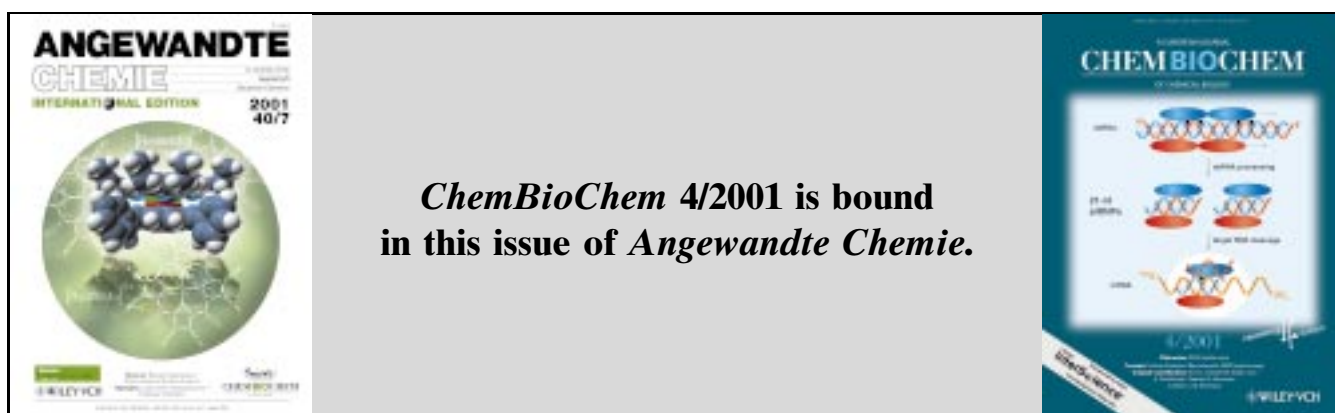


Cover Picture

James P. Collman, Roman Boulatov, and Geoffrey B. Jameson

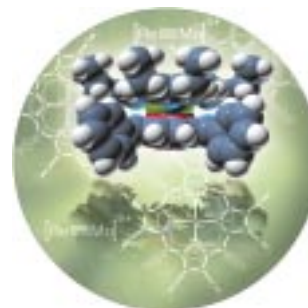
The cover picture shows the metalloporphyrin heterodimer $[(\text{tpp})\text{Mo}^{\text{IV}}\text{Re}(\text{oep})]^+$ with the novel $[\text{Mo}^{\text{IV}}\text{Re}]^{5+}$ core. The core represents the first example of a quadruple bond between elements of different triads, thus proving that heterometallic quadruple bonds are not limited to the Group 6 metals. From the space-filling model it is clear that there is no interaction between the stabilizing porphyrin ligands. The ORTEP plot in a projection along the Re–Mo axis emphasizes the perfectly eclipsed geometry of the porphyrins, which is unambiguous proof of the existence of the quadruple bond in the solid state. The diamagnetism and large magnetic anisotropy of the cation, as determined by ^1H NMR spectroscopy, indicate that the quadruple bond is retained in solution. A logical and well-defined synthetic route was used to synthesize the dimer, and can be extended to other metalloporphyrins to generate further novel quadruple bonds (the picture was generated by Marina Boulan, St. Petersburg, Russia), full details are reported by J. P. Collman et al. on p. 1271 ff.





COVER PICTURE

The cover picture shows the metalloporphyrin heterodimer $[(\text{tpp})\text{Mo}^{\text{IV}}\text{Re}(\text{oep})]^+$ with the novel $[\text{Mo}^{\text{IV}}\text{Re}]^{5+}$ core. The core represents the first example of a quadruple bond between elements of different triads, thus proving that heterometallic quadruple bonds are not limited to the Group 6 metals. From the space-filling model it is clear that there is no interaction between the stabilizing porphyrin ligands. The ORTEP plot in a projection along the Re–Mo axis emphasizes the perfectly eclipsed geometry of the porphyrins, which is unambiguous proof of the existence of the quadruple bond in the solid state. The diamagnetism and large magnetic anisotropy of the cation, as determined by ^1H NMR spectroscopy, indicate that the quadruple bond is retained in solution. A logical and well-defined synthetic route was used to synthesize the dimer, and can be extended to other metalloporphyrins to generate further novel quadruple bonds (the picture was generated by Marina Boulan, St. Petersburg, Russia), full details are reported by J. P. Collman et al. on p. 1271 ff.



An atomistic view of electrochemistry? Modern surface-science techniques applied to single-crystal electrodes with structurally well-defined surfaces allow electrochemists to study the metal/electrolyte interface and simple electrochemical reactions at a level of sophistication unheard of some twenty years ago.

Angew. Chem. **2001**, *113*, 1198–1220

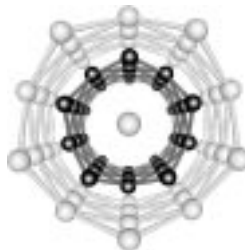
D. M. Kolb* 1162–1181

Electrochemical Surface Science

Keywords: electrochemistry • scanning tunneling microscopy • surface analysis • surface structure

Variety and individuality are characteristics of the crystal structures of the subhalides that can be obtained through the partial oxidation of the intermetallic phases of bismuth and an electron-rich transition metal. The spatial extent of the intermetallic structural region is mainly determined by the degree of oxidation. This results in “porous” and low-dimensional metals (see picture) as well as ionic and molecular cluster compounds.

Angew. Chem. **2001**, *113*, 1222–1234



M. Ruck* 1182–1193

From the Metal to the Molecule—Ternary Bismuth Subhalides

Keywords: bismuth • cluster compounds • intermetallic phases • low-dimensional metals • subvalent compounds

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>

The First Phosphine Oxide Ligand Precursors for Transition Metal Catalyzed Cross-Coupling Reactions: C–C, C–N, and C–S Bond Formation on Unactivated Aryl Chlorides

G. Y. Li*



Modular Pyridinyl Peptide Ligands in Asymmetric Catalysis: Enantioselective Synthesis of Quaternary Carbon Atoms Through Cu-Catalyzed Allylic Substitutions

C. A. Luchaco-Cullis,
H. Mizutani, K. E. Murphy,
A. H. Hoveyda*



Cyclic Dimers of Metalloporphyrins as Tunable Hosts for Fullerenes: A Remarkable Effect of Rhodium(III)

J.-Y. Zheng, K. Tashiro,
Y. Hirabayashi, K. Kinbara,
K. Saigo,* T. Aida,*
S. Sakamoto, K. Yamaguchi

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

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

Direct Observation of Surface-Controlled Self-Assembly of Coordination Cages by using Atomic Force Microscopy as a Molecular Ruler

S. A. Levi, P. Guatterri,
F. C. J. M. van Veggel,
G. J. Vancso, E. Dalcanele,
D. N. Reinhoudt*

Fluorinated Bis(enyl) Ligands through Metal-Induced Dimerization of Fluorinated Allenes

D. Lentz,* S. Willemsen

Probing Guest Geometry and Dynamics through Host-Guest Interactions

T. Kusukawa, M. Yoshizawa,
M. Fujita*

Minifullerenes, bizarre cages, and highly reactive guests are currently causing a stir in fullerene chemistry. An example is C_{20} , recently generated in the gas phase, which constitutes the smallest conceivable classical fullerene.

Angew. Chem. **2001**, *113*, 1235–1237



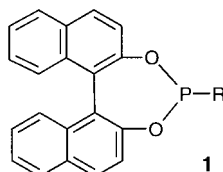
A. Hirsch* 1195–1197

New Cages and Unusual Guests:
Fullerene Chemistry Continues To Excite

Keywords: aromaticity •
cage compounds • fullerenes

Much better than their reputation are the rhodium(i) complexes of monophosphorus ligands, which were believed to be unsuitable for use in highly enantioselective hydrogenation reactions and have lain dormant and forgotten for 30 years. Now values of >99% *ee* have been reached in the hydrogenation of standard substrates when the ligand used is the binaphthol derivative **1**. As the synthesis of the monodentate ligands is often simpler than that of the more common diphosphorus ligands, a new and promising area of application has been opened up.

Angew. Chem. **2001**, *113*, 1237–1240



I. V. Komarov, A. Börner* .. 1197–1200

Highly Enantioselective or Not?—Chiral
Monodentate Monophosphorus Ligands
in the Asymmetric Hydrogenation

Keywords: asymmetric catalysis •
chelate complexes • hydrogenation •
P ligands • phosphanes

CORRESPONDENCE

“**[To bring] ... the essence of the world ...** [in each possible relation and from each point of view] to the clear and abstract perception of reason”. This is, according to Arthur Schopenhauer, the assignment of philosophy, and in Wallau’s interpretation, exactly this is accomplished by the logic of science established by Karl Popper for the field of empirical science. Therefore, its rejection by Jerome Berson in his essay “Kekulé Escapes, Popper Notwithstanding” is unfounded. This is a claim that Berson refutes in his reply.

Angew. Chem. **2001**, *113*, 1241–1243

Angew. Chem. **2001**, *113*, 1244–1245

W. M. Wallau* 1201–1203

Kekulé Escapes, Popper As Well

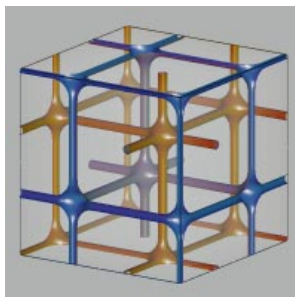
J. A. Berson* 1204–1205

Reply

Keywords: correspondence • falsification
criterion • Kekulé, August • philosophy
of science • Popper, Karl

COMMUNICATIONS

Two distinct channel systems are present in a polymer–inorganic nanocomposite, the structure of which is based on a bicontinuous plumber’s nightmare (a regular array of completely interconnected tubes; see picture). Calcination at high temperatures leads to a metal oxide containing mesoporous silica-type material with promise for application in separation technology and catalysis.



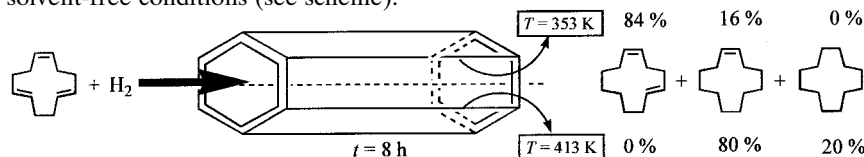
Angew. Chem. **2001**, *113*, 1248–1251

A. C. Finnefrock, R. Ulrich,
A. Du Chesne, C. C. Honeker,
K. Schumacher, K. K. Unger,
S. M. Gruner, U. Wiesner* .. 1208–1211

Metal Oxide Containing Mesoporous
Silica with Bicontinuous “Plumber’s
Nightmare” Morphology from a Block
Copolymer–Hybrid Mesophase

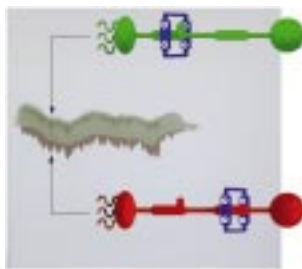
Keywords: block copolymers •
mesophases • mesoporous materials •
nanostructures • organic–inorganic
hybrid composites

The point of attachment of bimetallic Ru₆Sn particles which are anchored to the pore walls of a highly dispersed high-area mesoporous silica is found to be the tin atom, as indicated by in situ and ex situ measurements. This catalyst displays high activity for the low-temperature, selective hydrogenation of cyclic polyenes under solvent-free conditions (see scheme).



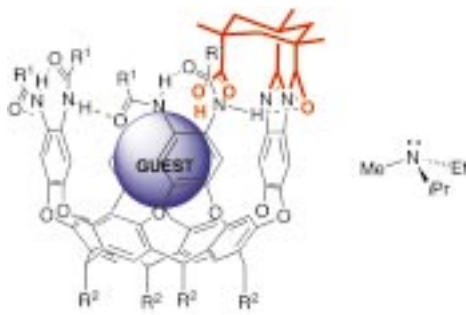
Angew. Chem. **2001**, *113*, 1251–1255

Separation of the two translational isomers by preparative thin-layer chromatography (see picture) and a kinetic study of their interconversion are possible when a central barrier is inserted between two stations on the rod section in the dumbbell component of a [2]rotaxane. This switchable [2]rotaxane incorporates a monopyrrolotetrathiafulvalene unit and a 1,5-dioxynaphthalene ring system within its rod section and the tetracationic cyclobis(paraquat-*p*-phenylene) as its ring component.



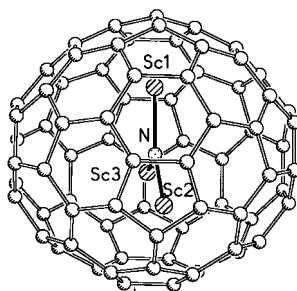
Angew. Chem. **2001**, *113*, 1256–1261

An introverted carboxy functionality of the cavitand shown, significantly alters the dynamics of nitrogen inversion of guest molecules, as well as the hydrogen bonding and guest tumbling in the inner recess. For example, NMR experiments indicate that N-inversion of ethylmethyloisopropylamine is several orders of magnitude slower in the cavitand than the rate observed in solution.



Angew. Chem. **2001**, *113*, 1261–1262

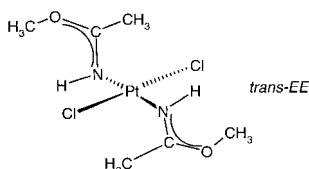
The unfavorable D_{3h} isomer of the C₇₈ fullerene cage is present in Sc₃N@C₇₈, an endohedral fullerene which has been prepared by the trimetallic nitride template process. The crystal structure of the fullerene–porphyrin adduct Sc₃N@C₇₈·[Co(oep)]·1.5 C₆H₆·0.3 CHCl₃ (oep = octaethylporphyrin) shows that the scandium atoms are located over the centers of the [6,6] ring junctions of pyracylene patches on the inner surface of the fullerene (see picture).



Angew. Chem. **2001**, *113*, 1263–1265



1,2-Intrastrand chelation is not unique for cisplatin adducts of nucleic acids, but is also possible for Pt complexes having a *trans* geometry. This possibility is demonstrated by the formation of an unprecedented cross-link of a *trans*-Pt-iminoether complex (*trans*-EE, see picture) with the A(N3) and G(N7) positions of the ribonucleotide r(ApG).



Angew. Chem. **2001**, *113*, 1266–1268

S. Hermans, R. Raja, J. M. Thomas,*
B. F. G. Johnson,* G. Sankar,
D. Gleeson 1211–1215

Solvent-Free, Low-Temperature,
Selective Hydrogenation of Polyenes
using a Bimetallic Nanoparticle Ru–Sn
Catalyst

Keywords: cycloalkenes • hydrogenation •
mesoporous materials • ruthenium •
supported catalysts

J. O. Jeppesen, J. Perkins, J. Becher,*
J. F. Stoddart* 1216–1221

Slow Shuttling in an Amphiphilic Bistable
[2]Rotaxane Incorporating a
Tetrathiafulvalene Unit

Keywords: isomerization • rotaxanes •
self-assembly • supramolecular chemistry •
tetrathiafulvalene

P. L. Wash, A. R. Renslo,
J. Rebek, Jr.* 1221–1222

Isolation of an Acid/Base Complex in
Solution Puts the Brakes on Nitrogen
Inversion

Keywords: amines • cavitands •
host–guest systems • kinetics •
nitrogen inversion

M. M. Olmstead, A. de Bettencourt-Dias,
J. C. Duchamp, S. Stevenson, D. Marciu,
H. C. Dorn,* A. L. Balch* .. 1223–1225

Isolation and Structural Characterization
of the Endohedral Fullerene Sc₃N@C₇₈

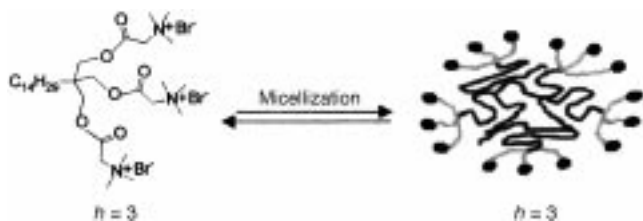
Keywords: fullerenes • nitrides •
scandium • structure elucidation

Y. Liu, C. Pacifico, G. Natile,
E. Sletten* 1226–1228

Antitumor *trans* Platinum Complexes can
Form Cross-Links with Adjacent Purine
Groups

Keywords: antitumor agents •
bioinorganic chemistry • coordination
chemistry • NMR spectroscopy •
nucleotides

Folding of hydrocarbon chains and reduction in micelle size are observed as the number of headgroups (h) on the new single-chain cationic surfactants increases from ($h = 1$) to bident ($h = 2$) or trident ($h = 3$, see picture). The aggregation number is dramatically decreased and the fractional charge on the micelle increases with the increase in the charge at the headgroup.



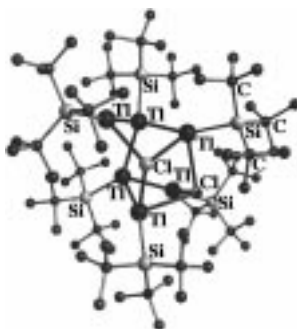
Angew. Chem. **2001**, *113*, 1278–1282

J. Haldar, V. K. Aswal, P. S. Goyal,
S. Bhattacharya* 1228–1232

Molecular Modulation of Surfactant
Aggregation in Water: Effect of the
Incorporation of Multiple Headgroups on
Micellar Properties

Keywords: chain structures • micelles •
small-angle neutron scattering •
surfactants • viscoelasticity

The largest Tl clusters to date with covalently linked Tl atoms are contained in the title compounds obtained from TlCl_3 and two molar equivalents of NaSi^tBu_3 in THF at -78°C . The structure of $(\text{Si}^t\text{Bu}_3)_6\text{Tl}_6\text{Cl}_2$, which contains two Tl_3Cl four-membered rings linked through the central Tl atoms and the Cl atoms, is depicted.



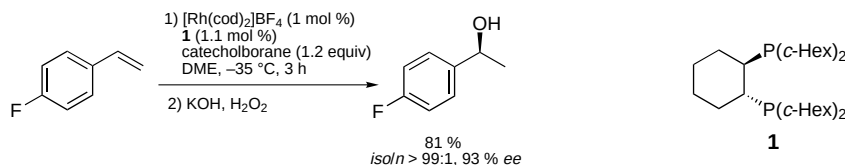
Angew. Chem. **2001**, *113*, 1275–1278

N. Wiberg,* T. Blank, H.-W. Lerner,
D. Fenske, G. Linti 1232–1235

$\text{R}_4^*\text{Tl}_3\text{Cl}$ and $\text{R}_6^*\text{Tl}_6\text{Cl}_2$ ($\text{R}^* = \text{Si}^t\text{Bu}_3$)—
The First Compounds with Larger
Clusters Containing Covalently Linked
Thallium Atoms

Keywords: cluster compounds • silicon •
structure elucidation • thallium

 **A double [2,3] sigmatropic rearrangement** enables the fast synthesis of novel C_2 -symmetrical 1,2-diphosphanes in good yields. These phosphanes (for example, **1**; $c\text{-Hex}$ = cyclohexyl) are highly efficient ligands for the rhodium-catalyzed asymmetric hydroboration of a wide variety of styrenes (see scheme). $\text{cod} = 1,5$ -cyclooctadiene; DME = 1,2-dimethoxyethane.



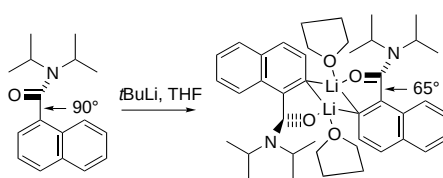
Angew. Chem. **2001**, *113*, 1272–1275

S. Demay, F. Volant,
P. Knochel* 1235–1238

New C_2 -Symmetrical 1,2-Diphosphanes
for the Efficient Rhodium-Catalyzed
Asymmetric Hydroboration of Styrene
Derivatives

Keywords: asymmetric catalysis •
hydroboration • P ligands • phosphanes •
rearrangement • rhodium

Despite the near-perpendicular arrangement of the amide group and aromatic ring in many tertiary aromatic amides, *ortho*-lithiation is still a very straightforward process. The first X-ray crystal structures of *ortho*-lithiated amides reveal why: the angle of twist is lessened to some degree, and the lithium ion lies far from the plane of the aromatic ring, with stabilization of the strained structure being achieved by dimerization (see scheme).



Angew. Chem. **2001**, *113*, 1282–1285

J. Clayden,* R. P. Davies,
M. A. Hendy, R. Snaith†,
A. E. H. Wheatley* 1238–1240

The First Crystallographic Evidence for
the Structures of *ortho*-Lithiated
Aromatic Tertiary Amides

Keywords: amides • lithiation • *ortho*-
metalation • solid-state structures

Atoms, bonds, clusters: The reaction of a meta-stable GaBr solution with trisyllithium ($\text{LiC}(\text{SiMe}_3)_3$) led to a novel cluster unit: two tetrahedral Ga_4R_3 units are linked through a Ga–Ga bond to give the Ga_8R_6 cluster ($\text{R} = \text{C}(\text{SiMe}_3)_3$; see picture; Ga: dark blue, C: light blue, SiMe_3 : not shown), which contains the prototype of a localized metal–metal bond.



A. Schnepf, R. Köppe,
H. Schnöckel* 1241–1243

A Ga_8R_6 Cluster as an Ideal Model for a Metal–Metal Bond?

Keywords: ab initio calculations • cluster compounds • gallium • metal–metal interactions

Angew. Chem. **2001**, *113*, 1287–1290

A “cracking” good performance: Cycloalkanes, which are easily accessible from the surplus aromatic products of petrochemistry, can be converted under hydrogen into a steamcracker feed consisting mainly of *n*-alkanes. The highest yields are obtained on zeolite H-ZSM-5 with tiny amounts of noble metals—a catalyst with a new type of cracking performance.

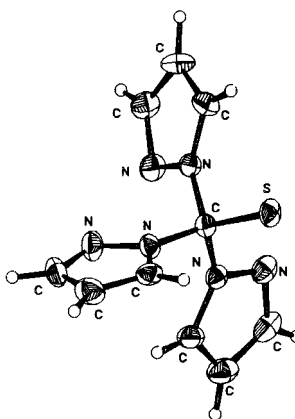
A. Raichle, Y. Traa, F. Fuder, M. Rupp,
J. Weitkamp* 1243–1246

Haag–Dessau Catalysts for Ring
Opening of Cycloalkanes

Keywords: cycloalkanes • Haag–Dessau catalysts • heterogeneous catalysis • petrochemistry • zeolites

Angew. Chem. **2001**, *113*, 1268–1272

Trifluoromethylthiolate $[\text{CF}_3\text{S}]^-$, which contains activated C–F bonds, can act not only as a nucleophile but also can undergo nucleophilic substitution by $\text{Me}_3\text{Si-Az}$ ($\text{Az} = \text{pyrazolyl}$, 1,2,4-triazolyl, imidazolyl) leading to the corresponding tris(azolyl)methylthiolates $[(\text{Az})_3\text{CS}]^-$ (the structure of the anion with $\text{Az} = \text{pyrazolyl}$ is shown), a potential new class of scorpionates. Tetrapyrrole-methane was isolated from the reaction with trimethylsilylpyrrole.



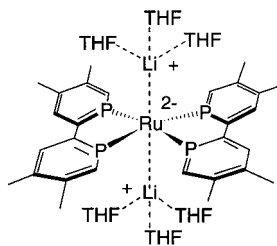
M. Müller, E. Lork,
R. Mews* 1247–1249

Tris(azolyl)methylthiolates: Another New
Scorpionate Class?

Keywords: C–F activation • N ligands • S nucleophiles • scorpionates • thiolates

Angew. Chem. **2001**, *113*, 1285–1287

Two partially reduced ligands and a d^8 -configured Ru^0 center are shown by extended Hückel calculations to be present in a ruthenium complex containing a dianionic $\text{Ru}(2-)$ center stabilized by the 2,2'-biphosphinine ligand. The ruthenium complex shown (and its iron analogue) adopts a square-planar geometry which is quite unusual for a ML_4 complex having a formal d^{10} electronic configuration.



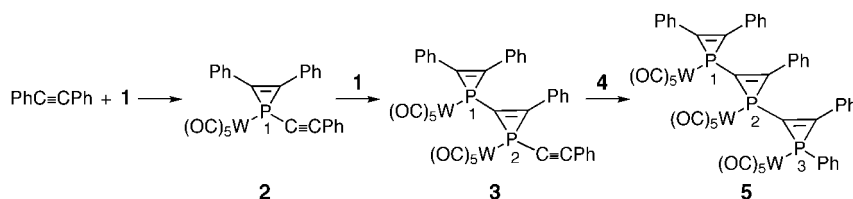
P. Rosa, N. Mézailles, L. Ricard,
F. Mathey, P. Le Floch,*
Y. Jean 1251–1253

Dianionic Iron and Ruthenium(2–)
Biphosphinine Complexes: A Formal d^{10}
Ruthenium Complex with a Square
Planar Geometry

Keywords: electronic structure • iron • P ligands • phosphinines • ruthenium

Angew. Chem. **2001**, *113*, 1291–1293

No end in sight: the mono-, bi-, and triphosphirenes **2**, **3**, and **5**, respectively, are prepared by a simple iterative method (see scheme; **1** = $[\text{Ph} \equiv \text{CPW}(\text{CO})_5]$, **4** = $[\text{PhPW}(\text{CO})_5]$); these oligomers offer numerous possibilities in coordination chemistry and catalysis. They can serve to create numerous other classes of polyphosphine chains by ring opening or ring expansion of the phosphirene units.



N. H. Tran Huy,* L. Ricard,
F. Mathey* 1253–1255

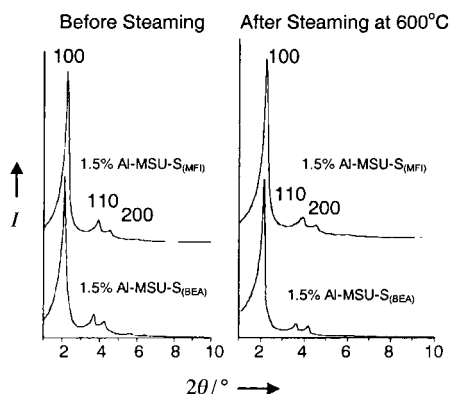
Stepwise Building of Polyphosphirene
Chains

Keywords: oligomers • P ligands • phosphirenes • small ring systems • tungsten

Angew. Chem. **2001**, *113*, 1293–1295

Protozeolitic nanoclusters or “zeolite seeds” templated by quaternary ammonium ions are shown to be effective precursors for the assembly of an improved class of aluminosilicate mesostructures, denoted MSU-S, which retain well-expressed hexagonal X-ray diffraction patterns and open mesopores even after exposure to steam at 600°C (see picture).

Angew. Chem. **2001**, *113*, 1295–1298



Y. Liu, W. Zhang,
T. J. Pinnavaia * 1255–1258

Steam-Stable MSU-S Aluminosilicate
Mesostructures Assembled from Zeolite
ZSM-5 and Zeolite Beta Seeds

Keywords: aluminosilicates •
heterogeneous catalysis • mesophases •
supramolecular chemistry • zeolites

Self-assembly of preformed aluminosilicate nanoclusters in the presence of templating micella provides a route to strongly acidic, hydrothermally stable mesoporous aluminosilicates with ordered hexagonal structures (MAS-5). Results show that the materials are similar to Beta zeolite and are highly active for the catalytic cracking of 1,3,5-triisopropylbenzene.

Angew. Chem. **2001**, *113*, 1298–1302

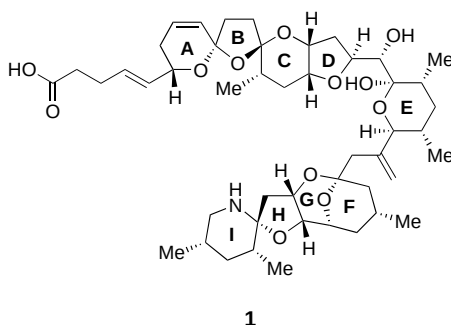
Z. Zhang, Y. Han, L. Zhu, R. Wang,
Y. Yu, S. Qiu,* D. Zhao,
F.-S. Xiao * 1258–1262

Strongly Acidic and High-Temperature
Hydrothermally Stable Mesoporous
Aluminosilicates with Ordered
Hexagonal Structure

Keywords: aluminosilicates •
heterogeneous catalysis • mesophases •
zeolites

As a causative agent of food poisonings, azaspiracid (1), a novel marine toxin isolated from the mussel *Mytilus edulis*, challenges the synthetic chemist with an intricate array of acetal and ketal structures. The construction of the FGHI ring system of azaspiracid was achieved by means of a key $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed cyclization to form the HI spirocycle. A final chemoselective intramolecular ketalization with $\text{Hg}(\text{OAc})_2$ formed the G ring, to afford the N-protected FGHI as a single diastereomer.

Angew. Chem. **2001**, *113*, 1302–1305

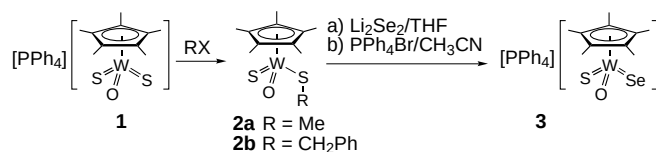


K. C. Nicolaou,* P. M. Pihko,
N. Diedrichs, N. Zou,
F. Bernal 1262–1265

Synthesis of the FGHI Ring System of
Azaspiracid

Keywords: cyclization • natural products •
spiro compounds • synthesis design

Oxygen, sulfur, and selenium all coordinate to the same tungsten atom in the mixed-chalcogenido complex $[\text{PPh}_4][\text{Cp}^*\text{W}(\text{O})(\text{S})(\text{Se})]$ (**3**; $\text{Cp}^* = \text{C}_5\text{Me}_5$), which has been prepared by the reaction of $[\text{Cp}^*\text{W}(\text{O})(\text{S})(\text{SR})]$ ($\text{R} = \text{Me}$ (**2a**), CH_2Ph (**2b**)) with Li_2Se_2 followed by cation exchange (see scheme). This unique mixed-chalcogenido complex is thermodynamically stable, and does not exhibit chalcogen-exchange reactions in solution.



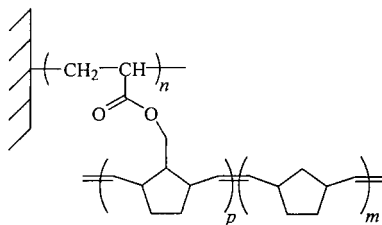
Angew. Chem. **2001**, *113*, 1306–1308

H. Kawaguchi, K. Tatsumi * 1266–1268

Synthesis of a Cp^* Complex of Tungsten
with Three Different Chalcogenido
(O^{2-} , S^{2-} , and Se^{2-}) Ligands

Keywords: chalcogens •
chiral complexes • selenium • sulfur •
tungsten

Controlling the adhesion: a poly-(norbornenylmethylene acrylate) coating was electrografted onto various conducting substrates, in a subsequent step, an initiator of ring-opening metathesis polymerization (ROMP) was attached to the norbornene pendant groups, and norbornene was polymerized, so forming a strongly adhering coating (see picture). This strategy which combines the “electrografting from” method and the more classical “grafting from” copolymerization is a novel powerful way to control adhesion, thickness, and the chemical properties of organic coatings.



Angew. Chem. **2001**, *113*, 1308–1311

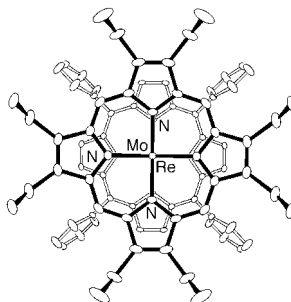
C. Detrembleur, C. Jérôme, M. Claes,
P. Louette, R. Jérôme* 1268–1271

Combination of Electrografting and Ring-Opening Metathesis Polymerization: An Efficient Way to Prepare Polynorbornene Brushes on Conducting Substrates

Keywords: coatings • electrochemistry • metathesis • polymer films • polymerization



Heterometallic quadruple bonds are very rare and although known since 1974, have been restricted to the Cr⁴Mo and the Mo⁴W cores. Now the synthesis and structure of a quadruply bonded Mo-Re heterodimer, [(tetraphenylporphyrin)-Mo⁴Re(octaethylporphyrin)]PF₆, is reported (see picture). This complex proves that quadruple bonds can exist between elements from different triads.



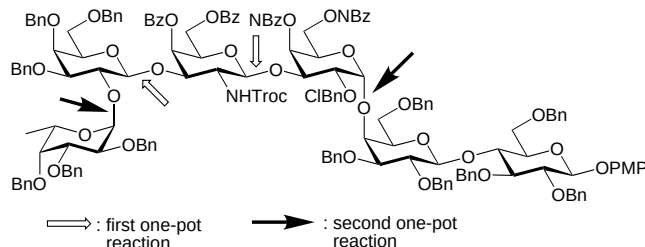
J. P. Collman,* R. Boulatov,
G. B. Jameson 1271–1274

The First Quadruple Bond Between Elements of Different Groups

Keywords: metalloporphyrins • metal–metal interactions • molybdenum • quadruple bonds • rhenium

Angew. Chem. **2001**, *113*, 1311–1314

Designer saccharides: The cancer antigen Globo H hexasaccharide has been synthesized from designed building blocks in a rapid, stereoselective, and high-yielding manner by using the reactivity-based one-pot strategy (see scheme) guided by the OptiMer computer program. Bn = benzyl, Bz = benzoyl, ClBn = *ortho*-chlorobenzyl, NBz = *para*-nitrobenzoyl, NHTroc = 2,2,2-trichloroethylcarbamate, PMP = *para*-methoxyphenyl.



Angew. Chem. **2001**, *113*, 1314–1317

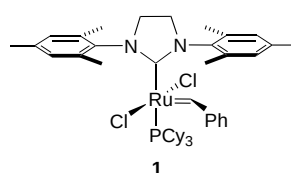
F. Burkhardt, Z. Zhang,
S. Wacowich-Sgarbi,
C.-H. Wong* 1274–1277

Synthesis of the Globo H Hexasaccharide Using the Programmable Reactivity-Based One-Pot Strategy

Keywords: combinatorial chemistry • Globo H • oligosaccharides • one-pot synthesis • synthetic methods



Electronic and steric properties of the substituents on the amide nitrogen govern the yield and rate of the cross-metathesis between a variety of α,β -unsaturated amides and olefins with **1** as the catalyst. This influence is the result of deactivation of the catalyst by chelation of the carbonyl group to the metal. However, an increase in catalyst loading compensates for the chelation effect.



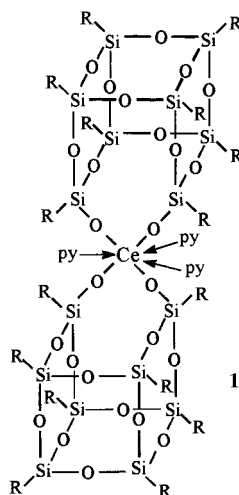
T.-L. Choi, A. K. Chatterjee,
R. H. Grubbs* 1277–1279

Synthesis of α,β -Unsaturated Amides by Olefin Cross-Metathesis

Keywords: amides • chelates • cross-coupling • metathesis • ruthenium

Angew. Chem. **2001**, *113*, 1317–1319

The diamagnetic Ce^{IV} complex 1 is the main product of the reaction of the Ce^{III} compounds [Ce{N(SiMe₃)₂}₃] or CeCl₃ with two equivalents of the polyhedral silsesquioxane (c-C₆H₁₁)₈Si₈O₁₁-(OH)₂ in the presence of pyridine (py). Compound **1** is a potential homogeneous analogue of silica-supported rare earth metal catalysts, and its novel synthesis may open routes to other metallasilsesquioxanes. R = cyclohexyl.



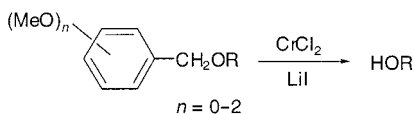
Y. K. Gun'ko,* R. Reilly,
F. T. Edelmann,*
H.-G. Schmidt 1279–1281

The First Ce^{IV} Metallasilsesquioxane
Complex: [Ce{(c-C₆H₁₁)₈Si₈O₁₃}₂(py)₃]

Keywords: catalysts • cerium •
O ligands • silicon

Angew. Chem. **2001**, *113*, 1319–1321

CrCl₂/LiI selectively cleave benzyl ethers and methoxy-substituted benzyl ethers (see scheme) in the order: C₆H₅CH₂OR < 4-MeOC₆H₄CH₂OR < 3,4-(MeO)₂-C₆H₃CH₂OR < 2,6-(MeO)₂C₆H₃CH₂OR. In contrast, C₆H₅CH₂OR is more readily cleaved than 2,6-(MeO)₂C₆H₃CH₂OR during catalytic hydrogenolysis while 3,4-(MeO)₂C₆H₃CH₂OR is cleaved faster than 2,6-(MeO)₂C₆H₃CH₂OR with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



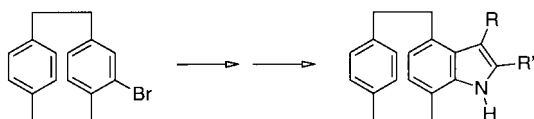
J. R. Falck,* D. K. Barma, R. Baati,
C. Mioskowski 1281–1283

Differential Cleavage of Arylmethyl
Ethers: Reactivity of
2,6-Dimethoxybenzyl Ethers

Keywords: chemoselectivity • chromium •
cleavage reactions • protecting groups •
reductions

Angew. Chem. **2001**, *113*, 1321–1323

Fancy drug candidates: The first preparation of indoloparacyclophanes is reported through the use of the Buchwald variant of the Fischer indole synthesis (see scheme). Receptor binding studies clearly demonstrated that the double-layered molecular scaffold can serve as an effective arylbioisostere.



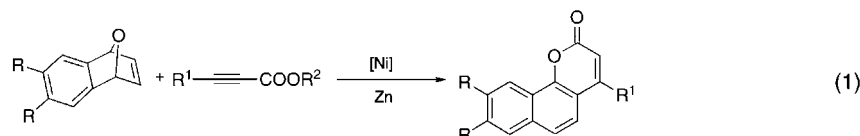
B. Ortner, R. Waibel,
P. Gmeiner* 1283–1285

Indoloparacyclophanes: Synthesis and
Dopamine Receptor Binding of a Novel
Arylbioisostere

Keywords: bioisosteres • cyclophanes •
Fischer indolization • indoles • receptors

Angew. Chem. **2001**, *113*, 1323–1325

7-Oxabenzonorbordienenes bearing various substituents react with propiolates in the presence of [NiBr₂(dppe)] (dppe = bis(diphenylphosphanyl)ethane) as a catalyst precursor and zinc powder to give benzocoumarin derivatives [Eq. (1)]. The one-pot reactions proceed at 80°C in acetonitrile, and the products are obtained in good yields with high regio- and stereoselectivity.



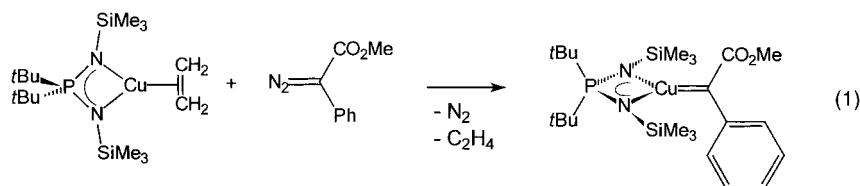
D. K. Rayabarapu, T. Sambaiah,
C.-H. Cheng* 1286–1288

Nickel-Catalyzed Highly Regio- and
Stereoselective Cyclization of
Oxanorborenones with Alkyl Propiolates:
A Novel Method for the Synthesis of
Benzocoumarin Derivatives

Keywords: alkenes • coumarins •
cyclization • nickel

Angew. Chem. **2001**, *113*, 1326–1328

A tailor-made copper ethylene complex was used to prepare solutions of highly reactive copper(I) carbene complexes of the d^{10} - ML_3 type which are active in olefin cyclopropanation and have been characterized unambiguously in situ [Eq. (1)]. Electronic and structural features of this novel class of compounds were determined by NMR spectroscopy.



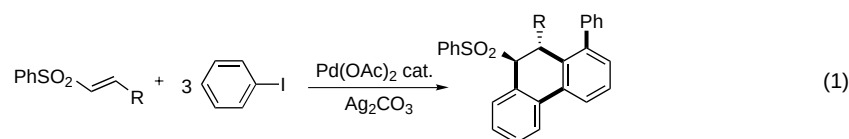
Angew. Chem. **2001**, *113*, 1328–1330

B. F. Straub, P. Hofmann* ... 1288–1290

Copper(I) Carbenes: The Synthesis of Active Intermediates in Copper-Catalyzed Cyclopropanation

Keywords: carbene complexes • copper • cyclopropanation • diazo compounds • N ligands

Four C–C bonds are formed in a single step by an intermolecular four-component cascade pathway. 1-Phenyl-9-phenylsulfonyl-9,10-dihydrophenanthrenes are formed in the palladium-catalyzed Heck-like reaction of α,β -unsaturated phenyl sulfones with three equivalents of iodobenzene in the presence of Ag_2CO_3 [Eq. (1)].



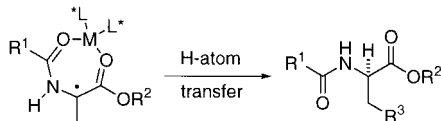
Angew. Chem. **2001**, *113*, 1331–1333

P. Mauleón, I. Alonso, J. C. Carretero* 1291–1293

Unusual Palladium-Catalyzed Cascade Arylation of α,β -Unsaturated Phenyl Sulfones under Heck Reaction Conditions

Keywords: Heck reaction • metallacycles • palladium • phenanthrenes • sulfones

Glycine radicals derived from conjugate radical additions to dehydroalanines complexed to chiral Lewis acids (L^*) undergo enantioselective H-atom transfer to furnish α -amino acids (see scheme). A variety of amino acids with *ee* values ranging from 27–85% can be prepared with good chemical efficiency.



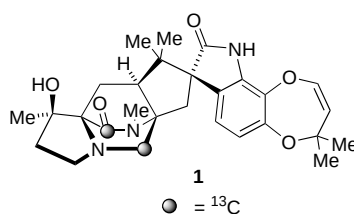
Angew. Chem. **2001**, *113*, 1333–1336

M. P. Sibi,* Y. Asano, J. B. Sausker 1293–1296

Enantioselective Hydrogen Atom Transfer Reactions: Synthesis of *N*-Acyl- α -Amino Acid Esters

Keywords: amino acids • enantioselectivity • hydrogen transfer • Lewis acids • radical reactions

Looking for the right path: An advanced metabolite involved in the biosynthesis of paraherquamide A (**1**) has been synthesized in a doubly ^{13}C -labeled form and shown to be incorporated into the potent anthelmintic alkaloid **1** by *Penicillium fellutanum*. The results are discussed in terms of a unified biogenesis of the paraherquamides and VM55599.



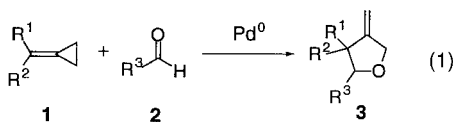
Angew. Chem. **2001**, *113*, 1336–1338

E. M. Stocking, J. F. Sanz-Cervera, R. M. Williams* 1296–1298

Studies on the Biosynthesis of Paraherquamide: Synthesis and Incorporation of a Hexacyclic Indole Derivative as an Advanced Metabolite

Keywords: biosynthesis • Diels–Alder reaction • isotopic labeling • metabolites • natural products

Multiply substituted tetrahydrofuran rings can be prepared by the [3+2] cycloaddition of alkylidenecyclopropanes **1** with aldehydes **2** [Eq. (1)]. In this reaction, the distal bond of the cyclopropane ring is cleaved, and 3-methylenetetrahydrofuran derivatives **3** are produced in good yields.



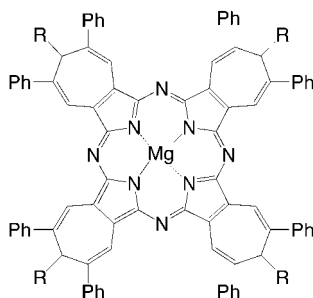
Angew. Chem. **2001**, *113*, 1338–1340

I. Nakamura, B. H. Oh, S. Saito, Y. Yamamoto* 1298–1300

Novel [3+2] Cycloaddition of Alkylidenecyclopropanes with Aldehydes Catalyzed by Palladium

Keywords: aldehydes • cycloaddition • heterocycles • palladium • synthetic methods

Both the size and symmetry of the π -conjugated systems change during dehydrogenation/hydrogenation cycles of a phthalocyanine analogue fused with four cycloheptatriene rings (see picture, R = H or Ph).



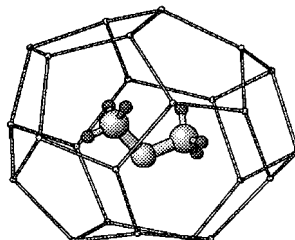
N. Kobayashi,* T. Nonomura,
K. Nakai 1300–1303

A Seven-Membered Carbon-Ring-Fused
Phthalocyanine Analogue in which the
 π System Changes during
Dehydrogenation/Hydrogenation Cycles

Keywords: dehydrogenation •
hydrogenation • phthalocyanines •
redox chemistry

Angew. Chem. **2001**, *113*, 1340–1343

Filling space with a host of cages: completely hydrophobic interactions between organic molecules and water are present in the novel clathrate hydrate that has dimethyl ether guests in three different cages. One of these cages is the previously unreported tetrakaidecahedron (4^5106^3) and is shown in the picture along with an encapsulated dimethyl ether molecule.



K. A. Udachin, C. I. Ratcliffe,
J. A. Ripmeester* 1303–1305

A Dense and Efficient Clathrate Hydrate
Structure with Unusual Cages

Keywords: clathrates • host–guest
systems • hydrates • supramolecular
chemistry • water

Angew. Chem. **2001**, *113*, 1343–1345

A simple hydride-transfer mechanism to produce alkyl cations occurs when isolated protonated hydrogen peroxide (HOOH_2^+) attacks the C–H bonds of alkanes (except methane) [Eq. (1)]. The chemical properties of HOOH_2^+ , which may serve as a model of the central catalytic motif of key biological systems, have been studied for the first time.



Å. M. Leere Øiestad, A. C. Petersen,
V. Bakken, J. Vedde,
E. Uggerud* 1305–1309

The Oxidative Power of Protonated
Hydrogen Peroxide

Keywords: C–H activation •
ion–molecule reactions • oxidation •
peroxides • protonation

Angew. Chem. **2001**, *113*, 1345–1349



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In the description of the cover picture of Issue 4 on p. 637 it should say $\text{Mes}^* = 2,4,6\text{-}t\text{Bu}_3\text{C}_6\text{H}_2$ instead of $\text{Mes}^* = 2,4,6\text{-}t\text{Bu}_3\text{C}_6\text{H}_3$.

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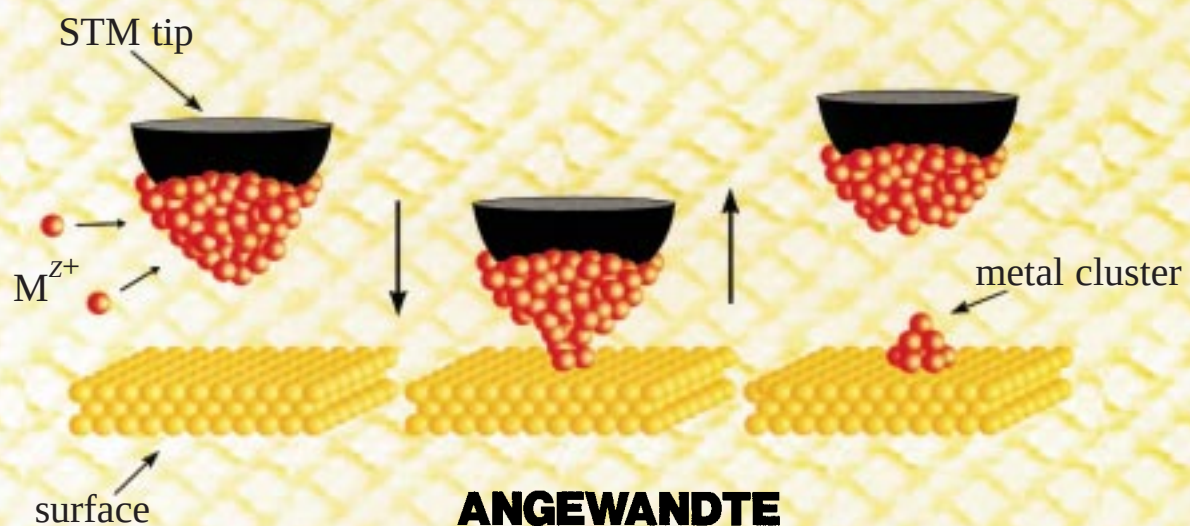
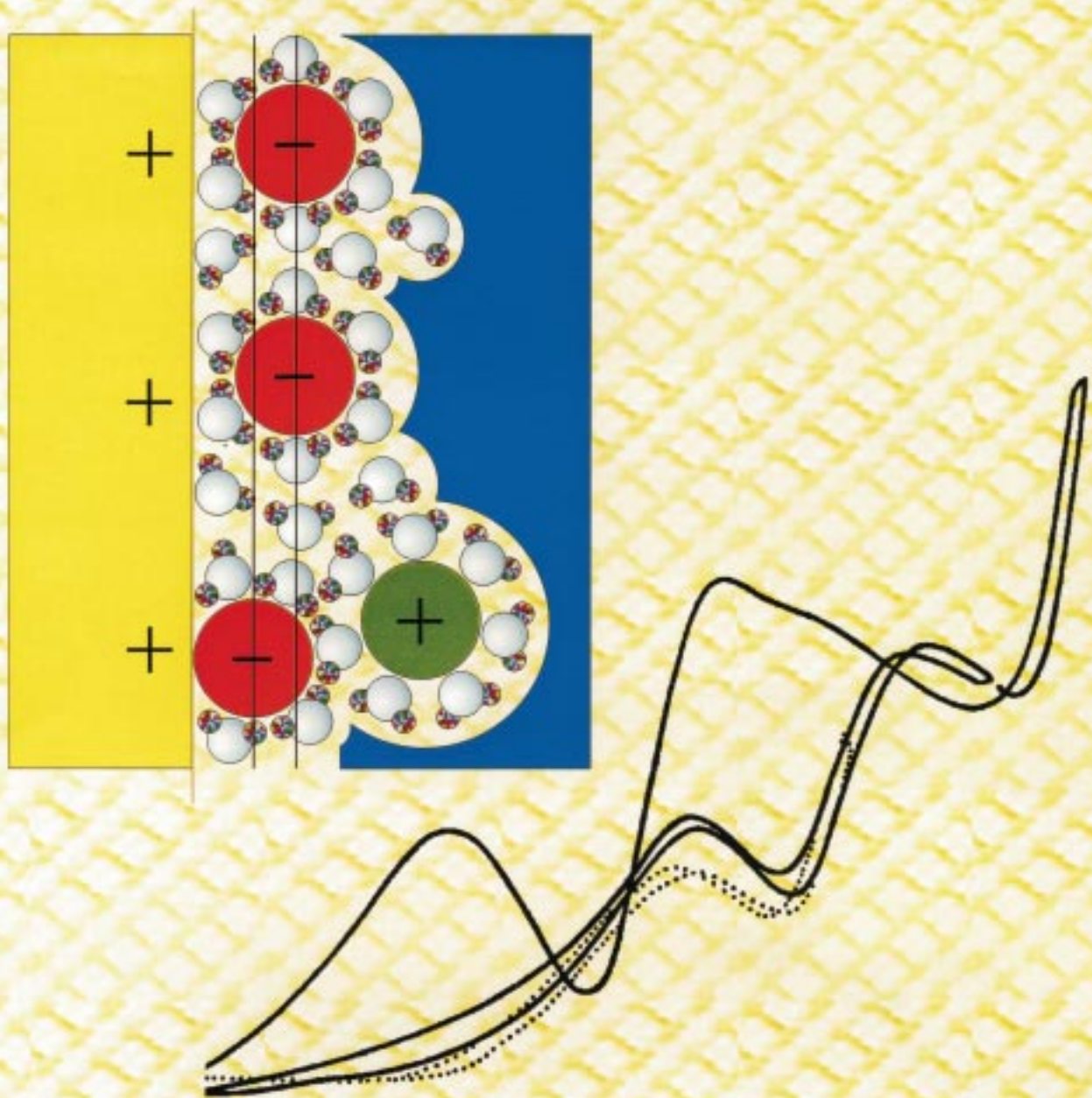
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electrochemical surface science



Electrochemical Surface Science**

Dieter M. Kolb*

The last 30 years have seen remarkable changes in interfacial electrochemistry, particularly in the kind of questions that were addressed in electrochemical studies. Ever since classical surface science, traditionally performed under ultrahigh vacuum conditions, has succeeded in describing surfaces and surface reactions on a molecular level,

electrochemists longed for a microscopic understanding of the solid/electrolyte interface and, at the same time, searched widely for new experimental ways to reach that goal. Herein, studies are described concerning the structure and the dynamics of bare and adsorbate-covered electrode surfaces and of metal deposition as a simple, yet im-

portant, electrochemical process. In all these cases, the scanning tunneling microscope plays a pivotal role emphasizing the surface-science approach to the problems.

Keywords: electrochemistry • scanning tunneling microscopy • surface analysis • surface structure

1. Introduction

Electrochemistry deals in the widest sense with chemical reactions that are connected with the transfer of electric charge. Typical examples are the oxidation (reduction) of Fe^{2+} (Fe^{3+}) [Eq. (1)] or the oxidation or deposition of a metal from solution [Eq. (2)].



The former is an electron-transfer reaction; the latter an ion-transfer reaction. Such reactions occur normally at the interface between an electrode, which in most cases is an electronic conductor, and the electrolyte, an ionic conductor. The electrochemical reaction acts as a switch between both types of conductivity and allows an electric current to pass the interface (faradaic current). In the absence of an electrochemical reaction, the interface blocks charge transport, behaving like a capacitor that can be charged or discharged (capacitive current). Electrochemical reactions can be driven and controlled by applying a voltage between the (working)

electrode and a counter electrode, or—if the reactions occur spontaneously—can provide electric current.^[1–3]

The traditional way of studying electrochemical processes is to measure currents and voltages. Both quantities, which can be easily determined with high precision, are inherently suited to monitor the reaction and to almost uniquely classify the electrochemical system. With the development of a sophisticated thermodynamic treatment for the interface between a mercury electrode and an aqueous solution by D. C. Grahame,^[4] bare and adsorbate-covered surfaces (of Hg) could be described precisely in terms of surface energies and surface excesses as a function of the applied potential.^[5, 6] With the development of instationary current and voltage techniques, reactions could be described by formal reaction kinetics.^[7, 8] The classical electrochemical methods laid the basis for a thermodynamic and formal-kinetics description of electrochemical processes and hence were—and still are—invaluable for the field. The models derived from such measurements, such as the electric double layer, however, were largely phenomenological.^[9] Nevertheless, they seemed to work and thereby served the purpose.

In the mid-1960s, surface science began to demonstrate its potential for providing information about solid surfaces on an atomic or molecular level. With an ever-increasing number of structure-specific and surface-sensitive techniques, mainly based on the electron as a probe (photoelectron spectroscopy and electron diffraction), detailed insights on ordered adsorption (superlattices), adsorption sites, surface band structures, bond lengths and so forth were obtained.^[10, 11] Of course, all these studies were performed under ultrahigh vacuum conditions (UHV) and hence were not directly applicable to electrochemical systems. Nevertheless, this surface science

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[**] This manuscript is based on the Bonhoeffer–Eucken–Scheibe lectures of the Deutsche Bunsengesellschaft, given by the author at Erlangen, Berlin, and Leipzig in 1999/2000.

has inspired and encouraged electrochemists to ask similar questions about the microscopic structure of the metal/electrolyte interface, about the influence of the surface structure on electrochemical reactions, and about the electronic and vibronic properties of adsorbates and their change with potential, to mention just a few. To find answers to such questions, however, required new routes involving new techniques, new types of electrodes, and new theoretical concepts.^[12]

2. The Experimental Basis of an Electrochemical Surface Science

Among the various requirements necessary to derive a microscopic picture of electrochemical processes, the following four in my opinion were the most crucial ones:^[13] 1) new techniques, 2) single-crystal surfaces with fully defined structures, 3) linking electrochemistry with UHV methods (ex situ approaches), and 4) new theoretical methods.

2.1. New Experimental Techniques

New experimental techniques were required that were able to provide information on a molecular basis but were applicable in situ. Quite obviously, these were optical spectroscopies. Reflectance spectroscopy in the visible and near-UV range, particularly electroreflectance, was among the first of the so-called nontraditional methods to address questions of the optical and electronic properties of adsorbates and thin metal or oxide overlayers.^[14] Later, this method was used to derive surface structure information by determining rotational anisotropies at normal incidence from linearly polarized light or involving surface band-structure effects.^[15] Then came surface-enhanced Raman spectroscopy, with which vibronic information became accessible.^[16] With the development of optical thin-layer cells for infrared studies a major barrier was shifted.^[17] In the end, almost the whole spectrum—from infrared to X-rays—became accessible for in situ studies. In situ IR spectroscopy began to yield invaluable information about reaction intermediates,^[18] whereas in situ X-ray diffraction and absorption provided structural

information of astounding precision and detail.^[19–22] Other nontraditional in situ techniques have joined in, such as the quartz-crystal microbalance for monitoring mass changes in the submonolayer range,^[23] spectroscopies based on nonlinear optics, such as second harmonic generation (SHG)^[24, 25] or sum-frequency generation (SFG),^[26] neutron scattering,^[27] and even NMR spectroscopy.^[28] A tremendous advance, however, came about with the scanning tunneling microscope, which soon after its invention for surface studies under UHV conditions^[29, 30] was adopted to electrochemical needs.^[31–33] This technique, which will play a dominant role in the studies described below, allows imaging of electrode surfaces in situ, in real space, and with atomic-scale resolution.

2.2. Single-Crystal Surfaces

For a detailed understanding of surface processes, the use of single-crystal electrodes with structurally well-characterized surfaces is highly desirable. Polycrystalline surfaces, routinely employed in the early days of electrochemical surface studies, are far too complicated for a reliable interpretation on an atomic level. Single-crystal surfaces need to be prepared and their structure characterized, which is by no means a trivial task for electrochemists. Since the classic method of preparing single-crystal surfaces involves sputtering and annealing of the crystal in a UHV chamber, the first systematic studies with single-crystal electrodes addressing the influence of the surface structure were performed with UHV-prepared samples in an apparatus that had a closed-transfer system between the electrochemical cell and UHV chamber.^[34–37] In parallel, single-crystal electrodes were prepared simply by mechanical and chemical or electrochemical polishing but without structural characterization; the quality of the data in retrospect varied from satisfactorily to unacceptable.

A major breakthrough was achieved when Clavilier et al. demonstrated that high-quality single-crystal platinum surfaces could be prepared simply with a Bunsen burner.^[38, 39] This so-called flame annealing, which was subsequently shown to work also for gold and silver,^[40] consisted of heating the crystal in the flame of a Bunsen burner for several seconds or minutes before it was quenched in ultrapure water and transferred to the electrochemical cell with a droplet of water



Dieter M. Kolb, born in 1942 in Amberg (Germany), studied physics at the Technical University, Munich. After postgraduate research with H. Gerischer, he received his doctorate from Munich in 1969. During 1969–71, he was a postdoctoral fellow at the Bell Laboratories, Murray Hill, studying the optical properties of electrode surfaces by reflectance spectroscopy. From 1971 until 1990, he was a senior scientist and head of a working group at the Fritz Haber Institute of the Max Planck Society in Berlin, where he pursued a surface-science approach to interfacial electrochemistry. In 1984, he was appointed Apl. Professor at the Freie Universität Berlin and, in 1990, appointed full professor at the Universität Ulm. His main research interest is electrochemical surface science, with emphasis on metal deposition, electrocatalysis, and electrochemical nanostructuring. He has received awards, among others, from the Deutsche Bunsengesellschaft, the International Society of Electrochemistry, and the American Electrochemical Society.

adhering to the polished surface. The latter was crucial in protecting the surface from airborne contaminants. This procedure was later modified, when it became evident that the heat shock during immersion of the still-hot crystal into water was detrimental to both surface structure and bulk crystallinity.^[41] The crystals were then allowed to cool to almost room temperature in air (gold) or in an inert (N_2 or Ar for silver) or reducing (H_2 or CO for platinum) atmosphere, which yielded large, atomically flat terraces.^[42, 43] In case of the three low-index faces of gold, flame annealing with subsequent slow cooling led to reconstructed surfaces, very much like those obtained in UHV by sputtering and annealing.^[44, 45] Two more observations helped to make single-crystal electrochemistry an easier game to play (at least with gold). 1) Thin gold films (about 200 nm thick) evaporated onto a special heat-resistant glass can be flame annealed to yield fairly good (111) surfaces. These are relatively cheap substitutes of massive Au(111) single crystals, which can be disposed of after use. 2) Besides thermal annealing, there is an electrochemical (room temperature) annealing to restore single crystallinity of a gold surface which had been maltreated, for example by alloy formation and dissolution.^[46] The effect is based on an anion-enhanced surface mobility of gold atoms and operates best in solutions containing specifically adsorbing anions, such as chloride, at potentials clearly positive of the potential of zero charge (pzc).^[47, 48]

2.3. Ex Situ Approaches

Historically, the ex situ approach to electrochemical surface science was extremely important for the development of this field. In the 1970s, there were no structure-sensitive techniques available for in situ studies. Hence, electrochemists adopted UHV techniques, particularly low-energy electron diffraction (LEED), to check the quality of UHV-prepared single-crystal surfaces before and after electrochemical treatment.^[49] UHV studies were then extended to strongly bound adsorbates, such as iodide,^[50] metal,^[51] or oxide overlayers;^[52] systems that were believed to undergo little or no changes after transfer into the UHV. Here, an important step forward was achieved by W. N. Hansen, when he showed that electrodes could be emersed with their electric double layer intact (see Section 3).^[53] The studies of emersed electrodes that followed and, to a lesser extent, the double-layer simulation studies (an attempt to compose the electric double layer under UHV conditions by adsorbing, for example, water and metal ions^[54]) yielded a wealth of information about bare and adsorbate-covered electrodes. Examples are the study of surface reconstruction^[55] or ordered adsorption occurring during metal-monolayer formation.^[37, 56]

2.4. Modern Theoretical Concepts and Methods

The fourth point that contributed in a significant way to the development of modern interfacial electrochemistry was the adoption of theoretical concepts and methods from solid-state physics or statistical mechanics, among others. This was

particularly important for a better understanding of the electric double layer or of the solvent structure near a charged wall in general. A good example is the “jellium” model for the description of metal surfaces, which was adopted by electrochemists to account for the influence of the metal side on the double-layer capacity.^[57, 58] Such an influence was safely established from measurements with solid electrodes but could not be satisfactorily explained by the earlier double-layer models, which only accounted for contributions from ions and water dipoles to the double-layer capacity. Other important results came from computer simulations of the electric double layer, which yielded new information about the spatial distribution of ions and water molecules near the electrode surface. One example thereof will be given in Section 3.1.

In the following, selected examples of electrochemical surface-science studies will be presented, to demonstrate the type of problems currently addressed in many electrochemical laboratories and, particularly, in the Department of Electrochemistry at the University of Ulm.

3. The Electric Double Layer

3.1. Double-Layer Models

The electric double layer is a central issue in electrochemistry. It is the place of electron and ion transfer, and the region where chemical and electric potentials are different from the neighboring phases, electrode and electrolyte. For generations of electrochemistry students, the electric double layer of a metal/electrolyte interface was described by a plate condenser of molecular dimensions (Figure 1): One plate is the metal surface with its excess charge, the other is formed by solvated ions at closest approach.^[9] Experimental values for the double-layer capacities of, say, silver single-crystal electrodes in 0.1 M solutions range between 20 and 50 $\mu F cm^{-2}$ with a pronounced maximum around the potential of zero charge (pzc). Assuming a “plate distance” of about 0.3 nm, the radius of a solvated ion, we obtain a relative dielectric constant of roughly 5–10 for the interfacial water, namely, for water molecules in a strong electric field. The solvated ions that form the outer Helmholtz plane (OHP, see Figure 1) and that are held in position by purely electrostatic forces are termed “nonspecifically adsorbed”. These are mainly solvated cations or anions with a strong solvation shell, such as fluoride. Most anions however (with their inherently weaker solvation shell) give away part of that solvation shell when entering the double layer to form a chemical bond with the electrode surface. These ions are termed “specifically adsorbed” and their centers form the inner Helmholtz plane (IHP, see Figure 1). Because the chemical interaction between (specifically adsorbed) anions and electrode surface causes more charge to be accumulated at the surface than required by electrostatics, countercharge (cations, in this case) is brought into the double layer for charge compensation. Consequently, while a linear potential drop is generally assumed for nonspecifically adsorbing ions, as for a plate condenser, specific adsorption of ions causes a steeper potential gradient (close to

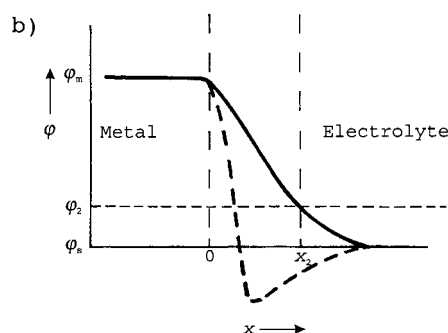
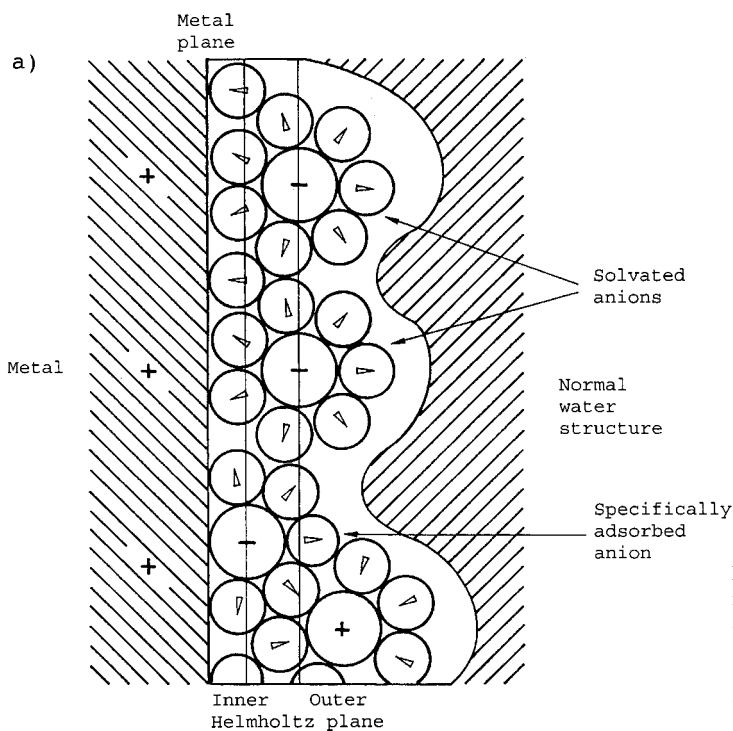


Figure 1. a) Model of the metal/electrolyte interface. b) Potential distribution across the electrochemical interface for a purely electrostatic interaction between solvated ions and the metallic surface (—) and for the case of specifically adsorbing anions (---).

the surface) and an “overshoot” of the potential with respect to the solution value before the latter is reached.

While this simple double-layer model works surprisingly well in that it can explain most of the experimental observations, a more detailed (and realistic) picture which, for example, takes the discreteness of a charge into account, is clearly desirable. Considerable advancement had been achieved during the last two decades, mainly by means of computer simulations.^[59, 60] An example is given in Figure 2, where for a 2.2 molal NaCl solution the densities of Na⁺ and Cl[−] as a function of distance z from the surface of a charged metal is shown, the latter being either positively or negatively charged.^[61] An oscillating density profile for $z < 10$ Å is clearly seen for both ions, similar to that for water (for example, its oxygen density), which reflects the “layering effect” found in liquids near a wall.^[62] We also see the closer approach of the anion due to specific adsorption. The very pronounced first density maximum for Na⁺ and Cl[−] allow

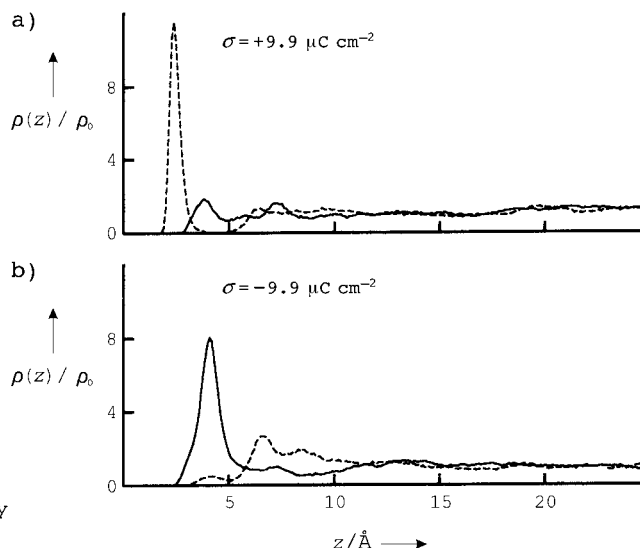


Figure 2. Normalized ion densities $\rho(z)/\rho_0$ for Na⁺ (—) and Cl[−] (---) near a positively (a) and a negatively (b) charged wall ($z=0$) in 2.2 M NaCl. Surface charges are +9.9 and −9.9 μC cm^{−2}, respectively. From ref. [61].

definition of planes which correspond directly to the outer and inner Helmholtz planes of the classical double-layer model (Figure 1).

A longstanding question in relation to the double-layer models concerns the electric field strength near metal surfaces. Applying an electrode potential 1 V positive or negative of the pzc, which according to our plate condenser model corresponds to a potential drop of 1 V across 0.3 nm, should give rise to extremely high electric field strengths of about 3×10^7 V cm^{−1}. With such large numbers, interesting and easily accessible experimental observations, such as electrochromism, were expected. In fact, the contrary seems to be the case. Electroreflectance studies of dye molecules adsorbed at gold electrodes led to estimated values which were about two orders of magnitude lower than the above mentioned value ($\approx 10^5$ V cm^{−1}^[63]). An obvious problem arises from the extremely small distance over which the high field strength exists. Classical dye molecules, which absorb in the visible region and hence are easily studied by in situ optical spectroscopies, are too large to be accommodated inside the double layer. Small molecules like CO have their absorption band in the far-UV range and hence are difficult to study in situ. There are, however, two pieces of information that point towards the high field expected near the surface of a metal electrode. These originate from surface-state spectroscopy and from ex situ ESCA measurements (ESCA = electron spectroscopy for chemical analysis).

3.2. Surface-State Spectroscopy

For gold and silver single-crystal electrodes in contact with an aqueous solution, there exist the very same electronic surface states that are found for such surfaces in UHV.^[64–66] It has been shown that the energetic position of surface states at metal/electrolyte interfaces relative to the bulk states of the metal depends on the electrode potential. Because surface

states penetrate significantly into the electric double layer—their “center of gravity” being assumed to be roughly 0.1 nm outside the metal, if one defines the metal surface by the location of the surface-atom cores—these states feel the potential drop across the double layer.^[67] Hence, the energy of the surface states changes differently than that of the bulk states when the electrode potential is altered. For example, when we change the electrode potential by 1 V in a positive (negative) direction, then the bulk states of the metal, including its Fermi level, are shifted exactly by 1 eV to higher (lower) electron binding energies; the energy shift of the surface states would be only a fraction of 1 eV depending on the fraction of the total potential drop that exists at the position of the surface states. With the total potential drop occurring, for example, over 0.3 nm and the surface states being located 0.1 nm away from the metal surface, the potential-induced shift in energy for surface states would only be $\frac{1}{3}$ of that for the bulk states (with reference to the potential in solution). For all three low-index faces of gold and silver, optical transitions from occupied bulk states into empty surface states have been observed. The transition energy $\hbar\omega$ would be expected to change with potential E according to $\delta\hbar\omega/\delta E \approx 0.3 \text{ eV V}^{-1}$, if the above described situation would hold and if a linear potential drop across the 0.3 nm region can be assumed. An experimental result for Au(100) in 0.5 M NaClO₄ is given in Figure 3, where the photon energy for an

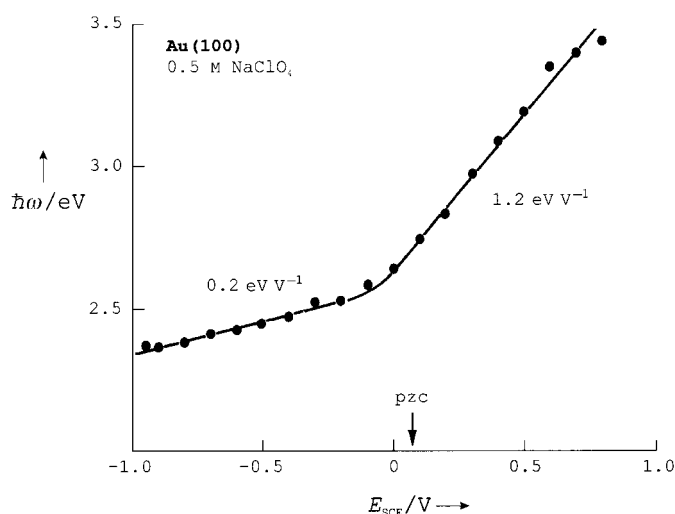


Figure 3. Optical excitation energy $\hbar\omega$ for the transition from bulk d-states into empty surface state B of Au(100) in 0.5 M NaClO₄ as a function of electrode potential. The potential of zero charge (pzc) is indicated by an arrow. From ref. [66].

optical transition from bulk d-states into the empty surface state B at $\bar{X}$ of the surface Brillouin zone is plotted as a function of electrode potential.^[66] For potentials negative of the pzc, where solvated (nonspecifically adsorbed) cations form the double layer, a shift of 0.2 eV V^{-1} has been measured, which is consistent with the simple plate-condensor model and a linear potential drop across the double layer. However, for potentials positive of the pzc, where specifically adsorbing anions set up an inner Helmholtz plane, a surprisingly large shift of 1.2 eV V^{-1} is observed. This value points towards a

high potential gradient near the metal surface that is felt by the surface states and that should be a result of the discrete nature of the ionic double-layer charge.

3.3. Ex Situ ESCA Measurements

Information about the potential gradient near the metal surface can also be obtained from measurements of the electrochemical shift for electron binding energies in ESCA spectra.^[68] This, of course, requires the withdrawal of the metal electrode with its electric double layer from the electrochemical environment and transfer to an UHV chamber. The emersion of electrodes from solution with its inherent loss of potential control and solution phase has been critically viewed by many electrochemists as far as compatibility with in situ information was concerned. However, in a number of rather thorough studies, it was shown that for a limited number of systems (which did include gold electrodes) the electrode can be emersed with its double layer essentially intact. We shall return to this point shortly. As we discussed above for surface states, any adsorbate, atom, ion, or molecule that is located inside the double layer will feel an electrostatic potential that is different from that for the bulk electronic states. In photoelectron spectroscopy, all electron binding energies, which includes those for adsorbates, are measured relative to the Fermi level of the substrate.^[69] Hence, the adsorbate's electronic states shift in energy with electrode potential (electrochemical shift) and, with our simple double-layer model, we can foresee the following two borderline cases: 1) no electrochemical shift, when the adsorbate is strongly electronically coupled to the substrate, and 2) an electrochemical shift of 1 eV V^{-1} , when the adsorbate resides at the outer Helmholtz plane and its electronic levels linked to those in solution. In several studies, electrochemical shifts of the order of 1 eV V^{-1} have been reported, even for strongly adsorbed molecules,^[70–73] which again suggests potential gradients near metal surfaces that are higher than those expected for our plate-condensor model. A remarkable observation is shown in Figure 4, where the electrochemical shifts for sulfate and water on Au(111) are reproduced.^[74] Much to our surprise, we found two clearly different shifts for the components of one and the same molecule, namely sulfate: Whereas for the S-2p_{3/2} level an shift of 1.3 eV V^{-1} was observed, only 0.4 eV V^{-1} was found for the O-1s level of the sulfate oxygen atom. It thus appears that the different atoms of sulfate feel different electrostatic potentials, which supports the idea of using small adsorbed molecules for sensing the spatial variation of the double-layer potential. Assuming the sulfate anion sits on the Au(111) surface with three oxygen atoms directed towards it, we expect a larger electrochemical shift for the more remote sulfur atom than for these three oxygen atoms, which is indeed the case (the fourth oxygen atom, of course, would be even further away from the metal surface and should show the largest electrochemical shift; however, its contribution may be masked by those from the three equivalent oxygen atoms close to the metal). Such simple geometric considerations may be too naive an approach to the microscopic structure of the

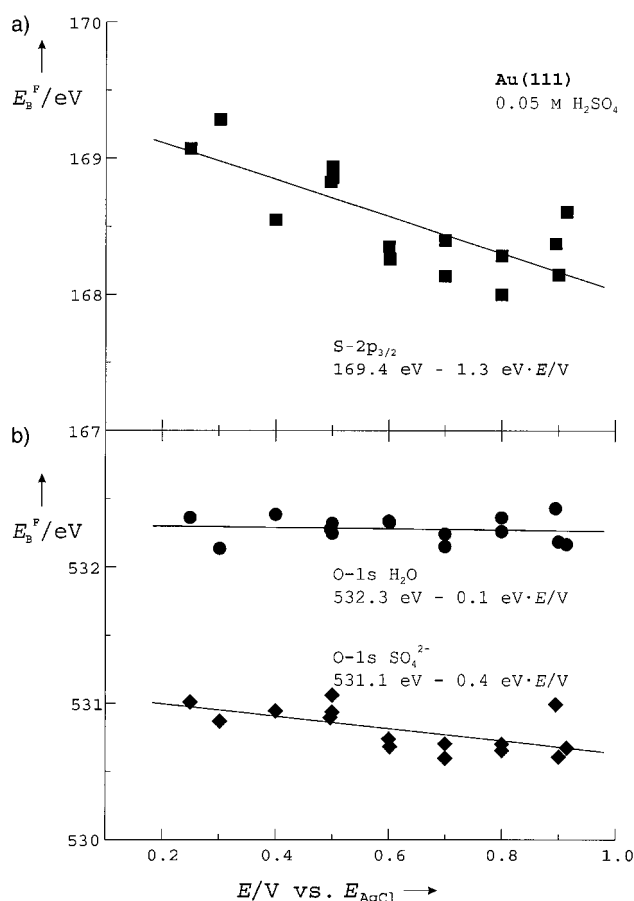


Figure 4. Dependence of electron binding energies E_B^F on the emersion potential E ("electrochemical" shift) for Au(111) in 0.05 M H_2SO_4 . a) $S-2p_{3/2}$ level of sulfate; b) $O-1s$ level of sulfate ($\blacklozenge$) and of H_2O ($\bullet$). From ref. [74].

electric double layer. What remains, however, is an interesting experimental observation that calls for a systematic study of electrochemical shifts in ESCA and for theoretical support. Also noteworthy is the vanishingly small electrochemical shift of the $O-1s$ signal that originates from water rather than from sulfate (Figure 4). This assignment can be unequivocally made from the *chemical* shift of $O-1s$. It implies that this water is bound to the metal surface.

As mentioned above, ex situ experiments are only meaningful for electrochemists if the electrode can be emersed with its electric double layer unchanged. A crucial test in this respect comes from work function measurements with emersed electrodes as a means of determining the potential drop across the double layer in the emersed state. As has been frequently stated, the work function and electrode potential represent one-and-the-same quantity, namely the electrochemical potential of the electrons in the metal. Hence, a 1:1 correlation is expected for the work function of emersed electrodes as a function of emersion potential if the potential drop across the double layer is retained during and after withdrawal of the electrode from the electrochemical cell. For gold electrodes, such a 1:1 relation has been found in numerous studies.^[75, 76] Equally important were deviations from the ideal 1:1 behavior, from which we learnt about double layer collapses after emersion and their origins.^[68, 77] Figure 5 shows the result from a recent study of Au(111) in

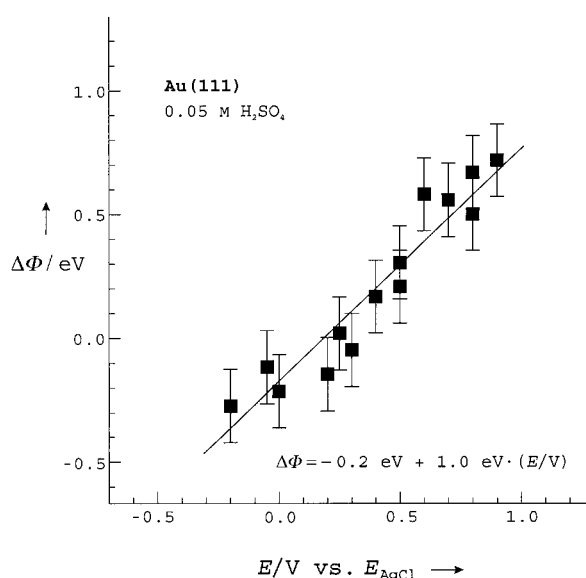


Figure 5. Changes in the work function $\Delta\Phi$ of an emersed Au(111) electrode as a function of emersion potential; $\Delta\Phi=0$ is referenced to the work function of a UHV prepared, bare Au(111)-(22 $\times$ $\sqrt{3}$) surface. From ref. [74].

0.05 M H_2SO_4 , which again demonstrates the 1:1 correlation between work function and emersion potential.^[74] The work function was determined from ESCA spectra by the cut-off of the secondary electron emission and referenced to that of the bare, reconstructed Au(111) surface after sputtering and annealing in the UHV chamber and before immersion into the electrolyte. Taking $\Phi=5.3$ eV for bare, reconstructed Au(111) from literature,^[78] the $\Delta\Phi$ axis of Figure 5 can be transformed into an absolute Φ -scale, which allows one to calculate the absolute electrode potential, namely, the potential of the normal hydrogen electrode (NHE) referenced to vacuum (in other words, the work function of NHE). With $E_{NHE} = -0.2$ V versus $Ag/AgCl$, we obtain a work function value of about 4.8–4.9 eV for the NHE. This number appears somewhat high but still falls into the 4.7–4.8 eV range obtained by similar methods^[76, 79] and by in situ optical spectroscopy.^[80] It is clearly at variance with the IUPAC-recommended value of 4.44 eV^[81] and adds to the on-going controversy between the two schools of thought.

4. Surface Reconstruction

In order to derive a microscopic picture of surface processes such as adsorption or deposition, single-crystal material is generally used, for which the surface structure is believed to be precisely known. This tacitly assumes that the atoms at the surface retain their bulk positions and hence the surface structure can be derived directly from the well-known bulk structure. Although most metal surfaces fulfill this expectation, some do not. The reason for the latter cases is that the highly asymmetrical environment of the surface atoms, due to missing neighbors, can lead to a rearrangement in the top layer. Typically, atoms at surfaces tend to acquire a more densely packed structure because of an increased electron

density between the surface atom cores.^[82] Such a rearrangement of surface atoms, which often involves local bond breaking and a change in surface symmetry, is called surface reconstruction.^[83, 84] Typical examples of such an effect are the bare low-index surfaces of gold which all reconstruct in order to reduce the surface energy. An eye-catching structural change due to surface reconstruction is seen with Au(100), which reconstructs into a hexagonal close-packed surface (hex structure) when prepared under UHV conditions.^[85] While for the bare surface the reconstructed state is energetically more favorable than the unreconstructed (1×1) state, the opposite is normally the case for adsorbate-covered surfaces, as adsorption is energetically more favorable on the less dense, unreconstructed surface.^[86] Because of an activation barrier for reconstruction, removal of the adlayer that was responsible for lifting of the reconstruction does not bring back the reconstructed surface; the latter process normally requires heating of the sample.

For gold single-crystal electrodes in contact with an aqueous solution, the very same reconstruction phenomena as for surfaces in UHV were observed.^[87, 88] Flame-annealed gold electrodes, to begin with, reconstruct in the same way as in UHV, namely Au(111)-($22 \times \sqrt{3}$), Au(100)-(hex), and Au(110)-(1×2) or -(1×3), and the reconstruction can be retained upon immersion into the electrolyte, provided certain precautions are met. Since specific adsorption of anions lifts the reconstruction, it is absolutely essential to immerse the reconstructed electrode under control of the potential, clearly negative of the pzc.^[44, 45]

Figure 6 shows the STM image of a freshly prepared (flame-annealed), reconstructed Au(100) surface in 0.05 M H_2SO_4 at $E_{\text{SCE}} = -0.2 \text{ V}$ (E_{SCE} = potential versus a saturated calomel electrode). The hexagonal arrangement of the surface atoms is clearly seen, together with the so-called reconstruction rows (they run vertically in Figure 6), which arise from the fact that the (hex)-structured surface is slightly buckled, since it is no longer congruent with the underlying second layer. The corrugation length of the reconstruction rows is 1.45 nm; its height is about 0.05 nm. These rows are a convenient sign of a (100) surface to be reconstructed in all those cases where atomic resolution is not obtained and, hence, where the hexagonal arrangement of the surface atoms cannot be seen directly. Well-prepared reconstructed Au(100) surfaces show large (hex)-structured domains with the reconstruction rows being aligned along monoatomic high steps. Very often a terrace is covered by a single domain.^[88, 89]

Since the optical as well as the electrochemical properties of reconstructed and unreconstructed Au(100) surfaces are

distinctly different, the existence of Au(100)-(hex) in an electrochemical environment has been shown well before the STM entered the scene.^[44, 90] In Figure 7, the electroreflectance (ER) spectra of reconstructed and unreconstructed

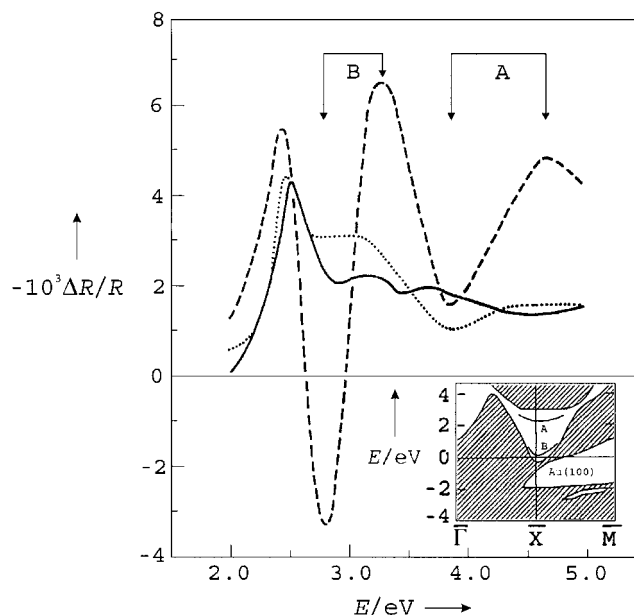


Figure 7. Normal-incidence electroreflectance spectra of Au(100)-(hex) (—), Au(100)-(1×1) (---), and Au(111) (•••) in 0.01 M HClO_4 . Inset: Surface band structure of Au(100)-(1×1) with surface states A and B. From refs. [15, 44].

Au(100) in 0.01 M HClO_4 are shown and that of Au(111) in the same electrolyte for comparison. Note that in ER spectroscopy, the normalized reflectance change $\Delta R/R$ with a change of electrode potential is measured. While the reconstructed Au(100)-(hex) surface exhibits an ER spectrum very similar to that of Au(111), the ER spectrum of the unreconstructed Au(100)-(1×1) differs vastly. The pronounced, derivative-like structures, labeled A and B in Figure 7, originate from optical transitions into the empty surface states A and B that are found at $\bar{X}$ of the surface Brillouin zone (see Figure 7 inset). The complete absence of the surface state features A and B (Figure 7) in the ER spectrum of Au(100)-(hex) leads, for certain wavelengths, to a pronounced difference in the optical response of reconstructed and unreconstructed Au(100) that has been utilized to study the kinetics of the (hex) $\rightarrow$ (1×1) structural transition.^[90] Furthermore, the electrochemical properties of (hex) and (1×1) surfaces differ markedly, mainly because the pzc values of both surfaces differ by about 220 mV. This is demonstrated in Figure 8. We recall that for dilute solutions—in this case 0.01 M HClO_4 —the double-layer capacity has a pronounced minimum at the pzc due to the contribution from the diffuse part of the double layer.^[1–3] Starting the measurement with a freshly flame-annealed, namely reconstructed, Au(100) electrode, a pzc of about +0.30 V versus SCE is observed, which is very close to that of Au(111). This is not unexpected as both surfaces have a hexagonal close-packed structure. Systematic studies have revealed that the specific

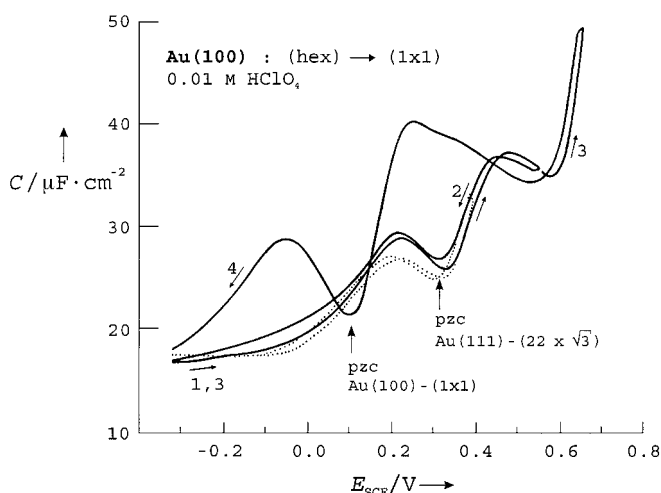


Figure 8. Double-layer capacity C as a function of electrode potential for Au(100)-(hex) in 0.01M HClO_4 with a transition from (hex) to (1×1) . Numbers refer to the scan sequence. The capacity curve for Au(111)-(22 $\times$ $\sqrt{3}$) is shown for comparison (••••). From refs. [44, 90].

adsorption of anions lifts reconstruction and the gold surface acquires the (1×1) structure. The transition potential depends on the type of anion and it shifts in negative direction with increasing strength of chemisorption.^[45] For 0.01M HClO_4 , the (hex) $\rightarrow$ (1×1) transition occurs around +0.6 V versus SCE. When the potential scan under the conditions shown in Figure 8 exceeds +0.6 V (scan 3), the reconstruction is lifted and the well-known capacity curve for the unreconstructed Au(100) emerges with its pzc at about +0.08 V versus SCE. The shift in pzc by 220 mV, which is connected with the (hex) $\rightarrow$ (1×1) transition, reflects a corresponding change of 0.22 eV in work function to lower values. This sudden shift in pzc with lifting of the (hex) reconstruction requires additional charging of the electrode surface to maintain the applied potential during the structural transition, and this gives rise to a pronounced current peak. This is shown in Figure 9 for Au(100) in 0.1M H_2SO_4 , where reconstruction is lifted already around +0.36 V (the exact value depending somewhat on the scan rate). This current peak has turned out to be a convenient

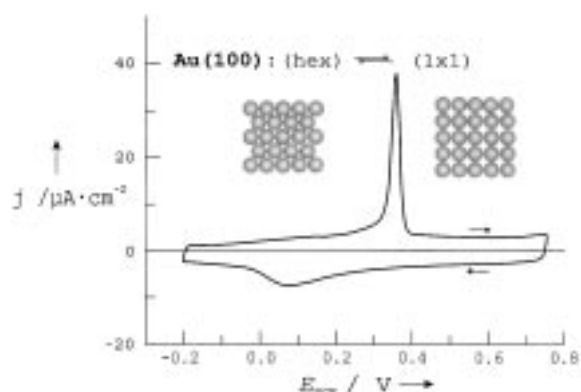


Figure 9. Cyclic current-potential curve for Au(100) in 0.1M H_2SO_4 starting at -0.2 V with a freshly prepared reconstructed surface. Scan rate: 50 mV s^{-1} . Lifting the (hex) reconstruction during the positive scan is seen by a pronounced current peak at +0.36 V. The subsequent scan in negative direction reflects the electrochemical behavior of Au(100)-(1 $\times$ 1). From ref. [88].

and easily accessible indicator for reconstruction: The peak potential is a measure for the stability range of the (hex) structure; the charge under the peak is a measure for the fraction of the electrode surface that is reconstructed.^[91]

A very remarkable observation can be made at the gold/electrolyte interface, which is not possible for UHV. Applying a negative potential (with respect to the pzc) to the unreconstructed Au(100) surface brings back the (hex) reconstruction.^[92] This *potential-induced* reconstruction has been observed for all three low-index gold faces. Under UHV conditions, the bare unreconstructed gold surfaces are in a metastable state; reconstruction of the uncharged surface is prevented at room temperature by an activation barrier. However, application of an electrode potential sufficiently negative of the pzc to the unreconstructed Au(100) surface will not only free the surface from anions but also lower the activation barrier to such an extent that reconstruction occurs within seconds or minutes, even at room temperature. This phenomenon has far-reaching consequences for electrochemical studies with gold single-crystal electrodes: The surface structure of the electrode becomes a function of potential! Only at potentials sufficiently positive of the pzc is the structure of the single-crystal surface that expected from the bulk structure. At negative potentials, however, a potential-induced reconstruction sets in to transform, for example, an Au(100) surface into one that is Au(111)-like. From the cyclic voltammogram of Figure 9, we can conclude that lifting the reconstruction is a much faster process than the $(1 \times 1) \rightarrow$ (hex) transition at negative potentials. Therefore, the potential scan in the negative direction (Figure 9), from +0.75 to -0.2 V, reflects in essence the double-layer capacity of Au(100)-(1 $\times$ 1). For the much faster $(1 \times 1) \rightarrow$ (rec.) transition of Au(111), potential-induced reconstruction spreads within a matter of seconds, which makes it very difficult, although not impossible, to perform experiments in the potential range negative of the pzc with an unreconstructed Au(111) surface. Since both structural transitions, potential-induced reconstruction and anion-induced lifting, require surface imperfections as nucleation centers to start the transition, these reactions can be suppressed to a great extent by working with surfaces as free of defects as possible. Electrochemical annealing has been shown to be important for protecting unreconstructed surfaces against potential-induced reconstruction.^[89, 93a]

Finally, a few words should be said about the topography of the unreconstructed Au(100) surface. Because the (hex) structure has a packing density about 25 % higher than that of Au(100)-(1 $\times$ 1), gold atoms are expelled from the surface during the (hex) $\rightarrow$ (1×1) transition. They coalesce and form monoatomic high islands of gold, which cover about one quarter of the surface. Such a surface is shown in Figure 10. I mention in passing that these islands undergo substantial Ostwald ripening after their formation, the rate of which depends significantly on the electrode potential (electrochemical annealing), and which helps to improve the smoothness of the surface. Nevertheless, it should remain borne in mind, that lifting of the reconstruction inevitably leads to a defect-rich surface, as the rims of the monoatomic high islands constitute surface imperfections.

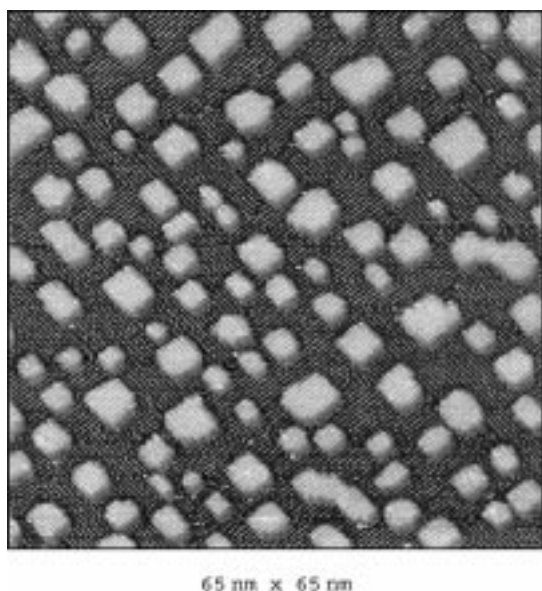


Figure 10. STM image of an unreconstructed Au(100) surface in 0.1M H_2SO_4 at +0.35 V versus SCE, recorded shortly after lifting of the (hex) reconstruction. The surface is strewn with monoatomic high islands of Au. The line pattern arises from ordered sulfate adsorption. From ref. [93b].

5. The Study of Adsorbates

Since many electrochemical reactions involve an adsorption step at some point, the study of adsorbates or adlayers is of particular interest for a mechanistic interpretation. However, adsorbed species often show extensive surface diffusion at room temperature and, hence, escape detection by the STM. In order to be able to image individual atoms, ions, or molecules on surfaces, the species under study has to be immobilized. This is normally achieved either by forcing the adsorbed species into a densely packed monolayer or allowing long-range order between the adspecies to lead to ordered adsorption, where lateral forces keep the entity in place. Ordered adlayers have become a favorite playground for STM studies, where important structure information combines with the fascination of “seeing” single atoms or molecules.^[94]

The formation of ordered adlayers, namely of adlayers where the atoms or molecules are arranged on the surface in a regular pattern, is often accompanied in cyclic voltammograms by a very pronounced current spike: This means the ordered adlayer is formed within a very narrow potential region, which is indicative of a first-order phase transition. A typical example is given in Figure 11, where the cyclic voltammogram for Au(111) in a sulfuric acid solution is shown. Besides the pronounced current peak at +0.3 V versus SCE on the potential scan in positive direction, which is due to lifting of the $(22 \times \sqrt{3})$ reconstruction, a pair of extremely narrow current spikes is noted around +0.73 V versus SCE, which was assigned to a phase transition in the anionic (sulfate) adlayer.^[95] The latter was indeed observed by structure-sensitive methods, such as in situ X-ray diffraction at grazing incidence^[96] and, in particular, the STM. Figure 12 shows an STM image of Au(111) in 0.1M H_2SO_4 , where the

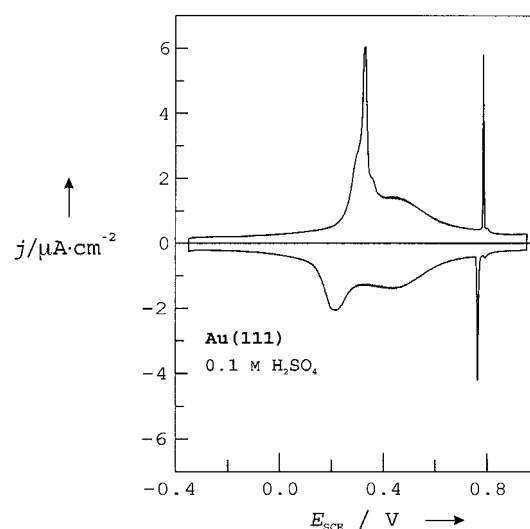


Figure 11. Cyclic current–potential curve for Au(111) in 0.1M H_2SO_4 starting with a freshly prepared reconstructed surface at –0.35 V. Scan rate: 10 mV s^{–1}.

potential was stepped during imaging from +0.65 to +0.80 V versus SCE (see arrow in Figure 12). At the former potential, the adsorbed sulfate (or bisulfate) ions are mobile and hence cannot be imaged with the STM. Instead, the surface atoms of the gold substrate are clearly visible and provide an internal

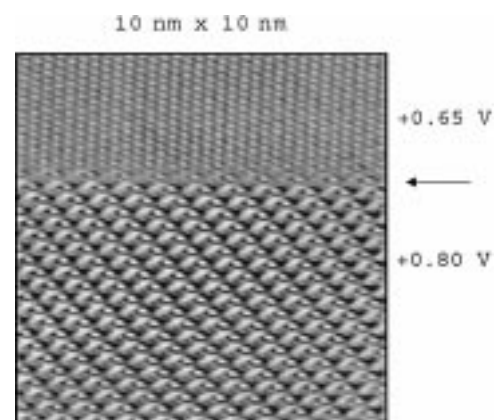


Figure 12. High-resolution STM image of Au(111) in 0.1M H_2SO_4 . The upper part shows the Au(111) surface, atomically resolved, at +0.65 V versus SCE; the lower part shows the ordered adlayer of sulfate, formed by a potential step to +0.80 V versus SCE.

calibration for lateral distances and crystallographic orientations. With the potential step to +0.80 V versus SCE, an ordered sulfate adlayer is formed instantaneously with, after LEED terminology, a $(\sqrt{3} \times \sqrt{7})\text{R}19.1^\circ$ superstructure. Although the image of the adlayer depends somewhat on the tunnel voltage, all research groups so far have unanimously reported two different reflexes, a main and a side maximum per unit cell, each corresponding to 0.2 monolayers (ML). Since the coverage of sulfate has been determined to 0.2 ML by chronocoulometric measurements,^[97] it had to be concluded that the main and side maxima belong to two different chemical species. It seems currently accepted that the side maximum corresponds to coadsorbed hydronium ions, while

the main reflexes are due to sulfate (or bisulfate). In the image of Figure 12, the main (sulfate) reflexes are rather broad with a lengthy shape, whereas the side maxima appear as small round spots which—interestingly enough—are exactly at positions of the gold atoms. This would imply that the coadsorbed hydronium ions occupy on-top positions, if the assignment of the side maxima is correct. I mention in passing that, due to thermal drift and inaccuracies in scanner calibrations, an internal standard for distances is almost mandatory for the safe determination of adsorbate structures from STM images. The most convenient standard is, naturally, the bare metal substrate, as demonstrated in Figure 12.

Another example of an ordered adlayer, formed out of specifically adsorbing anions, is given in Figure 13, which may also demonstrate the aesthetic of STM images. It shows a layer of tetrachloropalladate anions on Au(110) at +0.61 V versus SCE.^[98] Besides the formation of rows of anions, which

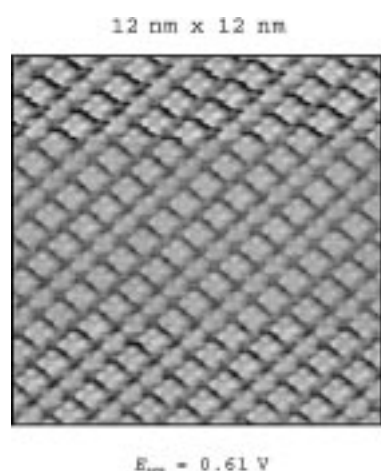


Figure 13. High-resolution STM image of an ordered adlayer of $[\text{PdCl}_4]^{2-}$ on Au(110) in 0.1M H_2SO_4 + 1 mM H_2PdCl_4 . From ref. [98].

is not unexpected for a substrate with two-fold symmetry, it is noteworthy that flat-lying $[\text{PdCl}_4]^{2-}$ ions are imaged as little pinwheels, a center reflex being surrounded by four reflexes arranged in a square. Considering the well-known square-planar structure of $[\text{PdCl}_4]^{2-}$, it appears that the fine structure in the image of each anion shows its atomic components, namely the palladium atom in the center and the four surrounding chloro ligands. High-resolution images like the one in Figure 13 nourish the hope that individual components of complex molecules—functional groups or even atoms—will be seen by STM.^[99, 100] This perspective seems particularly interesting for biological molecules.

A second group of ordered adlayers, which has been intensively studied by STM, are the self-assembled monolayers (SAMs).^[101] These are formed by molecules with a functional group that interacts strongly with the substrate. A classical system is alkanethiols on gold, particularly on Au(111), where the strong interaction between gold and sulfur leads to a stable and ordered adlayer upon mere immersion of the gold substrate into a thiol solution. Introduction of functional groups at the other end of the thiol allows for a chemical modification of electrode surfaces,

which bears great potential for future applications, for example in the areas of sensors or molecular electronics. Here again, STM has contributed significantly to the understanding of the adlayer properties by yielding detailed structural information. While most of the STM studies of alkanethiol SAMs so far were performed in UHV or in air, the number of investigations of SAM-covered gold surfaces in an electrochemical environment is steadily increasing.^[102] Although the structure of SAMs in many cases is the same in situ and ex situ, there are distinct features in an electrochemical system that attract attention. Of particular interest are potential-induced changes in the structure or the chemical state of SAMs which show a certain degree of reversibility. For example, there is an order–disorder transition in ethanethiol SAMs on Au(111) in 0.1M H_2SO_4 which is surprisingly reversible.^[103] An ordered ethanethiol layer is observed for $E > 0$ V versus SCE (Figure 14a) with domains

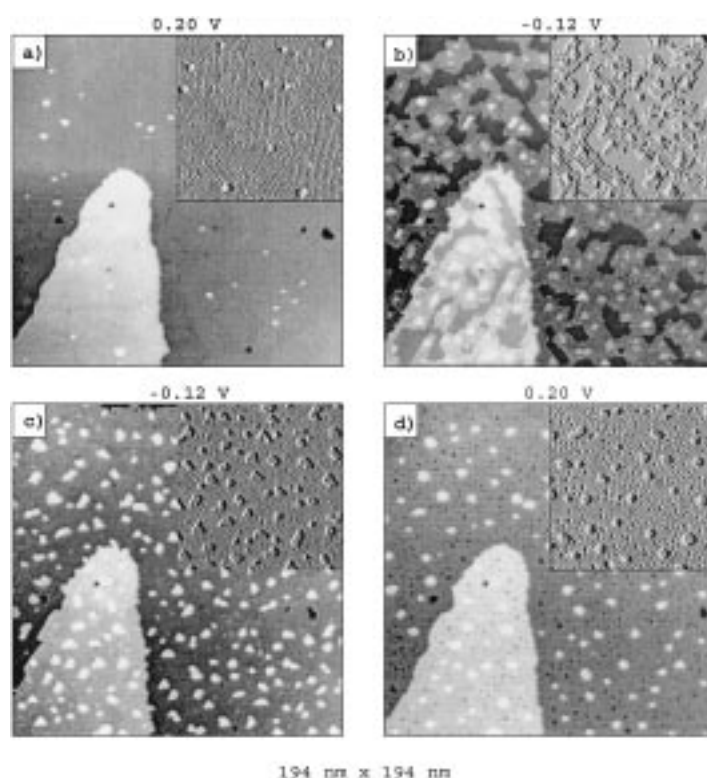


Figure 14. STM images of Au(111) in 0.1M H_2SO_4 covered with an ethanethiol self-assembled monolayer. The sequence shows the reversible transition between an ordered structure at +0.20 V and a disordered one at −0.12 V versus SCE. The upper right corner of the images has been shaded to improve contrast. From ref. [103].

of two distinctly different superstructures (a pinstripe ($p \times \sqrt{3}$) and a densely packed (4×3) structure; see the shadowed top-right quarter of Figure 14a), whereas for $E < -0.1$ V versus SCE a disordered state is found (Figure 14c). The disordered state, which cannot be molecularly resolved in STM images, appears to be less densely packed than the ordered one because small monomolecular high (0.3 ± 0.05 nm) islands are formed in that state, presumably from surface excess. Stepping the potential back to +0.20 V versus SCE (Figure 14d) causes the ordered structures ($(p \times \sqrt{3})$ and

(4 × 3) structures) to reappear, albeit in smaller domains and less perfectly ordered. The number of islands has decreased and small holes appear in the surface, to indicate that the extra amount of ethanethiol required for the more densely packed ordered state is only partly supplied by the islands. Hence, the degree of imperfection increases with each structural transition, similar to the case of reconstruction and lifting of reconstruction of gold surfaces.

An interesting complication during the order → disorder transition has been noted and is shown in Figure 14b. The transition produces a striped structure as an intermediate state which exists for a few minutes only and vanishes as the disordered state is completely formed. The stripes are separated by 1.7 nm and are aligned along the three main crystallographic directions of the gold substrate. Upon the potential step from +0.20 to −0.12 V versus SCE, first the ($p \times \sqrt{3}$) domains transform into the stripe structure and then the (4 × 3) structure, which is obviously more stable.

Quite surprisingly, the blocking power of the ethanethiol in the disordered state (for example, against metal deposition) is still high, to indicate that the SAM in the disordered state is also dense. The reversibility of the structure transition for this SAM signals an unexpectedly high surface mobility of these strongly bound molecules. I mention here in passing that the STM is generally assumed to image the sulfur atoms of the thiols rather than the alkane chains or end-substituted functionalized groups.

Another interesting feature of SAM-modified electrodes relates to potential-induced chemical changes of the adlayer. While the oxidative and reductive desorption or destruction of SAMs—deliberately or otherwise—has been frequently studied, investigations of potential-induced changes in the chemical state of SAMs, while they remain intact, are still rare. One such example refers to *p*-nitrothiophenol, which can be partially reduced to *p*-hydroxiaminothiophenol (Ar-NHOH) by applying a more negative potential. The latter shows a redox behavior due to a reversible switch between Ar-NHOH and Ar-NO, while the former one does not.^[104] Successful attempts of a tip-induced (and hence laterally confined) reduction of *p*-nitrothiophenol in a scanning electrochemical microscope cell was reported by Reda,^[105] who pursued the idea of a high-density storage device based on switching the oxidation state of single molecules.

A third class of ordered adlayers, which has been intensively studied by STM, comprises metal adsorbates formed by underpotential deposition (upd). The latter expression refers to the formation of a metal monolayer (in rare cases, of two monolayers) on a foreign metal substrate at potentials positive of the corresponding Nernst potential.^[106, 107] Such an apparent violation of the Nernst equation simply results from an interaction between adatom and substrate that exceeds in strength that between the adatoms. In a purely thermodynamic rationalization of upd, the activity of the metal $a_{\text{metal}} < 1$ has to be assumed.

Copper upd on Au(111) was one of the first systems for which ordered adsorption was shown to occur by structure-sensitive methods, such as ex situ electron diffraction^[108] and in situ STM.^[109] In sulfuric acid solutions, copper monolayer formation on Au(111) proceeds in three steps: Random

adsorption at low coverages, formation of a ($\sqrt{3} \times \sqrt{3}$)R30° superstructure (honeycomb structure with maximum coverage $\Theta_{\text{max}} = 2/3$), and finally a pseudomorphic (1 × 1) copper monolayer, that is, the copper adatoms occupy substrate lattice sites. Because the lattice constant of gold is about 12 % larger than that of copper, the pseudomorphic copper layer is strained. An interesting aspect of Cu/Au(111) is that anions play a structure-determining role.^[107, 110] The honeycomb structure at medium copper coverages, which is a rather unusual structure for a metal adsorbate, is observed only for sulfate-containing solutions, in which coadsorbed sulfate ions stabilize this structure by nesting in the copper hexagons.^[111, 112] Completely different adlayer structures were reported for copper upd in perchloric or chloride solutions.^[110]

Figure 15 shows the high-resolution STM image of a submonolayer amount of underpotentially deposited silver on Au(111). Silver upd on Au(111) starts with the successive

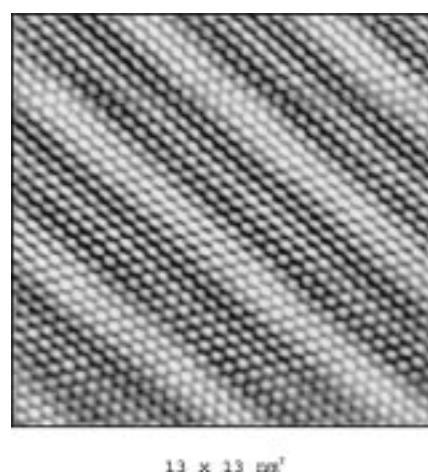


Figure 15. High-resolution STM image of the silver adlayer ($\Theta_{\text{Ag}} = 0.37$) on Au(111) in 0.05 M H_2SO_4 + 1 mM Ag_2SO_4 at +0.4 V versus Ag/Ag^+ . From ref. [113].

formation of three different hexagonal adlayer structures: A ($\sqrt{3} \times \sqrt{3}$)R30° arrangement with a limiting coverage of 0.33 ML; a distorted hexagonal-stripe pattern, shown in Figure 15 and which allows coverages up to 0.37 ML; and finally a (3 × 3) structure with a maximum coverage of 0.44 ML.^[113] The distorted hexagonal structure, given in Figure 15, can be obtained from the ($\sqrt{3} \times \sqrt{3}$)R30° lattice by a unidirectional compression of the latter by 10 %. The resulting misfit with the underlying substrate surface leads to the height modulation in the adlayer, reflected by the stripes in the STM image. The complete densely packed silver monolayer is (1 × 1) and free of strain, as silver and gold have practically identical lattice constants. This may also be the reason why a second silver layer even forms in the upd region, although only when very close to the Nernst potential.^[113]

6. The Initial Stages of Metal Deposition

Metal plating from solution is still a process of utmost industrial importance. Besides its use in classical areas, such as

protective overcoatings or improvement of the optical appearance of surfaces, electrolytic metal deposition has gained significant attention in various branches of the electronic industry, for example in circuit-board manufacturing, giant-magnetoresistance devices, or metal–semiconductor junctions. While the beginning of metal deposition on a foreign substrate has always been of considerable interest for fundamental research, for example in the study of electrocrystallization phenomena,^[114] the initial stages become increasingly relevant also for industrial science as the trend from micro- to nanoelectronics continues with demand for ever smaller products.

Metal deposition is well known to commence at surface defects, which act as nucleation centers for the new phase. Hence, for a detailed study of the nucleation and growth behavior, real-space imaging of the electrode surface is required. In this respect, STM is ideally suited for an atomistic view on the initial stages of metal deposition. Figure 16 shows two STM images of an Au(111) electrode in sulfuric acid

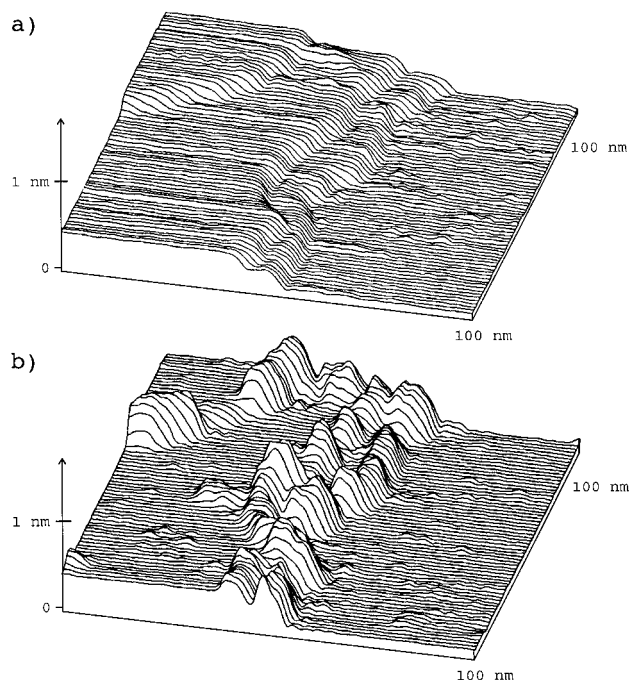


Figure 16. STM images of Au(111) in 5 mM H_2SO_4 + 0.05 mM CuSO_4 before (a) and during (b) Cu deposition. Nucleation and growth of copper occurs almost exclusively at the steps.

solution before and during deposition of bulk copper. As is clearly seen in Figure 16b, copper nucleates under these conditions almost exclusively at the monoatomic high steps of the gold substrate where the growing copper clusters decorate the surface defects. Substantial amounts of copper can be deposited at the steps while the flat terraces remain essentially copper free (except for the copper monolayer that has been formed at underpotentials and covers the substrate surface uniformly). Such a nucleation-and-growth habit of bulk metal inevitably leads to nonuniform, rough overlayers and hence run counter to the normal intentions of plating industry. There are, however, ways out of this dilemma: Addition of certain

groups of organic molecules, “levellers” and “brighteners”, can change either the nucleation or the growth behavior of the metal in such a way that smooth overlayers emerge.^[115] Although there exist some ideas about the action of additives, the detailed mechanism is still largely unknown; the undeniable successes of the plating industry are a result of trial-and-error and chemical intuition. Nevertheless, this is an important area where STM can and will add significantly to the understanding of additives in the future.^[116, 117]

As mentioned above, bulk copper deposition does not start on the bare Au(111) surface but rather on a pseudomorphic copper layer which was formed at underpotentials, namely, positive of the Nernst potential. Due to a considerable lattice mismatch between copper and gold of about 12 %, the first monolayer is strained and consequently the next copper atoms are not laid layer-by-layer but instead as clusters, presumably with the native lattice constants. This Stranski–Krastanov growth mode is quite common for metal systems with a lattice misfit: 3D growth on top of a pseudomorphic up layer. Layer-by-layer growth can be expected, and is indeed experimentally observed, for silver deposition on Au(111) because of the almost perfect match of the lattice parameters for both metals. The result are silver overlayers with large, atomically flat terraces, which even bury rough features of the gold substrate (such as step-bunching regions).^[113]

An interesting, yet at first sight puzzling, behavior was reported for copper deposition on Au(100), where again the first monolayer is formed at underpotentials.^[118] In this case, a total of ten copper layers was found to grow pseudomorphically, that is, with the lattice constant of gold. A similar observation had been reported earlier for copper on Ag(100), in which exactly eight pseudomorphic layers were grown before a sudden structural transition occurred.^[119] The unusually high number of pseudomorphic copper layers on Au(100) and Ag(100), despite the significant lattice misfit, was explained by the growth of body-centered cubic (bcc) rather than face-centered cubic (fcc) copper. Although fcc copper is the thermodynamically most stable form, model calculations have shown that the energy difference between bcc and fcc copper amounts to only 20–40 mV.^[120, 121] However, bcc Cu(100) fits almost perfectly onto Au(100) and obviously it is this perfect structural match that favors the initial growth of bcc copper on Au(100). The conclusions from STM measurements were supported by the results of a systematic, in situ surface X-ray scattering (SXS) study.^[122] Figure 17 shows the specular reflectivity of bare and copper-covered Au(100) as a function of the scattered wave vector component normal to the surface. The quasi-Bragg peak at $L=2.8$ results from the bcc copper overlayer. A detailed analysis of the specular reflectivity curves yielded values for the layer spacing in the copper film and for the gold/copper interface: The average copper–copper layer spacing was found to be 0.144 ± 0.002 nm, in good agreement with the expected value for bcc copper and with the STM-derived step heights on the copper overlayer of 0.15 ± 0.01 nm. For the average gold–copper spacing, a value of 0.174 ± 0.010 nm was obtained, which is practically identical to the average of the layer spacings for fcc gold and bcc copper.^[122]

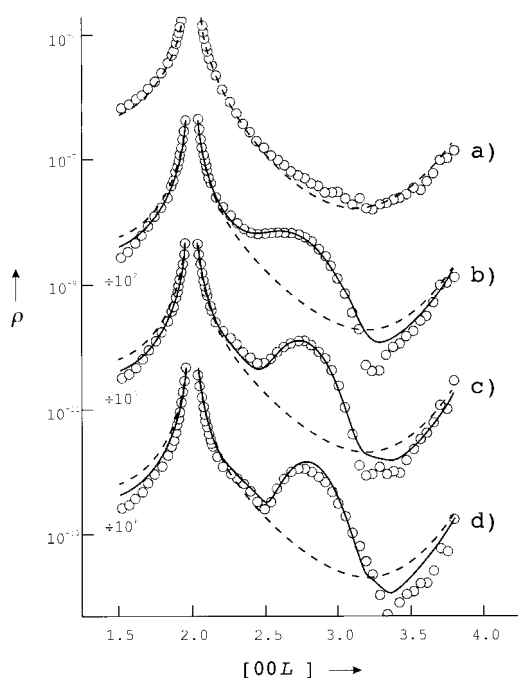


Figure 17. Specular reflectivity ρ of bare (a) and 4.2 (b), 6.7 (c), and 7.9 monolayers (d) of copper covering Au(100) in 0.05 M H_2SO_4 + 1 mM CuSO_4 as a function of the scattered wave vector component $[00L]$ normal to the surface. The quasi-Bragg peak at $L = 2.8$ is due to bcc Cu. From ref. [122].

With deposition of the eleventh copper layer on Au(100) (of the ninth copper layer on Ag(100)^[119]), the surface morphology changes abruptly: The surface appears striped, with a corrugation length of 6.2 ± 0.2 nm for the eleventh layer, 6.5 ± 0.2 nm for the twelfth layer, and a slight increase with each new copper layer. Figure 18 shows an STM image of

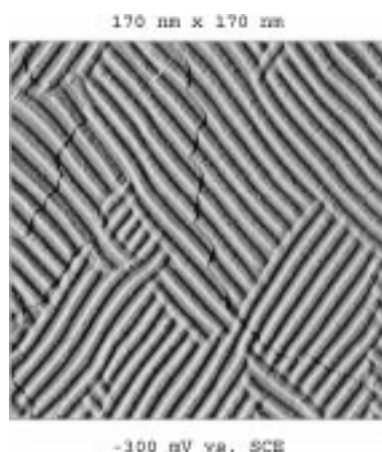


Figure 18. STM image (shaded) of Au(100) in 0.05 M H_2SO_4 + 1 mM CuSO_4 covered with approximately 13 to 15 Cu monolayers. The Cu overlayer shows the characteristic stripe structure. From ref. [118].

Au(100) covered with 13–15 monolayers of copper. The structure of the wavy overlayer is more difficult to determine. High-resolution STM images indicate a reduction of the copper next-neighbor distance from 0.29 nm in the pseudomorphic layers to 0.26 nm in the ridges of the wavy overlayer.^[118, 119] In situ SXS measurements suggest that the wavy

overlayer is composed of alternating orthorhombic and cubic stripes.^[123]

STM measurements had revealed that after dissolution of the eleventh and higher copper layers on Au(100), the same flat pseudomorphic surface reappeared, which was seen before deposition of the eleventh copper layer. This raised the interesting question about the fate of the ten pseudomorphic copper layers as deposition continues and the wavy structure appears: Do the first ten copper layers remain bcc as the wavy structure grows on top or is the bcc copper transformed into the wavy structure as the eleventh layer is deposited. This question was answered by in situ SXS and the result was quite surprising: With deposition of the eleventh copper layer on Au(100), the entire copper film (namely, all eleven layers) converts into the wavy structure; removal of the eleventh copper layer (or all layers in excess of ten) returns ten pseudomorphic copper layers.^[123] The high reversibility of this phenomenon, which shows that the bcc copper overlayer is stable, not just metastable, together with the fact that the structural transition is triggered exactly with the addition or removal of the eleventh layer, makes copper on Au(100) a good example of interesting electrochemical surface science. Not surprisingly, the very same phenomena were observed for copper on Ag(100), at least so far as STM studies are concerned (SXS measurements are still to be performed). Silver and gold have almost identical lattice constants, hence the very same arguments described above also hold for bcc Cu(100) on fcc Ag(100). Actually, the growth of bcc copper was first discovered in UHV studies during copper evaporation onto Ag(100) as substrate.^[124] As in the case of Au(100), copper deposition onto Ag(100) starts with the formation of bcc copper until a sudden transition into the wavy structure occurs. Quite remarkably, this transition takes place with laying the ninth copper layer and the pseudomorphic copper reappears as the ninth layer is oxidatively removed. The question remains as to which physical parameters of the substrate are responsible for the difference in critical thickness of the bcc overlayer.

A second example of metal deposition is given in Figure 19.^[125] It refers to the initial stages of palladium deposition on Au(111) and emphasizes once more the important role of surface defects, such as monoatomic high steps, as nucleation centers. The sequence of STM images starts with the bare Au(111) surface at +0.5 V versus SCE (Figure 19a), which shows one monoatomic high step and several monoatomic high gold islands, leftovers from lifting of the $(22 \times \sqrt{3})$ reconstruction. Stepping the potential to +0.48 V versus SCE, that is, into the upd region of palladium, nucleation and growth at the substrate step and at the rims of the gold islands is clearly seen (Figure 19b). Interestingly, there is a slight "chemical" contrast in the STM image, which makes the palladium layer appear higher than the gold, whereas on the basis of geometrical considerations the reverse should be observed. For example, the gold islands, the flat tops of which are still palladium-free, appear darker than the surrounding palladium that has nucleated at the island rims. This contrast is most likely caused by anion adsorption, which will differ for the two metals. As palladium deposition continues in a strictly two-dimensional fashion, the gold terraces become complete-

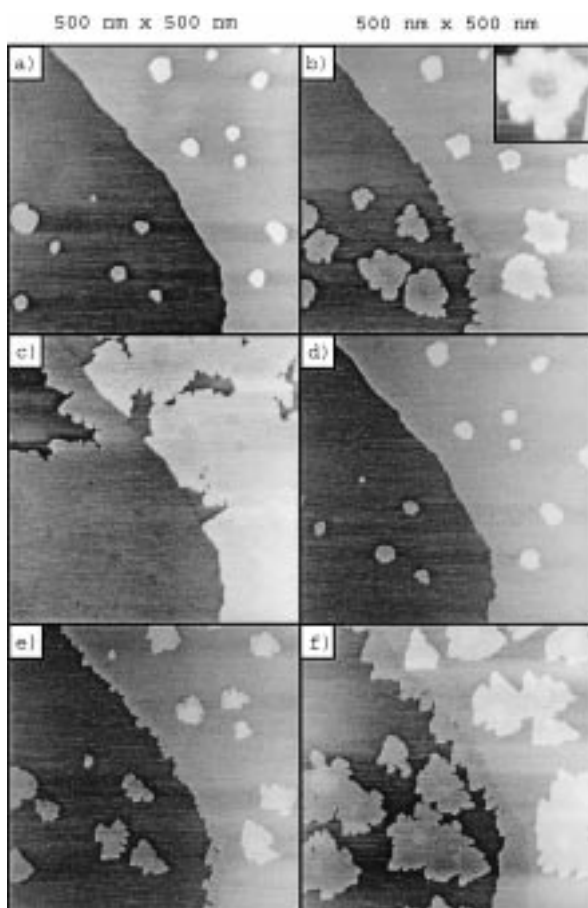


Figure 19. Sequence of STM images ($500 \times 500 \text{ nm}^2$) showing the initial stages of Pd deposition onto Au(111) from $0.1 \text{ M H}_2\text{SO}_4 + 0.1 \text{ mM H}_2\text{PdCl}_4$. Deposition potentials versus SCE: a) $+0.55 \text{ V}$ (bare gold surface; no Pd deposition); b, c) $+0.48 \text{ V}$; d) $+0.46 \text{ V}$; e, f) $+0.41 \text{ V}$. The inset in (b) has an increased height resolution to show more clearly the chemical contrast between Au (center) and Pd. From ref. [125].

ly covered by palladium nucleating at steps and growing onto the lower terrace, except for the gold islands, which obviously lack nucleation centers. A more negative potential is required to force palladium onto the gold island and the image in Figure 19d is practically identical to that of the bare gold surface (Figure 19a). Now the same process starts again for the second palladium layer, namely nucleation at the mono-atomic high step and the island rims (Figures 19e and f). However, before the second layer is complete, the third one begins to grow and, soon after, the fourth layer is formed. Hence, the palladium surface becomes increasingly defect-rich, although the terrace sites are still outnumbering the step sites. This is also reflected in cyclic voltammograms for adsorption processes such as copper upd on the palladium overlayer, which correspond to those for Pd(111) single-crystal electrodes. Thin palladium overlayers on the three low-index faces of gold (and of platinum, to be complete) have been shown to assume the crystallographic orientation of the substrate (if not pseudomorphic), which provides a relatively simple means of obtaining palladium single-crystal surfaces without the troublesome preparation of massive palladium crystals.^[126] Thin palladium overlayers have the advantage of showing very little hydrogen absorption,^[127] a

process which tends to mask other interesting reactions, such as hydrogen adsorption, for massive crystals.

In summarizing the described results, it is obvious that STM is a powerful technique for metal deposition studies, particularly for investigating the very initial stages of this process. The ability of this technique to combine real space imaging with nanometer, if not atomic, resolution leads to structure information of hitherto unprecedented quality which will not only substantially increase our understanding of nucleation and growth on an atomic level but will also be of great value in the attempt to tailor complex surface structures required for future nanotechnologies.

7. Nanostructuring of Electrode Surfaces

The continuing trend in microelectronics for miniaturization has launched a second career of the STM: It is not only a great technique for imaging surfaces with atomic-scale resolution, it is also a tool for positioning single atoms and molecules on surfaces at will and with atomic precision. The tip–substrate interaction at close distances (of the order of an atomic diameter or less), which for surface imaging is a much-feared problem as it may give rise to artifacts, had been successfully employed to move atoms or molecules with the tip along the surface. Impressive examples of this kind of surface nanostructuring have been published by several groups^[128–131] which operate under UHV conditions and often at low temperatures; a famous example is Eigler's quantum corral,^[132] which consisted of 48 iron atoms on Cu(111) arranged in a circle with the tip of an STM and demonstrated the wave nature of electrons in a very straightforward way.

Work on nanostructuring electrode surfaces started soon after the corresponding experiments in UHV, although the tip-generated entities had to be significantly larger than single atoms in order to survive in an electrochemical environment at room temperature. The first attempts of electrochemical nanostructuring involved tip-induced surface defects, generated either by mechanical contact (tip crashes) or by some sort of sputtering process (initiated by high-voltage pulses between the tip and substrate), which then acted as nucleation centers for metal deposition at predetermined positions.^[133, 134] More recently, metal clusters were shown to be positioned on metal and semiconductor surfaces by a two-step process that involved metal deposition from solution onto the STM tip, followed by a burstlike dissolution and redeposition on the sample within a narrow region directly underneath the tip.^[135, 136]

In the following, I will describe two different ways of nanostructuring electrode surfaces, as developed in our group, which deal with the spatially confined tip-induced substrate dissolution and tip-induced metal deposition. Two types of tip–substrate interaction, which can lead to the nanostructuring of surfaces, are sketched in Figure 20. Under normal imaging conditions, with typical values of $I_T = 2 \text{ nA}$ and $U_T = 50 \text{ mV}$, the tip–substrate distance s can be calculated from Equation (3).

$$I_T = R_0^{-1} U_T \exp(-A \sqrt{\phi_T} s) \quad (3)$$

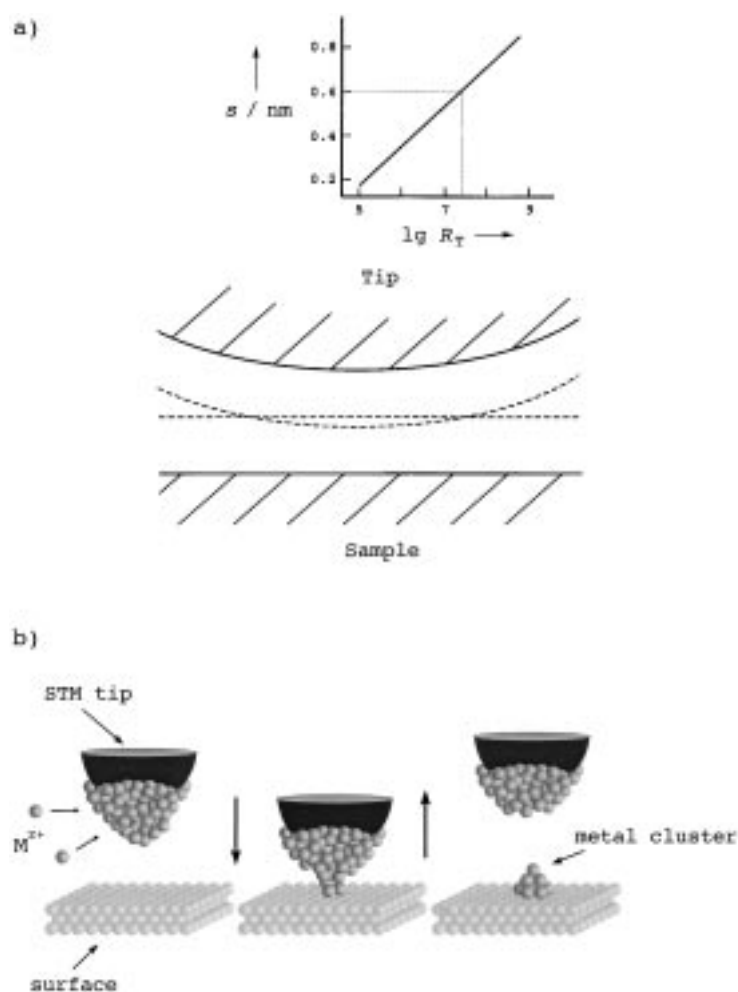


Figure 20. a) Schematic diagram of sample and tip with their electric double layers overlapping. The inset shows the dependence of the tunnel gap s on the tunnel resistance R_T for a tunnel barrier of 1.5 eV. From ref. [138]; b) Schematic representation of the jump-to-contact between a Cu-covered STM tip and an Au substrate. From ref. [139].

The term ϕ_T is the tunnel barrier, $A = 2\sqrt{2m_e}/\hbar = 10.25 \text{ eV}^{-1/2} \text{ nm}^{-1}$, and the point-contact resistance $R_0 = 12.90 \text{ k}\Omega$. With $\phi_T = 1.5 \text{ eV}$ (typical values of the tunnel barrier at metal/solution interfaces range between 1.0 and 2.0 eV^[137]), s equals about 0.6 nm. Considering the fact that the electric double layer of metal electrodes in concentrated solutions is an estimated 0.3 nm thick,^[1, 2] the double layers of substrate and tip begin to merge (Figure 20a) and the ideal picture of a noninteracting tip is no longer valid under these conditions. For example, contact with the reference electrode for the imaged area directly underneath the tip may be lost because the bulk electrolyte, which carries the reference potential, has been “squeezed” out. In a recent publication,^[138] it was demonstrated that a spatially confined copper dissolution directly underneath the tip can be achieved by applying a tip potential positive of the Cu/Cu^{2+} Nernst potential, despite the fact that the sample potential was held at a value negative of the Cu/Cu^{2+} equilibrium potential. Hence, copper is oxidatively dissolved underneath the tip and only there, although this process should not be possible at that sample potential. This effect is demonstrated in Figure 21 by

“drilling” a hole into the $\text{Cu}(111)$ surface. After imaging the $\text{Cu}(111)$ surface with a tip potential of 0 V versus Cu/Cu^{2+} (Figure 21a), the tip was positioned at a fixed location and a potential of +20 mV versus Cu/Cu^{2+} applied for 3 min. Although the sample potential was at –50 mV versus Cu/Cu^{2+} , a crater 14 nm deep and about 100 nm wide was generated at $I_T = 2 \text{ nA}$ (Figure 21b). Because the tip-induced copper dissolution depended so sensitively on the tip potential relative to the Nernst potential, it was inferred that the copper dissolution under these circumstances was a result of the direct tunneling from the redox system into the empty states of the tip.^[138] In this study, it was also shown that there is a smooth transition between imaging without much tip interference and tip-induced surface processing. Depending on the tip and sample potentials, the regimes of 1) tip-enhanced copper deposition, 2) mere surface imaging, or 3) tip-induced copper dissolution will dominate.

Most of the previously published work on nanostructuring deals with the deposition of small metal clusters at predetermined positions. The principle behind our method, which allows the formation of metal clusters in quick succession and without destroying the single crystallinity of the substrate, is as follows.^[139, 140] First, metal has to be deposited from solution onto the tip, which is achieved simply by choosing a tip potential negative of the Cu/Cu^{2+} equilibrium potential. Second, the metal-loaded tip has to approach the surface for a short period of time, during which a “jump-to-contact” takes place (Figure 20b). This jump-to-contact occurs at close distance between tip and sample (typically 0.3 nm or less) and requires a strong interaction between metal at the tip and substrate to initiate the jump. The resulting connective neck breaks upon the subsequent retraction of the tip, to leave a small metal cluster on the surface. As has been shown before on several occasions, this tip-induced cluster generation has been fully automated, with a microprocessor controlling not only the externally enforced tip approach which leads to the cluster formation but also the x - and y -position of the tip, which allows “writing” complex patterns on the surface.^[139] Figure 22 shows an array of 2500 copper clusters on an $\text{Au}(111)$ electrode, all about 0.6 nm high, which was accomplished within a few minutes. The clusters were generated by 2 ms voltage pulses to the z -piezo at a repetition rate of 120 Hz. The clusters are remarkably uniform in size and the pattern surmounts monoatomic high steps without any difficulty, to suggest that our technique of nanostructuring works also for slightly rough surfaces. Also noteworthy is the fact that despite the fabrication of many copper clusters at a fairly high rate (the largest array so far consisted of 10000 copper clusters^[141]), there is no sign of depletion of copper on the tip. The refilling of the tip during cluster fabrication by the on-going deposition reaction at the tip is surprisingly fast and—quite importantly—retains the high imaging quality of the tip. Therefore,

“drilling” a hole into the $\text{Cu}(111)$ surface. After imaging the $\text{Cu}(111)$ surface with a tip potential of 0 V versus Cu/Cu^{2+} (Figure 21a), the tip was positioned at a fixed location and a potential of +20 mV versus Cu/Cu^{2+} applied for 3 min. Although the sample potential was at –50 mV versus Cu/Cu^{2+} , a crater 14 nm deep and about 100 nm wide was generated at $I_T = 2 \text{ nA}$ (Figure 21b). Because the tip-induced copper dissolution depended so sensitively on the tip potential relative to the Nernst potential, it was inferred that the copper dissolution under these circumstances was a result of the direct tunneling from the redox system into the empty states of the tip.^[138] In this study, it was also shown that there is a smooth transition between imaging without much tip interference and tip-induced surface processing. Depending on the tip and sample potentials, the regimes of 1) tip-enhanced copper deposition, 2) mere surface imaging, or 3) tip-induced copper dissolution will dominate.

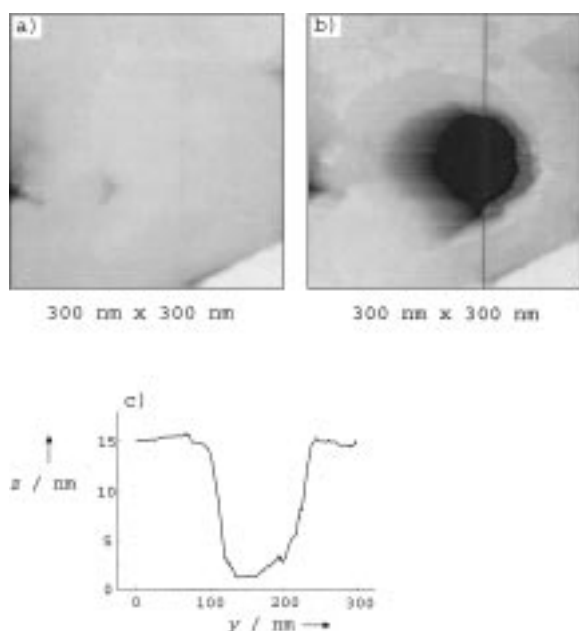


Figure 21. a) STM image of a Cu(111) surface in a Cu^{2+} containing solution at -50 mV versus Cu/Cu^{2+} . $E_{\text{tip}} = 0$ V versus Cu/Cu^{2+} . $I_T = 2$ nA. b) Same area, imaged after the tip was held at a fixed position for 3 min at $E_{\text{tip}} = +20$ mV versus Cu/Cu^{2+} and $E_{\text{sample}} = -50$ mV versus Cu/Cu^{2+} . c) Cross-section along the vertical line shown in (b). From ref. [138].

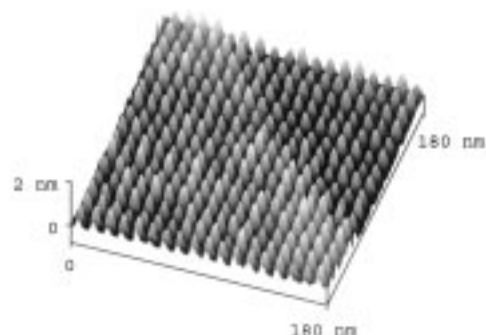
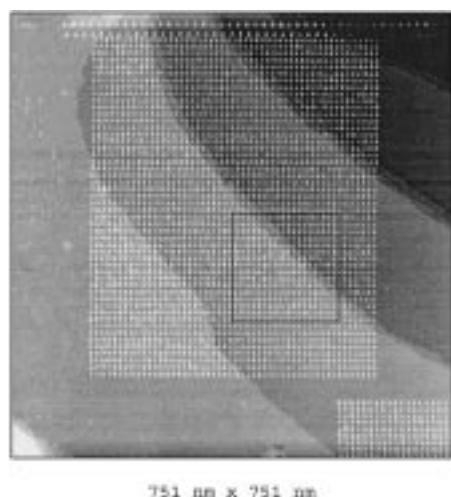


Figure 22. Array of 2500 Cu clusters on Au(111) in $0.05 \text{ M H}_2\text{SO}_4 + 1 \text{ mM CuSO}_4$, generated by 2500 voltage pulses to the z-piezo. The clusters are about 0.7 nm high. $E_{\text{sample}} = +10$ mV versus Cu/Cu^{2+} . The $180 \times 180 \text{ nm}^2$ section of the array demonstrates the uniformity in cluster size. In the top image, two more arrays of tip-induced Cu clusters are visible.

“writing” and “reading” are possible with one and the same tip.

A puzzling feature of the small, tip-induced metal clusters, which contain roughly 100 atoms, is their surprisingly high stability against anodic dissolution. Systematic studies of copper clusters on Au(111) have shown that they are stable at $+10$ mV versus Cu/Cu^{2+} for at least one hour and considerably higher “overpotentials”, say, 100 mV and more, have to be applied to dissolve the clusters completely.^[142] This effect is demonstrated in Figure 23 a, where the height of tip-induced

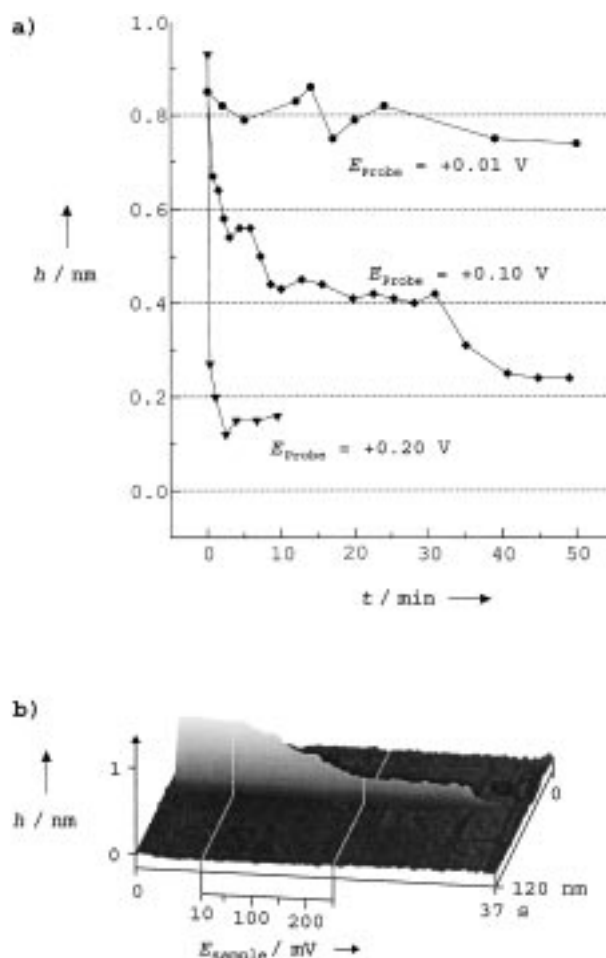


Figure 23. a) Heights h of three tip-induced Cu clusters on Au(111) in $0.05 \text{ M H}_2\text{SO}_4 + 0.1 \text{ mM CuSO}_4$ as a function of time for three different sample potentials (versus Cu/Cu^{2+}). From ref. [143]. b) Height h of a tip-induced Cu cluster on Au(111) as a function of sample potential. From ref. [143].

clusters is shown as a function of time for different dissolution potentials. At $+100$ mV versus Cu/Cu^{2+} , the layer-by-layer dissolution of the cluster is in particular clearly seen. Figure 23 b shows the cluster height as a function of electrode potential, which is scanned from $+10$ mV versus Cu/Cu^{2+} (to generate the cluster) to $+250$ mV versus Cu/Cu^{2+} (at which the cluster has disappeared completely).^[143] Interestingly, there seem to be distinct potential values at which partial dissolution of the clusters occurs. This points towards a quantum-size effect, with a 1 nm high copper cluster being stable up to 50 – 60 mV versus Cu/Cu^{2+} and a 0.6 nm high one

even up to about +180 mV versus Cu/Cu⁺⁺. In comparison, a 2.5 nm high, electrochemically deposited cluster dissolved at +10 mV versus Cu/Cu⁺⁺ within a few seconds and indicates that clusters of that size have bulk properties. However, more experimental data are required to safely establish quantum-size effects in small metal clusters.

8. Conclusions and Outlook

Electrochemical surface science, as a part of physical electrochemistry, has emerged in the endeavor both for an atomistic description of electrode/electrolyte interfaces and for a mechanistic interpretation of electrochemical processes. Significant progress was achieved during the last two decades, mainly through the adoption of experimental approaches and theoretical models of surface physicists. The use of single-crystal electrodes, of nontraditional methods such as in situ X-ray spectroscopies or STM, and of molecular dynamics calculations serve as such examples. Since structural information was most needed to reach our goal, scanning tunneling microscopy has come to play a major role among the many techniques available now to electrochemists. Quite naturally, studies so far were focused on surface structures rather than on dynamical processes or reactions, which would be the ultimate goal in electrochemistry. However, the information about surface reconstruction, about ordered adlayers, and about the initial stages of metal deposition, which has been obtained by STM and was presented here, is indeed amazing. This progress had not been foreseeable 20 years ago.

There are still many open questions that need to be answered. One of the oldest problems in electrochemistry, the structure of the metal/solution interface, is surprisingly far from being solved despite many attempts. The solution side, although handled quite well by theoretical models in the meanwhile, persistently escapes a thorough experimental characterization. This is particularly true for the properties of double-layer water, which are usually masked by those of the adjacent bulk solution. Much was learned from UHV experiments about the water–metal interaction^[144] and about the role of hydrogen bonds in determining the structure of water adlayers. There is interesting experimental evidence for high local-field strengths within the electric double layer, revealed, for example, by surface-state spectroscopy, but the various pieces of information still need to be combined to a complete picture. This process, however, seems painfully slow. Much more information is available about the metal side of the double layer, certainly as far as the structures are concerned. This is largely due to STM which indeed has advanced our knowledge in this respect tremendously. The ultimate goal in electrochemistry, however, is a detailed understanding of reactions, namely, electrically driven changes at electrode surfaces. After having investigated the structure for so many years at an atomic level, we will turn to the study of dynamic and kinetic phenomena. This will be a new and important role for the scanning probe microscopies: To adopt the instruments for recording structural changes at millisecond or even briefer time scales. Other techniques, particularly spectroscopic ones, will play a pivotal role, as they are capable of

monitoring changes, such as those due to reaction intermediates, at much shorter time scales.

A characteristic feature of electrochemistry always has been its strong and fruitful relation to applied research. Batteries and fuel cells, electrochemical classics, may serve as examples. The study of structure–reactivity relations by employing single-crystal electrodes of different crystallographic orientations or chemically modified by adlayers will be of utmost importance for a better understanding of electrocatalysis, such as for fuel cells. Solid-state ionics play a crucial role in electrochemical sensing as well as high-temperature power sources. Metal deposition from solution, particularly copper deposition, has recently received renewed interest for the fabrication of interconnects in microelectronics and for obtaining layered structures for GMR (giant-magnetoresistance) devices. Metal-deposition studies, especially of the initial stages, on the other hand, have a long tradition in fundamental electrochemistry, namely for looking at electrocrystallization phenomena or ion-transfer reactions.

With the implementation of modern surface-science techniques in electrochemistry and with the increasing awareness of the scientific community about the importance of solid/liquid interfaces (as opposed to, for example, solid/vacuum interfaces), electrochemical surface science in particular and electrochemistry in general has received wide-spread interest and thus, has become a truly interdisciplinary science with strong links to (UHV-based) surface science, organic synthesis, biochemistry, material science, micro- and nanotechnology, sensor technologies, and many others. This is certainly one of the strengths of electrochemistry, which will ensure continued interest in this area. There may be a price to pay: The danger of losing its own identity when the neighboring areas take over the electrochemical part. It will be a challenge for electrochemists to continue to play the central role in the many-faceted field of electrochemistry, which, I am sure, will have a bright future.

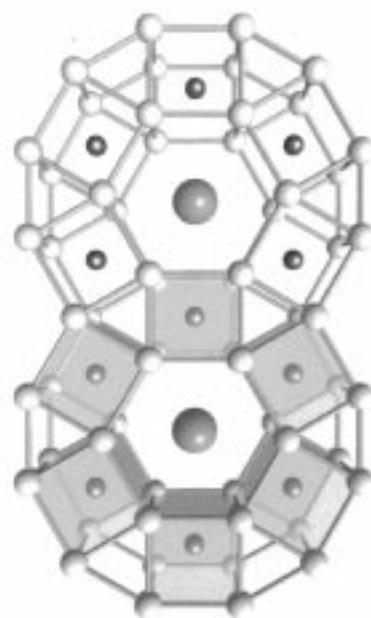
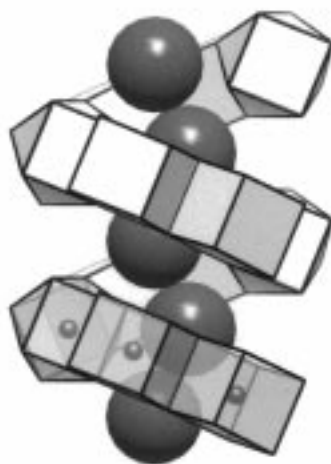
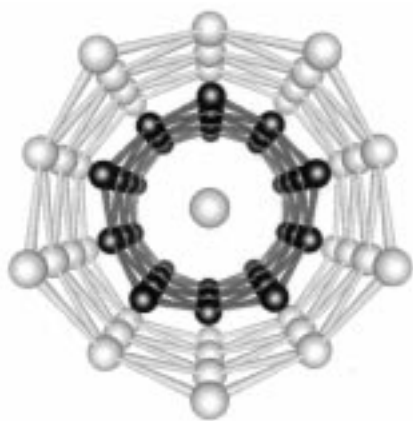
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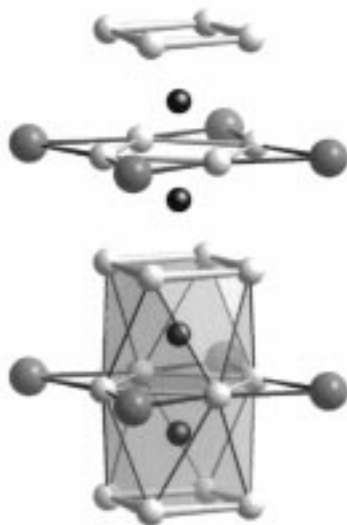
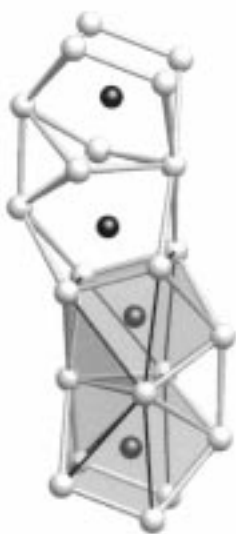
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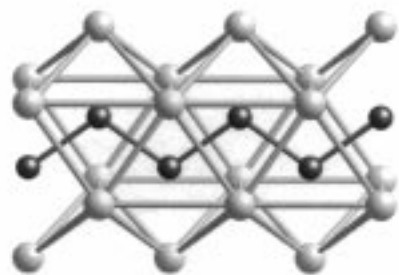
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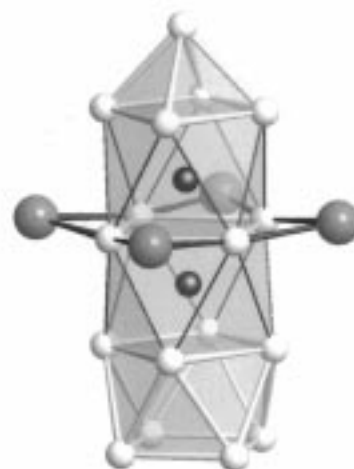
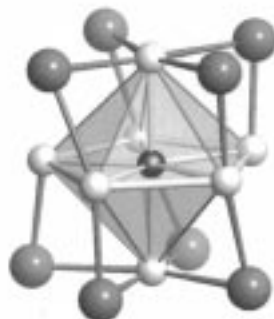
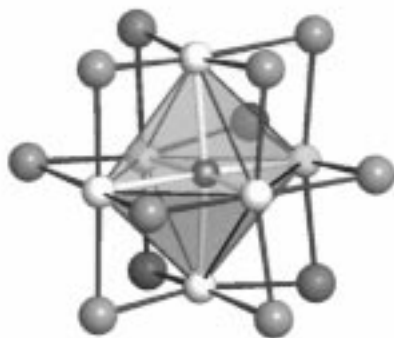
Low-Dimensional Metals



Subhalides



Bismuth Polycations



Cluster Compounds

From the Metal to the Molecule—Ternary Bismuth Subhalides

Michael Ruck*

Subvalent compounds, that is, metal-rich substances in which the average oxidation state of the cation is smaller than would be expected from the $(8 - N)$ rule, have proved to be a rich source of unexpected structural and physical features. The extraordinary structural chemistry generally observed in subvalent compounds is a consequence of the low and often non-integer oxidation states of the metal atoms coupled with the low concentration of valence electrons. Both factors can lead to a wide-range of bonding types within the same compound. A characteristic of

these compounds is the interplay between “metallic” regions, with delocalized electrons and mainly nonpolar bonds between the metal atoms, and “saltlike” regions, which are characterized by strong localization of the electrons and heteropolar exchange between the metal and nonmetal atoms. The volumes of the different structural regions as well as the extent to which they interpenetrate can vary from compound to compound. The ternary subhalides of bismuth belong to a new class of substances which cover the whole spectrum from parti-

ally oxidized “porous” metals, through one- and two-dimensional metals, up to semiconducting ionic or molecular cluster compounds. These subvalent compounds with their unusually high chemical stabilities provide excellent vehicles for further research and their potential is described in the following article.

Keywords: bismuth • cluster compounds • intermetallic phases • low-dimensional metals • subvalent compounds

1. Introduction

In spite of the difficulties, there is a certain satisfaction in establishing the rules and limitations of using localized bonding concepts to understand the binding in a large collection of atoms in the metallic state. Since practically all the typical physical properties of a metal depend on the almost free movement of electrons in the solid, the question arises: what happens when the freedom of movement of the conduction electrons is reduced by chemical means? Restricting the mobility of electrons to one dimension can affect quantum mechanical behavior and, as a result, macroscopic effects, which can be expected to be different from those of conventional three-dimensional metals. Further limitation must lead at some point to the crossing of the boundary between metallic and semiconducting behavior.

Solid-state chemistry can contribute to the investigation of this boundary area through the synthesis and characterization

of a range of chemically similar substances that demonstrate well-defined tiny steps in the transition between three-dimensional metallic and semiconducting materials. In a chemical sense, this typically involves metal-rich subvalent compounds. Famous examples are the suboxides and subnitrides of alkali and alkaline earth metals. Their structures can be roughly described as a metallic matrix in which ionic islands or rods are embedded.^[1] The saltlike building blocks mostly consist of oxygen or nitrogen-centered $[MX_6]$ octahedra that are either isolated or linked together by faces to form oligomeric or polymeric units. Less commonly observed are highly complex building blocks like, for example, the $[Ba_{14}CaN_6]$ cluster in $Na_{14}Ba_{14}CaN_6$ ^[2] or the $[O_7(Al_2Ba_{17})]$ cluster in $Ba_{17}Al_3O_7$.^[3] The latter subvalent metallate is also distinctive in that the Al atoms coexist as cationic and metallic species. In addition, the ternary and quaternary compounds provide a link to intermetallic phases, the structural motifs of which are also observed in the metallic matrices of subvalent compounds.

The metal-rich halides and chalcogenides of electron-deficient transition elements probably form the most extensive group of subvalent compounds.^[4] Structural investigations reveal that a large range of cluster types occur for these compounds although the M_6X_8 and M_6X_{12} types are dominant. Often these clusters are stabilized by interstitial atoms (e.g. H, B, C, N, platinum metals). Increasing the ratio of metal to

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nonmetal atoms leads, by progressive condensation of the clusters, to increasingly extended metallic regions.^[5]

Such subvalent compounds are not only known for electron-deficient s-, d-, and f-metals, but also for p-(semi-)metals albeit with far fewer examples. For example, recently significant progress has been made especially in research using the elements indium,^[6] tin,^[7] and bismuth.^[8] This research mainly concerns the ternary and quaternary oxides or halides of the aforementioned main group elements which contain electron-rich transition metals from Groups 8–10 as further components. Among these compounds, of particular note are the subhalides of bismuth, which show a large variation in metal/nonmetal ratios and range from partially oxidized intermetallic phases to complex salts and molecular solids. Consequently, there is a remarkable wealth of structural motifs that are not simply different arrangements of identical building blocks, but generally represent unique structures for each system.

The crystal structures of the binary bismuth halides already give a first impression of the structural variability, which is fully developed in the ternary phases. The bismuth monohalides $\text{BiBr}^{[9]}$ and $\text{BiI}^{[10]}$ like the metal-rich compounds $\text{Bi}_{14}\text{I}_4^{[11]}$ and $\text{Bi}_{18}\text{I}_4^{[12]}$ consist of one-dimensional (1D) infinite strips (Figure 1). The arrangement of the Bi atoms is similar to that in elemental bismuth, so that the overall impression is that the halogen atoms have acted as “chemical scissors” by cutting out strips from the element structure. Independent of this 1D character of the structural building blocks is that the electrons are mainly localized so that BiBr , which can be formulated as $(\text{Bi}^0)(\text{Bi}^{\text{II}})\text{Br}_{4/2}$, acts as a semiconductor.

Although their chemical composition differs only slightly from that of the monohalides the slightly halogen-rich compounds $\text{Bi}_6\text{Cl}_7^{[13]}$ and $\text{Bi}_6\text{Br}_7^{[9]}$ possess a completely different architecture: they contain polyhedral Bi_9^{5+} polycations (Figure 2), which are embedded in a coordination environment of halogenobismuthate(III) anions. Pictorially this can be regarded as a saltlike matrix in which “metallic” islands (more correctly, islands with metal–metal bonds) are scattered. It is possible to crystallize the Bi_9^{5+} polycations with complex counter ions as seen in compounds of the type $\text{Bi}_{10}\text{M}_3\text{X}_{18}$ ($\text{M} = \text{Zr}, \text{Hf}; \text{X} = \text{Cl}, \text{Br}$).^[14] Similarly, tetrachlorometallate(III) anions stabilize the antiprismatic Bi_8^{2+} ion in $\text{Bi}_8(\text{AlCl}_4)_2^{[15]}$ as well as the trigonal bipyramidal Bi_5^{3+} ion in $\text{Bi}_5(\text{AlCl}_4)_3^{[16]}$ and $\text{Bi}_5(\text{GaCl}_4)_3^{[17]}$

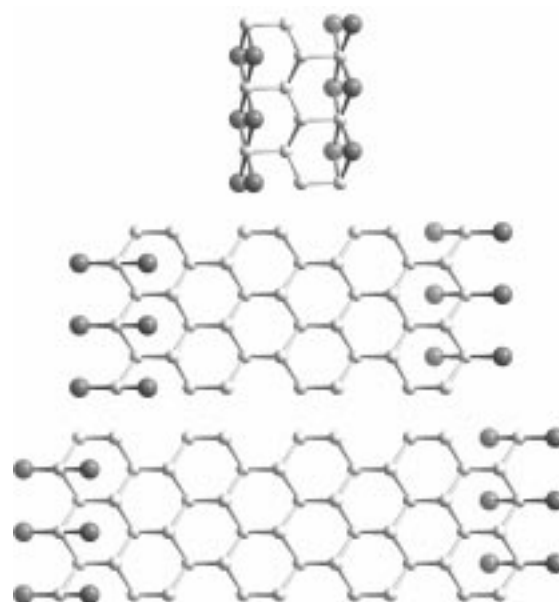


Figure 1. One-dimensional strings in the structures of BiI ($=\text{Bi}_4\text{I}_4$), Bi_{14}I_4 , and Bi_{18}I_4 . The Bi atoms are shown lightly shaded.

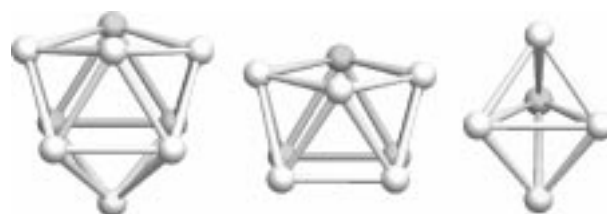


Figure 2. Homonuclear bismuth polycations in binary subhalides and halogenometallates: Bi_9^{5+} , Bi_8^{2+} , and Bi_5^{3+}

In the case of the new ternary bismuth subhalides, which will be described and discussed subsequently, we are concerned with subhalides of intermetallic phases rather than halogenometallates of the type mentioned above. The extent of the metallic areas for each structure serves as a means of categorizing the compounds. Starting with three-dimensional metals, the structures of which are disrupted by pores that are filled with anions, a reduction in the dimensionality of the metallic system ensues until finally, isolated clusters of metal atoms result. Firstly, a brief description of the synthesis of such compounds is given.



Michael Ruck was born in Pforzheim (Germany) in 1963 and began to study chemistry at the Universität Karlsruhe in 1984. After finishing his degree in the group of Hartmut Bärnighausen he moved in 1989 to the Max-Planck Institut für Festkörperforschung in Stuttgart. There he joined the group of Arndt Simon working on cluster compounds of the rare earth metals and completing his Ph.D. in 1991 at the Universität Stuttgart. Following this he returned to the Universität Karlsruhe where he completed his Habilitation in 1997 on ternary bismuth subhalogenides. In April 2000 he accepted a professorial position at the Institut für Anorganische Chemie at the Technische Universität Dresden. His research interests concern solid-state chemistry (subvalent compounds, low-dimensional systems, structure–property relationships, chemical bonding in the solid state) and crystallography (crystal chemistry, pseudo symmetry, twin formation).

2. The Partial Oxidation of Intermetallic Phases

In principle, the synthesis of the subhalides should proceed by heating the elements in an evacuated quartz ampoule. Mostly, it is found to be more convenient to use intermetallic phases or metal halides as starting materials. In some cases, it is necessary to add auxiliary reagents, such as niobium halides, which modify the partial pressures in the gas phase through various equilibrium processes but are not incorporated into the bismuth subhalides and can be easily separated after the reaction is complete. That electron-rich transition metals of Groups 8–10 are particularly suitable for the formation of ternary bismuth subhalides is because of a number of favorable factors:

- 1) With the exception of cobalt, these elements form intermetallic phases with bismuth. Previous studies suggest that this is a basic requirement for the formation of the corresponding subhalides. Consequently, we can speak of the partial oxidation of intermetallic phases.
- 2) The electronegativities of these transition metal elements hardly differ from that of bismuth so that the formation of strongly heteropolar bismuthides is unlikely.
- 3) Bromine and iodine oxidize these transition elements to di- or trihalides, high oxidation states, which make the formation of the subhalides improbable, are avoided.
- 4) The halides of these transition metals are volatile at temperatures at which bismuth and bismuth halides exist in the gas phase. This gives a route for the separation of the products from the gas phase.

Although many subhalides can be crystallized directly from the melt, in some cases the option of gas-phase transport can be used. The principle of subjecting two metals to a simultaneous chemical transport to deposit them as an intermetallic phase is well known, but has only recently been more thoroughly investigated.^[18] That subvalent compounds can also be deposited has been shown for the first time with the coupled transport of palladium and aluminum with iodide, whereby in addition to a variety of intermetallic phases the ternary subiodide Pd_5AlI_2 was formed.^[19]

For many reasons, it is difficult to synthesize pure bismuth subhalides, most of the compounds decompose and form peritectically. Frequently, the liquid phase separates below a critical temperature into a halogen-rich and an extremely halogen-deficient melt. In addition, at reaction temperatures which are usually over 400°C there are significant amounts of bismuth vapor and gas-phase bismuth halides, which precipitate out on cooling. Discovering suitable reaction conditions is made difficult by the often fragmentary nature of the phase diagrams. The calculation of transport equilibria also fails because of the paucity of thermodynamic data and insufficient knowledge regarding the gas-phase species. The possibility of observing new ternary bismuth subhalides in the ternary systems, where new compounds have already been discovered, as well as those, which up to now have looked less promising, cannot be ruled out.

The chemical properties of the binary and ternary subhalides of bismuth are particularly noteworthy. Remarkably, the compounds are only slightly sensitive to oxidation. In this way, they differ significantly from most other subvalent

compounds. All bismuth halides can be left exposed to the air for several days to several months without appreciable decomposition and some are even resistant to attack from dilute mineral acids.

3. “Porous” Metals

Bismuth forms two intermetallic phases with nickel, these are BiNi and Bi_3Ni , which decompose peritectically at 655°C and 469°C , respectively.^[20] If both elements are treated with iodine at temperatures higher than the decomposition temperature of Bi_3Ni , the subiodide $\text{Bi}_{5.6}\text{Ni}_5\text{I}$ is obtained by gas-phase transport.^[21]

That the crystals form as needles suggests a marked anisotropy of the crystal structure. The latter mostly consists of double-walled decagonal-cross-section tubes made up of Ni and Bi atoms (Figure 3). In each tube, the metal atoms are

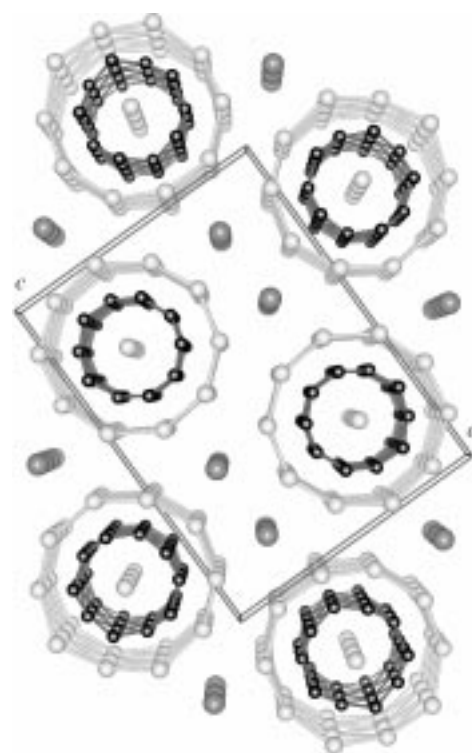


Figure 3. The crystal structure of $\text{Bi}_{5.6}\text{Ni}_5\text{I}$. Connecting lines highlight the intermetallic structural part formed by decagonal-cross-sectioned channels of Bi and Ni atoms. Ni atoms are shown in black.

arranged in regular pentagons, which are stacked in staggered conformations. On the central axis of the concentric tubes, there are additional Bi atoms so that compact metallic rods with a diameter of more than 1.1 nm result. Because of the noncrystallographic imposed symmetry of the rods, corresponding to a fivefold rotoinversion axis, close-packing of the rods is impossible. The remaining “pores” contain the iodide ions, which, however cannot be removed from the structure without decomposition of the subiodide.

$\text{Bi}_{5.6}\text{Ni}_5\text{I}$ is a moderately good conductor, and its resistance increases with temperature (Figure 4). The conduction of

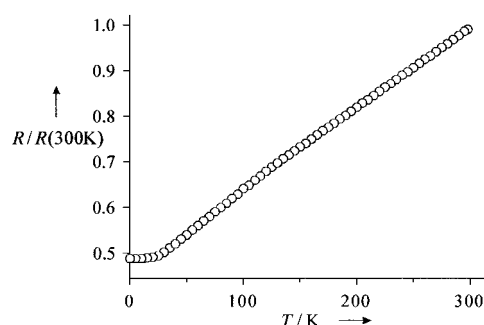


Figure 4. Temperature dependence of the electrical resistance of a crystal of $\text{Bi}_{5.6}\text{Ni}_5\text{I}$ measured parallel to the intermetallic rods of the structure.

the electrons takes place mostly in the interior of the individual intermetallic rods, since the double rows of the iodide ions are areas of electron localization and the metallic rods have only small contact areas. One could visualize a needle-crystal of $\text{Bi}_{5.6}\text{Ni}_5\text{I}$ as a bundle of parallel, partially isolated, metallic fibers.

$\text{Bi}_{12}\text{Rh}_3\text{Br}_2$, another “porous” metal, is built-up in a completely different way.^[22] The crystal structure is based on an open three-dimensional framework of rhodium-centered $[\text{RhBi}_{8/2}]$ cubes and square antiprisms, which share common edges (Figure 5). Bromide ions fill the chiral pores of the

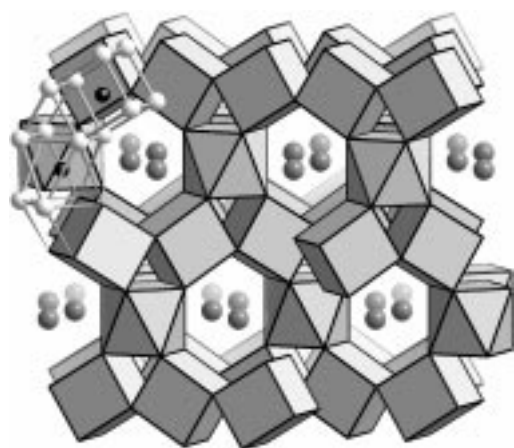


Figure 5. Section of the structure of $\text{Bi}_{12}\text{Rh}_3\text{Br}_2$. Edge-sharing $[\text{RhBi}_{8/2}]$ cubes and square $[\text{RhBi}_{8/2}]$ antiprisms form a network of chiral channels in which bromide ions are embedded.

intermetallic framework. Writing the sum formula of $\text{Bi}_{12}\text{Rh}_3\text{Br}_2$ as $(\text{Bi}_4\text{Rh})_3\text{Br}_2$ emphasizes the close correspondence to the intermetallic phase $\alpha\text{-Bi}_4\text{Rh}$. Similar to the subbromide, the cubic crystal structure of $\alpha\text{-Bi}_4\text{Rh}$ consists of edge-sharing $[\text{RhBi}_{8/2}]$ polyhedra.^[23] By calculating the electron localization function (ELF) for $\alpha\text{-Bi}_4\text{Rh}$ it was recently shown that the lone pairs of the Bi atoms are located at the surface of the polyhedra, pointing away from the metallic bonding inside the framework.^[24] This concept can be transferred to the partly oxidized subbromide $\text{Bi}_{12}\text{Rh}_3\text{Br}_2$, too. Thus, there is a comparable structural segregation of regions with largely delocalized electrons (conduction electrons inside the framework of $[\text{RhBi}_{8/2}]$ polyhedra) and areas with

high electronic localization (lone pairs on the framework surface and bromide ions in the pores).

4. Two-Dimensional Metals

Similar to $\text{Bi}_{12}\text{Rh}_3\text{Br}_2$, the intermetallic part of the structure of $\text{Bi}_{13}\text{Pt}_3\text{I}_7$ consists of edge-sharing $[\text{PtBi}_{8/2}]$ cubes (Figure 6).^[25] In this case, the linking of the polyhedra only occurs in two dimensions resulting in a planar net of the Kagomé type. The hexagonal prismatic voids in the net each provide space for an iodide ion. The layers in the structure are separated from each other by alternating layers of iodide ions and sheets made up of parallel $\infty[\text{BiI}_4^-]$ zigzag chains.

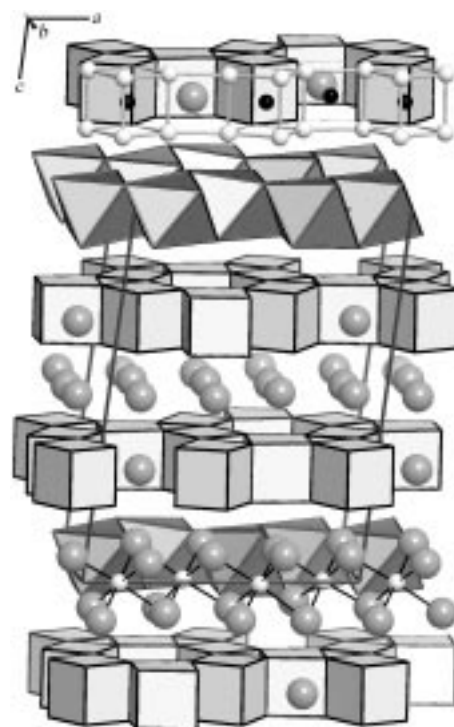


Figure 6. The crystal structure of $\text{Bi}_{13}\text{Pt}_3\text{I}_7$. The edge-sharing $[\text{PtBi}_{8/2}]$ cubes form a Kagomé net in which iodide ions fill the hexagonal prismatic holes. Monolayers of individual iodide ions and layers of tetraiodobismuthate(III) chains lie between the nets.

The cubic coordination of the Pt atoms is interesting since in the binary intermetallic phases the Pt atoms are always octahedrally surrounded by six Bi atoms. On the other hand a cubic environment for the Pt atoms is found in combination with the electron-deficient element lead in the compound Pb_4Pt .^[26] Formulating $\text{Bi}_{13}\text{Pt}_3\text{I}_7$ as $([\text{Bi}_4\text{Pt}]_3)^{4+}(\text{BiI}_4)^-(\text{I}^-)_3$ gives every $[\text{PtBi}_{8/2}]$ cube a charge of $+4/3$; thus it is still far from being isoelectronic with the $[\text{PtPb}_{8/2}]$ cube. Nevertheless, it seems that below a certain valence-electron concentration the cubic coordination for the Pt atom is favored.

The coordination number and mode change on moving from platinum to the lighter homologue nickel. The Bi/Ni system has already been mentioned above in connection with the subiodide $\text{Bi}_{5.6}\text{Ni}_5\text{I}$, which may be derived from the

intermetallic phase Bi_3Ni .^[27] The other phase, Bi_3Ni , can also be partially oxidized using halogens. Here, care must be taken during the preparation to ensure that the temperature does not exceed the peritectic point of Bi_3Ni .

This method can be successfully used for the synthesis of the isostructural compounds $\text{Bi}_{12.86}\text{Ni}_4\text{I}_6$ ^[28] and $\text{Bi}_{12.86}\text{Ni}_4\text{Br}_6$.^[29] The characteristic building blocks of the intermetallic phase Bi_3Ni are conserved in their structures.^[30] This involves monocapped trigonal prisms of Bi atoms, which are condensed through their two remaining uncapped rectangular faces to linear strings (Figure 7). As a consequence of the

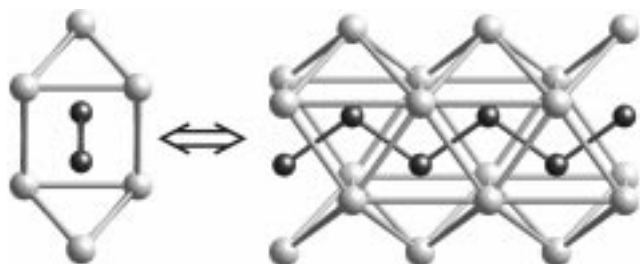


Figure 7. Two views of a prism string of composition $[\text{NiBi}_{1/3}\text{Bi}_{2/3}]_{\infty} = \text{Bi}_3\text{Ni}$.

prism condensation, the Ni atoms at the center of the Bi prisms form a zigzag chain. Although the Ni–Ni distances are comparatively short, they are nonbonding. These prism strings, corresponding to the composition $[\text{NiBi}_{1/3}\text{Bi}_{2/3}]_{\infty} = \text{Bi}_3\text{Ni}$, join together in a rod packing to give the intermetallic phase. In the subiodide $\text{Bi}_{12}\text{Ni}_4\text{I}_3 = (\text{Bi}_3\text{Ni})_4\text{I}_3$ the prism strings are no longer close packed, but form porous double layers (Figure 8). Iodide ions fill the channels and separate the double layers.

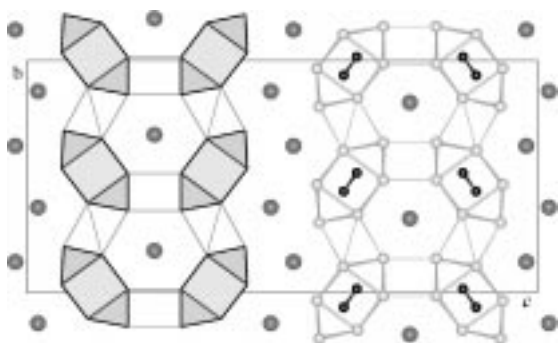


Figure 8. The crystal structure of $\text{Bi}_{12}\text{Ni}_4\text{I}_3$. The double layers consisting of Bi_3Ni prism strings are highlighted.

The halogen-richer subhalides of composition $\text{Bi}_{12.86}\text{Ni}_4\text{X}_6 = (\text{Bi}_3\text{Ni})_4(\text{Bi}_{0.86}\text{X}_4)\text{X}_2$ ($\text{X} = \text{Br}, \text{I}$) demonstrate an even smaller degree of connection between the intermetallic strings: deeply corrugated single layers are separated by isolated halide ions and halogenobismuthate groups (Figure 9). The nonstoichiometric formulation of the anions $(\text{Bi}_{0.86}\text{X}_4)$ hides a complicated sequence of short chains of *trans*-edge-sharing $[\text{BiX}_6]$ octahedra. Their varying lengths

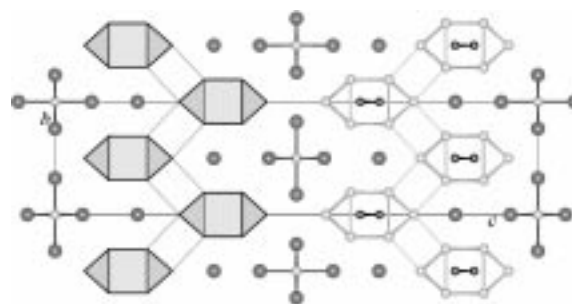


Figure 9. The crystal structure of $\text{Bi}_{12.86}\text{Ni}_4\text{I}_6$. Isolated iodide ions and oligomeric iodobismuthate(III) groups lie between deeply corrugated layers of Bi_3Ni prism strings.

manage the matching of the ionic and intermetallic parts of the structure.

As shown above, the contacts between the intermetallic strings become fewer with progressive oxidation, while the bond within a prism becomes stronger. This is demonstrated in the general shortening of the interatomic distances on going from Bi_3Ni to $\text{Bi}_{12.86}\text{Ni}_4\text{X}_6$. The variation in interatomic distances can be closely correlated to the changes in electron distribution (Table 1 and Figure 10). The oxidation leads to a drainage of electron density from the regions with metallic structure into the energetically low-lying states of the halogen atoms. Consequently, the energy states near the Fermi level, which are still occupied in Bi_3Ni , are emptied. Since these states possess antibonding character, the result of emptying

Table 1. Change in interatomic distances (in pm) on partial oxidation of Bi_3Ni with iodine.^[a]

	Bi_3Ni	$\text{Bi}_{12}\text{Ni}_4\text{I}_3$	$\text{Bi}_{12.86}\text{Ni}_4\text{I}_6$
Bi–Bi	348	333	328
Ni–Ni	263	255	252

[a] Bi–Bi corresponds to the distance between the capping Bi atom and the four adjacent Bi atoms of a trigonal prism. Compare Figure 7 and 10.

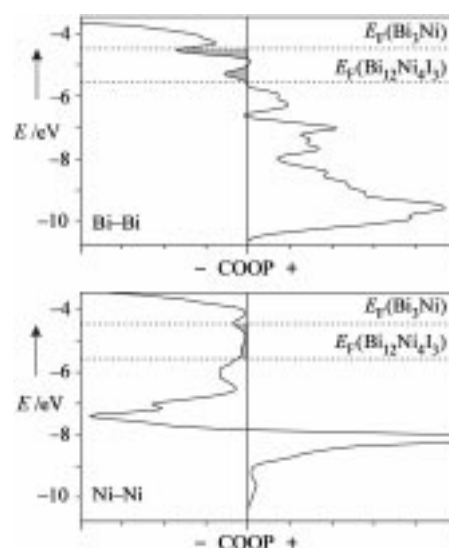


Figure 10. Emptying of the antibonding states through the lowering of the Fermi level (E_F) on oxidation of Bi_3Ni to $\text{Bi}_{12.86}\text{Ni}_4\text{I}_6$ (COOP = Crystal Orbital Overlap Population). See Table 1.

them is to produce a stronger chemical bond and shorter interatomic distances.

The modification of the electronic structure also affects the physical properties. Whilst Bi_3Ni can be described as non-magnetic, $\text{Bi}_{12.86}\text{Ni}_4\text{I}_6$ undergoes a magnetic-ordering change from a Pauli paramagnet to a band ferromagnet at 25 K.

5. Quasi One-Dimensional Metals

The transition from a two- to a one-dimensional metal is already initiated for the subbromide $\text{Bi}_{12.86}\text{Ni}_4\text{Br}_6$ and is fully established in another representative of the same ternary system: in the even more halogen-rich compound $\text{Bi}_{6.86}\text{Ni}_2\text{Br}_5 = (\text{Bi}_3\text{Ni})_2(\text{Bi}_{0.86}\text{Br}_4)\text{Br}$ the ${}^1_{\infty}[\text{NiBi}_{1/1}\text{Bi}_{6/3}]$ prism strings are entirely isolated from each other (Figure 11).^[31]

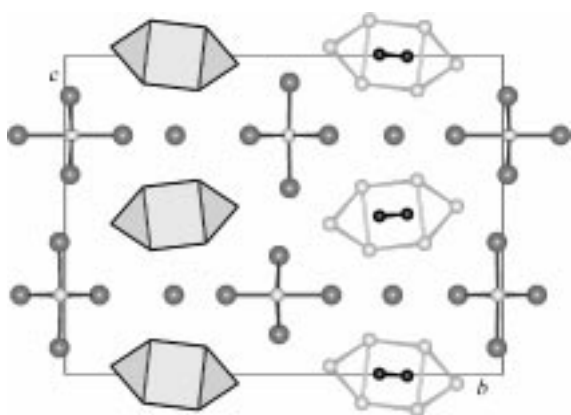


Figure 11. The incommensurate modulated crystal structure of $\text{Bi}_{6.86}\text{Ni}_2\text{Br}_5$ drawn in a simplified form as one unit cell. The Bi_3Ni prism strings are separated by bromide and bromobismuthate(III) anions.

The problem of the metrical inequality between the rather rigid intermetallic string and the bromobismuthate(III) anions is solved here through the formation of an incommensurately modulated crystal structure. This can be modeled by imagining that the ionic structural units of formula $(\text{Bi}_{0.86}\text{Br}_4)$ are made up of a complicated sequence of chains of varying lengths of *trans*-edge-sharing $[\text{BiBr}_6]$ octahedra that alternate between two orientations.

Clearly, only the electrons within the metallic bonding system of the 1D polyhedron strings show mobility. Still it is better to describe these as *quasi* one-dimensional metals, since according to the Peierls theorem completely one-dimensional metals should not exist, and here we are discussing three-dimensional, albeit strongly anisotropic solids.

That such compounds can indeed still possess metallic conductivity is demonstrated in the compound $\text{Bi}_9\text{Ir}_2\text{I}_3$ (Figure 12).^[32] This subiodide along with $\text{Bi}_9\text{Rh}_2\text{I}_3$ and $\text{Bi}_9\text{Rh}_2\text{Br}_3$ are members of a small group of compounds that although having the same stoichiometries are not isostructural. Their common structural feature is the form of the intermetallic part of the structure which is made up of isolated ${}^1_{\infty}[\text{MBi}_{1/1}\text{Bi}_{7/2}]$ polyhedral strings (Figure 13). In these, each metal (M) atom is surrounded by eight Bi atoms, which form a bicapped

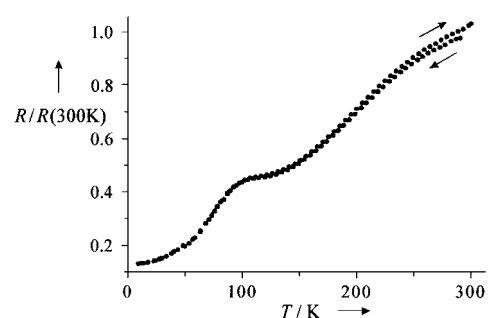


Figure 12. Temperature dependence of the electrical resistance of the quasi one-dimensional metal $\text{Bi}_9\text{Ir}_2\text{I}_3$.

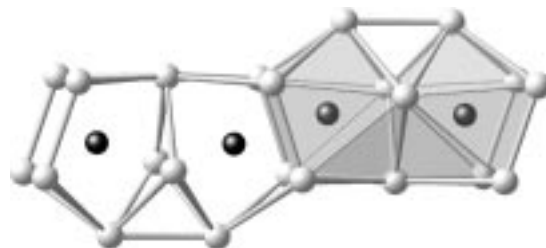


Figure 13. The slightly wavy string of face-sharing $[\text{MBi}_{1/1}\text{Bi}_{7/2}]$ polyhedra in BiM_2X_3 .

trigonal prism. The polyhedra are linked through the triangular and rectangular faces.

The simplest structural variant for the strings is found in $\text{Bi}_9\text{Rh}_2\text{I}_3$ where all the strings point in the same direction. In $\text{Bi}_9\text{Rh}_2\text{Br}_3$ and $\text{Bi}_9\text{Ir}_2\text{I}_3$ two orientations alternate in layers with a strict 2-1 or 2-2 sequence of the layers (Figure 14). The structural differences among the three packing types can be clearly seen: the ${}^1_{\infty}[\text{MBi}_{1/1}\text{Bi}_{7/2}]$ strings must have a significant influence on the translational period parallel to them. Since one is fixed by the intermetallic structural part, it is necessary to use the two other directions to accommodate the different space requirements of the bromide and iodide ions.

At this point, it is worth considering the remarkable crystal chemistry of the anions. In all the ternary bismuth subhalide structures discussed so far, the halide ions have had eight to twelve Bi atoms as nearest neighbors. Such high coordination numbers for anions are very unusual, though comparable coordination numbers (CN) are observed in metal-rich subsulphides like $\text{Ta}_6\text{S}^{[33]}$ with $\text{CN}(\text{S}) = 7$ and $\text{V}_3\text{S}^{[34]}$ with $\text{CN}(\text{S}) = 10$. From this point of view, the anions behave as if they were the third component of a ternary alloy. This feature no longer applies to the following compounds, where the halide ions adopt the more typical two- or threefold bridging positions. Examples for this are found in the columnar structures of Bi_4RuBr_2 and Bi_4RuI_2 .^[35] Both structures, which differ only in small details, consist of infinite strings of face-sharing square $[\text{RuBi}_{8/2}]$ antiprisms (Figure 15). The edges of alternate Bi_4 squares within a string are bridged by halide ions. The Ru atoms lying along the central axis are not arranged in an equidistant fashion, but instead form pairs. Using band-structure calculations it was shown that the comparatively short Ru–Ru distance is not the result of a direct bond as a consequence of Peierls distortion, but rather the result of strong bonds between the Ru atoms and the Bi atoms of the

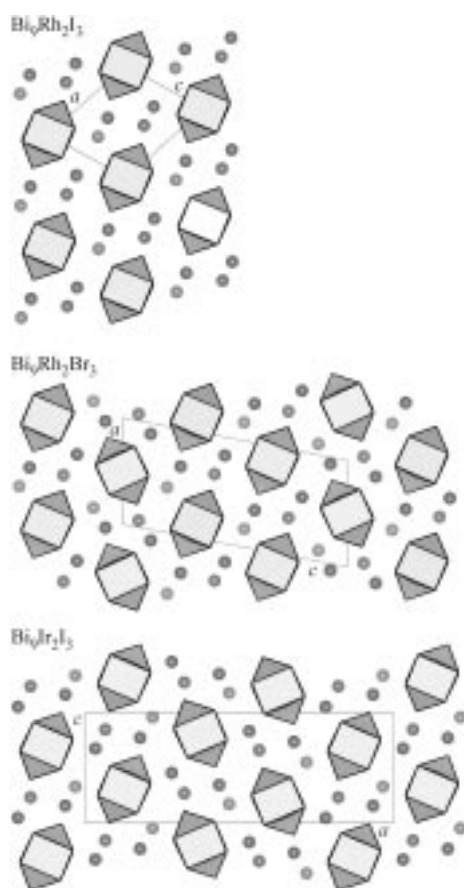


Figure 14. Different spatial arrangements of $\infty^1[\text{MBi}_{1/3}\text{Bi}_{7/3}]$ polyhedra strings in $\text{Bi}_9\text{Rh}_2\text{I}_3$, $\text{Bi}_9\text{Rh}_2\text{Br}_3$, and $\text{Bi}_9\text{Ir}_2\text{I}_3$.

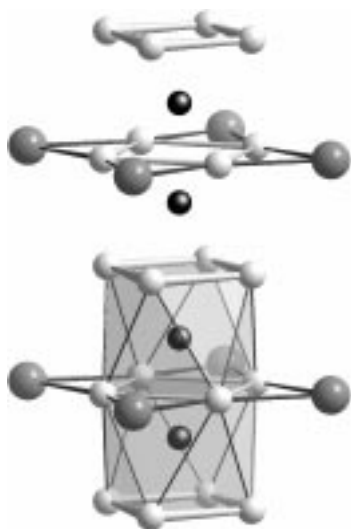


Figure 15. String of face-sharing square $[\text{RuBi}_{8/2}]$ antiprisms in the columnar structures of Bi_4RuBr_2 and Bi_4RuI_2 . The edges of the larger Bi_4 squares are bridged by halide ions.

halide-bridged Bi_4 squares, which are about three times as strong as the bonds to the halide-free Bi_4 squares.

The crystal structures of Bi_4RuBr_2 and Bi_4RuI_2 can be regarded as defect structures of the W_5Si_3 type. Here the Bi atoms occupy the cation sites whilst the two crystallographically different lattice sites of the silicide anions are occupied

by the halide ions and the Ru atoms, respectively. This remarkable analogy in crystal chemistry gives an indication of the electronic situation of the Ru atoms in the above-mentioned subhalides.

6. Ionic and Molecular Clusters

If we again apply the “chemical scissors” of oxidation to Bi_4RuBr_2 using bromine the 1D intermetallic string can be cut into pieces. The result is a significantly halogen-richer subbromide of formula $\text{Bi}_{24}\text{Ru}_3\text{Br}_{20}$.^[36] The isostructural chloride $\text{Bi}_{24}\text{Ru}_3\text{Cl}_{20}$ as well as mixed crystals of both compounds are also known.^[37]

The aforementioned snippets of the $\infty^1[\text{RuBi}_{8/2}]$ string enclose three face-sharing square antiprisms of Bi atoms (Figure 16). The stack is terminated on one side by a single Bi atom and contains only two Ru atoms; four bromide ions

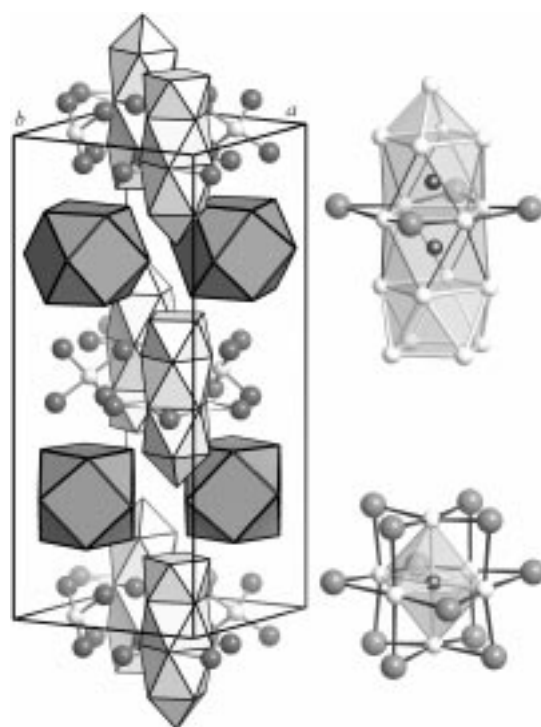


Figure 16. The crystal structure of $\text{Bi}_{24}\text{Ru}_3\text{Br}_{20}$. The cuboctahedra $[\text{RuBi}_6\text{Br}_{12}]^{2-}$ cluster and the $[\text{Ru}_2\text{Bi}_{17}\text{Br}_4]^{3+}$ stacks are shown in detail.

surround the central four-membered ring of Bi atoms. An alternative description of the arrangement of atoms in the $[\text{Ru}_2\text{Bi}_{17}\text{Br}_4]$ stack involves the segregation into a square antiprism of Bi_8^{2+} ions, a square-based pyramid of Bi_5^+ ions, and the $[\text{Ru}_2\text{Bi}_4\text{Br}_4]$ central unit. The assignment of the charges on the polycations is based on modified Wade’s rules, in which each Bi atom contributes three 6p electrons to the bonding in the cluster.^[38] The Bi_5 pyramid has the appearance of a *nido* cluster and consequently should be stable with 14 cluster electrons (CE), leading to an overall charge of +1. Analogously, the Bi_8^{2+} square antiprism forms an *arachno* cluster (22 CE), and the Bi_5^{3+} trigonal bipyramid described in the Introduction (see Figure 2) a *closo* cluster (12 CE).

In $\text{Bi}_{24}\text{Ru}_3\text{Br}_{20}$ the charge compensation is reached through two different anionic components: cuboctahedral $[\text{RuBi}_6\text{Br}_{12}]^{2-}$ cluster and $[\text{BiBr}_4]^-$ groups. Within the $[\text{RuBi}_6\text{Br}_{12}]^{2-}$ clusters, six Bi atoms coordinate the central Ru atom octahedrally (Figure 16); bromide ions bridge the twelve edges of the octahedron. Whilst the short Bi–Ru contacts can be mainly described as covalent single bonds, the edge lengths of the octahedra preclude any significant interaction between the Bi atoms.

A comparison with the crystal structure of BiBr is highly informative: in the $[\text{RuBi}_6\text{Br}_{12}]^{2-}$ cluster each Bi atom is coordinated by four bridging Br atoms and perpendicular to these by an Ru atom. In the chain-structure of $\text{BiBr} = (\text{Bi}^0(\text{Bi}^{\text{II}})\text{Br}_{4/2})$, each outer Bi^{II} is bonded to four bridging Br atoms in addition to a perpendicular inner Bi^0 atom (see Figure 1). Thus, the $(\text{Bi}^{\text{II}}\text{Br}_2)$ partial structures in BiBr and in $[\text{RuBi}_6\text{Br}_{12}]^{2-}$ clusters have the same relationship to each other as the chain structure of $\alpha\text{-PdCl}_2$ and the cluster structure of $\beta\text{-PdCl}_2$.^[39] Formally, it is possible to separate the $[\text{RuBi}_6\text{Br}_{12}]^{2-}$ ion into a neutral $(\text{Bi}^{\text{II}}\text{Br}_2)_6$ shell and an internal Ru atom with a $-II$ oxidation state. By using the electron-counting rules of complex chemistry we expect that with six Bi–Ru bonds there is a total of 16 valence electrons (VE) on the central atom. Although no definitive statement concerning the actual charge distribution can be made, the suggestion of a partial negative charge on the Ru atom is supported by the topology of the $[\text{RuBi}_6\text{Br}_{12}]$ cluster: the cluster corresponds to a portion of the NaCl lattice, in which Ru and Br atoms both occupy the anion positions. In addition, many examples of similarly constructed clusters can be cited, in which interstitial atoms surrounded by positively charged atoms must clearly be described as possessing anionic character.^[4, 40]

The subhalides $\text{Bi}_{14}\text{Si}_2\text{MI}_{12}$ and $\text{Bi}_{12-x}\text{MX}_{13-x}$ represent the final step in the transition from extensive intermetallic and saltlike areas to an ionic lattice of small charged units, along which $\text{Bi}_{24}\text{Ru}_3\text{Br}_{20}$ with its oligomeric $[\text{Ru}_2\text{Bi}_{17}\text{Br}_4]$ cluster stacks represent an intermediate state. The arrangement of the ionic building blocks in $\text{Bi}_{14}\text{Si}_2\text{MI}_{12}$ and in $\text{Bi}_{12-x}\text{MX}_{13-x}$ display the CsCl structure type.

The two quaternary phases with the formula $[\text{Bi}_{14}\text{Si}_2\text{MI}_{12}]$ ($M = \text{Rh}, \text{Ir}$) consist of $[\text{Bi}_8\text{Si}_2]^{3+}$ ions and $[\text{MBi}_6\text{I}_{12}]^{3-}$ ions (Figure 17).^[41] The assignment of the charges comes from a band-theory treatment which reveals that all the bonding or nonbonding orbitals of the cuboctahedral $[\text{MBi}_6\text{I}_{12}]^{3-}$ cluster should be filled (18 VE for M). The $[\text{Bi}_8\text{Si}_2]^{3+}$ polyhedron consists of a square antiprism of Bi atoms with each of the square faces capped by an Si atom. Thus, the cation is topologically equivalent to the molecule 1,10-dicarba-*closo*-decaboran(10)^[42] and to the anionic cluster *closo*- $[\text{Li}_2\text{Sn}_8]^{4-}$.^[43] Unlike them, the $[\text{Bi}_8\text{Si}_2]^{3+}$ cation has three cluster electrons more than would be expected for a *closo* polyhedron (22 CE) according to Wade's rules. The double degeneracy of the antibonding HOMO, which contains the three surplus electrons, is abolished by a small but detectable distortion of the $[\text{Bi}_8\text{Si}_2]^{3+}$ ion (Jahn–Teller distortion).

The ionic description as a cluster salt corresponds to the semiconducting nature of $\text{Bi}_{14}\text{Si}_2\text{IrI}_{12}$. However, a small thermal activation is sufficient to overcome the band gap of

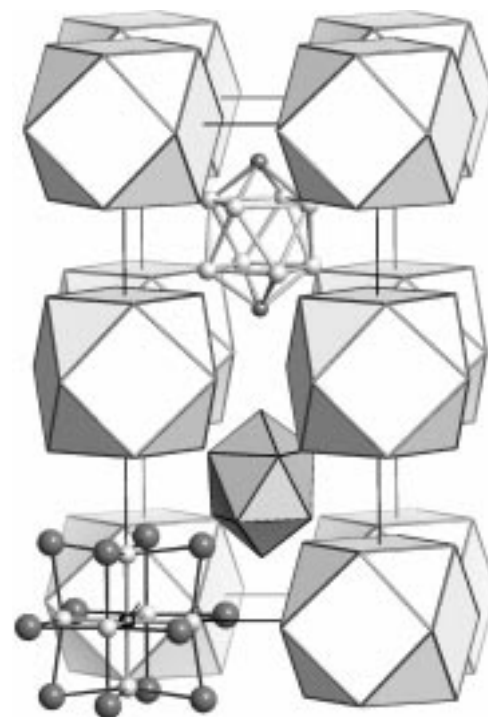


Figure 17. The crystal structure of $\text{Bi}_{14}\text{Si}_2\text{IrI}_{12}$ with $[\text{Bi}_8\text{Si}_2]^{3+}$ polyhedra and $[\text{IrBi}_6\text{I}_{12}]^{3-}$ cuboctahedra.

about 0.1 eV and thereby mobilize the electrons. The magnetic properties of $\text{Bi}_{14}\text{Si}_2\text{IrI}_{12}$ are of note: the paramagnetism of the unpaired electrons is overlaid by such a dominant diamagnetic component that the susceptibility remains in the negative region even to very low temperatures (Figure 18).

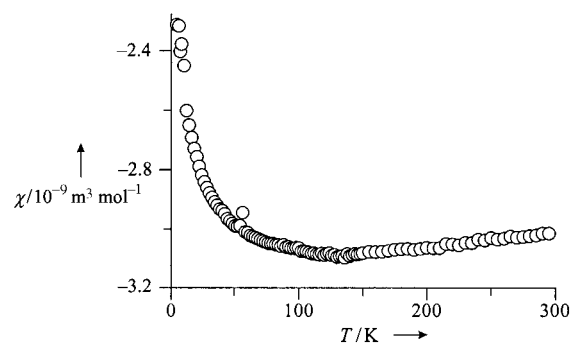


Figure 18. Temperature dependence of the molar magnetic susceptibility of $\text{Bi}_{14}\text{Si}_2\text{IrI}_{12}$.

The subhalides of average formula $\text{Bi}_{12-x}\text{MX}_{13-x}$ ($M = \text{Rh}, \text{Ir}$; $X = \text{Cl}, \text{Br}$; $x < 1$) show a phase range, because of tiny changes of the relative proportions of the building units.^[44] These building blocks include the homonuclear polycations Bi_5^+ and Bi_6^{2+} as well as the cluster anions $[\text{MBi}_6\text{X}_{12}]^-$ and $[\text{MBi}_6\text{X}_{13}]^{2-}$ (Figure 19). Whilst the square-based pyramidal Bi_5^+ ion with 14 CE can easily be classified as a *nido* cluster, with the distorted “octahedral” Bi_6^{2+} ion things are not so simple. The seeming contradiction between the 16 CE, which suggest a *nido* cluster, and the apparently closed cage is resolved on closer examination: the shape of the Bi_6^{2+} cation

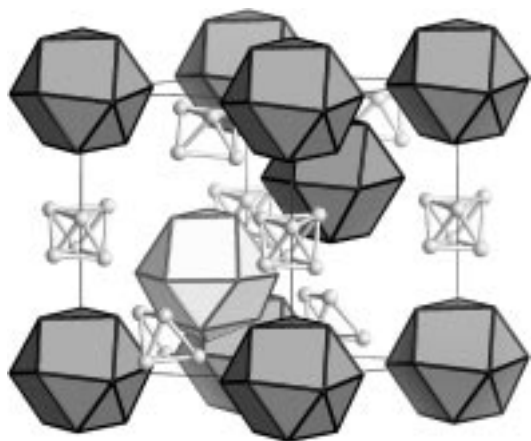


Figure 19. Crystal structure of $\text{Bi}_{11.67}\text{IrBr}_{12.67} = \text{Bi}_{34}\text{Ir}_3\text{Br}_{37}$ with Bi_5^+ and Bi_6^{2+} polycations as well as $[\text{IrBi}_6\text{Br}_{12}]^{2-}$ cubooctahedra (shaded) and $[\text{IrBi}_6\text{Br}_{13}]^{2-}$ clusters (light).

deviates significantly from that of a regular octahedron so that it is as if a seventh atom has been removed from a hypothetical *closo* cluster.

As expected, the subbromide $\text{Bi}_{11.67}\text{IrBr}_{12.67} = \text{Bi}_{34}\text{Ir}_3\text{Br}_{37}$ is a diamagnetic semiconductor with a substantial electric resistance. The black color of the compound indicates that the band gap must lie below the energy of visible light.

The unexpected termination to the series of known ternary bismuth subhalides occurs with the compound Bi_7RhBr_8 .^[45] This subbromide no longer consists of bismuth polycations and cluster anions but rather of a single type of uncharged unit (Figure 20). Even in the $[\text{RhBi}_7\text{Br}_8]$ molecules the differing electronic requirements of the components are manifested. Two apparently incompatible coordination geometries sit side-by-side: a pentagonal bipyramid about the central Rh atom and an almost square-planar coordination of the apical Bi atoms by bromide ions.

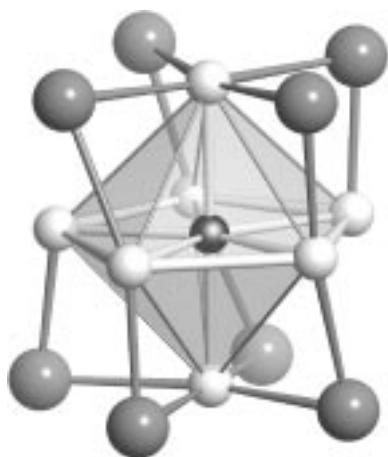


Figure 20. Molecular $[\text{RhBi}_7\text{Br}_8]$ cluster.

The bonding is also correspondingly difficult to understand: from *ab initio* calculations we expect that the Bi atoms in the central five-membered ring are bonded to each other through 5-center-4-electron bonds.^[46] Assuming that a) the seven Bi atoms are bound by single covalent bonds to the Rh atom and b) the square-planar coordinated apical Bi atom can be

assigned the oxidation state +II, we can formulate Bi_7RhBr_8 as $(\text{Bi}_5^{\text{VI}})(\text{Bi}^{\text{II}})_2\text{Rh}^{\text{II}}(\text{Br}^{\text{I}})_8$ with 18 VE for the transition metal.

7. Conclusion and Outlook

Intermetallic phases of bismuth and a transition metal from Groups 8–10 can be partially oxidized with halogens. In the resulting ternary subhalides the mobility of the conducting electrons becomes more restricted with increasing oxidation. The resulting range of compounds stretches from “porous” three-dimensional metals, that are interspersed with anions ($\text{Bi}_{5.6}\text{Ni}_5\text{I}$, $\text{Bi}_{12}\text{Rh}_3\text{Br}_2$), through two-dimensional ($\text{Bi}_{13}\text{Pt}_3\text{I}_7$, $\text{Bi}_{12}\text{Ni}_4\text{I}_3$, $\text{Bi}_{12.86}\text{Ni}_4\text{X}_6$) and one-dimensional systems ($\text{Bi}_{6.86}\text{Ni}_2\text{Br}_5$, $\text{Bi}_9\text{M}_2\text{X}_3$, Bi_4RuX_2), to semi-conductors with very small ($\text{Bi}_{14}\text{Si}_2\text{MI}_{12}$) or moderately large band gaps ($\text{Bi}_{24}\text{Ru}_3\text{X}_{20}$, $\text{Bi}_{12-x}\text{MX}_{13-x}$, Bi_7RhBr_8).

The synthetic possibilities offered by using chlorine and fluorine on the intermetallic phases are yet to be explored. Since these halogens are more oxidizing, we can expect to see cluster salts with even higher halogen contents and with band gaps falling in the visible region.

In the general phase diagram (Figure 21), the subhalides described above are grouped in the phase area that lies

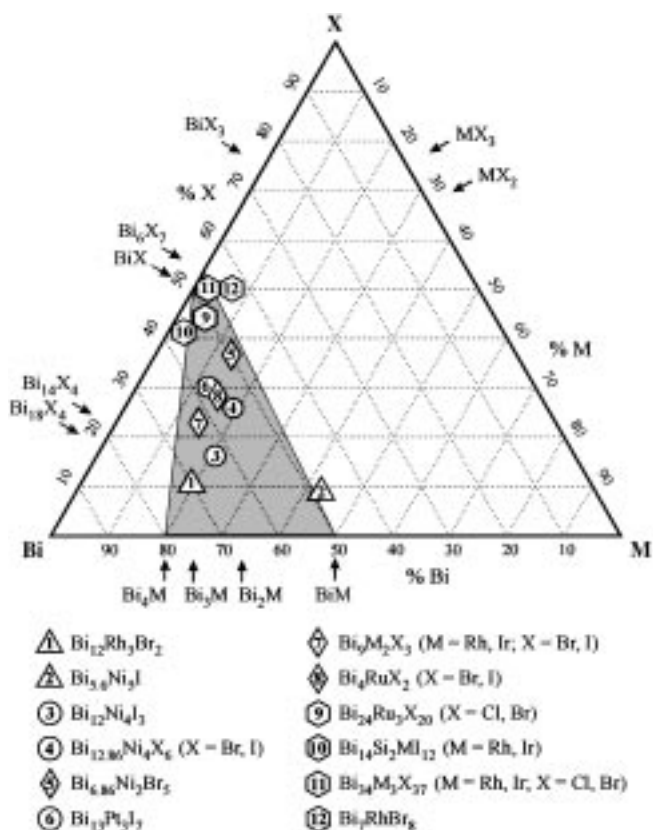


Figure 21. Generalized phase diagram of the ternary system bismuth, transition metal (M), and halogen (X) showing the known ternary phases. The bismuth and silicon components for the quaternary compounds $\text{Bi}_{14}\text{Si}_2\text{MI}_{12}$ are combined. The symbols indicate for the intermetallic structural part whether it is three-dimensional (triangle), two-dimensional (circle), one-dimensional (diamond) or made up of isolated clusters (hexagon).

between the pseudo-binary "intersections" $\text{BiX}-\text{Bi}_4\text{M}$ and $\text{Bi}_6\text{X}_7-\text{BiM}$. The bismuth content varies between 70 at. % in $\text{Bi}_{12}\text{Rh}_3\text{Br}_2$ and 44 at. % in Bi_7RhBr_8 , the halogen content between 12 at. % in $\text{Bi}_{5,6}\text{Ni}_5\text{I}$ and 50 at. % in Bi_7RhBr_8 . The trend is that a higher halogen content is linked to a lower transition metal content without, however, there being a true correlation between the ratios of the elements.

For all the currently known compounds it is the case that the halide ions have no direct contact to the transition metals, but rather are exclusively bonded to the Bi atoms. As a result, a higher halogen content leads to a larger surface area of the intermetallic structural region formed by the Bi atoms. In this way, the ordering of the subhalides according to increasing oxidation state corresponds to the ordering in terms of increasing penetration of intermetallic and saltlike structural regions.

The decrease of the intermetallic structural regions with increasing degree of oxidation leads inevitably to a gradual change in the chemical bonding. The metallic bonding which is present in the particularly halogen-deficient compounds and stretches in one, two, or, three dimensions through the crystal is replaced by the many-centered bonds in isolated clusters and finally turns into covalent single bonds between the transition metal and the bismuth atoms.

The strong bonding within the areas of the structure built up from metal atoms is an important factor in stabilizing the ternary bismuth subhalides. This is true not only for the intermetallic strings discussed in detail above for the subhalides $\text{Bi}_{12}\text{Ni}_4\text{I}_3$, $\text{Bi}_{12,86}\text{Ni}_4\text{X}_6$, and $\text{Bi}_{6,86}\text{Ni}_2\text{Br}_5$ derived from Bi_3Ni , but also for the various types of cluster. The stability of the chemical bonds is reflected by the remarkable chemical inertness observed in the bismuth subhalides.

In view of the relatively robust and largely isolated building blocks in the solid state, the question arises as to the whether these could be stabilized in solution through the use of bulky ligands as has been observed for aluminum,^[47] gallium,^[48] and indium^[49] clusters. Experiments to synthesize ligand-stabilized bismuth clusters starting from Bi_6Br_7 have recently led to the tetramer $[\text{Bi}(\text{Si}(\text{SiMe}_3)_3)]_4$.^[50] Such four-membered rings made up of Bi atoms are, however, also accessible using other routes.^[51]

The question regarding the valencies of the transition metal atoms in ternary subhalides is still to be resolved. Crystal chemistry and bonding theory both indicate that, contrary to conventional ideas, negative oxidation states occur: apparently transition metals and halide ions repel one another in the crystal structures of the subhalides and are shielded from each other by the positively charged Bi atoms. There are also various structural parallels to well-known, heteropolar compounds (e.g. NaCl or W_5Si_3) which show that the transition metals in the ternary bismuth subhalides occupy the typical anion positions in such structures.

This point of view is further supported by population analyses based on extended Hückel calculations, which assign partial negative charges to the transition metals in all these compounds. It is possible that the driving force for this is that the relatively electron-rich elements of Groups 8–10 can complete their shells by only taking up a few extra electrons (to give s^0d^{10} or s^2d^{10} configurations or else, 16 or 18 VE

according to electron-counting rules). To shed further light on the problem, comparative Mößbauer spectroscopy studies on the iridium-containing subvalent compounds of bismuth, tin, and indium as well as related intermetallic phases are underway. In parallel, quantum mechanical calculations using density functional theory should give a more reliable picture of the chemical bonding.

A further characteristic of the crystal structures of nearly all the ternary bismuth subhalides is the inherent pseudo symmetry. This is because the symmetry of the intermetallic structural part cannot be applied to the whole structure. The discrepancy between the high symmetry of substantial portions of the structure and the significantly lower symmetry of the total structure leads to many crystallographic problems, which have been extensively discussed elsewhere.^[31]

The particular appeal of the bismuth subhalide class of substances lies in their highly differentiated structures and bonding relationships. In view of the individual and, in practically all cases, novel solutions to achieve the optimum bonding situation in the solid state, demonstrated for all of the ternary systems described here, it is virtually impossible to predict the composition or crystal structures of yet to be discovered representatives. The discovery of unusual new subhalides can certainly be expected.

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New Cages and Unusual Guests: Fullerene Chemistry Continues To Excite

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Since Krätschmer, Huffman et al. discovered^[1] the synthetic route to fullerenes^[2] in macroscopic quantities over ten years ago, ever-expanding research into the chemistry of these molecular allotropes of carbon has developed. Alongside the isolation of numerous higher fullerenes^[3] and endohedral derivatives,^[4] the specific synthesis of exohedral fullerene adducts^[5] is particularly prominent. With the development of several exohedral addition reactions and the ability to exert close control over the regioselectivity of multiple additions,^[6] made-to-measure fullerene derivatives have become accessible. Because of the unique properties of fullerenes, such as their spherical, rigid form, the ability to incorporate endohedral guests,^[4] easily reversible electron transfer properties,^[7] minimal reorganization energy leading to exceptional photo-physical properties^[8] and remarkable free-radical scavenging properties, interesting materials such as superconductors^[10] and derivatives with noteworthy biological activity^[11] such as HIV-protease inhibition^[12] and high potential for neuroprotection^[13] have been produced. From the beginning, fullerene chemistry has also been shaped by the sometimes unexpected discovery of exceptionally attractive structures derived from the parent systems. Examples include heterofullerenes,^[14] open clusters^[15] and supramolecular aggregates.^[16] The sequence of startling developments continues.

To illustrate this, here a selective gallery of new fullerenes distinguished by their unusual structural properties will be presented. For example, Prinzbach et al. recently detected unambiguously the smallest fullerene, C_{20} (**1**), in the gas phase.^[17] This is so remarkable because this fullerene consists only of condensed, unsaturated five-membered rings and thus exhibits an enormously high strain energy. The smallest fullerene that can be isolated as a stable compound is C_{60} , in

which all of the five-membered rings are surrounded by six-membered rings and so the isolated pentagon rule (IPR) is satisfied. A well-known phenomenon that one observes in the mass spectra of “normal” fullerenes is *shrink wrapping*, in which successive C_2 fragments are “spat out”, leading to the formation of smaller fullerenes.^[5a] However, the smallest fullerene that can be produced in the gas phase in this manner is C_{32} .

The production of C_{20} was made possible by the use of dodecahedrane, $C_{20}H_{20}$, as the starting material by Prinzbach et al., which is the stable, perhydrogenated form of C_{20} . This was exhaustively brominated with preservation of the carbon framework, then subjected to a gas-phase debromination. The fullerene structure of the C_{20} thus formed was confirmed by photoelectron spectroscopy. These spectra leave open the possibility that C_{20} exhibits Jahn–Teller distortion. These results were recently supported by calculations showing that, in neutral C_{20} , not all of the π orbitals are fully occupied.^[18] On the other hand, it was predicted that the closed-shell C_{20}^{2+} system is undistorted and highly diatropic and that the recently described $2(N+1)^2$ rule for spherical aromaticity is satisfied.^[18] Indeed, the intensities of the C_{20}^{2+} signals imply remarkable kinetic stability of the minifullerene. *Note added in proof* (February 20, 2001): the photoelectron spectra of C_{20}^{2-} have recently been confirmed by theoretical calculations, M. Saito, Y. Miyamoto, *Phys. Rev. Lett.*, in press.

The production of fullerene derivatives with highly unusual forms is possible in principle by the exohedral addition of multiple addends to the C_{60} parent molecule. This was recently strikingly shown in the crystal structure analysis of $C_{60}F_{18}$ (**2**), originally synthesized in 1996 (Figure 1).^[19] Following the specific addition of the fluorine atoms in the form of a

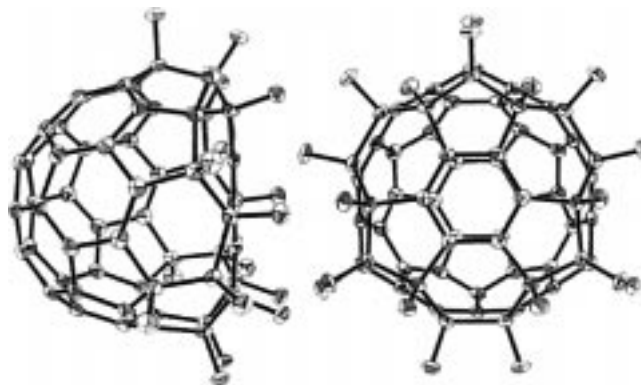
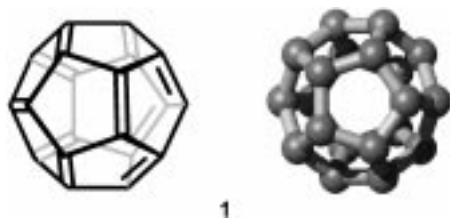
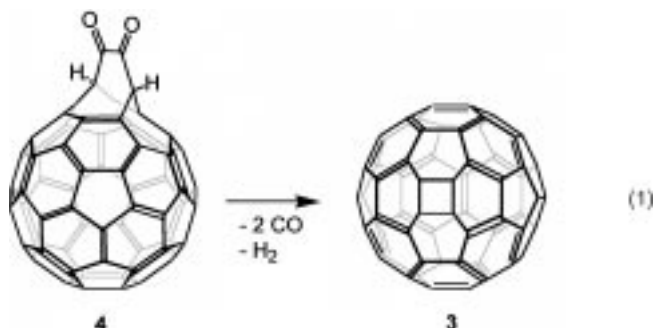


Figure 1. Two projections of the structure of $C_{60}F_{18}$ (**2**) (ORTEP).

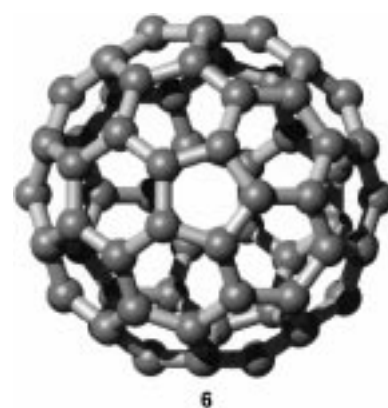
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belt and the consequent formation of 18 sp^3 -hybridized C atoms, a half-flattened molecule in the shape of a tortoise results. The most striking feature of the bonding is the presence of an isolated benzene ring on the belly of the tortoise. In contrast with C_{60} itself, all of the bond lengths within this six-membered ring are identical. It is possible that the potential formation of this aromatic substructure is a driving force behind the regioselectivity of the 18-fold fluorination of C_{60} . Recently, the same group isolated a highly symmetrical isomer of $C_{60}F_{20}$, which exhibits a Saturn-like conformation, containing two independent corannulene subunits connected by a $(CF)_{20}$ chain.^[20] Other π -electron substructures within the fullerene core were recently generated by Rubin et al.^[21] and Diederich et al.,^[22] with the synthesis of new hexaadducts exhibiting novel D_3 - and D_2 -symmetrical addition patterns.

C_{70} is the second IPR fullerene after C_{60} . Therefore, no stable fullerenes are to be expected between C_{60} and C_{70} . Besides normal fullerenes, however, conceptual and non-classical fullerenes may be envisaged. Nonclassical fullerenes include rings of other sizes together with the five- and six-membered rings. As an example of a nonclassical fullerene, Rubin et al. recently identified C_{62} (**3**) in the gas phase, arising from the inclusion of an additional four-membered ring into C_{60} .^[23] The instability of **3** is indicated by a very small HOMO–LUMO gap of 1.84 eV, compared with 2.76 eV in C_{60} . Compound **3** was synthesized by the fragmentation of diketone **4** [Eq. (1)], made by a series of cycloadditions. Laser desorption Fourier transform mass spectrometry resulted in a very effective fragmentation to the radical anion by stepwise removal of two CO groups and two H atoms from **4**.



The recent preparation of complexes such as $Sc_3N@C_{80}$ (**5**) has caused a great sensation in the field of endohedral fullerenes.^[24] It has emerged that the presence of small quantities of N_2 in a fullerene reactor allows the synthesis of new endohedral fullerenes, such as the trigonal-planar Sc_3N unit encased in the high-symmetry, icosahedral C_{80} cage **6**. The exact structure of **5** was determined by X-ray crystal structure analysis. ^{13}C NMR spectroscopic investigations have shown that, at room temperature, the Sc_3N unit is free to move in the C_{80} cage and so only two signals for the C atoms in C_{80} are observed. This C_{80} isomer is a third icosahedral fullerene alongside C_{20} and C_{60} and has an unstable and antiaromatic, ground-state, open-shell structure as an empty cage and has not yet been isolated. In the case of **5**, the cage is stabilized by six negative charges which result in aromaticity.^[18]



Another striking development with endohedral fullerenes was the synthesis of $N@C_{60}$ (**7**), which was the first example of encapsulation of a nonmetal atom.^[25] It is particularly surprising that the enclosed nitrogen exists as a single atom and no bonding to the fullerene framework is apparent. The fullerene therefore represents a trap for extremely reactive atomic nitrogen. This phenomenon is due to the fact that curvature results in the inner surface of the fullerene cage being inert, whilst the outer surface is distinguished by high reactivity.^[26] The formation of a covalent bond with the enclosed N atom, which has a half-filled p-shell (three unpaired electrons) and so displays minimal electron affinity, would lead to a distinct rise in the strain energy of the total system. Thanks to the absence of relaxation mechanisms, the lowest ESR linewidths yet observed occur in the spectra of **7**.^[27] The wavefunction of the enclosed N atom is influenced by subsequent exohedral adduct formation with one or more addends. This is caused by the altered cage structure of the adducts. The analogous complexes $N@C_{70}$ and $P@C_{60}$ are made in a similar way to $N@C_{60}$, by bombarding a thin layer of fullerene on a cathode with energy-rich N^+ or P^+ ions, respectively.^[25]



These selected examples from more recent fullerene chemistry truly emphasize what high potential for unusual structures with novel properties is associated with this class of substances. It remains clear that fullerene chemistry is still at an early stage and one may anticipate future surprises.

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Highly Enantioselective or Not?—Chiral Monodentate Monophosphorus Ligands in the Asymmetric Hydrogenation

Igor V. Komarov and Armin Börner*

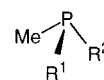
The development was over before it had really begun—this was certainly true for the use of monodentate chiral monophosphorus ligands in rhodium(1) catalysts for enantioselective hydrogenation reactions. Initially everything seemed very promising. In 1965 Wilkinson and co-workers discovered that $[\text{RhCl}(\text{PPh}_3)_3]$ catalyzes the hydrogenation of olefins.^[1] Only a few months later Vaska and Rhodes reported the use of *trans*-coordinated bis(monophosphane) iridium complexes in the reduction of alkenes.^[2] Monophosphane ligands were also prominent in other newly discovered metal catalysts, whereas *cis*-chelating diphosphanes, such as bis(diphenylphosphanyl)ethane greatly reduced the rate of hydrogenation. Mechanistic studies showed that the dissociation of a phosphane from Wilkinson's complex is essential for the initiation of the catalytic cycle. For this reason bidentate diphosphane ligands were regarded as unsuitable since the chelate effect enhances their binding to the metal center.^[3]

In 1968, the suggestion from Horner and co-workers to employ chiral monophosphanes for the enantioselective hydrogenation of prochiral olefins was both timely and logical.^[4] Two Monsanto chemists, Knowles and Sabacky, realized this idea only a few months later through the use of a rhodium complex with the P-chiral ligands PAMP (*o*-anisylmethylphenylphosphane **1a**) and CAMP (*o*-anisylcyclohexylmethylphosphane **1b**) for the hydrogenation of atropic acid.^[5] They generated hydratropic acid in a 15 % optical yield. With this report itaconic acid (ItH_2) began its career as a prochiral test substrate, it was reduced with a 3 % optical yield.

1a: $\text{R}^1 = o\text{-MeOC}_6\text{H}_4$, $\text{R}^2 = \text{Ph}$ (PAMP)

1b: $\text{R}^1 = o\text{-MeOC}_6\text{H}_4$, $\text{R}^2 = \text{cyc-C}_6\text{H}_{11}$ (CAMP)

1c: $\text{R}^1 = \text{Ph}$, $\text{R}^2 = n\text{-C}_3\text{H}_7$

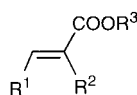
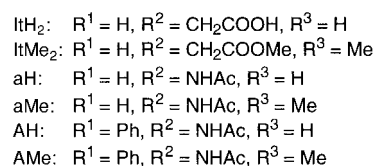


Still in the same year Horner et al., now showed that prochiral styrene could be hydrogenated in up to 8 % optical yield by using an in situ formed Rh^{I} complex of methylphenyl-*n*-propylphosphane (**1c**).^[6] Clearly the disappointingly low enantioselectivities were a deciding factor that greatly hindered the rapid adoption of the new hydrogenation method.

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In addition came the blinkered focus on P-chiral phosphane ligands, the synthesis of which, at that time, was relatively complicated and did not always proceed without racemization.

The situation changed drastically in 1971 when Dang and Kagan reported the synthesis and use of (*R,R*)-DIOP, the first

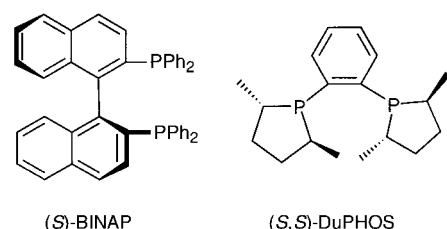


chiral diphosphane ligand.^[7] The corresponding Rh^I complex was used for the hydrogenation of (*Z*)-*N*-acetylaminocinnamic acid (AH) and promptly gave an optical yield of 72 % and almost quantitative conversion—all this with the rhodium complex of a diphosphane! Three requirements were central to the design of DIOP 1) maximum conformational rigidity of the ligand, 2) strong coordination to the metal center 3) use of a ligand with chemically equivalent phosphorus atoms.^[8]

It remains for chemical historians to analyze the reasons in all their complexity for the change in the direction of research, from mono- to diphosphane ligands, that now followed. The simple preparation of enantiomerically pure (*R,R*)-DIOP from naturally occurring (+)-tartaric acid, the typically short hydrogenation times with seven-ring chelates, and the, for that time, impressive enantioselectivities even for the reduction of other substrates no doubt played an important role and stimulated the search for similarly effective (diphosphane)

ligands. In the following years huge numbers of this type of ligand were prepared and tested in particular in the normal-pressure hydrogenation of the substrates itaconic acid (ItH_2), *N*-acetylaminocinnamic acid (aH), and (*Z*)-*N*-acetylaminocinnamic acid (AH), or their methylesters (ItMe_2 , aMe, AMe)—substrates which are still the standards against which hydrogenation catalysts are measured.^[9]

Milestones in the development of the diphosphane family include the establishment of BINAP^[10] and DuPHOS.^[11] The potential offered by the chiral diphosphane complexes of



ruthenium^[12] and iridium^[13] in hydrogenation was also recognized. In parallel investigations into the mechanism of the enantioselective hydrogenation^[14] and the influence of the ligand parameters on it were carried out.^[15] Diphosphinites^[16]

and more recently diphosphonites^[17] and diphosphites^[18] as well as hybrid ligands^[19] have also been shown to be similarly effective to diphosphanes.

That in 1972 Knowles and co-workers achieved an optical yield of 90 % in the hydrogenation of unsaturated *N*-acetylphenylalanine precursors with an Rh catalyst containing the monophosphane CAMP, was completely lost in the euphoria over the bidentate ligands.^[20] In the subsequent 30 years as far as enantioselective hydrogenation is concerned monophosphorus ligands have been living in the shadows. Of course, every now and then chiral monophosphane ligands would be prepared, but usually only as intermediates on the road towards more efficient and hopefully unpatented diphosphorous ligands.

Almost ironically it is Kagan, who with DIOP initiated the rapid development of the chelating diphosphane ligands and who has had such a lasting influence on this area, who recently in a retrospective over monophosphanes, with regard to enantioselective hydrogenation, came to the following conclusion: “We can expect that they [monophosphanes] will play a role of increasing importance in many aspects of organometallic catalysis. We hope that this review will encourage practitioners of asymmetric catalysis to consider the potential of chiral monodentate phosphines and to investigate this area which has been quite neglected till now”.^[21]

This impulse from such a respected source found an unexpectedly rapid response. In the last few months several groups have reported the use of monophosphorus ligands in highly enantioselective hydrogenation reactions, whereby different oxidation states of the trivalent phosphorus atom have received attention. Leading the way Guillen and Fiaud reported as early as 1999 a rhodium complex of 1,2,5-triphenylphospholane (**2a**), a monodentate species of the DuPHOS-type, that reduces AMe with 82 % *ee* (Table 1).^[22, 23] Incidentally this ligand is closely related to 2,5-dimethylphospholane **2b** the compound that stands at the beginning of the development of the bidentate DuPHOS by Burk et al., but on grounds of its poor enantioselectivity in hydrogenation

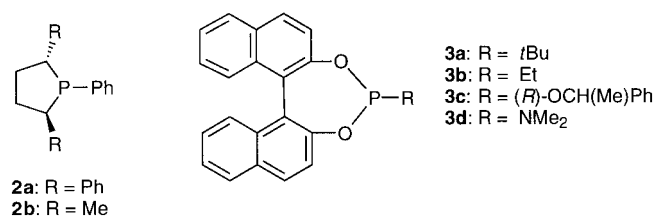


Table 1. Highly enantioselective Rh-catalyzed hydrogenation with monophosphorus ligands.

Ligand	Substrate	<i>ee</i> [%]	Author(s), Ref.
2a	AMe	82–92 (<i>S</i>)	Fiaud ^[22, 23]
(<i>S</i>)- 3a	aMe	92 (<i>R</i>)	Orpen and Pringle ^[26]
(<i>R</i>)- 3b	aMe	94 (<i>S</i>)	Reetz ^[27]
(<i>R</i>)- 3b	ItMe ₂	90 (<i>R</i>)	Reetz ^[27]
(<i>S</i>)- 3c	ItMe ₂	> 99 (<i>S</i>)	Reetz ^[28]
(<i>S</i>)- 3d	AMe	98.4 (<i>R</i>)	de Vries and Feringa ^[30]
(<i>S</i>)- 3d	AH	97.1 (<i>R</i>)	de Vries and Feringa ^[30]
(<i>S</i>)- 3d	aMe	> 99 (<i>R</i>)	de Vries and Feringa ^[30]
(<i>S</i>)- 3d	aH	98.7 (<i>R</i>)	de Vries and Feringa ^[30]
(<i>S</i>)- 3d	ItH ₂	96.6 (<i>S</i>)	de Vries and Feringa ^[30]

reactions (maximum 60 % *ee*)^[24] has since only been used as a synthetic building block on the way to bidentate ligands.^[25]

In 2000 Orpen, Pringle, and co-workers attained the hydrogenation of aMe in 92 % *ee* with the asymmetric monophosphonite **3a** and thus a higher enantioselectivity than is possible with comparable *C*₂-symmetric diphosphonite analogues.^[26] With this publication the widely accepted dominance of the bidentate diphosphorus ligands was questioned for the first time. Reetz and Sell showed in response that through the exchange of the *tert*-butyl group for an ethyl group (**→3b**) the enantioselectivity can be increased further.^[27] With the same catalyst *ItMe*₂ was also hydrogenated with a respectable 90 % *ee*. However, in spite of this a related diphosphonite ligand when tested delivered >99 % *ee*. The old rule that chelating diphosphorus ligands are superior still appeared to hold.

A clear tie in regard to performance, with enantioselectivities that could not be topped, was achieved with the use of monodentate binaphtholphosphites and phosphoramidites. Reetz and Mehler prepared the monophosphite **3c**.^[28] The corresponding catalyst induces >99 % *ee* in the hydrogenation of *ItMe*₂. Particularly noteworthy is the high substrate: rhodium ratio of up to 5000:1, that still guarantees complete conversion in 20 h under normal pressure. Surprisingly the configuration of the chiral carbon atom of the benzyl ether does not play any kind of role. The enantioselectivity of this type of ligand is dominated by the chiral binaphthyl unit, in complete contrast to other P substituents, for example, sterically demanding aryloxy groups, that have a very significant influence on the enantioselectivity and conversion.

Phosphoramidites, a ligand class that has only recently been introduced into asymmetric hydrogenation, in the form of hybrid chelate ligands,^[29] induce excellent enantioselectivity as monodentate ligands. Thus de Vries, Feringa, and co-workers could reduce standard substrates in >96 % *ee* with a rhodium complex based upon the binaphtholphosphoramidite **3d**, once the solvent and reaction temperature had been optimized.^[30]

It is noticeable that all the ligands that induce a high enantioselectivity are phosphorus derivatives of binaphthol. Based on the crystal structure of a Pt^{II} complex with monophosphonite ligands Orpen and Pringle have proposed a plausible explanation that could be helpful in the development of other selective monophosphorus ligands.^[26] Through the *cis* coordination both the sterically demanding monophosphonite ligands take up an exceptionally stable configuration around the metal center, through which rotation about the P–O bond is reduced. In this conformation the two biaryl fragments point out of the plane of the projection in what is described as edge-on arrangement. In a virtual coordination system two diagonally opposing squares are occupied (Figure 1 A). The squares at the top left and bottom right are not effectively occupied, because of the planar arrangement of the two phenyl groups in the plane of the projection (face-on). From investigations with chelating diphosphorus ligand complexes it is known that such an alternating edge/face arrangement^[31] can support the diastereo-differentiating coordination of a prochiral substrate through the minimization of repulsive interactions.^[32] In

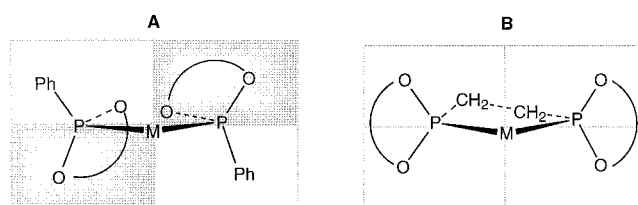


Figure 1. Monodentate (A) and chelating (B) binaphthyl ligands on a metal center and their effect on the stereoselective occupation of the squares.

contrast, by the *cis* coordination of the diphosphonite ligands the rotamer stabilized is that in which the biaryl units are in the face-on orientation; none of the squares is favored (Figure 1 B). Thus the chances of diastereomeric recognition of the prochiral substrate are greatly reduced.

On the basis of this general model^[33] and supported by first semiempirical calculations from de Vries and Feringa^[30] it is clear that for the mechanism of chiral transfer in asymmetric hydrogenation, mono- and diphosphorus ligands do not necessarily fundamentally differ.^[34] The requirement originally laid down by Kagan, that the catalyst must be conformationally rigid, is clearly also achievable with two appropriate monodentate monophosphorus ligands. As a consequence of these results the strategic decision as to whether one should favor mono- or diphosphorus ligands comes down to the principle question asked of every asymmetric catalyst: is it highly enantioselective or not?

Clearly the potential that chiral monophosphorus ligands have in hydrogenation reactions is far from exhausted, a hypothesis that is supported by the well known and excellent results from other asymmetric catalytic reactions.^[21] Naturally the demands for the design of monophosphorus ligands that effect high enantioselectivity are higher, something that should stimulate the search for new principles for the selective stabilization of diastereomeric catalysis intermediates, for example, by secondary interactions between the ligand and the metal or substrate.^[35] The synthesis of monophosphorus ligands is often simpler than that of diphosphorus compounds, which is justification enough to look closer at these types of ligands that in the past were often undervalued.

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Kekulé Escapes, Popper As Well

W. Martin Wallau*

"The virtue will not be taught, as little as the genius ... therefore we would be foolish to expect that our ... ethics would arise virtuous men, nobles and saints, and also that our aesthetics would arise poets, artists and musicians."^[1] Because of this statement of Arthur Schopenhauer it is obviously also foolish to expect from our science philosophies the creation of scientists or even support for the practical scientific work. Therefore it is not astonishing, that Jerome A. Berson in his essay "Kekulé Escapes, Popper Notwithstanding",^[2] in which he applies the theoretical guidelines of science, proposed by Sir Karl Raimund Popper, especially the falsification criterion, to the real events of the development of Kekulé's formula of benzene, comes to the conclusion, that "the issue of whether a theory is logically testable can hardly be of great concern to the working chemist",^[2] because a logic of science, as Popper's, cannot be a practical guidance for the education of scientists.^[3]

Furthermore Berson shows in his argumentation, that Popper's falsification criterion, applied to Kekulé's formula of benzene, had led to its rejection by the community of organic chemists of the 19th century, and "much of the development of the subject in that period would have been retarded",^[2] and he concludes, that this shows, "why we should resist attempts to force our research efforts onto this Procrustean bed",^[2] because "the progress of chemical research cannot be reasonably expected to stand still until enough time has passed for the means finally to emerge that can test a theory by the falsification protocol."^[2] Therefore he rejects the logic of science, attributed to Popper, especially the falsification criterion as a useless "Procrustean bed".

However, to recognize the significance of philosophical theories and the knowledge derived from them, one must first be clear what philosophy actually can do. Schopenhauer answers this question, with the quotation: "The philosophy can nowhere do more, than to interpret and explain the existing, to bring to the clear and abstract perception of reason, the essence of the world, which *in concreto*, this is as a sense, is pronounced clearly to everybody, but this in each possible relation and from each point of view."^[1]

However, a philosophy which will do this, had naturally to be able to describe the occurrences of an actual scientific

development. But this is exactly what Popper's theory, in Berson's description, apparently does not do, because there its statements are in discrepancy to the actual development. To decide if this is because of the theory or Berson's interpretation of it, one must scrutinize in a practical way Popper's own description:

"Early during this period I developed further my ideas about the *demarcation between scientific theories* (like Einstein's) and *pseudoscientific theories* (like Marx's, Freud's, and Adler's). ... I shall say here a few more words on the *problem of demarcation* and my solution.

- 1) As it occurred to me first, the problem of demarcation was not the problem of demarcating science from metaphysics but rather the problem of demarcating science from pseudoscience. ...
- 2) My main idea ... was this. If somebody proposed a scientific theory he should answer, ..., the question: "Under what conditions would I admit that my theory is untenable?" In other words what conceivable facts would I accept as refutations, or falsifications, of my theory?
- 3) I had been shocked by the fact that the Marxists ... and the psychoanalysts ... were able to interpret any conceivable fact as a verification of their theories. This, ..., led me to the view that only attempted refutations which did not succeed *qua* refutations should count as "verifications".
- 4) I still uphold (2). But when a little later I tentatively introduced the idea of *falsifiability ... of a theory as a criterion of demarcation*, I ... found that every theory can be "immunized" ... If we allow such immunization, then every theory becomes unfalsifiable. Thus we must exclude at least some immunizations.

On the other hand, I also realized that we must not exclude all immunizations, not even all which introduced *ad-hoc* auxiliary hypothesis. For example the observed motion of Uranus might have been regarded as a falsification of Newton's theory. Instead the auxiliary hypothesis of an outer planet was introduced *ad-hoc*, thus immunizing the theory. This turned out to be fortunate; for the auxiliary hypothesis was a testable one, ..., and it stood up to tests successfully. ...

In spite of the fact that all this was clearly stated in my *Logik der Forschung* ... a number of legends were propagated about my views.^[4] First, that I had introduced falsifiability as a meaning criterion rather than as a criterion of demarcation. Secondly, that I had not seen that immunization was always possible, and ... [that] therefore ... none [theory] could simply

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be described as “falsifiable”. In other words my own results were, in these legends, turned into reasons for rejecting my approach.”^[5, 6]

So Berson’s description of Popper’s philosophy must be corrected in three points. 1) As a philosophy Popper’s logic of science is not to be understood as a concrete guideline,^[3] but serves as all sciences as a description of the “essence of the world”.^[1] 2) The falsification criterion is contrary to the legend, by which Berson was taken in, not the fundamental characteristic (criterion of meaning) of science in Popper’s mind, but serves merely to its demarcation from pseudo-science.^[7] 3) A *fundamental* prohibition of the ad-hoc rescue of falsified theories, as it is stated by Berson, belongs also to the sphere of the legend and not to the structure of Popper’s thoughts.^[7]

As the falsification criterion cannot be seen as the central point of Popper’s theory, the revised version of Popper’s philosophy, gives special emphasis to the statement quoted by Berson, “that progress can be made only by a series of conjectures and refutations.”^[2] Popper illustrates this central point of his theory using a “four step scheme, that is characteristic for the science theory.”^[8] and that “appears in the following way: 1) *The older problem*; 2) *conjectural formation of theories*; 3) *attempts to their elimination* by critical discussion, including experimental test; 4) *the new problems*, which arise from the critical discussion of our theories.”

In the confrontation with the development of Kekulé’s formula of benzene, Popper’s revised logic has now to show, if it is in agreement with the real occurrences of the 19th century. These events are, in terms of the above scheme, as follows: 1) the *older problem*: The proposition of an appropriate chemical formula for benzene; 2) *conjectural formation of theories*: The description of benzene as 1,3,5-cyclohexatriene. The next step:

3) *attempts to their elimination* through critical discussion and experimental tests, is the critical point in Popper’s scheme, and therefore it needs a more detailed explanation. The experimental results obtained during the scrutiny of Kekulé’s hypothesis, show, because of the absence of the expected two *ortho* isomers, that the proposed structure represents only a very inexact approximation of the reality, and that therefore, the assumption benzene might be 1,3,5-cyclohexatriene, should be eliminated from the canon of the valid theories of organic chemistry. On account of this “falsification”,^[9] Ladenburg proposed his prism structure, which Berson points out, according to the state of the art of that time “does not suffer this deficiency” (the missing two *ortho* isomers).^[2, 10]

In agreement with Popper’s logic of science, Kekulé tries to immunize his structure proposal. Popper says on this score: “... often even a real scientist will try to defend a theory ... against attempts of falsification. From the point of view of science theory this is absolutely welcome; because how could we otherwise distinguish between *real* falsifications and *apparent* falsifications?”^[11]

On this occasion, as Berson emphasizes, Kekulé abstains to “bring into play ... escape mechanisms as the possibility that the properties of the two isomers called by his original theory

were so similar that the compounds were experimentally indistinguishable,”^[2] and also on the remark, that “one could not be sure that further isomers might not be found sometime in the future.”^[2] These immunizations would escape the experimental test and would be, according to Popper, forbidden.

Instead of this approach Kekulé proposes, to rescue his formula of benzene, “a completely new and unprecedented hypothesis which significantly modified his theory”,^[2] as an ad-hoc rescuing hypothesis. Berson describes these hypothesis in the following way: “Kekulé’s new argument amounts to the assertion that he wrote double and single bonds in benzene to keep track of the tetravalence of carbon, not to represent their actual nature. Instead, all C–C bonds ... are *equivalent*. He suggested that the best explanation ... for this new type of bonding was given by his collision theory.”^[2]

However, the here described ad-hoc rescuing hypothesis, “the molecule is regularly hexagonal”,^[2] *together* with the “collision theory” or rather its simplified formulation as bond oscillation, proposed for its justification, is according to Popper’s logic of science allowed, because its introduction increases the “degree of falsifiability of the system”. Certainly, Berson correctly emphasizes: “In Kekulé’s time ... techniques ..., which today provide direct information about molecular symmetry ... and convince ... that the assumption of equivalent C–C bonds ... is true, lay decades in the future.”^[2] But Popper says explicitly, “that the use of a theory for the purpose of *predicting* some specific event is just another aspect of its use for the purpose of explaining such an event. And since we test a theory by comparing the events predicted with those actually observed, our analysis also shows how theories can be *tested*.”^[12]

The application of Kekulé’s theory in the 19th century and “the tremendous flowering of synthesis and the discovery of an abundance of new reactions and structures”^[2, 13] resulting from this application, shows that the scrutiny of its prediction was possible with the methods of the 19th century and that it therefore indeed was undertaken on a broad range of “falsification experiments”. This scrutiny led to “the growing conviction that, *for whatever reason*, the C1–C2 and C1–C6 bonds in benzene were structurally equivalent.”^[2] This “*for whatever reason*”, stated by Berson, is nothing else but the fourth step in Popper’s scheme, “*the new problems*, which arise from the critical discussion.”^[8]

However, for the 19th century, which was caught up in the classical mechanics (“collision theory”)^[2] these new problems were soluble only by “hypotheses of embarrassment”,^[2, 14] and the development of quantum mechanics in the 20th century was necessary to propose, returning to the starting step of Popper’s scheme, *conjectural theories* for these now *older problems*.

Thus, the course of the scientific development corresponds perfectly with Popper’s statements, although his logic of science, published in 1934, was unknown by the scientists involved. That Popper’s logic of science really brings, “which *in concreto*, this is as a sense, is pronounced clearly to everybody, to ... the ... abstract perception of reason”,^[1] shows besides the above confrontation of the theory with the occurrences described by Berson, especially his own statement: “... our decision on whether to continue to use the

theory must be based upon pragmatic considerations: does it predict new phenomena or rationalize a body of information?"^[2, 15] Here he acts "*in concreto*"^[1] in the same way, as it is described by Popper's logic of science, that he scrutinizes theories using their predictions and their possible explanations. Therefore his explicit disapproval of Popper's thoughts, especially the "criterion of falsification" is unfounded.

Nevertheless, one can be of the opinion, "that the philosophers are wasting our time and their own".^[2] Because for what serves a philosophy, which only puts into words, which ("*in concreto*, this is as a sense"^[1]) is already known? To give a tentative explanation for the waste of my and the reader's time on this article, we can think about the ethics mentioned by Schopenhauer^[1] in the following way. Certainly they will not "arise virtuous men, nobles, and saints", but one will concede, that the maxims proposed there, could be used in the sense of the Categorical Imperative, *as the basis of a universally valid legislation*, which would allow the virtuous men to be virtuous, the nobles to be noble, and the saints to be sacred, without being victims of the immorality.

In the same way Popper's call for a critical discussion can serve as basis of a science code, which guarantees this call. Also the significance of the falsification criterion should be emphasized here, because if one rejects it as a "Procrustean bed"^[2] the empirical science loses its distinctive feature from the occasionally successful pseudosciences. And a social situation, in which the science without a severe demarcation criterion to pseudoscience could run into trouble, is conceivable. For instance to justify why public funds are used for pharmaceutical research, while well sold, that is socially accepted scientific(?) books, show that with a handful of blooms, picked at a peaceful brook, diseases can be controlled, and without side effects. But if we support Berson, we cannot refuse *esoteric theories*, his argument that their rejection "does not take into account the historical context",^[2] and that therefore their present application, even at the expense of the empirical science, cannot be opposed, because logically future scrutiny of their statements is not ruled out.

[1] A. Schopenhauer, *Sämtliche Werke, Bd. 2* (Ed.: A. Hübscher), Brockhaus, Wiesbaden, **1972**, p. 321, quoted from A. Schopenhauer, *Die Welt als Wille und Vorstellung, Bd. I*, Reclam, Stuttgart, **1990**, pp. 387–388; own translation.

[2] J. A. Berson, *Angew. Chem.* **2000**, *112*, 3173–3176; *Angew. Chem. Int. Ed.* **2000**, *39*, 3045–3047.

- [3] That Popper does not intend to draw up actual guidances is confirmed by the following quotation: "I believe that the function of a scientist or of a philosopher is to solve scientific or philosophical problems, rather than to talk about what he or other philosophers are doing or might do." (K. R. Popper, *Conjectures and Refutations*, Routledge & Kegan, London, **1969**, p. 66).
- [4] Remark of Popper on the text: see Chap. 1 of K. R. Popper *Conjectures and Refutations: The Growth of Scientific Knowledge*, Routledge & Kegan, London, **1963** and later editions.
- [5] Remark of Popper on the text; for a much fuller discussion see sections 2, 3, and 5 in: Replies to My Critics: *The Philosophy of Karl Popper* (*Library of Living Philosophers, Vol. II* (Ed.: P. A. Schilpp)), Open Court, La Salle, **1974**.
- [6] K. R. Popper, *Unended Quest. An Intellectual Autobiography*, Fontana/Collins, London, Glasgow, **1974**, pp. 41–42.
- [7] This statement is based on Popper's own statement in [6].
- [8] K. R. Popper, *Alles Leben ist Problemlösen*, Piper, München, **1994**, p. 32; own translation.
- [9] If, as Berson states explicitly in his reply (next article), the equivalence of all C–C bonds is already embodied in the original theory, the actual observation of only one *ortho* isomer is not an experimental falsification.
- [10] If Kekulé's theory of 1865 already embodies the equivalence of all C–C bonds, Ladenburg's critic concerns only its graphical presentation, or points to a *new* problem (why the bonds are equivalent?; step 4 in Popper's scheme), respectively. To jeopardize the original theory, Ladenburg's alternative should not only solve the problem of equivalent bonds, which it solves only apparently,^[2] but it should also solve "all these problems, which the old theory already had solved, at least as well." (K. R. Popper, ref. [8], p. 28; own translation). However, Berson's description does not show this. Therefore the "collision theory" is not an ad-hoc hypothesis to rescue the *unjeopardized* original theory, but rather an independent hypothesis to solve *new* i.e. *other* problems. Berson's discussion of its validity as an ad-hoc auxiliary hypothesis is therefore invalid and unnecessary.
- [11] K. R. Popper, ref. [8], p. 26; own translation.
- [12] K. R. Popper, *The Open Society and its Enemies, Vol. II*, Princeton University Press, Princeton, **1971**, pp. 262–263.
- [13] That only the original theory was tested and applied in the 19th century, as Berson says in his reply, means that the "collision theory" was ignored and had no share in the mentioned successes.
- [14] The "collision theory" is such a *hypothesis of embarrassment* to solve a *new* problem: the nature of the bond in benzene and the chemical bond in general. In this field the progress really was at a standstill until not only a new theory (quantum mechanics) for its description, but also "until enough time has passed for the means finally to emerge that can test a theory by the falsification protocol."^[2]
- [15] With this attitude would Berson apply the "collision theory" himself? By his own statement it does not predict new phenomena, and the experiments realized in the 19th century were rationalized with the original theory.

Reply

Jerome A. Berson*

The critique^[1] by Dr. Wallau of my article^[2] raises a number of interesting points. In the interest of brevity, I have chosen to respond here only to those of major contention. These are:

- 1) "As a philosophy Popper's logic of science is not to be understood as a concrete guideline, but serves as all sciences as a description of the "essence of the world".
- 2) The falsification criterion is contrary to the legend, by which Berson was taken in, not the fundamental characteristic (criterion of meaning) of science in Popper's mind, but serves merely to its demarcation from pseudoscience.
- 3) A *fundamental* prohibition of the ad-hoc rescue of falsified theories, as it is stated by Berson, belongs also to the sphere of the legend and not to the structure of Popper's thoughts."

These opinions of Dr. Wallau cannot be reconciled with numerous statements in Popper's writings. That Popper intended his logical deductions to be the basis of a scientific methodology, a set of guidelines to action, is widely accepted among philosophers of science and is discussed in many writings on the methodology of science.^[3–10] Moreover, it also is clear in passages including among others the following from Popper's *Conjectures and Refutations*:^[11]

p. 27: "...if you are interested in the problem which I tried to solve by my tentative assertion, you may help me by criticizing it as severely as you can; if you can design some experimental test which you think might refute my assertion, I shall gladly, and to the best of my powers, help you to refute it."

p. 31: "...the work of the scientist consists in putting forward and testing theories."

p. 42: "According to my proposal, what characterizes the empirical method is its manner of exposing to falsification, in every conceivable way, the system to be tested. Its aim is not to save the lives of untenable systems but, on the contrary, to select the one which is by comparison the fittest, by exposing them all to the fiercest struggle for survival."

p. 50: "...I shall try to establish the rules, or if you will the norms, by which the scientist is guided when he is engaged in research or in discovery."

p. 53: "Methodological rules are here regarded as *conventions*. They might be described as the rules of the game of empirical science..."

p. 54, in a section entitled *A Theory of Method*: "Just as chess might be defined by the rules proper to it, so empirical science may be defined by means of its methodological rules. In establishing these rules we may proceed systematically. First a supreme rule is laid down which serves as a kind of norm for deciding upon the remaining rules, and which is thus a rule of a higher type. It is the rule which says that the other rules of scientific procedure must be designed in such a way that they do not protect any statement in science against falsification. Methodological rules are thus closely connected both with other methodological rules and with our criterion of demarcation. But the connection is not a strictly deductive or logical one. It results, rather, from the fact that the rules are constructed with the aim of ensuring the applicability of our criterion of demarcation; thus their formulation and acceptance proceeds according to a practical rule of a higher type."

In other words, the falsification criterion of demarcation is not identical to a complete methodological set of rules, but it acts as the "supreme rule" from which the other procedural rules are derived as corollaries. The rule prohibiting ad-hoc rescues without enhanced vulnerability is a corollary which Popper himself derived from his supreme rule of falsification.

Another indication that Popper's logic was intended to lead the working scientist becomes clear when we remember that he, like most other philosophers of science, uses historical case studies in support of his procedural recommendations. The argument for case studies is set out, for example, by Hesse,^[12] who proposes that not only should philosophers use historical cases in the development and refinement of their methodology, but also that scientists should give attention to methodological considerations in their work:

"Firstly, a logic of science ... should supplement mere description with *normative considerations* [emphasis supplied]. This is because it presupposes that there are norms or criteria of 'good science' in terms of which scientists judge scientific theories, and that these have some elements, perhaps tacit, of internal logical coherence and rationality ... [ultimately] the relation of logic and [historical] cases will be one of mutual comparison and correction."

Do philosophers intend their case studies to be historical analyses leading to philosophical conclusions, or normative recommendations specifying *actions* for scientists to carry out? From the very nature of the enterprise of philosophy of science, I think the answer must be "both". If the growth and

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success of science in the past can be analyzed according to some philosophical system, this analysis amounts to a recommendation to scientists that they adhere to the same historically proven kinds of procedure in the future. We find a similar conclusion in a passage from Kuhn.^[5] In response to Feyerabend's question^[13] whether we should read Kuhn's remarks about scientific development as *descriptions* or *prescriptions*, Kuhn writes:

"The answer, of course, is that they should be read both ways at once. If I have a theory of how and why science works, it must necessarily have implications for the way in which scientists should behave if their enterprise is to flourish."

Dr. Wallau also objects to my previous discussion^[2] of Popper's criterion in *The Logic of Scientific Discovery* (p. 80 ff.),^[14] which requires that an ad-hoc rescuing hypothesis must predict something new, an event not predicted by the original jeopardized theory. I showed that Kekulé's rescuing collision hypothesis did not meet this criterion. Dr. Wallau now states that: "the application of Kekulé's theory in the 19th century ... shows that the scrutiny of its prediction was possible with the methods of the 19th century and that it therefore indeed was undertaken on a broad range of falsification experiments".

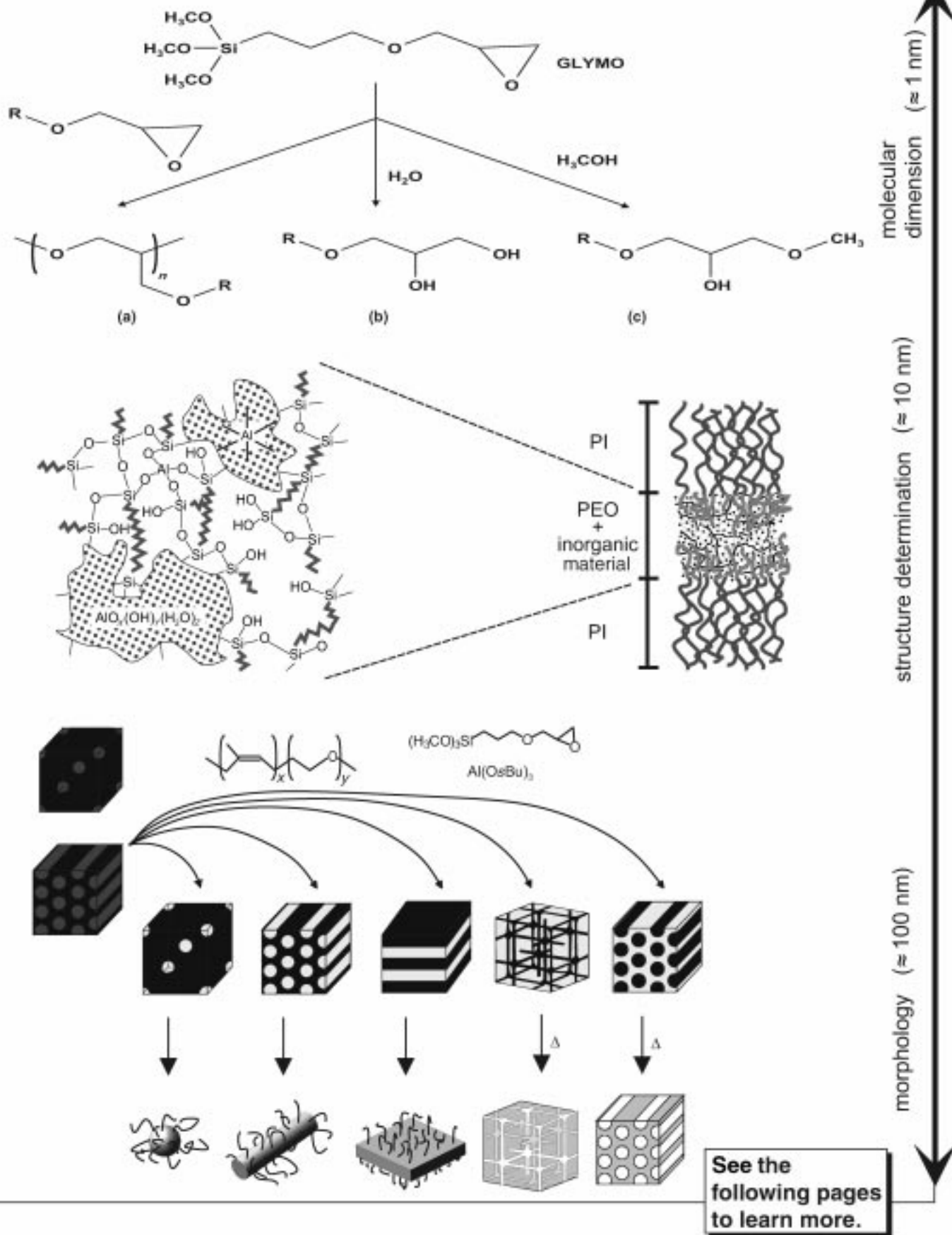
This formulation precisely misses the point. The experiments to which Dr. Wallau refers were of a type that were designed or could be interpreted to test the idea that all C–C bonds of benzene were equivalent. But the *original* Kekulé theory of 1865 *already embodied* this idea. The *rescuing collision hypothesis* of 1872, proposed only to explain C–C bond uniformity in benzene, did not predict anything further than did the original theory. So all the tests of the 19th century and for decades after were tests of the *original* 1865 theory and could not have falsified the collision hypothesis. Actually, in practical terms, one may question whether the collision hypothesis has been falsified even today, except in the broadest sense. It is true that it has been superseded by quantum mechanics, which by general agreement offers a much more satisfactory account of chemical bonding and many other phenomena. Thus, the emergence of quantum mechanics can be said to provide a good reason for rejecting

the collision hypothesis, but I know of no single experimental test that has disproved the latter.

Dr. Wallau^[1] believes that Popper did not intend his falsification scheme and its corollaries to provide guidelines or rules for action by scientists. I conclude that this does not agree with many statements to the contrary by Popper himself, nor is it compatible with philosophical practice in the development of scientific methodology. The assertion^[1] that Kekulé's collision hypothesis did not violate Popper's prohibition regarding ad-hoc rescuing hypotheses conflicts with historical fact.

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A rational approach to polymer-directed ceramic hybrid morphologies



Metal Oxide Containing Mesoporous Silica with Bicontinuous “Plumber’s Nightmare” Morphology from a Block Copolymer–Hybrid Mesophase**

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The synthesis of mesoporous materials by using organic molecules as structure-directing agents or templates is an area of rapid growth with diverse applications, such as separation technology and catalysis. Block copolymers can be regarded as macromolecular analogues of low molecular weight surfactants.^[1] Use of block copolymers was recently shown to extend the pore sizes of ordered porous silica to hundreds of Ångströms.^[2–5] Combined principles of polymer, colloidal, and inorganic chemistries were used to synthesize materials with uniform and adjustable pore sizes and with thick, hydrothermally stable walls.^[6] Both two-dimensional hexagonal structures and three-dimensional cubic morphologies with more accessible pores have been synthesized. The synthetic strategy has been generalized for various metal oxides and hierarchical oxide structures.^[7–9]

Recently, we showed that unprecedented morphology control is obtained for nanostructured materials by changing from conventional silicon precursors to organically modified ceramic (ormocer) precursors in the block copolymer directed synthesis.^[4] Most of the mesophase morphologies observed in block copolymers or copolymer–homopolymer mixtures have been obtained for such organic–inorganic hybrid materials.^[10] The basis for this morphological control is a unique polymer–ceramic interface which can be characterized by solid-state NMR techniques.^[11] The hydrophilic blocks of the amphiphilic copolymers are completely integrated into the ceramic phase. This leads to a “quasi-two-phase system” that allows for a more rational design of hybrid morphology based on the current understanding of the phase behavior of block copolymers and copolymer–homopolymer mixtures.^[12]

Here we describe the block copolymer directed preparation, characterization, and properties of metal oxide containing mesoporous silica in an area of the block copolymer phase space where a double Gyroid phase might be expected.^[12] Ordered bicontinuous nanoporous and nanorelief materials with the Gyroid morphology have been realized in ultrathin films.^[13] The synthesis of such structures in the bulk is still a challenge. To our surprise the data presented below on the bulk materials, both before and after calcination, are consistent with a “Plumber’s Nightmare”^[14] morphology. This refers to subtle, poorly understood differences of phase behavior between the present hybrid materials and block copolymer–homopolymer mixtures. Because of its interwoven and regular, branched cubic bulk structure, the resulting mesoporous material is expected to provide excellent mass-transfer kinetics in catalytic and separation technologies. The approach based on ormocer–block copolymer combinations may therefore significantly expand the property profile of mesoporous materials.

An amphiphilic diblock copolymer, namely, poly(isoprene-*b*-ethylene oxide) (PI-*b*-PEO), with a total number average molecular weight of 16.4 kg mol^{−1} and a volume fraction of PEO of 35 % was used as the structure-directing agent. Anionic polymerization was employed to obtain this polymer with a narrow molecular weight distribution (polydispersity < 1.1).^[15] The pure diblock copolymer exhibits a melt morphology of hexagonally packed PEO cylinders in a PI matrix, as expected for such a volume fraction.^[12] Mixing of the ormocer precursors (3-glycidyloxypropyl)trimethoxysilane (GLYMO) and aluminum *sec*-butoxide with the diblock copolymer in a molar ratio of 80:20 was performed by using a recently described procedure.^[10]



The volume fraction of the PI phase of the as-made material was calculated to be 0.36. It is assumed that there is no phase mixing between the PI (density 0.91 g cm^{−3}) and the inorganic/PEO phase (density 1.4 g cm^{−3}).^[10] The organic–inorganic nanocomposite was then calcined to obtain a mesoporous material. Calcination was achieved by heating in several stages up to 600 °C in air with an overall heating rate of approximately 1 K min^{−1}. Elemental analysis after calcination indicated 0.1 wt % C and 1.5 wt % H. The weight loss, measured by thermogravimetric analysis (TGA) as 75 %, compared well with the theoretical prediction of 78 %.

Bright-field transmission electron microscopy (TEM) data on as-made and calcined materials are shown in Figure 1. Bright areas correspond to the minor phase that either consists of PI (uncalcined) or voids (calcined), while dark areas correspond to the major PEO-rich ceramic phase. For both samples the classic cubic fourfold and threefold orientations are shown. In particular, in the case of the calcined material it is easy to identify thin, connected volumes (channels) with fourfold and threefold (“wagonwheel”)

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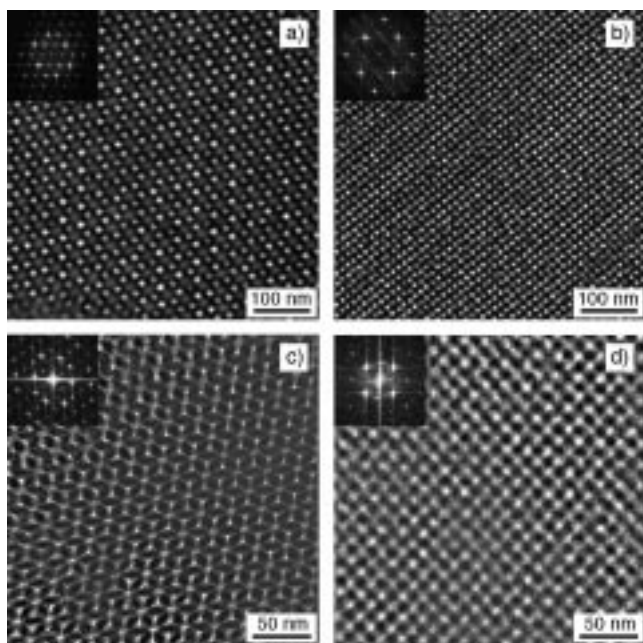


Figure 1. Bright-field TEM images from as-made (top) and calcined material (bottom) highlighting the threefold (a, c) and fourfold (b, d) projections of the cubic phase. The images from calcined material exhibit even greater contrast due to the removal of all organic moieties. This allows for the convenient identification of the bicontinuous nature of the structure. Insets in each panel show the computed Fourier diffraction patterns. These materials show a striking degree of order over broad regions.

orientations, typical of a bicontinuous cubic structure. Furthermore, as demonstrated by scanning electron microscopy (SEM), the materials show a remarkably large average grain size (data not shown). It was not uncommon to find grains spanning the entire area of a grid mesh (approximately 100 μm in diameter). The beautiful micrographs therefore suggest the existence of a highly ordered bicontinuous cubic mesostructure.

We performed small-angle X-ray scattering (SAXS) experiments on both as-made and calcined samples to identify the underlying symmetry and further elucidate the long-range structure (Figure 2). The X-ray patterns indicate a high degree of ordering, out to $q^2 = h^2 + k^2 + l^2 = 50$ and $q^2 = 32$ reciprocal lattice units for the as-made and calcined samples, respectively. This is remarkable, given that the structure is highly disordered on length scales of a few Ångströms. Consistent with the large grain sizes observed by electron microscopy, the distinct peaks in the images imply that the X-ray beam ($< 0.1 \text{ mm}^2$) averages

only over a limited number of crystallites with different orientations. Beneath each SAXS image in Figure 2 is a plot of the peak positions. By using systematic algorithms,^[16] a structure was solved for each set of peaks that could originate from a single microdomain within the scattering volume. The peaks are colored according to the microdomain; peaks are visible from five microdomains within the uncalcined image, and from six microdomains within the calcined image.

It is usually difficult to determine the lattice symmetries of classic powder diffraction patterns consisting of a limited number of concentric rings. The inclusion of azimuthal information, such as is present in Figures 2a and 2b, places strong constraints on the possible symmetry groups and unit cell lengths of the sample. The reciprocal-space SAXS data is consistent with $Im\bar{3}m$ symmetry, and the lattice basis lengths were determined to be 630 and 395 Å for the as-made and calcined samples, respectively, consistent with the analysis of the TEM data.

Figure 3 contrasts two structures derived from infinite periodic minimal surfaces, namely, the Plumber's Nightmare and the Gyroid. The TEM data strongly suggest a bicontinuous cubic morphology. The TEM data, together with the X-ray $Im\bar{3}m$ symmetry, suggest a Plumber's Nightmare-like phase,^[14] and exclude the Gyroid and Double Diamond.^[12] A detailed description of the X-ray analysis will be presented

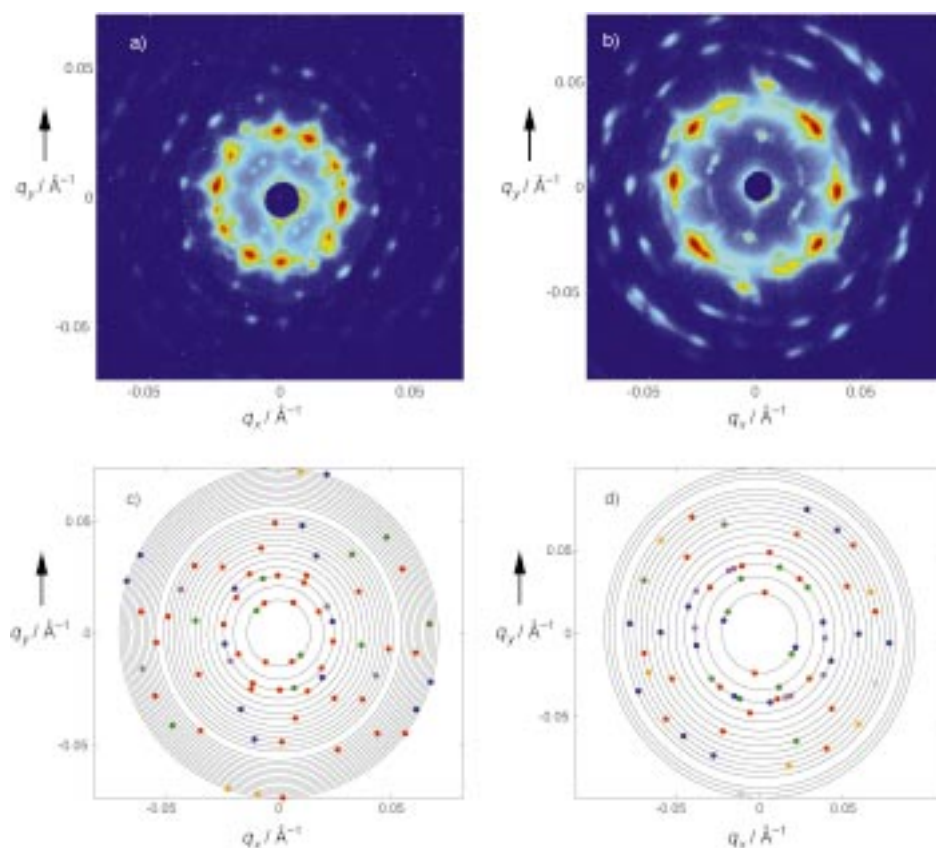


Figure 2. SAXS images (top) obtained from as-made (a) and calcined (b) samples. The false-color scale (ascending from blue to red) corresponds to logarithmic X-ray intensity. Indexed peak positions (bottom) for as-made (c) and calcined (d) samples. Peaks from the same crystallite are colored identically. All of these peaks can be assigned to five microdomains within the scattering volume for the as-made (c), and six microdomains for the calcined sample (d). The radii of the circles are given by $q = \sqrt{(h^2 + k^2 + l^2)}$, where h, k, l are integers allowed by the $Im\bar{3}m$ symmetry group. The apparent gap results because $q^2 = 28$ units is not the sum of any three squares of integers.

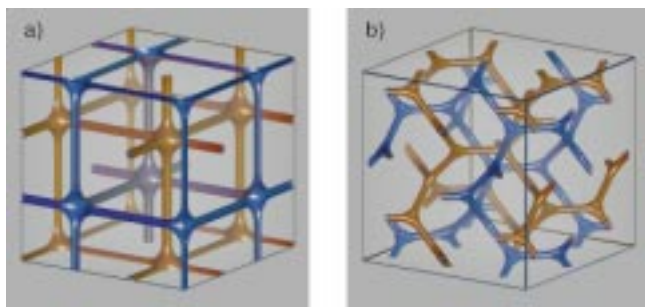


Figure 3. Real-space image of a stick structure derived from the Plumber's Nightmare (a). For comparison, the real-space image of a Gyroid-derived structure is shown (b). The graphics were generated by using the following website: <http://msri.org/publications/sgp/SGP/>. Blue and brown colors serve to distinguish the two distinct three-dimensional channel systems.

elsewhere.^[16] A powder-diffraction pattern of a block copolymer derived mesoporous silicate, with a very different structure formation process, was also reported to be consistent with $Im\bar{3}m$ symmetry.^[6] However, in that case the limited number of diffracted orders necessarily meant that the symmetry assignment was more tentative.

It is striking that the symmetry is so well-preserved after calcination, even though the lattice constant falls to approximately 60% of the value for the uncalcined material (the cell volume drops to about 25%). This indicates that the bonding network formed by the inorganic precursors is extremely robust. This may be a general feature of the block copolymer derived ormocer materials. After calcination the bulk material consists of an aluminosilicate matrix interwoven with two discrete, continuous nanochannel systems that do not touch each other (see Figure 3) and result in a mesoporous material with open and accessible pores. Indeed, it exhibits a nitrogen sorption isotherm of type IV according to BDDT classification, with a specific surface area of $300 \text{ m}^2 \text{ g}^{-1}$ according to the Brunauer–Emmett–Teller (BET) method (data not shown).^[17] Calculation of the pore size distribution from the desorption branch of the isotherm reveals a slightly bimodal pore size distribution with an average pore diameter according to Barrett–Joyner–Halenda (BJH) of 8.9 nm .^[18] The specific pore volume can be calculated by the Gurvitch rule to be 0.47 mL g^{-1} .^[19] From earlier NMR studies, we know that about half of the aluminum is incorporated in the silicon network as fourfold-coordinated aluminum. Calcination of the as-made material leads to an increase in the amount of such in-frame aluminum with respect to the precursor material and thus provides a pathway to materials with acid catalytic activity.

In summary, we have described the synthesis and characterization of a metal oxide containing mesoporous silica from a block copolymer–hybrid mesophase. Using a combination of SAXS and TEM we have shown that the structure of the mesophase is most consistent with the $Im\bar{3}m$ cubic space group associated with the bicontinuous Plumber's Nightmare morphology. The structure exhibits unusually large grain sizes ($10\text{--}100 \mu\text{m}$) and is preserved after calcination. Nitrogen-sorption isotherms clearly demonstrate the accessibility of the resulting interwoven networks of channels. Finally we have demonstrated that by this synthetic method, metal oxides

imperative for catalytic applications^[20] (e.g., alumina, titania) can be incorporated conveniently. In analogy with monomer–surfactant–water systems, we expect to find a variety of bicontinuous cubic phases as the stoichiometric ratios of PI, PEO, and inorganic components are altered.^[21] This may elucidate the origin for the occurrence of the present Plumber's Nightmare symmetry rather than the Gyroid symmetry. Studies along these lines are now underway.

Experimental Section

Adsorption and desorption isotherms were measured at 77 K on a Quantachrome Autosorb 6B (Quantachrome Corporation, Boynton Beach, FL). The samples were outgassed at 423 K and 1 mPa for 13 h before measurements were made.

TEM: The organic–inorganic hybrid sample was used as synthesized. The calcined sample was manually powdered and embedded in UHU glue (Henkel). Ultrathin sections (thickness $50\text{--}100 \text{ nm}$) were produced with a Leica-ultramicrotome (UCT) at -55°C . Sections were floated off the diamond knife onto aqueous DMSO solution, transferred to grids, and investigated unstained. TEM was performed on a Leo 912 Ω (tungsten filament) operated at 120 kV with an objective aperture angle of 16.5 mrad . All images were taken in the elastically filtered imaging mode. Contrast of the unstained, uncalcined samples was very weak, but the morphology of the samples could be clearly observed at a defocus of about $2.5 \mu\text{m}$. The organic–inorganic (aluminosilicate) hybrid appears as the dark phase. Images were recorded with a slow-scan CCD camera (lateral resolution 1000×1000 pixels, 14-bit gray values), and fast Fourier transforms were calculated by means of an SIS-AnalySIS[®] image-processing system.

SAXS: $\text{Cu}_{K\alpha}$ X-rays ($\lambda = 1.54 \text{ \AA}$) were generated on a Rigaku RU300 rotating-anode generator, focused by Franks mirror optics, and then imaged with a home-built 1000×1000 CCD detector (as in ref. [22]). The data of the uncalcined sample were recorded with 42 exposures over 9.3 h , to maximize the signal-to-noise ratio and dynamic range. The calcined sample only required 12 exposures totaling 18 min . The q -dimensions of each image were calibrated with silver behenate ($d = 58.376 \text{ \AA}$) and silica sphere ($R = 278 \text{ \AA}$) references. (The reader is referred to ref. [16] for more details of the SAXS data treatment and analysis.)

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Solvent-Free, Low-Temperature, Selective Hydrogenation of Polyenes using a Bimetallic Nanoparticle Ru–Sn Catalyst**

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 Brian F. G. Johnson,* Gopinathan Sankar, and
 David Gleeson

Progress in making solvent-free chemical conversions much more feasible than they are at present awaits the development of highly active (and selective) heterogeneous catalysts. Not only must the sites at which turnover occurs be of high intrinsic activity, their concentration (per unit mass) must also be large. Moreover, diffusion of reactant species to, and of products away from, such sites must also be facile.^[1]

Herein we demonstrate how freely accessible active sites on bimetallic nanoparticles, finely dispersed and firmly anchored along the interior surfaces of high area (around 800 m² g^{−1}) mesoporous silica function as highly effective catalysts for a number of selective hydrogenations that are of considerable significance for chemical and fine-chemical production. Such heterogeneous nanocatalysts may be readily prepared^[2–5] from mixed-metal carbonylates and introduced in a spatially uniform fashion along the pores (around 30 Å diameter) of

the silica host. Their atomic structure is straightforwardly established,^[1, 6–8] from in situ X-ray absorption and FTIR measurements.

Tin has been widely used as a “promoter” in heterogeneous catalysis, and has been shown to increase dramatically the selectivity of ruthenium catalysts in a variety of chemical transformations. These usually involve the selective hydrogenation of a carbonyl group in the vicinity of a conjugated or isolated double bond, such as the hydrogenation of benzoic acid and fatty esters to their corresponding alcohols^[9, 10] or the hydrogenation of acrolein and its derivatives.^[11] It has been suggested that the effect of tin is, besides others, to deactivate selectively certain catalytic sites on the surface thereby impeding undesirable side reactions.^[10, 12] Other explanations, such as alloying and its consequential electronic influences, have also been proposed.^[11]

The chemical conversions upon which we focus herein consist of the hydrogenation of cyclic polyenes: 1,5,9-cyclododecatriene, 1,5-cyclooctadiene, and 2,5-norbornadiene. The monoenes of all three polyenes are used extensively as intermediates in the synthesis of bicarboxylic aliphatic acids, ketones, cyclic alcohols, lactones, and other intermediates. The selective hydrogenation of 1,5,9-cyclododecatriene to cyclododecane and cyclododecene is industrially important in the synthesis of valuable organic and polymer intermediates, such as 12-lauro lactam and dodecanedioic acid,^[13] which are important monomers for nylon 12, nylon 612, copolyamides, polyesters, and coating applications.

A wide variety of homogeneous and heterogeneous hydrogenation catalysts such as Raney nickel,^[14] palladium,^[15] platinum,^[16] cobalt,^[17] and mixed transition-metal complexes have been previously used for the above-mentioned hydrogenations.^[18, 19] But all the reactions entailed the use of organic solvents (such as *n*-heptane, benzonitrile, and so forth),^[13, 20–22] and some required utilization of efficient hydrogen donors such as 9,10-dihydroanthracene, often at temperatures in excess of 300 °C, to achieve the desired selectivities.^[23] Recently, Reetz et al.^[24] have shown that entrapment of palladium clusters in micro/mesoporous hydrophobic sol–gel matrices prevents undesired agglomeration of the clusters, to result in active catalysts for the hydrogenation of 1,5-cyclooctadiene.

Previously, we have described the catalytic performance of other, finely dispersed bimetallic catalysts (Ag–Ru,^[2] Cu–Ru,^[3] and Pd–Ru,^[4]), some of which possessed remarkable properties. Herein we report the catalytic performance of a supported carbidic Ru₆Sn nanoparticle and compare it with that of the above-mentioned bimetallic nanocatalysts. In particular, we highlight the changing selectivity (in the hydrogenation of 1,5,9-cyclododecatriene and other polyenes) as a function of operating temperature and degree of conversion.

The compound (PPN)[Ru₆C(CO)₁₆SnCl₃] (PPN: bis(triphenylphosphane)iminium cation) is obtained in a two step reaction from the known carbido–hexaruthenium cluster [Ru₆C(CO)₁₇]. Details of the preparation along with the single-crystal X-ray structure of the anion [Ru₆C(CO)₁₆SnCl₃][−] (**1**), have been given elsewhere,^[25] as have the corresponding details for the neutral species

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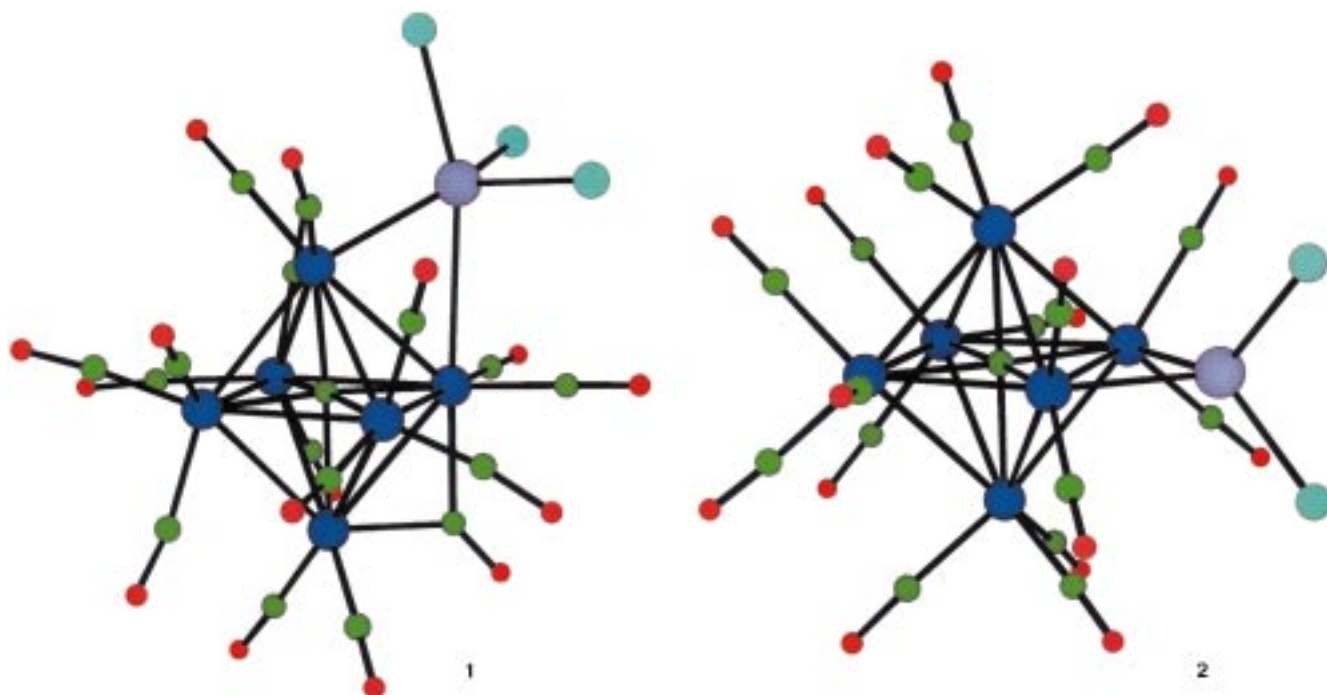


Figure 1. Molecular structures of $[\text{Ru}_6\text{C}(\text{CO})_{16}\text{SnCl}_3]^-$ **1** and $[\text{Ru}_6\text{C}(\text{CO})_{16}\text{SnCl}_2]$ **2**, as determined by X-ray crystallography.

$[\text{Ru}_6\text{C}(\text{CO})_{16}\text{SnCl}_2]$ (**2**; see Figure 1). This latter compound can be obtained by chloride abstraction from **1** or directly by reacting $[\text{Ru}_6\text{C}(\text{CO})_{17}]$ with SnCl_2 . The mesoporous silica was loaded with cluster **1** by making a slurry in ether/dichloromethane, stirring for 48 h under nitrogen, and filtering.^[3] The pink solid obtained was then washed with ether and dried under vacuum. The same procedure was used for the incorporation of cluster **2** within the mesopores. However, a small amount of nonadsorbed compound was lost in the filtrate, demonstrating the less favorable interaction of this neutral species with the surface hydroxyl groups of MCM-41, when compared to its charged analog **1**.

The catalytic precursor material **1**/MCM-41, which was characterized by FTIR (using a purpose-built evacuable cell^[7]), revealed that the carbonyl cluster was still intact within the pores. This was confirmed by extended x-ray absorption fine structure (EXAFS) analysis, which showed that the structure of the pure, unsupported carbonyl cluster is exactly identical to that of the species adsorbed into the mesoporous silica.

The frequency characteristics of the terminal carbonyl groups disappeared totally at a heat-treatment temperature of 200 °C. During this activation procedure—and concomitant with the loss of all carbonyl ligands—the metallic core of the cluster becomes firmly anchored to the siliceous surface (Figure 2).

The EXAFS data, recorded in situ,^[2,3] showed significant changes in the coordination environment of both the tin and ruthenium centers (Figure 3). The best fit for the ruthenium K-EXAFS data yielded a structure for the denuded bimetallic catalyst consisting of mainly ruthenium neighbors. To obtain a better fit for the low k data, it was necessary to include a carbon neighbour. The Ru–Ru and Ru–C distances and the coordination number of 2.67 and 2.07 Å, and 3 and 1,

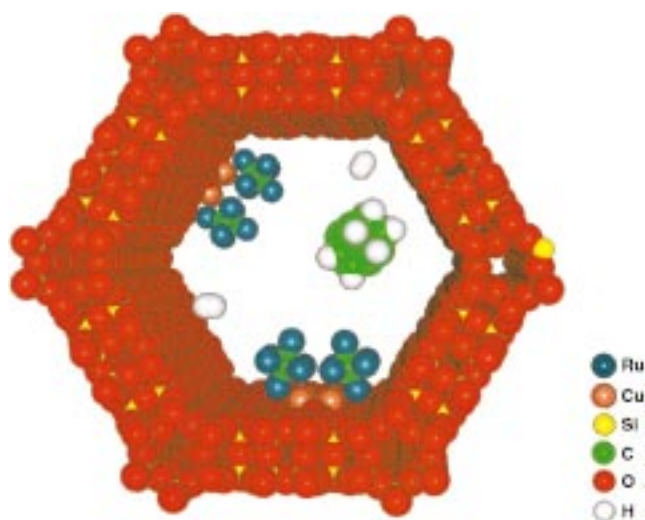


Figure 2. Computer graphic model of $\text{Cu}_4\text{Ru}_{12}\text{C}_2$ nanocatalyst clusters anchored through pendant silanol groups to the inner walls of mesoporous silica (MCM-41). This nanocatalyst is akin to Ru_6Sn and other clusters described in the text. A typical reactant (1,5,9-cyclododecatriene) and H_2 are also shown in the mesopore channel (diameter around 30 Å).

respectively, suggest that the arrangement of Ru, C, and Sn are quite similar to that of the starting material. Upon removal of the carbonyl ligands the Ru–Ru distances decreased from an average value of around 2.8 to 2.67 Å. It is not directly feasible to detect the Ru–Sn interaction, since only one of the six ruthenium centers has a close contact with the tin atom. Similarly, from the Sn K-edge, two of the chlorine neighbors are completely replaced by the oxygen atoms, and the best fit is obtained by taking two Sn–O, one Sn–Cl, and one Sn–Ru interaction,^[26] which shows that the tin atom is the anchoring point of the bimetallic, nanoparticle

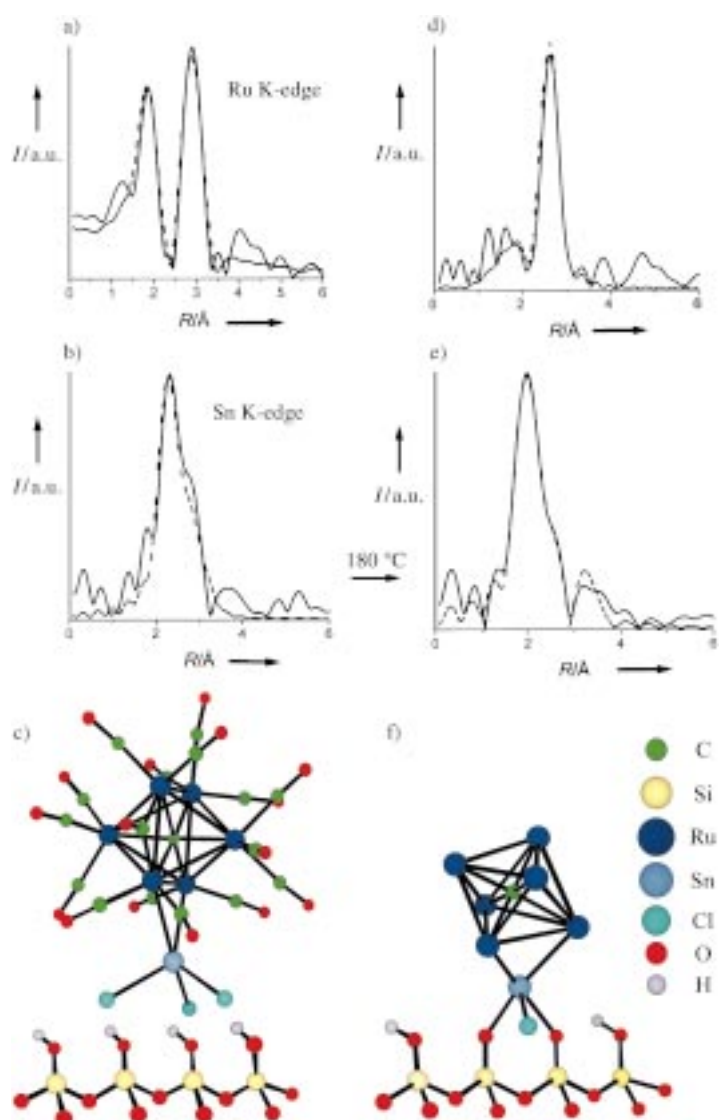


Figure 3. Fourier transform of the EXAFS a) at the Ru K-edge and b) Sn K-edge (of the $[\text{Ru}_6\text{C}(\text{CO})_{10}\text{SnCl}_3]^-$ cluster anchored on MCM-41. c) The single crystal-derived structure is broadly consistent with the experimental EXAFS data. Fourier transforms of the d) Ru K-edge and e) Sn K-edge EXAFS of the decarbonylated (by mild thermolysis at 180°C in vacuum for 1 h) catalysts. f) Local structure of the activated catalyst, derived from the analysis of the EXAFS data. Solid and dashed lines in (a), (b), (d) and (e) represent the experimental and calculated data, respectively.

catalyst on the silica surface. Taking these results into account, we propose a model for the active denuded cluster that is shown in Figure 3 f. We found that cluster **2** could not be freed completely from its residual chlorine ligands; in fact, the Ru K-edge EXAFS data could be refined only on the assumption that a residual chlorine atom was attached to the ruthenium centers. Furthermore, this denuded material derived from cluster **2** is not catalytically active.^[27]

High-angle, annular dark-field (HAADF) scanning transmission electron microscopy (STEM),^[1, 5] shows (Figure 4) how well the nanoparticle catalysts are distributed within the mesopores of the silica support both prior to and after catalytic testing (see below). No dramatic change in the structure of the material (such as sintering of the nano-

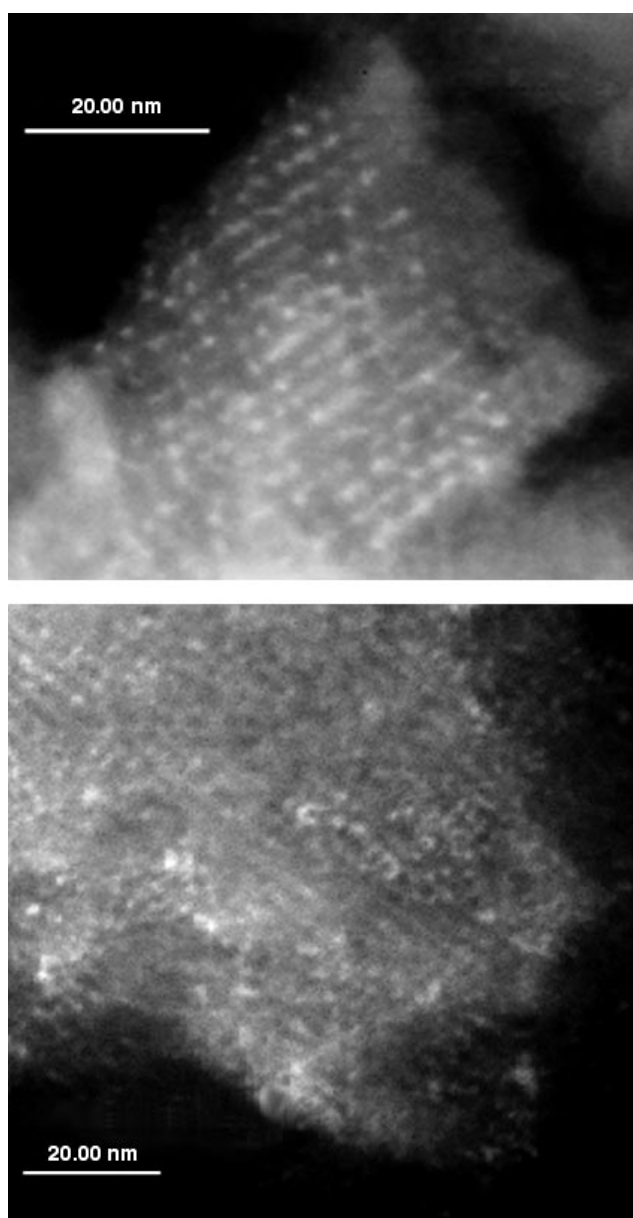


Figure 4. High-angle, annular dark field electron micrographs of the $\text{Ru}_6\text{Sn}/\text{MCM-41}$ catalyst a) prior to and b) after catalytic use.

particles or breakdown of the MCM-41 matrix) occurs during catalysis. This demonstrates both the robust nature of the nanoparticle catalyst and its effective anchoring to the walls of the high-area silica. The overall composition and the invariance of the ratio of the two metals were deduced from energy-dispersive X-ray analysis on both the as-prepared and used specimens of catalyst. Consistent with the fact that no Sn–Sn bond were detected by EXAFS, this indicates that each nanoparticle is derived from an intact cluster core made of six ruthenium atoms, one carbon atom and a single atom of tin.

The marked dependence of temperature upon selectivity in the catalytic hydrogenation of 1,5,9-cyclododecatriene is shown in Figure 5, from which we note that, even as low as 80°C , this solvent-free hydrogenation to cyclododecene is 70% selective and well in excess of 90% at 100°C . This

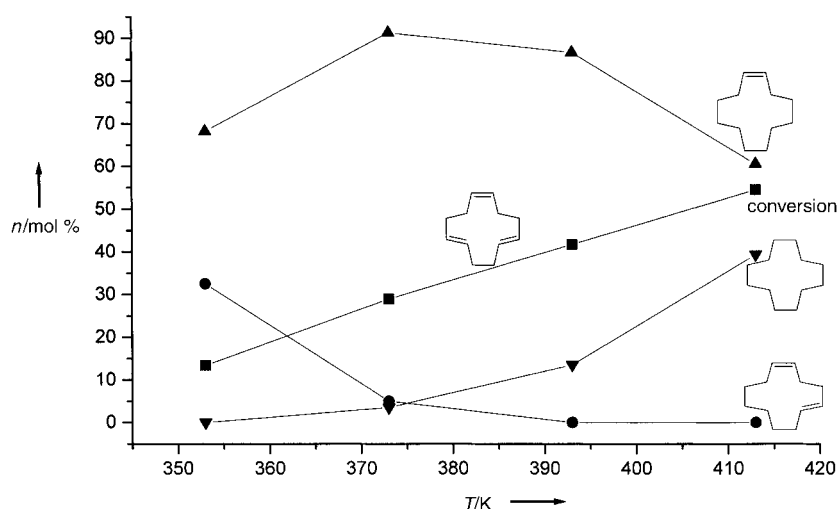


Figure 5. The effect of temperature on the hydrogenation conversion (■) of the product selectivity is marked in terms of singly (●), doubly (▲), and fully (▼) hydrogenated products of 1,5-cyclododecatriene with the Ru_6Sn catalyst.

particular selective hydrogenation falls off in efficiency with further increase in temperature, and conversion to the fully hydrogenated cyclododecane is progressively favored. It is noteworthy that conversion to the cyclododecadiene on the other hand is favored at the lowest test temperature (80 °C). By contrast, the Pd_6Ru_6 catalyst reported earlier^[4] displays very little selectivity for the 1,5-cyclododecadiene or cyclododecene, even at temperatures as low as 40 °C. By comparison with three other bimetallic catalysts ($\text{Cu}_4\text{Ru}_{12}$, $\text{Ag}_4\text{Ru}_{12}$ and Pd_6Ru_6), we note that precursor **1** yields the bimetallic catalyst (Ru_6Sn) with the best performance, so far as selective hydrogenation of one of the two double bonds in the hydrogenation of 1,5-cyclooctadiene is concerned (Figure 6).

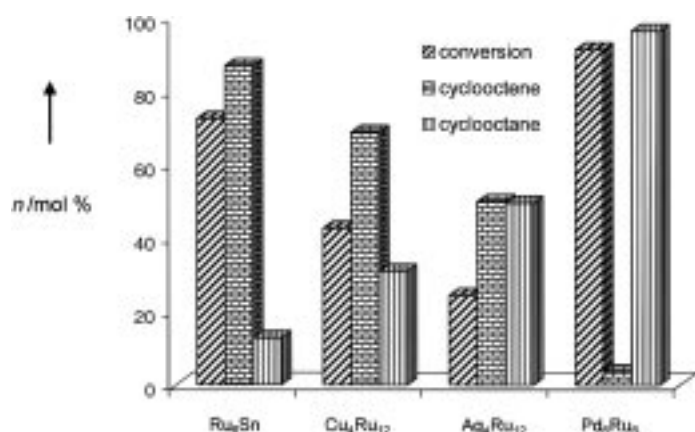


Figure 6. Comparison of catalytic performance and degree of selectivity for the hydrogenation of 1,5-cyclooctadiene, after 24 h, at 353 K. (See Table 1 for reaction conditions).

Further scope for fine-tuning both the conversion and selectivity is obtained by varying the contact times, for a range of polyenes (Table 1). It is particularly interesting that, in the case of 2,5-norbornadiene, the conditions (and catalyst) may be so chosen as to produce a high yield of either norbornene

or norbornane. It is also evident from Table 1 that bimetallic nanoparticle catalysts are far superior in performance to their monometallic analogs and more importantly yield a higher selectivity for hydrogenated products, which shows a synergism between the two components of the bimetallic nanoparticle. We established in separate experiments that monometallic Ru_6 and Pd anchored on MCM-41 were inactive for the above-mentioned reactions. Considerable scope clearly exists, with the principles that we have outlined here and previously to develop other, solvent-free systems for the selective conversion of organic compounds.

We have demonstrated how to regulate the selectivity of nanocatalysts for solvent-free hydrogenations by changing the nature of the constituents in its active phase.

Experimental Section

Electron Microscopy: The images were obtained on a VG HB501 field-emission STEM microscope. A small amount of activated catalyst was ground and suspended in hexane by ultrasonic treatment. A holey carbon film supported on a copper grid was dipped into the solution and allowed to dry in the air before introduction to the microscope. The sample dispersed on the grid was further dried inside the preparation chamber of the microscope by heating at ca. 100 °C under a light bulb and then was left under high vacuum overnight before acquiring the images.

EXAFS: Ru and Sn K-edge EXAFS data were collected at station 9.2 at the Daresbury Synchrotron Laboratory, which operates at 2 GeV and a typical current in the range of 150 to 250 mA. This station is equipped with a quick scanning Si(220) double-crystal monochromator, ion chambers for measuring incident (I_0), transmitted (I_t) beam intensities, and a 13 element Canberra fluorescence detector. In a typical experiment 150 mg of the sample was pressed into a self-supporting wafer and loaded in to the in situ cell.^[28] The cell was evacuated to around 4×10^{-3} Torr and the catalyst was heated to 180 °C at 5 K min^{-1} and retained at this temperature for around 1 h before cooling it to room temperature. All the EXAFS experiments were performed in the fluorescence mode and 10 scans were taken to improve the signal to noise ratio. The data processing was done using the suite of programs available at Daresbury, namely, EXCALIB, EXBROOK, and EXCURV98. The summed data were analysed without Fourier filtering and a full multiple scattering procedure was employed to analyse all the data sets, in particular when carbonyl species and second silicon neighbors were included in the analysis.

Catalysis: The catalytic testing was carried out in a high-pressure stainless steel reactor (Cambridge Reactor Design) lined with PEEK (polyetheretherketone). Nanoparticle bimetallic catalyst (20 mg) was activated (473 K, 2 h, in the presence of hydrogen (0.5 MPa) prior to the hydrogenation reaction. The reactor was then depressurised and cooled to room temperature, before introducing the substrate (50 g; see Table 1) and internal standard (mesitylene, 2.5 g). The vessel was pressurised with hydrogen (30 bar) and heated to the desired temperature with continued stirring (400 min^{-1}). During the reaction, small aliquots were removed, using a mini-robot autosampler, to enable the kinetics to be studied. The products of the reaction were analysed with gas chromatography (GC, Varian, Model 3400 CX) employing a HP-1 capillary column ($25 \text{ m} \times 0.32 \text{ mm}$) and flame ionisation detector. The identity of the products was confirmed by LC-MS (Shimadzu, QP 8000).

Both the Ru_6Sn and Pd_6Ru_6 bimetallic nanoparticle anchored catalysts were reused six or seven times for the hydrogenation of 1,5-cyclooctadiene and 1,5,9-cyclododecatriene without appreciable loss in catalytic activity or

Table 1. Hydrogenation of polyenes—comparison of catalysts.

Catalyst	Substrate	<i>t</i> [h]	<i>T</i> [K]	Conv. [mol %]	TOF ^[a] [h ^{−1}]	Prod. dist. [mol %]		
						A	B	
Ru ₆ Sn/MCM-41	1,5-cyclooctadiene	8	353	11.7	1980	100	–	
		24		72.5	4090	86.9	12.8	
Cu ₄ Ru ₁₂ /MCM-41	1,5-cyclooctadiene	8	353	11.5	690	70.4	29.2	
		24		42.7	1422	68.8	31.0	
Ag ₄ Ru ₁₂ /MCM-41	1,5-cyclooctadiene	8	353	9.0	465	57.3	42.5	
		24		24.4	1316	50	49.6	
Pd ₆ Ru ₆ /MCM-41	1,5-cyclooctadiene	8	353	36.9	2012	15.7	84.5	
		24		91.4	4965	3.6	96.5	
Ru ₆ /MCM-41	1,5-cyclooctadiene	24	353	2.5	141	–	36.2	
Pd/MCM-41	1,5-cyclooctadiene	24	353	7.3	212	–	100	
						C	D	E
Ru ₆ Sn/MCM-41	1,5,9-cyclododecatriene	8	353	4.7	530	84.0	15.8	–
		24		13.4	503	32.5	68.2	–
Ru ₆ Sn/MCM-41	1,5,9-cyclododecatriene	8	373	17.2	1940	17.2	82.4	–
		24		28.9	1130	5.0	91.3	3.5
Ru ₆ Sn/MCM-41	1,5,9-cyclododecatriene	8	393	28.2	3280	6.8	87.0	6.0
		24		41.7	1785	–	86.7	13.5
Ru ₆ Sn/MCM-41	1,5,9-cyclododecatriene	8	413	39.1	4400	–	80.2	19.5
		24	–	54.5	2170	–	60.5	39.3
Pd ₆ Ru ₆ /MCM-41	1,5,9-cyclododecatriene	8	353	47.2	3320	–	48.2	51.5
		24		62.0	1975	–	36.2	63.6
Pd ₆ Ru ₆ /MCM-41	1,5,9-cyclododecatriene	8	373	64.9	5350	–	11.7	88.5
		24		86.2	3200	–	6.2	95.7
						F	G	
Ru ₆ Sn/MCM-41	2,5-norbornadiene	8	333	51.4	10210	88.6	11.3	
		24		89.3	5960	46.8	53.3	
Pd ₆ Ru ₆ /MCM-41	2,5-norbornadiene	8	333	76.4	11 176	24.7	75.1	
		24		98.7	6855	2.5	97.6	

[a] TOF = [(mol_{substr})(mol_{cluster})⁻¹h⁻¹]. Reaction conditions: substrate ≈ 50 g; catalyst = 25 mg; H₂ pressure = 30 bar; A = cyclooctene; B = cyclooctane; C = 1,9-cyclododecadiene; D = cyclododecene; E = cyclododecane; F = norbornene; G = norbornane; .

selectivity. In addition, the following experiments were performed to rule out the possibility of leaching:

- In a typical experiment (see Table 1 and Figure 6), the solid catalyst was filtered from the reaction mixture (when hot) after 8 h, and the reaction was continued with the resulting filtrate for a further 16 h. No significant change in conversion or product selectivity was observed, indicating that the metal ions leached out (if any) are not responsible for the observed activity and selectivity.
- The resulting filtrate (at the end of the reaction, after 24 h) was independently analyzed by ICP and AAS for free or dissolved metal (Sn, Pd, Ru) ions, and only trace amounts (<3 ppb) were detected.

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Slow Shuttling in an Amphiphilic Bistable [2]Rotaxane Incorporating a Tetrathiafulvalene Unit**

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The mechanically interlocked components of nondegenerate catenanes and rotaxanes^[1] can be induced to switch between different ground-state geometries (co-conformations) in response to either physical (light activation) or chemical (redox or pH changes) stimuli.^[2] Since the ring and dumbbell components of these highly ordered molecular assemblies can be induced to perform relative motions, such as circumrotation^[3] (rotary motion) and shuttling^[4] (linear motion), catenanes and rotaxanes^[1] are now prime candidates for the construction of artificial molecular machines^[5, 6] and the fabrication of molecular electronic devices.^[7, 8] In recent years, a number of different protocols, based on self-assembly,^[9] have been developed^[3, 4, 10] for the template-directed synthesis^[11] of rotaxanes. Among the desirable features for the redox-controllable, amphiphilic [2]rotaxanes that have been employed to fabricate single-molecule-thick electrochemical junctions in electronic devices are 1) the siting of redox-active units along the rod section of the dumbbell component and 2) the presence of both hydrophobic and hydrophilic groups as stoppers at the ends of the dumbbell component.

In the context of such devices, the tetrathiafulvalene (TTF) unit (which has found widespread use^[12] in materials chemistry) is an ideal redox-active unit in view of its excellent π -electron-donating properties. It forms^[13] a strong green 1:1 complex ($K_a = 8000 \text{ M}^{-1}$ in MeCN)^[4c] with cyclobis(paraquat-*p*-phenylene)^[14] (CBPQT⁴⁺) for incorporation into a redox-switchable [2]rotaxane also containing a 1,5-dioxynaphthalene (DNP) ring system which also interacts, but somewhat more weakly^[15] with CBPQT⁴⁺ to afford a red color in the process. Although a TTF unit and a DNP ring system have been incorporated^[16] into the crown ether ring component of a redox-switchable [2]catenane, which has already been employed in the fabrication of a solid-state electronically reconfigurable switch,^[7] no rotaxanes containing these two recognition sites for a CBPQT⁴⁺ component have been described in the literature.^[17] Here, we report the template-directed synthesis of an amphiphilic bistable [2]rotaxane (Figure 1) in which the ring component is CBPQT⁴⁺ and the dumbbell component—containing a monopyrrolo-TTF unit and a DNP ring system within its rod section—is terminated by a hydrophilic dendritic stopper at one end and a hydro-

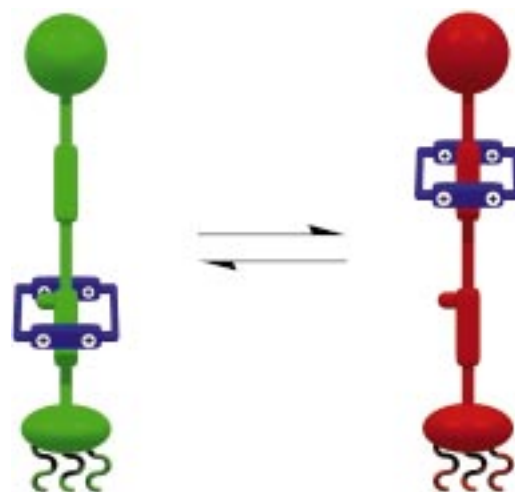


Figure 1. The concept of a slow molecular shuttle with a knob hindering the interconversion between the green and red translational isomers of an amphiphilic bistable [2]rotaxane.

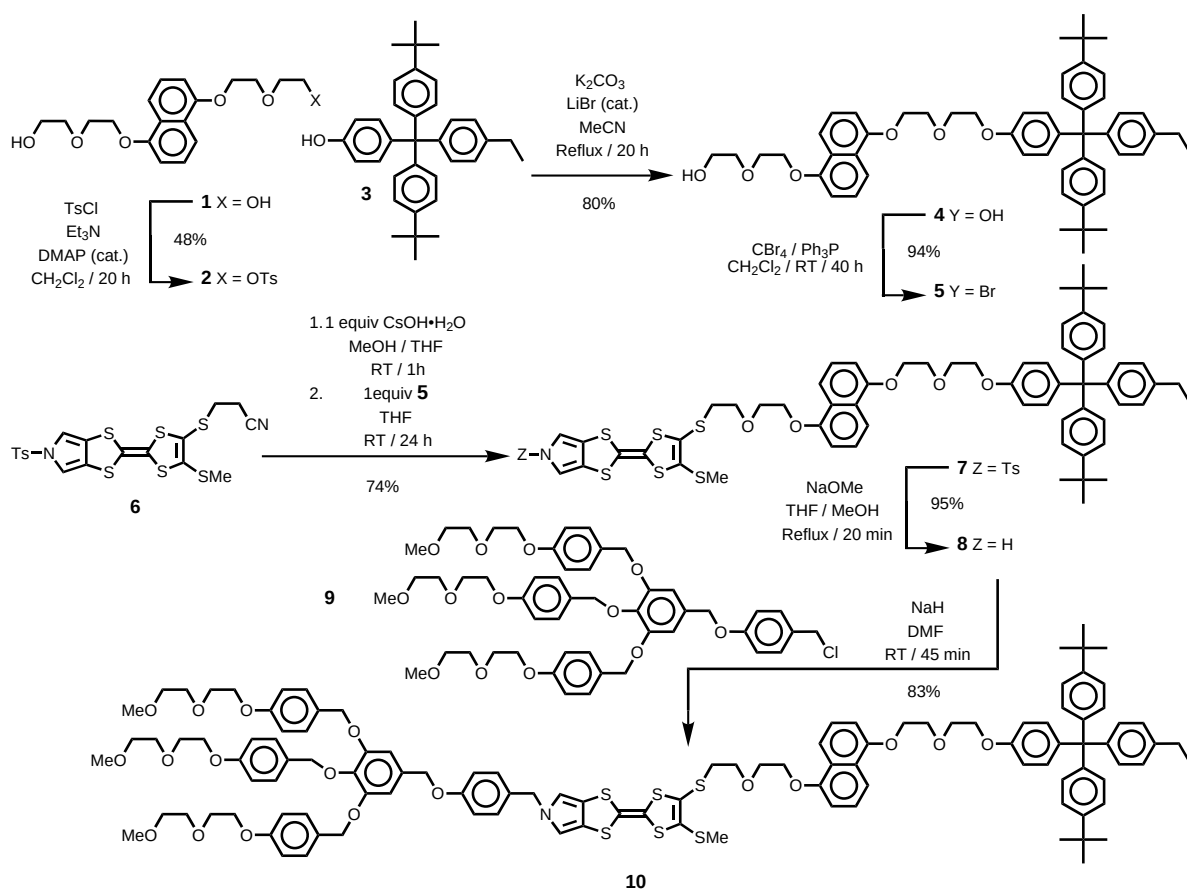
phobic tetraarylmethane stopper at the other end.^[18] Furthermore, we demonstrate the separation of the two possible translational isomers and discuss the kinetic and thermodynamic processes involved in the slow interconversion of the two isomers.

The dumbbell-shaped compound **10** was synthesized as illustrated in Scheme 1. The monotosylate **2** was obtained in 48 % yield by reaction of the diol^[19] **1** with one equivalent of *p*-toluenesulfonyl chloride (TsCl). Alkylation of the hydrophobic tetraarylmethane-based stopper^[10d, 18] **3** with **2** in MeCN in the presence of K₂CO₃ gave (80 %) the alcohol **4**, which was subsequently brominated using CBr₄ and Ph₃P in CH₂Cl₂ to afford the bromide **5** in 94 % yield. A solution of the recently described^[18, 20] asymmetric monopyrrolo-TTF building block **6** in THF was treated with one equivalent of CsOH·H₂O. This procedure generated the TTF-monothiolate, which was alkylated with one equivalent of the bromide **5** to afford the TTF derivative **7** in 74 % yield. Removal of the tosyl protecting group was carried out in near quantitative yield by refluxing **7** in THF/MeOH (1/1) in the presence of an excess of NaOMe. An 83 % yield of compound **10** was obtained following N-alkylation of the pyrrole unit in **8** with the hydrophilic stopper^[18] **9** in DMF containing NaH. Self-assembly of the [2]rotaxane **13**·4PF₆ was achieved (Scheme 2) in 23 % yield using **10** as the template for the formation of the encircling CBPQT⁴⁺ unit from its dicationic precursor^[3] **11**·2PF₆ and 1,4-bis(bromomethyl)benzene (**12**). The molecular shuttle was isolated as an analytically pure brown solid after column chromatography using a solution of NH₄PF₆ in Me₂CO as eluent. The fast atom bombardment mass spectrum (FAB-MS) of this brown solid shows intense peaks at *m/z* 2921, 2776, 2631, 1388, 1316, and 1243 which correspond to the [M - PF₆]⁺, [M - 2PF₆]⁺, [M - 3PF₆]⁺, [M - 2PF₆]²⁺, [M - 3PF₆]²⁺, and [M - 4PF₆]²⁺ ions, respectively.

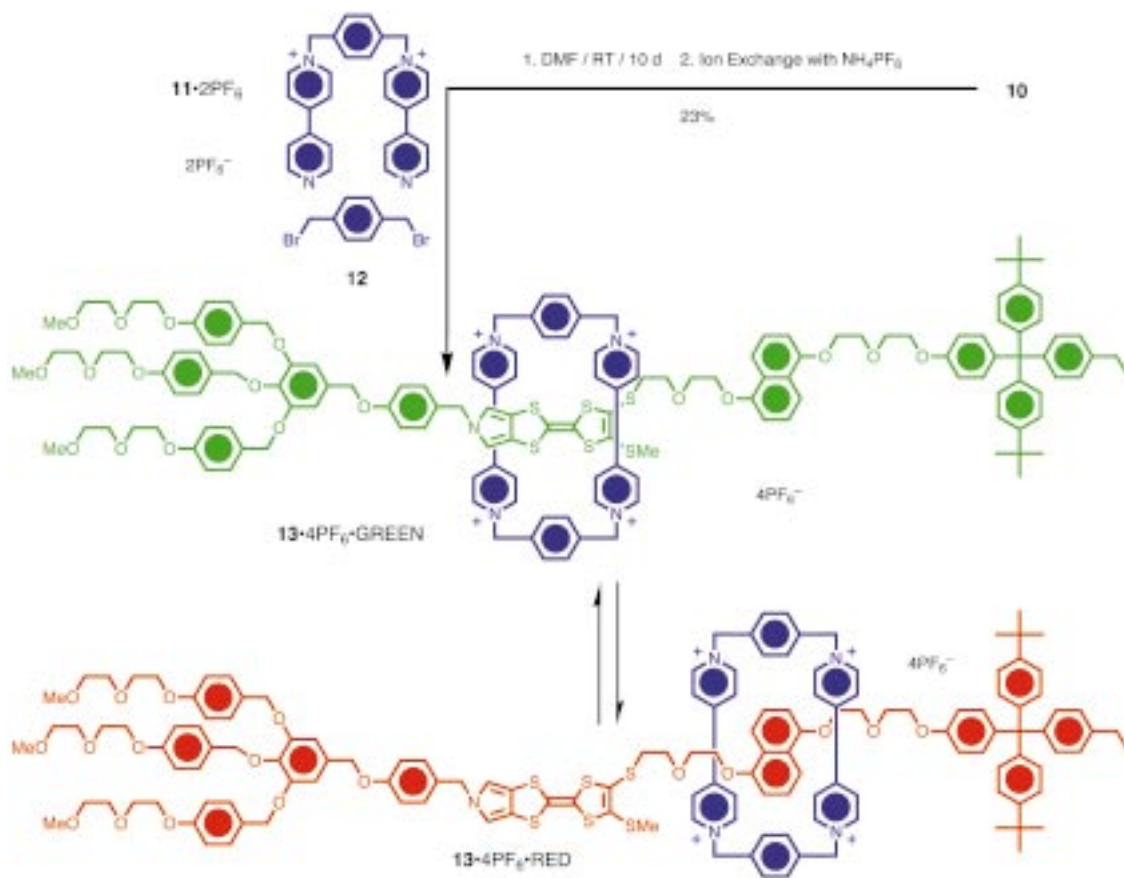
UV/Vis and ¹H NMR spectroscopy indicated the presence of the two stable translational isomers present in the isolated product. The UV/Vis spectrum (Figure 2, curve a) recorded in Me₂CO showed a broad charge-transfer (CT) absorption

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Scheme 1. Synthesis of the dumbbell-shaped compound **10**.



Scheme 2. Template-directed synthesis of the [2]rotaxane **13**·4PF₆⁻.

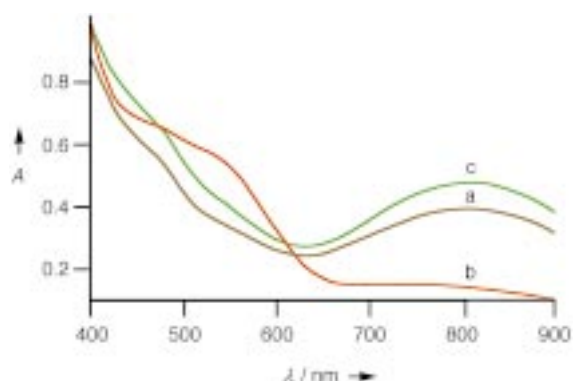


Figure 2. Absorption spectra (Me_2CO , 298 K) recorded on a solution of an equilibrium mixture of the [2]rotaxanes $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{GREEN}$ and $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ (curve a) and of the [2]rotaxane $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ (curve b) and the [2]rotaxane $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{GREEN}$ (curve c) immediately after their isolation. Allowing the red solution of $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ to stand for 24 h at room temperature regenerates the “original” spectrum (curve a).

band centered on 805 nm ($\epsilon = 810 \text{ M}^{-1} \text{ cm}^{-1}$)—which is characteristic^[13] of co-conformations containing a TTF unit located “inside” CBPQT^{4+} —and a CT absorption band observed as a shoulder at 540 nm ($\epsilon = 670 \text{ M}^{-1} \text{ cm}^{-1}$)—which results from the DNP moiety being located “inside” the cyclophane.^[19, 21] The ^1H NMR spectrum (400 MHz) recorded at 298 K in $(\text{CD}_3)_2\text{CO}$ showed (Figure 3) two singlets at $\delta = 2.64$ and 2.47, which can be assigned to the SMe resonances

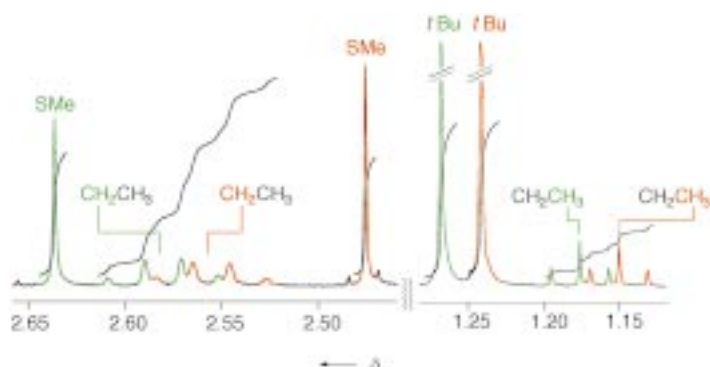


Figure 3. Partial ^1H NMR spectrum of an equilibrium mixture of the [2]rotaxanes $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{GREEN}$ and $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ recorded at 400 MHz in $(\text{CD}_3)_2\text{CO}$ at 298 K.

attached to the TTF unit in $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{GREEN}$ and $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$, respectively.^[22] The ratio of the two translational isomers was estimated from the integrals of the two different SMe resonances to be approximately 1:1.

Thin-layer chromatography (TLC) of $\mathbf{13} \cdot 4\text{PF}_6$ showed green and red spots with similar intensities, thus indicating the existence of two isolable translational isomers—one in which CBPQT^{4+} encircles the TTF unit (namely, $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{GREEN}$) and another in which CBPQT^{4+} encircles the DNP ring system (namely, $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$). By employing preparative thin-layer chromatography (PTLC), it was possible (Figure 4) to isolate the red translational isomer ($\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$). The UV/Vis spectrum (Figure 2, curve b) of $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ reveals a CT absorption band which is observed as a shoulder at 540 nm. This band results from the DNP moiety

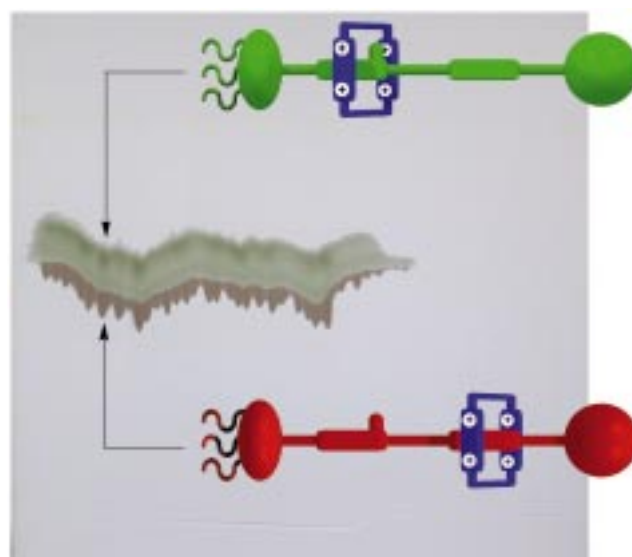


Figure 4. A preparative thin-layer chromatogram (see Experimental Section) showing the separation of $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ from $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{GREEN}$.

being located “inside” CBPQT^{4+} . Furthermore, no absorption band is observed in the region 750–850 nm where the CT interaction resulting from the TTF moiety being located “inside” the tetracationic cyclophane would occur. Leaving the red solution to stand for 24 h at room temperature gives back the “original” spectrum (Figure 2, curve a). The kinetics of the shuttling of CBPQT^{4+} from the DNP recognition site in $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ to the TTF recognition site was investigated by ^1H NMR spectroscopy. The ^1H NMR spectrum (500 MHz) of $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ was recorded (Figure 5a) at 230 K in

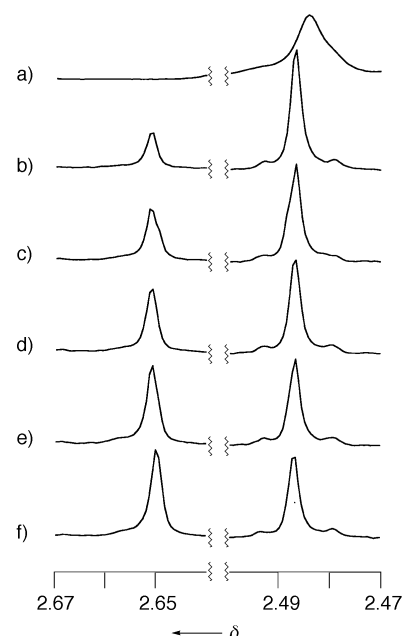


Figure 5. Partial ^1H NMR spectra (500 MHz) of the isolated [2]rotaxane $\mathbf{13} \cdot 4\text{PF}_6 \cdot \text{RED}$ recorded in $(\text{CD}_3)_2\text{CO}$ at a) 230 K/0 h, b) 300 K/1 h, c) 300 K/3 h, d) 300 K/5 h, e) 300 K/8 h, f) 300 K/21 h. The singlet at $\delta = 2.49$ corresponds to the SMe resonance when CBPQT^{4+} encircles the 1,5-dioxynaphthalene ring system and the singlet at $\delta = 2.65$ corresponds to the SMe resonance when CBPQT^{4+} encircles the TTF unit.

(CD₃)₂CO and shows, as expected, only one signal for the SMe protons as a singlet resonating at $\delta = 2.49$. The sample was heated subsequently to 300 K and the shuttling of CBPQT⁴⁺ from the DNP recognition site in **13**·4PF₆·RED to the TTF recognition site was followed using the SMe resonances as the probe (Figure 5b–f). After 21 h at 300 K, the system had equilibrated and a 1:1 mixture of **13**·4PF₆·RED and **13**·4PF₆·GREEN was re-established (Figure 5f). As a consequence of these spectroscopic variations the color of the solution changed from red to brown. By employing a first-order kinetic treatment^[23] a rate constant of $k = 2 \times 10^{-5} \text{ s}^{-1}$ was obtained for the slippage of CBPQT⁴⁺ over the SMe group, in the direction from **13**·4PF₆·RED to **13**·4PF₆·GREEN. The corresponding free energy of activation ($\Delta G^\ddagger$) for this isomerization is 24 kcal mol⁻¹.

Although it was not possible to isolate a sufficient amount of **13**·4PF₆·GREEN from the PTLC experiment to follow its interconversion into **13**·4PF₆·RED by ¹H NMR spectroscopy, it proved possible to shift the equilibrium between the two translational isomers from 1:1 to 9:1 in favor of **13**·4PF₆·GREEN by heating a solution of the brown 1:1 mixture in (CD₃)₂SO to 425 K. The color of the solution changed from brown to green upon heating to 425 K. The solution was then quenched at 273 K (ice bath) and the conversion of **13**·4PF₆·GREEN into **13**·4PF₆·RED was followed at 300 K using the signals for the protons on the monopyrrolo-TTF unit and the DNP ring system as a probe. On this occasion, a first-order rate constant of $3 \times 10^{-4} \text{ s}^{-1}$ was obtained for the slippage of CBPQT⁴⁺ over the SMe group in the direction from **13**·4PF₆·GREEN to **13**·4PF₆·RED. The associated $\Delta G^\ddagger$ value is 22 kcal mol⁻¹.

In summary, we have devised and completed the synthesis of an amphiphilic bistable [2]rotaxane comprising two different recognition sites, a TTF unit and a DNP ring system, for CBPQT⁴⁺. The steric hindrance exhibited by the SMe group situated between the two recognition sites has made it possible to isolate the translational isomer **13**·4PF₆·RED and to study the kinetics of the shuttling of the tetracationic cyclophane between the two recognition sites. The process, which is accompanied by a clearly detectable color change, can also be followed by ¹H NMR and UV/Vis spectroscopy. This new amphiphilic rotaxane is currently being assessed for its ability to self-organize into monolayers as a prelude to its introduction into devices.

Experimental Section

5: Ph₃P (0.70 g, 2.67 mmol) was added portionwise to a solution of **4** (1.75 g, 2.20 mmol) and CBr₄ (0.88 g, 2.65 mmol) in anhydrous CH₂Cl₂ (15 mL) at room temperature. The reaction mixture was stirred for 16 h, whereupon additional CBr₄ (0.88 g, 2.65 mmol), followed by Ph₃P (0.70 g, 2.67 mmol) was added and the reaction mixture was stirred for another 24 h. After concentration, the residue was purified by column chromatography (SiO₂, CH₂Cl₂/hexane 2/1). The colorless band ($R_f = 0.3$) was collected and the solvent evaporated to afford a colorless oil, which was repeatedly dissolved in CH₂Cl₂ (3 × 50 mL) and concentrated to provide **5** (1.77 g, 94 %) as an analytically pure white semisolid. ¹H NMR (CDCl₃, 200 MHz, 298 K): $\delta = 1.26$ (t, $J = 7.6$ Hz, 3H), 1.33 (s, 18H), 2.65 (q, $J = 7.6$ Hz, 2H), 3.54 (t, $J = 6.2$ Hz, 2H), 3.94–4.10 (m, 8H), 4.14–4.19 (m, 2H), 4.28–4.36 (m, 4H), 6.80–6.89 (m, 4H), 7.06–7.15 (m, 10H), 7.24–7.42 (m, 6H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H); ¹³C NMR (CDCl₃, 50 MHz, 298 K): $\delta = 15.4, 28.3, 30.5, 31.5, 34.4, 63.2$ (CAr₄), 67.4, 68.0, 69.8, 70.0, 70.2, 71.6

(6 × CH₂O, 1 × CH₂O signal missing/overlapping), 105.8 (2 signals), 113.3, 114.7, 114.9, 124.2, 125.2, 125.3, 126.7, 126.8 (2 signals), 130.8, 131.1, 132.3, 139.9, 141.4, 144.3, 144.7, 148.3, 154.3, 154.4, 156.6; FAB-MS: m/z (%): 858 (30) [$M+2$]⁺, 856 (27) [M]⁺; elemental analysis calcd (%) for C₃₃H₆₁BrO₅ (857.95): C 74.20, H 7.17; found: C 74.36, H 7.20.

7: A solution of **6**^[18, 20] (0.27 g, 0.51 mmol) in anhydrous THF (35 mL) was degassed (Ar, 10 min) before a solution of CsOH·H₂O (0.090 g, 0.54 mmol) in anhydrous MeOH (3.5 mL) was added dropwise by syringe over a period of 1 h at room temperature. The mixture was stirred for 15 min, whereupon a solution of the bromide **5** (0.46 g, 0.54 mmol) in anhydrous THF (5 mL) was added in one portion and the reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated and the resulting yellow residue was dissolved in CH₂Cl₂ (100 mL), washed with brine (100 mL) and H₂O (2 × 100 mL), and then dried (MgSO₄). Removal of the solvent gave a yellowish orange semisolid, which was purified by column chromatography (SiO₂, CH₂Cl₂/hexane 4/1). The broad yellow band ($R_f = 0.3$) was collected and concentrated to afford a yellow semisolid, which was repeatedly dissolved in CH₂Cl₂ (2 × 20 mL) and concentrated to give **7** (0.47 g, 74 %) as an analytically pure yellow semisolid. FAB-MS: m/z (%): 1252 (100) [M]⁺; elemental analysis calcd (%) for C₆₉H₇₃NO₇S₇ (1252.78): C 66.15, H 5.87, N 1.12; found: C 66.34, H 6.02, N 1.05.

8: Compound **7** (0.42 g, 0.34 mmol) was dissolved in anhydrous THF/MeOH (1/1, 50 mL) and degassed (Ar, 10 min) before NaOMe (25 % solution in MeOH, 1.1 mL, 0.27 g, 5.0 mmol) was added in one portion. The yellow solution was refluxed for 20 min and cooled to room temperature, whereupon the solvent was evaporated. The yellow residue was dissolved in CH₂Cl₂ (100 mL), washed with H₂O (3 × 100 mL), and dried (MgSO₄). Removal of the solvent gave a yellow semisolid, which was subjected to column chromatography (SiO₂, CH₂Cl₂). The yellow band ($R_f = 0.5$) was collected and concentrated to give **8** (0.35 g, 95 %) as an analytically pure yellow solid. FAB-MS: m/z (%): 1098 (100) [M]⁺; elemental analysis calcd (%) for C₆₂H₆₇NO₃S₆ (1098.60): C 67.78, H 6.15, N 1.27; found: C 67.81, H 6.15, N 1.24.

10: Compounds **8** (0.23, 0.21 mmol) and **9**^[18] (0.21 g, 0.23 mmol) were dissolved in anhydrous DMF (10 mL) and degassed (Ar, 10 min) before NaH (0.021 g of a 60 % suspension in mineral oil, 0.53 mmol) was added. The reaction mixture was stirred for 45 min at room temperature, which resulted in the initial yellow solution becoming more orange. H₂O (40 mL) was added, followed by the addition of brine (40 mL). The yellow precipitate was filtered and dried. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂/EtOAc 2/1). The yellow band ($R_f = 0.4$) was collected and the solvent evaporated to afford a yellow oil, which was repeatedly dissolved in CH₂Cl₂ (3 × 20 mL) and concentrated to yield **10** (0.34 g, 83 %) as an analytically pure yellow semisolid. ¹H NMR (CD₃COCD₃, 400 MHz, 298 K): $\delta = 1.17$ (t, $J = 7.6$ Hz, 3H), 1.26 (s, 18H), 2.38 (s, 3H), 2.57 (q, $J = 7.6$ Hz, 2H), 3.05 (t, $J = 6.4$ Hz, 2H), 3.26 (s, 9H), 3.45–3.48 (m, 6H), 3.60–3.63 (m, 6H), 3.74–3.79 (m, 6H), 3.81 (t, $J = 6.4$ Hz, 2H), 3.90–4.00 (m, 6H), 4.05–4.13 (m, 8H), 4.24–4.27 (m, 4H), 4.88 (s, 2H), 4.96 (s, 2H), 5.00 (s, 6H), 6.72 and 6.75 (AB, $J = 2.1$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 2H), 6.80 (d, $J = 9.1$ Hz, 2H), 6.83 (s, 2H), 6.88–6.93 (m, 8H), 7.03–7.12 (m, 10H), 7.15 (d, $J = 8.7$ Hz, 2H), 7.22–7.33 (m, 8H), 7.36 (d, $J = 8.8$ Hz, 4H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.82 (d, $J = 8.5$ Hz, 1H); FAB-MS: m/z (%): 1966 (100) [M]⁺; elemental analysis calcd (%) for C₁₁₂H₁₂₇NO₁₈S₆ (1967.60): C 68.37, H 6.51, N 0.71; found: C 68.17, H 6.49, N 0.66.

13·4PF₆: A solution of **10** (0.28 g, 0.14 mmol), **11**·2PF₆^[3] (0.30 g, 0.42 mmol), and **12** (0.11 g, 0.42 mmol) in anhydrous DMF (10 mL) was stirred for 10 d at room temperature (after approximately 1 d the color changed to dark green and a white precipitate was formed). The green suspension was subjected directly to column chromatography (SiO₂) and recovered **10** was eluted with Me₂CO, whereupon the eluent was changed to Me₂CO/NH₄PF₆ (1.0 g NH₄PF₆ in 100 mL MeCO) and the brown band containing **13**·4PF₆ was collected. Most of the solvent was removed under vacuum ($T < 30^\circ\text{C}$) followed by the addition of H₂O (50 mL). The resulting precipitate was collected by filtration, washed with Et₂O (20 mL), and dried to afford the [2]rotaxane **13**·4PF₆ (0.10 g, 23 %) as an analytically pure brown solid. M.p. 150 °C (decomposed without melting); FAB-MS: m/z (%): 2921 (4) [$M - \text{PF}_6$]⁺, 2776 (9) [$M - 2\text{PF}_6$]⁺, 2631 (6) [$M - 3\text{PF}_6$]⁺, 1966 (3), 1388 (10) [$M - 2\text{PF}_6$]²⁺, 1315.5 (13) [$M - 3\text{PF}_6$]²⁺, 1243 (6) [$M - 4\text{PF}_6$]²⁺; elemental analysis calcd (%) for C₁₄₈H₁₅₉F₂₄N₃O₁₈P₄S₆·2H₂O

(3068.12): C 57.26, H 5.29, N 2.26; found: C 56.86, H 5.19, N 2.11. Preparative thin-layer chromatography (PTLC) was performed at room temperature on UNIPLATE silica gel PTLC plates with Me₂CO/NH₄PF₆ (1.0 g NH₄PF₆ in 100 mL Me₂CO) as eluent. Immediately after elution, the red band containing **13**·4PF₆·RED was extracted into Me₂CO. The solvent was removed under vacuum (*T* < 10 °C) and the red residue dissolved in (CD₃)₂CO to give a red solution, which was cooled to –78 °C in a Me₂CO/dry ice bath. Although **13**·4PF₆·GREEN seems to be less polar than **13**·4PF₆·RED, it was only possible to extract an extremely small amount of **13**·4PF₆·GREEN from the silica on the PTLC plate. The UV/Vis spectrum recorded in (CD₃)₂CO at 298 K of this fraction shows, as expected, only a broad charge-transfer (CT) absorption band centered on 801 nm.

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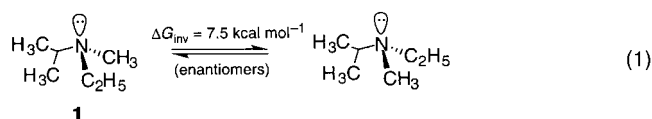
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Isolation of an Acid/Base Complex in Solution Puts the Brakes on Nitrogen Inversion**

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Acid/base interactions pervade chemistry and dominate molecular recognition in biology. The isolation of individual acid/base complexes can be achieved in the gas phase at low pressures^[1] and in the solid or glassy states within inert matrices. In solution, rapid diffusion permits the frequent exchange of acid/base partners and the characterization of individual complexes requires the fastest of spectroscopic techniques. We have recently introduced a synthetic host that features an inwardly directed carboxy group on its concave surface,^[2] and we apply it here to the study of isolated acid/base interactions. The results augur well for the observation and characterization of short-lived intermediates in these receptacles.

The effects are demonstrated with the amine base *N*-ethyl-*N*-methyl-*N*-isopropylamine [**1**, Eq. (1)]. This base features

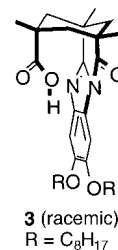


one of the simplest amines with a stereogenic nitrogen atom and its behavior has been closely examined in solution.^[3, 4] The nitrogen atom inverts rapidly at room temperature, a motion that can be frozen out at low temperatures. The activation barrier for inversion/rotation—the process that converts the molecule into its mirror image—is approximately 7.5 kcal mol^{−1} at 160 K in CBrF₃. Extrapolated to room temperature, the rate of racemization is about 10⁷ s^{−1}.

The same amine shows starkly different behavior within the racemic receptacle molecule **2** (Figure 1).^[2] The inversion/rotation of **1** within **2** is slow on the NMR timescale at room temperature, and even at 323 K. A portion of the NMR spectrum of **1** in **2** is shown and highlights the consequences of amine complexation: large upfield shifts, emergence of coupling details, an overall expansion of the spectrum, and the doubling of its resonances. The last feature reflects the modest (about 2:1) diastereoselectivity of the racemic receptacle for the amine enantiomers.

The guest exchange rates into and out of **2** are slow on the NMR timescale and separate signals are seen for free and bound guest.^[5] Steric barriers—mechanical bonds—isolate the amine from the bulk solution and costly conformational changes (including the rupture of hydrogen bonds) are necessary to allow the passage of molecules into and out of the cavity. The rate of this process for **1**, as measured by an exchange spectroscopy (EXSY) experiment, is 2 s^{−1} at room temperature and corresponds to a barrier of about 17 kcal mol^{−1}. However, EXSY experiments on the bound guest failed to show exchange between diastereomeric complexes, even at 323 K. Accordingly, the lowest energy path for interconversion of diastereomers of the complex involves dissociation to the free components in solution and then their recombination.

What causes the large energetic barrier to the process of Equation (2): the interconversion of the diastereomeric complexes of **1** within **2**? The attractive forces between the acid and base must contribute but they cannot be a large factor. The model (racemic) acid **3** was used as a model for estimating the effects of acid/base attraction. The carboxy groups of both **2** and **3** are derived from Kemp's triacid^[6, 7] and are attached to the aromatic residues through an *N*-acylbenzimidazole function; they are inherently chiral. Complexes of **3** with **1** exchange/interconvert rapidly on the NMR timescale in CH₂Cl₂ at ambient temperature, and low temperatures are required to distinguish the diastereomers. Dynamic NMR experiments show an activation barrier of 10.5 ± 0.5 kcal mol^{−1} for the exchange process at the coalescence temperature ($T_c = 230$ K). There is nothing unusual about this acid/base pair: the complex of **1** with 2,2-dimethylpropionic (pivalic) acid also shows a barrier of 10.3 kcal mol^{−1} at $T_c = 230$ K for the inversion/rotation of the amine.



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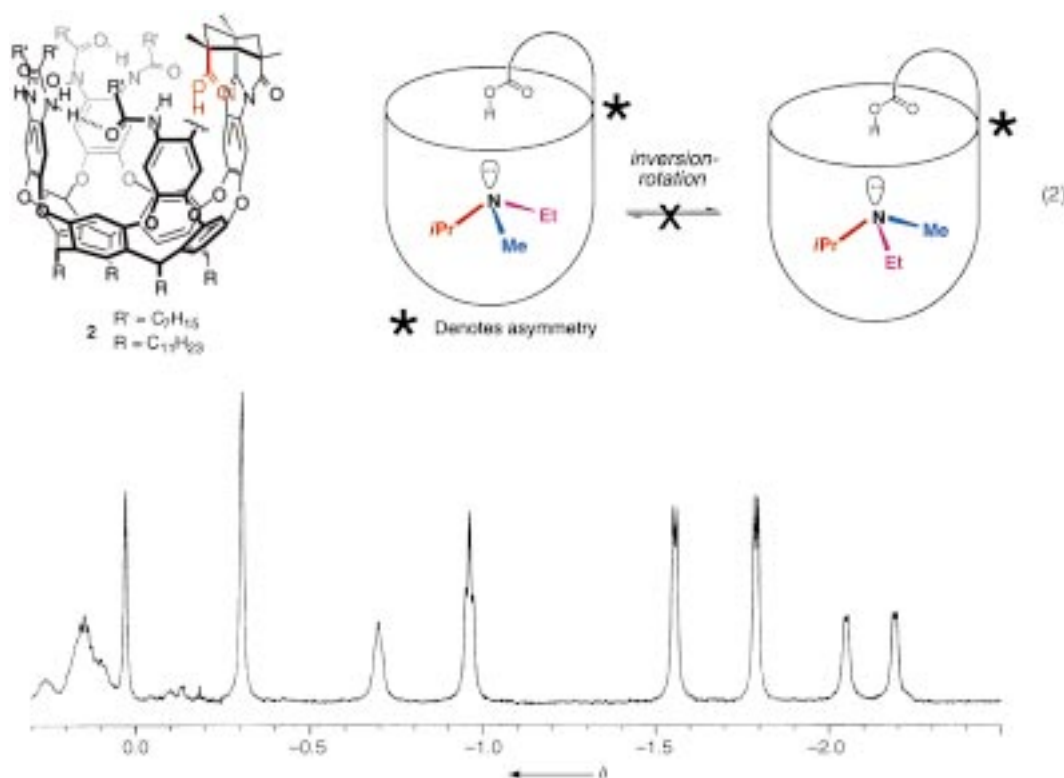


Figure 1. Top: Introverted acid receptacle **2**. It is represented as a cartoon in the hypothetical Equation (2). Bottom: Upfield region of the NMR spectrum of the amine **1** with added **2** in CDCl_3 at room temperature.

Perhaps the nature of the amine–carboxy interaction inside the cavity of **2** is special. It might range from a hydrogen bond to a salt bridge or even an ion pair depending on the dielectric constant of the microenvironment. This value is unknown and, if calculations of protein interiors are any indication, it is likely to remain so.^[8] For the time being we feel that the steric barriers to inversion/rotation and tumbling of the amine must contribute considerably to the difficulties of Equation (2).^[9]

In conclusion, isolation of a guest can be accomplished in solution through formation of “molecule-within-molecule” complexes, for example, with covalently bonded structures such as carcerands^[10] and cryptophanes,^[11] in reversibly formed capsules held together with hydrogen bonds,^[12] or with metal–ligand interactions.^[13] The receptacle **2** offers an additional feature that makes its microenvironment unique to physical organic chemistry: it surrounds the amine base with steric barriers and provides a built-in acid, which is trained on the base held inside. The partners are frozen into a close association that restricts diffusion and resists conformational changes^[14] such as inversion/rotation and tumbling. In this respect the behavior of **1** in **2** is reminiscent of the carceroisomerism^[15] seen in covalently bound molecule-within-molecule complexes. In another respect, the receptacle resembles the naturally occurring examples of inwardly directed and physically isolated functional groups found at the active sites enzymes and receptors.

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Isolation and Structural Characterization of the Endohedral Fullerene $\text{Sc}_3\text{N@C}_{78}$ **

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Although fullerenes with metals encapsulated within a cage of carbon atoms have been known since the beginning of fullerene chemistry,^[1] progress in exploring their chemical, physical, and structural properties has been limited by the low yields of the endohedral fullerenes produced. Conducting the normal Krätschmer–Huffman arc method for fullerene preparation using graphite rods doped with trivalent metal oxides in a dynamic atmosphere that contains dinitrogen and helium results in the enhanced production of endohedral fullerenes. A recently reported example is the preparation of $\text{Sc}_3\text{N@C}_{80}$, which contains a planar Sc_3N unit within a fullerene cage of I_h symmetry.^[2, 3] Performing this trimetallic nitride template (TNT) process with scandium(III) oxide doped graphite rods yields not only $\text{Sc}_3\text{N@C}_{80}$ but two other novel endohedral products: $\text{Sc}_3\text{N@C}_{68}$, in which the carbon cage must violate the isolated pentagon rule,^[4] and $\text{Sc}_3\text{N@C}_{78}$. The three fullerenes were isolated in relative yields of 8:1:1, respectively; $\text{Sc}_3\text{N@C}_{78}$ is more abundant than any of the other conventional metallofullerenes such as $\text{Sc}_2\text{@C}_{84}$. These isomers have been isolated through a three-step high-pressure liquid chromatography (HPLC) procedure.^[5] Figure 1 shows the mass spectra of the purified samples of the three endohedral fullerenes, along with color photographs of solutions of them in carbon disulfide. Note that each different cage imparts a distinctive color to the sample. The UV/Vis absorption spectrum of air-stable $\text{Sc}_3\text{N@C}_{78}$ in carbon disulfide is shown in Figure 2. Prominent maxima are seen at 460 and 623 nm with shoulders at longer wavelengths. Here we report the detailed structural characterization of $\text{Sc}_3\text{N@C}_{78}$. Endohedral fullerenes with a C_{78} cage are uncommon and to our knowledge none have been isolated as yet in significant quantities.

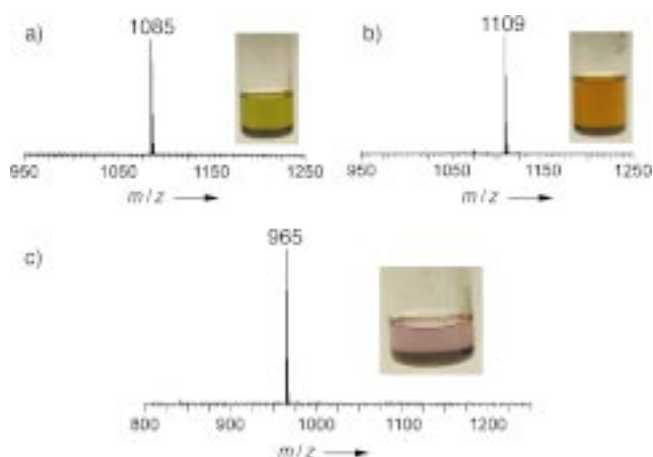


Figure 1. Mass spectra of purified samples of $\text{Sc}_3\text{N@C}_{78}$ (a); $\text{Sc}_3\text{N@C}_{80}$ (b); and $\text{Sc}_3\text{N@C}_{68}$ (c). The insets show the colors of solutions of the respective samples in carbon disulfide.

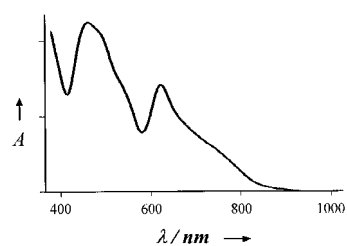


Figure 2. The UV/Vis spectrum of $\text{Sc}_3\text{N@C}_{78}$ in carbon disulfide.

There are five isomers for the empty C_{78} cage itself (with symmetries $D_3(78:1)$, $C_{2v}(78:2)$, $C_{2v'}(78:3)$ (two distinct isomers), $D_{3h}(78:4)$, and $D_{3h'}(78:5)$ (two distinct isomers)) which obey the isolated pentagon rule.^[6] Three of these five isomers have been isolated.^[7–9] These isomers have been identified as having D_3 , C_{2v} , and $C_{2v'}$ symmetry on the basis of their ^{13}C NMR spectra. The relative yields of the three isomers have been shown to depend on the helium pressure during the synthesis.^[10] Theoretical calculations indicate that the potential energies of the five isomers increase in the following order: $C_{2v'}(78:3) < C_{2v}(78:2) < D_3 < D_{3h}(78:4) < D_{3h'}(78:5)$.^[11, 12] Thus, the three most stable isomers have been separated and identified while the two highest energy isomers, both with D_{3h} symmetry, have not yet been found in conventionally prepared fullerene soot.

Black crystals of $\text{Sc}_3\text{N@C}_{78} \cdot [\text{Co}(\text{oep})] \cdot 1.5\text{C}_6\text{H}_6 \cdot 0.3\text{CHCl}_3$ (**1**, oep = octaethylporphyrin) were obtained by the slow diffusion of solutions of $\text{Sc}_3\text{N@C}_{78}$ in benzene and $[\text{Co}^{\text{II}}(\text{oep})]$ in chloroform.^[13] Figure 3 shows a diagram of the individual molecular components. The fullerene is cradled within the cavity provided by the cobalt porphyrin and its eight ethyl groups. The dimensions of the non-fullerene components are entirely normal.

The fullerene component suffers from disorder, which has been satisfactorily modeled. Three orientations of the C_{78} cage, which has been treated as a rigid group with $D_{3h'}(78:5)$ geometry (with the central [6,6] ring junctions of pyracylene patches lying in the horizontal mirror plane) using idealized coordinates, have been found with relative site occupancies of 0.25, 0.15, and 0.10. Since the fullerene is situated on a mirror

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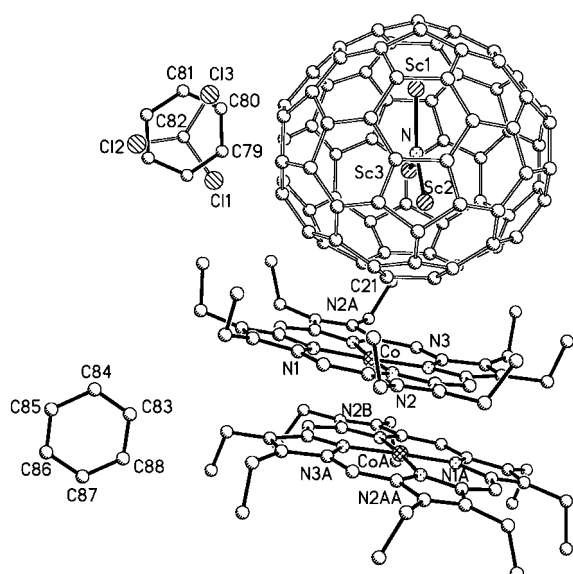


Figure 3. A view of the structure of **1** that shows the relative orientation of all the components. Only the major (0.25 %) orientation of the $\text{Sc}_3\text{N}@C_{78}$ molecule is shown. At one site, which is partially occupied by 0.5 benzene and 0.3 chloroform molecules (top left), the two molecules are shown superimposed.

plane that does not coincide with any of the mirror planes of the C_{78} cages, each of these orientations also generates a second C_{78} cage. Three orientations of the Sc_3 portion have also been identified with fractional occupancies again of 0.25, 0.15, and 0.10.

Figure 4 shows two orthogonal views of the $\text{Sc}_3\text{N}@C_{78}$ molecule in its major orientation. The N–Sc distances are 1.988(7) (Sc1), 1.983(15) (Sc2), and 2.125(5) Å (Sc3), and the Sc–N–Sc angles are Sc1–N–Sc2 130.3(5), Sc1–N–Sc3 113.8(5), and Sc2–N–Sc3 115.9(5)°. The flat Sc_3N portion is oriented so that it lies near the horizontal mirror plane of the C_{78} cage. In this orientation each scandium atom lies over a [6,6] ring junction within a pyracylene patch. The shortest C–Sc distances fall in a narrow range: Sc1–C37 2.058(3), Sc1–C38 2.107(3), Sc2–C6 2.058(16), Sc2–C7 2.024(16), Sc3–C66 2.075(4), and Sc3–C67 2.106(5) Å.

All five isomeric C_{78} cages have been examined within the model described above, and the $D_{3h}(78:5)$ isomer clearly produces the best fit. For example, although the $C_{2v}(78:3)$ isomer differs from the $D_{3h}(78:5)$ isomer only by a single Stone–Wales transformation^[14] (which involves reorientation of the inner C–C bond in a pyracylene patch) introduction of the $C_{2v}(78:3)$ isomer into the major orientation results in an increase in the *R* factor by about 2 % and in a much less uniform distribution of the thermal ellipsoids throughout the C_{78} cage. Introduction of other isomers produces even poorer agreement with the data.

Figure 4 also shows the relative orientations of the three different Sc_3 subunits. Significantly, all three orientations of the Sc_3N group have analogous dispositions and dimensions with regard to the three different orientations of the C_{78} cage. Thus the threefold axis of the major orientation of the C_{78} cage makes an angle of 5.9° with the normal to the Sc1–Sc2–Sc3 plane, while the threefold axes of the C_{78} cages with 0.15

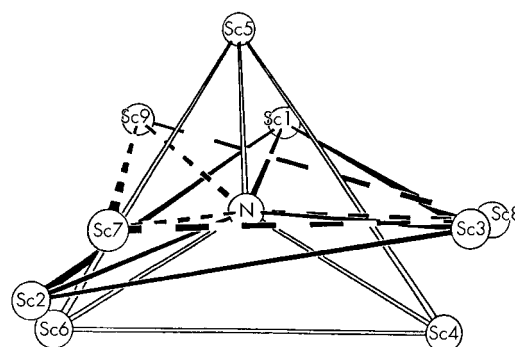
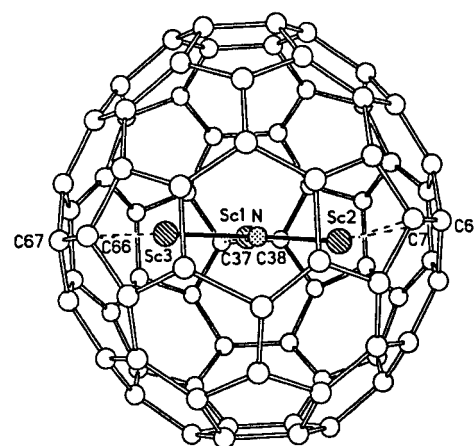
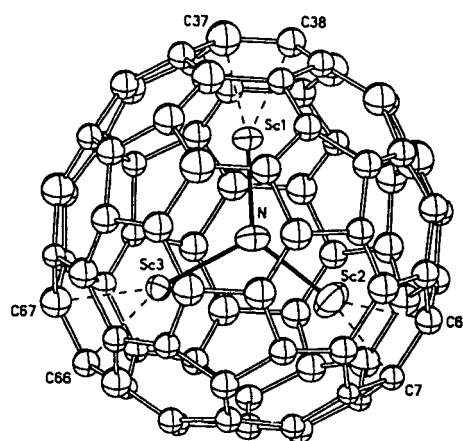


Figure 4. Two orthogonal views of the major form (0.25 site occupancy) of the $\text{Sc}_3\text{N}@C_{78}$ molecule in **1**, and a digram showing the relative orientations of the three different triangular Sc_3 units.

and 0.10 occupancy make angles of 9.6 and 9.9°, respectively with the normal to the Sc4–Sc5–Sc6 and Sc7–Sc8–Sc9 plane, respectively. It is particularly important to note that in each of these orientations the Sc_3N portion lies near the horizontal mirror plane of the C_{78} cage, and each scandium ion is situated over two carbon atoms at [6,6] ring junctions within pyracylene patches of the cage. Such sites are completely analogous

to the sites where metal atoms coordinate on the outside of fullerenes.^[15, 16] This orientation differs from that seen in $\text{ErSc}_2\text{N@C}_{80}$ and $\text{Sc}_3\text{N@C}_{80}$ where the metal atoms are located closest to individual carbon atoms of the icosahedral C_{80} cage.^[17] However, the C_{80} cage with I_h symmetry lacks any pyracylene patches, and the Sc–C interactions seen in $\text{Sc}_3\text{N@C}_{78}$ are impossible for this C_{80} cage. Consequently, $\text{Sc}_3\text{N@C}_{78}$, with the metal ions centered above [6,6] ring junctions within pyracylene patches, provides a better paradigm for metal ion/fullerene interactions than does $\text{Sc}_3\text{N@C}_{80}$.

After completion of the X-ray crystallographic analysis, the 125.78 MHz ^{13}C NMR spectrum of $\text{Sc}_3\text{N@C}_{78}$ was obtained in $\text{CS}_2/10\% [\text{D}_6]\text{acetone}$ (9:1) with $[\text{Cr}(\text{acac})_3]$ (acac = acetylacetonate anion) as a relaxation reagent. As expected for a cage with D_{3h} symmetry, eight lines (three with half intensity) were observed at $\delta = 155.60$ (1), 151.23 (0.5), 150.50 (1), 143.16 (0.5), 142.48 (1), 135.34 (1), 133.84 (0.5), 132.97 (1) (relative intensity).

With the knowledge that $\text{Sc}_3\text{N@C}_{78}$ has a C_{78} cage with D_{3h} symmetry, it is now clear that the TNT process generates carbon-cage isomers in each of the three new products— $\text{Sc}_3\text{N@C}_{80}$, $\text{Sc}_3\text{N@C}_{68}$, and $\text{Sc}_3\text{N@C}_{78}$ —that are different from the isomers of the corresponding empty cage fullerenes. Thus $\text{Sc}_3\text{N@C}_{80}$ exists with an I_h cage, whereas empty C_{80} has been found to exist as the D_2 and D_{5d} isomers;^[18, 19] $\text{Sc}_3\text{N@C}_{78}$ has a D_{3h} cage, while empty C_{78} has been isolated as the D_3 and two C_{2v} isomers; and finally although $\text{Sc}_3\text{N@C}_{68}$ exists, no empty cage C_{68} is formed in the conventional fullerene preparations.^[20]

Experimental Section

Cored graphite rods (6-mm diameter) were filled with CoO (180 mg) and a mixture of Sc_2O_3 and graphite powder (4/96 w/w). These rods were vaporized in a Krätschmer–Huffman electric-arc generator under a dynamic atmosphere of He/N_2 (1250/20 mL min^{−1}). The resulting soot from four graphite rods was extracted with cold CS_2 to yield a soluble extract (200 mg) of fullerenes and endohedral metallofullerenes. After chromatographic isolation, 1–2 mg (0.5–1% yield of soluble extract) of purified $\text{Sc}_3\text{N@C}_{78}$ was obtained with an overall yield from the total available carbon (graphitic powder and rods) of about 0.2%.

Crystals of **1** were obtained by layering a green solution of about 0.5 mg of $\text{Sc}_3\text{N@C}_{78}$ in 0.5 mL of benzene over a red solution of 2.5 mg of $[\text{Co}^{\text{II}}(\text{oep})]$ in 1.5 mL of chloroform. The two solutions were allowed to diffuse together over five days and black crystals gradually formed.

Crystal data for **1**: black parallelepiped, $0.08 \times 0.08 \times 0.05 \text{ mm}^3$, monoclinic, space group $C2/m$, $a = 25.124(2)$, $b = 14.9400(13)$, $c = 19.533(2) \text{ \AA}$, $\beta = 93.720(2)^\circ$, $V = 7316.3(11) \text{ \AA}^3$, $\lambda = 0.77490 \text{ \AA}$, $Z = 4$, $\rho_{\text{calcd}} = 1.662 \text{ Mg m}^{-3}$; $\mu(16 \text{ KeV}) = 2.16 \text{ mm}^{-1}$; ω scans, $2\theta_{\text{max}} = 61.6^\circ$; $T = 110(2) \text{ K}$; 41 718 reflexes collected; 7058 independent ($R_{\text{int}} = 0.056$) included in the refinement; min/max transmission = 0.85/0.92; Patterson and difference Fourier methods solution (SHELXS-97, Sheldrick, 1990); full-matrix least squares based on F^2 (SHELXL-97; Sheldrick, 1998); $R = 0.1175$, $wR = 0.3026$ for all data; conventional $R1 = 0.1107$ computed for 7058 observed data ($>2\sigma(I)$) with 27 restraints and 404 parameters. The data were collected at the Stanford Synchrotron Radiation Laboratory (SSRL), which is funded by the U.S. Department of Energy and the National Institute of Health. The diffractometer employed a Huber Kappa goniometer and Area Detector Systems Corp 2×2 matrix Quantum-4 CCD detector. The monochromator was a double-crystal “pin-post” type. Two runs were merged and scaled. The first run used $0.5^\circ \phi$ scans of 1 s exposure at a detector distance of 80 mm. The second run used 2 s exposures and a 70 mm distance. The fullerene molecule was refined as a rigid group in three different orientations by using idealized coordinates. Crystallographic data (exclud-

ing structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-148633. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

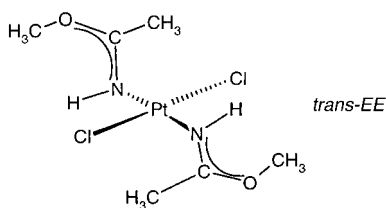
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Antitumor *trans* Platinum Complexes can Form Cross-Links with Adjacent Purine Groups**

Yangzhong Liu, Concetta Pacifico, Giovanni Natile, and Einar Sletten*

The structure–activity relationship behind the high efficacy of *cis*-diamminedichloroplatinum(II) (*cis*-DDP) in the treatment of cancers is still not fully understood (for recent reviews see reference [1]). There is a general consensus on the important role played by cisplatin in forming intrastrand (N7,N7) cross-links between adjacent purine bases. The clinically ineffective *trans* isomer cannot form these types of adducts. However, it has been shown recently that several analogues of *trans*-DDP can exhibit antitumor activity comparable to that of *cis*-DDP.^[2–5] Of particular interest is a group of iminoether derivatives with the formula *trans*-[PtCl₂(iminoether)₂] which was shown to be endowed with significant antitumor activity in vivo.^[3–6] Surprisingly, these compounds were much more cytotoxic than their *cis* isomers towards tumor cells.^[2] The major DNA lesion formed by such iminoether compounds occurs through the formation of a monoadduct with the N7 nitrogen atom of a purine base. A detailed HPLC and NMR spectroscopic analysis of a DNA duplex consisting of 5'-d(CCTCG*CTCTC) and its complement 5'-d(GAGAGC-GAGG) platinated by *trans*-[PtCl₂{(*E*)-HN=C(OMe)Me}₂] (*trans*-EE) has recently been reported.^[7]



We have now characterized several adducts of *trans*-EE with the ribonucleotide r(ApG) by high-pressure liquid chromatography (HPLC) as well as by ¹H and ¹⁵N NMR spectroscopy. Small fractions of the 1:1 reaction mixture of *trans*-EE and ApG were analyzed by HPLC at several time

intervals. The distribution of the species is shown for two different time periods in Figure 1. Initially, one major species (**M1**) formed which attains a maximum concentration of 70 % of the total products after about 8 h. This adduct is then transformed into two new species, **M2** and **M3**, which reach a steady-state equilibrium after about three weeks with a ratio of **M2**:**M3** of about 2:1.

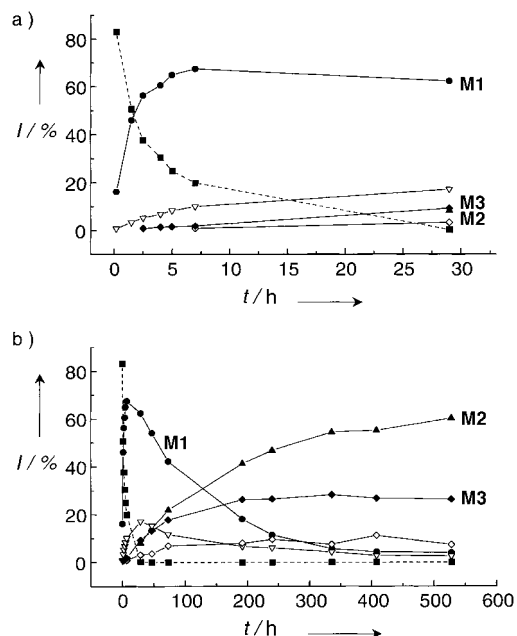


Figure 1. Distribution of the species in the reaction mixture for the platination of r(ApG) with *trans*-EE over 0–30 h (a) and 0–3 weeks (b).

Our previous work on the reaction of *trans*-EE with GMP and AMP shows that platinum binds to the N7 position to form monoadducts which are gradually transformed to diadducts in the presence of excess mononucleotides.^[8] The reaction with GMP is much faster (*t*_{1/2} = 3.5 h) than with AMP (*t*_{1/2} = 23 h). The adduct **M1** is formed relatively fast (*t*_{1/2} = 1.6 h) in the reaction between *trans*-EE and r(ApG), and is subsequently converted into **M2** within days (*t*_{1/2} = 101 h). **M1** is characterized as a monochloro adduct at G-N7; a downfield shift of the G-H8 resonance by 0.45 ppm is in accord with platination at N7. The two minor components probably represent the solvated G-N7 and A-N7 monoadducts (the time-dependent HPLC patterns for this latter adduct and for **M1** are similar to those observed for the solvolysis of the monoadducts with AMP and GMP, respectively).^[8]

The NMR spectrum of **M2** shows two unexpected features for the adenosine residue: an extreme downfield shift (3.68 ppm) for the anomeric proton A-H1' to 9.55 ppm and a large downfield shift (0.82 ppm) of the aromatic proton A-H2 to 8.85 ppm (Figure 2). In addition, most of the other sugar protons on the adenosine residue exhibit significant downfield shifts. The assignments of these chemical shifts are based on COSY and ROESY spectra and also by comparison with the chemical shifts of free r(ApG), both in the present study and from that carried out by van Hemelryck et al.^[9] (see Supporting Information). The assignments of A-H2 and A-H8 were also confirmed by measuring the *T*₁ relaxation times.

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

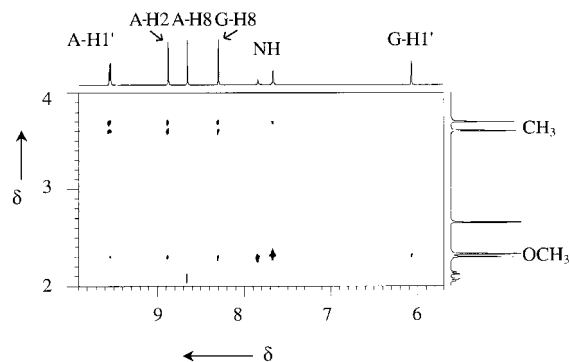


Figure 2. A section of the ROESY spectrum of adduct **M2** in D₂O (δ values are referenced to $\delta(\text{HDO})=4.952$). A total of 2048 complex points in t_2 were collected for each of the 256 t_1 increments, and 72 transients were averaged for each increment. The iminoether NH signal is slowly exchanged with D₂O during one day at 280 K.

The plots of chemical shifts versus pH (Figure 3) show no significant changes for the A-H2 and A-H8 protons over the entire pH range (1–11). The pK_a value for a free A-N1 proton is normally found around 3.5 and 1.2–1.5 for an unplatinated

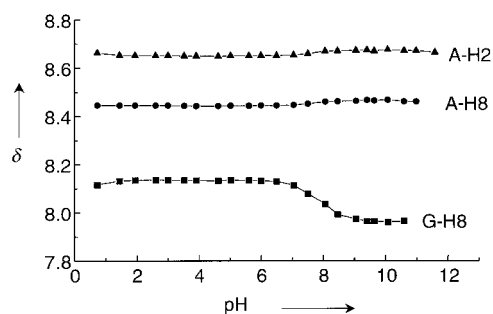


Figure 3. ¹H NMR chemical shifts versus pH for A-H2, A-H8, and G-H8 in adduct **M2**.

and N7-platinated adenine group, respectively. The absence of a shift change in this region may indicate either platination at A-N1 or, alternatively, platination at A-N3; the latter would produce a pK_a shift for A-N1 outside the pH range explored. The pK_a values estimated for N7 and N1 in N3-platinated N6,N6,N9-trimethyladenine were 0.3 and –1.2, respectively.^[10] Therefore, platination at A-N3 could account for both the titration experiment and the very large downfield shifts of A-H1' and A-H2 since they would come right inside the deshielding cone of the platinum center. The deshielding effect of the platinum center could also account for the downfield shift of most of the sugar protons on the adenosine unit.

M2 also exhibits a downfield shift of 0.45 ppm for the G-H8 proton, which supports the coordination of platinum at G-N7. The plot of the G-H8 signal against pH (Figure 3) shows an inflection point at pH 7.5 which corresponds to N1 (de)protonation of a platinated G-N7 residue. In the adduct of *cis*-DDP with r(ApG), where platinum coordinates at A-N7 and G-N7, the pK_a value measured for G-N1 was 7.8,^[9] which is thus in good agreement with our results.

For stereochemical reasons *trans* Pt compounds are unable to coordinate to two sites simultaneously if they involve either

A-N7/G-N7 or A-N1/G-N7. Consequently, if G-N7 is one of the binding sites the second binding site must be at A-N3. Although this model might appear rather unusual (considering that N1 is appreciably more basic than N3), support is also provided by the natural abundance 2D [¹H,¹⁵N] HMBC NMR spectra (see Supporting Information), which show that the resonances for G-N7 and A-N3 are shifted upfield by 99 and 83 ppm, respectively, while the other nitrogen atoms exhibit only minor downfield shifts. These nitrogen shifts compare nicely with the platinum-induced shifts of GMP and AMP adducts.^[8]

The dicoordination model was optimized by energy-minimization calculations (BIOSYM)^[11] using distance constraints obtained from the ROESY spectra. The *trans-EE* ligand was initially fixed in the conformation determined by an X-ray structure analysis.^[12] In the final calculation only the platinum and the four nitrogen atoms were fixed in a square-planar arrangement. The resultant geometry of the structure was in qualitative agreement with the experimental data (Figure 4).

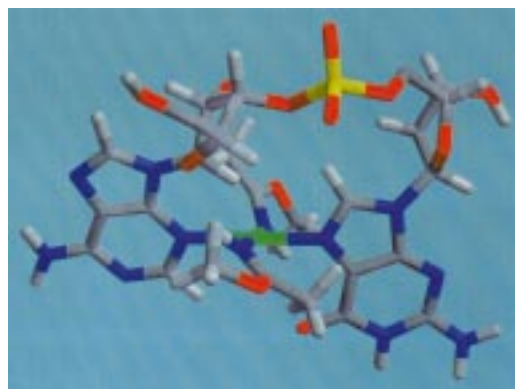


Figure 4. Energy-minimized structure of the *trans-EE*/r(ApG)(N3,N7) chelate.

In this model A-H1' is located close to the platinum center (2.29 Å), which explains the very large (3.68 ppm) metal-induced downfield shift resulting from the paramagnetic anisotropy of platinum. Large downfield shifts are typical for protons at a pseudoaxial position above the platinum center in a square-planar complex.^[13] A short Pt...H distance of 2.53 Å was observed in the crystal structure of *trans*-[PtCl₂(benzoquinoline)(PET₃)] which corresponded to the downfield shift (in solution) of 2.75 ppm for the signal in the NMR spectrum.^[13]

The NMR spectra of **M3**, the second major component formed at long reaction times, are distinctly different from those obtained for **M1** and **M2**. The integration of the 1D spectra indicates that the composition of **M3** corresponds to a *trans-EE*:r(ApG) ratio of 2:1. Moreover, the A-H8 and G-H8 signals are shifted downfield by 0.83 and 0.70 ppm, respectively, which clearly indicates platination of both residues at N7. Therefore the formation of **M3** can be explained by the presence of a slight excess of the platinum complex in the reaction sample which leads to the formation of a dimetalated r(ApG).

The platination of oligonucleotides by *trans*-DDP has been shown to produce intrastrand 1,3-(N7,N7) cross-links with d(GpTpG),^[14] d(GpCpG),^[15] d(GpApG),^[16] and a 1,3-(N1,N7) cross-link with d(ApGpG).^[17] Monoadducts and interstrand cross-links were mainly formed in the reaction with double-stranded DNA;^[18] *trans*-DDP was considered unable to form 1,2-intrastrand d(GpG) or d(ApG) adducts as a result of its structure.^[17] Thus, the stable adduct **M2** represents a new and unprecedented chelation geometry for a *trans* platinum complex. Although the chelation process is relatively slow, the N3-Pt-N7 structure may be of biological relevance since A-N3 is readily exposed to platination in the minor groove. The involvement of the N3 atom of adenine as an alkylation site^[19] and in the cleavage reaction of hammerhead ribozyme has recently been demonstrated.^[20] This study is presently being extended to other ribo- and deoxy-dinucleotides.

Experimental Section

trans-EE was synthesized according to a literature procedure.^[12] r(ApG) was purchased from Sigma. *trans-EE* (2.3 mg, 5.6 μ mol) was added to 5 mL of a 1 mM solution of r(ApG) (5 μ mol, pH 4.0) at room temperature in the dark. Samples were collected for HPLC detection at various time intervals. Samples were lyophilized and dissolved in D₂O (0.5 mL) and the ROESY NMR spectra (mixing time 300 ms, 3 mm sample, pH 3.9, *T* = 280 K) were recorded on a Bruker DRX 600 instrument. The pH values were measured on a Philips PW 9420 pH meter. HPLC was performed on a Waters 626 LC instrument using Millennium 32 software and a reverse-phase Waters Symmetry C8 column with gradient elution (0–50% methanol in 50 mM NaClO₄ at a flow rate of 0.8 mL min⁻¹).

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Molecular Modulation of Surfactant Aggregation in Water: Effect of the Incorporation of Multiple Headgroups on Micellar Properties**

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Surfactant molecules self-organize in water,^[1] often producing nearly spherical aggregates called micelles in dilute solutions, and lyotropic mesophases at higher concentrations. The polar headgroups of these aggregates lie near the bulk aqueous phase, whereas the hydrocarbon chains extend inwardly to avoid unfavorable water contacts. Electrostatic interactions between the headgroups determine their relative positions and separations in an aggregate. The correlation of the molecular structure of various surfactants with the aggregate type produced upon self-assembly is important as surfactant solutions are useful in a number of household, industrial, and scientific applications.^[2]

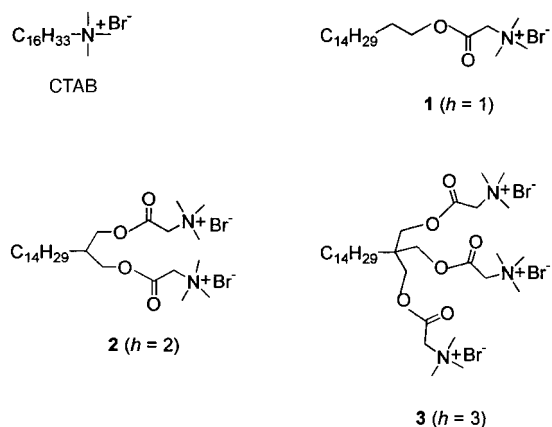
Molecular design of surfactants of widely varying architectures offers an excellent opportunity for tailoring surfactant aggregation behavior and the resulting complex fluid properties. For instance, dimeric or oligomeric surfactants that consist of two or more conventional surfactant units connected at the headgroup by a suitable spacer are attracting attention because of the number of unusual properties that they manifest.^[3]

In ionic micelles, surfactant molecules such as cetyltrimethylammonium bromide (CTAB) also ionize in aqueous solution and the corresponding micelles are aggregates of

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the resulting CTA⁺ ions. However, the ionization is far from complete on a micellar surface. The Br[−] counterions, tend to stay near the CTA⁺ micellar surface. The shape, size, fractional charge of the micelle, and the inter-micellar interaction depend on the distribution and nature of these counterions.^[4]

It was however, not clear whether a surfactant will form micelles, if several charged headgroups are incorporated on one end of a single hydrocarbon chain of the surfactant molecule. This is because with every increase in the number of charges, the micellar surface demands a progressively smaller aggregation number, which is not consistent with the micellar volume that has to be filled. In such a situation does the surfactant behave like a salt, for example NaCl, where the surfactant is fully ionized (as is NaCl into Na⁺ and Cl[−] ions) and there is no aggregation of cations? To address this fundamental question, we have synthesized a novel class of cationic surfactants with multiple headgroups and herein we show for the first time that they indeed form micelles.

The newly designed surfactants **2** and **3** are intriguing, since for a given hydrophobic part, the cationic headgroup charges (h) are increased two or three times over that of the reference surfactant, which bears a single cationic headgroup (**1**, $h = 1$). The critical micelle concentration (cmc) for each surfactant was determined at 25 °C by plotting the values of the pyrene fluorescence intensity ratio I_3/I_1 , against the surfactant concentration.^[5] For each surfactant reproducible breaks were observed indicating the onset of micellization. The cmc values obtained using this procedure were ~1.0 mM (**1**), 3.5 mM (**2**), 3.7 mM (**3**), and the value obtained using the same method for CTAB (0.8 mM) was consistent with the cmc value reported.^[5]

To investigate the aggregate microstructures of these surfactants in water we used small angle neutron scattering (SANS), a noninvasive technique that provides information on colloidal particles of a length of 10–1000 Å. SANS has been used to obtain structural details about complex fluids of diverse origin. These include micellar solutions,^[6a] microemulsions,^[6b] polymers,^[6c] proteins,^[6d] materials,^[6e] and biological samples.^[6f] Since neutrons have an irregular variation of scattering length for various elements, the contrast between the particle and the matrix can be easily varied to enhance the signal. Thus SANS is an ideal technique to obtain information about the micellar shape, size, aggregation number, charge on the micelle, the extent of hydration, and the inter-micelle interaction.^[7, 8] SANS experiments involve measurement of

differential scattering cross section ($d\Sigma/d\Omega$) as a function of wave vector transfer Q .

SANS distributions from micellar solutions of the surfactants CTAB and **1–3** at a fixed surfactant concentration and temperature are shown in Figure 1. All the distributions show

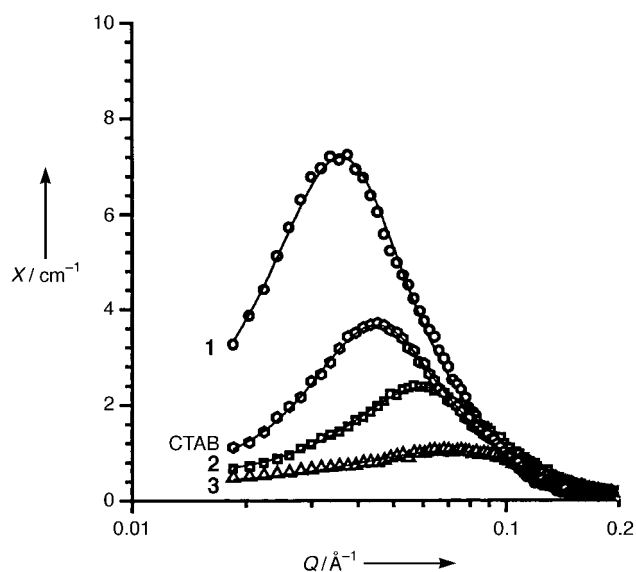


Figure 1. SANS distributions of micellar solutions of CTAB and the newly synthesized surfactants **1–3** at a concentration of 50 mM and 40 °C. Q = wave vector transfer; X = cross section.

well-defined peaks characteristic of suspensions of charged particles.^[6a] The SANS distribution from a suspension of charged particles or a micellar solution is determined by the product of two terms, namely, the intra-particle structure factor $P(Q)$ and the inter-particle structure factor $S(Q)$. $P(Q)$ depends on the shape and size of the particle, $S(Q)$ on the inter-particle distance and the inter-particle interaction potential. The peak in the SANS distribution is the consequence of a corresponding peak in the inter-particle structure factor $S(Q)$. Usually this peak occurs at $Q_m \approx 2\pi/d$, where d is the average distance between micelles and Q_m is the value of Q at the maximum of the peak. Since Q_m was found to vary with the number of headgroups (h), one can conclude that inter-micelle distance and hence the number density (n) of micelles is not the same for the above surfactant solutions even when they have identical surfactant concentrations. This also suggests that the aggregation number (N) (the number of molecules that form a micelle) of the micelles varies with the number of headgroups. The actual value of N was determined by analyzing the data using the method of Hayter and Penfold.^[7] In addition, this analysis provided information about the micellar dimensions and the fractional charge ($\alpha = Z/N$, where Z is charge on the micelle).

These results demonstrate that micelles are indeed formed from all the surfactants tested here irrespective of the number of headgroups (h). The aggregation number (N) decreases with an increase in h . This is understandable as with larger headgroup sizes and enhanced electrostatic repulsion, as in the cases with $h = 2$ and $h = 3$, greater micellar surfaces are

required and fewer surfactant molecules can be accommodated in a single micellar aggregate.

Compared with the surfactant **1** ($h = 1$), CTAB micelles have a considerably lower aggregation number ($N = 135$ vs 244, Table 1) at the same concentration and temperature, even though the CTAB micelles also have a single Me_3N^+ headgroup per hydrocarbon chain. It is possible that the

Table 1. Micellar parameters of the surfactants CTAB and **1–3**.^[a]

Surfactant	$N^{[b]}$	α	Semi-minor axis $b = c$ [Å]	Semi-major axis a [Å]	a/b
1	244	0.08	24.5	66.9	2.73
2	48	0.23	17.3	36.2	2.10
3	20	0.27	14.5	27.3	1.88
CTAB	135	0.14	22.0	37.3	1.70

[a] All the SANS spectra were performed at 40 °C using 50 mm micellar solutions. [b] The aggregation number, N , is calculated from the relation $N = \pi a b^2 / 3 v$ where, a = semi-major axis, b = semi-minor axis and v = volume of the surfactant monomer (Tanford's equation (C. Tanford, *J. Phys. Chem.* **1972**, 76, 3020–3024)).

surfactant **1** is more tightly associated in the micellar aggregate because of the presence of an ester linkage $[-\text{OC}(\text{O})-]$ between the Me_3N^+ headgroups and the hydrocarbon chain. The presence of this linkage facilitates intermonomer association through dipolar interactions. Furthermore since these ester linkages are located near the “Stern-layer” region^[9] of the micelles, strong hydrogen bonding interactions among the surfactant molecules can occur through interfacially associated water molecules.^[10]

The drop in the aggregation number (N) on an increase in the number of headgroups (Table 1) is expected as with each rise in the number of cationic headgroups the charge repulsion between the headgroups becomes more pronounced. To accommodate these unfavorable electrostatic consequences the hydrocarbon chains in the micelles of multiheaded surfactants take up severely bent conformations (Figure 2) leading to the formation of an increasingly “disorganized” collection of surfactant molecules in the resulting micellar aggregate. In such “porous” aggregates, the hydrophobic core of micelles has a more aqueous environment. By comparison, in micelles of surfactants bearing a single charge on the headgroup the hydrocarbon chains are considerably more extended, and the terminal CH_3 group buried deeply in the core. Noteworthy is that at the surfactant concentration of 50 mM, micelles are prolate ellipsoidal ($a \neq b = c$) in all the samples including CTAB. The semi-major axis (a) and the semi-minor axis (b) are given in Table 1; both a and b and the axial ratio a/b decrease when h is increased.

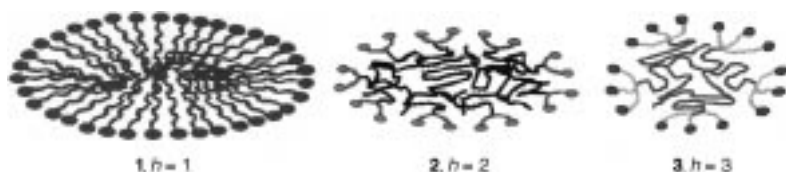


Figure 2. Schematic representation of multiheaded surfactant micelles where chain coiling is required to alleviate inter-surfactant headgroup repulsion within the aggregate.

Fractional charge (α) is a measure of the dissociation of the counterion of surfactant molecules present in the micelle. Analysis of the SANS data (Table 1) gives a fractional charge of 0.08 for the surfactant with single headgroup ($h = 1$). This means that only 8% of the counterions (Br^-) are dissociated from the micelle of this surfactant leaving the remaining 92% bound.

The data in Table 1 also show that α increases with the number of headgroups on the surfactant. This is not surprising if the equilibrium dissociation constant increases linearly with the number of cationic headgroups per surfactant molecule, then one could expect, $\alpha_2 = 2\alpha_1$, and $\alpha_3 = 3\alpha_1$ where α_1 , α_2 , α_3 represent fractional charges on the single-, double-, and triple-headed surfactant respectively. However, from Table 1, we see that $\alpha_2 > 2\alpha_1$, suggesting far greater dissociation of the counterions in the case of micelles of a double-headed surfactant than would be expected merely from doubling the number of headgroups of the single-headed surfactant. Double-headed surfactants require more room at the headgroup level than that needed for the packing of two single-headed surfactants in a micelle. This is because the positive charges located on each of the two heads of **2** tend to stay as far apart as possible as a result of electrostatic repulsion. In addition, with an increase in charge, the headgroup hydration increases facilitating greater ionization.

Although the Me_3N^+ units on the triple-headed surfactant **3** tend to stay as far apart as possible, the intermolecular repulsion between individual surfactants in the micelle increase steeply. As a consequence, the aggregation number of these micelles is considerably lower than that in **2**. To alleviate the headgroup level repulsion and to fill up the micellar volume, the hydrocarbon chains in these micelles take up bent conformations. While increased charge facilitates hydration, the hydrocarbon chain coiling regulates the extent of the increase in the fractional charge (α_3).

Additives such as $\text{KBr}^{[11]}$ (0.1M) or sodium salicylate ($\text{Na-Sal}^{[12a-f]}$ (0.01M) induce pronounced micellar growth of CTAB (0.1M) leading to marked increases in the viscosity of the resulting micellar solutions. This has been attributed to the transition from spherical to rod-like morphology.^[12e] While surfactant **1** also showed similar behavior in the presence of Na-Sal (0.01M) or KBr (0.1M), such changes in viscosity could not be brought about with the micelles of either **2** or **3** even with very high concentrations of the above additives. This prompted us to examine rheological properties of each surfactant solution^[12a-d] in the presence of Na-Sal at a chosen Na-Sal -to-surfactant ratio of 25 mM Na-Sal and 50 mM surfactant (see Experimental Section).

Soon after mixing the samples, CTAB- $\text{Na-Sal}/\text{W}$ or **1**- $\text{Na-Sal}/\text{W}$ (where W = water) developed into thick, viscous masses. Oscillatory shear experiments were conducted at a torque ramp from 0.001 to 100 Pa to find the stress where these materials were in the linear response region. Shear stress of 1.5 Pa and 1.0 Pa was used for solutions of CTAB and **1**, respectively, Figure 3. In both figures, the curves describing G' and G'' cross as the frequency increases, indicating that these materials are more elastic than viscous at higher

frequencies. In Figure 3a, G' reaches a plateau and G'' first has a maximum, then a minimum, and finally increases with increasing frequency. In contrast in Figure 3b, both G' and G'' curves continue to slope upward with increasing frequency.

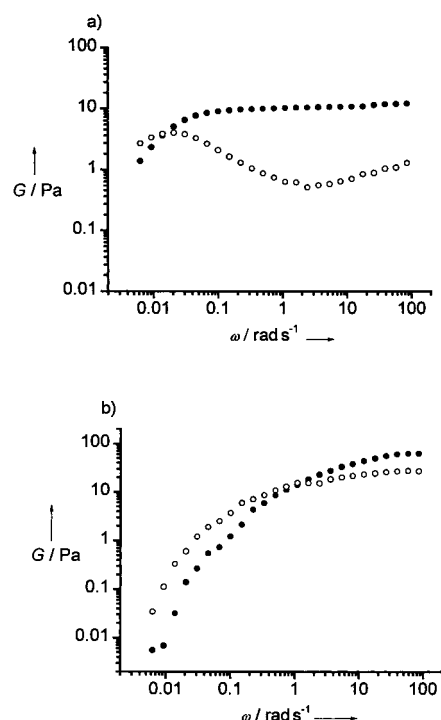


Figure 3. The dependence of storage moduli, G' (●) and loss moduli, G'' (○) as a function of shear rate for a solution containing 50 mM surfactant and 25 mM Na-Sal. a) CTAB; and b) **1** ($h=1$).

In the case of mixtures of solutions containing Na-Sal and either **2** or **3** which remained as *free-flowing* solutions, the oscillatory shear experiments were attempted at several different stress values from 0.003 Pa to 10 Pa. However, it was not possible to perform oscillatory shear experiments with **2**-Na-Sal/W or **3**-Na-Sal/W as the viscosity of these samples did not change significantly from that of the surfactant solutions alone. This observation indicates that these samples were inelastic although they might be a little more viscous than water and suggests that there is no significant change in the micellar structure of **2** and **3** in the presence of Na-Sal. This result clearly shows that the number of headgroups on the surfactant molecule could significantly modulate the organic-salt-induced micellar growth.

In summary we have observed some unusual effects associated with the micellar aggregation properties of surfactants with two or three cationic headgroups. We find for the first time that the hydrocarbon chains in the micelles from surfactants bearing multicharged headgroups are highly folded. The maximum number of charged headgroups that can be attached onto a single hydrocarbon chain so that micelle formation is still feasible remains to be examined. The counterion distributions around the micelles from surfactants with multiple headgroups also need to be elucidated.

Experimental Section

Synthesis: The compounds **1** ($h=1$), **2** ($h=2$), and **3** ($h=3$) were synthesized by esterification of 1-hexadecanol, 2-hydroxymethyl-hexadecanol or 2,2-dihydroxymethyl-hexadecanol, respectively, with 1.1, 2.2, and 3.3 equivalents of 2-bromoacetyl bromide in the presence of Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) in $\text{CH}_2\text{Cl}_2/\text{THF}$ (1/1). After purification, the respective bromoacetylated products were quaternized with NMe_3 in dry acetone in screw-top pressure tube. Pure surfactants **1** (yield 98%), and **2** (87%) were obtained upon repeated recrystallizations from CHCl_3/n -hexane, and $\text{CHCl}_3/\text{EtOAc}$ respectively. **3** (65%) was purified by repetitive precipitation from $\text{CHCl}_3/\text{EtOAc}/n$ -hexane mixture. **2** and **3** were found to be extremely hygroscopic.

Selected spectroscopic and analytical data for the new surfactants: **1:** IR (KBr): $\tilde{\nu} = 1751 \text{ cm}^{-1}$ (C=O); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.88$ (t, 3H, CH_3), 1.25 (s, 26H, $13 \times \text{CH}_2$), 1.63–1.70 (m, 2H, $\text{CH}_2\text{CH}_2\text{O}$), 3.67 (s, 9H, $3 \times \text{N}^+\text{CH}_3$), 4.18 (t, 2H, CH_2O), 4.99 (s, 2H, CH_2N^+); ESI-MS (HP1100LC-MSD): $[M^+]$ ($\text{C}_{21}\text{H}_{44}\text{NO}_2$) $^+$: calcd: 342.3, found: 342.2; elemental analysis (%) for $\text{C}_{21}\text{H}_{44}\text{NO}_2\text{Br}$ calcd: C 59.7, H 10.5, N 3.31; found: C 59.54, H 10.63, N 2.95. **2:** IR (KBr): $\tilde{\nu} = 1749 \text{ cm}^{-1}$ (C=O); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.88$ (t, 3H, CH_3), 1.26 (s, 26H, $13 \times \text{CH}_2$), 2.12–2.18 (m, 1H, CHCH_2O), 3.62 (s, 18H, $6 \times \text{N}^+\text{CH}_3$), 4.03 (dd, 2H, $2 \times \text{CHCH}_2\text{H}_2\text{O}$), 4.44 (dd, 2H, $2 \times \text{CHCH}_2\text{H}_2\text{O}$), 5.50 (s, 4H, $2 \times \text{CH}_2\text{N}^+$); ESI-MS (HP1100LC-MSD): $[M^{2+}]$ ($\text{C}_{27}\text{H}_{56}\text{N}_2\text{O}_4$) $^{2+}$ Br^- (78.91): calcd: 551.3, found: 551.3, $[M^{2+}]$ ($\text{C}_{27}\text{H}_{56}\text{N}_2\text{O}_4$) $^{2+}$ Br^- (80.91): calcd: 553.3, found: 553.4, $[M^{2+}]/2$: calcd: 236.2, found: 236.1; elemental analysis (%) for $\text{C}_{27}\text{H}_{56}\text{N}_2\text{O}_4 \cdot \text{Br}_2 \cdot \text{H}_2\text{O}$: calcd: C 49.85, H 8.99, N 4.3; found: C 49.53, H 8.97, N 3.9. **3:** IR (KBr): $\tilde{\nu} = 1751 \text{ cm}^{-1}$ (C=O); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.88$ (t, 3H, CH_3), 1.26 (s, 26H, $13 \times \text{CH}_2$), 3.36 (s, 27H, $9 \times \text{N}^+\text{CH}_3$), 4.25 (s, 6H, $3 \times \text{CH}_2\text{O}$), 5.57 (s, 6H, $3 \times \text{CH}_2\text{N}^+$); ESI-MS (HP1100LC-MSD): $[M^{3+}]$ ($\text{C}_{33}\text{H}_{68}\text{N}_3\text{O}_6$) $^{3+}$ 2Br^- (78.91): calcd: 760.3, found: 760.3, $[M^{3+}]$ ($\text{C}_{33}\text{H}_{68}\text{N}_3\text{O}_6$) $^{3+}$ Br^- (80.91): calcd: 762.3, found: 762.4, $[M^{3+}]/2$ Br^- (80.91): calcd: 764.3, found: 764.3, $[M^{3+}]/3$ Br^- (80.91): calcd: 340.7, found: 340.7, $[M^{3+}]/2$ Br^- (80.91): calcd: 341.7, found: 341.6, $M^{3+}/3$: calcd: 200.8, found: 200.9; elemental analysis (%) for $\text{C}_{33}\text{H}_{68}\text{N}_3\text{O}_6 \cdot \text{Br}_3 \cdot \text{H}_2\text{O}$: calcd: C 46.05, H 8.2, N 4.88; found: C 45.67, H 8.05, N 4.43.

CMC Measurements: In a Hitachi model F-4500 fluorescence spectrometer, steady-state fluorescence emission ($\lambda_{\text{ex}} = 310 \text{ nm}$) because of pyrene doped in micellar solutions was measured at 25°C . The cmc values were determined from the plots of the concentrations of the respective surfactant versus the ratio (I_3/I_1) of the intensities of the third (I_3) and the first (I_1) vibronic peaks in the emission spectra.

SANS Measurements: Neutron-scattering experiments were performed at 40°C on a 1.85 m (sample to detector distance) SANS spectrometer equipped with a linear position-sensitive detector, (LPSD) at the Dhruva reactor, Trombay, India. To provide a good contrast between the micelle and the solvent, surfactant solutions (50 mM) were prepared in D_2O . The spectrometer made use of a BeO filter as the monochromator. The mean wavelength (λ) of the incident neutron beam is $5.2 \text{ \AA}$. The wave vector transfer Q ($=4\pi\sin\theta/\lambda$, where 2θ is the scattering angle) in SANS spectrometers is small, typically in the range 0.001 to $1.0 \text{ \AA}^{-1}$. The Q range of the instrument is 0.018 – $0.32 \text{ \AA}^{-1}$. To obtain low Q values, the SANS instrument used large wavelength ($\sim 5 \text{ \AA}$) neutrons and small scattering angles (~ 0.5 – 10°). The data were corrected for detector background sensitivity, empty cell scattering and sample transmission factors. The D_2O intensity was subtracted from that of the sample. The corrected intensities were normalized to absolute cross-section units. The experimental points were fitted using nonlinear least-squares routine. The SANS distributions have been analyzed by Hayter-Penfold method.^[7] The original model, which was valid for spherical micelles, has subsequently been modified for other aggregation shapes.

Rheological Measurements: The sample solutions for rheological measurements were mixtures of aqueous solutions of surfactant and sodium salicylate (Na-Sal). Solutions were prepared by adding water to weighed quantities of the respective surfactant and Na-Sal and the mixture was heated $>50^\circ\text{C}$ to ensure complete dissolution. The final concentrations of surfactant and Na-Sal were 50 mM and 25 mM respectively. All the solutions were left standing for 1 day at ambient temperature to reach equilibrium. The rheological properties of the above mixtures were measured with a Rheolyst TA Instrument (model AR1000, cone and plate geometry with a

truncation gap of 53 μm). The radius of the cone was 20 mm, and the angle between the cone and plate was 2°. The experiments were performed at 35 °C for the single-headed surfactant **1** and at 25 °C for CTAB, **2**, and **3**. Both the steady shear (flow-step) and oscillatory shear (stress control) measurements were performed and the measurements were taken over a frequency sweep range of 0.001 to 100 s⁻¹. The rheometer has a built-in computer which converts the torque measurements into either G' (the storage modulus) and G'' (the loss modulus) in oscillatory shear experiments or viscosity in flow-step measurements.

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R^{*}₄Tl₃Cl and R^{*}₆Tl₆Cl₂ (R^{*} = Si*t*Bu₃)—The First Compounds with Larger Clusters Containing Covalently Linked Thallium Atoms**

Nils Wiberg,* Thomas Blank, Hans-Wolfram Lerner, Dieter Fenske und Gerald Linti

Dedicated to Professor Hansgeorg Schnöckel on the occasion of his 60th birthday

Many compounds of the compositions TlR₃ and TlR (R = inorganic, organic group) exist with thallium in the oxidation states +III and +I^[1] (the Tl–R bonds in the former compounds are more covalent in nature, those in the latter more electrovalent), whereas very few compounds of the composition TlR₂ with thallium in the oxidation state +II are known to date. They form dimers R₂Tl–TlR₂ with a covalent Tl–Tl bond (Tl–Tl 2.914 (R = Si(SiMe₃)₃),^[2] 2.966 (R = Si*t*Bu₃),^[3] 2.881 Å (R = Si*t*Bu₂Ph)^[4]). A few Tl^I compounds also have Tl–Tl bonds; however, as weak interactions with Tl–Tl distances >3.3 Å these vary significantly from the strong interactions in the three reported dithallanes with Tl–Tl distances <3.0 Å (e.g. (PhCH₂)₅C₅Tl⋯TlC₅(CH₂Ph)₅: Tl–Tl 3.632 Å;^[5] [(Me₃Si)₃CTl]₄: Tl–Tl 3.322 and 3.627 Å;^[6] {MeSi[N(Tl)*t*Bu]₃}₂ has a Tl–Tl distance in the intermediate range (3.146 Å) and in addition several very weak Tl–Tl interactions;^[7] in {MeC[CH₂N(Tl)SiMe₃]₃}₂ and other Tl^I amides Tl–Tl interactions exclusively occur with very large Tl–Tl distances (>3.6 Å)^[8]). Thallium cluster compounds containing more than two covalently linked thallium atoms were hitherto unknown.

We obtained compounds of this type, namely the trithallane R^{*}₄Tl₃Cl (**1**) and the hexathallane R^{*}₆Tl₆Cl₂ (**2**), in the attempt to synthesize sterically overloaded disupersilylthallium chloride R^{*}₂TlCl (R^{*} = supersilyl = Si*t*Bu₃) analogously to the preparation of R^{*}₂ECl (E = Al, Ga, In)^[9] from the trihalide ECl₃ and two molar equivalents of supersilylsodium NaR^{*} in tetrahydrofuran (THF). Treatment of TlCl₃ in THF at –78 °C with NaR^{*} in the molar ratio 1:2 leads to the slow (several hours) formation of a red-brown reaction solution as well as a

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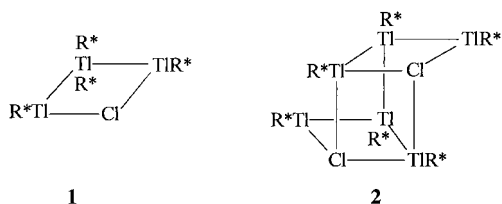
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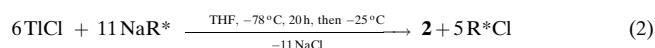
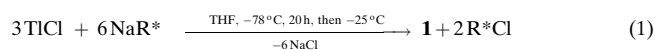
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black-brown precipitate. From the THF solution at -25°C or from a toluene solution obtained from extraction of the precipitate with toluene (-78°C) and likewise kept at -25°C , the compounds **1** and **2**, respectively (at least **1** forms in the THF solution very slowly at -25°C), crystallized in the course of several months. The nature of fraction of the precipitate which remained after extraction with toluene has still to be clarified (oligomeric TIR^* ?).

The red trithallane **1** and the black hexathallane **2** probably form according to the Equations (1) and (2). Both Tl cluster



compounds are air-, moisture-, and light-sensitive and thermolyze in C_6D_6 at room temperature slowly and very slowly, respectively, leading to the formation of R^*Cl (dissolved in C_6D_6) and a black precipitate (oligomeric TIR^* ?), which at 100°C in the presence of C_6D_6 slowly transforms into elemental thallium and deuterated supersilane R^*D (supersilyl radicals probably form initially, which dimerize quickly and reversibly and stabilize slowly and irreversibly on addition of hydrogen: $2\text{R}^*\cdot \rightleftharpoons (\text{R}^*)_2$; $\text{R}^*\cdot + \text{C}_6\text{D}_6 \rightarrow \text{R}^*\text{D} + \text{C}_6\text{D}_5\cdot$).^[10]

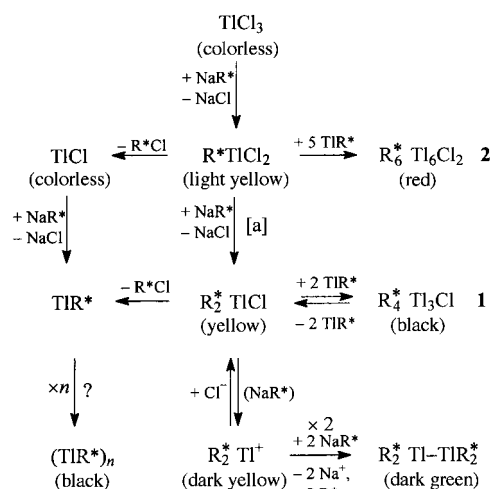
The mechanism of the reactions of TlCl_3 and NaR^* leading to **1** and **2** is still not completely clear. Possibly, the supersilation of TlCl_3 initially leads to the compounds R^*TlCl_2 and R_2^*TlCl (Scheme 1), which through R^*Cl elimination decompose into TlCl and TIR^* , respectively. The TIR^*

molecules formed directly in this way or indirectly after the supersilation of TlCl oligomerize or insert into the $\text{Tl}-\text{Cl}$ bonds of R^*TlCl_2 and R_2^*TlCl five and two times, respectively.

Studies on the reaction of TlCl_3 with varying amounts NaR^* as well as on the thermolysis of the intermediate products formed hereby support these hypotheses for the formation of **1** and **2**. Thus, the reaction of TlCl_3 with the equimolar amount of NaR^* in THF at -78°C indeed leads to a solution of light yellow dichlorosupersilylthallane R^*TlCl_2 .^[11] With two molar equivalents of NaR^* in THF at low temperatures it is not chlorodisupersilylthallane R_2^*TlCl that is formed but—as described—the trithallane **1** and the hexathallane **2** (rapid heating of a solution of $\text{TlCl}_3/2\text{NaR}^*$ cooled to -78°C in THF to room temperature leads exclusively to R^*Cl and a black precipitate). The yellow thallane R_2^*TlCl was obtained finally after many failed attempts (e.g. $\text{TlCl}_3 + \text{NaR}^*$, MgR_2^* , ZnR_2^* ; $\text{Ti}_2\text{R}_4^* + \text{HCl}$, Ph_3CCl) by addition of Me_3SiCl to a solution of TlCl_3 and three molar equivalents of NaR^* in THF at -78°C ; Me_3SiR^* was formed as a by-product.^[12] On heating the corresponding solution without adding Me_3SiCl , dark green tetrasupersilyldithallane Ti_2R_4^* is formed, which is also accessible from TlBr and NaR^* .^[3] Possibly, in the present case a compound is formed initially that contains disupersilylthallonium R_2^*Ti^+ (counterion R^*NaCl^- ?; see Scheme 1). The cations could react with Cl^- donors such as Me_3SiCl to give R_2^*TlCl , whereas in the absence of Me_3SiCl they would be slowly reduced by excessive NaR^* to give Ti_2R_4^* (Scheme 1). The dark yellow cation R_2^*Ti^+ also forms from R_2^*TlCl on addition of AlCl_3 in CD_2Cl_2 .^[13]

Whereas the thermal decomposition of the thallane R^*TlCl_2 dissolved in THF into TIR^* and TlCl (Scheme 1) already occurs at -50°C , the thallane R_2^*TlCl decomposes very slowly (over a period of many days) in C_6D_6 even at room temperature via **1** to give R^*Cl and the above-mentioned black precipitate (oligomeric TIR^* ?), which at higher temperatures—as already mentioned—is transformed into Tl and R^*D . Thus, TIR^* , which is formed slowly thermolytically from R_2^*TlCl , could in statu nascendi react with R_2^*TlCl to give trithallane **1**, which, in turn, would decompose even slower with the release of supersilylthallium, which has a tendency to oligomerize. Since R_2^*TlCl does not occur in the solutions of $\text{TlCl}_3/2\text{NaR}^*$ in THF, which at low temperatures lead to **1** and **2**, another compound (which still has to be identified; $\text{R}^*\text{ClTi}-\text{TlClR}^*$?) derived from R^*TlCl_2 and NaR^* must be responsible for the formation of **1** and **2**.

Figures 1 and 2 show the structures of the molecules **1** and **2** in the crystal.^[14] The central structural element of the trithallane **1** is a planar Tl_3Cl four-membered ring (sum of angles 359.91°) with a $\text{R}^*\text{Tl}-\text{R}_2^*\text{Tl}-\text{R}^*\text{Tl}$ chain ($\text{Tl}-\text{Tl}$ 2.92 Å (av)). The Si_2Tl plane of the R_2^*Tl unit is almost perpendicular (89°) to the Tl_3Cl plane. The hexathallane **2** contains two Tl_3Cl four-membered rings with $\text{R}^*\text{Tl}-\text{R}^*\text{Tl}-\text{R}^*\text{Tl}$ chains ($\text{Tl}-\text{Tl}$ 2.93 Å (av)), which are linked with each other through the central Tl atoms ($\text{Tl}-\text{Tl}$ 2.85 Å). As a result of additional $\text{Tl}-\text{Cl}$ bonds between the Tl_3Cl four-membered rings, these are, in contrast to those in **1**, no longer planar (sum of angles 344.3° (av); dihedral angle $\text{Tl}-\text{Tl}-\text{Cl}-\text{Tl}$ in the rings 135.8° (av)).



Scheme 1. The reaction of TlCl_3 with NaR^* . [a] This reaction proceeds via an unidentified compound.

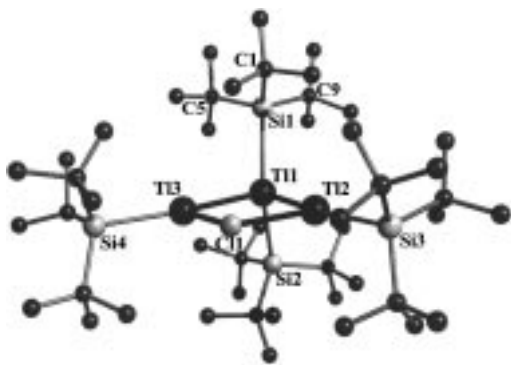


Figure 1. Molecular structure of **1** in the crystal (SCHAKAL plot; atoms with arbitrary radii; the hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: Tl1–Tl2 2.9093(7), Tl1–Tl3 2.9262(8), Tl2–Cl1 2.808(3), Tl3–Cl1 2.803(3), Tl1–Si1 2.641(3), Tl1–Si2 2.645(3), Tl2–Si3 2.678(3), Tl3–Si4 2.696(3), Si–C 1.944 (av); Si1–Tl1–Si2 143.9(1), Si1–Tl1–Tl2 105.55(7), Si2–Tl1–Tl2 101.04(6), Si1–Tl1–Tl3 103.51(9), Si2–Tl1–Tl3 102.32(7), Tl2–Tl1–Tl3 85.85(3), Si3–Tl2–Cl1 101.24(11), Si3–Tl2–Tl1 166.70(9), Cl1–Tl2–Tl1 92.06(7), Si4–Tl3–Cl1 101.60(10), Si4–Tl3–Tl1 166.58(7), Cl1–Tl3–Tl1 91.82(7), C5–Si1–C9 111.5(10), C–Si–C 110.9 (av), C–Si–Tl 107.6 (av).

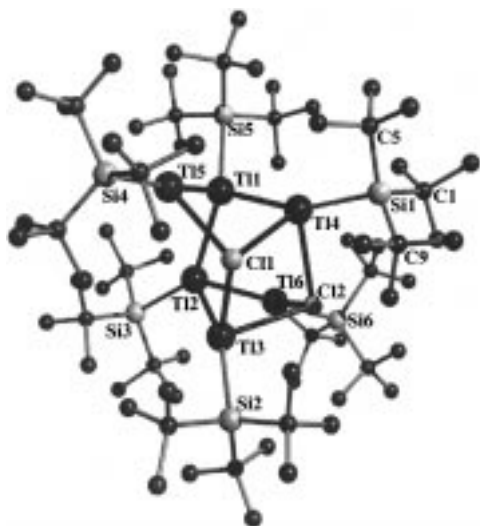


Figure 2. Molecular structure of **2** in the crystal (SCHAKAL plot; atoms with arbitrary radii; the hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°] of one of the two almost identical $R_3^+Ti_3Cl$ units and its linkage with the other unit: Tl1–Tl2 2.854(2), Tl1–Tl5 2.908(2), Tl1–Tl4 2.944(2), Tl4–Cl2 2.918(6), Tl4–Cl1 2.984(7), Tl5–Cl1 2.866(7), Tl1–Si5 2.630(7), Tl4–Si1 2.715(6), Tl5–Si4 2.680(8), Si–C 1.951 (av); Si5–Tl1–Tl2 137.1(2), Si5–Tl1–Tl5 112.4(2), Tl2–Tl1–Tl5 94.83(5), Si5–Tl1–Tl4 113.8(2), Tl2–Tl1–Tl4 100.89(5), Tl5–Tl1–Tl4 84.11(4), Si1–Tl4–Cl2 99.7(2), Si1–Tl4–Tl1 159.6(2), Cl2–Tl4–Tl1 99.1(1), Si1–Tl4–Cl1 105.3(2), Cl2–Tl4–Cl1 82.0(2), Tl1–Tl4–Cl1 85.4(1), Si4–Tl5–Cl1 99.2(2), Si4–Tl5–Tl1 172.5(2), Cl1–Tl5–Tl1 88.3(1), Tl5–Cl1–Tl3 103.6(2), Tl5–Cl1–Tl4 84.1(2), Tl3–Cl1–Tl4 91.9(2), C–Si–C 111.7 (av), C–Si–Tl 107.3 (av).

Experimental Section

NaR^* (0.513 g, 11.3 mmol) in THF (25 mL) was added dropwise to a solution of $TiCl_3$ (1.74 g, 5.60 mmol) in THF (50 mL) at $-78^\circ C$. The initially orange solution (NaR^*) was transformed slowly at $-78^\circ C$ into a dark red-brown suspension. After a reaction time of 20 h the mixture was filtered at $-78^\circ C$ to separate the insoluble components. Compound **1** (0.350 g, 0.240 mmol; 13 %) precipitated as red crystals from the filtrate, which had been concentrated to about 30 mL and kept at $-25^\circ C$, over the course of six months. The separated dark brown precipitate was extracted

with toluene (30 mL; $-78^\circ C$). Black crystals of **2** (0.500 g, 0.200 mmol; 21 %) precipitated from the extract at $-25^\circ C$ over the course of six months. **1**: ^1H NMR (C_6D_6 , TMS, internal): δ = 1.395 (br.; 2SiBu₃), 1.410 (br.; 2SiBu₃); $^{13}C\{^1H\}$ NMR (C_6D_6 , TMS, internal): δ = 23.10 (6CMe₃), 23.70 (6CMe₃), 33.70 (6CMe₃), 33.89 (6CMe₃); $^{29}Si\{^1H\}$ NMR (C_6D_6 , TMS, external): δ = 99.1 (d; $^1J(Si,^{203,205}Ti)$ = 1431, 1436 Hz; 2SiBu₃), 100.2 (d; $^1J(Si,^{203,205}Ti)$ = 1450, 1455 Hz; 2SiBu₃). **2**: ^1H NMR ($[D_8]toluene$, TMS, internal): δ = 1.371 (d; $^4J(H,Tl)$ = 1.33 Hz; 4SiBu₃), 1.393 (br.; 2SiBu₃); ^{13}C and ^{29}Si NMR in $[D_8]toluene$: not observed. Note: In a repeat of the reaction, NMR spectra (^1H , ^{13}C , ^{29}Si) of the filtrate cooled to $-25^\circ C$ were recorded immediately after heating to room temperature and thereafter at certain intervals (replace THF for C_6D_6). They show that at $-25^\circ C$ the trithallane **1** is formed only slowly (in the course of weeks) from an unidentified precursor ($R^*ClTi-TiClR^*$) (^1H NMR (C_6D_6 , TMS, internal): δ = 1.36 (d; $^4J(H,Tl)$ = 3.74 Hz); $^{29}Si\{^1H\}$ NMR (C_6D_6 , TMS, external): δ = 97.1 (d; $^1J(Si,^{203,205}Ti)$ = 1447, 1441 Hz). According to the NMR spectra the solution contained only traces of hexathallane **2**.

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- [11] The existence of the thallane R^*TiCl_2 at low temperatures ($^{29}Si\{^1H\}$ NMR (THF, $-50^\circ C$): δ = 62.2 (d, $^1J(Si,^{203,205}Ti)$ = 513.6, 516.7 Hz; SiBu₃) is supported not only by the smooth thermolytic decomposition into R^*Cl and $TiCl$, but also by the reaction with LiPh, which affords diphenylsupersilylthallane R^*TiPh_2 . ^1H NMR (C_6D_6 , TMS, internal): δ = 1.120 (br.; SiBu₃), 7.18, 7.43 (each m; *o*-, *p*-, *m*-H of 2Ph); $^{13}C\{^1H\}$ NMR (C_6D_6 , TMS, internal): δ = 28.45, 32.77 (3CMe₃, 3CMe₃), 127.41, 127.50, 129.00, 141.70 (*m*-, *p*-, *o*-, *i*-C of 2Ph); ^{29}Si NMR: not observed.
- [12] According to X-ray structure analysis (in collaboration with H. Nöth, M. Warchhold), the air-, water-, and light-sensitive thallane R^*TiCl_2 , which is obtained from pentane at $-23^\circ C$ in the form of yellow plates, has a planar Si_2TiCl framework and thus contains—unlike Me_2TiCl^{II} —no linear $[RTiR]^+$ ions (possibly the very different sizes of the ions $R_3^+Ti^+$ and Cl^- prevent the formation of an energy-poor ionic crystal). ^1H NMR (C_6D_6 , TMS, internal): δ = 1.319 (br.; 2SiBu₃); $^{13}C\{^1H\}$ NMR (C_6D_6 , TMS, internal): δ = 28.35, 32.75 (each v br.; 6CMe₃, 6CMe₃; the former signal is a doublet with $^3J(C,Tl)$ = 55 Hz); ^{29}Si NMR: not observed; MS: m/z (%): 603 (67) [$M^+ - Cl$], 581 (22) [$M^+ - C_4H_9$], 405 (90) [$M^+ - SiBu_3$], 205 (100) [Tl^+] (each correct isotopic pattern).
- [13] Disupersilylthallonium tetrachloroaluminate $[R_3^+Ti]^+[AlCl_4]^-$, which had hitherto not been obtained as crystals suitable for an X-ray structural analysis: ^1H NMR (CD_2Cl_2 , TMS, internal): δ = 1.40 (br.; 2SiBu₃); $^{13}C\{^1H\}$ NMR (CD_2Cl_2 , TMS, internal): δ = 27.39, 33.25 (each v br.; 6CMe₃, 6CMe₃); ^{29}Si NMR: not observed; ^{27}Al NMR (CD_2Cl_2 , $Al(NO_3)_3$ in D_2O , external): δ = 101.14 ($AlCl_4^-$; full width at half maximum 140 Hz).

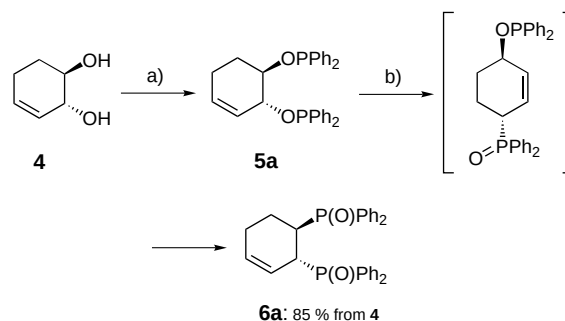
[14] Crystal structure analyses: **1**: monoclinic, space group $C2/c$, $a = 2511.8(5)$, $b = 1309.2(3)$, $c = 4291.8(9)$ pm, $\beta = 101.37(3)^\circ$, $V = 13.84(1)$ nm³, $Z = 4$; $\rho_{\text{calcd}} = 1.473$ Mg m⁻³, $\mu = 7.109$ mm⁻¹, $F(000) = 6040$. Data collection: $2\theta = 3.86\text{--}48.14^\circ$, $-18 \leq h \leq 28$, $-13 \leq k \leq 13$, $-49 \leq l \leq 49$, 24666 reflections, of which 9010 were independent ($R_{\text{int}} = 0.0781$) and 611 refined. All non-hydrogen atoms were refined anisotropically and the H atoms were included in calculated positions, $R_1 = 0.0663$, $wR_2 = 0.1794$ ($F > 4\sigma(F)$), $\text{GOF}(F^2) = 1.083$; max. residual electron density 2.556 e Å⁻³. **2**: triclinic, space group $P\bar{1}$, $a = 1548.9(3)$, $b = 1738.7(4)$, $c = 2097.4(4)$ pm, $\alpha = 78.37(3)$, $\beta = 68.79(3)$, $\gamma = 77.12(3)^\circ$, $V = 5.0877(18)$ nm³, $Z = 2$; $\rho_{\text{calcd}} = 1.473$ Mg m⁻³, $\mu = 9.621$ mm⁻¹, $F(000) = 2396$. Data collection: $2\theta = 4.22\text{--}51.84^\circ$, $-18 \leq h \leq 18$, $-21 \leq k \leq 21$, $-25 \leq l \leq 25$, 55309 reflections, of which 18432 were independent ($R_{\text{int}} = 0.0939$) and 829 refined. All non-hydrogen atoms were refined anisotropically and the H atoms were included in calculated positions, $R_1 = 0.1313$, $wR_2 = 0.4136$ ($F > 4\sigma(F)$), $\text{GOF}(F^2) = 1.851$; max. residual electron density 17.506 e Å⁻³. The crystals of **2** are extremely thin, very small platelets, and therefore the data set was strongly influenced by absorption effects. An absorption correction could not be performed. Several maxima of similar size occur which are all located at the periphery of the molecule (60–150 pm from the H atoms). If only data up to $2\theta = 44^\circ$ are considered for the refinement of the structure, the structural parameters are altered only slightly: $R_1 = 0.128$; max. residual electron density 13.40 e Å⁻³. The intensities were measured with a STOE-IPDS diffractometer with a CCD area detector (MoK α radiation, $\lambda = 0.71073$ Å). The crystals were mounted in perfluoropolyether oil; $T = 183(2)$ and $193(2)$ K, respectively. The structures were solved by using direct methods and refined against F^2 for all observed reflections. (Structure solution with SHELXS 94, refinement using SHELXL 93). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-150538 (**1**) and CCDC-150539 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

New C₂-Symmetrical 1,2-Diphosphanes for the Efficient Rhodium-Catalyzed Asymmetric Hydroboration of Styrene Derivatives**

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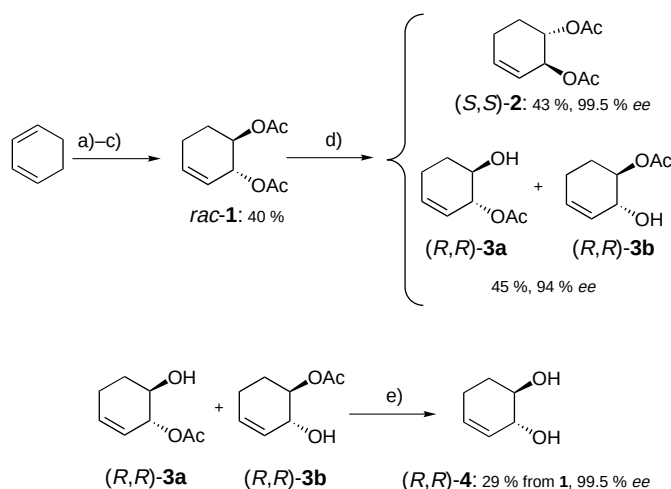
Chiral 1,2-diphosphanes are important ligands for asymmetric metal catalysis.^[1] Their synthesis is challenging especially if the stereoselective formation of secondary carbon–phosphorus bonds is desired. Recently, we have developed a method^[2] that provides a stereoselective synthesis of cyclic 1,2-diphosphane oxides using a tandem [2,3] sigmatropic

rearrangement of diphenylphosphinites that are readily available from the corresponding unsaturated 1,2-diols (Scheme 1). Herein we report the use of this rearrangement for a practical preparation of new chiral 1,2-diphosphanes and their application in highly efficient rhodium-catalyzed asymmetric hydroborations.



Scheme 1. Tandem [2,3] sigmatropic rearrangement of diphenylphosphinite. a) ClPPh₂, 4-DMAP, Et₂O, RT; b) toluene, reflux, 42 h.

The racemic mixture of the diacetate **1** is prepared in three steps in about 40% overall yield starting from 1,3-cyclohexadiene.^[3] This diacetate is easily resolved using *Pseudomonas fluorescens* lipase^[4] to afford the chiral diacetate (*S,S*)-**2** (43% yield, 99.5% *ee*) and a mixture of monoacetates (*R,R*)-**3** (45% yield, 94% *ee*; Scheme 2). The two enantio-



Scheme 2. Preparation of the optically pure diol (*R,R*)-**4**. a) Br₂ (1 equiv), CHCl₃, 5 °C; b) 1 M KOH, H₂O, RT, 96 h; c) Ac₂O (2 equiv), pyridine, RT, 12 h; d) *Pseudomonas fluorescens* lipase, pH 7, buffer, 38 °C; e) NaOMe (1 equiv), MeOH, RT, 1 h; f) recrystallization from AcOEt.

meric diols (*R,R*)-**4** and (*S,S*)-**4** are obtained in optically pure forms after saponification and recrystallization from AcOEt in yields of 29 and 31%, respectively (from **1**). These compounds have been prepared on a multigram scale and are a convenient starting material for a range of new chiral phosphanes of interest for metal catalysis.

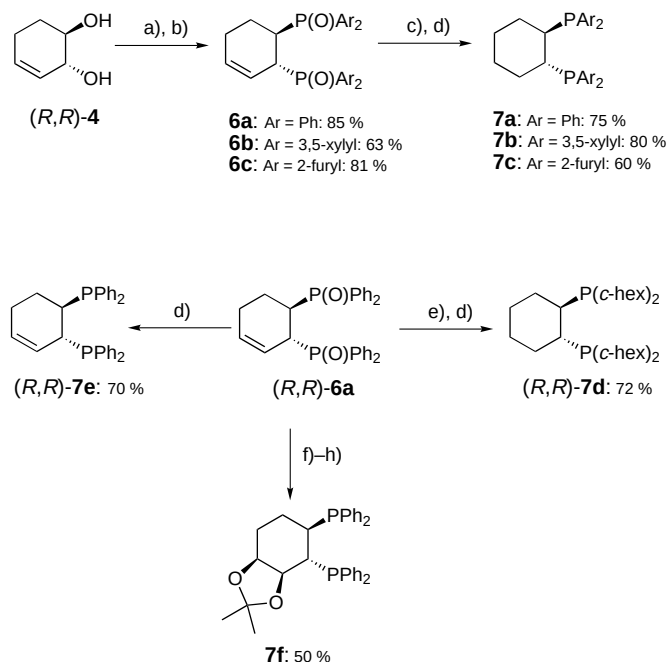
The reaction of (*R,R*)-**4** with several diarylchlorophosphanes^[5] provides the corresponding diphosphinites **5a–c** which undergo a smooth [2,3] sigmatropic rearrangement in

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

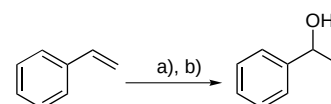
toluene (for **5a** and **5b**; reflux, 42 h) or in mesitylene (for **5c**; 170 °C, 17 h) to afford the corresponding phosphane oxides **6a–c** in 63–85 % yield (Scheme 3). These phosphane oxides



Scheme 3. Preparation of the diphosphanes **7a–f**. a) ClPAr_2 (2.05 equiv), 4-DMAP (2.1 equiv), Et_2O , RT, 30 min; b) toluene or mesitylene, reflux; c) Pd/C, H_2 , AcOH, 60 °C, 18 h; d) HSiCl_3 (20 equiv), toluene, autoclave, 110 °C, 14 h; e) Raney Ni in excess, 40 bar H_2 , EtOH, 90 °C, 12 h; f) OsO_4 (0.1 equiv), NMO (3 equiv), pyridine (3 equiv), $t\text{BuOH}$, H_2O , reflux, 6 h; g) HSiCl_3 (30 equiv), toluene, autoclave, 130 °C, 18 h; h) $\text{Me}_2\text{C}(\text{OMe})_2$ (excess), PTSA (cat.), CH_2Cl_2 , THF, RT, 12 h.

are readily converted into the corresponding saturated phosphanes (**7a–c**) in a two-step sequence (1. H_2 , Pd/C, AcOH, 65 °C, 18 h; 2. HSiCl_3 (20 equiv), toluene, 110 °C, autoclave, 14 h) in satisfactory overall yield (60–80 %). Alternatively, the phenyl rings can also be readily reduced with a Raney nickel catalyst^[6] in 90 % yield to give the (*R,R*)-1,2-bis(dicyclohexylphosphanyl)cyclohexane (**7d**) in 80 % yield after subsequent reduction with HSiCl_3 .^[7] The direct reduction of **6a** with HSiCl_3 provides the unsaturated diphosphane **7e**. The treatment of **6a** with a catalytic amount of OsO_4 (10 mol %), *N*-methylmorpholine *N*-oxide (NMO; 3 equiv), and pyridine (3 equiv) in $t\text{BuOH}/\text{H}_2\text{O}$ (reflux, 6 h) affords stereoselectively^[8] a *cis*-1,2-diol, which leads to the diphosphane **7f** in 50 % yield after reduction of the phosphane oxide (HSiCl_3 , 30 equiv, toluene, 130 °C, 18 h) and ketal formation ($\text{Me}_2\text{C}(\text{OMe})_2$, *p*-toluenesulfonic acid (PTSA; cat.), CH_2Cl_2 , THF, RT, 12 h).

The catalytic activity of rhodium complexes of these new phosphanes in enantioselective hydroboration reactions was investigated.^[9] The hydroboration of styrene with catecholborane in the presence of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (1 mol %; cod = 1,5-cyclooctadiene) and the chiral diphosphanes **7a–f** (1.2 mol %) furnishes, after oxidative workup (KOH, H_2O_2), 1-phenylethanol with high regioselectivity (> 99:1) and variable enantioselectivity (Scheme 4 and Table 1). The diphos-



Scheme 4. Rhodium-catalyzed asymmetric hydroboration of styrene with ligands **7a–f**. a) $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (1.0 mol %), **7a–f** (1.2 mol %), catecholborane (1.2 equiv), solvent; b) 3 M KOH, H_2O_2 .

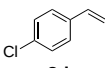
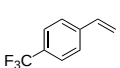
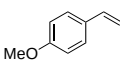
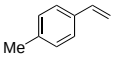
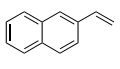
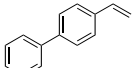
Table 1. Rhodium-catalyzed enantioselective hydroboration of styrene using ligands **7a–f**.

Entry	Ligand	Solvent	<i>T</i> [°C]	<i>ee</i> [%] (config.)
1	7a	$\text{Et}_2\text{O}:\text{CH}_2\text{Cl}_2$ (4:1)	– 60	8 (<i>S</i>)
2	7b	$\text{Et}_2\text{O}:\text{CH}_2\text{Cl}_2$ (4:1)	– 60	65 (<i>R</i>)
3	7c	$\text{Et}_2\text{O}:\text{CH}_2\text{Cl}_2$ (4:1)	– 60	65 (<i>S</i>)
4	7d	DME	– 35	92 (<i>S</i>)
5	7e	DME	– 40	8 (<i>R</i>)
6	7f	DME	– 40	15 (<i>R</i>)

phanes **7a**, **7e**, and **7f** (entries 1, 5, and 6 of Table 1) produce low enantioselectivities which are independent of the reaction conditions. However, the electron-rich diphosphane **7b** provides (*R*)-1-phenylethanol with 65 % *ee* using a mixture of diethyl ether and CH_2Cl_2 (4:1) as the solvent for the reaction. This mixture was found to be superior to THF, dimethoxyethane (DME), *tert*-butyl methyl ether, toluene, and mixtures of these solvents. Interestingly the electron-poor diphosphane **7c** (entry 3, Table 1) provides the (*S*)-alcohol; this result shows the importance of the electron density of the phosphorus center on the enantioselectivity.^[10] Finally, the best results are obtained with the very electron-rich diphosphane **7d**. In this case, (*S*)-1-phenylethanol is obtained in 92 % *ee* (DME, – 35 °C, 3 h) with a regioselectivity greater than 99:1 (Table 1, entry 4). A lower reaction temperature results in no reaction, while a higher temperature results in lower enantioselectivity and regioselectivity.

The diphosphane **7d** has been applied to the hydroboration of other styrene derivatives to evaluate the scope of this new ligand under standard conditions (1 mol % of catalyst in DME at – 35 °C; Table 2). In all cases the regioselectivity is excellent. Irrespective of the electronic nature of the substituents, their position and size have a profound effect on the enantioselectivity. Indeed, all the styrene derivatives with a

Table 2. Rhodium-catalyzed enantioselective hydroboration of styrene derivatives using ligand **7d**.

Entry	Substrate	Conversion [%] (<i>t</i> [h])	Regio-selectivity	<i>ee</i> [%] (config.)	Yield ^[c] [%]
1		100 (3)	> 99:1	92 (<i>S</i>)	85
2		100 (3)	> 99:1	93 (<i>S</i>)	81
3		86 (15)	> 99:1	76 (<i>S</i>)	62
4		100 (2)	> 99:1	85 (<i>S</i>)	84
5		98 (4)	98:2	58 (<i>S</i>)	80
6		84 (17)	99:1	93 (<i>S</i>)	69
7		98 (4)	98:2	92 (<i>S</i>)	82
8		100 (5)	> 99:1	91 (<i>S</i>)	83
9		74 (17) ^[a]	97:3	74 (<i>S</i>)	64
10		62 (17) ^[b]	97:3	84 (<i>S</i>)	50

[a] Reaction performed with 2 mol % of catalyst at -28°C . [b] Reaction performed with 2 mol % of catalyst at -35°C . [c] Yield of the analytically pure product.

substituent in the *para* position give enantioselectivities between 84 and 93 % *ee* (Table 2, entries 2, 4, 6, 7, and 10), except for the *para*-trifluoromethylstyrene (58 % *ee*; Table 2, entry 5), which is the only styrene bearing a pure electron-withdrawing group (only $-I$, no $+M$ effect). Enantioselectivities lay between 74 and 91 % *ee* when the substituents are in the *meta* position (Table 2, entries 3, 8, and 9). *ortho*-Fluorostyrene is hydroborated under these conditions with a regioselectivity greater than 99:1, but with only 56 % *ee*. Remarkably, the use of ligand **7c** solves the problem of the hydroboration of 2-substituted styrenes (Table 3). Reactions were performed with 1 mol % of catalyst in a mixture of DME and toluene (3:2) at -75°C . The high rate of these hydroborations is surprising, with most reactions being completed within 1 h at this low temperature. Enantioselectivities lay between 77 and 82 % and regioselectivities are also good.

Table 3. Rhodium-catalyzed enantioselective hydroboration of 2-substituted styrene derivatives using ligand **7c**.^[a]

Entry	Substrate	Regio-selectivity	<i>ee</i> [%] (config.)	Yield ^[b] [%]
1		86:14	77 (<i>S</i>)	75
2		97:3	82 (<i>S</i>)	84
3		97:3	81 (<i>S</i>)	86
4		94:6	82 (<i>S</i>)	81

[a] Reaction is performed with 2 mmol of styrene derivatives, 1 mol % of $[\text{Rh}(\text{cod})_2]\text{BF}_4$, 1.05 mol % of ligand **7c**, and 1.2 equivalents of catecholborane in a mixture of DME and toluene (3:2) at -75°C ; the conversion was 100 % after 1 h. [b] Yield of analytically pure product.

In summary, the [2,3] sigmatropic rearrangement of chiral unsaturated 1,2-diphosphinites allows an effective and original preparation of chiral diphosphanes. We have also shown the high efficiency of these diphosphanes in the asymmetric hydroboration of styrene derivatives. The modular approach for the preparation of these ligands is a great advantage since various substituents can be attached to the phosphorus center.

Experimental Section

Typical procedure for the double [2,3] sigmatropic rearrangement: Preparation of (1*R*,2*R*)-1,2-bis(diphenylphosphanyl)-3-cyclohexene (**6a**): (1*R*,2*R*)-1,2-dihydroxy-3-cyclohexene (**4**, 10 mmol, 1.14 g), 4-dimethylaminopyridine (DMAP; 21 mmol, 2.1 equiv, 2.57 g), and diethyl ether (120 mL) were added under argon to a 250-mL flask equipped with a magnetic stirrer. Pure chlorodiphenylphosphane (20.5 mmol, 2.05 equiv, 4.60 g) was added dropwise to the homogeneous solution. The resulting suspension was stirred for 0.5 h and then filtered under argon over a short pad of dry silica gel. The precipitate was washed twice with diethyl ether (20 mL). The ether solution was evaporated under reduced pressure and the resulting crude diphosphinite was diluted with toluene (80 mL). This solution was heated under argon to reflux for 42 h. The solvent was evaporated after cooling the reaction mixture to RT. Crude **6a** was recrystallized from AcOEt to yield a colorless crystalline solid (4.09 g, m.p. 201–202 °C, 85 % yield from **4**).

Typical procedure for the preparation of (1*R*,2*R*)-1,2-bis(dicyclohexylphosphanyl)cyclohexene (**7d**): Unsaturated phosphane oxide **6a** (2.41 g, 5 mmol), Raney nickel (5 g, rinsed with ethanol prior to use), and ethanol (20 mL) were placed in an autoclave under argon. The autoclave was heated at 90 °C for 20 h with vigorous magnetic stirring under hydrogen (40 bar). After cooling the autoclave and purging with argon, the Raney nickel was filtered off and rinsed with AcOEt. The solvents were evaporated under reduced pressure. The reaction was complete and gave only one product as judged by ^{31}P NMR spectroscopic analysis of the crude reaction mixture. The white and waxy residue was recrystallized from *n*-heptane/ CH_2Cl_2 to give **6h** as colorless needles (2.29 g, 90 % yield). The phosphane oxide **6h** (2 mmol) was placed under argon in an autoclave with toluene (30 mL) and trichlorosilane (4 mL, 40 mmol, 20 equiv) and heated for 14 h at 110 °C. After cooling the reaction mixture to RT, it was transferred in a 100-mL flask filled with argon. The excess toluene and trichlorosilane were evaporated under a high vacuum (10–2 Torr). The residue was dissolved in toluene (25 mL) and carefully hydrolyzed at 0 °C

with degassed 3 M KOH (10 mL). The mixture was stirred at RT for 30 min. The two layers were then separated and the organic phase dried (MgSO₄) under argon. The resulting clear yellow organic phase was filtered and transferred by cannulation into a second flask flushed with argon. The toluene was evaporated and the crude diphosphane **7d** washed with dried degassed methanol (2 × 5 mL). After filtration, traces of the solvent were removed under high vacuum (2 h) to yield **7d** as a white microcrystalline solid (m.p. 126–128 °C), which was stored under argon (0.76 g, 80 % yield).

Typical procedure for the hydroboration with **7d**: A mixture of [Rh(cod)₂]₂BF₄ (8.1 mg, 0.020 mmol) and diphosphane **7d** (11.5 mg, 0.024 mmol) in dry DME (5 mL) was stirred for 10 min at RT in a 10-mL Schlenk tube under argon. Styrene or a derivative (2 mmol) was added to the resulting orange solution. The homogeneous mixture was cooled to –35 °C and stirred at this temperature for 15 min before adding freshly distilled catecholborane dropwise (2.4 mmol, 0.26 mL). The catecholborane dissolved in the DME and some gas evolved from the reaction mixture. The reaction was monitored by sampling. Aliquots were taken, treated with KOH (3 M) and 30 % H₂O₂, and extracted with diethyl ether or dichloromethane. The samples were then analyzed by chiral GC (Chirasil DEX-CB column) or chiral HPLC (OD or OJ columns) to determine the conversion (using *n*-decane as an internal reference) and enantiomeric excess. The regioselectivity was determined by ¹H NMR spectroscopic analysis of the final crude reaction mixture after oxidative work-up. The products were purified by chromatography on silica (pentane/diethyl ether) to afford the corresponding alcohols.

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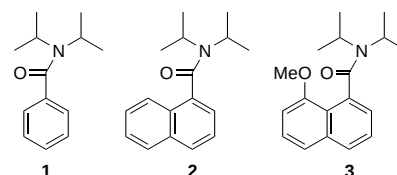
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The First Crystallographic Evidence for the Structures of *ortho*-Lithiated Aromatic Tertiary Amides**

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Directed metalation is arguably the most selective way of making regiospecifically substituted aromatic rings. The use of directed *ortho*-metalation involving amide-type functional groups (secondary and tertiary amides, carbamates, and oxazolines) has revolutionized the synthesis of complex benzenoid aromatic compounds over the last 15 years:^[1] several recent total syntheses have involved important *ortho*-lithiation steps.^[2] The four classes of substituents mentioned are not only the best directors of lithiation—with their electron-rich oxygen centers which promote the “complex-induced proximity effect”^[3] and withdraw electron density from the ring—but also the most versatile.^[2c]

It is, therefore, surprising how little is known of the products of *ortho*-lithiation reactions. Kinetic-isotope-effect evidence^[4] suggests the reaction proceeds by a rate-determining deprotonation of an initial substrate–organolithium complex. It is assumed that O–Li coordination is maintained from reactive complex through to products, though for tertiary amides (the best directing group of all^[5]) such coordination poses severe geometric difficulties. Even in the simple benzamide **1**, the tertiary amide group lies twisted out of the aromatic ring plane for steric reasons,^[6, 7] inhibiting direct O-coordination to a 2-lithio group. The angle of twist affects the rate of lithiation,^[6] but even amides which have little flexibility to rotate far from perpendicular, for example, **2** and **3**, still undergo efficient *ortho*-lithiation.^[7, 8]



Herein we report the first crystal structures of the products of tertiary-amide-directed *ortho*-metalation reactions. These go some way towards clarifying the nature of the O–Li coordination in *ortho*-lithiated amides, and also towards

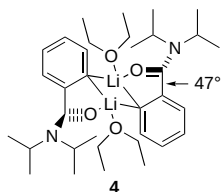
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explaining the surprising ease with which hindered tertiary amides may be *ortho*-lithiated, despite their twisted geometry.

Treatment of *N,N*-diisopropylbenzamide **1** in diethyl ether at -78°C with one equivalent of *t*BuLi gave a yellow solution.



On storage at -30°C , crystals were formed which were identified by NMR spectroscopy (see Experimental Section) as being of an *N,N*-diisopropyl-2-lithiobenzamide-diethyl ether complex **4**. The X-ray structure^[9] of these crystals showed that in the solid state **4** is a dimer in which an $(\text{LiC})_2$ core is stabilized by the O-centers of the amide carbonyl functionalities and of Et_2O (Figure 1).

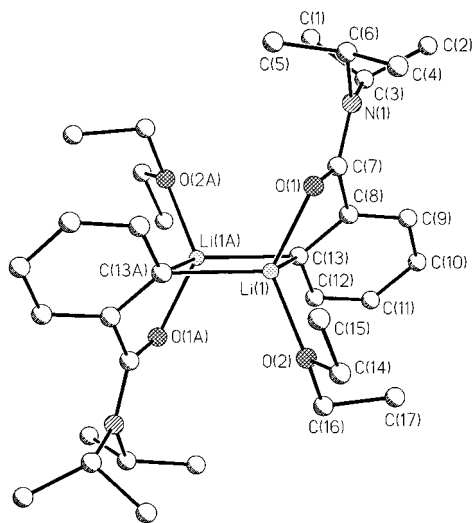


Figure 1. Molecular structure of **4**; hydrogen atoms and disorder in the Et_2O molecules are omitted for clarity.

An $(\text{LiX})_2$ unit is not uncommon in species of the type $[(\text{RLi} \cdot \text{L})_n]$ in which R is an imide ($\text{X} = \text{N}$),^[10] alkoxide,^[11] enolate^[12] ($\text{X} = \text{O}$), or aryl ($\text{X} = \text{C}$)^[13] residue and L is a monodentate Lewis base (THF, Et_2O etc.). The Li–C bonds in the core of **4** vary in a fashion explicable by viewing the structure as an aggregate of two monomeric organolithium fragments with their metal centers stabilized by intramolecular coordination to the oxygen atom of the amide group ($\text{Li}(1) - \text{O}(1) = 1.936(3) \text{ \AA}$). Each lithium ion lies close to the plane of the amide system (dihedral angle $\text{N}(1) - \text{C}(7) - \text{O}(1) - \text{Li}(1) = 161.1^{\circ}$), which is itself twisted at an angle of 46.8° to the aromatic ring. The strain imposed by this twist means that the intramolecular C–Li bond is long and weak ($\text{Li}(1) - \text{C}(13) = 2.303(4) \text{ \AA}$) and that the lithium center lies well out of the plane of the aromatic ring. Dimerization allows the formation of a stronger metal–carbon bond ($\text{Li}(1) - \text{C}(13\text{A}) = 2.176(4) \text{ \AA}$) lying surprisingly close to the aromatic plane (dihedral angle $\text{C}(7) - \text{C}(8) - \text{C}(13) - \text{Li}(1\text{A}) = 21.0^{\circ}$).

In a similar way, reaction of *N,N*-diisopropyl-1-naphthamide **2** in THF at -78°C with one equivalent of *t*BuLi gave a yellow suspension which dissolved at reflux. Storage of the resultant solution at -30°C afforded yellow crystals of the

N,N-diisopropyl-2-lithionaphthamide-THF complex **5** (see Experimental Section). The X-ray structure^[14] revealed that in the solid state **5** is also a dimer (for which there are two molecules of lattice THF) in which an $(\text{LiC})_2$ core is stabilized by amide groups and O centers from THF (Figure 2). As with **4**, the structure of **5** suggests that dimerization accompanies the intramolecular amide-group coordination of each lithium center

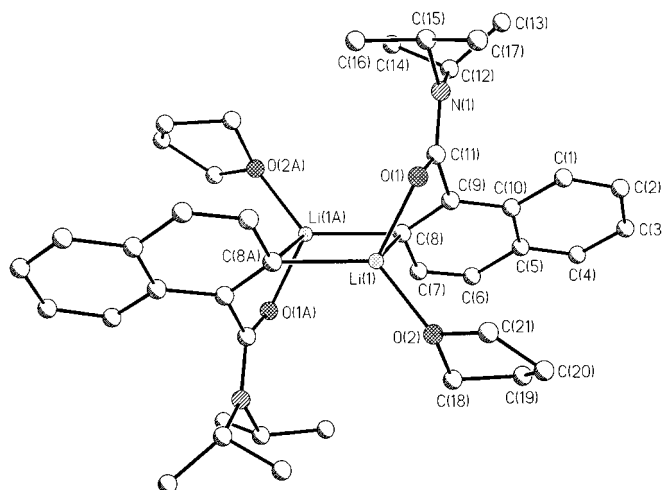
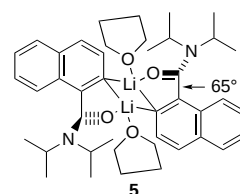


Figure 2. Molecular structure of **5**; hydrogen atoms and disorder in the THF molecules are omitted for clarity.

($\text{Li}(1) - \text{O}(1) = 1.974(4) \text{ \AA}$). The significant lengthening of this bond as compared with its analogue in **4** is accompanied by lengthening of the intramolecular C–Li bond ($\text{Li}(1) - \text{C}(8) = 2.389(4) \text{ \AA}$). Relative to **4**, these changes result from the even greater 65° dihedral angle between the amide group and the aromatic ring in **5**. The amide group and ring plane in naphthamides and in 2-substituted benzamides typically lie almost perpendicular,^[6, 7] and the 65° dihedral angle must represent a compromise between maintaining intramolecular C–Li–O bonding and minimising steric hindrance.

The solid-state structures of both **4** and **5** establish for the first time that the oxygen coordination of the lithium center is maintained in *ortho*-lithiated aromatic tertiary amides, despite the deviation from coplanarity^[6, 7] of the amide group and the aryl system in precursors **1** and **2**. The structures show that the formation of a four-membered $(\text{LiC})_2$ ring is ideally suited to stabilization of the metal by the amide carbonyl group, but the increased strain evident in the lengthened bonds of **5** accounts for the slower rates of lithiation of these twisted amides relative to their coplanar analogues.^[6]

Complexes **4** and **5** represent rare examples of β -lithiated amides.^[15] Solid-state structures of *ortho*-lithiated benzenoid derivatives have been reported with a variety of *saturated* directing groups^[16] but the crystal structures of **4** and **5** are the first to incorporate *ortho*-metalated carbonyl-substituted aromatic rings. *Ortho*-lithiated compounds containing *unsaturated* directing groups have been characterized only for polymetalated stilbenes,^[17] sulfones,^[18] and sulfoximines.^[19]

In conclusion, the isolation and characterization of **4** and **5** afford a significant insight into the *ortho*-lithiation-directing effects of tertiary amides. Complexation of the lithium center by the amide C=O group, as expected, is crucial to the stability of the metalated species, and this mode of coordination is achieved by lessening the amide–arene twist angle. Solution studies on both **4** and **5** will form the basis of future work with preliminary NMR spectroscopy pointing to rather complicated solution behavior. Hence **5** dissolves in [D₈]THF to give five observable solution species (#1–#5, see Experimental Section). Further, we intend, by the use of theoretical methods, to probe the mechanism by which directed *ortho*-lithiation occurs and also hope to extend the study to the metalation of other, more complex, atropisomeric tertiary amides with a view to gaining a better understanding of the stereochemistry of these unusual chiral organolithium species and their reactions.^[20]

Experimental Section

4: *t*BuLi (0.8 mL, 1.7 M in pentane, 1.3 mmol) was added to a solution of *N,N*-diisopropylbenzamide **1** (0.26 g, 1.25 mmol) in Et₂O (10 mL) under nitrogen at –78 °C. The resultant yellow solution was transferred directly to a –30 °C freezer. Yellow crystals of **4** were obtained after 4 h at this temperature. Yield 65%; m.p. 101 °C (decomp.); elemental analysis calcd (%) for C₁₇H₂₈LiNO₂: C 71.56, H 9.89, N 4.91; found: C 71.29, H 9.89, N 5.10; ¹H NMR (400 MHz, [D₈]THF, –40 °C, TMS): δ = 7.39–7.28 (m, 4H; Ph), 3.82 (sept, ³J(H,H) = 6.7 Hz, 1H; NCH), 3.55 (sept, ³J(H,H) = 6.7 Hz, 1H; NCH), 3.37 (q, ³J(H,H) = 7.0 Hz, 4H; OEt₂), 1.49 (d, ³J(H,H) = 6.8 Hz, 6H; Me), 1.12 (t, ³J(H,H) = 7.0 Hz, 6H; OEt₂), 1.12 (d, ³J(H,H) = 6.5 Hz, 6H; Me).

5: *t*BuLi (0.6 mL, 1.7 M in pentane, 1 mmol) was added to a solution of *N,N*-diisopropyl-naphthylamide **2** (0.26 g, 1 mmol) in THF (2 mL) under nitrogen at –78 °C. The yellow suspension which formed was warmed to room temperature and dissolved at reflux on the addition of THF (1 mL). The resultant solution was stored at –30 °C for 2 d whereupon yellow crystals of **5** were deposited. Yield 25%, m.p. 286–288 °C; elemental analysis calcd (%) for C₃₀H₂₇Li₂N₂O₆: C 73.98, H 8.88, N 3.45; found: C 76.90, H 7.54, N 5.63; ¹H NMR (400 MHz, [D₈]THF, –70 °C, TMS): δ = 8.37–7.52 (m, 6H; Ph), 3.89 (m, 0.8H; 0.4NCH#1), 3.76 (m, 0.8H; 0.8NCH#2), 3.62 (m, 4.2H; THF + 0.2NCH#3 + 0.06NCH#4), 3.25 (m, 0.4H; 0.4NCH#5), 1.77 (m, 4H; THF), 1.64 (m, 2.4H; 0.8Me#2 + 0.4Me#5), 1.44 (d, ³J(H,H) = 6.3 Hz, 1.2H; 0.8Me#2), 1.39 (d, ³J(H,H) = 6.3 Hz, 1.2H; 0.8Me#2), 1.20 (d, ³J(H,H) = 6.5 Hz, 1.2H; 0.4Me#5), 1.13 (d, ³J(H,H) = 6.3 Hz, 1.2H; 0.8Me#2), 1.07 (d, ³J(H,H) = 6.6 Hz, 0.2H; 0.06Me#4), 1.01 (d, ³J(H,H) = 6.6 Hz, 0.2H; 0.06Me#4), 0.90 (d, ³J(H,H) = 6.0 Hz, 0.6H; 0.2Me#3), 0.72 (d, ³J(H,H) = 5.9 Hz, 1.2H; 0.4Me#1), 0.10 (d, ³J(H,H) = 6.0 Hz, 0.6H; 0.2Me#3), –0.03 (d, ³J(H,H) = 5.9 Hz, 1.2H; 0.4Me#1).

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A Ga₈R₆ Cluster as an Ideal Model for a Metal–Metal Bond?*

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Hansgeorg Schnöckel*

*Dedicated to Professor Kurt Dehnicke
on the occasion of his 70th birthday*

In the 1960s the primary interest in simple cluster compounds such as [(CO)₃CpW–WCp(CO)₃], [(CO)₅Mn–Mn(CO)₅], and ClHg–HgCl lay in the bond between the metal atoms, since here the complex bonding situation in metals is reduced to a two-electron–two-center (2e2c) bond.^[1] Since the ligands, such as halogen atoms or CO, undergo strong interactions with the metal atoms and thus strongly influence the bond between the two metal atoms, such a bonding situation is fundamentally different from that in metals.

Therefore compounds of the type Y₃X–XY₃ (X, Y = metal atoms, that is two linked Y₃X tetrahedra) with bonding interactions between the Y atoms are of particular significance. However, there are to date only a few examples in which some of the metal atoms are replaced by nonmetal atoms: X = C, Y = Co,^[2] Y = Fe;^[3] X = N, Y = Au;^[4] X = Hg, Y = Pt,^[5] and X = (As,Co), Y = Co.^[6] The only species known to us which approaches the desired model compound is [Ir₈(CO)₂₂]^{2–},^[7] in which a Ir₂ unit is bound on both sides to an Ir₃CO₁₁ group, and some of the CO ligands function as bridging ligands. Thus to date there is no simple model compound for a typical metal–metal bond as defined by the above-mentioned limitations, in which eight identical metal atoms, in the form of two linked M₄ tetrahedra, form 13 metal–metal bonds (2 × 6 + 1), but only six metal–ligand bonds.

Recently, however, we have achieved a first step in this direction through the synthesis of an Al₇R₆ cluster,^[8] in which two Al₄ tetrahedra are linked through a “naked” Al atom, such that 12 metal–metal contacts are present together with six metal–ligand bonds. Herein we present the first molecular example for an ideal metal–metal bond as defined by the above-mentioned criteria, in which in a Ga₈R₆ unit two Ga₄ tetrahedra are linked through a common “naked” Ga atom. C(SiMe₃)₃ (trisyl) groups were used as ligands, with which both the first Ga₄R₄ cluster^[9] and recently a Ga₁₉ species were obtained.^[10]

Reaction of trisyllithium dissolved in toluene at –78 °C with a solution of Ga^IBr in toluene/THF (obtained by cocondensation of the high-temperature molecule GaBr) resulted in a solution that was stable at room temperature. After removal of the solvent, a black residue remained. Extraction with pentane and subsequently with toluene gave

black filtrates in each case; a Ga-centered Ga₁₉ cluster was crystallized from the toluene solution,^[10] and we have now also obtained black crystals in the form of hexagonal platelets from the pentane extract. The results of the X-ray structure analysis show that these crystals are the neutral octagallane [Ga₈C(SiMe₃)₃]₆ (**1**) (Figure 1).

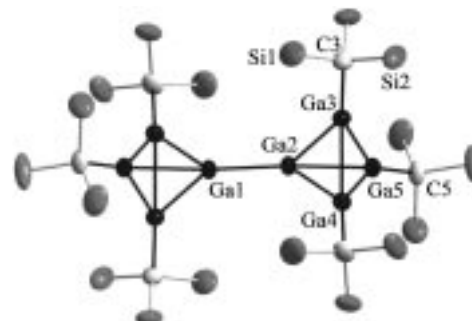


Figure 1. Molecular structure of **1** (without methyl groups; thermal ellipsoids 50%). Selected bond lengths [pm] and angles [°]: Ga1–Ga2 261.43(11), Ga2–Ga3 260.54(8), Ga2–Ga4 260.54(8), Ga2–Ga5 264.03(11), Ga3–Ga4 264.81(9), Ga3–Ga5 263.65(8), Ga3–C3 204.8(4), Ga5–C5 204.3(5); Ga1–Ga2–Ga3 142.97(2), Ga1–Ga2–Ga5 147.11(4), Ga3–Ga2–Ga4 61.09(3), Ga2–Ga4–Ga5: 60.49(3), Ga2–Ga4–Ga3 59.455(13), C5–Ga5–Ga2 143.61(16), C3–Ga3–Ga4 146.75.

The Ga–Ga distances in **1** vary within a narrow range (260.5–264.8 pm), and consequently the angles within the triangular faces of the tetrahedra deviate by a maximum of 1° from the ideal value of 60°. The ligands are bound to the gallium atoms with an average Ga–C distance of 204.5 pm. The Ga–Ga as well as the Ga–C bonds in **1** are significantly shorter than those in the tetrahedral complex [Ga₄C(SiMe₃)₃]₄ (*d*(Ga–Ga) = 268.3, *d*(Ga–C) = 207.4 pm (av)). This finding shows that the C(SiMe₃)₃ ligand has a large steric demand and thus in situations in which steric overloading occurs such as in Ga₄R₄ compounds leads to increased bond lengths in the Ga₄ framework and in the Ga–R bonds.

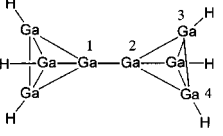
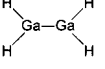
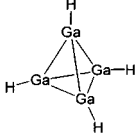
Since as outlined in the introduction the structural element depicted in Figure 1 of two tetrahedral M₄R₃ units linked by a metal–metal bond is hitherto unknown for clusters containing one element, we have examined this archetype of a metal–metal bond in more detail by carrying out density functional theory (DFT) calculations^[11] on the model compound Ga₈H₆ (**1a**). The results of these calculations are given in Table 1 and are compared to the analogous results for Ga₂H₄ (**1b**) and Ga₄H₄ (**1c**).

As expected the charges of the Ga atoms in the listed compounds differ only slightly. The central Ga atoms in **1a** bear a slightly negative partial charge (in contrast to the positive partial charges, for example, in localized metal–metal bonds mentioned in the introduction such as in ClHg–HgCl), so that these species contain metal–metal interactions that are close to metallic metal–metal bonds, which for the first time allows a comparison of an extensively localized bond in a molecular unit with the delocalized bonding in metals. However, the distances found for **1** differ from the ones calculated for **1a** with regard to absolute values

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Table 1. Ga–Ga distances $d(\text{Ga–Ga})$, force constants f , charges q , and ^{71}Ga NMR shifts δ of the calculated model compounds **1a–1c**.

Compound			
	Ga_8H_6 1a	Ga_2H_4 1b	Ga_4H_4 1c
$d(\text{Ga–Ga})$ [pm]	253.8 (Ga1–Ga2) 259.4 (Ga2–Ga3) 255.8 (Ga3–Ga4)	246.2	256.7
f [mdyn Å ^{−1}]	0.8 (Ga1–Ga2)	1.1	0.6
q	−0.1 (Ga1) 0.0 (Ga3)	0.1	0.0
$\delta(^{71}\text{Ga})$	1028 (Ga1) 942 (Ga3)	705	986

and their progression. This finding is plausible since the sterically highly demanding $\text{C}(\text{SiMe}_3)_3$ group leads to very long Ga–Ga bonds such as found in the Ga_4R_4 compound.^[9] This bulkiness of the ligand framework also results in an increase of the central Ga–Ga distance in **1**, as can be clearly seen in the space-filling model (Figure 2).

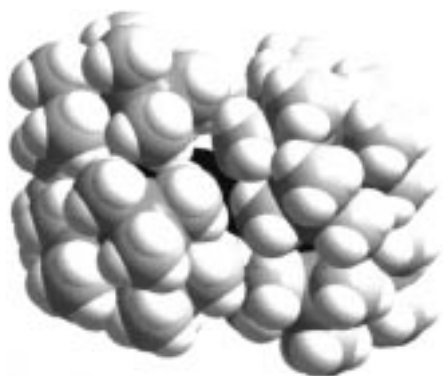


Figure 2. Space-filling model of **1**.

Without these repulsive interactions the central Ga–Ga bond, as the calculations show, should be significantly shorter than the other Ga–Ga bonds, since the central Ga_2 unit is mainly based on $2e2c\text{-}\sigma$ bonding (HOMO, a_{1g}), whereas the six remaining Ga–Ga bonds in the $(\text{RGa})_3\text{Ga}$ units are based on four delocalized molecular orbitals (a_{1g} , t_{2u}).

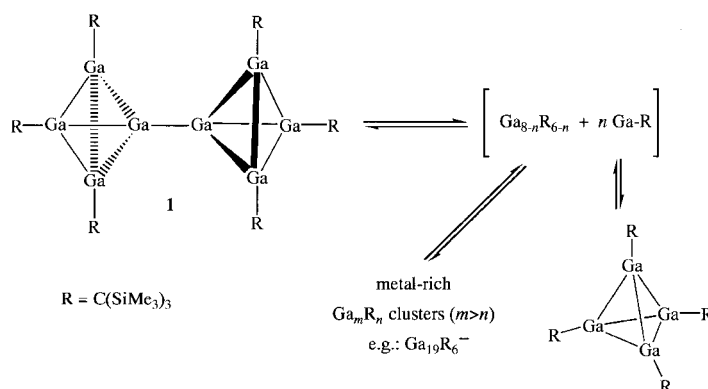
Parallel to the Ga–Ga distances, the corresponding Ga–Ga force constants also change, that is the Ga–Ga bond of Ga_2H_4 is significantly stronger (1.1 mdyn Å^{−1})^[12] than the one of the central Ga_2 unit in **1**. In contrast, the latter is slightly larger than the one of the Ga_4H_4 tetrahedron **1c**. Evidently, the strong delocalization of the electrons within the two Ga_4 fragments leads to this destabilization of the linking Ga–Ga bond in **1**. This bond lengthening should be even larger on increasing the coordination numbers at the central Ga atoms, for example, the linkage of two octahedral or icosahedral Ga_n polyhedra through common Ga–Ga bonds.

The electronic relationship of **1** to a corresponding Ga_4R_4 unit is already clear through the differing color (**1** is black, Ga_4R_4 in contrast red). This finding is in agreement with the

results of DFT calculations, according to which significantly different HOMO–LUMO distances were calculated for **1a** and Ga_4H_4 : 1.27 and 2.46 eV, respectively.

The calculated ^{71}Ga shifts for **1a** and **1c** must be considered together with the experimental and theoretical results for a Ga_{19} cluster ($[\text{GaGa}_{12}(\text{GaR})_6]^-$; $\text{R} = \text{C}(\text{SiMe}_3)_3$):^[10] In this case calculations show that the signals of the naked Ga atoms (GaGa_{12}) are considerably low-field shifted in comparison to those of the six ligand-bearing Ga atoms; note also that the nature of the ligands strongly influences the shift of the “naked” atoms. Their resonance shifts to higher fields on going from H through CH_3 to $\text{C}(\text{SiMe}_3)_3$ as ligand. The signals shifted to highest field were found in the ligand-free Ga cluster Ga_{13}^- . Thus the as yet not observed shift of the central Ga atoms in **1** will probably lie significantly shifted to high field in comparison to those calculated in **1a**, whereas the shift of the ligand-bearing Ga atoms will probably be only slightly influenced. Shifts to high field of “naked” Ga atoms, which could for the first time be experimentally confirmed for the Ga_{19} cluster, thus seem to be typical for “metallically” bound metal atoms. The slight shift to high field of the central Ga atoms in **1a** in comparison to the shift in **1c** shows, however, that the electronic environment of the central Ga_2 unit in **1a** is very similar to that in the tetrahedral **1c**. A change of the situation with signals further shifted to high field is only expected for the central Ga_2 unit when the coordination numbers for these atoms increase, that is, when, for example, two icosahedral clusters are linked through a Ga–Ga bond. Such compounds would then be even better model compounds for an isolated metal–metal bond.

In addition to the described special characteristics with regard to structure and bond theory, the formation of **1** also gives an indication of the reactions occurring in solution. For instance, **1**, as a key compound in the construction of larger clusters, could be in equilibrium with other metal-rich species and GaR oligomers (Scheme 1).



Scheme 1. Postulated mechanism of the formation of the metalloid Ga_{19} cluster from **1**.

Compound **1** is the first model compound for a metal atom contact^[13] in the form of a nano-metal wire. In this context the results presented here should provide the stimulus or be the gauge for future theoretical and experimental investigations on the reaction between metal atom clusters from their primary contact to their fusion to give larger clusters.

Experimental Section

In a 250-mL bulb $\text{LiC}(\text{SiMe}_3)_3$ (1.5 g, 6.3 mmol) was placed in toluene (25 mL). After the solution had been cooled to -78°C , GaBr (15 mL of a 0.3 M solution in toluene/THF (3/1), 5 mmol) was added. The reaction mixture was slowly allowed to warm to room temperature, during which the solution became dark red to black. The solvent was then removed in vacuum. The black residue was extracted with pentane. A few black crystals of **1** in the form of hexagonal platelets precipitated from the dark brown pentane extract.

Crystal structure data of **1**: $\text{Ga}_8(\text{C}(\text{SiMe}_3)_3)_6$, $M_r = 1891.3$, crystal dimensions $0.3 \times 0.6 \times 0.6$ mm, monoclinic c , space group $C2/m$, $a = 13.203(3)$, $b = 24.704(5)$, $c = 17.382(4)$ Å, $\beta = 103.86(3)^\circ$, $V = 5504.3(19)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.175$ g cm⁻³, μ_{Mo} = 2.150 mm⁻¹, $2\theta_{\text{max}} = 51.74^\circ$, 16186 measured reflections, 5446 independent reflections ($R_{\text{int}} = 0.0841$), absorption correction: numerical (min./max. transmission 0.1630/0.4012), $R_1 = 0.0466$, $wR_2 = 0.1388$. Stoe-IPDS diffractometer ($\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å), 200 K). The structure of **1** was solved by direct methods and refined against F^2 for all observed reflections. Programs used: SHELXS and SHELXTL (G. M. Sheldrick, Universität Göttingen). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151247. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Haag–Dessau Catalysts for Ring Opening of Cycloalkanes

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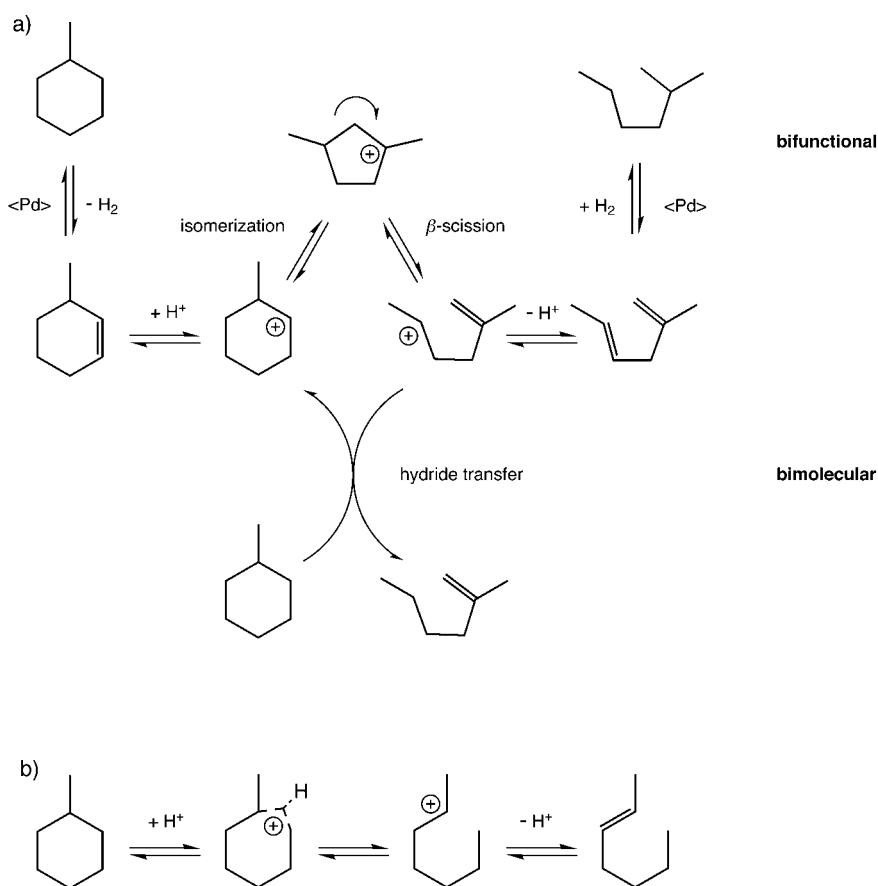
With the advent of the Auto Oil Programme of the European Union, the aromatics content of gasoline has to be reduced from 45 vol % in 1999 to 42 and 35 vol % in 2000 and 2005, respectively.^[1] Therefore, western Europe will probably face a surplus of aromatics, especially toluene, soon. One of the major sources of aromatics is pyrolysis gasoline, a by-product from steamcracking of naphtha for the production of ethene and propene. Given the large growth rate of demand for ethene^[2] and propene^[3] that is generally forecasted, the production of pyrolysis gasoline—and, hence, of aromatics—will necessarily increase as well. For the conversion of aromatics into a premium synthetic steamcracker feedstock (consisting mainly of ethane, propane, and *n*-butane), two process variants have recently been introduced. In variant 1, the aromatics are directly converted with hydrogen on a bifunctional zeolite catalyst;^[4] in variant 2, cycloalkanes, which can easily be obtained from aromatics by state-of-the-art hydrogenation processes, are hydroconverted on acidic zeolite catalysts.^[5] In both cases, pyrolysis gasoline is ultimately recycled into the steamcracker and thus removed from the market.

Recently, we observed that the selectivity to *n*-alkanes with two and more carbon atoms (C_{2+} -*n*-alkanes) is very high during the conversion of methylcyclohexane on catalysts that contain noble metals in such small amounts that they can be classified neither as typically bifunctional nor as monofunctional. We report here on these results and their mechanistic implications.

To begin with, the salient mechanistic features of catalytic ring opening of cycloalkanes are briefly sketched (Scheme 1): On bifunctional catalysts, methylcyclohexane is dehydrogenated on metallic sites, and the resulting cycloalkenes are protonated to carbenium ions on acidic sites. Usually, skeletal isomerization into highly branched isomers occurs first, whereupon classical β -scission can proceed. Finally, the diene formed is hydrogenated on a metal site (Scheme 1 a, top).^[6, 7] On monofunctional acidic catalysts, two different mechanisms can be operative:^[8, 9] On the one hand, β -scission of classical carbenium ions is possible, but the latter can now only form through a bimolecular hydride transfer (Scheme 1 a, bottom). On the other hand, methylcyclohexane can be directly protonated forming a nonclassical carbonium ion with a three-center, two-electron bond in the transition state (Haag–Dessau cracking, Scheme 1 b). If ring opening is accompanied by secondary cracking steps, isoalkanes (no

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Scheme 1. Mechanisms for ring opening of cycloalkanes: a) classical (bifunctional or bimolecular) and b) nonclassical cracking.

methane and ethane due to the instability of primary carbenium ions) will predominantly be formed in the first case due to the preceding isomerization, while *n*-alkanes (including methane and ethane) will be the dominant products in the second case. Under increased pressure of hydrogen, only saturated compounds and no alkenes are obtained in the product stream, even on the metal-free acidic catalysts. This can be accounted for by activation of hydrogen on the acid sites.^[5] As a measure of the contribution of the two mechanisms, Wielers et al.^[10] introduced the so-called cracking mechanism ratio (CMR), which is defined as the ratio of the yields of C_1 and C_2 hydrocarbons to the yield of isobutane.

On the basis of these generally accepted mechanistic concepts, an attempt will be made to rationalize the experimental data obtained on H-ZSM-5 zeolites. During the conversion of methylcyclohexane at 250 °C, three types of reactions can be observed on all catalysts: a) isomerization to ethylcyclopentane and dimethylcyclopentanes, b) ring opening to *n*-heptane and its isomers, and c) secondary cracking to propane and isobutane or *n*-butane (Figure 1). The formation of all these products can readily be accounted for by reactions via carbenium ions; no contribution of nonclassical Haag–Dessau cracking has to be invoked at this low reaction temperature. On the typically bifunctional catalysts (0.2 or 1.0 wt % Pd), the conversion is clearly higher (approximately 9%) than on the catalysts with no or only small amounts of palladium (approximately 3%). In addition, the isomerization

products are formed with considerably higher selectivity on the bifunctional catalysts, whereas the selectivities to the secondary cracking products remain comparably small, which indicates an efficient desorption mechanism on these catalysts.^[6] At this low conversion, methylcyclohexene molecules formed on metal sites displace the products of isomerization or ring opening from the acidic sites to a large extent before secondary cracking can take place.

On all catalysts, the yields of cycloalkanes and of isoalkanes exhibit maxima and then start to decrease with increasing conversion (Figure 2), whereas the yields of C_{2+} -*n*-alkanes (the desired synthetic steamcracker feedstock) and methane (a very undesirable product) increase monotonously. This could be due to ever faster cracking reactions and to an increasing influence of nonclassical Haag–Dessau cracking. A closer examination of the temperature dependence of C_{2+} -*n*-alkane formation reveals significant differences between the various catalysts (Figure 3): On the typically bifunctional catalysts, the selectivities to C_{2+} -*n*-alkanes are considerably smaller than those on the monofunctional acidic catalyst, and this is true for all temperatures

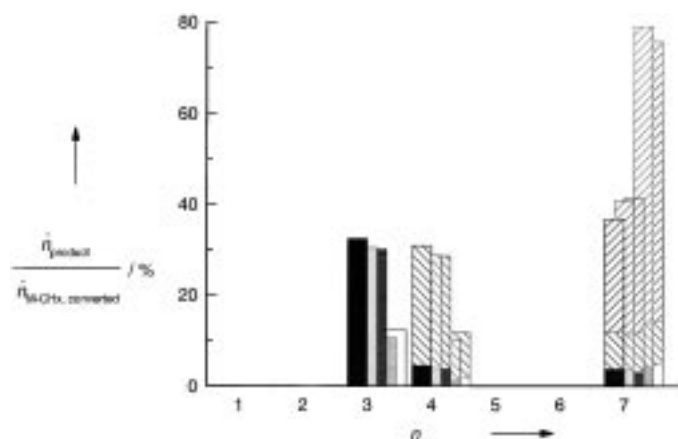


Figure 1. Molar fractions of the products with *n* carbon atoms during the conversion of methylcyclohexane on H-ZSM-5 catalysts with 0 (black), 0.001 (light gray), 0.01 (dark gray), 0.2 (medium gray), and 1.0 (white) wt % of palladium at 250 °C. Forwards shading (///): cycloalkanes; backwards shading (\\): isoalkanes; solid color: *n*-alkanes; aromatics are not formed.

applied. In contrast, on the catalysts with 10 or 100 ppm of palladium, slightly less C_{2+} -*n*-alkanes are formed at low temperatures compared to the acidic catalyst, but significantly more at 400 °C. With the temperature dependence of the CMR value depicted in Figure 4, these differences become even more striking: On all catalysts, the CMR value, and hence the proportion of nonclassical cracking via carbonium

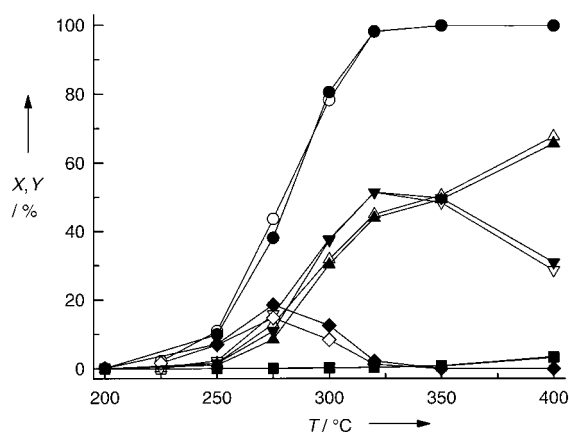


Figure 2. Temperature dependence of the conversion of methylcyclohexane on zeolite H-ZSM-5 with 0.2 wt % of palladium (full symbols) or 0.4 wt % of platinum (open symbols). X: conversion, Y: yield. $\circ$, $\bullet$: X(methylcyclohexane); $\triangle$, $\blacktriangle$: Y(C₂₊-n-alkanes); ∇ , $\blacktriangledown$: Y(isoalkanes); $\square$, $\blacksquare$: Y(methane); $\diamond$, $\blacklozenge$: Y(cycloalkanes); aromatics were not formed.

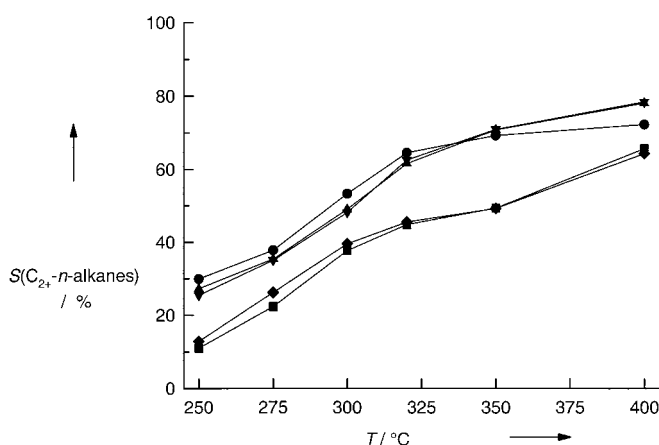


Figure 3. Temperature dependence of the selectivity to *n*-alkanes with two and more carbon atoms ($S_{\text{C}_{2+}\text{-}n\text{-alkanes}}$) during the conversion of methylcyclohexane on H-ZSM-5 catalysts with 0 (●), 0.001 (▲), 0.01 (▼), 0.2 (■), and 1.0 (◆) wt % of palladium.

ions versus classical β -scission of carbenium ions (through the bimolecular or bifunctional mechanism), increase with increasing temperature. Similar trends have already been observed by Haag and Dessau^[8] during cracking of hexane isomers on acidic zeolites and interpreted in terms of a high activation energy of the nonclassical cracking route. On typically bifunctional catalysts, this nonclassical cracking

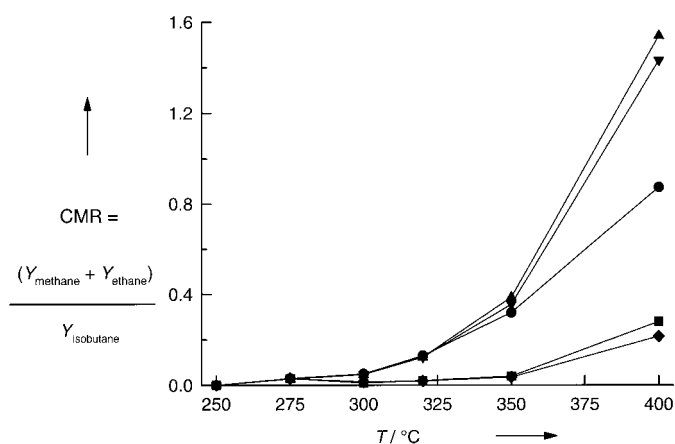


Figure 4. Temperature dependence of the cracking mechanism ratio (CMR) value during the conversion of methylcyclohexane on H-ZSM-5 catalysts with 0 (●), 0.001 (▲), 0.01 (▼), 0.2 (■), and 1.0 (◆) wt % of palladium.

occurs only to a small extent. The dehydrogenation of methylcyclohexane is now efficiently catalyzed, hence there is a relatively high steady-state concentration of unsaturated hydrocarbons (for example, methylcyclohexenes), which are much more strongly adsorbed on the acidic sites than the saturated compounds. This results in a relatively high concentration of classical carbenium ions and a low concentration of nonclassical carbonium ions, hence the classical β -scission clearly dominates ($\text{CMR}_{400^\circ\text{C}} \approx 0.3$, Table 1). The β -scission can also take place on monofunctional acidic catalysts. However, the carbenium ions have to form in a sterically demanding, bimolecular hydride transfer (Scheme 1a, bottom). Thus, bimolecular classical cracking is, especially under sterical constraints as in the medium-pore zeolite ZSM-5, accompanied by nonclassical cracking, indicated by a significantly higher CMR value (0.9 at 400 °C). Even higher values (approximately 1.5 at 400 °C) could be observed on H-ZSM-5 zeolites with 10 or 100 ppm of palladium, which indicates that nonclassical Haag–Dessau cracking is very much favored on these catalysts.

Of course, it would be desirable to perform such comparisons of the catalytic properties of various zeolites at low conversion. However, because of its higher activation energy, Haag–Dessau cracking becomes only significant at temperatures around 400 °C, and at these high temperatures low conversions would have been very difficult to achieve, even

Table 1. Conversion of methylcyclohexane at 400 °C on various H-ZSM-5 catalysts with different weight contents of Pd or Pt.

	0 ppm Pd	10 ppm Pd	100 ppm Pd	0.2 % Pd	1.0 % Pd	0.4 % Pt
$X_{\text{M-CHX}}$ [%]	100	100	99.8	100	100	100
Y_{Me} [%]	3.9	5.0	3.5	3.5	2.5	3.5
Y_{Et} [%]	10.4	15.4	12.3	6.1	4.5	6.0
Y_{Pr} [%]	48.6	51.7	51.5	47.8	47.0	48.5
Y_{nBu} [%]	12.4	10.6	13.7	12.6	12.7	13.1
Y_{nPr} [%]	1.0	0.5	0.9	0.2	0.2	0.3
$Y_{\text{C}_{2+}\text{-}n\text{-alkanes}}$ [%]	72.4	78.2	78.4	66.7	64.4	67.9
$Y_{\text{isoalkanes}}$ [%]	22.4	15.9	17.7	29.8	33.1	28.6
$Y_{\text{cycloalkanes}}$ [%]	0.0	0.0	0.1	0.0	0.0	0.0
$Y_{\text{aromatics}}$ [%]	1.3	0.9	0.3	0.0	0.0	0.0
CMR	0.86	1.54	1.44	0.33	0.22	0.34

with a drastic increase of the weight hourly space velocity (WHSV).

Tentatively, we attribute the prevalence of Haag–Dessau cracking on the catalysts with small amounts of palladium to the lack of an efficient formation mechanism for carbenium ions: On the one hand, there are not enough metal sites to dehydrogenate methylcyclohexane at a sufficiently high rate for the bifunctional mechanism to proceed. On the other hand, the number of metal sites suffices for a reasonably fast hydrogenation of the reaction products. This impedes the hydride transfer and, therefore, the classical cracking mechanism. This explanation is supported by the fact that, at the high partial pressure of hydrogen applied (6 MPa), hydrogenation should be favored over dehydrogenation. Hence, the formation of carbenium ions through both classical mechanisms is hindered.^[11] Conversely, Haag–Dessau cracking is favored by a higher number of free acidic sites, which becomes especially visible at the high temperatures and with the pronounced spatial constraints which promote this mechanism.

A significantly higher proportion of nonclassical cracking on the catalysts with 10 or 100 ppm of palladium is in line with the maxima of the yields of C_{2+} -*n*-alkanes and methane, as well as with the minimum of the yield of isoalkanes (Figure 5 and Table 1). A rival mechanism for the formation of methane

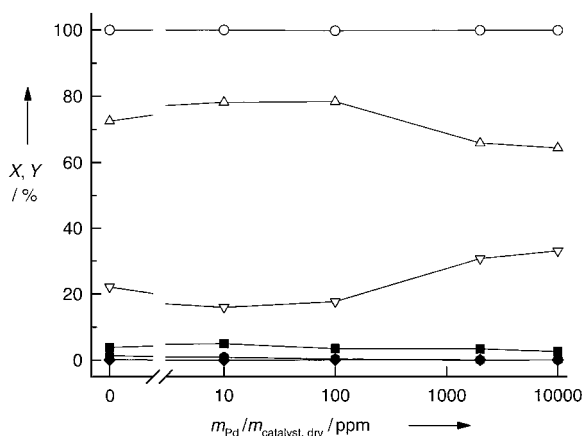


Figure 5. Effect of the palladium content on the conversion of methylcyclohexane on Pd/H-ZSM-5 catalysts at 400 °C. X: conversion, Y: yield. ○: X(M-CHx), △: Y(C_{2+} -*n*-alkanes), ▽: Y(isoalkanes), ■: Y(methane), ◆: Y(cycloalkanes), ●: Y(aromatics).

and ethane by hydrogenolysis on the metal^[11] can, in all probability, be ruled out, because if it were operative the yields of methane and ethane would be expected to increase with increasing palladium content. In addition, the fact that the molar amount of the metal is important, but not its nature (Figure 2 and Table 1, 0.4 wt % Pt corresponds to about the same amount of metal as 0.2 wt % Pd), represents independent evidence against a contribution of hydrogenolysis under the reaction conditions applied here.

In conclusion during the conversion of methylcyclohexane, maximal yields of *n*-alkanes with two and more carbon atoms, which are very desirable components for a synthetic steam-cracker feedstock, are not obtained on monofunctional acidic

or on typically bifunctional catalysts, but on Pd/H-ZSM-5 zeolites with very small contents of noble metal in the range of approximately 10–100 ppm (approximately 78 % at 400 °C). Such catalysts can be classified neither as monofunctional nor as bifunctional but, in the light of the present study, they represent rather a new type of catalyst, which we refer to as Haag–Dessau catalysts because the salient feature of the cracking performance of these catalysts is an unusually high contribution of nonclassical Haag–Dessau cracking.

Experimental Section

Zeolite ZSM-5 ($n_{Al}/(n_{Si} + n_{Al}) = 4.8\%$, that is, $n_{Si}/n_{Al} = 20$, crystal size: $1.5 \times 0.5 \times 0.5 \mu m$) was hydrothermally synthesized as previously reported.^[12] After ion exchange with aqueous solutions of ammonium nitrate and palladium(II) or platinum(II) tetraamminochloride, the samples were pre-treated successively in flows of N_2 (12 h), air (2 h), N_2 (1 h), and H_2 (7 h) at 400 °C. This yielded catalysts with 0 (<90), 10 (<90), 100 (92), 2.0×10^3 (2.0×10^3), and 10×10^3 (10×10^3) ppm of palladium and 3.7×10^3 (4.0×10^3) ppm of platinum (referenced to the dry catalyst; the values given are calculated from the amount of metal salt used and in parentheses are the analytical values obtained by atomic emission spectroscopy with inductively coupled plasma (AES/ICP)). The catalytic experiments were performed in a stainless steel flow-type apparatus with a fixed-bed reactor. The mass of dry catalyst (particle size between 0.2 and 0.3 mm), the total pressure, the partial pressure of methylcyclohexane at the reactor inlet, and the WHSV were 500 mg, 6.0 MPa, 65 kPa, and $0.68 h^{-1}$, respectively. Product analysis was achieved by capillary gas chromatography. No change of conversion, yields, or CMR value was observed due to the length of time on stream within 10 h. The experimental data given here were obtained after about 90 min on stream.

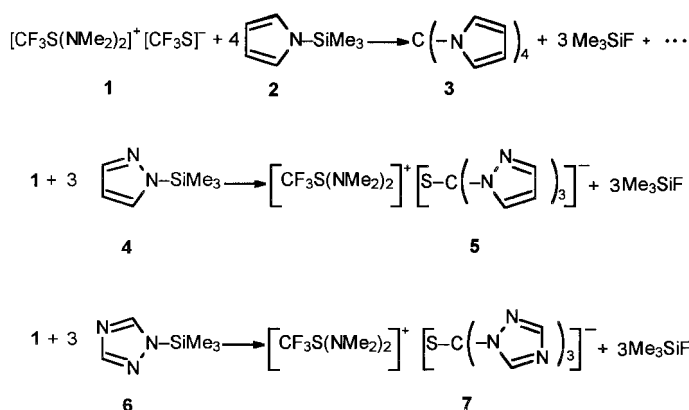
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Tris(azoly)methylthiolates: Another New Scorpionate Class?

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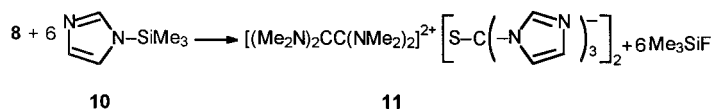
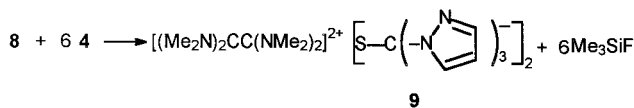
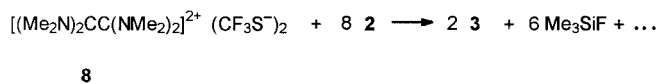
The trimethylsilyldifluorosilicate ion $[\text{Me}_3\text{SiF}_2]^-$ (usually used as its sulfonium salt $\text{A}^+[\text{Me}_3\text{SiF}_2]^-$ ($\text{A}^+ = [(\text{Me}_2\text{N})_3\text{S}]^+$ (TAS),^[1] $[(\text{Me}_2\text{N})_2\text{SCF}_3]^+$ (CF_3BAS),^[2] $[(\text{Me}_2\text{N})_3\text{SO}]^+$ (TAOS)^[3]) behaves like a “naked” fluoride due to its very weak, long^[4] and thus, extremely reactive Si–F bond.^[5] It is particularly well suited to the nucleophilic cleavage of Si–element bonds.^[6] The considerable lengthening of the C–F bond in the anions $[\text{OCF}_3]^-$ (139 pm)^[7] and, less markedly, $[\text{SCF}_3]^-$ (134–135 pm),^[8] (compared to C–F bond lengths in covalent or cationic CF_3S derivatives (130–131 pm)) leads one to expect a significant activation of these bonds. Whereas $[\text{OCF}_3]^-$ only acts as a fluoride source,^[9] it is known that $[\text{SCF}_3]^-$ reacts as a nucleophile to give trifluoromethylthioethers in high yield.^[8, 10, 11] In reactions of $[\text{CF}_3\text{S}(\text{NMe}_2)_2]^+[\text{SCF}_3]^-$ (**1**)^[12] with the silylated azoles **2**, **4**, and **6**, we have been able to show that in $[\text{SCF}_3]^-$ ions the C–F bond is so highly activated that it reacts even at temperatures below 0 °C (Scheme 1).



Scheme 1.

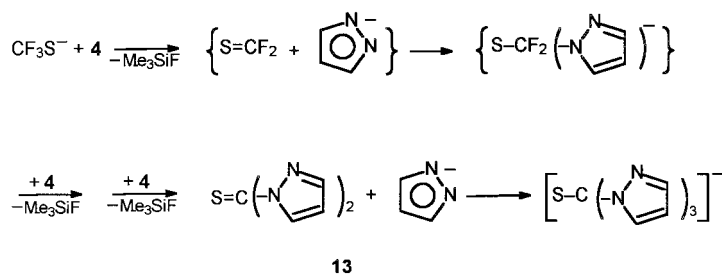
Here, a surprising reaction path is observed: the anion acts as a nucleophile and is itself the target of nucleophilic attack. Tetrapyrrolemethane (**3**) is isolated from trimethylsilylpyrrole, whereas with trimethylsilylpyrazole (**4**) and 1,2,4-trimethylsilyltriazole (**6**) the reaction stops at the tris(azoly)methylthiolates **5** and **7**, respectively.

As expected, these reactions are virtually independent of the counterion. The very stable salt **8**, which was recently reported by Kolomeitsev et al.,^[8] undergoes analogous reactions at slightly higher temperatures (Scheme 2). A proposal for the reaction path of the formation of the tris(azoly)methylthiolates is given in Scheme 3. The last step of this reaction

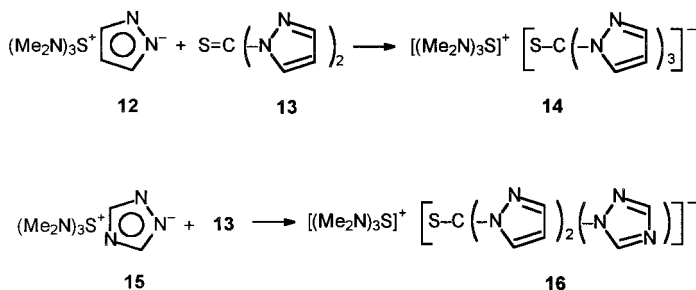


Scheme 2.

scheme is the addition of the pyrazole anion to the bis(pyrazoly)thioether **13**. This step was confirmed by the direct reaction of **13**^[13] with **12**^[14] and **15**^[14], respectively. The corresponding products **14** and **16** are formed quantitatively at room temperature in CH_3CN as solvent (Scheme 4).



Scheme 3.



Scheme 4.

Kläui and co-workers recently reported the synthesis of $[(\text{pyr})_3\text{CSO}_3]^-$ (pyr = pyrazoly)^[15] which is closely related to our tris(azoly)methylthiolates. This tris(pyrazoly)methane-sulfonate which was synthesized from lithium tris(pyrazoly)methane and $\text{SO}_3 \cdot \text{NMe}_3$ is a water-soluble, hydrolysis-stable analogue of the tris(pyrazoly)borates,^[16] which could play a very important role as a novel scorpionate^[17] ligand in coordination chemistry. These investigations have also shown that the starting material $\text{Li}[\text{C}(\text{pyr})_3]$ can be used as a versatile reagent for the synthesis of further tris(pyrazoly)methane derivatives.^[15] It is not known whether the thiolates we have described can be synthesized by the reaction of the salt with sulfur.

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The tris(azolyl)methylthiolates **5**, **7**, **9**, **11**, and **16**, as well as tetra(pyrrolyl)methane (**3**) were unambiguously characterized by X-ray structure analyses. As an example the structure of the tris(pyrazolyl) salt **5** is shown in Figure 1. Selected bond

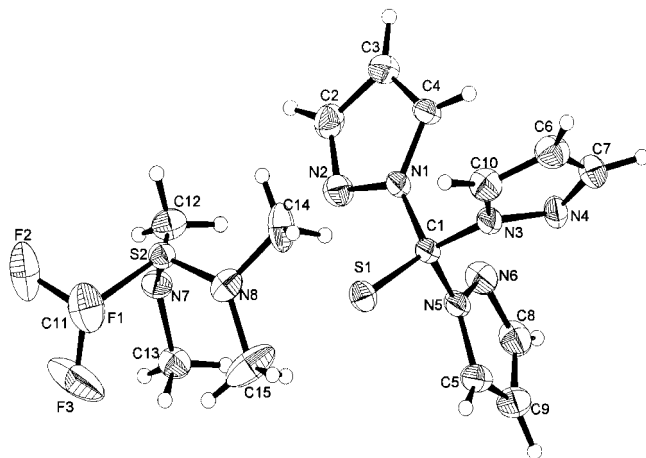


Figure 1. Structure of the salt **5** with average bond lengths [pm] and selected bond and torsion angles [°]. Anion: C1-S 178.8, C1-N1 147.6, N1-N2 135.5, N2-C2 132.6, C2-C3 139.7, C3-C4 136.6, C4-N1 135.4; N1-C1-N3 105.8(2), N3-C1-N5 107.1(2), N5-C1-N1 107.0(2), S1-C1-N1 113.1(2), S1-C1-N3 110.9(2), S1-C1-N5 112.6(5); S1-C1-N1-N2 – 54.9(3), S1-C1-N3-N4 153.9(2), S1-C1-N5-N6 152.1(2); cation: C-F 131.2, S-N 160.6, C-S 185.4, C-N 147.2; N7-S2-N8 119.96(13), N8-S2-C11 100.79(14), N7-S2-C11 99.00(13); sum of the angles at N7 353.8, at N8 355.7°.

lengths and angles of the anions are compared with those of the $\text{Ti}^+[(\text{pyr})_3\text{CSO}_3]^-$ (**A**)^[16] in Table 1. Whereas the central SCN_3 framework of the tris(azoly)thiolates is virtually independent

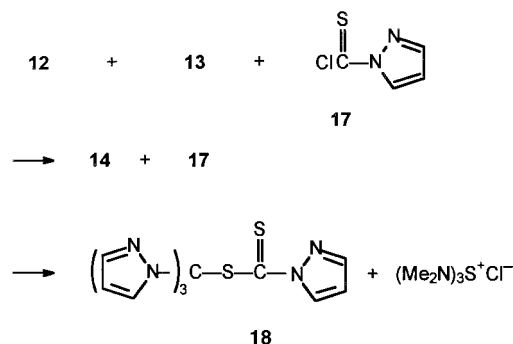
Table 1. Comparison of selected average bond lengths and angles of **A**, **5**, **9**, **7**, and **11**.

	A	5	9	7	11
S–C [pm]	189.1	178.8	177.8	176.9	177.4
C–N [pm]	145.2	147.6	148.3	148.2	148.1
N–N [pm]	137.3	135.5	135.7	–	–
N–C–S [°]	109.7	112.2	111.8	112.6	112.7
N–C–N [pm]	109.2	106.6	107.0	106.3	106.0

of the particular azolyl group, we observe a considerable difference between the [(pyr)₃CS]⁻ and the [(pyr)₃CSO₃]⁻ ions. In particular, the C–S distance in the methanesulfonate **A** is 10 pm longer than in the thiolate anions. Coulombic repulsion between the strongly positive S^{VI} center and the, likewise, positively polarized central carbon lead to the bond lengthening, the somewhat increased coulombic attraction leads to a shortening of the C–N bonds. The higher electron density in the C–S bond of the thiolates leads to an opening of the S-C-N angle and a compression of the N-C-N angle.

We expect interesting coordination chemistry for the tris(azolyl)methylthiolates and investigations are underway. This class of compounds is not only important for coordination chemistry, but also as a nucleophile in organic chemistry as shown, for example, by the reaction of $[(\text{Me}_2\text{N})_3\text{S}]^+[\text{pyr}]^-$ (**12**) with a mixture of $\text{ClC}(\text{S})(\text{pvr})$ (**17**) and bis(pyrazolyl)-

thioketone **13** (Scheme 5). We isolated a mixture of (pyr)₃CSC(S)(pyr) (**18**) and [(Me₂N)₃S]⁺Cl⁻. The formation of **18** can be formally explained by a nucleophilic attack by **14** on ClC(S)(pyr).



Scheme 5.

Experimental Section

General procedure: In a N₂ dry-box the salt **1** or **8** (0.75–1 mmol), respectively, was placed into one side of a two-armed lambda-shaped glass vessel fitted with a Teflon valve. A small excess of the trimethylsilylazole was placed, by a syringe, into the second arm under dry N₂. CH₃CN (10 mL) was condensed at –196 °C by using a vacuum line onto the salt **1** or **8**. At –40 °C the silylazoles were slowly poured onto the salt solutions. Whereas **1** already reacted readily at –10 °C, the reaction with **8** finished after 30 min at room temperature. The formation of tetrapyrrolemethane (**3**) from **8** and **2** required more than 24 h. In the case of the reactions of **8** the silylazoles could also be added directly to the salt solutions at room temperature. Me₃SiF, formed as by-product, was removed in vacuum, the reaction solution was layered with diethyl ether (30 mL) at –40 °C and the reaction vessel kept still in a cryostat bath at this temperature for one week. Most of the unreacted starting materials and decomposition products were removed by decantation of the liquid from the crystals. After condensing off the solvent the crystals were washed with diethyl ether and the volatiles removed under vacuum.

The tris(azolyl)methanethiolate salts were isolated in yields of 80–90 %. The salts decomposed in moist air.

3: Yield 90%; m.p. 130°C, ¹H NMR (CD₃CN, 20°C): δ = 6.6 (⁴J(AA') = 1.0, ³J(AB) = 3.2, ⁴J(AB') = 1.5 Hz, 2H), 6.3 (³J(BB') = 2.0 Hz, 2H).

5: Yield 92 %; m.p. 119 °C, ¹H NMR (CD₃CN, 20 °C): δ = 3.2 (q, ⁵J(H,F) = 0.8 Hz), 6.1 (dd, ³J(H,H) = 2.5, 1.6 Hz), 7.3 (dd, ³J(H,H) = 1.6, ⁴J(H,H) = 0.9 Hz), 8.1 (dd, ³J(H,H) = 2.5, ⁴J(H,H) = 0.9 Hz); ¹⁹F NMR (CD₃CN, 20 °C): δ = −58.3 (tridecet, ⁵J(F,H) = 0.8 Hz).

7: Yield 92 %; m.p. 120 °C, ¹H NMR (CD₃CN, 20 °C): δ = 3.2 (q, ⁵J(H,F) = 0.8 Hz), 7.8 (d, ⁴J(H,H) = 0.7 Hz), 8.9 (d, ⁴J(H,H) = 0.7 Hz); ¹⁹F NMR (CD₃CN, 20 °C) δ = −58.3 (tridecet, ⁵J(F,H) = 0.8 Hz).

9: Yield 87 %; m.p. 116 °C, ¹H NMR (CD₃CN, 20 °C): δ = 3.0 (s), 3.3 (s), 6.1 (dd, ³J(H,H) = 2.5, 1.6 Hz), 7.3 (dd, ³J(H,H) = 1.6, ⁴J(H,H) = 0.8 Hz), 8.0 (dd, ³J(H,H) = 2.5, ⁴J(H,H) = 0.8 Hz).

11: Yield 83%; m.p. 114 °C, ¹H NMR (CD₃CN, 20 °C): δ = 3.0 (s), 3.3 (s), 7.1 (dd, ³J(H,H) = 1.8, ⁴J(H,H) = 0.9 Hz), 7.6 (dd, ³J(H,H) = 1.8, 1.4 Hz), 8.1 (dd, ³J(H,H) = 1.4, ⁴J(H,H) = 0.9 Hz).

X-ray structure analysis: Crystals were grown by slow diffusion of diethyl ether into CH₂CN solutions of the compounds at −40°C. Crystals suitable for X-ray structure analysis were fixed to a glass fiber by Kel-F oil and measured on a Siemens P4 four-circle diffractometer with graphite-monochromated MoK α radiation at −100°C.

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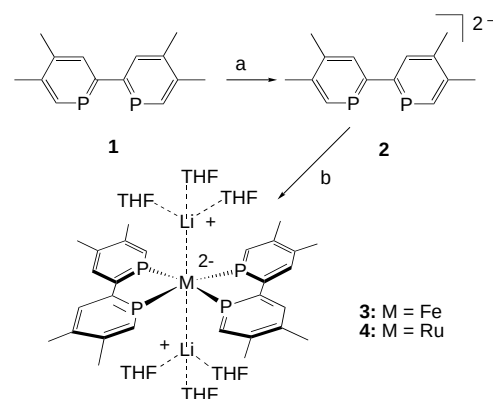
Dianionic Iron and Ruthenium(2 –) Biphosphinine Complexes: A Formal d^{10} Ruthenium Complex with a Square Planar Geometry**

Patrick Rosa, Nicolas Mézailles, Louis Ricard,
François Mathey, Pascal Le Floch,* and Yves Jean

Though the Collman's reagent $[\text{Fe}(\text{CO})_4]^{2-}$ is probably one of the most popular and useful reagents in organic synthesis,^[1] our knowledge of dianionic Group 8 metal complexes still remains limited. In addition to the carbonyl ruthenium analogue $[\text{Ru}(\text{CO})_4]^{2-}$, only a few other complexes are known: the complete series of PF_3 derivatives $[\text{M}(\text{PF}_3)_4]^{2-}$ ($\text{M} = \text{Fe}, \text{Ru}, \text{Os}$),^[2] the isocyanide complexes $[\text{Ru}(\text{CNR})_4]^{2-}$ synthesized by Cooper and co-workers,^[3] and the amazing Jonas' iron complexes $[\text{Fe}(\text{C}_2\text{H}_4)_4]^{2-}$ and $[\text{Fe}(\text{cod})_2]^{2-}$ ($\text{cod} = \text{cycloocta-1,5-diene}$).^[4] We have begun to explore the use of sophisticated phosphinine-based ligands in an effort to design phosphorus equivalents of carbonyl ligands.^[5] This we recently illustrated by the successful stabilization of an Au^0 center encapsulated in a silacalix-[4]-phosphinine macrocycle^[6] and the synthesis of dianionic 2,2'-biphosphinine complexes of Group 4^[7] and 9 metals.^[8] Herein we report the successful stabilization of dianionic Fe and Ru 2,2'-biphosphinine complexes.

All our syntheses were carried out using dianion **2** which is readily obtained by reduction of 2,2'-biphosphinine **1** (tmbp) using lithium in excess.^[9] Reaction of two equivalents of **2** with one equivalent of $[\text{FeCl}_2(\text{thf})_{1.5}]_n$ or $[\text{Ru}(\text{cod})(\text{acac})_2]$ ($\text{acac} = 2,4\text{-pentanedione}$, acetylacetonate) in THF at low temperature, yielded complexes **3** and **4**, respectively, which were isolated as highly moisture and oxygen sensitive powders (Scheme 1).

The formulation of these two complexes was confirmed by NMR spectroscopic data (^1H and ^{13}C). To gain more structural information, an X-ray crystal structure analysis of complex **4** was carried out (Figure 1).^[10] Remarkably, the overall geometry of **4** is not tetrahedral as usually observed for ML_4 d^{10} complexes,^[8] but square planar;^[11] the iron complex **3** is assumed to have the same structure. The two biphosphinines are roughly located in the same plane ($\theta = 7.29^\circ$, θ being the interplane angle) and the two cationic $[\text{Li}(\text{thf})_3]^+$ units are located above and below the plane in apical positions. Though the structure roughly resembles an octahedron, the $\text{Ru} \cdots \text{Li}$ separation (2.740(3) Å) is long and exceeds the sum of the covalent radii (2.60 Å) indicating only a very weak, mainly



Scheme 1. Syntheses of **3** and **4**: a) Li (excess), THF, 25 °C, 2 h. b) $[\text{FeCl}_2(\text{thf})_{1.5}]_n$ or $[\text{Ru}(\text{cod})(\text{acac})_2]$, THF –80 °C → RT.

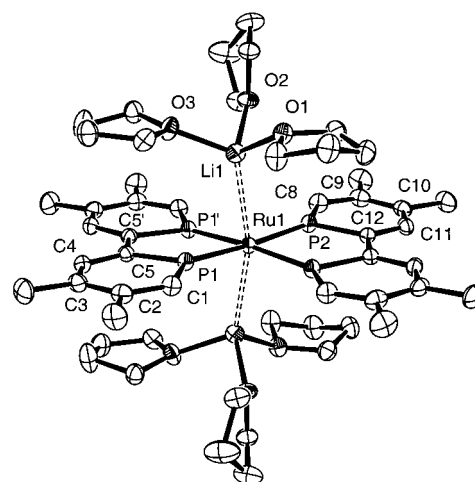
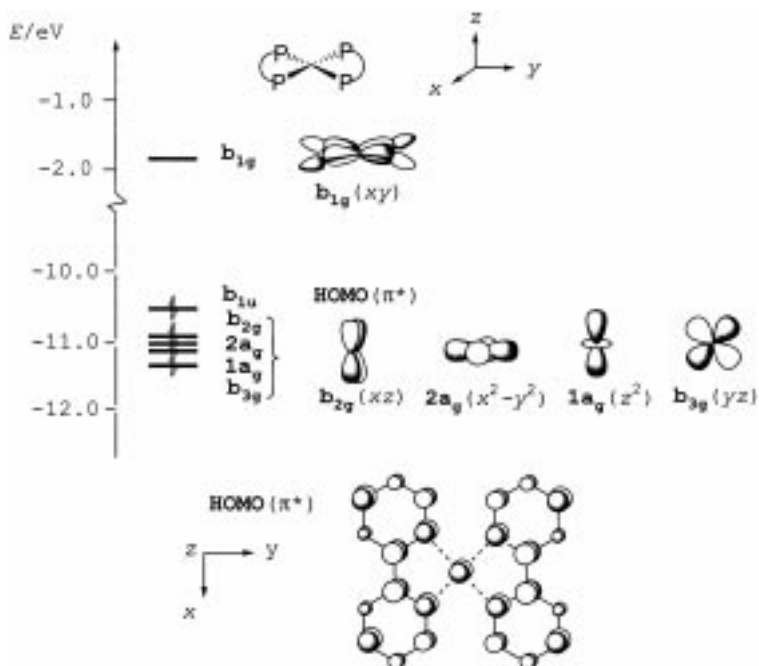


Figure 1. Molecular structure of **4**. Thermal ellipsoids are set at the 50% probability level. The hydrogen atoms are omitted for clarity. Important distances [Å] and angles [°]: Ru1-P1 2.2131(5), Ru1-P2 2.2168(5), $\text{Ru1} \cdots \text{Li1}$ 2.740(3), P1-C5 1.777(2), P1-C1 1.740(3), C1-C2 1.381(3), C2-C3 1.418(3), C3-C4 1.393(3), C4-C5 1.395(2), C5-C5' 1.436(3), Li1-O1 2.015(3), Li1-O2 1.984(4), Li1-O3 2.001(4); P1-Ru1-P2 174.85(2), P1-Ru1-Li1 82.89(7), P1-Ru1-P1' 79.19(2), P2-Ru1-Li1 91.99(7), C5-P1-C1 102.12(8), P1-C1-C2 125.6(2), C1-C2-C3 122.8(2), C2-C3-C4 121.8(2), C3-C4-C5 127.0(2).

electrostatic, interaction between the Ru and Li centers. This structure markedly differs from that of the iron carbonyl derivative^[12] as well as that of the Jonas' complex $[\text{Fe}(\text{C}_2\text{H}_4)_4][[\text{Li}(\text{tmeda})_2]$ ($\text{tmeda} = N,N,N',N'$ -tetramethyl 1,2-ethanediamine) in which Fe-Li and C-Li bonds are found.^[4] Another interesting structural feature is provided by the internal bond distances in the two ligands. Apparently, a significant electronic transfer occurs from the metal into the π^* LUMO of the biphosphinine as shown by the shortening of the C–C connection between the two rings (average 1.437 Å in **4** vs. 1.490 Å in **1**) and the lengthening of the internal P=C bonds (1.770 Å in **4** vs. 1.736(4) Å in **1**). All distances in the cycles are similar to those found in the radical anion $1^{\cdot-}$.^[13] A first insight to this particular geometry was given by extended Hückel (EH) calculations^[14, 15] on the $[\text{Ru}(\text{bp})_2]^{2-}$ ion ($\text{bp} = \text{C}_{14}\text{H}_{16}\text{P}_2$ parent compound). The analysis of the electronic structure reveals that only the four low-lying d orbitals of this square-planar complex are actually occupied. The two extra

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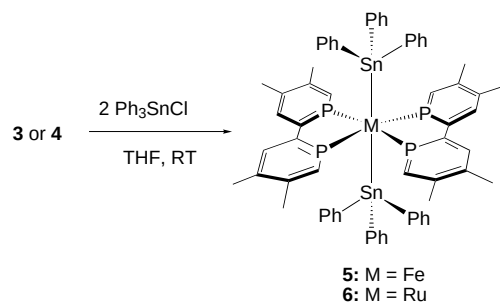


Scheme 2. Electronic structure of the $[\text{Ru}(\text{bp})_2]^{2-}$ complex (five highest occupied MOs and the vacant fifth orbital of the d block). Symmetry labels are given assuming an idealized D_{2h} symmetry. For the sake of clarity, only the metal contribution is drawn for the four occupied d orbitals.

electrons are located in the b_{1u} orbital which is depicted in Scheme 2. This orbital results from the in-phase combination of the π^* LUMO on each biphosphinine ligand which is further stabilized by a bonding interaction with the parallel p metal orbital. Therefore, the formal $d^{10} [\text{Ru}(\text{bp})_2]^{2-}$ complex is in fact a d^8 ruthenium species coordinated by two radical anions $1^{\cdot-}$. This electron counting is consistent with the square-planar geometry observed and rationalizes the bond length changes in the biphosphinine ligands upon coordination to the metal center.

Though a significant part of the electron density resides on the ligands, the metal centers in **3** and **4** remain the reaction center when triphenyltin chloride is used as reagent and complexes $[\text{M}(\text{tmbp})_2(\text{Ph}_3\text{Sn})_2]$ **5** and **6** were isolated as very stable solids (Scheme 3). The structure of the iron complex **5** was confirmed by an X-ray crystal structure analysis (not shown).

Further studies aimed at investigating the reactivity of these new dianionic Fe and Ru(2-) species are currently underway.



Scheme 3. Syntheses of **5** and **6**.

Experimental Section

General procedure for the syntheses of complexes **3** and **4**: Biphosphinine **1** (123 mg, 0.50 mmol) was treated with excess lithium at 25 °C in THF (10 mL). After 2 h, the green solution obtained (dianion **2**) was cooled to -80 °C and $[\text{Ru}(\text{cod})-(\text{acac})_2]$ (92 mg, 0.23 mmol) or $[\{\text{FeCl}_2(\text{thf})_{1.5}\}_n]$ (53 mg, 0.23 mmol) were added. After stirring for 5 min, the red solution obtained was slowly warmed to 25 °C. The solvent was evaporated and the resulting red solid was washed with diethyl ether (10 mL). The high sensitivity of **3** and **4** towards oxygen and moisture, and the presence of traces of LiCl salts precluded the determination of yields and satisfactory elemental analyses. Suitable crystals of **4** for X-ray structure analysis were grown from THF solution in a sealed tube at -18 °C. Crystals were separated from the mother liquor at this temperature to avoid dissolution and then protected with paratone oil for handling.

3: ^{31}P NMR (81 MHz, $\text{C}_6\text{D}_6\text{O}$, 25 °C): δ = 196.9 (s); ^1H NMR (200 MHz, $\text{C}_6\text{D}_6\text{O}$, 25 °C): δ = 2.29 (s, 12 H; Me), 2.40 (s, 12 H; Me), 7.94 (m, 4 H, $\text{H}_{3,3'}$ or $\text{H}_{6,6'}$), 8.12 (m, 4 H, $\text{H}_{3,3'}$ or $\text{H}_{6,6'}$); ^{13}C NMR (200 MHz, $\text{C}_6\text{D}_6\text{O}$, 25 °C): δ = 22.5 (s, Me), 24.45 (s, Me), 115.4 (m, $\text{C}_{4,4'}$ or $\text{C}_{5,5'}$), 126.3 (m, $\text{C}_{3,3'}$ or $\text{C}_{6,6'}$), 133.9 (m, $\text{C}_{3,3'}$ or $\text{C}_{6,6'}$), 139.2 (m, $\text{C}_{4,4'}$ or $\text{C}_{5,5'}$), 144.2 (m, $\text{C}_{2,2'}$).

4: ^{31}P NMR (81 MHz, $\text{C}_6\text{D}_6\text{O}$, 25 °C): δ = 188.7 (s); ^1H NMR (200 MHz, $\text{C}_6\text{D}_6\text{O}$, 25 °C): δ = 2.37 (s, 12 H; Me), 2.52 (s, 12 H; Me), 8.03 (m, 4 H, $\text{H}_{3,3'}$ or $\text{H}_{6,6'}$), 8.12 (m, 4 H, $\text{H}_{3,3'}$ or $\text{H}_{6,6'}$); 8.21 (m, 4 H, $\text{H}_{3,3'}$ or $\text{H}_{6,6'}$); ^{13}C NMR (50 MHz, $\text{C}_6\text{D}_6\text{O}$, 25 °C): δ = 22.7 (s, Me), 24.3 (s, Me), 116.1 (m, $\text{C}_{4,4'}$ or $\text{C}_{5,5'}$), 126.5 (m, $\text{C}_{3,3'}$ or $\text{C}_{6,6'}$), 133.2 (m, $\text{C}_{6,6'}$ or $\text{C}_{3,3'}$), 138.5 (m, $\text{C}_{4,4'}$ or $\text{C}_{5,5'}$), 146.3 (m, $\text{C}_{2,2'}$).

General procedure for the syntheses of complexes **5** and **6**: Dianionic complexes **3** and **4**, prepared as above in THF, were treated with Ph_3SnCl (175 mg, 0.5 mmol) at 25 °C. After stirring for 10 min, the solvent was evaporated and the resulting solid was washed twice with diethyl ether (10 mL) and then dissolved in CH_2Cl_2 (10 mL). After filtration on celite, the solvent was evaporated. After standing in THF for several days, **5** and **6** were isolated as orange crystals.

5: Yield 231 mg (70 %); m.p. > 220 °C; elemental analysis (%) calcd for $\text{C}_{64}\text{H}_{62}\text{FeP}_4\text{Sn}_2$: C 61.58, H 5.01; found: C 61.65, H 4.90; ^{31}P NMR (81 MHz, CDCl_3 , 25 °C): δ = 231.9 (pseudo t, $^2J(\text{P},\text{Sn}) = 326.0$ Hz); ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 2.45 (s, 24 H, Me), 6.37–6.99 (m, 30 H, ShPh_3), 7.93–8.17 (m, 8 H, $\text{H}_{3,3'}$ and $\text{H}_{6,6'}$); ^{13}C NMR (50 MHz, CDCl_3 , 25 °C): δ = 23.1 (s, Me), 22.5 (virtual t, AXX' , $\Sigma J(\text{C},\text{P}) = 5.0$ Hz, Me), 126.9 (pseudo t, $^4J(\text{C},\text{Sn}) = 9.7$ Hz, C_{para} SnPh_3), 127.1 (pseudo t, $^3J(\text{C},\text{Sn}) = 40.4$ Hz, C_{meta} SnPh_3), 129.7 (m, $\text{C}_{3,3'}$), 130.2 (m, $\text{C}_{5,5'}$ or $\text{C}_{4,4'}$), 137.2 (pseudo t, $^2J(\text{C},\text{Sn}) = 33.4$ Hz, C_{ortho} SnPh_3), 141.0 (m, $\text{C}_{6,6'}$), 145.8 (s, C_q ShPh_3), 146.0 (m, $\text{C}_{4,4'}$ or $\text{C}_{5,5'}$), 151.1 (m, $\text{C}_{2,2'}$).

6: Yield 144 mg (40 %); m.p. > 220 °C; elemental analysis (%) calcd for $\text{C}_{64}\text{H}_{62}\text{RuP}_4\text{Sn}_2$: C 59.42, H 4.83; found: C 59.31, H 4.90; ^{31}P NMR (81 MHz, CDCl_3 , 25 °C): δ = 221.0 (pseudo t, $^2J(\text{P},\text{Sn}) = 193.3$ Hz); ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 2.45 (s, 12 H, Me), 2.48 (s, 12 H, Me), 6.49–6.88 (m, 30 H, SnPh_3), 8.11–8.26 (m, 8 H, $\text{H}_{3,3'}$ and $\text{H}_{6,6'}$); ^{13}C NMR (50 MHz, CDCl_3 , 25 °C): δ = 22.2 (s, Me), 24.1 (m, Me), 126.5 (pseudo t, $^4J(\text{C},\text{Sn}) = 9.7$ Hz, C_{para} SnPh_3), 126.9 (pseudo t, $^3J(\text{C},\text{Sn}) = 40.0$ Hz, C_{meta} SnPh_3), 130.6 (m, $\text{C}_{3,3'}$), 131.1 (m, $\text{C}_{5,5'}$ or $\text{C}_{4,4'}$), 137.2 (pseudo t, $^2J(\text{C},\text{Sn}) = 34.7$ Hz, C_{ortho} SnPh_3), 139.9 (m, $\text{C}_{6,6'}$), 146.0 (s, C_q SnPh_3), 146.0 (m, $\text{C}_{4,4'}$ or $\text{C}_{5,5'}$), 151.1 (m, $\text{C}_{2,2'}$).

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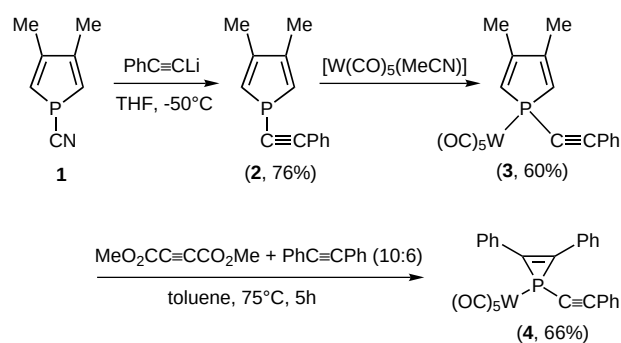
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Stepwise Building of Polyphosphirene Chains

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As a result of its very peculiar structural and electronic properties, the phosphirene ring occupies a special niche in carbon–phosphorus heterocyclic chemistry.^[1] Whereas the foundations of its chemistry are now well established, almost nothing is known about oligomeric or macrocyclic molecules containing several phosphirene units. Recently, both 2,2'-biphosphirenes^[2] and the related 2,2'-bisphosphiranes^[3] have been described, but their syntheses cannot be easily extrapolated to yield higher oligomers. Herein, we wish to present an iterative approach which opens a route to a new class of polyphosphirenes.

Our initial idea was to synthesize a 1-alkynylphosphirene derivative and to investigate the reactivity of its C≡C triple bond toward terminal phosphinidene complexes. For this purpose, we needed to prepare an alkynylphosphinidene precursor. Accordingly, we first synthesized the 1-alkynylphosphole **2** and the corresponding P–W(CO)₅ complex **3** from the 1-cyanophosphole **1**.^[4] Fearing a [P+C≡C] self-condensation of the alkynylphosphinidene intermediate, we then decided to combine the synthesis of the 7-phosphanorbornadiene precursor^[5] with its generation and trapping by a reactive alkyne such as diphenylacetylene (tolan).^[6] On that basis, **3** was allowed to react with a 10:6 mixture of dimethyl acetylenedicarboxylate and tolan. Tolan proved to compete efficiently with the self-condensation of the phosphinidene intermediate and the desired 1-alkynylphosphirene complex **4** was obtained in satisfactory yield (Scheme 1).

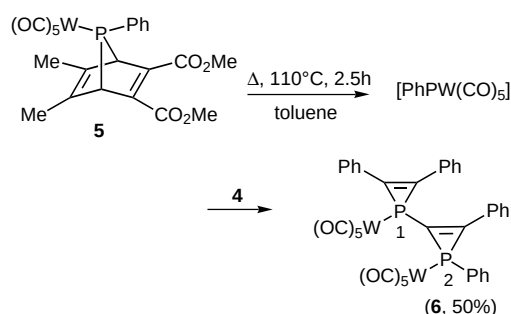


Scheme 1. Synthesis of a 1-alkynylphosphirene complex.

The C≡C triple bond of **4** is highly hindered by the phosphirenyl substituent, nevertheless, a typical terminal phosphinidene complex such as [PhPW(CO)₅] readily cycloadds to it to give the 1,2'-biphosphirene **6** (Scheme 2).

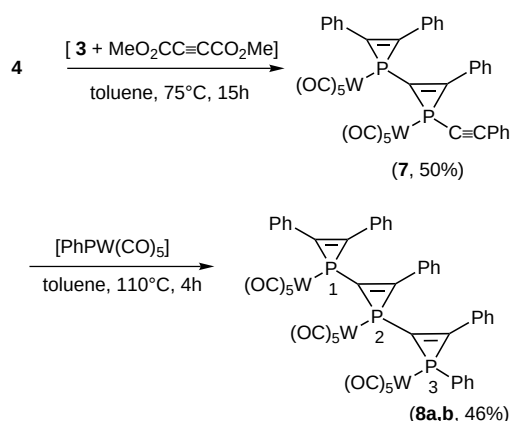
The ³¹P NMR spectrum of **6** confirms the presence of the two phosphirene rings: δ(³¹P) = -186.5 (P1), -142.6 (P2),

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Scheme 2. Synthesis of a 1,2'-biphosphirene complex.

$^2J_{\text{PP}} = 11$ Hz. At this point, it is interesting to recall that, in many cases, terminal phosphinidene complexes insert into the ring P–C2 bond of 2-alkynylphosphirenes, thus preventing the formation of the expected 2,2'-biphosphirenes.^[7] Clearly, a 2-alkynyl substituent weakens the ring P–C bonds, whereas a 1-alkynyl substituent does not. This success led us to attempt the condensation of **4** with the system $[\mathbf{3} + \text{MeO}_2\text{C}-\text{C}\equiv\text{C}-\text{CO}_2\text{Me}]$, the synthetic equivalent of the 7-phosphanorbornadiene precursor of $[\text{PhC}\equiv\text{CPW}(\text{CO})_5]$ employed above. This new experiment was again successful (Scheme 3).



Scheme 3. Synthesis of a triphosphirene complex.

The ^{31}P NMR parameters of **7** are very similar to those of **6**, except that the two phosphorus nuclei resonate at almost the same frequency: $\delta(^{31}\text{P}) = -184.0$ and -187.1 , $^2J_{\text{PP}} = 16$ Hz. Noteworthy is that **7** was formed as a minor by-product in the synthesis of **4**. The availability of **7** gave us the possibility to check the validity of our iterative approach. By using the method which converts **4** into **6** we could transform **7** into the triphosphirene **8** (Scheme 3).

The triphosphirene **8** was formed as a 1:1 mixture of two diastereomers showing characteristic ^{31}P NMR spectra: **8a**: $\delta(^{31}\text{P}) = -188.5$ (P1), -169.8 (P2), -139.3 (P3), $^2J_{\text{P1,P2}} = 4$ Hz, $^2J_{\text{P2,P3}} = 14$ Hz; **8b**: $\delta(^{31}\text{P}) = -187.0$ (P1), -173.8 (P2), -139.0 (P3), $^2J_{\text{P1,P2}} = 9$ Hz, $^2J_{\text{P2,P3}} = 21$ Hz. These two isomers were difficult to separate by standard chromatographic procedures. However, a slow recrystallization in hexane/toluene yielded pure crystals of **8a**. The X-ray data are presented in (Figure 1).^[8] The structural parameters of the first phosphirene ring (P1) are very close to those of the prototypical 1,2,3-triphenylphosphirene complex $[(\text{PhC})_2\text{PhPW}(\text{CO})_5]$.^[6] Both

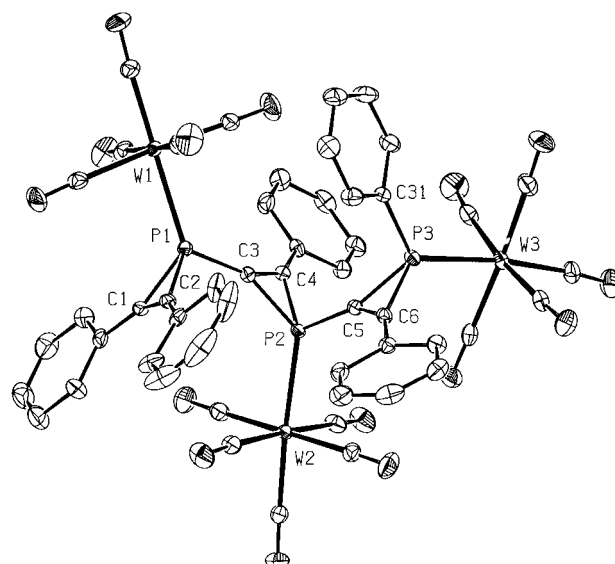


Figure 1. Structure of **8a**. Hydrogen atoms are omitted for clarity. Selected distances [Å] and angles [$^\circ$]: P1–C1 1.793(5), P1–C2 1.781(5), P1–C3 1.804(5), P1–W1 2.473(1), C1–C2 1.324(7), P2–C3 1.809(5), P2–C4 1.803(5), P2–C5 1.788(5), C3–C4 1.326(6), P2–W2 2.469(1), P3–C5 1.818(4), P3–C6 1.796(5), P3–C31 1.818(5), P3–W3 2.488(1), C5–C6 1.321(7); C1–P1–C2 43.5(2), C1–P1–C3 103.5(2), C1–P1–W1 125.9(2), C2–P1–C3 104.6(2), C2–P1–W1 124.8(2), C3–P2–C4 43.1(2), C3–P2–C5 106.7(2), C3–P2–W2 129.7(1), C4–P2–C5 105.4(2), C4–P2–W2 127.5(2), C5–P3–C6 42.9(2), C5–P3–C31 106.5(2), C5–P3–W3 124.8(1), C6–P3–C31 106.5(2), C6–P3–W3 124.9(2).

the second (P2) and third rings (P3) show elongated P–C ring bonds. This might be the result of steric compression, which tends to increase the distances between the bulky P–W units. However, as we have seen, this weakening of the ring P–C bonds does not interfere with the $[\text{P}+\text{C}\equiv\text{C}]$ condensation process. This process is both original and useful, and appears to have no equivalent in the related silirene field.^[9] Finally, the formation of a small amount of **7** during the synthesis of **4** indicates that the possibility exists to create longer oligophosphirene chains using a one-pot procedure. Since various techniques exist to obtain free phosphirenes from their complexes,^[10] an interesting coordination chemistry can be built around such chains.

Experimental Section

2, 3: A solution of the lithium salt of phenylacetylene (1.3 equiv) in diethyl ether was added at -50°C to a solution of 1-cyano-3,4-dimethylphosphole (**1**)^[4] (7 g, 5×10^{-2} mol) in THF (150 mL). The mixture was then stirred for 0.5 h at RT. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with hexane/dichloromethane (4/1) to yield **2** (8 g, 76%): ^{31}P NMR (81 MHz, THF): $\delta = -40.6$. Complex **3**: ^{31}P NMR (CDCl_3): $\delta = -25.3$ ($^1J(\text{P,W}) = 219.7$ Hz); ^{13}C NMR (50 MHz, CDCl_3): $\delta = 17.7$ (d, $^3J(\text{C,P}) = 13.3$ Hz; Me), 77.9 (d, $^1J(\text{C,P}) = 76.0$ Hz; P–C $\equiv$ C), 108.1 (d, $^2J(\text{C,P}) = 13.8$ Hz, P–C $\equiv$ C), 121.4 (s; PhC $\equiv$ C, C_{ipso}), 127.0 (d, $^1J(\text{C,P}) = 50.2$ Hz; CH–P), 152.1 (d, $^2J(\text{C,P}) = 12.2$ Hz; Me–C $\equiv$), 196.2 (d, $^2J(\text{C,P}) = 7.5$ Hz; cis–CO), 199.5 (d, $^2J(\text{C,P}) = 18.5$ Hz; trans–CO); ^1H NMR (200 MHz, CDCl_3): $\delta = 2.19$ (s; Me), 6.36 (d, $^2J(\text{H,P}) = 38.1$ Hz; CH–P); MS (^{184}W): m/z (%): 536 (10) [M^+], 396 (100) [$M^+ - 5\text{CO}$]; elemental analysis (%) calcd for $\text{C}_{18}\text{H}_{15}\text{O}_3\text{PW}$: C 42.53, H 2.42; found: C 42.78; H 2.46.

4: A solution of **3** (2.15 g, 5 mmol), dimethyl acetylenedicarboxylate (1.25 mL, 10 mmol) and diphenylacetylene (1.1 g, 6.25 mmol) in toluene (10 mL) was heated at 70 – 75°C for 5 h. After evaporation of the solvent, the residue was purified by column chromatography eluting with hexane/

dichloromethane (10/1). Phosphirene complex **4** was isolated as yellow crystals (2 g, 66%). ^{31}P NMR (81 MHz, CDCl_3): $\delta = -201.0$ ($^1J(\text{P},\text{W}) = 294.9$ Hz); ^{13}C NMR (50 MHz, CDCl_3): $\delta = 89.3$ (d, $^1J(\text{C},\text{P}) = 18.8$ Hz; $\text{P}-\text{C}\equiv\text{C}$), 93.9 (d, $^2J(\text{C},\text{P}) = 5.8$ Hz; $\text{P}-\text{C}\equiv\text{C}$), 120.9 (s; $\text{C}\equiv\text{C}-\text{Ph}$, C_{ipso}), 195.9 (d, $^2J(\text{C},\text{P}) = 9.1$ Hz; *cis*-CO), 198.4 (d, $^2J(\text{C},\text{P}) = 34.8$ Hz; *trans*-CO); MS: m/z (%): 634 (6) [M^+], 494 (100) [$M^+ - 5\text{CO}$]; elemental analysis (%) calcd for $\text{C}_{27}\text{H}_{15}\text{O}_5\text{PW}$: C 51.10, H 2.36; found: C 51.48, H 2.42.

6: Biphosphirene **6** was isolated as light yellow crystals by chromatography with hexane/dichloromethane (4/1). ^{13}C NMR (50 MHz, CDCl_3): $\delta = 137.4$ (d, $^1J(\text{C},\text{P}) = 5.4$ Hz; C_{ipso} Ph-P), 143.2 (pseudo t, $^1J(\text{C},\text{P}) \sim ^2J(\text{C},\text{P}) = 13.6$ Hz; Ph-C(P)=C-P); MS: highest mass 785 [$M^+ - 10\text{CO} - \text{H}$].

7: Biphosphirene **7** was isolated as a yellow powder by chromatography with hexane/dichloromethane (10/1). ^{13}C NMR (50 MHz, CDCl_3): $\delta = 89.5$ (d, $^1J(\text{C},\text{P}) = 23.6$ Hz; $\text{P}-\text{C}\equiv\text{C}$), 95.2 (d, $^2J(\text{C},\text{P}) = 6.5$ Hz, $\text{P}-\text{C}\equiv\text{C}$), 120.5 (s; $\text{C}\equiv\text{C}-\text{Ph}$, C_{ipso}), 144.6 (pseudo t, $^1J(\text{C},\text{P}) \sim ^2J(\text{C},\text{P}) = 15$ Hz; PhC(P)=C-P); MS: highest mass 632; elemental analysis (%) calcd for $\text{C}_{40}\text{H}_{20}\text{O}_{10}\text{P}_2\text{W}_2$: C 44.07, H 1.85; found: C 44.03, H 1.75.

8: Triphosphirene **8** was isolated as light yellow crystals by chromatography with hexane/dichloromethane (4/1); elemental analysis calcd (%) calcd for $\text{C}_{31}\text{H}_{25}\text{O}_{15}\text{P}_3\text{W}_3$: C 40.24, H 1.66; found: C 39.98, H 1.56.

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Steam-Stable MSU-S Aluminosilicate Mesostructures Assembled from Zeolite ZSM-5 and Zeolite Beta Seeds**

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The structural integrity of Al-MCM-41 and related mesoporous aluminosilicate molecular sieves has been significantly improved in recent years through direct assembly and post-synthesis treatment methods.^[1] Nevertheless, the hydrothermal instability and mild acidity remain inferior to conventional zeolites and limit potential applications in petroleum refining and fine chemicals synthesis.^[2] One might expect to improve both the stability and acidity of these materials if zeolite-like order could be introduced into the pore walls. One approach, first introduced by van Bekkum and co-workers,^[3] is to transform the preassembled walls of Al-MCM-41 into zeolitic structures by post-assembly treatment with a microporous zeolite structure director, such as tetrapropylammonium cations. More recent studies have shown that the walls of the mesostructure can indeed be converted to a zeolitic product, but the microporous zeolite phase (ZSM-5) is segregated from the mesostructure, giving rise to ZSM-5/MCM-41 composites.^[4] These composites exhibited an enhancement in acidity for hydrocarbon cracking in comparison to mechanical mixtures of ZSM-5 and MCM-41 and an improvement in steam stability for purely siliceous composites.^[4c]

We recently reported an alternative approach to more acidic and hydrothermally stable mesostructures based on the direct assembly of nanoclustered aluminosilicate precursors that normally nucleate zeolite type Y crystallization.^[5] These protozeolitic species, known as "zeolite seeds", promote zeolite nucleation by adopting AlO_4 and SiO_4 connectivities that resemble the secondary building units of a crystalline zeolite.^[6] The assembly of the Na^+ -nucleated zeolite type Y (faujasitic) seeds under hydrothermal conditions in the presence of cetyltrimethylammonium ions afforded hexagonal MSU-S mesostructures with Si/Al ratios in the range 1.6:1 to 10:1. The replacement of Na^+ by NH_4^+ ions in the as-made mesostructure, followed by calcination in the presence of the surfactant, afforded exceptionally acidic and steam-stable mesostructures. However, the steam stability was enhanced by structure-stabilizing occlusions of carbon that formed during the calcination process. That is, the steam stability at 800 °C was in part a consequence of the exceptional acidity of a framework that formed structure-stabilizing carbon, and not entirely a result of an intrinsically stable framework.

Here we also make use of protozeolitic nanoclusters to form exceptionally acidic and steam-stable aluminosilicate

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- [8] X-ray structure data for **8a**: crystal dimensions $0.40 \times 0.16 \times 0.16$, monoclinic, $P2_1/n$, $a = 12.467(5)$, $b = 18.565(5)$, $c = 22.346(5)$ Å, $\beta = 91.220(5)^\circ$, $V = 5171(3)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.955$ g cm⁻³, $\mu = 6.817$ cm⁻¹, $F(000) = 2872$, $\theta_{\text{max}} = 30.03^\circ$, hkl ranges: $-13-17$; $-21-26$; $-31-25$, 33543 data collected, 15050 unique data ($R_{\text{int}} = 0.0699$), 12185 data with $I > 2\sigma(I)$, 649 parameters refined, $\text{GOF}(F^2) = 1.008$, final R indices: $R1 = 0.0414$, $wR2 = 0.1095$; max/min residual electron density 2.082(0.251)/-3.219(0.251) e Å⁻³. Data collection was with a Nonius Kappa CCD diffractometer, ϕ and ω scans, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å), graphite monochromator, $T = 150$ K, structure solution with SIR97, refinement against $F2$ (SHELXL97) with anisotropic thermal parameters for all non-hydrogen atoms, calculated hydrogen positions with riding isotropic thermal parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151986. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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mesostructures, but the zeolitic seeds are formed from *organic* structure directors. Moreover, the Si/Al ratios are much *higher* ($>10.0:1$) than the ratios needed to template faujasitic (FAU) zeolite seeds ($\sim 1.6:1$ – $10.0:1$). The resulting mesostructures, unlike those formed from FAU seeds, are remarkably steam stable even in the absence of occluded coke. Since many organic cations are known to function as zeolite-nucleating agents,^[7] zeolite seeds templated by organic cations promise to be much more versatile for the supramolecular assembly of aluminosilicate mesostructures that are intrinsically steam stable.

The zeolite seeds of interest in the present work nucleate the crystallization of pentasil zeolites ZSM-5 (MFI) and Beta (BEA). Aqueous solutions of nanoclustered MFI and Beta seeds (Si/Al = 67:1) were prepared by using tetrapropylammonium (TPA⁺) and tetraethylammonium (TEA⁺) templates, respectively.^[8] For comparison purposes, conventional aluminosilicate anions were prepared by using tetramethylammonium ions (TMA⁺) in place of TPA⁺ and TEA⁺. TMA⁺ is not known to function as a template for MFI or BEA zeolite seeds. The solids formed through the evaporation of each of the aluminosilicate solutions afforded amorphous X-ray diffraction patterns. However, the IR spectra of the solids formed from MFI and BEA zeolite seeds revealed distinct vibrations between 550–600 cm⁻¹. In contrast, no IR bands were observed in this range for the conventional aluminosilicate anions formed from TMA⁺ hydroxide. A band near 550 cm⁻¹ in pentasil MFI and BEA zeolites is indicative of the presence of five-membered rings.^[9] Thus, the presence of an analogous band for the TPA⁺ and TEA⁺ aluminosilicate precursors verified the presence of pentasil zeolite subunits, even though MFI and Beta nanocrystals are absent.

Hexagonal aluminosilicate mesostructures, denoted MSU-S_(MFI) and MSU-S_(BEA), were assembled by reaction of the

respective zeolite seed solutions with cetyltrimethylammonium bromide (CTAB) at a surfactant to silica ratio of 0.25:1 at 150 °C for two days. An equivalent procedure was used to assemble conventional TMA⁺ aluminosilicate precursors into a disordered MCM-41 mesostructure. The as-made products were calcined at 550 °C to remove surfactant, treated with 0.1M NH₄NO₃ at room temperature to displace exchangeable sodium ions, and then calcined again at 550 °C to convert NH₄⁺ at exchange sites to protons. Chemical analysis indicated the absence of occluded carbon and a Si/Al ratio in agreement with the ratio contained in the initial zeolite seeds.

Figure 1 illustrates the X-ray diffraction (XRD) patterns of calcined 1.5% Al-MSU-S_(MFI) and 1.5% Al-MSU-S_(BEA) before and after exposure to 20% (v/v) water vapor in N₂ at 600 and 800 °C for 5 h. The XRD results clearly indicate that the mesostructures retain hexagonal order upon steaming. Disordered 1.5% Al-MCM-41 also retained some XRD order after exposure to steam at 600 °C, but at 800 °C the mesostructure was almost completely lost (XRD patterns not shown). The disorder initially associated with the 1.5% Al-MCM-41 sample is not responsible for the collapse of the mesostructure at 800 °C. Even well-ordered Al-MCM-41 samples with four hexagonal *hkl* reflections have been shown^[5] to exhibit a loss of mesostructure upon steaming at 800 °C.

Figure 2 provides the N₂ adsorption and desorption isotherms for 1.5% Al-MSU-S_(MFI) and 1.5% Al-MSU-S_(BEA). Table 1 provides the surface areas, framework pore sizes, and pore volumes for 1.5% Al-MSU-S_(MFI) and 1.5% Al-MSU-S_(BEA) and compares them with those for 1.5% Al-MCM-41 formed under equivalent conditions. The 1.5% Al-MSU-S mesostructures retain more than 95% of their surface areas and more than 87% of their framework pore volumes with little or no pore contraction after exposure to steam at 600 °C.

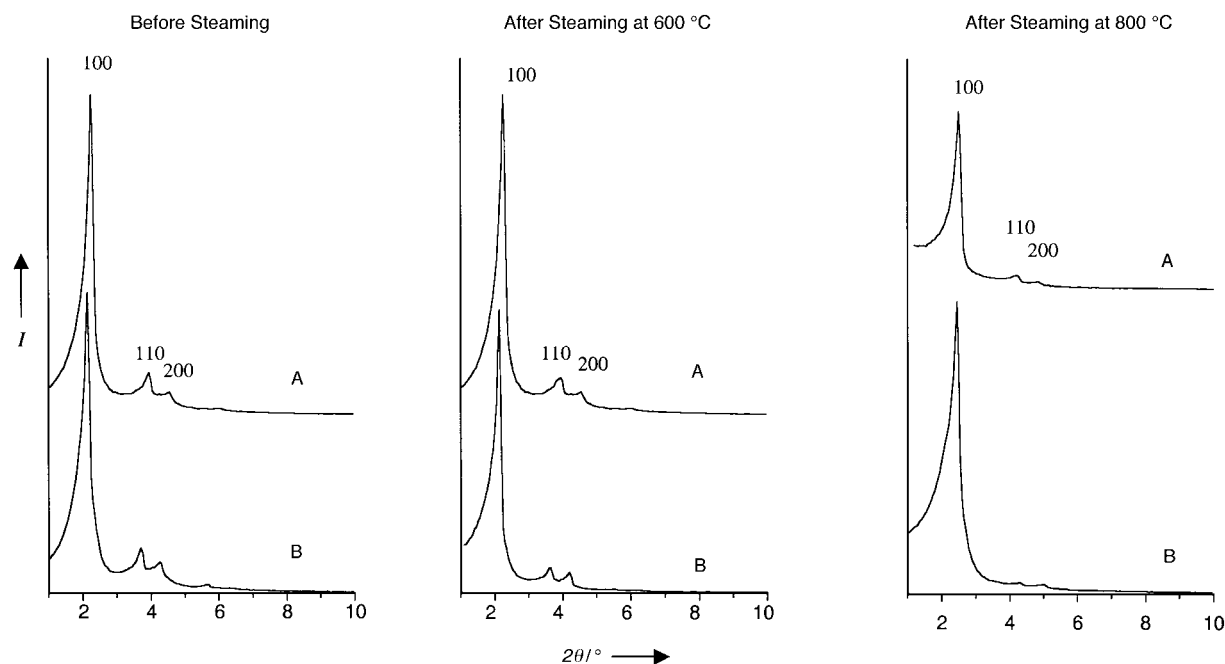


Figure 1. XRD patterns of calcined (550 °C, 4 h) mesoporous aluminosilicate molecular sieves before and after steaming at 600 °C and 800 °C for 5 h: A) hexagonal 1.5% Al-MSU-S_(MFI) prepared from zeolite ZSM-5 seeds; B) hexagonal 1.5% Al-MSU-S_(BEA), prepared from zeolite Beta seeds. The intensity scale is the same for the samples before and after steaming. Hexagonal unit cell parameters are provided in Table 1.

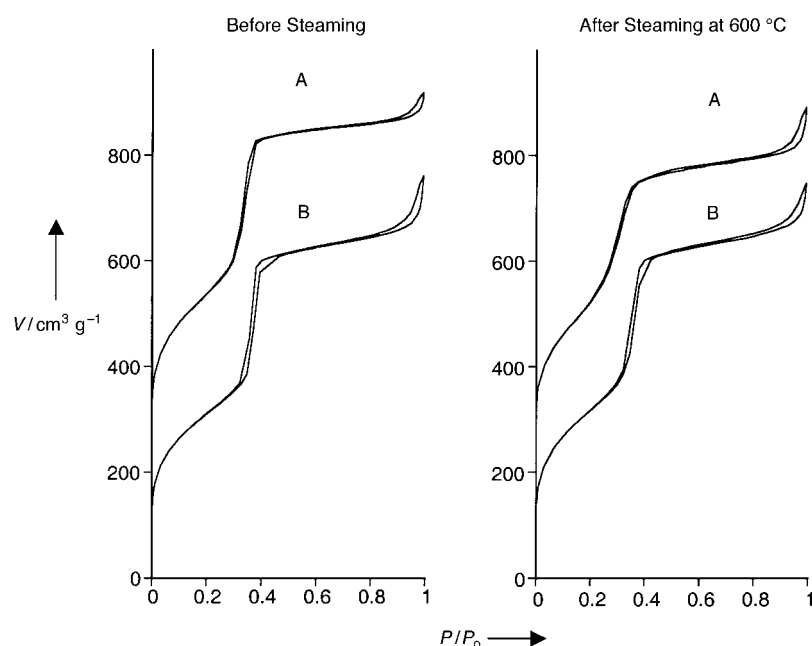


Figure 2. N₂ adsorption/desorption isotherms for calcined (550 °C, 5 h) mesoporous aluminosilicate molecular sieves before and after steaming (20 vol% H₂O in N₂, 600 °C, 5 h): A) 1.5 % Al-MSU-S_(MFI) B) 1.5 % Al-MSU-S_(BEA). The isotherms are offset by 200 cm³ g⁻¹ for clarity.

Table 1. Textural properties and cumene conversions for mesoporous aluminosilicate sieves.

Sample	Unit cell dimension <i>a</i> ₀ [Å]	Surface area [m ² g ⁻¹]	Pore volume [cm ³ g ⁻¹]	Pore diameter [Å]	Cumene conversion ^[a] [%]
1.5 % Al-MSU-S _(MFI)					
calcined	45.3	1231	1.06	36.8	32.3
steamed 600 °C, 5 h	44.5	1192	0.93	34.7	–
steamed 800 °C, 5 h	36.6	849	0.44	24.3	–
1.5 % Al-MSU-S _(BEA)					
calcined	47.3	1124	1.06	39.1	31.5
steamed 600 °C, 5 h	46.7	1065	0.94	38.0	–
steamed 800 °C, 5 h	37.0	885	0.46	26.4	–
1.5 % Al-MCM-41 ^[b]					
calcined	46.4	1013	1.08	38.7	11.7
steamed 600 °C, 5 h	35.2	639	0.39	20.1	–
steamed 800 °C, 5 h	–	55	–	–	–

[a] Reaction conditions: 6 mm i.d. fixed bed quartz reactor; 200 mg catalyst; cumene flow rate, 4.1 μmol min⁻¹; N₂ carrier gas, 20 cm³ min⁻¹; conversions reported after 60 min on-stream at 300 °C. [b] 1.5 % Al-MCM-41 was prepared by the direct assembly of conventional aluminosilicate anions formed from sodium aluminate, fumed SiO₂, and TMAOH.

In contrast, 1.5 % Al-MCM-41 assembled from conventional aluminosilicate anions retains only 63 % of its surface area and 36 % of its framework pore volume under equivalent steaming conditions. Upon increasing the steaming temperature to 800 °C, we find that both MSU-S aluminosilicate mesostructures retain long-range hexagonal order (cf., Figure 1) and substantial mesoporosity (cf., Table 1), whereas the mesoporosity of MCM-41 is completely lost. Also, as we have shown previously^[5] that “ultrastable” grafted forms of Al-MCM-41^[1b] are destroyed completely under these steaming conditions.

The supramolecular assembly of steam-stable MSU-S mesostructures from zeolite MFI and Beta seeds is not

limited to the 1.5 % Al-MSU-S compositions illustrated here. These same nanoclusters also can be used to assemble steam-stable MSU-S mesostructures with Si/Al ratios in the range ~20:1–300:1. Also, in contrast to previously reported MSU-S derivatives assembled from faujasitic zeolite type Y seeds (denoted here as MSU-S_(FAU)), MSU-S_(MFI) and MSU-S_(BEA) are intrinsically stable and do not require the presence of occluded carbon for steam stability.

²⁷Al MAS NMR spectroscopy indicates that more than 90 % of the aluminum centers in calcined 1.5 % Al-MSU-S_(MFI) and 1.5 % Al-MSU-S_(BEA) are in tetrahedrally coordinated sites. In accord with the tetrahedral siting of aluminum, the Brønsted acidity of these steam-stable mesostructures was verified through cumene cracking experiments. Cumene conversions for calcined forms of 1.5 % Al-MSU-S_(MFI), 1.5 % Al-MSU-S_(BEA), and 1.5 % Al-MCM-41 at 300 °C are provided in Table 1. Clearly, the Al-MSU-S derivatives are far more active acid catalysts than the equivalent Al-MCM-41 prepared from conventional aluminosilicate precursors. These results, together with the steam-stability properties, suggest that MSU-S_(MFI) and MSU-S_(BEA) may be suitable acid catalysts for the processing of high molecular weight petroleum fractions that can not be adequately refined over microporous zeolites.

We propose that the hydrothermal stability and catalytic activity of MSU-S_(MFI) and MSU-S_(BEA) arise from zeolite-like subunits of AlO₄ and SiO₄ tetrahedra in the framework walls of the mesostructures. Evidence for the retention of a protozeolitic connectivity of tetrahedra was provided by IR spectroscopy. The band in the 550–600 cm⁻¹ region, which is characteristic of five-membered ring subunits,^[9] is well-expressed in the spectra of MSU-S_(MFI) and MSU-S_(BEA), but not for the MCM-41 derivative (Figure 3).

Finally, as we noted earlier, many organic cations are known to function as zeolite-nucleating agents.^[7] Further advancements in the steam stability and acidity of aluminosilicate

mesostructures may therefore be anticipated through the incorporation of other zeolitic subunits in the framework walls.

Experimental Section

MFI seeds^[8a] (Si/Al=67:1) were prepared by the reaction of 1.0 M tetrapropylammonium (TPA⁺) hydroxide (6.7 mmol), sodium aluminate (0.50 mmol, Strem Chemicals, Inc), and fumed silica (33.3 mmol, Aldrich Chemicals) in water (1270 mmol) at 50 °C for 18 h. The same stoichiometric ratio of tetraethylammonium (TEA⁺) hydroxide, sodium aluminate, fumed silica, and water was used to prepare a solution of BEA seeds^[8b] at 100 °C. MSU-S_(MFI) and MSU-S_(BEA) mesostructures were assembled by reaction of the respective zeolite seeds solutions with CTAB (8.65 mmol) at 150 °C for

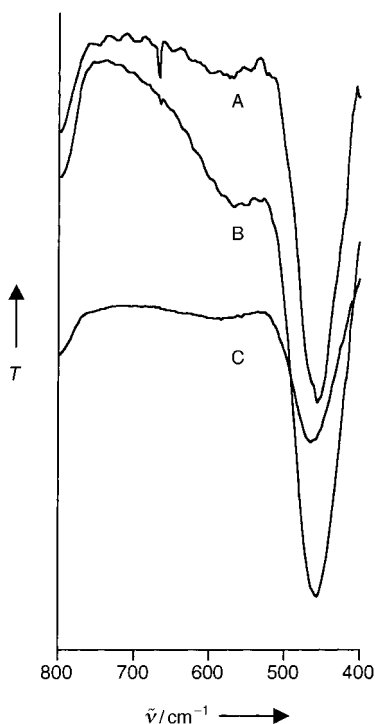


Figure 3. IR spectra of calcined mesostructures: A) 1.5% Al-MSU-S_(MFI) assembled from zeolite ZSM-5 seeds, B) 1.5% Al-MSU-S_(BEA) assembled from zeolite Beta seeds, and C) 1.5% Al-MCM-41 formed from conventional aluminosilicate precursors.

two days. Al-MCM-41 (Si/Al = 67:1) also was assembled at 150 °C from conventional aluminosilicate precursors formed at 35 °C using tetramethylammonium (TMA⁺) in place of TEA⁺ and TPA⁺.

X-ray diffraction patterns were recorded on a Rigaku Rotaflex diffractometer using CuK α radiation ($\lambda = 1.542$ Å). N₂ adsorption and desorption isotherms were determined on a Micromeritics ASAP 2000 sorptometer at –196 °C. The samples were outgassed under 10^{–5} Torr at 150 °C. ²⁷Al NMR spectra were recorded on a Varian VXR-400S spectrometer with a 7-mm zirconia rotor and a spinning frequency of 4 kHz. IR spectra of samples in the form of KBr pellets were recorded by using a Nicolet IR/42 spectrometer.

Cumene cracking reactions were performed in a 6 mm i.d. fixed bed quartz reactor with 200 mg catalyst. The cumene flow rate was 4.1 $\mu\text{mol min}^{-1}$ in a 20 cm³ min^{–1} carrier stream of N₂. Cumene conversions were reported under steady-state conditions after 60 min on stream at 300 °C.

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Strongly Acidic and High-Temperature Hydrothermally Stable Mesoporous Aluminosilicates with Ordered Hexagonal Structure**

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Mesoporous molecular sieves such as hexagonally ordered MCM-41 have attracted considerable attention because of their potential use as versatile catalysts and catalyst supports for the conversion of large molecules.^[1–16] However, the acidity and hydrothermal stability of these mesostructured materials are relatively low compared with those of zeolites, which strongly influences their practical applications in industrial catalytic reactions of petroleum.^[1] Despite several successful examples of stabilizing aluminosilicate mesostructures at low temperatures (in boiling water, 100 °C), for example by synthesizing materials with thick pore walls by using triblock copolymers,^[3] by removing silanol groups by silylation,^[14] by employing salt effects,^[15] by using the co-templating approach,^[16] and by post-treatments,^[5–8] the acidity and hydrothermal stability of these mesostructures at high temperature (800 °C) are still lower than those of microporous aluminosilicate zeolites.

It is well known that microporous zeolites are very stable, commercial catalysts, and the MFI-type and Beta zeolites, which contain structure building units of 5-rings (T–O–T, T = Si and Al), exhibit extremely high acidity and hydrothermal

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stability. Notably, several zeolite structure-directing agents (aluminosilicate nanoclusters) for syntheses with primary and secondary structure building units have been reported recently,^[17–19] one of which has been shown to be particularly suitable for the synthesis of Beta zeolite.^[19]

Here we demonstrate that strongly acidic and high-temperature hydrothermally stable mesoporous aluminosilicates with ordered hexagonal structure can be synthesized by self-assembly of preformed aluminosilicate nanoclusters with templating micella. Our results show that the materials obtained contain primary and secondary building units similar to those of microporous Beta zeolite. In addition the materials are highly active for the catalytic cracking of 1,3,5-triisopropylbenzene and have longer catalyst lifetimes for use in the alkylation of isobutane with butene than MCM-41 and HZSM-5. This should open the door for the application of mesoporous materials as acidic catalysts for the conversion of large molecules.

Strongly acidic and hydrothermally stable mesoporous aluminosilicates (denoted as MAS-5) with ordered hexagonal structures were hydrothermally synthesized from silica and sodium aluminate in the presence of co-templates of tetraethylammonium hydroxide (TEAOH) and cetyltrimethylammonium bromide (CTAB).

The small-angle X-ray diffraction (XRD) pattern for the as-synthesized sample of MAS-5 shows four well-resolved peaks (Figure 1 A) that can be indexed as (100), (110), (200), and (210) reflections associated with hexagonal symmetry. The (100) peak reflects a d spacing of 4.441 nm ($a_0 = 51.33$ Å). After calcination in air at 550 °C for 4 h, thermogravimetric analysis (TG) of the sample shows a weight loss of 51 %, which was attributed to the removal of organic templates of TEAOH and CTAB, and the XRD pattern (Figure 1 B) shows that the four diffraction peaks are still observed, confirming

that hexagonal MAS-5 is thermally stable. A similarly high degree of mesoscopic order is observed for hexagonal MAS-5 even after calcination to 900 °C. Interestingly, after treatment of the calcined sample in boiling water for 300 h (Figure 1 C), and even after treatment of the calcined sample at 600 °C for 4 h or at 800 °C for 2 h in flowing water vapor (Figure 1 D), the XRD patterns also show similar peaks assigned to hexagonal symmetry, suggesting that MAS-5 is extremely hydrothermally stable even at high temperature.

Figure 2 shows temperature-programmed desorption of ammonia (NH₃-TPD) curves on MAS-5, MCM-41, H-ZSM-5, and H-Beta with similar SiO₂/Al₂O₃ ratios (78:1–84:1). Evidently, the desorption temperature for ammonia on MAS-5 is much higher than that on MCM-41 with a similar SiO₂/Al₂O₃ ratio, and the curve shape is very similar to that of H-Beta, indicating that the acidic strength and amount of

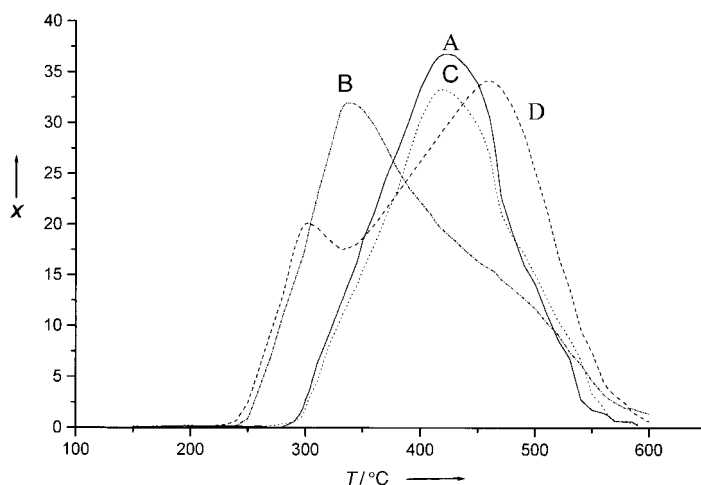


Figure 2. NH₃-TPD curves on A) MAS-5, B) MCM-41, C) H-Beta, and D) HZSM-5. X = amount of desorbed NH₃.

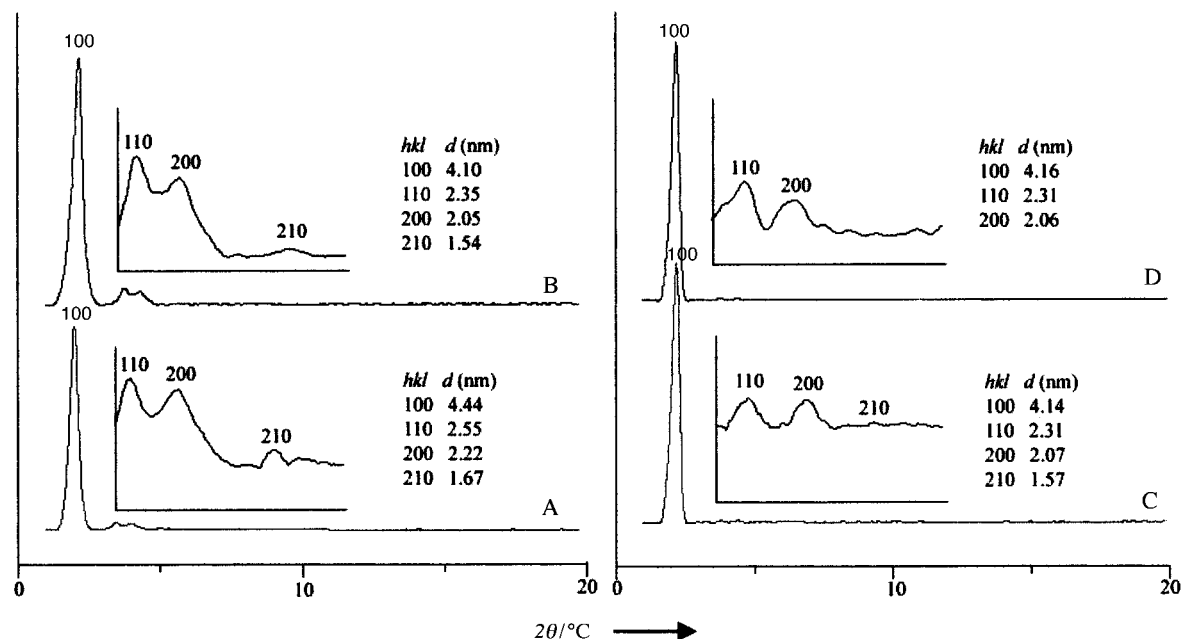


Figure 1. XRD patterns of A) as-synthesized MAS-5; B) calcined MAS-5 at 550 °C for 4 h; C) calcined MAS-5 after treatment in boiling water for 300 h; D) calcined MAS-5 after treatment with 100 % water vapor at 600 °C for 4 h or calcined MAS-5 after treatment with 100 % water vapor at 800 °C for 2 h. The XRD patterns were measured with a Siemens D5005 diffractometer.

MAS-5 are similar to those of H-Beta zeolite, which is much stronger than that of MCM-41. Moreover, the IR spectrum recorded for pyridine adsorption over MAS-5 shows a much stronger band at 1545 cm^{-1} than that over MCM-41, indicating that MAS-5 has a much higher concentration of Brønsted acidic sites than MCM-41.

The transmission electron microscopy (TEM) image of calcined MAS-5 shows well-ordered hexagonal arrays of mesopores with one-dimensional (1D) channels, and further confirms that MAS-5 has a two-dimensional (2D) $p6mm$ hexagonal mesostructure.^[2] From the high dark contrast in the TEM image of this sample, the distance between mesopores is estimated to be 48 Å , which is in good agreement with that determined from XRD.

The N_2 adsorption–desorption isotherm of calcined MAS-5 exhibits a typical adsorption curve of type IV, which is attributed to the mesoporous structure. Correspondingly, the pore-size distribution for calcined MAS-5 shows narrow uniform pore with a mean value of 27 Å . Combined with the XRD results, we estimate that the thickness of the mesoporous wall is about 21 Å . Furthermore, a high BET surface area of $1150\text{ m}^2\text{ g}^{-1}$ and a large pore volume of $1.17\text{ cm}^3\text{ g}^{-1}$ were observed.^[1, 2]

IR, UV-Raman, and NMR spectroscopy were used to characterize the primary and secondary building units (PSBU) of MAS-5. The IR spectrum of calcined MAS-5 (Figure 3) exhibits four sharp bands between 410 and

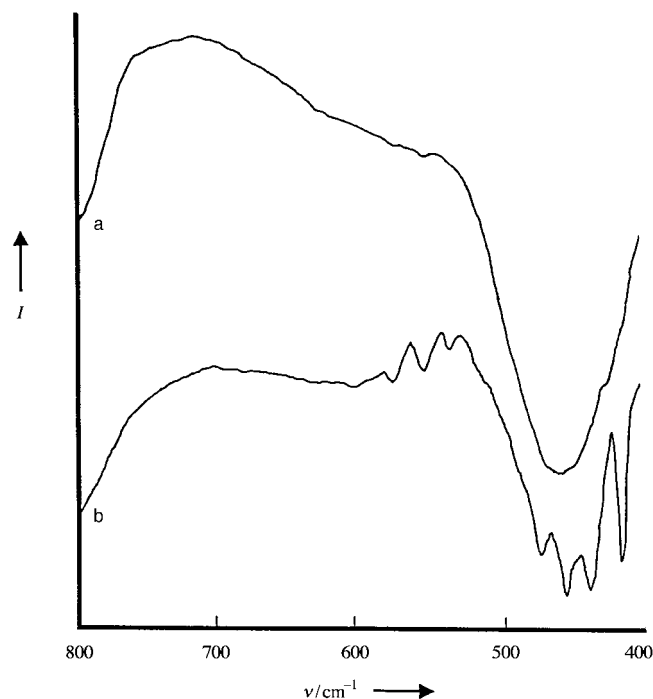


Figure 3. IR spectra of a) MCM-41 and b) MAS-5 after removal of organic templates.

480 cm^{-1} and other notable bands between 520 and 600 cm^{-1} , which are characteristic of 6- and 5-rings of T-O-T (T = Si or Al), respectively.^[20] In contrast, MCM-41 only exhibits a broad band at 455 cm^{-1} ; the UV-Raman spectrum of MAS-5 shows characteristic bands at 340 and 390 cm^{-1} , which are assigned to 5-rings of T-O-T (Figure 4),^[21] in addition to the

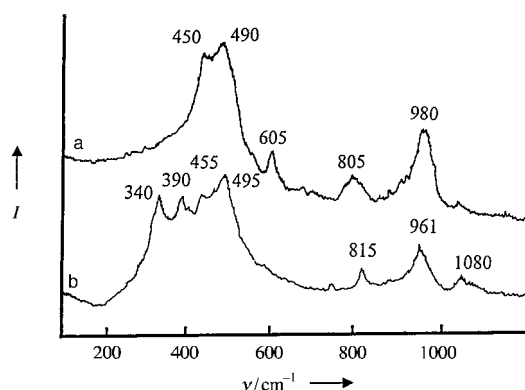


Figure 4. UV Raman spectra of a) MCM-41 and b) MAS-5.

bands at 455 and 495 cm^{-1} for the 4-rings of T-O-T. In contrast, MCM-41 exhibits bands at 450 , 490 , and 605 cm^{-1} , which are assigned to 4- and 3-rings in the amorphous phase of aluminosilicates;^[12, 22] the ^{27}Al NMR spectrum shows that the full-width half-height (FWHH) of MAS-5 is similar to that of Beta zeolite, but much narrower than that of MCM-41. Additionally, the ^{27}Al NMR spectrum for MAS-5 displays a peak at $\delta = 61$; in contrast, this peak appears at $\delta = 55$ for MCM-41. These results suggest that the aluminum environment in MAS-5 is much more similar to that in Beta zeolite than in amorphous MCM-41.^[23] All of these results indicate that MAS-5 contains PSBU of 5- and 6-rings of T-O-T,^[20–23] similar to those in aluminosilicate zeolites such as Beta zeolite.

Catalytic activities determined for the cracking of 1,3,5-triisopropylbenzene over various catalysts are given in Table 1. HZSM-5 is almost inactive due to its relatively small pore size and the large diameter of the molecule to be cracked. MCM-41 shows high activity; however, it completely loses its activity after its treatment in boiling water for 6 h or at 600°C for 2 h. Interestingly, our calcined MAS-5 displays both higher activity and longer catalyst lifetimes than those of MCM-41. Moreover, when MAS-5 is treated in boiling water for 300 h, or even when it is treated at 600°C for 4 h or at 800°C for 2 h, it still shows high catalytic activity. These results also confirm that MAS-5 is strongly acidic and is highly hydrothermally stable, suggesting that it is a good candidate catalyst for industrial cracking of petroleum.

Catalytic alkylation of isobutane with butene (Figure 5) shows that MAS-5 exhibits higher activity than calcined MCM-41 with a similar $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio. This is attributed to the strongly acidic sites of MAS-5. Furthermore, MAS-5 has the longest catalyst lifetimes of the catalysts studied, which is attributed to the relatively low coke formation. In addition, the products obtained over a MAS-5 catalyst display higher octane values than those obtained over the other samples measured.

MAS-5 is proposed to form by the self-assembly of aluminosilicate species co-templated by TEOH and CTAB. In our case, the TEOH template assembles aluminosilicates to form precursors in which the PSBU are similar to those in Beta zeolite. These precursors are further self-assembled with CTAB micella to give hexagonal mesoporous structures, which contain PSBU similar to those of Beta zeolite, that are

Table 1. Catalytic activities in the cracking of 1,3,5-triisopropylbenzene on various catalysts.^[a]

Sample	SiO ₂ /Al ₂ O ₃	Treatment	Conversion [%]	Reaction temperature [°C]
HZSM-5	84:1	–	1.7	250
HMCM-41	80:1	–	65.8	250
HMCM-41	80:1	boiling water for 6 h	< 0.1	250
HMCM-41	80:1	treated with 100 % water vapor at 600 °C for 2 h	< 0.1	250
MAS-5	81:1	–	78.8	250
MAS-5	81:1	boiling water for 300 h	79.1	250
MAS-5	81:1	treated with 100 % water vapor at 600 °C for 4 h	78.9	250
MAS-5	80:1	treated with 100 % water vapor at 800 °C for 2 h	77.5	250
MAS-5	123:1	–	87.0	320
MAS-5	81:1	–	90.1	320
MAS-5	59:1	–	95.2	320

[a] Catalytic reactions were performed by pulse injections, and the data presented are the results after 10 injections. In each run, 50 mg of catalyst was used, the pulse injection contained 0.4 µL of the reactant, and the reaction flow rate was 53.7 mL min^{−1}.

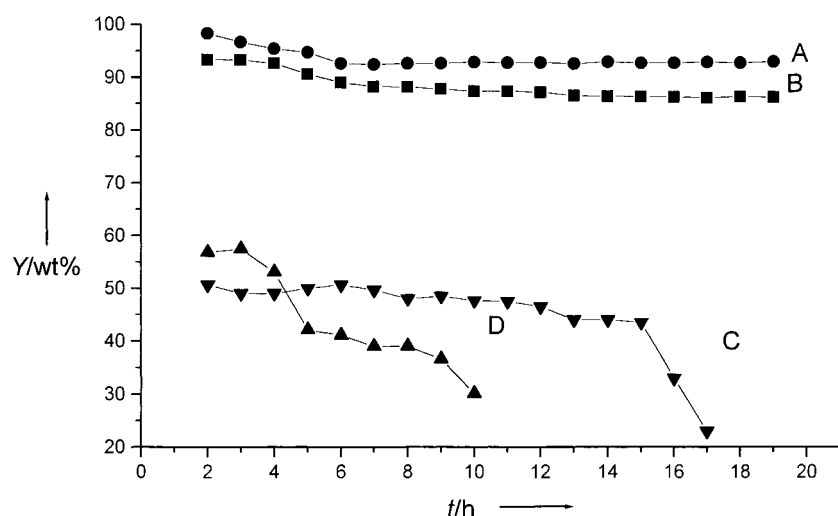


Figure 5. Catalytic conversion (Y) of 2-butene in the alkylation of isobutane with butene versus reaction time over various catalysts (each 0.5 g): A) MAS-5, B) H-Beta, C) MCM-41, and D) HZSM-5. Reaction temperature 25 °C; isobutane/butene ratio of 12:1; 1-butene/2-butene ratio of 8:1; WHSV = 9 h^{−1}.

hydrothermally stable even at high temperature, strongly acidic, resulting in excellent catalytic activity.

The aluminosilicate precursors were well characterized by IR spectroscopy. Prior to the formation of aluminosilicate precursors, the IR spectrum shows a broad band at 460 cm^{−1}, which is attributed to structure building units of amorphous aluminosilicates.^[20] After the formation of these aluminosilicate precursors, the IR spectrum exhibits a notable bands between 520 and 600 cm^{−1}, which are characteristic of 5-rings.^[20]

Experimental Section

Synthesis: Strongly acidic and hydrothermally stable mesoporous aluminosilicates (denoted as MAS-5) with ordered hexagonal structures were hydrothermally synthesized from silica and sodium aluminate in the presence of co-templates of tetraethylammonium hydroxide (TEAOH) and cetyltrimethylammonium bromide (CTAB) with a molar ratio of Al₂O₃/SiO₂/TEAOH/CTAB/H₂O at 1.0/7.0–350/10.0–33.0/12.0–32.0/500–2000. The molar ratio of SiO₂/Al₂O₃ in the products varied between 6.0:1–350:1.

Typical runs for the preparation of MAS-5: 1) Sodium aluminate (0.236–1.36 g), sodium hydroxide (0.11–0.4 g), and tetraethylammonium hydroxide (26–36 g; 20 wt % aqueous solution) were mixed in a plastic vessel.

Then fume silica (10.086 g) was added, and the mixture was stirred for several hours. After the solution became homogeneous, the resulting mixture was transferred to a Teflon-lined stainless-steel autoclave and heated to 100–150 °C for several hours, which led to the aluminosilicate precursors. 2) CTAB (1.18–1.92 g) and deionized water (25 g) were mixed, and then added to the aluminosilicate precursors (9.8 g). The resulting mixture was transferred to a Teflon-lined stainless-steel autoclave, heated at 100–150 °C in an oven. 3) After crystallization for 48 h, the solid product was filtered, washed with water, and dried at 80 °C in air for 12 h. 4) The sample was calcined at 550 °C for 6 h in an oxygen flow to remove the templates TEAOH and CTAB. 5) The protonated form of the sample was prepared by ion-exchange with NH₄Cl, followed by calcination at 500 °C for 2 h.

Characterization: XRD patterns were obtained with a Siemens D5005 diffractometer using CuK_α radiation. TEM images and electron diffraction (ED) patterns were recorded by using a Philips CM200FEG instrument with an acceleration voltage of 200 kV. The nitrogen isotherms of the sample were measured by using a Micromeritics ASAP 2010 system. The samples were outgassed for 2 h at 400 °C before the measurements. The pore-size distribution was calculated by using the Barrett–Joyner–Halenda (BJH) model. ²⁷Al NMR spectra were recorded on a Bruker MSL-300WB spectrometer, and chemical shifts were referenced to [Al(H₂O)₆]³⁺. The Si/Al ratio of the samples was measured by using a Perkin–Elmer 3300 DV ICP, by NMR spectroscopy, and by chemical analysis.

IR spectra of the samples and IR spectra of pyridine adsorbed on the samples were recorded on an FT-IR spectrometer (PE 430) with a resolution of 1 cm^{−1}. Before measurement of the pyridine adsorption, the samples were pressed to thin wafers (5 mg cm^{−2}), and were placed into a quartz cell with CaF₂ windows. The sample disks were evacuated at 400 °C for 2 h (10^{−5} Torr) and cooled down to room temperature, then the disks were exposed to pyridine (10 Torr) at room temperature. The IR spectra were recorded after adsorption at room temperature for 1 h and evacuation at 150 °C for 1 h.

UV-Raman spectra were recorded on an UV-Raman spectrometer built at the State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics. The UV line at 244 nm was generated from a Coherent Ionva 300 Fred ultraviolet laser equipped with an intracavity frequency-doubling system based on a β-barium borate (BBO) crystal. The laser power at the sample was kept below 4.0 mW. The scattered Raman light was collected at 180°. The spectral resolution was estimated to be 1.0 cm^{−1}. Powders of samples were pressed into pellets with diameters of 1.0 cm and then placed in the sample holder.

TPD-NH₃ curves were performed in the range of 120–600 °C; the temperature was increased at a rate of 15 °C min^{−1}. The adsorption of

ammonia on the sample was performed at room temperature; the subsequent removal of ammonia was carried out at 120 °C for 1 h in flowing pure nitrogen.

Catalytic reactions: Two catalytic reactions were used to characterize the catalytic performance of the prepared materials, and analyses of the catalytic products were carried out using GC-8A and GC-17A (Shimadzu Co.) instruments equipped with TCD and FID detectors. Catalytic cracking of 1,3,5-triisopropylbenzene was performed by the pulse method. Samples were calcined at 600 °C for 5 h to burn off any residual organic template. The catalytic testing was performed according to the following standard conditions: catalyst mass: 0.051 g; reaction temperatures in the range of 250–320 °C (no thermal cracking); the ratio of catalyst to 1,3,5-triisopropylbenzene or isopropylbenzene at 0.4 μL per 0.051 g. Nitrogen was used as carrier gas; flow rate 0.92 mL s^{-1} .

The catalytic alkylation of isobutane with butene was investigated at 2 MPa by using a stainless-steel apparatus equipped with a one-through stainless-steel flow reactor. Typical reactions were carried out with 0.5 g of catalyst and an isobutane/butene ratio of 12:1, and a 1-butene/2-butene ratio of 8:1; the WHSV was 9 h^{-1} at a reaction temperature of 25–100 °C.

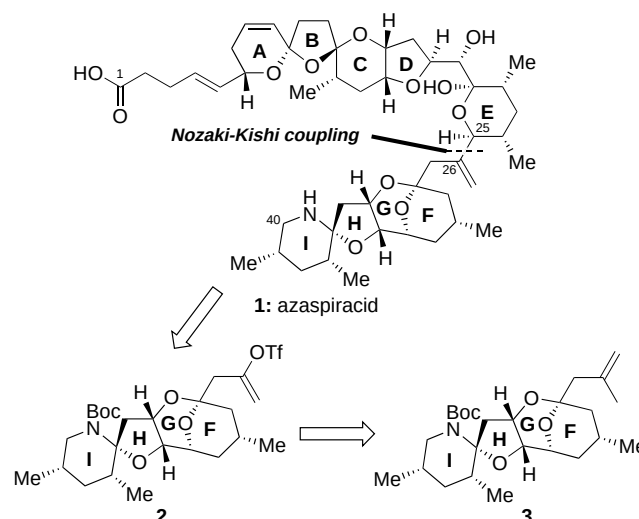
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Synthesis of the FGHI Ring System of Azaspiracid**

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Azaspiracid (**1**, Scheme 1), a novel marine toxin isolated from the mussel *Mytilus edulis* in Killary Harbor, Ireland, represents a new class of marine metabolites unrelated to any



Scheme 1. Structure of azaspiracid (**1**) and retrosynthetic analysis leading to FGHI ring framework **3** via key intermediate **2**.

previously known agents of diarrhetic shellfish poisoning.^[1] This seasonally occurring toxin displays an unusually complex molecular assembly – it harbors a total of nine rings, eight of which are part of acetal or ketal structures – namely, an azaspiro ring system fused to a 2,9-dioxacyclo[3.3.1]nonane ring and a trioxadispiroketal fused to a tetrahydrofuran ring. Adding to the serious challenge posed by such a molecular framework, the absolute stereochemistry of the molecule and the relative stereochemistry between the ABCDE and the

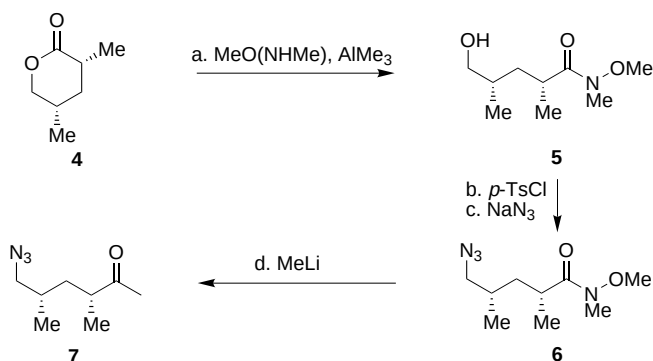
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FGHI domains remain unknown. Azaspiracid (**1**) is a potent toxin in vivo, and exhibits mouse lethality at 0.2 mg kg⁻¹. The biological basis of the toxicity, however, also remains a mystery. These intriguing questions posed by the chemistry and biology of azaspiracid should be addressable through chemical synthesis.^[2] Herein we report the first synthesis of the C26–C40 tetracyclic FGHI domain of azaspiracid by a novel strategy that affords the protected ring system in an enantiomerically pure form.

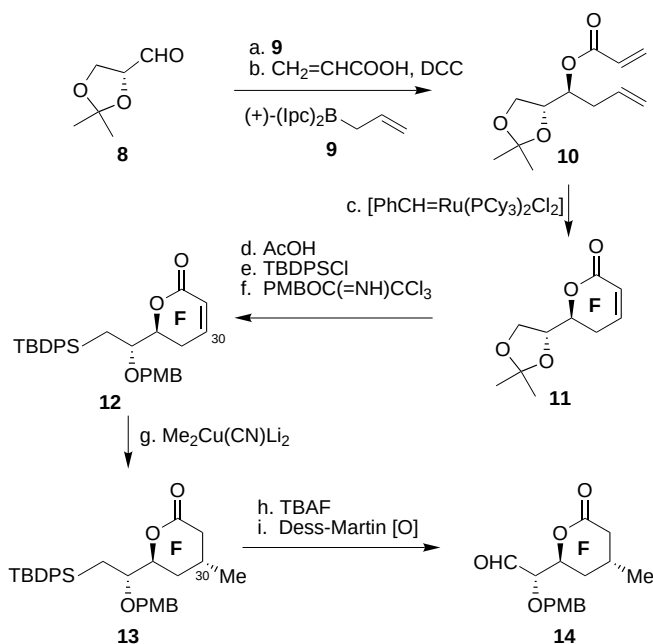
As shown in Scheme 1, azaspiracid (**1**) can be retrosynthetically dissected at the C25–C26 bond, thus dividing the molecule into the ABCDE and the FGHI domains. The synthetic rationale for this strategic disconnection arises not only from issues of convergency, but also from the need to synthesize the ABCDE and the FGHI ring systems separately in a manner that allows access to both enantiomers of each subunit. Thus, a Nozaki–Kishi disconnection led to triflate **2**, which is accessible, in principle, from olefin **3** by ozonolysis and formation of an enol triflate.

Scheme 2 outlines the synthesis of the I-ring precursor, ketone **7**. Starting from the known^[3] lactone **4**, ring opening with AlMe₃ and MeO(NHMe) gave the Weinreb amide **5** in 96% yield.^[4] Tosylation of the primary alcohol, followed by azide displacement afforded azide **6** in 92% overall yield. Finally, treatment of the latter compound (**6**) with MeLi resulted in a clean conversion into ketone **7** (82%).



Scheme 2. Preparation of azidoketone **7**: a) MeO(NHMe)·HCl (5.0 equiv), AlMe₃ (2.0 M in toluene, 5.1 equiv), THF, –15 °C, 2 h, 96%; b) *p*-TsCl (1.5 equiv), Et₃N (5.0 equiv), CH₂Cl₂, 25 °C, 18 h, 96%; c) NaN₃ (2.0 equiv), DMF, 25 °C, 76 h, 96%; d) MeLi (1.25 M in Et₂O, 1.0 equiv), THF, –78 °C, 40 min, 82%. *p*-TsCl = *para*-toluenesulfonyl chloride.

The synthesis of the F-ring aldehyde is presented in Scheme 3. Allylboration of *D*-isopropylidene glyceraldehyde^[5] (**8**) with the Brown chiral allylborane **9**^[6] proceeded in 88% yield and 97:3 diastereoselectivity. Acylation of the resulting alcohol with acrylic acid and 1,3-dicyclohexylcarbodiimide (DCC) smoothly yielded acrylate **10** (73%). A remarkably efficient ring-closing metathesis reaction^[7] within **10** then afforded unsaturated lactone **11** in 95% yield. Acid-catalyzed deprotection of the acetonide, selective silylation of the primary alcohol with *tert*-butyldiphenylsilyl chloride (TBDPSCI) and protection of the secondary hydroxy group as the 4-methoxybenzyl (PMB) ether^[8] furnished lactone **12** in 76% yield over three steps. Methylcupration with Me₂Cu(CN)Li₂ served as an excellent method to install the C30

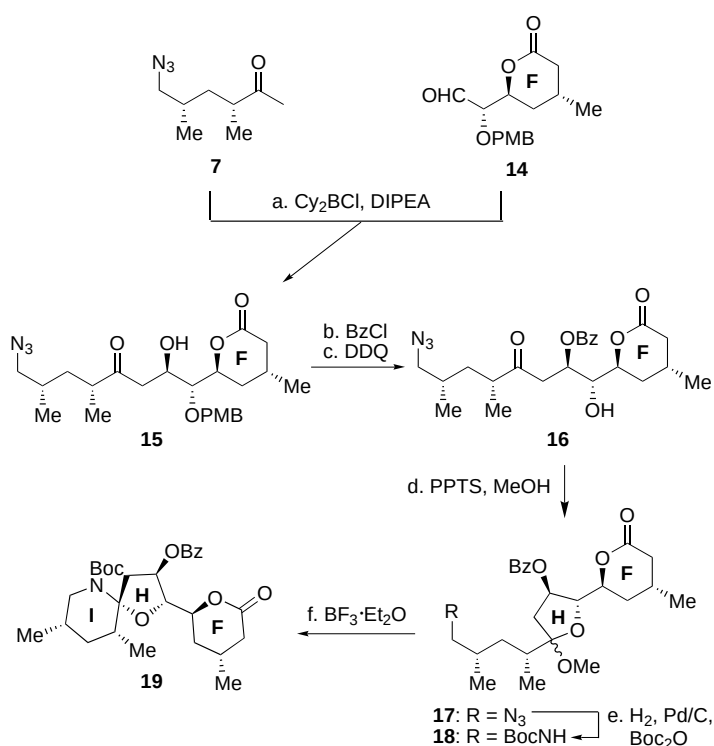


Scheme 3. Synthesis of the F ring aldehyde **14**: a) **9** (2.0 equiv), Et₂O, –100 °C, 6 h, 88% (97:3 selectivity); b) acrylic acid (1.8 equiv), DCC (2.0 equiv), 4-DMAP (0.08 equiv), CH₂Cl₂, 25 °C, 40 h, 73%; c) [PhCH= Ru(PCy₃)₂Cl₂] (0.05 equiv), CH₂Cl₂, reflux, 4 h, 95%; d) AcOH/H₂O (3/1), 65 °C, 2 h; e) TBDPSCI (1.5 equiv), Et₃N (3.0 equiv), 4-DMAP (0.08 equiv), CH₂Cl₂, 0–25 °C, 5 h; f) PMBOC(=NH)CCl₃ (2.0 equiv), TrBF₄ (0.025 equiv), Et₂O, 0 °C, 20 min, 76% over three steps; g) Me₂Cu(CN)Li₂ (1.5 equiv), Et₂O, –78 °C, 10 min, 97%; h) TBAF (1.0 M in THF, 1.25 equiv), THF, 25 °C, 3 h, 89%; i) Dess–Martin periodinane (1.4 equiv), pyridine (10.0 equiv), CH₂Cl₂, 0 °C, 2 h, 95%. Ipc = isopinocampheyl, 4-DMAP = 4-(dimethylamino)pyridine, TrBF₄ = triphenylcarbenium tetrafluoroborate.

methyl group in a highly diastereoselective fashion to afford **13** in 97% yield as the only detectable stereoisomer.^[9] The synthesis of aldehyde **14** was completed by a tetra-*n*-butylammonium fluoride (TBAF) mediated cleavage of the *tert*-butyldiphenylsilyl (TBDPS) group (89%) followed by oxidation of the liberated hydroxy group with Dess–Martin periodinane (95%).

With both building blocks **7** and **14** in hand, our next task was the aldol-facilitated union of the two fragments. Efforts to utilize a chelation-controlled Mukaiyama aldol process under the conditions of Reetz and Kessler (SnCl₄, –78 °C)^[10] resulted only in extensive decomposition of the aldehyde. We then turned to boron-mediated aldol reactions as mild alternatives. Thus, enolization of ketone **7** with (Cy)₂BCl (Cy = cyclohexyl) and *N,N*-diisopropylethylamine (DIPEA)^[11] followed by reaction with aldehyde **14** gave aldol **15** in 82% yield as a single isomer (Scheme 4). The aldol product in this case represented the undesired *anti* diastereoisomer (corresponding to the Felkin product).^[12] However, we were confident that the stereochemistry at this newly formed chiral center could be corrected after the formation of the spirocycle as long as we could obtain the correct spiro stereochemistry.

Although a few methods for the construction of azaoxaspirane junctions are known,^[13] our goal was to develop a method that would allow the direct synthesis of the spirocycle



Scheme 4. Synthesis of azaspiro compound **19**: a) Cy_2BCl (1.3 equiv), DIPEA (1.5 equiv), CH_2Cl_2 , $-78 \rightarrow -40^\circ\text{C}$, 5 h, 82% (>30:1 diastereoselectivity); b) BzCl (3.0 equiv), pyridine, 0°C , 2 h, 96%; c) DDQ (1.5 equiv), $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10/1), 0°C , 8 h, 98%; d) PPTS (0.2 equiv), MeOH, 25°C , 1.5 h; e) H_2 , 10% Pd/C (20% by weight), Boc_2O (4.0 equiv), EtOAc, 25°C , 3.5 h, 76% over two steps; f) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.1 equiv), CH_2Cl_2 , 0°C , 10 min, 60%. Bz = benzoyl, Boc = *tert*-butoxycarbonyl.

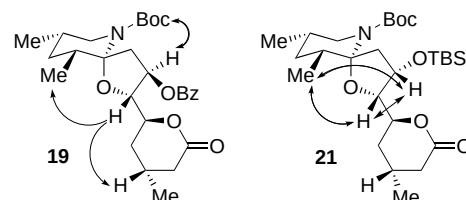
in a protected form, which would facilitate handling and purification. We projected that the acid-catalyzed construction of the azaoxaspiro system would require relatively harsh conditions because of the basic character of the nitrogen atom. However, we envisaged that by suitable protection of the nitrogen atom, cyclization with relatively mild acids or Lewis acids might become feasible. As shown in Scheme 4, we began with the protection of **15** as a benzoate (96%). Subsequent deprotection of the PMB ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave keto alcohol **16** in 98% yield. This compound was then further activated towards cyclization by formation of the mixed methyl ketal **17** with pyridinium *para*-toluenesulfonate (PPTS) in MeOH (ketal **17** was isolated as a 2:1 mixture of anomers). Hydrogenolysis of the azide in the presence of di-*tert*-butyl dicarbonate (Boc_2O)^[14] afforded carbamate **18** in 76% yield over two steps. The stage was now set for the crucial spirocyclization. Although the use of protic acids to effect this transformation led mostly to decomposition of the starting material, we were gratified to observe that exposure of **18** to a catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at 0°C resulted in the rapid formation of the desired spirocycle **19** in 60% yield (Table 1).^[15] NOE studies of **19** confirmed the formation of the correct spiro stereochemistry (Scheme 5).

The remaining tasks consisted of the inversion of the stereochemistry at C34, the attachment of the methallyl side chain, and final cyclization to close ring G. An oxidation-

Table 1. Selected data for compounds **19** and **3**.

19: $R_f = 0.78$ (silica gel, ethyl acetate:hexanes 1:1); $[\alpha]_D^{20} = -13.1^\circ$ (CHCl_3 , $c = 1.14$); IR (film) $\tilde{\nu}_{\text{max}} = 2959, 2924, 1720, 1365, 1274, 1159, 1110, 1068, 858, 713 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 8.00$ (dd, $J = 8.4, 1.4 \text{ Hz}$, 2H), 7.56 (tt, $J = 7.5, 1.1 \text{ Hz}$, 1H), 7.43 (t, $J = 7.9 \text{ Hz}$, 2H), 5.67 (dt, $J = 7.3, 2.2 \text{ Hz}$, 1H), 4.49 (dt, $J = 8.1, 4.8 \text{ Hz}$, 1H), 4.27 (dd, $J = 8.1, 1.8 \text{ Hz}$, 1H), 3.71 (ddd, $J = 13.2, 4.0, 1.8 \text{ Hz}$, 1H), 3.32 (dd, $J = 16.2, 7.4 \text{ Hz}$, 1H), 2.93 (dd, $J = 13.2, 11.3 \text{ Hz}$, 1H), 2.62 (dd, $J = 16.5, 5.7 \text{ Hz}$, 1H), 2.54 (dd, $J = 15.8, 2.2 \text{ Hz}$, 1H), 2.24 (m, 1H), 2.15 (dd, $J = 16.5, 9.2 \text{ Hz}$, 1H), 2.01 (ddd, $J = 13.9, 7.7, 6.2 \text{ Hz}$, 1H), 1.99 (ddq, $J = 10.2, 6.6, 3.7 \text{ Hz}$, 1H), 1.73 (ddd, $J = 13.9, 6.6, 4.4 \text{ Hz}$, 1H), 1.61 (m, 1H), 1.57 (m, 1H), 1.46 (s, 9H), 1.30 (m, 1H), 1.11 (d, $J = 7.0 \text{ Hz}$, 3H), 0.97 (d, $J = 6.6 \text{ Hz}$, 3H), 0.85 (d, $J = 6.6 \text{ Hz}$, 3H); ^{13}C NMR (150 MHz, CDCl_3): $\delta = 171.0, 165.8, 155.7, 133.1, 129.9, 129.6, 128.4, 99.3, 85.8, 80.3, 76.6, 75.9, 50.7, 41.0, 38.4, 37.7, 31.8, 30.9, 30.3, 28.4, 23.4, 21.2, 18.8, 17.2$; HR-MS (Matrix-assisted laser desorption/ionization (MALDI)): calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_7\text{Na}^+$ [$M + \text{Na}^+$]: 524.2619, found 524.2613

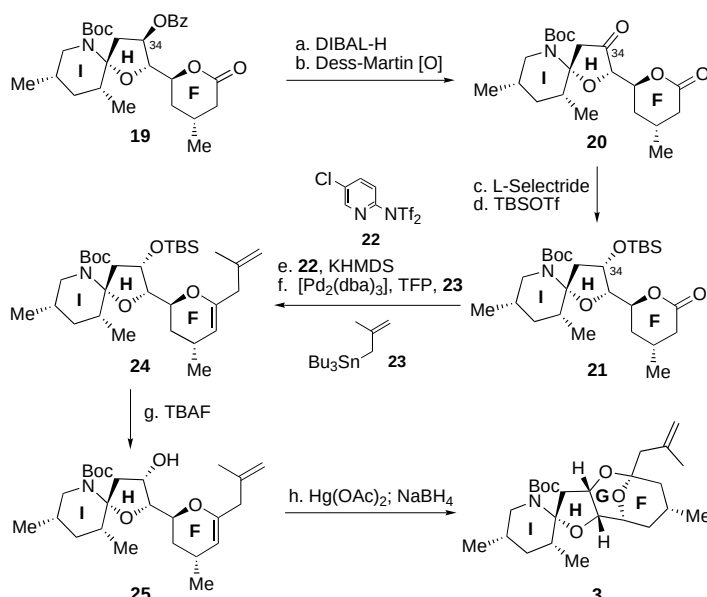
3: $R_f = 0.56$ (silica gel, ethyl acetate:hexanes 4:1); $[\alpha]_D^{20} = +4.6^\circ$ (CH_2Cl_2 , $c = 0.22$); IR (film) $\tilde{\nu}_{\text{max}} = 2925, 1591, 1492, 1446, 1373, 1225, 1190, 1115, 928, 747 \text{ cm}^{-1}$; ^1H NMR (500 MHz, $[\text{D}_6]\text{acetone}$): $\delta = 4.77$ (m, 1H), 4.73 (dt, $J = 5.1, 2.4 \text{ Hz}$, 1H), 4.69 (m, 1H), 4.19 (br d, $J = 4.9 \text{ Hz}$, 1H), 3.82 (dd, $J = 5.1, 0.9 \text{ Hz}$, 1H), 3.68 (m, 1H), 3.64 (m, 1H), 3.19 (dd, $J = 13.2, 11.8 \text{ Hz}$, 1H), 2.21 (AB, $J = 13.2 \text{ Hz}$, $\nu_{\text{ab}} = 20.8 \text{ Hz}$, 2H), 2.17 (dd, $J = 14.7, 5.1 \text{ Hz}$, 1H), 2.16 (m, 1H), 2.00 (ddq, $J = 11.0, 6.2, 4.1 \text{ Hz}$, 1H), 1.77 (t, $J = 0.7 \text{ Hz}$, 3H), 1.77–1.72 (m, 2H), 1.60–1.50 (m, 2H), 1.42 (s, 9H), 1.37 (dt, $J = 12.6, 5.3 \text{ Hz}$, 1H), 1.29 (m, 1H), 1.24 (dd, $J = 13.6, 12.5 \text{ Hz}$, 1H), 0.88 (d, $J = 6.2 \text{ Hz}$, 3H), 0.81 (d, $J = 6.6 \text{ Hz}$, 3H), 0.79 (d, $J = 6.6 \text{ Hz}$, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta = 156.1, 143.3, 114.9, 97.6, 97.1, 79.3, 78.8, 74.2, 72.3, 51.3, 50.2, 42.5, 40.9, 39.9, 37.4, 35.8, 32.3, 28.7, 25.1, 24.4, 23.2, 19.0, 16.8$; HR-MS (MALDI): calcd for $\text{C}_{25}\text{H}_{41}\text{NO}_5\text{Na}^+$ [$M + \text{Na}^+$]: 458.2877, found 458.2864



Scheme 5. Selected NOE interactions observed in intermediates **19** and **21**.

reduction sequence accomplished the inversion task (Scheme 6). Thus, simultaneous reduction of the benzoate group and of the lactone with diisobutyl aluminum hydride (DIBAL-H) and oxidation of the resulting hydroxy groups with Dess–Martin periodinane gave ketone **20** (66% over two steps). A highly selective reduction of **20** with lithium tri-*sec*-butylborohydride (L-Selectride) gave an intermediate alcohol as a single isomer (84%). Protection of the resulting alcohol with *tert*-butyldimethyl trifluoromethanesulfonate (TBSOTf) furnished **21** in 68% yield.^[16] Diagnostic NOE enhancements observed in the NMR spectra of **21** (Scheme 5) confirmed the illustrated stereochemistry.

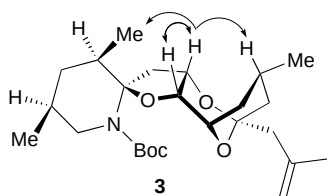
For the installation of the methallyl side chain, functionalization of the lactone as the ketene acetal triflate^[17] or phosphate^[18] and subsequent Stille coupling with methallyl-*n*-tributyltin (**23**) appeared particularly attractive, since the resulting enol ether could readily be engaged in the formation of the final ketal under mild conditions. Towards this end, treatment of lactone **21** with potassium bis(trimethylsilyl)-amide (KHMDs) and **22** gave the intermediate ketene acetal triflate in 75% yield. Stille coupling (**23**, $[\text{Pd}(\text{dba})_3] \cdot \text{CHCl}_3$ (dba = *trans,trans*-dibenzylideneacetone), tri-2-furylphosphine (TFP))^[19] effected the smooth displacement of the



Scheme 6. Synthesis of the FGHI ring system **3**: a) DIBAL-H (1.0 M in CH_2Cl_2 , 4.0 equiv), toluene, -78°C , 10 min; b) Dess–Martin periodinane (3.0 equiv), pyridine (20 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 1 h, 66% over two steps; c) L-Selectride, (1.0 M in THF, 2.0 equiv), THF, -78°C , 20 min, 84%; d) TBSOTf (1.1 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2 , -78°C , 15 min, 68%; e) **23** (15 equiv), KHMDS (0.5 M in toluene, 10.0 equiv), THF, $-20 \rightarrow 0^\circ\text{C}$, 30 min, 75%; f) LiCl (3.0 equiv), $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (0.05 equiv), tri-2-furylphosphine (0.43 equiv), methallyltributylstannane (5.0 equiv), THF, 25°C , 10 h, 86%; g) TBAF (1.0 M in THF, 3.0 equiv), THF, 25°C , 2 h, 93%; h) $\text{Hg}(\text{OAc})_2$ (3.5 equiv), THF:H₂O (3:1), -5°C , 20 min, then NaBH_4 (excess), 65% based on 75% conversion. DIBAL-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl.

triflate group (OTf) with the methallyl side chain to afford enol ether **24** in 86% yield. Finally, desilylation with TBAF gave the alcohol **25** in 93% yield, thus setting the stage for the final ring closure.

Our initial attempts at intramolecular ketalization with PPTS were not very encouraging. Although the desired FGHI spiro ring system **3** was indeed formed in 68% yield (based on 68% conversion), the product was obtained as an inseparable mixture of spiro isomers. We then turned our attention to other electrophiles. In spite of the presence of the potentially reactive methallyl side chain, we felt that the higher reactivity of the enol ether should allow a chemoselective reaction to take place at the enol double bond. Fortunately, exposure of **25** to $\text{Hg}(\text{OAc})_2$ in THF/H₂O (3:1) at -5°C followed by quenching with NaBH_4 ^[20] effected a smooth cyclization into the desired FGHI ring system **3** in 65% yield (based on 75% conversion), with none of the undesired spiroisomer observed (Table 1). Remarkably, this mild mercurycyclization reaction also left the methallyl side chain intact. Scheme 7 displays the three-dimensional shape of **3** with the observed NOE effects, which confirm the assigned stereochemistry.



Scheme 7. Three-dimensional representation of **3** and representative NOE interactions confirming the indicated stereochemistry.

In conclusion, the synthesis of the protected FGHI domain of azaspiracid (**1**) has been achieved in 23 linear steps from known starting materials. The unusual nature of this intricately carved portion of the molecule necessitated the search for novel conditions to effect the required key cyclizations. The power of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to catalyze the expedient formation of the HI spirocycle and the effectiveness of $\text{Hg}(\text{OAc})_2$ -mediated intramolecular ketalization have ultimately resulted in the first successful synthesis of the FGHI ring system of this novel target in a protected and enantiomerically pure form. Significantly, as both enantiomers of the starting materials utilized in this synthesis are readily available, the route described herein can provide material for continuing efforts toward the total synthesis of azaspiracid (**1**), determination of its absolute and relative stereochemistries, and for chemical biology studies.

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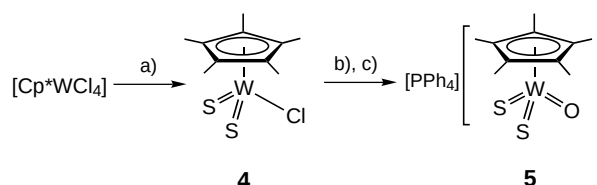
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Synthesis of a Cp* Complex of Tungsten with Three Different Chalcogenido (O²⁻, S²⁻, and Se²⁻) Ligands**

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The number of compounds containing terminal chalcogenido ligands has been increasing during the last decade.^[1] However, aside from derivatives of tetrachalcogenidometalates [M(E)₄]ⁿ⁻, mixed chalcogenido complexes are rare.^[2,3] In particular, it is difficult to prepare mononuclear complexes having both M=S and M=Se multiple bonds. This is because of the lack of an appropriate synthetic route to such complexes, difficulty arises from the propensity of chalcogenido ligands to bridge metal atoms and from the tendency of metal chalcogenides to undergo complicated ligand-exchange reactions in solution.^[3,4] In this context, the title complex ion [Cp*W(O)(S)(Se)]⁻ (Cp* = η⁵-C₅Me₅) is unique in that three different atoms of Group 16 coordinate the Cp*W fragment. It is also noted that this anionic species is a new type of chiral transition metal compound. Recently we developed a new method to prepare a series of the trithio and triseleno complexes of Group 5 and 6 transition metals having a Cp* ligand, and reported high yield syntheses of [Li(thf)₂][Cp*M(S)₃] (M = Nb, Ta),^[5] [PPh₄][Cp*M(S)₃] (M = Mo, W),^[6] and their seleno analogues for M = Ta, W.^[7] We found by NMR spectroscopic analysis in CD₃CN that a mixture of [PPh₄][Cp*W(S)₃] (**1**) and [PPh₄][Cp*W(Se)₃] (**2**) remained intact for a prolonged period, and showed no sign of ligand exchange to form mixed seleno/thio complexes. This observation prompted us to seek the preparation of the mixed-chalcogenido complex [PPh₄][Cp*W(O)(S)(Se)] (**3**) which is reported here.

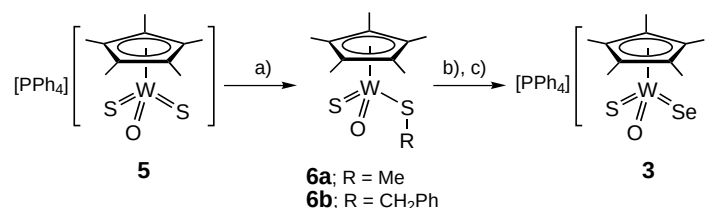
To synthesize the target molecule **3**, we first attempted the replacement of the terminal sulfide(s) of **1** by an oxygen or selenium atom. However, the reaction of **1** with a small amount of water caused partial decomposition of the complex, and the formation of a mononuclear oxo/thio complex was not discernible, while Li₂Se₂ did not react with **1**. Neither could we find a rational way to substitute the terminal selenide(s) of **2**. A successful, but less direct, route begins with the high yield (89%) synthesis of a dithio/chloro complex [Cp*W(S)₂Cl] (**4**) by the reaction of [Cp*WCl₄] with 1 equivalent of Me₃SiSCH₂CH₂SSiMe₃ (Scheme 1).^[8] Apparently C–S bond cleavage occurs, along with the liberation of the Me₃Si group. This reaction contrasts to the formation of [Cp*W(S)₃]⁻ upon treatment of [Cp*WCl₄] with LiSCH₂CH₂SLi, in which all the chlorides are substituted by thio ligands.



Scheme 1. Synthesis of **4** and **5**; reagents: a) Me₃SiSCH₂CH₂SSiMe₃/THF; b) H₂O/Et₃N/THF; c) PPh₄Br/CH₃CN.

The relatively mild reactivity of Me₃SiSCH₂CH₂SSiMe₃ toward [Cp*WCl₄] may be a reason for the formation of **4**. While an attempt to introduce seleno ligand(s) into **4** by reaction with Li₂Se₂ and subsequent cation exchange of the product with PPh₄Br resulted in a mixture of **1** (16%), [PPh₄][Cp*W(S)₂(Se)] (34%), and [PPh₄][Cp*W(S)(Se)₂] (5%),^[9] addition of a small amount of H₂O to a THF solution of **4** in the presence of NEt₃ gave [Cp*W(O)(S)₂]⁻. This dithio/oxo complex anion was isolated as an analytically pure phosphonium salt [PPh₄][Cp*W(O)(S)₂] (**5**) in 77% yield. Geoffroy et al reported that the reaction of [Cp*WCl₄] with H₂S in the presence of NEt₃ produced [NEt₃H][Cp*W(O)(S)₂] in low yield along with [Cp*₂W₂(S)₂(μ-S)₂], [Cp*₂W₂(S)₂(S₂)], and [NEt₃H][Cp*W(S)₃].^[10]

We have reported that alkylation reactions of **1** occur readily with various alkylhalides (RX), producing a series of [Cp*W(S)₂(SR)] compounds.^[6a] The remaining thio ligands are inert to alkylhalides, so that only one sulfide of **1** is alkylated. The reaction of **5** with CH₃I or PhCH₂Br proceeded in a similar manner, and [Cp*W(O)(S)(SR)] (R = CH₃ (**6a**), CH₂Ph (**6b**)) were isolated in 98% and 92% yields, respectively. Finally, a terminal selenide was introduced successfully by the reaction of **6a** or **6b** with Li₂Se₂ and PPh₄Br, and the desired oxo/thio/seleno complex [PPh₄][Cp*W(O)(S)(Se)] (**3**) was obtained in 64% or 57% yield, respectively (Scheme 2). Elemental analysis of **3–6a,b** for H, C, S, and



Scheme 2. Synthesis of **3** and **6**; reagents: a) MeI or PhCH₂Br/CH₃CN; b) Li₂Se₂/THF; c) PPh₄Br/CH₃CN.

X-ray fluorescence microanalysis for P, S, Se, and W are satisfactory. The ¹H and ⁷⁷Se NMR (for **3**) ascertained their purity. The negative ion electrospray ionization mass spectrum (EI-MS) of **3** measured at room temperature in acetonitrile exhibits an intense isotope cluster corresponding to [Cp*W(O)(S)(Se)]⁻, which fits very well to the theoretical isotope pattern (Figure 1). The complex [Cp*₂V₂(μ-O)(μ-S)(μ-SeTe)] containing four different chalcogenides in the bridge system between the two Cp*V units has been observed and characterized by NMR spectroscopy and mass spectrometry, although not isolated in a pure form.^[2f]

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[**] We thank Prof. Roger E. Cramer for careful reading of the manuscript; Cp = C₅Me₅.

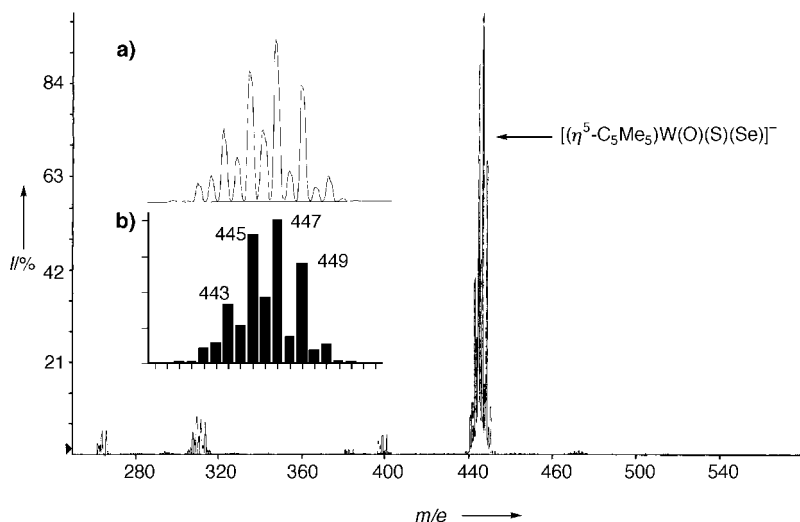


Figure 1. Negative ES mass spectrum of **3** in CH₃CN; a) observed spectrum of the mass ion, b) theoretical isotope pattern.

The mononuclear nature of these complexes has been established by single-crystal X-ray diffraction analyses for **3–5**, and **6b**,^[11] and they assume a common three-legged piano-stool geometry. In the X-ray structure of **3** (Figure 2), disorder between thio and seleno groups was observed, as is often the case, the chloro and thio groups of **4** are also disordered. Therefore we could not obtain accurate lengths for the W–Cl, W=S, and W=Se bonds of **3** and **4**.

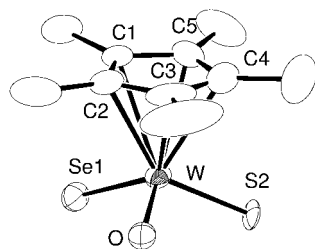


Figure 2. X-ray structure of the anion of **3**, only the major components of the disordered S and Se atoms are shown.

However, the oxo position is unique in the structure of **3**, and the oxo and thio groups of **5** are not disordered. Noteworthy here is that the centroid of the C₅Me₅ pentagon of **3** and **5** is not situated exactly above the metal atom, but is shifted toward the oxo ligand.^[12] Thus the two W–C bonds approximately *trans* to the W=O unit are longer by 0.071 Å (for **3**) or by 0.065 Å (for **5**) than the other W–C bonds. We attribute this deformation to the stronger *trans* influence of the oxo ligand relative to the thio/seleno ligands. The W=O and W=S bonds of **5** are 1.755(6) and 2.205(3) Å, respectively, which fall in the normal range of those found for terminal oxo and thio ligands bound to tungsten.^[13] The W=O and W=S bond lengths are somewhat longer than those of **6b** (1.732(9) and 2.150(4) Å), because one thio group of **5** is replaced by a thiolato ligand. The W=S bond length of **5** is also slightly longer than the W=S bond of **1** (2.188(2)–2.199(2) Å), indicating that the *trans* influence of the oxo ligand is in fact stronger than that of the thio ligand. The infrared and Raman spectra of **3** show strong absorptions can be assigned to the W=O stretch at $\tilde{\nu}$ = 871 and 870 cm^{−1}, the corresponding band of **5** both appear at $\tilde{\nu}$ = 869 cm^{−1}. The difference between thio- and seleno-coordination does not affect the W=O stretching frequencies. We observed two W=S stretching bands in the infrared and Raman spectra of **3**, both at 450 and 444 cm^{−1},

while those infrared bands of **4** and **5** are at 499, 486 cm^{−1}, and 454, 434 cm^{−1}, respectively. The W=Se stretching band for **3** appears at 287 cm^{−1} (infrared) or 286 cm^{−1} (Raman), comparable to those of [PPh₄][Cp*W(Se)₃] (**2**) and [W(Se)₄]^{2−}.^[2a, 7b]

Complex **3** is thermodynamically stable, and does not show a propensity for chalcogenide scrambling reactions in CH₃CN. Determination of the stereochemistry at tungsten in the reaction of **6a,b** → **3**, and the separation of the enantiomers of **3** and **6a,b** are in progress.

Experimental Section

3: Addition of **6a** (0.28 g, 0.68 mmol) in THF (10 mL) to Li₂Se₂ (0.31 g, 1.80 mmol) in THF (10 mL) at 0 °C gave a red suspension. The mixture was stirred for 1 h at room temperature. After centrifugation to remove insoluble material, the red supernatant solution was evaporated to dryness. The residue was dissolved in CH₃CN (10 mL), and a solution of PPh₄Br (0.26 g, 0.62 mmol) in CH₃CN (5 mL) was added. Concentration and cooling to −20 °C afforded of **3** (0.34 g, 64% yield) as red crystals; ¹H NMR (500 MHz, CDCl₃): δ = 7.6–8.0 (m, 20H; PPh₄), 2.10 (s, 15H; Cp*); ⁷⁷Se NMR (95.3 MHz, CDCl₃, Me₂Se): δ = 1027; IR (Nujol): $\tilde{\nu}$ = 871 (W=O), 450, 444 (W=S), 287 (W=Se) cm^{−1}; Raman: $\tilde{\nu}$ = 870 (W=O), 450, 444 (W=S), 286 (W=Se) cm^{−1}; ESI-MS (negative mode, CH₃CN); *m/z* 447 ([Cp*W(O)(S)(Se)][−]); X-ray fluorescence: W:S:Se:P = 1.00:0.98:1.06:1.10; elemental analysis calcd (%) for C₃₄H₃₅OPSSeW: C 51.99, H 4.49, S 4.08; found: C 52.24, H 4.36, S 4.22. A THF (10 mL) solution of **6b** (0.35 g, 0.71 mmol) was treated with Li₂Se₂ (0.36 g, 2.10 mmol) in THF (10 mL), and a workup similar to the one described above, using PPh₄Br (0.27 g, 0.64 mmol), yielded **3** (0.32 g, 57%).

4: Me₃SiSCH₂CH₂SSiMe₃ (3.93 mmol) in THF (40 mL) was added to a slurry of [Cp*WCl₄] (1.81 g, 3.93 mmol) in THF (50 mL) at room temperature. The mixture was stirred at room temperature for 3 h, producing a dark brown homogeneous solution. After removal of the volatiles, the residue was extracted with toluene (60 mL × 2). The toluene solution was concentrated and allowed to stand overnight at −20 °C producing **4** as dark red crystals (1.46 g, 89%); ¹H NMR (500 MHz, CDCl₃): δ = 2.35 (s; Cp*); IR (Nujol): $\tilde{\nu}$ = 499, 486 (W=S) cm^{−1}; EI-MS; *m/z* 418 [*M*⁺]; X-ray fluorescence: W:S:Cl = 1.00:2.03:0.92; elemental analysis calcd (%) for C₁₀H₁₅ClS₂W: C 28.69, H 3.61, S 15.32; found: C 28.77, H 3.58, S 15.30.

5: A mixture of NEt₃ (1.0 mL, 7.2 mmol) and H₂O (0.10 mL, 5.5 mmol) was added to a THF (80 mL) solution of **4** (1.06 g, 2.53 mmol) at room temperature. This immediately produced an orange suspension. After 30 min of stirring, the solution was dried over MgSO₄. After centrifugation to remove insoluble material a solution of PPh₄Br (0.95 g, 2.27 mmol) in CH₃CN (20 mL) was added to the supernatant solution. Concentration and cooling to −20 °C afforded **5** (1.44 g, 77%) as orange crystals; ¹H NMR (500 MHz, CDCl₃): δ = 7.6–8.0 (m, 20H; PPh₄), 2.09 (s, 15H; Cp*); IR (Nujol): $\tilde{\nu}$ = 869 (W=O), 454, 434 (W=S) cm^{−1}; Raman: $\tilde{\nu}$ = 869 (W=O), 454, 434 (W=S) cm^{−1}; ESI-MS (negative mode, CH₃CN); *m/z* 399 ([Cp*W(O)(S)₂][−]); X-ray fluorescence: W:S:P = 1.00:1.98:0.91; elemental analysis calcd (%) for C₃₆H₃₅OPS₂W: C 55.29, H 4.78, S 8.68; found: C 54.97, H 4.56, S 8.31.

6a: Iodomethane (90 μ L, 1.44 mmol) was added to a solution of **5** (0.97 g, 1.31 mmol) in CH₃CN (40 mL) at room temperature. The reaction mixture immediately formed a red solution and was stirred for 30 min. The solvent was removed in vacuo. The resulting solid was extracted with toluene (20 mL) and PPh₄I was removed by centrifugation. The supernatant solution was evaporated to leave **6a** (0.53 g, 98%) as a red crystalline powder; ¹H NMR (500 MHz, CDCl₃): δ = 3.05 (s, 3H; SMe), 2.23 (s, 15H; Cp*); IR (Nujol): $\tilde{\nu}$ = 910 (W=O), 482 (W=S) cm^{−1}; EI-MS; *m/z* 414 [*M*⁺], 399 [*M*⁺ − CH₃]; elemental analysis calcd (%) for C₁₁H₁₈OS₂W: C 31.90, H 4.38, S 15.48; found: C 31.77, H 4.28, S 15.19.

6b: A CH₃CN solution of **5** (0.81 g, 1.10 mmol) was treated with benzyl bromide (0.14 mL, 1.18 mmol), and a workup similar to the one described

above yielded **6b** (0.49 g, 92 %) as red microcrystals; ^1H NMR (500 MHz, CDCl_3): δ = 7.1–7.4 (m, 5 H; SCH_2Ph), 4.63 (d, J = 12.5 Hz, 1 H; SCH_2Ph), 4.33 (d, J = 12.5 Hz, 1 H; SCH_2Ph), 2.23 (s, 15 H; Cp*); IR (Nujol): $\tilde{\nu}$ = 911 ($\text{W}=\text{O}$), 482 ($\text{W}=\text{S}$) cm^{-1} ; EI-MS: m/z 490 [M^+], 399 [$M^+ - \text{CH}_2\text{Ph}$]; elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{22}\text{OS}_2\text{W}$: C 41.64, H 4.52, S 13.08; found: C 41.72, H 4.66, S 12.98.

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Combination of Electrografting and Ring-Opening Metathesis Polymerization: An Efficient Way to Prepare Polynorbornene Brushes on Conducting Substrates**

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Nowadays, increasing attention is paid to films of polymer chains covalently bonded to solid surfaces.^[1, 2] This strategy is very useful to modify the surface properties of inorganic materials, to improve the interfacial bonding in composites, and to prepare novel inorganic–organic hybrids.^[3, 4] In addition to this technique that consists of the chemical bonding of preformed end-reactive chains to the surface (“grafting onto” method), polymer brushes can be formed by the “grafting from” method, that is, the initiation and growth of the chains from the solid surface. When this substrate is electrically conducting, electropolymerization has proved to be a powerful method to deposit polymers that highly adhere to the substrate.^[5–7] Indeed, the electroreduction of monomers of the (meth)acrylate type at an appropriate potential leads to the rapid formation of an homogeneous polymer film on the cathode whatever its shape (plate, fiber) and nature (metal, carbon, indium tin oxide (ITO) glass).^[8, 9] That the polymer is chemisorbed onto the substrate is confirmed by insolubility in a good solvent for the polymer and by peeling tests.^[10, 11]

However, as a result of the formation of an insulating poly(meth)acrylate film on the cathode, the substrate is rapidly passivated (rendered inactive) which limits the film thickness (<100 nm). Moreover, monomers that contain protic functions (alcohol, amine, carboxylic acid, etc.) cannot be electrografted because of their reduction at the same or at a less cathodic potential than the (meth)acrylate.

The recent development of well-defined and highly active catalysts by the groups of Schrock^[12] and Grubbs^[13] has also reactivated interest in the ring-opening metathesis polymerization (ROMP) of cycloolefins, particularly for applications in solid-phase chemistry.^[14–17] Therefore, a combination of living ROMP and electrografting appears to be a promising strategy to overcome the limitations of the electrografting process. Indeed, the thickness of the polymer film “grafted” to the electrode could be easily tuned by a second step of “grafting from” polymerization of cycloolefins. Moreover, advantage can be taken of the compatibility of the Grubbs

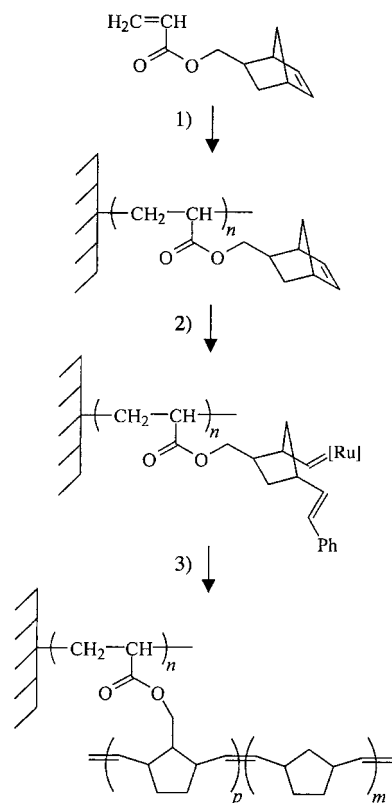
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catalyst with a wide-range of functional norbornenes to impart additional functionality to the surface of the conducting substrate.

The first step of the new process of surface modification reported herein relies on the electrografting of an acrylate, the ester group of which can be further used to initiate the ROMP of a cycloolefin. Scheme 1 shows the whole process that has



Scheme 1. Reaction scheme for the entire process. 1) Electrografting of NBE-A by cathodic polarization of the conducting substrate in DMF/TEAP mixture. 2) Grubbs initiator fixation by 5 min immersion in a dichloromethane solution; [Ru] = ruthenium complex. 3) ROMP by dipping in the NBE solution at room temperature.

been tested first for norbornenylmethacrylate (NBE-A). Figure 1 compares the voltammogram recorded for the reduction of norbornene (NBE; curve A) and NBE-A (curve B) using a Cu wire as the cathode in DMF treated with tetraethyl ammonium perchlorate (TEAP). Two distinct phenomena are observed in the case of NBE-A as is usually reported for the electroreduction of acrylates, these are, electrografting of PNBE-A to the cathode at the less cathodic potential (peak I), and initiation of the polymerization in solution concomitant to the degrafting of the originally formed film (peak II).^[18] The cathode is thus passivated as soon as the reduction occurs, which results in the dramatic decrease of the current intensity beyond peak I. For NBE, no reduction occurs (curve A) which confirms the stability of NBE in the potential range of interest for this process.

Whenever the applied potential is that corresponding to the top of peak I, the electrode is passivated after a few seconds, since peak I is no longer observed during a second potential

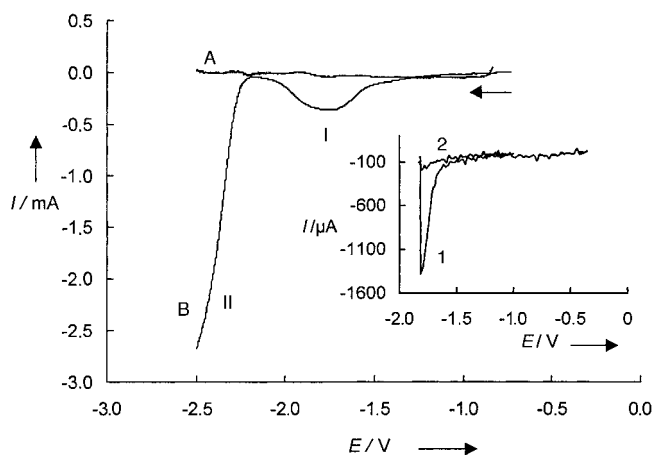


Figure 1. Cyclic voltammogram of A) NBE (0.75 M) and B) NBE-A (0.75 M) and TEAP (0.05 M) solution in DMF I) Grafting peak. II) Polymerization in solution. Inset: enlargement of the peak I recorded on steel plate cathode 1) first scan, 2) second scan.

scan (inset in Figure 1). The deposition of the insulating film, which is not visible to the naked eye, has been confirmed by X-ray photoemission spectroscopy (XPS; Table 1); the experimental C1 and O1 curves are nicely fitted by taking into account the chemical structure of the expected grafted poly(norbornenylmethacrylate).

Table 1. XPS data of the grafted P(NBE-A).

Atom	Position [eV]	Width	Area	% [a]	Theoretical amount [%]
C1	288.85	2.35	298	8.65	9.09
C2	286.83	1.26	298	8.65	9.09
C3	286.01	1.21	298	8.65	9.09
C4	285.05	1.40	2550	74.04	72.73
O1	533.34	2.27	778.9	50.00	50.00
O2	532.20	1.69	778.9	50.00	50.00

[a] Atomic experimental amount [%].

To attach the polymerization catalyst to the poly(NBE-A) coated surface, the modified electrode was dipped in a solution of the Grubbs catalyst (40 mg of Grubbs catalyst in 10 mL CH_2Cl_2) for five minutes and then rinsed three times with pure dichloromethane to remove any excess catalyst. Finally, the exposure of this modified substrate to a solution of NBE in CH_2Cl_2 (concentrations ranging from 0.1 M to 0.5 M), for a period of 10 to 30 minutes resulted in the “grafting from” polymerization.

The poly(NBE) (PNBE) grafted steel electrodes were washed extensively with dichloromethane, a good solvent for PNBE, and dried. Since only half of the electrode surface was dipped into the NBE-A solution during electrografting, only this part of the surface could initiate the NBE polymerization. Accordingly this part of the surface was covered by a white film of PNBE, visible to the naked eye, which confirms at least

qualitatively the successful grafting of polyNBE from the P(NBE-A) grafted film.

The FT infrared reflection absorption spectroscopy (IR-RAS) analysis of the PNBE film shows three characteristic peaks of high intensity at 2955, 2860, and 964 cm^{-1} . The absorption at 964 cm^{-1} is typical of the *trans* double bonds of PNBE. Additional peaks of lower intensity are also observed at 1467, 1423, and 742 cm^{-1} . The *cis* double bonds of PNBE actually absorb at 742 cm^{-1} .^[19] Figure 2A shows that the

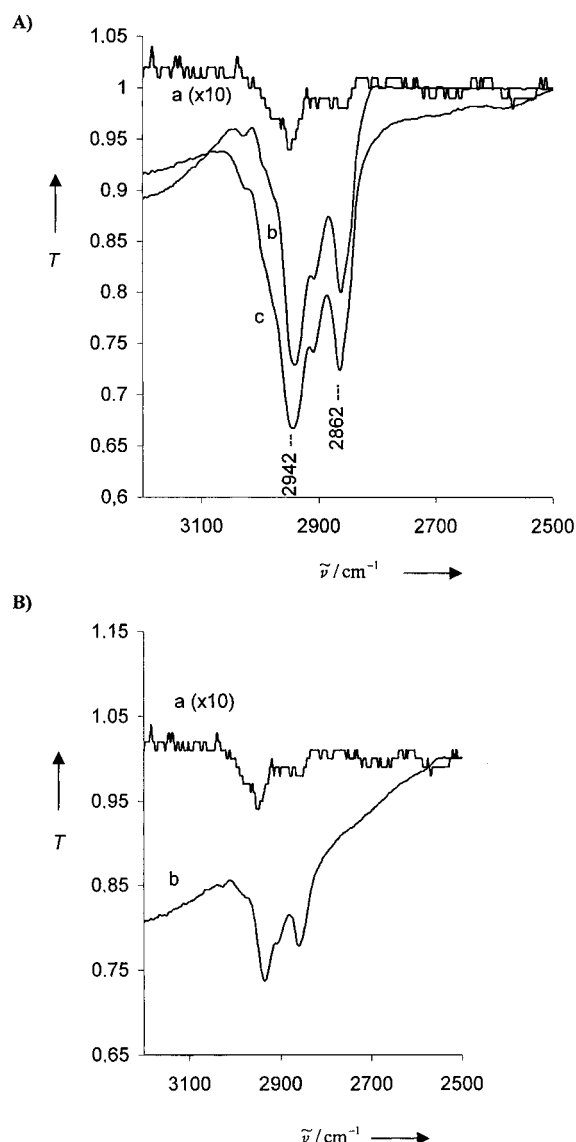


Figure 2. FTIR-RAS spectra of grafted PNBE films on steel, A) after 10 min polymerization from a CH_2Cl_2 solution with various NBE monomer concentrations: a) 0.1M, b) 0.25M, c) 0.5M. B) From a 0.1M NBE solution in CH_2Cl_2 after various polymerization times at room temperature: a) 10 min, b) 30 min.

intensity of the FTIR-RAS peaks of PNBE in the 3200–2500 cm^{-1} range increases with the NBE monomer concentration at constant polymerization time, which indicates a parallel increase in the PNBE film thickness. The same observation holds whenever the polymerization time is increased at constant monomer concentration (Figure 2B).

Evaluation by SEM (scanning electron microscopy) of the film prepared from the 0.1M NBE solution in 10 min shows the film to be about 6 μm thick.

Figure 3 is a comparison of the surface of the steel electrode before and after grafting as observed by SEM. The PNBE film covers completely and homogeneously the treated surface to the point where the roughness of the original surface is totally masked.

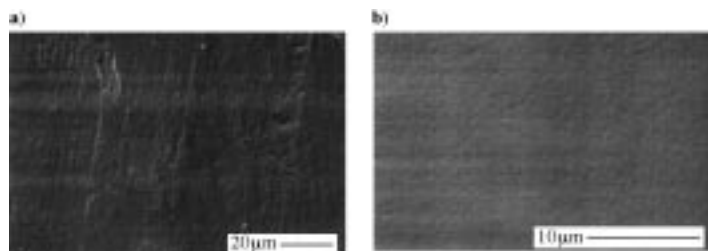


Figure 3. SEM images of a) neat steel, b) PNBE grafted onto steel.

The adhesion of the PNBE film onto steel has also been estimated by peeling tests. The surface adhesion, that is the peeling energy required to detach a standard scotch tape (3M-Acrylic foam 4930) from the neat surface is 1850 Jm^{-2} . This adhesion increases to 2400 Jm^{-2} when the test is repeated in case of the PNBE grafted surface. This value is however smaller than the actual adhesion energy, since the polymer film remains attached to the substrate after peeling.

The versatility of the electrochemical technique allows this coating method to be extended to various types of solid substrates. Electrografting of NBE-A followed by ROMP of NBE has been found successful not only on steel but also on copper wires, carbon plates, and carbon fibers. Figure 4 illustrates the SEM image of PNBE-modified fibers after extensive washing of the PNBE with dichloromethane in a Soxhlet apparatus for 13 days.

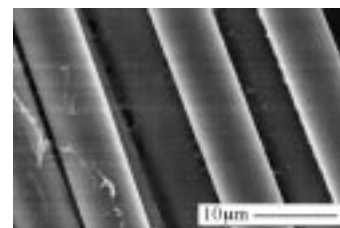


Figure 4. SEM image of PNBE grafted onto carbon fibers.

The electrografting of a conducting substrate by a polyacrylate film (such as poly(NBE-A)) which can be used further to initiate the growth of a polymer brush (e.g. of PNBE) is thus an efficient technique to control the thickness of well-adhering polymer films. Advantage can be taken of the brush in the development of electrochemical sensors. Moreover, the coating of steel, for example, by a thick hydrophobic polymer film is a very useful way to impart corrosion protection. For instance, the PNBE coating has proved highly successful in protecting steel against corrosion (copper test). Indeed, whenever a drop of an acidic aqueous solution of CuSO_4 is deposited onto neat steel and on steel

coated by PNBE, the oxidation of the neat surface is immediate as evidenced by the very fast formation of metallic Cu. In contrast, the coated surface remains unchanged at least for 12 h (Figure 5).

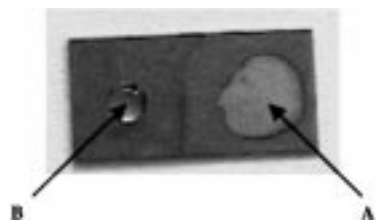


Figure 5. Steel plate after application of two drops of a CuSO_4 solution: A) neat steel: copper from the reaction with CuSO_4 ; B) PNBE grafted steel: the drop of CuSO_4 solution does not react.

Modification of carbon fibers by well-adhering polymer chains that contain reactive double bonds is also of importance in the field of composite materials. Finally the general concept illustrated in this paper can be extended to the ROMP of functionalized NBE, so paving the way to functionalized surfaces with tunable properties.

Experimental Section

NBE-A was prepared by reaction of 5-norbornene-2-methanol (41 mmol) with excess acryloyl chloride (123 mmol) in the presence of triethylamine (123 mmol), and dried before use.

Monomers, solvents, and conducting-salt were dried before use. Electrochemical experiments were carried out in a one-compartment cell with a platinum pseudoreference counter-electrodes with a PAR EG&G potentiostat (Model 273A). All the experiments were carried out in a glovebox under a dried inert atmosphere.

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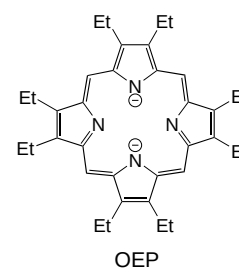
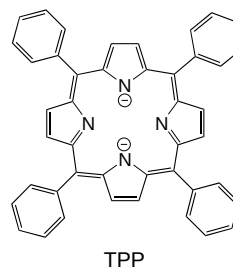
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The First Quadruple Bond Between Elements of Different Groups**

James P. Collman,* Roman Boulatov, and Geoffrey B. Jameson

Whereas many homonuclear quadruply bonded compounds are known,^[1] heteronuclear analogs remain rare. Discovery of the first bridged heteronuclear quadruple bond in 1974^[2] was followed by the synthetically more challenging preparation of the unbridged Mo^4W unit in 1984.^[3] Yet to date, fewer than twenty such heterometallic systems have been characterized, all containing either the Cr^4Mo or the Mo^4W core. We report here the preparation of the first compound with a quadruple bond between elements from different triads: the heterometallic "dimer" $[(\text{tpp})\text{Mo}^4\text{Re}(\text{oep})]\text{PF}_6$ (**1**) (TPP = *meso*-tetraphenylporphyrin dianion, OEP = octaethylporphyrin dianion).



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

The formation of a quadruple bond requires at least four valence orbitals and exactly eight valence electrons (Figure 1) to occupy all of the bonding and none of the antibonding orbitals of the $[M^4-M']^{x+}$ core. The unique preference of

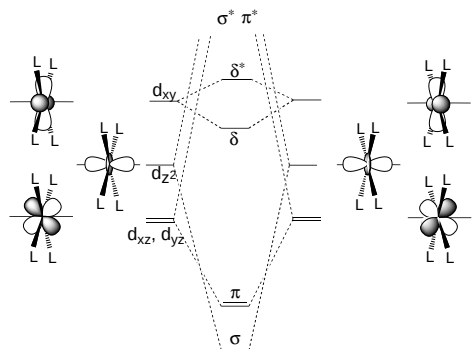
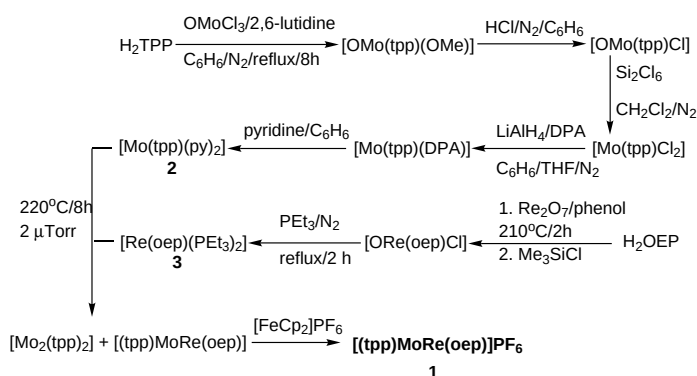


Figure 1. Qualitative MO diagram of metal–metal bonding between two square-planar ML_4 units.

unbridged $L_4M^4-M'L'_4$ complexes for an eclipsed conformation, in which nonbonding repulsions are strongest, is the direct result of the drive to maximize the $d_{xy}-d_{xy}$ overlap. The effect of the polarity of the quadruple bond on its properties remains one of the unsettled issues of chemical bonding. Bridged Mo^4-W bonds are often shorter, or have higher force constants, than their homonuclear counterparts,^[4] while the properties of the unbridged Mo^4-W bonds are approximately the average of those of their homonuclear congeners.^[5] Quadruply bonded metallocporphyrin dimers are excellent systems to study this issue. Porphyrins (por) such as TPP and OEP combine the high binding affinity of a chelating ligand with almost no bridging capacity. They provide a symmetrical, relatively rigid, square-planar coordination environment. Their steric bulk can be modified by peripheral substitution, while preserving the general structural motif of the core.^[6] Moreover, our synthetic strategy for metallocporphyrin dimers is applicable to many transition metals, permitting systematic studies of M^4-M' entities. In contrast, a lack of general preparative methods has limited the variety of accessible quadruple bonds in non-porphyrin environments.

The OEP–TPP combination in **1** was chosen on the basis of its complementary substitution pattern, which eliminates unfavorable steric interactions between the peripheral groups in both the eclipsed and staggered conformations of the dimer, thereby minimizing steric perturbation of the metal–metal bond. In addition, a heteroleptic dimer should be free of the solid-state disorder common for heterodimetallic systems, wherein the two crystallographic sites for metal ions are randomly occupied.

The synthesis of **1** starts with metalation of the corresponding porphyrins (Scheme 1). Although such reactions are usually carried out at high temperatures and proceed in only moderate yields,^[7] we were able to achieve high-yielding Mo insertion under mild conditions.^[8] This finding makes accessible Mo complexes of highly functionalized, temperature-sensitive porphyrins. The heterodimer is obtained by high-vacuum solid-state pyrolysis of mixtures of the monometallic



Scheme 1. Synthesis of $[(tpp)MoRe(oep)]PF_6$ (**1**). DPA = diphenylacetylene. See the Experimental Section and Supporting Information for experimental details.

precursors **2** and **3**. Loss of thermally labile axial ligands generates four-coordinate (tpp)Mo and (oep)Re fragments, which randomly dimerize to a mixture of hetero- and homodimers. Precursors of comparable thermal stability should produce such fragments in nearly equimolar amounts during the pyrolysis, thus maximizing the yield of the heterodimer. This criterion dictates the combination of axial ligands used to maintain the mononuclearity of **2** and **3**. Isolation and purification of **1** is achieved with cycles of selective oxidation and reduction.^[9]

In the solid state, **1** adopts the fully eclipsed conformation, unequivocally proving the presence of the quadruply bonded Mo^4-Re moiety (Figure 2). In contrast, bis-porphyrin “sand-

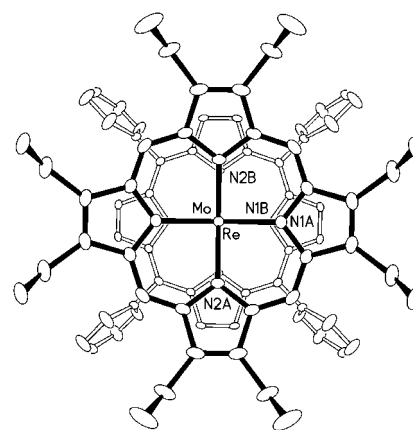


Figure 2. ORTEP view of the cation in **1** along the Re–Mo vector (thermal ellipsoids for 20% probability). The perspective is exaggerated to better show the perfectly eclipsed alignment of the porphyrin ligands. Hydrogen atoms are omitted.

wich” compounds, $(por)_2M$, wherein the relative orientation of the macrocycles is determined by purely steric interactions, invariably adopt a staggered geometry.^[10] Among all $[d-d]^8-9$ metallocporphyrin dimers studied to date, various degrees of deviation from an eclipsed conformation have been observed, which in some cases leads to annihilation of the δ bond (Table 1).^[11–13] For example, as a result of severe steric repulsions between the phenyl substituents, the d^4-d^4 $[Mo_2(tpp)_2]$ dimer adopts an N–Mo–Mo–N dihedral angle of

Table 1. Electronic configurations (e.c.) of the frontier orbitals, metal–metal bond orders (b.o.) and metric parameters (in [°] or [Å]) of selected d^{8–9} metalloporphyrin dimers.

Dimer	e.c.	b.o.	N–Mo–M–N	Mo–M	N ₄ –N ₄ ^[a]	Mo–N ₄ ^[b]	M–N ₄ ^[b]
[(tpp)Mo⁴Re(oep)]⁺	σ²π⁴δ²	4	0	2.236	3.120	0.492	0.392
[(tpp) ₂ Mo ₂] ^[11]	σ ² π ⁴ δ ²	4	18	2.239	3.208	0.458	
[(oep)MoRu(tpp)] ^{+[12]}	σ ² π ⁴ δ ² (π*) ¹	3.5	4.5	2.211	3.11	0.562	0.334
	σ ² π ⁴ (d _{xy}) ² (π*) ^{1[c]}	2.5	43	2.181	3.05	0.578	0.295
[(oep)MoOs(tpp)] ^{+[13][d]}	σ ² π ⁴ (d _{xy}) ² (π*) ^{1[c]}	2.5	42	2.24	3.14	0.58	0.31

[a] Distance between the least-squares planes of the chelating nitrogen atoms. [b] Displacement of the metal ion from the least-squares plane of the chelating nitrogen atoms. [c] Although the HOMO of the *neutral* dimers was unequivocally determined to be π*, there is at present no experimental evidence that would favor either a σ²π⁴(d_{xy})²(π*)¹ (b.o. = 2.5) or a σ²π⁴(d_{xy})²(d_{xy})¹ (b.o. = 3) description of the metal–metal bonding in the corresponding *cations*. However, irrespective of the precise description of the Mo–M bonding (M = Ru, Os), the important point in the context of the present discussion is that the d⁹ configuration of [(oep)MoM(tpp)]⁺ does not necessarily yield a δ bond. [d] The bonding in the [MoOs]⁵⁺ core was originally described as σ²π⁴δ²(π*)¹ giving an overall bond order of 3.5; however, at the observed N–Mo–Os–N' dihedral angle of 42° no more than 10% of the maximum δ–δ overlap remains (ref. [1], p. 20). Therefore, [(oep)MoOs(tpp)]⁺ should more precisely be considered as having a metal–metal bond order of 2.5 with a pair of nearly nonbonding d_{xy} atomic orbitals.

18°. In contrast, the complementary substitution pattern of the OEP–TPP pair and the d⁸ electronic configuration of the [Mo⁴Re]⁵⁺ core engender to **1** a perfectly eclipsed conformation. Common for all metalloporphyrin dimers, the resulting steric crowding is partially relieved by distortions of the macrocycles (see Table 1). Both metal ions in **1** are significantly displaced from the mean plane of the coordinating nitrogen atoms, while the porphyrin cores experience substantial “doming” distortions (Figure 3). Consequently, the closest OEP–TPP contact occurs between the corresponding nitrogen atoms, N_{OEP}⋯N_{TPP} (3.11(1) Å).

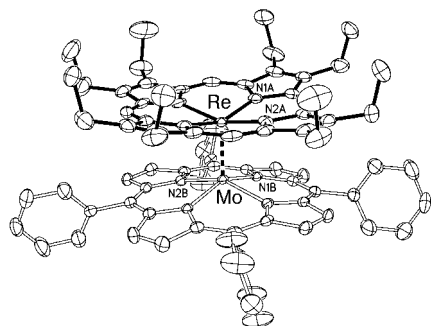


Figure 3. Side view of the cation in **1** showing the doming of the porphyrin ligands (thermal ellipsoids for 40% probability). Hydrogen atoms are omitted.

As a result of the high bond order, the Mo–Re distance in **1** is by far the shortest ever reported for a Mo–Re unit (Table 2). It falls within the range of Re⁴Re bond lengths but is slightly longer than the bonds in the Mo⁴Mo cores. Notably, metalloporphyrin dimers possess comparable met-

Table 2. Metal–metal distances in **1** and related dimers.

Moieties	M–M distance, range [Å]	
	Nonbridging ligands	Bridging ligands
[(tpp)Mo⁴Re(oep)]⁺	2.236	
Mo ⁴ Mo ^[a]	2.110–2.175 ^[b]	2.010–2.186
Re ⁴ Re ^[a]	2.188–2.296	2.178–2.260
Re⋯Mo ^[c]	2.844–3.184	2.656–3.199

[a] Compiled from data in ref. [1]. [b] Excludes [Mo₂(tpp)₂]. [c] Compiled from Cambridge Structural Database.

al–metal separations, irrespective of the formal bond orders (see Table 1).

The diamagnetic σ²π⁴δ² ground-state configuration of **1** and its 1:1 TPP-to-OEP ratio are confirmed by solution ¹H NMR spectroscopy. The chemical shift differences (Δδ_{endo/exo}) within the diastereotopic pairs of protons (Figure 4) in **1** point to a significant magnetic anisotropy. This phenomenon is observed whenever two porphyrin macrocycles, at least one of which containing phenyl groups, are positioned in parallel at a relatively close separation. In order to relieve the ensuing steric congestion, the phenyl groups tilt back, which places their *endo* protons into the deshielding region of the combined magnetic field of the porphyrin ring currents. The magnetic anisotropy experienced by the diastereotopic pairs of such protons is dependent on the interporphyrin separation, as this separation affects both the strength of the combined magnetic field and the degree to which the phenyl rings are “tilted back”. Nonetheless, the Δδ_{endo/exo} values in **1** are larger than those observed for other bis-porphyrin systems with comparable interporphyrin separations, such as [Th(tpp)₂] (Table 3).^[14, 15]

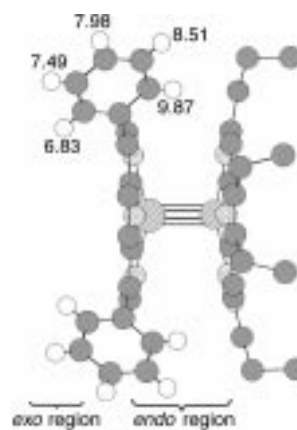


Figure 4. Chemical shifts (δ vs. TMS) of the *endo* and *exo* protons of the phenyl substituents in [(tpp)Mo⁴Re(oep)]⁺. All other hydrogen atoms are omitted.

Table 3. Chemical shifts of the phenyl hydrogen atoms and the interporphyrin distances in selected bis-porphyrin complexes.

Compound	Ct–Ct ^[a]	<i>ortho</i> – <i>endo</i> / <i>exo</i> (Δδ _{endo/exo}) ^[b]	<i>meta</i> – <i>endo</i> / <i>exo</i> (Δδ _{endo/exo}) ^[b]
[(tpp)Mo⁴Re(oep)]⁺	3.514	9.87/6.83 (3.04)	8.51/7.49 (1.02)
[Ce(tpp)(oep)] ^[14]	3.38	9.68/6.40 (3.28)	8.25/7.25 (1.00)
[Th(tpp) ₂] ^[15]	3.47	9.33/6.56 (2.77)	8.00/7.23 (0.77)
[Mo ₂ (tpp) ₂] ^[11]	≥ 3.7	9.28/6.90 (2.38)	7.92/7.38 (0.54)

[a] Distance between the least-squares planes of 24 atoms of the porphyrin core. [b] Chemical shifts (δ vs. TMS in CDCl₃) and the differences for the diastereotopic pairs of the *ortho* and *meta* protons of the phenyl groups.

The additional contribution may be attributable to the Mo⁴–Re bond, by analogy with the very large diamagnetic anisotropies of Mo⁴–Mo bonds.^[16] However, whereas the Mo⁴–Mo unit has a *deshielding* effect on the *endo* groups (corresponding to a negative magnetic anisotropy), the Mo⁴–Re moiety in **1** apparently causes *shielding* of the *endo* protons. This may reflect different electronic properties of heteronuclear and homonuclear quadruple bonds.

Experimental Section^[17]

All operations were performed under strictly anaerobic and anhydrous conditions. A mixture of [Mo(tpp)(py)₂] **2** (25 mg, 30 μmol) and [Re(oep)-(PEt₃)₂] **3** (8 mg, 8.4 μmol) was lyophilized by rapid removal of the solvent (C₆H₆, 2.5 mL). The resulting amorphous solid was pyrolyzed at 220°C under vacuum (2 μTorr) for 8 h. The pyrolysis was repeated five times, the solids from these five batches were combined (ca. 150 mg),^[18] dissolved in C₆H₆ (10 mL), and the solution was filtered through a celite plug on to [Cp₂Fe]PF₆ (20 μmol, obtained by evaporating 800 μL of a 25 mM stock solution in acetonitrile in the reaction vial) and the mixture was stirred overnight. The precipitate of [Re(oep)(PEt₃)₂]PF₆ (and some **1**) was filtered, and the filtrate was treated with another 20 μmol portion of [Cp₂Fe]PF₆ to yield after 12 h, crude **1** as a dark-brown solid (the C₆H₆ filtrate contained mostly [Mo₂(tpp)₂] and a small amount (<10%) of [OMo(tpp)] along with [Cp₂Fe] and some [(oep)ReMo(tpp)]). The precipitate was treated with [Cp₂Co] (18 μmol, 40 mM stock solution in C₃H₆) in C₆H₆ for 24 h. The remaining solids ([Cp₂Co]PF₆ and an unidentified Re(oep) species) were separated, and the filtrate (mostly [(tpp)MoRe(oep)]) was subjected to two cycles of oxidation with [Cp₂Fe]⁺ followed by reduction with [Cp₂Co] exactly as described above. The main impurity isolated in these subsequent redox cycles was an unidentified Re(oep) species. Recrystallization of the precipitate of the final oxidation from CH₂Cl₂/toluene (1/3) yielded **1** (12 mg, 7.2 μmol, 17% yield based on [Re(oep)(PEt₃)₂]). ¹H NMR (500 MHz, CDCl₃, TMS): δ = 10.10 (s, 4H; *meso*-H, Re(oep)), 9.86 (d, ³J(H,H) = 7 Hz, 4H; *ortho-endo*-H_{ph}, Mo(tpp)), 8.51 (t, ³J(H,H) = 8 Hz, 4H; *meta-endo*-H_{ph}, Mo(tpp)), 8.47 (s, 8H; β-pyrrolic, Mo(tpp)), 7.97 (t, ³J(H,H) = 8 Hz, 4H; *p*-H_{ph}, Mo(tpp)), 7.50 (m, 4H; *meta-exo*-H_{ph}, Mo(tpp)), 6.82 (d, ³J(H,H) = 7.5 Hz, 4H; *ortho-exo*-H_{ph}, Mo(tpp)), 4.35 (m, 8H; CH₂, Re(oep)), 4.14 (m, 8H; CH₂, Re(oep)), 0.86 (t, ³J(H,H) = 7.5 Hz, 24H; CH₃, Re(oep)).

Crystal data for **1**·3 C₆H₅CH₃ (C₁₀₁H₉₆F₆MoN₈PRE): *M*_r = 1848.97, orthorhombic, space group *Pmma*, *a* = 26.350(5), *b* = 15.516(3), *c* = 9.802(2) Å; *V* = 4007.6(14) Å³, *Z* = 2 (imposing *mm2* symmetry on **1**), ρ_{calcd} = 1.532 g cm⁻³, absorption coefficient 1.757 mm⁻¹, *F*(000) = 1888, reflections collected 18484, independent reflections 3642, GOF = 1.132, *R* = 0.05457, *wR*₂ = 0.1344. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149919. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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- [18] The exact composition of this mixture could not be determined quantitatively due to paramagnetism of [(oep)ReMo(tpp)] and unreacted [Re(oep)(PEt₃)₂]. A small sample of the mixture was oxidized stepwise by adding small portions of [Cp₂Fe]PF₆ until mostly diamagnetic NMR spectra were observed. These indicated that the major species in the sample were [(oep)ReMo(tpp)], [Re(oep)-(PEt₃)₂], and [Mo₂(tpp)₂] in ca. 1:(<1):(<3) ratio.

Synthesis of the Globo H Hexasaccharide Using the Programmable Reactivity-Based One-Pot Strategy**

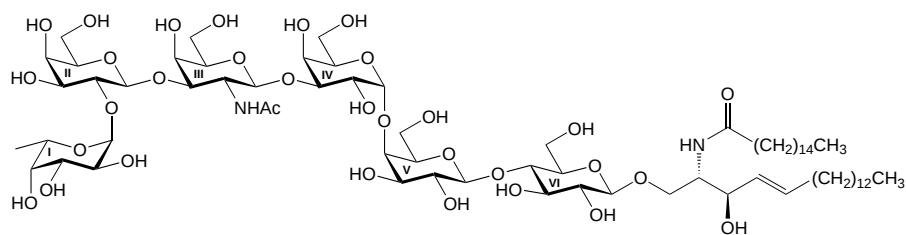
Fred Burkhart, Zhiyuan Zhang, Shirley Wacowich-Sgarbi, and Chi-Huey Wong*

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

Carbohydrate antigens are the most abundantly expressed antigens on the surface of most cancer cells.^[1] Globo H (Scheme 1), a glycosyl ceramide, was isolated and identified as an antigen on prostate and breast cancer cells.^[2] Its immunofunction has been characterized by Mênard et al.^[3] and Kuryashov et al.^[4] The use of this molecule as a vaccine for breast and prostate cancer has been studied by Danishefsky and co-workers.^[5]

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Scheme 1. The Globo H glycolipid.

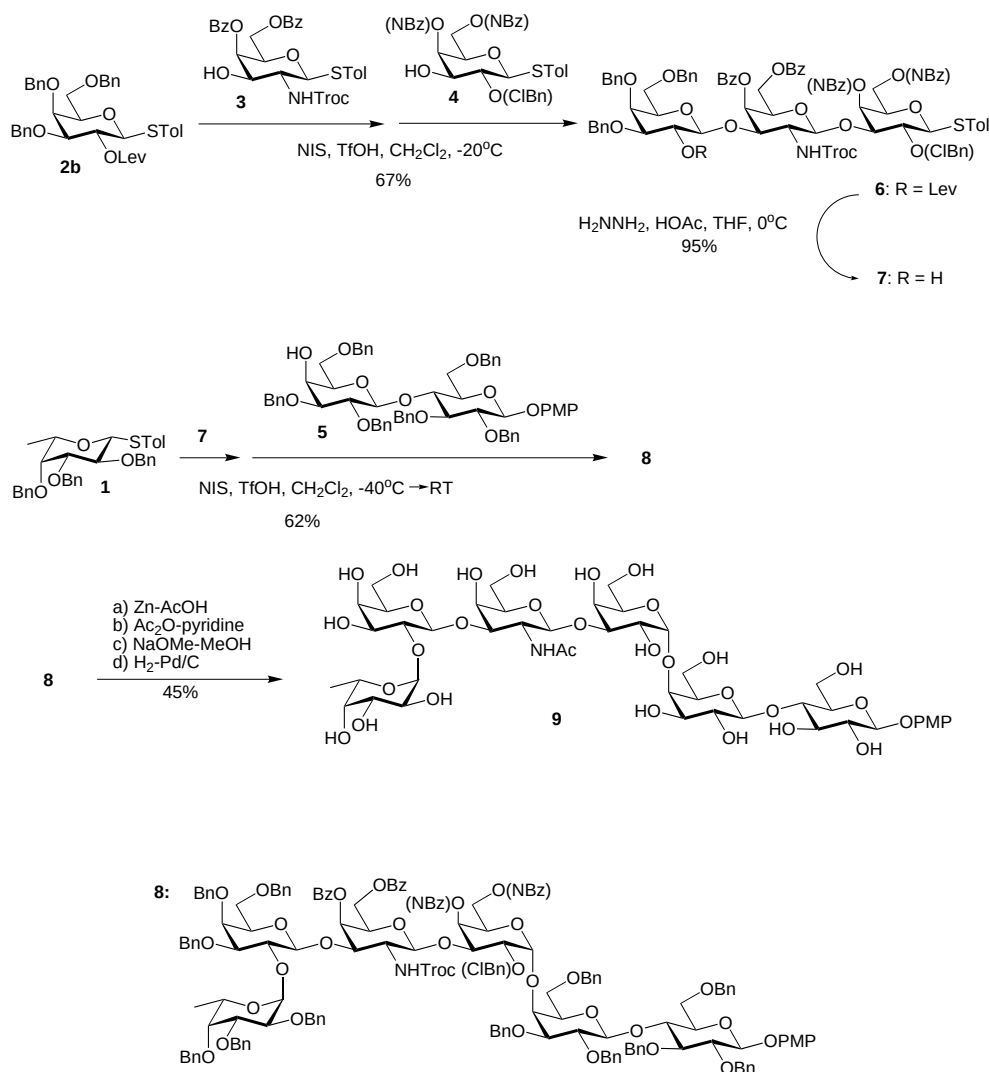
The first synthesis of the saccharide moiety of Globo H was reported by Danishefsky and co-workers using the glycal assembly strategy.^[6] Lassaletta and Schmidt synthesized the Globo H hexasaccharide with the trichloroacetimidate methodology.^[7] Another very effective synthesis of the saccharide moiety of Globo H was published by Zhu and Boons.^[8] However, controlling the β -selectivity of the coupling between rings II and III was a problem.

Herein we present a new method for the synthesis of the Globo H hexasaccharide using the anomeric reactivity-based one-pot strategy developed by Ley and co-workers^[9] and this group.^[10] Our programmable one-pot approach uses a computer program called “OptiMer” to guide the selection of appropriate tolylthioglycoside building blocks from a large pool for the one-pot synthesis.^[10] With this strategy, oligosaccharides containing three to six monosaccharides are rapidly assembled in minutes or hours by mixing the selected building blocks in sequence, with the most reactive one first. No intermediate work-up and purification is required except for the final deprotection/isolation step. The “relative reactivity” (against peracetyltolylthiomannoside) of each building block serves as an “identity tag” to identify or decode the structure of the target oligosaccharide. This approach thus represents a new method of combinatorial chemistry suitable for the synthesis of single-molecule libraries. Currently there are 80 building blocks in the database; expansion of the database (to approximately 300 building blocks) is necessary to cover the synthesis of most oligosaccharides.

Control of the stereoselectivity of each glycosylation

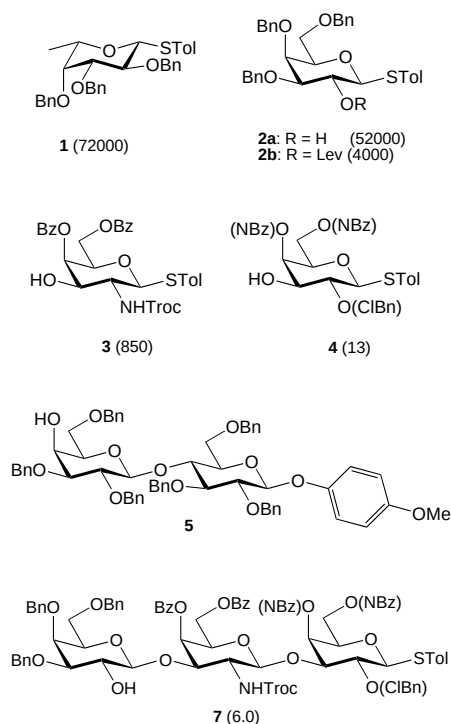
and the generation of a significant reactivity difference between the thio-glycosides are crucial for the successful synthesis of an oligosaccharide with the one-pot strategy. Our strategy for the Globo H saccharide synthesis involved the use of two one-pot reactions separated by a selective deprotection step to fully control the α and β selectivities (Scheme 2). The

first one-pot reaction was to build the two β -linkages connecting rings II, III, and IV to form **6**, which would then be converted into the trisaccharide building block **7**. The second one-pot reaction was to build the two α -linkages, between rings I and II and between rings IV and V, to form the protected Globo H saccharide **8**, through the sequential reaction of **1**, **7**, and **5**. We decided to use a levulinate as a temporary protecting group on the 2-position of galactose II (that is, **2b**), which would be removed selectively after the first one-pot reaction. Based on the knowledge of what affects the reactivity of a building block,^[10] compounds **1–5** were



Scheme 2. One-pot synthesis of the Globo H hexasaccharide. Bn = benzyl, Bz = benzoyl, ClBn = *ortho*-chlorobenzyl, Lev = levulinate, NBz = *para*-nitrobenzoyl, NHTroc = 2,2,2-trichloroethylcarbamate, NIS = *N*-iodosuccinamide, PMP = *para*-methoxyphenyl, Tf = triflate = trifluoromethanesulfonyl, Tol = tolyl = *para*-methylphenyl.

designed and synthesized (Scheme 3). The reactivities were mainly tuned by using electron-donating groups (benzyl ether and 2,2,2-trichloroethylcarbamate) and electron-withdrawing groups (benzoyl, *p*-nitrobenzoyl, and *o*-chlorobenzyl ethers).



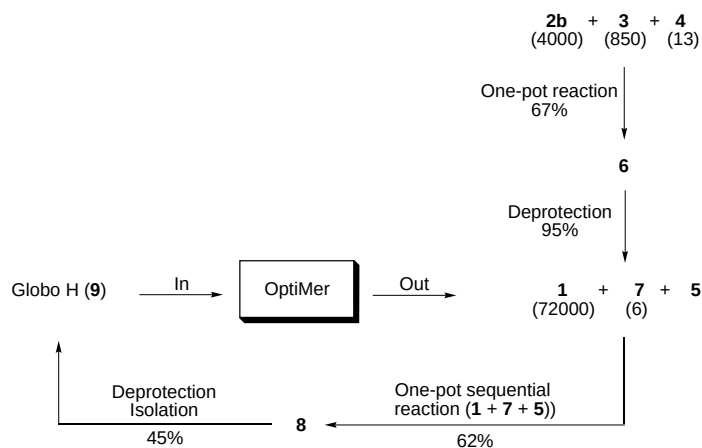
Scheme 3. The building blocks **1**–**5** and **7** were designed for the synthesis of the Globo H hexasaccharide. The relative reactivity values (against peracetyltolylthiomannoside, as determined by HPLC^[10]) are given in brackets.

Compounds **1**^[10] and **5**^[11] have been described previously. Thioglycosides **2a** and **2b** were prepared with the procedure analogous to that described by Sinaý and co-workers.^[12] The syntheses of glycosyl donors **3** and **4** were straightforward and required standard protecting group manipulations. Reactivities of those compounds were determined by HPLC as described previously.^[10] As shown in Scheme 3, the reactivity differences of the designed compounds are in a suitable range for a successful one-pot synthesis.

The three-step-synthesis of fully protected Globo H derivative **8** is outlined in Scheme 2. The first one-pot reaction built up the two β -linkages from compounds **3** (1 equiv), **2b** (1.5 equiv), and **4** (1.5 equiv). *N*-iodosuccinimide and triflic acid were used as promoters. The desired trisaccharide **6** was isolated in 67% yield. Deprotection of the levulinate using hydrazine in a mixture of THF and acetic acid at 0°C gave building block **7** in 95% yield.^[13] The reactivity of this compound relative to peracetyltolylthiomannoside is 6.0, similar to that of building block **4**. The second one-pot reaction formed the two α -linkages of Globo H. Thus, the fully protected Globo H derivative **8**^[13] was assembled in 62% yield, using donor **1** (1.8 equiv), compound **7** (1 equiv), and acceptor **5** (2.5 equiv). It is worth pointing out that all glycosyl linkages were built stereoselectively, and the overall yield after two one-pot assemblies and one deprotection step was 41% yield. Finally, the protecting groups on compound **8** were removed to give the deprotected Globo H hexasaccharide **9** in

45% yield.^[13] The *p*-methoxyphenyl group (PMP) was used in order to give us the possibility to independently deprotect the reducing end to further functionalize for biological purposes.

We have demonstrated the stereoselective synthesis of the hexasaccharide moiety of the tumor-associated antigen Globo H through the programmable one-pot synthesis strategy (Scheme 4). The building blocks developed for the synthesis



Scheme 4. Overall strategy for the programmed one-pot synthesis of the Globo H hexasaccharide. The numbers in parenthesis are the relative reactivities (against peracetyltolylthiomannoside).

contain mono-, di-, and trisaccharides and have been entered into the OptiMer database. They were assembled in two separate one-pot reactions performed stereoselectively in good overall yields. We believe that this new synthetic strategy has potential for use in the rapid synthesis of Globo H and analogues, including the aglycon moiety, for identification of the optimal structure to be used in vaccine development. The programmable one-pot strategy should also be applicable to the structure–activity relationship study of other complex oligosaccharides. Work is in progress to develop another one-pot synthesis of the Globo H saccharide using the disaccharide of rings II and III as a building block to react with **1**, followed by **4** and **5**. The result will be published in due course.

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- [13] Compound **7** was characterized by ^1H NMR spectroscopy, with HMQC and COSY analyses, and high-resolution mass spectrometry. ^1H NMR (600 MHz, CDCl_3): δ = 7.06–8.30 (ArH), 5.87 (d, J = 1.8 Hz, 1H; H4), 5.57 (d, J = 2.1 Hz, 1H; H4'), 5.34 (d, J = 7.1 Hz, 1H; NH), 4.77 (d, J_{CH} = 159.4 Hz, 1H; H1'), 4.57 (d, J = 9.6 Hz, J_{CH} = 154.3 Hz, 1H; H1), 4.34 (d, J = 7.9 Hz, J_{CH} = 162.9 Hz, 1H; H1''); HR-MS $[M+\text{Na}]^+$ calcd for $\text{C}_{84}\text{H}_{77}\text{N}_3\text{O}_{24}\text{S}_1\text{Cl}_4\text{Na}$: 1706.3264; found: 1706.3344. Compound **8** was characterized by ^1H NMR spectroscopy, with HMQC analysis, and high-resolution mass spectrometry. ^1H NMR (600 MHz, CDCl_3): δ = 6.75–8.23 (ArH), 6.40 (d, J = 7.0 Hz, 1H; NH), 6.07 and 5.61 (d, J = 3.1, 3.5 Hz, 1H each; H4'' and H4'''), 5.39 and 5.25 (d, J = 3.1, 4.0 Hz, 1H each; two α -H1), 5.23, 4.81, 4.47, and 4.34 (d, J = 8.3, 7.9, 7.5 Hz, four β -H1), 0.88 (d, J = 7.0 Hz, 3H; H6^{fu}). MS (MALDI-TOF) calcd for $\text{C}_{165}\text{H}_{161}\text{Cl}_4\text{N}_3\text{O}_{40}$: 2963; found: 2963. Removal of the protecting groups on compound **8** by steps including Zn–AcOH, Ac_2O –pyridine, NaOMe–MeOH, and H_2 –Pd/C gave the *N*-acetylated Globo H hexasaccharide **9**, confirmed by NMR. ^1H NMR (600 MHz, CD_3OD): δ = 7.04, 6.83 (d, J = 9.2 Hz, 2H each; ArH), 5.22, 4.93 (d, J = 4.0, 4.0 Hz, 1H each; two α -H1), 4.55, 4.52, 4.45 (d, J = 8.3, 7.5, 7.5 Hz, 1H each; three β -H1), 2.00 (s, COCH_3), 1.08 (d, J = 6.6 Hz, 3H; H6^{fu}). HR-MS $[M+\text{Na}]^+$ calcd for $\text{C}_{45}\text{H}_{71}\text{NO}_{31}\text{Na}$: 1144.3902, found 1144.3928.

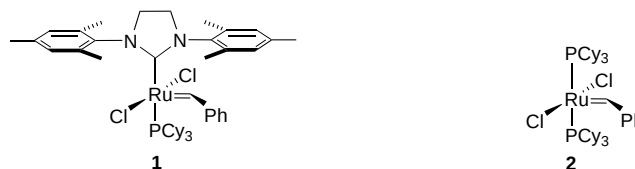
Synthesis of α,β -Unsaturated Amides by Olefin Cross-Metathesis**

Tae-Lim Choi, Arnab K. Chatterjee, and Robert H. Grubbs*

Dedicated to Professor Gilbert Stork on the occasion of his 80th birthday

Over the past few years, olefin metathesis has become a useful reaction in organic,^[1] polymer^[2] and bioorganic chemistry.^[3] Among olefin metathesis reactions, ring-closing metathesis (RCM) and ring-opening metathesis polymerization

(ROMP) have received the most attention. However, cross-metathesis (CM) is also of increasing utility in C=C bond formation under mild conditions.^[4, 5] The synthesis of trisubstituted^[6] and functionalized alkenes^[7] by cross-metathesis has become possible due to the development of the more active and more stable catalyst **1**, containing the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand.^[8] Catalyst **1** not only has



activity comparable to early transition metal catalysts, but also retains the functional group tolerance comparable to catalyst **2**.^[9] Herein, we report a versatile cross-coupling reaction of various α,β -unsaturated amides with terminal olefins and styrene, and that the CM efficiency is affected by the substituents on the amide nitrogen.

Several unsaturated amide substrates were screened for CM with terminal olefins (Table 1). Initially, dimethylacryl-

Table 1. Cross-metathesis reactions with terminal olefins^[a] and styrene.^[b]

Entry	Acrylamide	Terminal olefin ^[c]	Isolated yield of CM [%] ^[d] Terminal olefin Styrene (<i>E/Z</i>)
1a		I	3 : 39 (25:1) 4 : 25
1b ^[e]		I	3 : 83 (25:1)
2		I	5 : 77 6 : 57
3		II	7 : 80 8 : 62
4		II	9 : 89 (60:1) 10 : 66
5		III	11 : 89 12 : 69
6		II	13 : 90 14 : 69
7		II	15 : 97 (28:1) 16 : 83
8		II	17 : 100 (40:1) 18 : 87
9		I	19 : 87 (60:1) 20 : 40 ^[f]
10		II	21 : 100 22 : 63

[a] Reaction with 5 mol % catalyst **1** and 1.25 equiv terminal olefin (0.2 M in CH_2Cl_2) at 40 °C for 15 hours. [b] Reaction with 5 mol % catalyst **1** and 1.9 equiv styrene (0.2 M in CH_2Cl_2) at 40 °C for 15 hours. [c] See Scheme 1 for the chemical formulas. [d] Isolated ratio or no *cis* product observed by ^1H NMR spectroscopy. The compound numbers are used in the Supporting Information. [e] Reaction with 10 mol % catalyst **1** and 1.5 equiv terminal olefin. [f] Yield determined by ^1H NMR spectroscopy.

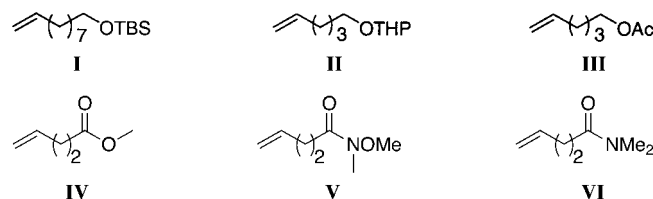
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

amide (entry 1a) was tried and a disappointingly low yield of 39% of CM product was obtained. However, upon using higher catalyst loading and a higher excess of terminal olefin, the yield was improved to 83% (entry 1b). Other substrates showed good to excellent yields ranging from 77 to 100% with excellent diastereoselectivity (>25:1 *trans:cis*). Particularly valuable is the compatibility with Weinreb amides^[10] (entry 4) and oxazolidinone imides (entry 9).^[11] These functional groups are widely used in organic synthesis (for example oxazolidinone imides in asymmetric reactions^[12] such as Michael additions,^[13] aldol,^[14] and Diels–Alder reactions^[15]) and CM provides synthons for further manipulations. In an unexpected related result, CM of acrylic acid gave a quantitative yield of the cross product (entry 10). Thus, this route provides an efficient method for the synthesis of a variety of acrylic acids that avoids harsh reaction conditions such as oxidation of alcohols to acids. In addition, it has been demonstrated that, in the presence of catalyst **1**, not only simple terminal olefins but also styrenes react with functionalized olefins in high yields.^[16] The yields with styrene are lower and show a similar trend (ranging from 25 to 87%) to CM with terminal olefins (Table 1).

Electron-donating substituents, such as alkyl groups, on the amide nitrogen resulted in lower yields, whereas electron-withdrawing substituents gave higher yields of cross products. These observations suggest that the amide carbonyl group is chelated to the metal center (**A** in Scheme 2), whereby the



Scheme 1. Formulas of the terminal olefins in Table 1 and Figure 1.

degree of chelation would depend on the electron density at the oxygen atom. As chelation decreases catalyst turnover the nitrogen substituents would affect the CM yields.^[17] Chelation effects in olefin metathesis catalysts are not unprecedented. Schrock et al. isolated a metallacyclobutane moiety possessing a 4-membered chelate with Mo- and W-based catalysts.^[18] Although Ru-based catalysts are much less oxophilic than those of the early metals, and the more electron-rich catalyst **1** should be even less prone to chelation than **2**,^[19] chelation to form 5- and 6-membered rings with both catalyst **1** and **2** has been previously observed or proposed.^[20] Moreover, amides having more electron-rich carbonyl groups have a higher propensity for chelation. In addition, dicyclohexylacrylamide (entry 2) gave a higher yield in CM than dimethylacrylamide (entry 1a), despite the similar electronic properties. Steric interactions between the cyclohexyl groups and the bulky imidazolyldiene ligand of **1** should decrease carbonyl chelation and increase catalyst turnover.

Kinetic studies were performed in order to obtain detailed information about the CM reactions with terminal olefins (see *Supporting Information*). As expected, the more electron-rich amides reacted more slowly than electron-poor amides. Most

notably, when dimethylacrylamide was the CM partner, only 33% of the terminal olefin had participated in CM or dimerization after 1 hour. In contrast, when diphenylacrylamide was used, 93% of the terminal olefin participated in metathesis reactions in the same period of time. This strongly supports our speculation that a chelation effect of electron-rich amides slows down the metathesis activity by lowering catalytic turnover.

A further kinetic study of the homodimerization of four terminal olefins (Figure 1) provided support for the proposed catalyst inhibition by chelation.^[21] Of the four olefins, the

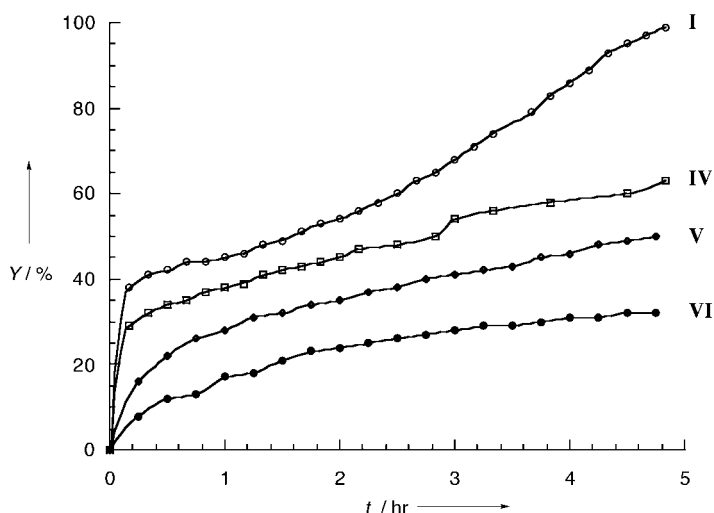
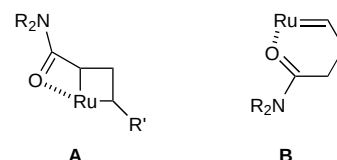


Figure 1. Kinetic studies of various terminal olefins (**I**, **IV**–**VI**) by ¹H NMR spectroscopy. See Scheme 1 for the chemical formulas.

nonfunctionalized terminal olefin **I** dimerized fastest, followed by the other substrates (**IV**, **V**, then **VI**). The fact that the rate of dimerization decreases as the electron density on the carbonyl group increases (**IV** < **V** < **VI**) supports the six-membered chelate intermediate (**B** in Scheme 2).^[22]



Scheme 2. Proposed structures of chelation in the CM reaction.

In conclusion, α,β -unsaturated amides are excellent cross-metathesis partners with terminal olefins and styrene. This method allows for an efficient one-step formation of functionalized α,β -unsaturated amides under mild conditions. More electron-rich amides give lower yields due to lower metathesis activity resulting from carbonyl chelation to the Ru center.

Experimental Section

Full procedures and the characterization data are given in the *Supporting Information*.

General procedure: To a flask charged with amide (1.0 equiv in CH_2Cl_2 ; 0.2 M) catalyst **1** (0.05 equiv in CH_2Cl_2) was added by cannulation followed by addition of either terminal olefin (1.25 equiv) or styrene (1.9 equiv) via

syringe. The flask was fitted with a condenser and refluxed under argon for 15 h. The reaction was monitored by thin-layer chromatography. After the solvent was evaporated, the product was purified directly on a silica gel column.

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The First Ce^{IV} Metallasilsesquioxane Complex: [Ce{(c-C₆H₁₁)₈Si₈O₁₃)}₂(py)₃]^{***}

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Metallasiloxanes containing Si-O-M functional groups (M = main group metal, transition metal, or f-block element) have been envisaged as molecular analogues of zeolites due to their astonishing geometrical relationship.^[1] In recent years, the chemistry of metallasilsesquioxanes has been extensively covered.^[2] Metallasilsesquioxanes of rare earth metals might be important as homogeneous analogues of silica-supported rare earth metal catalysts and rare earth silicates, which are potential materials for optoelectronics. Hence, this area of research is of considerable interest for several fields of chemistry, including catalysis and materials science. However, investigations on metallasilsesquioxanes of rare earth metals are often hampered by difficulties with crystallization and characterization of these compounds. Here we report the synthesis and structural investigation of the first Ce^{IV} metallasilsesquioxane, a possible homogeneous model of Ce^{IV} silicate oxidation catalysts, and a new synthetic route, which may provide access to other novel metallasilsesquioxane complexes.

Treatment of [Ce{N(SiMe₃)₂}]₃ with two equivalents of (c-C₆H₁₁)₈Si₈O₁₁(OH)₂^[3] in diethyl ether in the presence of an excess of pyridine exclusively afforded the diamagnetic complex [Ce{(c-C₆H₁₁)₈Si₈O₁₃)}₂(py)₃] (**1**). Compound **1** could also be prepared by direct reaction of anhydrous CeCl₃ with two equivalents of (c-C₆H₁₁)₈Si₈O₁₁(OH)₂ in THF/pyridine, albeit in somewhat lower yield (Scheme 1). Surprisingly, in both cases cerium was oxidized to the tetravalent oxidation state. The compound gave satisfactory C, H, N analyses and was fully characterized by IR and ¹H, ¹³C, and ²⁹Si NMR spectra, as well as X-ray single-crystal diffraction.

The IR spectrum (KBr) of **1** exhibited characteristic pyridine bands at 1599 and 750 cm⁻¹. ¹H NMR spectroscopy in [D₆]benzene gave a complex spectrum for a diamagnetic compound with broad multiplets between δ = 0.91 and 2.12 for the methine and methylene protons of the c-C₆H₁₁ substituents. The spectrum also showed three characteristic signals attributable to pyridine. In the ¹³C NMR spectrum the

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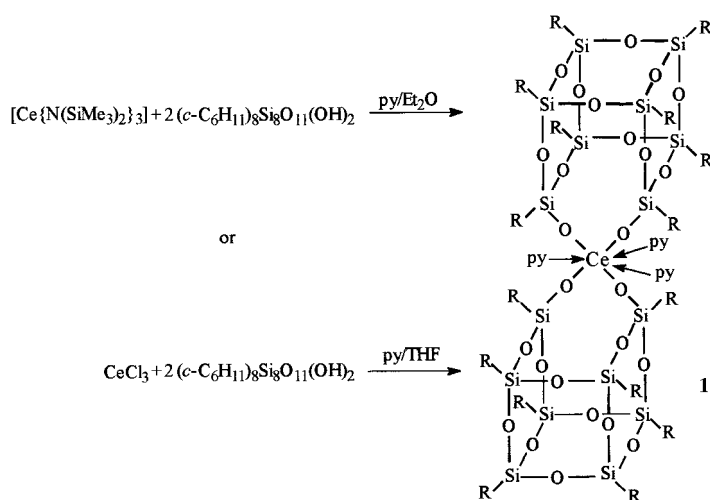
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Scheme 1. Two alternative syntheses of **1**. R = *c*-C₆H₁₁.

methine signals are slightly farther upfield ($\delta = 24.04$ – 25.96) than the methylene signals ($\delta = 27.46$ – 28.77). The ²⁹Si NMR spectrum showed three signals at $\delta = -60.68$, -63.81 , and -69.59 in a 2:4:2 ratio. The NMR signals of **1** were slightly shifted relative to the corresponding signals for the starting ligand, but they were in good accordance with the previously reported structure (from NMR data) of the free ligand.^[3a]

X-ray quality crystals of **1** were grown from a concentrated solution in pyridine/diethyl ether at room temperature.^[4] Compound **1** is the first metallasilsesquioxane derived from the recently discovered polyhedral $\{(c\text{-C}_6\text{H}_{11})_8\text{Si}_8\text{O}_{13}\}^{2-}$ ligand.^[3] The central Ce atom is coordinated by four oxygen atoms of two siloxane ligands and by three nitrogen atoms of three pyridine molecules to give a distorted pentagonal-bipyramidal arrangement (Figure 1). The O(5) and O(5A) atoms are in axial and O(1), O(1A), N(1), N(1A), and N(2) are in equatorial positions. Some of the angles between two

axial ($161.5(2)^\circ$) and axial and equatorial ligands ($89.56(12)$, $96.32(12)$, $99.26(9)$, $86.66(13)$, $77.98(13)^\circ$) differ significantly from the ideal angles of 180 and 90° , respectively, and the pentagonal bipyramid is very distorted. However, the angles between equatorial ligands ($71.43(9)$, $75.12(14)$, $68.1(2)$, $142.9(2)$, $141.66(14)$ and $145.93(11)^\circ$) are quite close to those for an ideal pentagon (72 or 144°).

No structurally characterized cerium(IV) siloxane derivatives are available for comparison. However, the Ce^{III} siloxane complex $[\text{Ce}(\text{OSiPh}_3)_3(\text{thf})_3] \cdot \text{thf}$ ^[5] and several Ce^{IV} alkoxide complexes have been previously reported.^[6] As expected, the Ce–O bond lengths ($2.167(3)$ and $2.177(3)$ Å) in **1** are substantially shorter than those to the OSiPh₃ ligands in the Ce^{III} complex ($2.208(4)$, 2.224 , and 2.234 Å)^[5] but longer than those to the *Or*Bu ligands ($2.026(5)$ and $2.023(5)$ Å) in the Ce^{IV} complex $[\text{Ce}(\text{OrBu})_2(\text{NO}_3)_2(\text{HOCrBu})_2]$. The Ce–O distances are also comparable to those in $[\text{Ce}(\text{OrBu})_2(\mu\text{-OrBu})_2(\mu_3\text{-OrBu})_2\text{Na}_2(\text{dme})_2]$ for the terminal *Or*Bu ligands ($2.136(4)$ – $2.146(4)$ Å).^[6] The Ce–N distances are equal ($2.655(4)$ Å) for two of the pyridine ligands (N(1) and N(1A)), but shorter ($2.610(6)$ Å) for the third (N(2)), presumably for steric reasons. The pyridine molecule that contains N(2) is sterically hindered by two adjacent *c*-C₆H₁₁ groups. The Si–O distances range from $1.589(3)$ to $1.634(3)$ Å (av 1.615 Å), which is comparable to 1.603 Å for an idealized tetrahedral Si–O distance in the framework of silicates.^[7]

The X-ray structure is not quite consistent with the NMR data considered above. According to the structure, Si(2) and Si(3) should not be chemically equivalent to Si(5) and Si(8), and consequently four (not three) ²⁹Si NMR signals and two (not one) different sets of resonances for pyridine ligands should be observed. Complex **1** is clearly not rigid in solution, and fast exchange between the fully and partially pyridine-solvated forms of the compound presumably occurs. The solvation–desolvation exchange process is too fast to be observed on the NMR timescale.

The most striking result is that despite starting from Ce^{III} precursors selective formation of a Ce^{IV} complex occurred in all cases. A similar phenomenon has been noticed before only in the formation of uranium(IV)–silsesquioxane complexes from different U^{IV} precursors.^[2d] We propose that the pathway includes initial formation of an anionic Ce^{III} complex $(\text{pyH})\text{-}[\text{Ce}((c\text{-C}_6\text{H}_{11})_8\text{Si}_8\text{O}_{13})_2(\text{py})_x]$. The steric and electronic properties of the silsesquioxane silanolate ligands render metal centers more Lewis acidic than conventional alkoxide or siloxide ligands do. Coordination of the OH groups to Ce facilitates the elimination of H⁺ and the formation of the pyH^+ cation. A related anionic aluminosilsesquioxane is the recently reported compound $(\text{HNEt}_3)[\{(c\text{-C}_6\text{H}_{11})_7\text{Si}_7\text{O}_9(\text{OSiMe}_3)_2\text{Al}\} \cdot \text{C}_6\text{H}_{14}]$.^[8] Finally we note that the Ce^{III} intermediate is most likely oxidized by the skeletal oxygen atom of the silsesquioxane ligand to give the final product **1**. Oxidation by oxygen or a hydroperoxide, which might be present in THF or diethyl ether, is less plausible, because the solvents were stored over K/Na–benzophenone under argon and were freshly distilled shortly before the experiments.

The novel reaction pathway described here may provide access to other novel types of metallasilsesquioxane complexes in oxidation reactions.

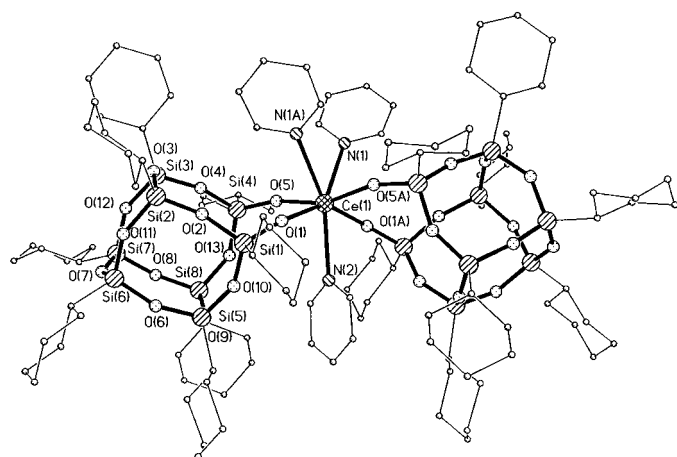


Figure 1. Structure of **1** in the crystal. Selected bond lengths [Å] and angles [$^\circ$]: Ce(1)–O(1) $2.167(3)$, Ce(1)–O(5) $2.177(3)$, Ce(1)–N(2) $2.610(6)$, Ce(1)–N(1) $2.655(4)$; O(1)–Ce(1)–O(1A) $142.9(2)$, O(1)–Ce(1)–O(5) $89.56(12)$, O(1A)–Ce(1)–O(5) $96.32(12)$, O(5)–Ce(1)–O(5A) $161.5(2)$, O(1)–Ce(1)–N(2) $71.43(9)$, O(5)–Ce(1)–N(2) $99.26(9)$, O(1)–Ce(1)–N(1A) $75.12(14)$, O(1)–Ce(1)–N(1) $141.66(14)$, O(5)–Ce(1)–N(1) $77.98(13)$, O(5)–Ce(1)–N(1A) $86.66(13)$, N(1A)–Ce(1)–N(1) $68.1(2)$, N(2)–Ce(1)–N(1) $145.93(11)$.

Experimental Section

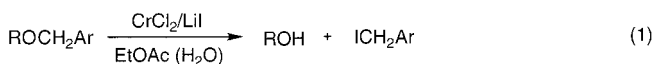
The ligand (*c*-C₆H₁₁)₈Si₈O₁₁(OH)₂ was prepared according to a procedure previously described by Feher et al.^[3] A solution of (*c*-C₆H₁₁)₈Si₈O₁₁(OH)₂ (2.52 g, 2.3 mmol) in diethyl ether (60 cm³) was added to [Ce{N(SiMe₃)₂}₃]^[9] (0.713 g, 1.15 mmol) at ca. 20 °C. The mixture was stirred for 3 h. Pyridine (2.1 g, 23 mmol) was added, and the mixture was stirred for 24 h. The mixture was then filtered, and the filtrate was concentrated to ca. 20 cm³ in vacuo. Pale yellow crystals of **1** were gradually deposited. Further concentration of the remaining mother liquor (ca. 10 cm³) in vacuo and cooling to –22 °C afforded an additional crop of crystals of **1** (total yield: 1.97 g, 67%). Analysis calcd for C₁₁₄H₁₉₁CeN₃O₂₆Si₁₆: C 53.4, H 7.45, N 1.6; found: C 52.9, H 7.36, N 1.4; ¹H NMR (400 MHz, [D₆]benzene, 22 °C): δ = 8.86 (m, 6H; py), 7.0 (m, 3H; py), 6.8 (m, 6H; py), 2.12–1.27 (brm, 160H; CH₂ in *c*-C₆H₁₁), 1.04 (m, 16H; CH in *c*-C₆H₁₁); ¹³C NMR (125 MHz, [D₆]benzene, 22 °C): δ = 150.45, 136.28, 123.76 (py), 28.77, 28.36, 28.12, 27.92, 27.62, 27.46 (CH₂), 25.96, 25.16, 24.04 (CH); ²⁹Si NMR (99 MHz, [D₆]benzene, 22 °C): δ = –60.68, –63.81, –69.59 (2:4:2); IR (KBr): $\tilde{\nu}$ = 2923, 2850, 1599, 1448, 1108, 1067, 949, 847, 823, 750, 700, 622, 518, 403 cm^{–1}. Alternatively, complex **1** was prepared by heating anhydrous CeCl₃ (0.152 g, 0.615 mmol) for 24 h in THF under reflux and subsequent treatment with (*c*-C₆H₁₁)₈Si₈O₁₁(OH)₂ (1.35 g, 1.23 mmol) in THF/pyridine (75 cm³, 4/1). Crystallization from a concentrated solution in pyridine gave crystals of **1** (yield: 0.87 g, 55%).

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Differential Cleavage of Arylmethyl Ethers: Reactivity of 2,6-Dimethoxybenzyl Ethers**

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Protecting groups (PGs) serve a fundamental, albeit often under-appreciated, role in synthesis.^[1] The interplay of their physico-chemical properties, availability, economics, and, most importantly, their selective manipulation significantly influences their ultimate utility. Consequently, milder or more selective methodology applicable to the existing repertoire of PGs and the development of new PGs with different reactivities have the potential to expedite progress along a broad front. Herein, we describe a convenient, high-yield protocol for the selective cleavage of arylmethyl ethers with stoichiometric chromium(II) chloride/lithium iodide in moisture-containing EtOAc [Eq. (1)].^[2] We also highlight the 2,6-dimethoxybenzyl moiety^[3] as a versatile and cost-effective^[4] PG that extends the range of options for the selective removal of arylmethyl ethers.



The scope of the de-*O*-benzylation by CrCl₂/LiI^[5] was evaluated with a panel of representative arylmethyl ethers (Table 1). Unsubstituted benzyl ethers were smoothly cleaved at 75 °C in moisture-containing^[6] EtOAc to give, after aqueous isolation, the corresponding alcohol and benzyl iodide (e.g., the conversion of **1** into **2** (Table 1, entry 1)) in good to excellent yields. There was little or no reaction when we used CrCl₂ or LiI alone,^[7] CrCl₂/LiBr, or CrCl₂/*n*-Bu₄NI.^[8] On the other hand, CrI₂ was just as effective as CrCl₂/LiI, but its expense precluded further exploration. Yields were much lower in *N,N*-dimethylformamide, 1,2-dimethoxyethane, and acetonitrile; the use of THF was limited by its reaction with the reagent.

p-Phenylbenzyl ether^[9] **3** likewise gave rise to **2** (Table 1, entry 2) in excellent yield under similar conditions as **1**. Notably, glycerol derivative **4** furnished secondary alcohol **5** (Table 1, entry 3) as the sole product. Such regioselectivity is reminiscent^[10] of other transition metal promoted de-*O*-

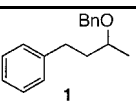
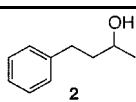
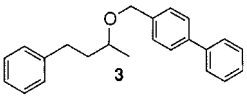
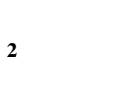
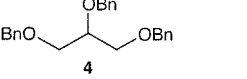
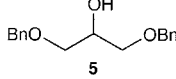
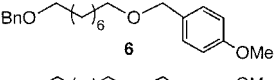
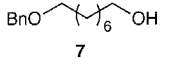
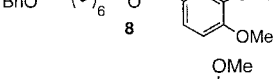
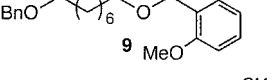
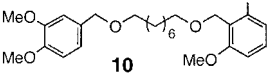
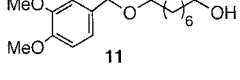
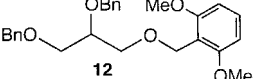
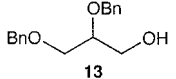
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Table 1. Cleavage of benzylic ethers.^[a]

Entry	Benzyl ether	Alcohol	Time [h]	Yield [%]
1			12	92
2			14	92
3			8	95
4			10	85
5			8	95
6			3	98
7			2	85
8			3	95

[a] Reaction conditions: CrCl₂ (3 equiv), LiI (4 equiv), 75 °C, EtOAc:H₂O (1:0.005 v:v).

benzylations of **4** and suggests that a comparable cyclic chelation mechanism is operative, i.e., chromium coordinates to two or more oxygen atoms, thus rendering the benzylic carbon atom susceptible to nucleophilic attack by iodide (see below). The preferential cleavage of the electron-rich methoxy-substituted arylmethyl moieties of **6** (Table 1, entry 4) and **8** (Table 1, entry 5) in the presence of an unsubstituted benzyl ether is consistent with this hypothesis and prompted us to investigate the reactivity of 2,6-dimethoxybenzyl ethers whose stereoelectronic properties should enhance Cr coordination and accelerate displacement (Figure 1).

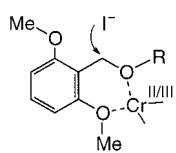
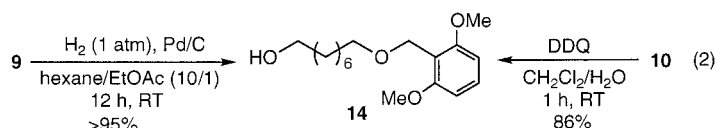


Figure 1. Coordinated intermediate.

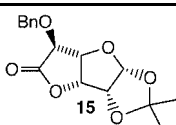
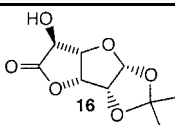
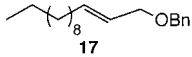
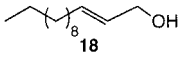
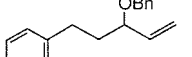
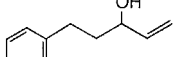
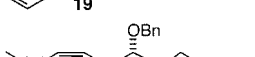
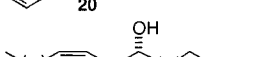
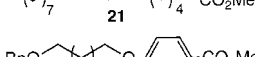
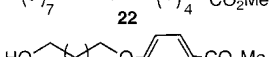
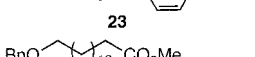
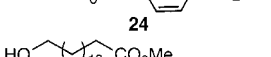
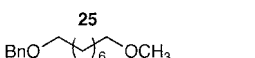
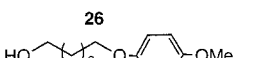
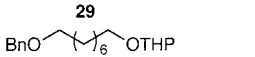
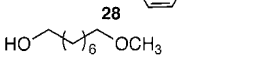
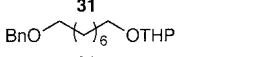
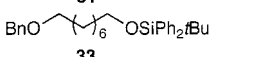
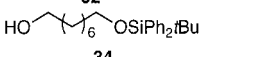
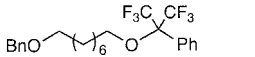
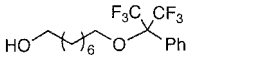
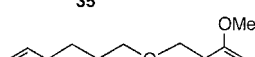
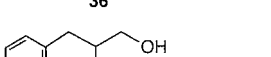
The expectation of greater reactivity was validated by the facile liberation of **7** from **9** (Table 1, entry 6) in just 3 hours. Indeed, the 2,6-dimethoxybenzyl ether in **10** (Table 1, entry 7) was cleaved more readily with CrCl₂/LiI than was its 3,4-dimethoxybenzyl analogue and, as illustrated by the example of **12** (Table 1, entry 8), could even overcome the regiochemical bias displayed by glycerol **4** (Table 1, entry 3). Alternatively, the benzyl group in **9** or the 3,4-dimethoxybenzyl group in **10** could be selectively cleaved to **14** using conventional methodology (Eq. (2); DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone). In contrast with the simple benzyl ethers discussed above, the 2,6-dimethoxybenzyl iodide by-product was converted under the reaction conditions into the corresponding chromium(III) intermediate,



which could be intercepted by electrophiles such as benzaldehyde, or gave 2,6-dimethoxytoluene upon quenching with water.^[11]

Since the utility of a PG is ultimately linked to its ease of manipulation in the presence of other functional groups, a brief survey of the compatibility of the debenzylolation conditions with some common functional groups was deemed important. Application of the standard deprotection conditions to D-glucuronolactone derivative **15** was instructive since alcohol **16** was obtained in good yield without compromising the anomeric center, acetonide, or lactone (Table 2, entry 1).^[12] Primary (Table 2, entry 2) and secondary (Table 2, entry 3) allylic ethers **17** and **19**, respectively, showed no indications of isomerization or dehydration, nor did *cis* olefin **21** (Table 2, entry 4). In contrast, application of the popular^[1] debenzylolation reagents Me₃SiI, Na/NH₃, or H₂/Pd to **17** and **19** under typical conditions proved unsatisfactory and resulted

Table 2. Functional group specificity.^[a]

Entry	Substrate	Alcohol	Time [h]	Yield [%]
1			16	82
2			12	89
3			11	89
4			12	89
5			16	87
6			14	92
7			12	88
8			16 ^[b]	82
9			24 ^[b]	80
10			18 ^[b]	89
11			16	86
12			11 ^[b,c]	89

[a] Reaction conditions: CrCl₂ (3 equiv), LiI (4 equiv), 75 °C, EtOAc:H₂O (1:0.005 v:v). [b] 65 °C. [c] CrCl₂ (6 equiv), LiI (10 equiv).

in iodine-containing by-products, hydrogenolysis of the allylic alcohol, and/or olefin saturation.

Methyl benzoate **23**, aliphatic ester **25**, and phenolic ether **27** readily afforded alcohols **24–28** (Table 2, entries 5–7), respectively. However, it was necessary to reduce the temperature and increase the reaction times for methyl ether **29**, tetrahydropyran (THP) **31**, and silyl ether **33** (Table 2, entries 8–10) to avoid any concomitant loss of these functional groups. 1,1,1,3,3,3-Hexafluoro-2-phenylisopropyl (HIP) ethers,^[13] although classified as benzyl ethers, were stable to CrCl_2/LiI treatment, for example, **35** was converted into **36** (Table 2, entry 11). On the other hand, amines such as **37** tended to retard de-*O*-benzylation, but this could be surmounted with the use of excess reagent (Table 2, entry 12).

Experimental Section

De-*O*-benzylation procedure: An arylmethyl ether (1 equiv) was added to a purple suspension of CrCl_2 (3 equiv) and LiI (4 equiv; Aldrich Chem. Co, 99.99%) in a solution of $\text{EtOAc}/\text{H}_2\text{O}$ (1:0.005 v/v, 10 mL/100 mg arylmethyl ether). The reaction was heated at the indicated temperature (Tables 1 and 2) for 2–24 h, then cooled to room temperature, quenched with water, and extracted three times with Et_2O . The combined organic extracts were washed with saturated sodium sulfite solution and water, then dried and evaporated in vacuo. Chromatographic purification of the residue afforded the corresponding free alcohol.

Preparation of 2,6-dimethoxybenzyl bromide:^[3] 2,6-Dimethoxytoluene (1 equiv) was heated at reflux with *N*-bromosuccinimide (NBS; 1.1 equiv) and benzoyl peroxide (2 mol %) in carbon tetrachloride (10 mL/1.5 g 2,6-dimethoxytoluene) for 30 min. After cooling the reaction mixture to room temperature, the precipitated succinimide was removed by filtration and the solvent was evaporated in vacuo to give crude 2,6-dimethoxybenzyl bromide (95%), which was sufficiently pure to be used without further purification.

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- [5] Anhydrous LiI (99.99%) from Aldrich gave a consistently good result, whereas samples purchased from Acros were inconsistent.
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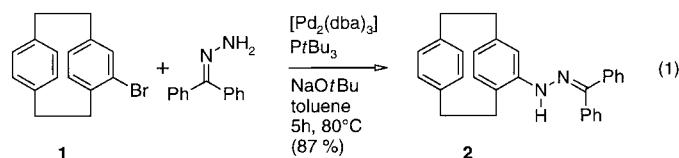
Indoloparacyclophanes: Synthesis and Dopamine Receptor Binding of a Novel Arylbioisostere**

Birgit Ortner, Reiner Waibel, and Peter Gmeiner*

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

Investigating the reaction of arylhydrazines with ketones in his laboratory in Erlangen, Emil Fischer discovered the formation of indoles.^[1,2] Very recent work published by Buchwald et al. and also by Hartwig further extended the scope of the Fischer indole synthesis.^[3,4] The major improvement of this variant is the Pd-catalyzed preparation of *N*-arylbenzophenone hydrazones used as key intermediates. As part of our exploration of novel types of pharmacophoric elements, we recently found that enyne moieties and azaderivatives thereof can serve as nonaromatic arylbioisosteres.^[5] Furthermore, the pyrazolo[1,5]pyridine nucleus turned out as an effective indole bioisostere.^[6] As an extension of these studies, we were intrigued by the question whether a double-layered [2.2](4,7)indoloparacyclophane system with its close proximity of the face-to-face aromatic rings coupled to the rigid and highly strained skeleton could be exploited as a pharmacophoric element being able to coordinate to highly specific receptor binding sites.^[7]

For the preparation of the hitherto unknown [2.2]indoloparacyclophane ring system,^[8,9] we planned to take advantage of Buchwald's variant of the Fischer indole synthesis.^[3] Thus, we tried to prepare the *N*-([2.2]paracyclophanyl)benzophenone hydrazone **2** by Pd-catalyzed cross-coupling reaction of benzophenone hydrazone with 2-bromo[2.2]paracyclophane **1**, readily available by bromination of [2.2]paracyclophane [Eq. (1)].^[10] Our initial attempts using 1.0 mol % $\text{Pd}(\text{OAc})_2$



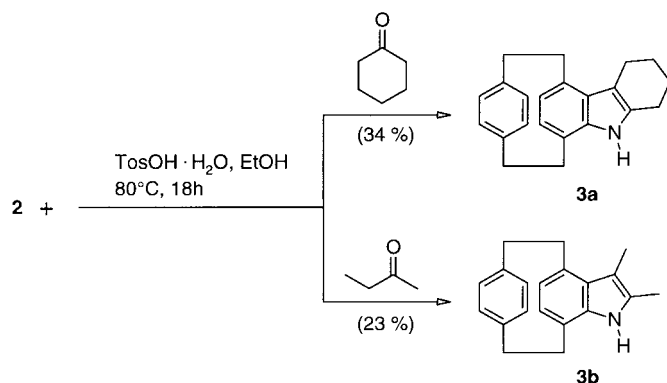
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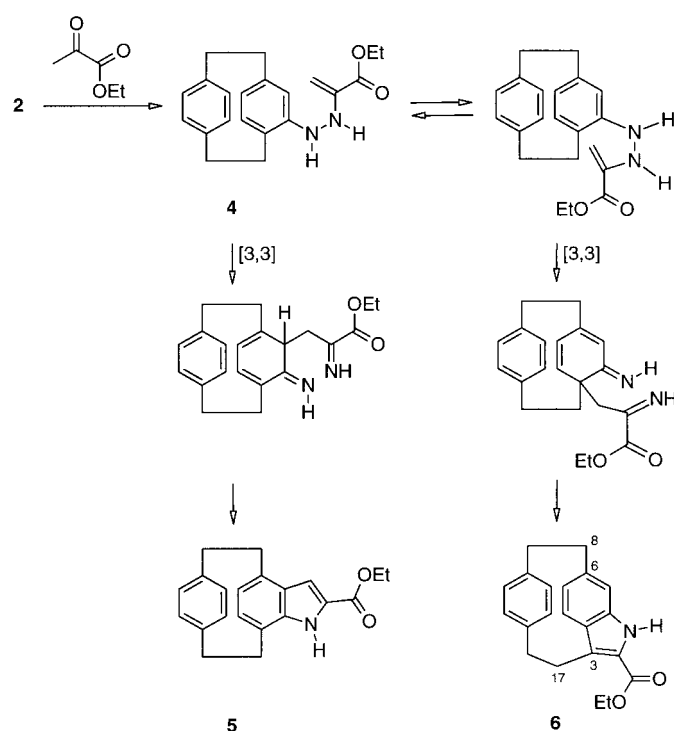
and 4.0 mol % PPh_3 failed to promote cross-coupling. Further investigations examining the utility of catalysts based on the reagents $\text{Pd}(\text{OAc})_2$ (or $[\text{Pd}_2(\text{dba})_3]$, dba = dibenzylideneacetone) and $\text{P}(o\text{-Tol})_3$ (or DPPF 1,1'-bis(diphenylphosphanyl)-ferrocene) furnished small amounts of the desired coupling product **2**.^[11] Further improvement was observed with the Pd/BINAP catalyst system resulting in formation of the cyclophanyl hydrazone **2** in 20 % yield. Superior activity resulted with a catalyst composed of $[\text{Pd}_2(\text{dba})_3]$ and the sterically demanding PrBu_3 ^[12] ligand facilitating a clean conversion of the starting material to the coupling product **2** in 87 % yield.

We next turned our attention to the following reaction steps involving cleavage of the hydrazone, condensation of the resulting paracyclophanylhydrazine with an enolizable ketone and, finally, Fischer cyclization. Employing Buchwald's one-pot protocol, the benzophenone hydrazone **2** was treated with cyclohexanone and TosOH in refluxing EtOH, which led to the formation of the fused [2.2](4,7)indoloparacyclophane **3a** in 34 % yield (Scheme 1). Analogously, the 2,3-dimethyl derivative **3b** could be synthesized starting from the central precursor **2** and butanone.



Scheme 1. Synthesis of the double-layered indoles **3a** and **3b**. Tos = *para*-Toluenesulfonyl.

Subjecting ethyl pyruvate and the hydrazone **2** to identical conditions gave a 1:1 reaction mixture separable by preparative HPLC (10- μ silica gel, hexane/EtOAc 9/1). Depending on the direction of cyclization, both the typical Fischer cyclization product **5** and the rearranged (3,6)indoloparacyclophane **6** were formed, as depicted in Scheme 2. Atypical Fischer indolizations of *ortho*-substituted phenylhydrazones including *ipso*-cyclization paired with [1,2], [1,3], [1,4], and [1,5] alkyl shifts are reported in the literature.^[13] Only one rearrangement is described from the benzene ring to the C3 position of the pyrrole moiety.^[14] Obviously, the reaction sequence leading to the atypical cyclization product **6** involves an *ipso*-directed [3,3] sigmatropic rearrangement of the intermediate ene-hydrazine followed by imine/enamine tautomerization, alkyl shift and cyclization under loss of ammonia. Since we did not observe atypical indolizations for the synthesis of the indoloparacyclophanes **3a** and **3b**, we reason that the carboxylic ester functionality, favoring the formation of an enamine intermediate, facilitates the alternative reaction pathway.



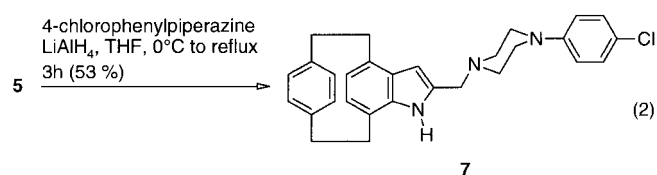
Scheme 2. Typical and atypical indolizations. One-pot synthesis: $\text{TosOH} \cdot \text{H}_2\text{O}$ (2 equiv), ethyl pyruvate, EtOH (1 equiv), reflux, 18 h (**5**: 23 %; **6**: 23 %). Synthesis step by step: 1. $\text{TosOH} \cdot \text{H}_2\text{O}$ (5 equiv), $\text{HOCH}_2\text{CH}_2\text{OH}$, HCl/EtOH , reflux, 18 h; 2. ethyl pyruvate (1 equiv), EtOH, 70 °C, 5 h (61 %); 3. TosOH (1.5 equiv), C_6H_6 , reflux, 45 min (42 % **5**).

Careful NMR studies including HMQC, HMBC, and NOE experiments unambiguously proved the structures of the double-layered indoles **5** and **6**. Multiple bond correlations between the methylene protons and the neighbored aromatic carbon atoms demonstrated the substitution pattern of the aromatic ring systems. In detail, the connectivities of the rearranged (3,6)indolocyclophane **6** were unambiguously proved by heteronuclear correlations between $\text{H}17_{\text{anti}}$ and C2, C3, and C3a and between $\text{H}8_{\text{anti}}$ and C5, C6, and C7, respectively. Based on the aromatic protons H4, H5, and H7, three-bond correlations to the respective aromatic carbon atoms C6/C7a, C3a/C7, and C3a/C5 were diagnostic for localizing the quaternary carbon atoms. In combination with difference NOE measurements the heteronuclear correlation experiments enabled us to assign all ^1H and ^{13}C NMR resonances of the structural isomers **5** and **6** completely. Quantum mechanical calculations of the indolocyclophanes **5** and **6** choosing the AM1 parameter set^[15] in MOPAC gave minimal-energy structures clearly demonstrating boat shapes for the benzene moieties and a significantly crooked indole nucleus for the (3,6)-isomer **6**. It is interesting to note that the final heats of formation obtained by the SCF calculations were similar ($\Delta\Delta H = 1.2 \text{ kcal mol}^{-1}$) when the rearranged isomer **6** was predicted more stable.

To circumvent the difficult purification process involved in the preparation of pure **5**, which should be used as an intermediate for the synthesis of bioactive compounds, we tried to avoid the formation of the side product **6**. It turned out to be useful to perform the synthesis step by step (see

legend to Scheme 2). Deprotection of the benzophenone hydrazone **2** under acidic conditions was facilitated by ethylene glycol which effectively traps benzophenone. After extraction, the liberated hydrazine was reacted with ethyl pyruvate to furnish the condensation product **4**. Finally, cyclization of pure **4** under relatively mild conditions resulted in formation of the typical indolization product **5** without rearrangement.

In order to investigate whether the double-layered [2,2](4,7)indoloparacyclophane moiety can serve as an indole bioisostere, we envisioned to synthesize the test compound **7** which is structurally related to piperazinylmethylindoles that were recently described as strong and selective dopamine D4 receptor ligands.^[16] Employing a one-step process, pre-treatment of (4-chlorophenyl)piperazine with LiAlH₄ and subsequent addition of the carboxylic ester **5** resulted in formation of the reductive amination product **7** [Eq. (2)].



The test compound **7** and the dopamine receptor antagonist clozapine, known as a valuable antipsychotic drug, were evaluated in vitro for their abilities to displace [³H]spiperone from the cloned human dopamine receptors D2_{long}, D2_{short},^[17] D3,^[18] and D4.4^[19] being stably expressed in CHO cells (Table 1).^[5a] The D1 affinities were determined by employing bovine striatal membrane preparations and the D1 selective antagonist [³H]SCH 23390. The data prove that the double-

Table 1. Dopamine receptor binding (K_i values (nM)) of the test compound **7** compared to the antipsychotic drug clozapine.^[a]

compound	D1	D2 _{long}	D2 _{short}	D3	D4.4
7	1500	2500	1100	410	35
clozapine	420	41	28	960	16

[a] Data are based on the means of 2–4 experiments performed in triplicate at eight concentrations.

layered indolocyclophane **7** displays strong and selective affinity for the dopamine D4 receptor subtype which is of special interest for the treatment of neuropsychiatric disorders. These results clearly demonstrate that sterically demanding cyclophane derivatives are, in fact, capable of approaching and recognizing highly specific transmembrane receptor binding sites. Further investigations including enantiopure indolocyclophanes are currently in progress.

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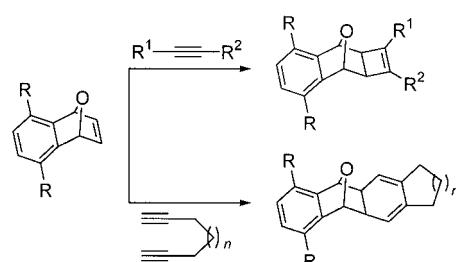
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Nickel-Catalyzed Highly Regio- and Stereoselective Cyclization of Oxanorbornenes with Alkyl Propiolates: A Novel Method for the Synthesis of Benzocoumarin Derivatives**

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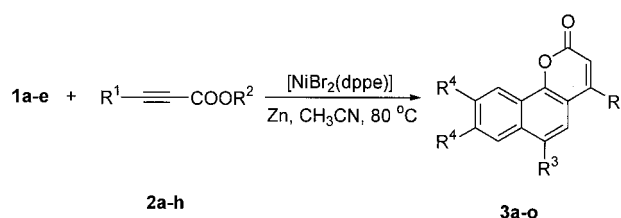
Transition metal catalyzed cyclizations of alkenes and alkynes are powerful methods for the synthesis of various carbocyclic and heterocyclic compounds.^[1] Recently, we^[2, 3] and others^[4, 5] observed that nickel complexes effectively catalyze the cycloaddition of 7-oxa- and 7-azabenzonorbornadienes with alkynes to give [2+2]^[2] and [2+2+2]^[3a,b] cycloadducts (Scheme 1). The reactions of alkenes with



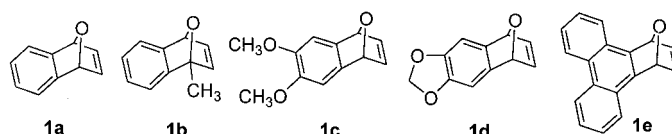
Scheme 1. Ni-catalyzed [2+2] and [2+2+2] cycloaddition of 7-oxabenzonorbornadienes with alkynes.

alkynes depend greatly on the reaction conditions. Here we report a new cyclization of 7-oxabenzonorbornadienes and alkyl propiolates with catalysis by nickel complexes to give benzocoumarin derivatives with remarkably high regio- and stereoselectivity (Scheme 2). The coumarins are an important class of naturally occurring compounds, many of which exhibit useful biological activity.^[6] Benzo-annulated coumarin derivatives are also known as electron-transporting emitters.^[7] However, the traditional methods for synthesizing benzocoumarin derivatives are limited by poor yields and harsh reaction conditions.^[8] The present nickel-catalyzed reaction provides a very convenient method for the one-pot synthesis of benzocoumarins under mild conditions. In addition, the catalytic mechanism for product formation is of interest.

Treatment of 7-oxabenzonorbornadiene (**1a**) with methyl butyn-2-olate (**2a**) in the presence of [NiBr₂(dppe)] (dppe = bis(diphenylphosphanyl)ethane) and zinc metal powder in acetonitrile at 80 °C gave the cyclization product **3a** in 87 % yield. The structure of **3a** was confirmed by ¹H and ¹³C NMR spectroscopy, mass spectrometry, and X-ray structure analysis.^[13] To the best of our knowledge, this cyclization is



- 2a:** R¹ = CH₃, R² = CH₃
2b: R¹ = Ph, R² = CH₂CH₃
2c: R¹ = *n*Bu, R² = CH₃
2d: R¹ = (CH₂)₄CH₃, R² = CH₃
2e: R¹ = SiMe₃, R² = CH₂CH₃
2f: R¹ = CH₂OCH₃, R² = CH₃
2g: R¹ = CH=CHCOOCH₃, R² = CH₃
2h: R¹ = H, R² = CH₃



Scheme 2. Cyclization of 7-oxabenzonorbornadienes **1** with alkyl propiolates **2**. Spectroscopic data of the new compounds can be found in the supporting information.

unprecedented. Control experiments showed that in the absence of either [NiBr₂(dppe)] or zinc metal, the desired product was not obtained.

The phosphine ligand employed is crucial to the success of the present catalytic reaction. A bidentate phosphine is required for the reaction to proceed. Among several bidentate phosphine ligands examined, dppe gave the best results and afforded **3a** in 95 % yield. Other bidentate phosphines such as 1,1'-bis(diphenylphosphanyl)ferrocene (dppf), methylenebis(diphenylphosphane) (dppm), and 1,3-propanediylbis(diphenylphosphane) (dppp) are less effective, giving **3a** in 53, 47, and 26 % yield, respectively. Nickel complexes of monodentate phosphines that are efficient catalysts for the [2+2]^[2] and [2+2+2]^[3a,b] cycloaddition of **1a** with various alkynes are essentially inactive in the formation of **3a**.

The choice of solvent is also vital to the catalytic reaction. The best solvent is acetonitrile, in which **3a** was obtained in 95 % yield. Dimethylformamide is also effective (44 % yield). In THF and toluene, only the [2+2+2] cycloadduct was observed,^[3] while no cycloaddition product was detected in dichloromethane.

Under similar conditions, **1a** underwent cyclization with a variety of substituted alkyl propiolates **2** to give the corresponding benzocoumarin derivatives. Thus, the reaction of **1a** with **2b–e** gave the corresponding benzocoumarin derivatives **3b–e** in good yields (see Scheme 2 and Table 1). Alkyne **2f** gave, in addition to **3f** (70 %), the naphthalene derivative **4f** (21 %; entry 6). The reaction of propiolate **2g** with **1a** did not give any desired cyclization product under standard conditions, but proceeded smoothly in the presence of one equivalent of acetic acid to give **3g**. The α,β -unsaturated carbon–carbon double bond of **2g** is hydrogenated in **3g**. Unsubstituted propiolate **2h** reacts with **1a** to give **4h** in 57 % yield instead of the cyclization product. The present Ni

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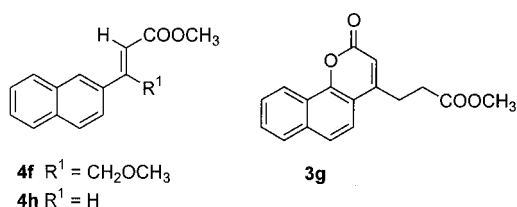
[**] We thank the National Science Council (NSC 89-2119-M-007-010) and the Ministry of Education (89-FAO4-AA) of the Republic of China for support of this research.

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Table 1. Results of nickel-catalyzed cyclization of 7-oxanorbornadienes **1** with propiolates **2**.^[a]

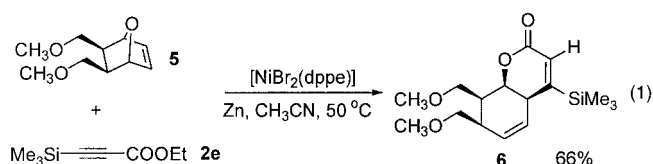
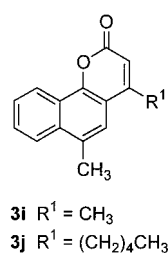
Entry	Alkene	Alkyne	Product (yield [%]) ^[b]
1	1a	2a	3a (87)
2	1a	2b	3b (75)
3	1a	2c	3c (89)
4	1a	2d	3d (83)
5	1a	2e	3e (60) ^[d]
6	1a	2f	3f (70) + 4f (21)
7 ^[c]	1a	2g	3g (68)
8	1a	2h	4h (57)
9	1b	2a	3i (62)
10	1b	2d	3j (71) ^[d]
11	1c	2a	3k (80)
12	1c	2c	3l (72)
13	1d	2a	3m (65) ^[d]
14	1d	2d	3n (56)
15	1e	2a	3o (73)

[a] Unless stated otherwise, all reactions were carried out with [NiBr₂(dppe)] (0.05 mmol), Zn (2.75 mmol), **1** (1.0 mmol), **2** (1.2–2.0 mmol), and CH₃CN (3.0 mL) at 80 °C for 12 h under 1 atm N₂. [b] Yield of isolated product. [c] 1.0 mmol of acetic acid was added. [d] Yield determined by ¹H NMR spectroscopy with mesitylene as internal standard.



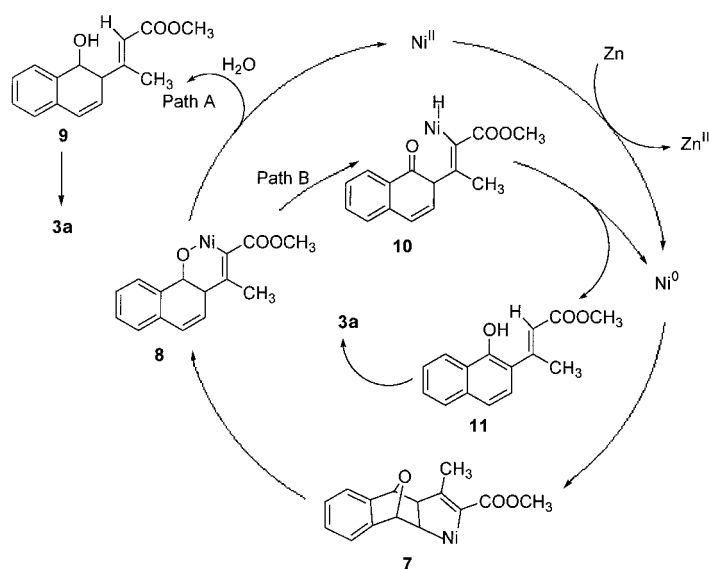
catalyst system is inactive for the cyclization of EtO₂CC≡C-CO₂Et with **1a**. The results of these studies are summarized in Table 1. All benzocoumarin products show a characteristic peak at around δ = 6.4 in the ¹H NMR spectrum for the olefinic α-proton of the lactone ring. The presence of an α,β-unsaturated carbonyl group in these benzocoumarins is evidenced by a signal at δ ≈ 160 in the ¹³C NMR spectrum and a strong absorption at about 1710 cm⁻¹ in the IR spectrum. Naphthalene derivatives **4f** and **4h** were also fully characterized by spectroscopic methods. The alkenyl substituents on both products have *trans* stereochemistry according to the results of NOE experiments with **4f** and the coupling constant (16 Hz) of the two olefinic protons of **4h**.

The present cyclization was successfully extended to substituted 7-oxabenzonorbornadienes **1b–e** and **5** [see Eq. (1)]. The reaction of **1b**, which bears a methyl group at a bridgehead atom, with alkynes **2a** and **2d** gave regioselectively benzocoumarins **3i** and **3j** in 62 and 71 % yield, respectively. Similarly, treatment of substituted 7-oxabenzonorbornadienes **1c** and **1d** with propiolates gave the corresponding benzocoumarins in moderate to good yields (Table 1, entries 11–14), and the reaction of **1e** with **2a** afforded **3o** in 73 % yield. The cyclization of substituted 7-oxanorbornene **5** with **2e** in CH₃CN at 50 °C also proceeded smoothly in completely regio- and stereoselective^[9] fashion to give tetrahydrocoumarin **6** [Eq. (1)]. This product was fully characterized by



spectroscopic methods. In the ¹H NMR spectrum, the four characteristic methine signals appear at δ = 4.82, 3.21, 2.53, and 2.13. The ¹³C NMR data, the results of DEPT experiments, and MS data are also consistent with the proposed structure. It is noteworthy that tetrahydrocoumarins are intermediates for the synthesis of natural products.^[10]

The mechanism for benzocoumarin formation is intriguing in view of the extensive bond-formation and bond-breaking processes required. While the detailed pathway is not clear, key steps are proposed in Scheme 3 for the synthesis of **3a** on



Scheme 3. A plausible catalytic cycle for benzocoumarin formation.

the basis of the above results and the established nickel chemistry. The reduction of [NiBr₂(dppe)] by zinc likely initiates the catalytic reaction. Coordination of both **1a** and **2a** to Ni^{II} followed by cyclometalation forms a nickelacyclopentene^[11, 12] intermediate **7**. Subsequent β-oxy elimination to form **8** and protonation give the intermediate organic product **9** and an Ni^{II} species (path A). The latter is reduced by Zn to regenerate the Ni⁰ catalyst, while **9** undergoes *cis–trans* isomerization, dehydrogenation, and lactonization to give the final benzocoumarin product. Compound **9** may be considered as a reductive coupling product of **1a** and **2a**. Evidence supporting this intermediate comes from the observation of products **4f**, **4h**, and tetrahydrocoumarin **6** [Eq. (1)]. Presumably, **4f** and **4h** are obtained from dehydration of the corresponding reductive coupling products similar in structure to **9**, while **6** results from *cis–trans* isomerization followed by cyclization of the reductive coupling product of **5** and **2e**. Another pathway (B) involving β-hydride elimination of **8** to give ketone **10** cannot be ruled out. The intermediate then undergoes reductive elimination and tau-

toomerization to afford naphthol **11**. Further *E/Z* isomerization and subsequent lactonization provide product **3a**.

In conclusion, we have demonstrated a novel nickel-catalyzed cyclization of tricyclic alkenes **1** with propiolates **2** to give benzocoumarins or tetrahydrocoumarins in a one-pot reaction. More detailed studies on the scope, mechanism, and utility of this reaction are in progress.

Experimental Section

General procedure for the cyclization of 7-oxabenzonorbornadienes **1** with alkyl propiolates **2**: Freshly distilled CH₃CN (3.0 mL) and **2** (1.2–2.0 mmol) were added to **1** (1.00 mmol), [NiBr₂(dppe)] (0.05 mmol), and zinc powder (0.180 g, 2.75 mmol) under nitrogen. The reaction mixture was heated with stirring at 80 °C for 12 h and then cooled and stirred in air for 15 min. The mixture was filtered through Celite and silica gel and washed with dichloromethane. The filtrate was concentrated, and the residue was purified on a silica gel column with hexane/ethyl acetate as eluent to afford the desired cyclization product **3**.

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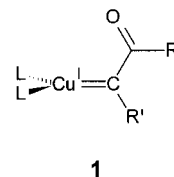
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Copper(I) Carbenes: The Synthesis of Active Intermediates in Copper-Catalyzed Cyclopropanation**

Bernd F. Straub and Peter Hofmann*

The cyclopropanation of olefins with α -carbonyldiazoalkanes mediated by homogeneous copper catalysts has been known for more than 30 years, and was the first reported example of enantioselective transition metal catalysis.^[1] Despite this long history, copper(I) α -carbonyl carbene complexes of type **1**, which are generally assumed to be the active intermediates, have remained undetected so far.^[2] It is crucial to know their structure in solution to understand the enantiomeric and diastereomeric selectivities that can be achieved if chiral spectator ligands are utilized in cyclopropanation catalysis.^[3]



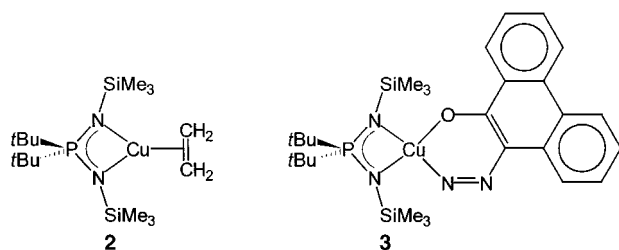
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L = nitrogen or oxygen donor ligand
R = alkyl, aryl, alkoxy, amide
R' = aryl, acyl

Copper carbene complexes in the literature are limited to the linear d¹⁰-ML₂ type, with Wanzlick–Arduengo carbene ligands substituted with strong donor groups.^[4] These complexes are inactive in cyclopropanation chemistry. Generally, nickel-triad and coinage-metal carbene complexes of the d¹⁰-ML₃ type are scarce,^[5] probably as a result of the antibonding interaction between the metal d¹⁰ subshell and the sp² lone pair of a singlet carbene fragment.^[6]

We have recently introduced an extremely basic, sterically demanding, and highly symmetric iminophosphoramidate ligand into organometallic copper chemistry.^[7] It stabilizes otherwise elusive or labile copper coordination modes by enhanced metal-to-ligand back donation and by steric shielding of the copper fragment.^[7] We used the stable and neutral copper(I) ethylene complex **2**^[7a] to isolate the α -carbonyldiazoalkane complex **3**, which is a stabilized model for

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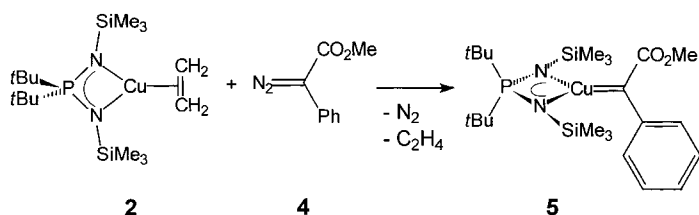
[**] B.F.S. thanks the Fonds der Chemischen Industrie for a doctoral fellowship.



intermediates in the catalytic cyclopropanation cycle.^[7b] However, **3** does not cyclopropanate olefins.

From density functional theory studies of less-congested model systems, a low-energy pathway for N₂ extrusion has been calculated, which leads to copper(I) carbenes.^[7b, 8] The neutral precursor compound **2**, which allows convenient associative ligand substitution at the metal fragment, seemed ideal to provide access to copper(I) carbenes by reaction with α -carbonyldiazo compounds in solution.

Ethylene complex **2** reacts with methyl 2-phenyl-2-diazoacetate (**4**) in [D₈]toluene, C₆D₆, or pentane at ambient temperature to yield an intensely violet solution, after evolution of N₂ (Scheme 1). A single new copper complex is formed in a steady-state concentration of 15 to 25 % of the ethylene complex concentration. This species was unambiguously identified as copper(I) carbene **5** by ¹H, ¹³C{¹H}, ²⁹Si{¹H}, and ³¹P{¹H} NMR spectroscopy.



Scheme 1. Formation of copper(I) carbene **5**.

All of diazoalkane **4** had been consumed within an hour at ambient temperature, to give 2,3-diphenyl maleate and fumarate derivatives as the main decomposition products. Complex **5** started to disappear as soon as **4** was completely consumed. Within a few minutes, all of **5** had decomposed, and the violet color had faded. Upon cooling a reaction mixture of **2**, **4**, and **5** to -33°C , the steady-state concentration of carbene complex **5** was maintained for several hours without significant evolution of nitrogen.

The main evidence for the structure of carbene complex **5** was derived from the ¹³C{¹H} NMR signal of the carbene carbon atom at $\delta = 229.9$ (Figure 1). The downfield ¹³C NMR signal for the carbonyl carbon atom of complex **5** at $\delta = 177.9$ also indicates the presence of an electrophilic carbene center. Both ¹³C NMR signals disappear as the thermal decomposition of **5** goes to completion, or as **5** is consumed by the addition of styrene (see below). Low-temperature fast-atom bombardment (LT-FAB) mass spectra of solutions containing **5** confirm the presence of the molecular ion (m/z 531.2).

The *tert*-butyl groups of the iminophosphanamide ligand of **5** remain diastereotopic on the NMR time scale even at 28°C

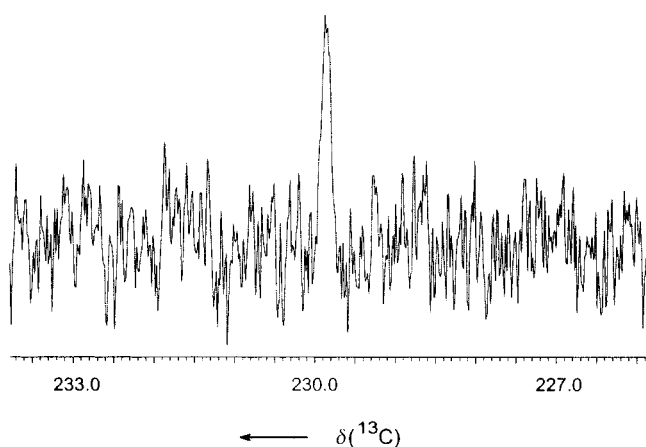


Figure 1. ¹³C{¹H} NMR spectrum of **5** in [D₈]toluene (-33°C , 75.47 MHz), showing the signal for the carbene carbon atom.

(Figure 2), which proves that the the PN₂Cu chelate ring and the carbene plane are mutually orthogonal. The rotational barrier of the carbene fragment around the Cu–C double bond must amount to at least 60 kJ mol⁻¹.

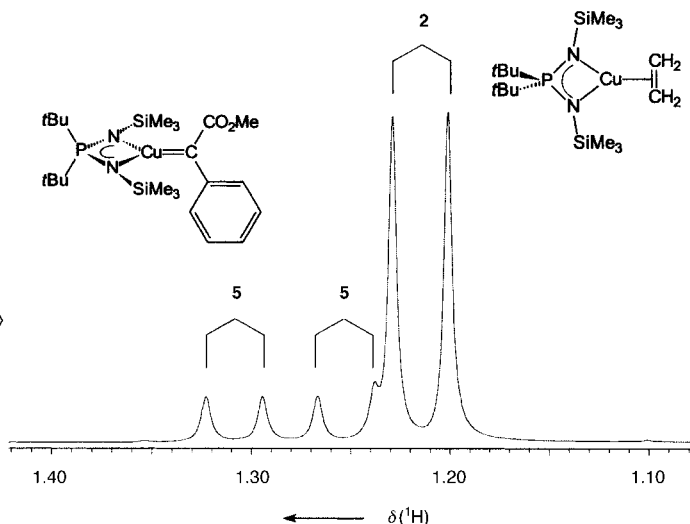


Figure 2. ¹H NMR spectrum (C₆D₆, 500.13 MHz, 28°C) of the *tert*-butyl region of carbene complex **5** ($J_{\text{PH}} = 14$ Hz) and of ethylene complex **2** ($J_{\text{PH}} = 14$ Hz).

Variable temperature (VT) ¹H NMR spectroscopy shows a coalescence of the signals for the diastereotopic *ortho*-phenyl protons of carbene complex **5** at $-70 \pm 4^{\circ}\text{C}$ and 300.13 MHz (Figure 3). The upfield signal for the *ortho* protons overlaps with those of diazoalkane **4** and of the fumarate and maleate derivatives present in solution, and thus cannot be observed. However, an activation barrier of $\Delta G^{\ddagger} = (36.8 \pm 3.0) \text{ kJ mol}^{-1}$ for the rotation of the phenyl group can be derived from the coalescence temperature and the observed chemical shift data for the *ortho* protons.

In the transition state **5**[‡], the carbene center cannot withdraw electron density from the π system of the phenyl ring. The observed rotational barrier of the phenyl substituent is in accordance with the electrophilic character of the carbene carbon atom in **5** and a qualitative description of

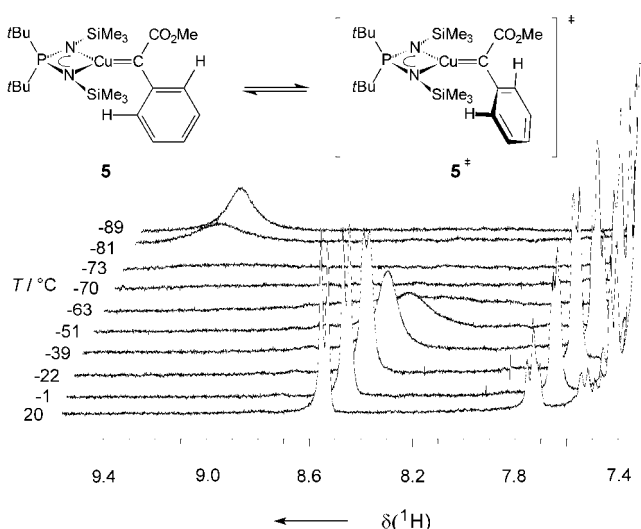


Figure 3. VT ^1H NMR spectra showing coalescence of the signals for the *ortho* phenyl protons ($^3J_{\text{HH}} = 8\text{ Hz}$) of carbene complex **5** in $[\text{D}_8]\text{toluene}$ at 300.13 MHz. At low temperatures, the upfield signal overlaps with other signals.

the complex as a Fischer-type carbene. The ^{31}P and ^{29}Si chemical shifts of **5** indicate that the carbene ligand is a better π acceptor than ethylene, but a weaker one than, for example, an η^2 -coordinated maleic anhydride.^[8a]

The intense violet color ($\lambda_{\text{max}} = 496\text{ nm}$ in pentane) can be rationalized by either a $\pi \rightarrow \pi^*$ transition of the copper–carbon double bond with predominant metal-to-ligand charge-transfer character, or by an excitation from a former sp^2 carbene lone pair localized in the copper–carbon σ bond to the π^* lowest unoccupied molecular orbital (LUMO) with primarily carbene p-orbital character.

The addition of styrene to solutions containing **5** leads to the disappearance of the violet color of the reaction mixture within several seconds at room temperature, even in the presence of excess **4**. This observation is consistent with the assignment of **5** as a copper(I) carbene species. Only traces of **5** remain detectable by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy, and the styrene was cyclopropanated to give a mixture of *cis*- and *trans*-methyl-1,2-diphenylcyclopropanecarboxylate (ratio greater than 8:1).^[9] This result is strong evidence that the active species in copper-catalyzed cyclopropanation reactions are indeed copper(I) carbene complexes, as proposed in the literature.^[2, 3, 10]

When the steric shielding is increased by replacing the CO_2Me group of **4** with a bis(4-chlorophenyl)methyl ester group, or by introducing a 9-phenanthryl substituent and an isopropyl ester moiety, the resulting carbene complexes are slightly more stable and have very similar spectroscopic properties. However, the isolation of any analytically pure copper(I) carbene complexes and of single crystals suitable for X-ray diffraction studies has so far been hampered by the high solubility of our systems with iminophosphanamide ligands, and remains a challenging task.

In summary, the first copper(I) carbenes have been synthesized and characterized spectroscopically in solution. Their structural features and their concomitant reactivity patterns are fully consistent with the mechanistic scenario put forward

by Pfaltz and co-workers for explaining and predicting product distributions in enantioselective copper-catalyzed cyclopropanations.^[3] Mechanistic studies utilizing **5** and its congeners, as well as quantum-chemical investigations, are presently being pursued in our laboratory and will be reported separately.

Experimental Section

Diazoalkane **4** was prepared according to a literature procedure^[11] and was purified by short-path distillation at 10^{-3} mbar . $[\text{D}_8]\text{Toluene}$ and C_6D_6 were dried over CaH_2 and saturated with argon. Ethylene complex **1** was prepared according to ref. [7a].

5: Methyl 2-phenyl-2-diazoacetate (**4**) (98 mg) was dissolved in $[\text{D}_8]\text{toluene}$ (0.5 mL) in an NMR tube, and ethylene complex **1** (58 mg) was added. The solution instantly became intensely violet, and gas evolution was observed.

Spectroscopic data of **5**: ^1H NMR (500.13 MHz, C_6D_6 , 28°C): $\delta = 8.68$ (d, $^3J_{\text{HH}} = 8\text{ Hz}$, 2H; *ortho*- C_6H_5), 3.61 (s, 3H; OCH_3), 1.31 (d, $^3J_{\text{PH}} = 14\text{ Hz}$, 9H; $\text{C}(\text{CH}_3)_3$), 1.25 (d, $^3J_{\text{PH}} = 14\text{ Hz}$, 9H; $\text{C}(\text{CH}_3)_3$), 0.24 (s, 18H; SiMe_3), the signals for *meta* and *para* phenyl protons overlap with signals of diazoalkane **4**, and of diphenyl fumarate and maleate derivatives; $^{13}\text{C}\{^1\text{H}\}$ NMR (125.76 MHz, $[\text{D}_8]\text{toluene}$, -33°C): $\delta = 229.9$ (s; $\text{Cu}=\text{C}$), 177.9 (s; CO), 27.3 (brs; $\text{C}(\text{CH}_3)_3$), 27.2 (brs; $\text{C}(\text{CH}_3)_3$), 4.9 (s; $\text{Si}(\text{CH}_3)_3$), phenyl, methoxy, and quaternary *tert*-butyl carbon signals cannot be assigned unambiguously; $^{29}\text{Si}\{^1\text{H}\}$ NMR (59.63 MHz, C_6D_6 , 25°C): $\delta = -10.2$ (d, $^2J_{\text{SiP}} = 12.2\text{ Hz}$); $^{31}\text{P}\{^1\text{H}\}$ NMR (121.49 MHz, $[\text{D}_8]\text{toluene}$, 25°C): $\delta = 64.3$ (s + satellites, $^2J_{\text{SiP}} = 12.6\text{ Hz}$, $^1J_{\text{CP}} = 63\text{ Hz}$); UV/Vis (pentane) $\lambda_{\text{max}} = 496\text{ nm}$ ($\epsilon \approx 10^3\text{ M}^{-1}\text{cm}^{-1}$); LT-FAB:^[12] m/z (%): 531.2 (1.8; $[\text{M}^+]$); VT ^1H NMR ($[\text{D}_8]\text{toluene}$, 300.13 MHz): *ortho*- C_6H_5 , $T_c = -70 \pm 4^\circ\text{C}$, $k_c = (700 \pm 100)\text{ Hz}$; external temperature calibration by using MeOH.

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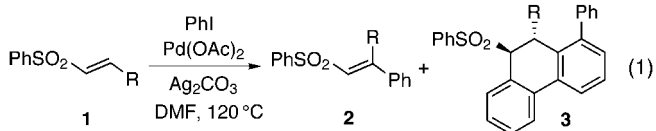
Unusual Palladium-Catalyzed Cascade Arylation of α,β -Unsaturated Phenyl Sulfones under Heck Reaction Conditions**

Pablo Mauleón, Inés Alonso, and Juan C. Carretero*

Over the last two decades the Heck reaction has emerged as one of the most versatile tools for the synthesis of carbon-substituted alkenes.^[1] The mechanism of this reaction is generally accepted to proceed through an oxidative addition/*syn*-carbopalladation/*syn*- β -hydrogen elimination sequence. The Heck reaction is also the origin of a fascinating variety of cascade reactions in which the key common feature is the formation, after the carbopalladation step, of a σ -alkylpalladium(II) intermediate lacking a suitable β -hydrogen *syn* with respect to the palladium center.^[1, 2] A particularly interesting case is that in which the σ -alkylpalladium(II) complex undergoes an intramolecular C–H activation process to give a palladacycle intermediate.^[3]

In our research into the use of substituted vinyl sulfones in stereoselective synthesis,^[4] we envisaged that acyclic β,β' -disubstituted- α,β -unsaturated sulfones could be stereoselectively prepared by simple Heck arylation of α,β -unsaturated sulfones through the seemingly evident *syn*-carbopalladation/*syn*- β -hydrogen elimination pathway.^[5] However, we describe herein that the palladium-catalyzed reaction of *trans*- α,β -unsaturated phenyl sulfones with excess iodobenzene/ Ag_2CO_3 proceeds by an intermolecular four-component cascade reaction to give 1-phenyl-9-phenylsulfonyl-9,10-dihydrophenanthrenes in which four C–C bonds are formed in a single step.

To test the behavior of vinyl sulfones in intermolecular Heck reactions,^[6] we began by treating the model substrate **1a** (see Eq. (1), Table 1, R = *i*Pr)^[7] with iodobenzene under



typical Heck reaction conditions: $\text{Pd}(\text{OAc})_2$ (10 mol %), K_2CO_3 , *N,N*-dimethylformamide (DMF), 120 °C. However, only the base-catalyzed isomerization of the vinyl sulfone to form the corresponding allyl sulfone was observed.^[8] Therefore, we turned our attention to the use of Ag_2CO_3 , a milder base that has proved to be very efficient in the Heck reactions of α,β -unsaturated sulfoxides.^[9] The reaction of **1a** with iodobenzene (1 equiv) and Ag_2CO_3 (200 mol %) in DMF at

Table 1. Palladium-catalyzed reaction of *trans*- α,β -unsaturated sulfones **1** with iodobenzene.

Entry ^[a]	Olefin	R	2 : 3 ^[b]	Yield ^[c] [%] (3 ^[d] [%])
1	1a	<i>i</i> Pr	2a : 3a 5:95	86 (69)
2	1b	<i>n</i> Pent	2b : 3b 12:88	82 ^[e]
3	1c	Cy	2c : 3c 10:90	84 ^[e]
4	1d	Ph	2d : 3d 3:97	82 (63)
5	1e	β -Naph	2e : 3e 8:92	85 (61)
6 ^[f]	1f	H	2d : 3d 4:96	78 (60)

[a] Reaction conditions: PhI (10 equiv), $\text{Pd}(\text{OAc})_2$ (10 mol %), Ag_2CO_3 (200 mol %), DMF, 120 °C, 3–5 days. [b] Determined by ^1H NMR spectroscopy of the crude mixtures. [c] Yields of mixtures of **2** and **3** after flash chromatography (compound **3** was only partially separated). [d] Yield of pure compound **3** after recrystallization. [e] Dihydrophenanthrenes **3b** and **3c** could not be crystallized. About 10–15 % of pure **3b** or **3c** was obtained after flash chromatography (toluene:*i*Pr₂O 100:1). [f] 250 mol % of Ag_2CO_3 was used.

120 °C for 72 h gave a mixture of four compounds: the starting vinyl sulfone (32 %), the isomerized allyl sulfone (30 %), the expected Heck product **2a** (26 %), and, quite surprisingly, the dihydrophenanthrene **3a** (21 %; Eq. (1)). The yield of **3a** improved progressively in the presence of increasing amounts of iodobenzene since the formation of **3a** requires the participation of three molecules of iodobenzene. The optimal **2a**:**3a** ratio was obtained in the presence of ten equivalents of iodobenzene^[10] (**2a**:**3a** 5:95, Table 1, entry 1).

In order to determine the versatility of this unprecedented Heck-type cascade process on acyclic alkenes, the arylation of several *trans*- α,β -unsaturated phenyl sulfones **1**^[7] was studied (Table 1, entries 1–5).

Remarkably, the cascade product **3** predominated largely over the Heck product **2** (**2**:**3** ratio from 12:88 to 3:97, 82–86 % yields of mixtures of **2** and **3**) with both β -alkyl- (Table 1, entries 1–3) and β -aryl-substituted vinyl sulfones (Table 1, entries 4–5). Although compounds **2** and **3** could not be completely separated by standard flash chromatography because of their very similar chromatographic mobilities (R_f values), pure compounds **3** were readily obtained in most cases by further recrystallizations (61–69 % yields in pure crystalline form). The structure of the dihydrophenanthrenes **3** was first studied by NMR spectroscopy and mass spectrometry, and the *trans* configuration at C9–C10 was unambiguously proved by the X-ray structure analyses^[11] of **3a** and **3d** (Figure 1).

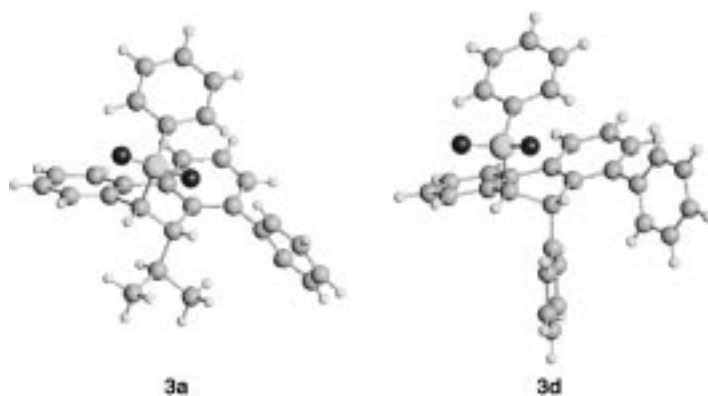


Figure 1. Crystal structures of **3a** and **3d**.

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

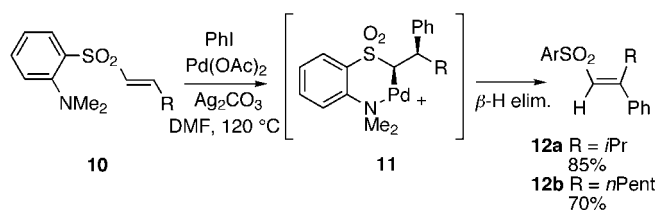
We were delighted to observe that even the simple phenyl vinyl sulfone **1f** (entry 6) reacted with iodobenzene to give mainly the dihydrophenanthrene **3d**, which showed that four molecules of iodobenzene took part in an even more elaborate cascade process involving the formation of five C–C bonds. This result can be readily explained by assuming that the β -unhindered vinyl sulfone **1f** first undergoes a fast Heck reaction to give the *trans*-disubstituted olefin intermediate **1d**, which then reacts in situ with iodobenzene to afford **3d** through the four-component cascade process (entry 4). Accordingly, **1d** was isolated in 82% yield when the palladium-catalyzed reaction of **1f** was carried out in the presence of a stoichiometric amount of iodobenzene instead of a large excess (10 equiv).

This cascade reaction is similar to the palladacycle-mediated formation of 2:1 and 3:1 coupling products described by Catellani et al.^[12] and de Meijere and co-workers^[13] in the palladium-catalyzed reactions of halobenzenes with norbornene, a cyclic alkene widely used in interrupted Heck reactions because the *syn*- β -hydrogen elimination step is not feasible. Taking these precedents into account, Scheme 1 outlines a simplified mechanistic hypothesis for the formation of the dihydrophenanthrenes **3**.

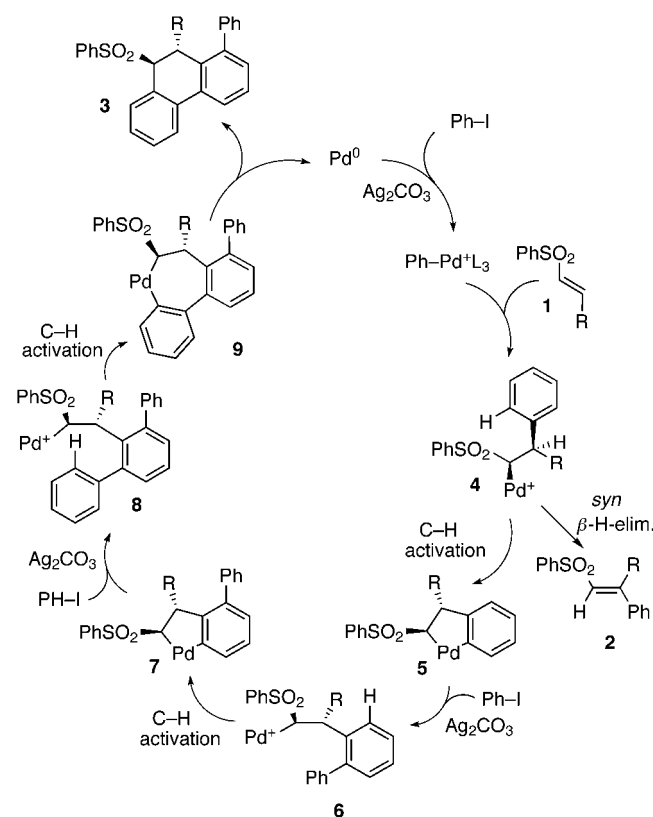
The first step after the oxidative addition of iodobenzene to the Pd⁰ catalyst would be the regioselective *syn*-insertion of the cationic phenylpalladium species into the C–C double bond in the presence of Ag₂CO₃ to form the sulfonylalkylpalladium intermediate **4**. Unlike the usual behavior of acyclic alkenes, the complex **4** would evolve faster through a C–H

activation process, to give the five-membered palladacycle^[14] **5**, than by *syn* β -hydrogen elimination to yield the Heck product **2**. The intermediate **5** could react further with iodobenzene to give the σ -alkylpalladium intermediate **6**, possibly through an oxidative addition/reductive elimination pathway via a Pd^{IV} palladacycle intermediate.^[15, 16] The repetition of the same mechanistic sequence at the next available *ortho* positions would lead successively to the formation of the intermediates **7** and **8**. Finally, a third C–H activation process would give the seven-membered palladacycle^[17] **9**, which would afford the main product **3** after reductive elimination.

In this cascade process the intramolecular C–H activation steps seem to require the participation of highly electrophilic σ -alkylpalladium(II) species, as it is necessary to use Ag₂CO₃ as a base. Furthermore, the *trans*- α,β -unsaturated 2-(*N,N*-dimethylamino)phenyl sulfones **10**^[7], which can potentially coordinate palladium, exclusively underwent a normal Heck reaction to give the *E*-trisubstituted olefins **12**,^[18] possibly via Pd–N coordinated intermediates^[19] **11** (Scheme 2).



Scheme 2. Heck reaction of α,β -unsaturated sulfones **10** with iodobenzene (Ar = *o*-(Me₂N)C₆H₄).



Scheme 1. Mechanistic proposal for the palladium-catalyzed cascade reaction of vinyl sulfones **1** with iodobenzene. (The ligands at the palladium center have been omitted for clarity.)

In conclusion, the behavior of *trans* α,β -unsaturated phenyl sulfones under arylation Heck conditions differs from that of all previously studied acyclic 1,2-disubstituted alkenes. In the presence of Ag₂CO₃ the palladium-catalyzed reactions with iodobenzene occur through an intermolecular four-component cascade process, which involves one unit of vinyl sulfone and three units of iodobenzene, rather than by a normal Heck arylation. Further synthetic transformations of the resulting 9,10-dihydrophenanthrenes **3**, as well as studies to ascertain the steric and electronic requirements of this type of cascade reaction with acyclic alkenes are in progress.

Experimental Section

3a: A mixture of *trans* 1-phenylsulfonyl-3-methyl-1-butene (**1a**; 81 mg, 0.38 mmol), silver carbonate (213 mg, 0.77 mmol, 200 mol %), Pd(OAc)₂ (8.7 mg, 0.038 mmol, 10 mol %), iodobenzene (0.43 mL, 3.86 mmol, 1000 mol %), and DMF (2 mL) was heated at 120 °C under an argon atmosphere and stirred vigorously. After 72 h (thin-layer chromatography control), the mixture was allowed to cool to room temperature, diluted with Et₂O (20 mL), filtered through celite, and washed with water (20 mL). The organic layer was dried (MgSO₄) and evaporated. The residue was analyzed by ¹H NMR spectroscopy and purified by flash chromatography (hexane/diethyl ether 10:1) to give a 5:95 mixture of **2a**:**3a** (86% yield). This mixture was recrystallized from diethyl ether to afford 10-isopropyl-1-phenyl-9-phenylsulfonyl-9,10-dihydrophenanthrene (**3a**, 117 mg, 69% yield).

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Enantioselective Hydrogen Atom Transfer Reactions: Synthesis of *N*-Acyl- α -Amino Acid Esters**

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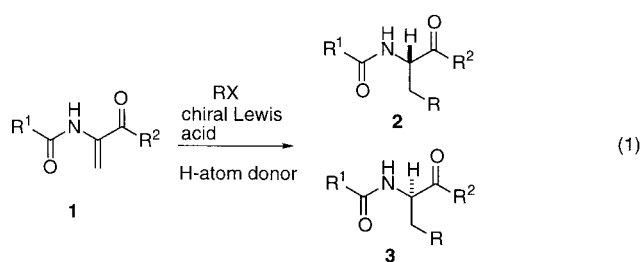
Enantioselective proton-transfer reactions (enolate protonations) have been investigated in detail for over a decade and even catalytic variants have been demonstrated.^[1] In contrast, enantioselective hydrogen atom transfer reactions have begun to emerge only recently.^[2] In principle, these reactions can be carried out in two distinct ways: 1) by H-atom transfer from a chiral reagent to a radical, or alternatively 2) by H-atom transfer from an achiral reagent to a radical complexed to a chiral source. Nanni and Curran,^[3a] Metzger and co-workers,^[3b,c] Roberts and co-workers,^[3d] and Schiesser and co-workers^[3e] have reported examples of reactions using chiral H-atom transfer reagents. On the other hand, only a few examples of H-atom transfer to radicals complexed to chiral Lewis acids have been noted in the literature.^[4] We have shown that enantioselective conjugate additions proceed with high chemical efficiency and selectivity using a chiral Lewis acid derived from M²⁺ metal salts in conjunction with a bisoxazoline prepared from aminoindanol.^[5] Herein we show that conjugate radical addition to *N*-acylamido acrylates **1** mediated by a chiral Lewis acid followed by an enantioselective H-atom transfer furnishes a variety of α -amino acid derivatives (**2** or **3**) with good to excellent efficiency [Eq. (1)].

Diastereoselective H-atom transfer reactions to captodative radicals derived from *N*-acylamido acrylates in both acyclic^[6] and cyclic^[7] systems proceed with moderate to good selectivity.^[8] In contrast, enantioselective variants of these reactions have not been reported and this work constitutes the first example of such a process. We began our experiments

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with the addition of an ethyl radical to differentially substituted α -amino acrylates. Preliminary experiments were designed to arrive at the optimal substitution at the nitrogen and the ester oxygen atoms for chemical efficiency as well as selectivity. The following reaction conditions were used as standard conditions: five equivalents of ethyl iodide/two equivalents of tributyltin hydride, triethylborane/O₂ as an initiator, and with CH₂Cl₂ as the solvent at -78°C . A preliminary non-Lewis acid mediated reaction indicated that conjugate addition was not facile at low temperature (<5% yield of the product after 3 h). The addition of a Lewis acid facilitated the addition. A chiral Lewis acid (1.3 equiv) derived from magnesium perchlorate and bisoxazoline (**4**) was employed in the initial screening experiments [Eq. 2, Table 1].^[9] *N*-Benzoyl and benzyloxycarbonyl (CBZ) substituents were not effective (entries 1 and 2). Of the four different *N*-acyl groups investigated the 2-naphthoyl substituent gave the highest *ee* value of 85% (entry 4). It is interesting to note that the corresponding 1-naphthoyl substituent gave much lower selectivity (entry 3). The next series of experiments examined the effect of the ester substituent. Of the three variations the smaller methyl group in conjunction with the *N*-2-naphthoyl group furnished the highest *ee* values

(entries 4–6). Having settled on the *N*-acyl and ester substituents, a brief study of the Lewis acid was undertaken. Of the different Lewis acids investigated Mg(ClO₄)₂ gave the highest selectivity as well as chemical yield (compare entry 4 with entries 7–10). Variations in the stoichiometry and/or the nature of the tin H-atom transfer reagent did not show any improvements in the selectivity (entries 10–13). Tris(trimethylsilyl)silane was ineffective as a H-atom transfer reagent (entry 14).

The addition of a variety of nucleophilic radicals of various size and functionality to **1d** under the optimal conditions was undertaken [Eq. (3); Table 2]. Examination of the data in

Table 2. Conjugate radical addition to dehydroalanines followed by enantioselective H-atom transfer.^[a]

Entry	RX	Prod.	Yield [%] ^[b]	<i>ee</i> [%] (config.) ^[c]
1	AcBr	6	76	80
2	MeOCH ₂ Br	7	71	65
3	EtI	8	72	85 (<i>R</i>)
4	<i>i</i> BuI	9	76	79
5	<i>i</i> PrI	10	62	83 (<i>R</i>)
6	<i>c</i> HexI	11	62	55 (<i>R</i>)
7	<i>t</i> BuI	12	54	27 (<i>R</i>)

[a] For the general reaction conditions see the Supporting Information. *c*Hex = cyclohexyl. [b] Yields are for isolated products and materials purified by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. For the establishment of the configuration see the Supporting Information.

Table 1. Enantioselective H-atom transfer to glycine radicals: Effect of the *N*-acyl and ester substituents on the selectivity.^[a]

Entry	Compd	R ¹	R ²	Lewis acid	H-Atom donor (equiv)	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	1a	Ph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	62	17
2	1b	OBn	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	61	22
3	1c	1-naph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	55	47
4	1d	2-naph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	72	85
5	1e	2-naph	Bn	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	57	68
6	1f	2-naph	<i>t</i> Bu	Mg(ClO ₄) ₂	Bu ₃ SnH (2)	56	71
7	1d	2-naph	Me	MgBr ₂	Bu ₃ SnH (2)	57	27
8	1d	2-naph	Me	MgI ₂	Bu ₃ SnH (2)	36	16
9	1d	2-naph	Me	Mg(OTf) ₂	Bu ₃ SnH (2)	33	3
10	1d	2-naph	Me	Zn(OTf) ₂	Bu ₃ SnH (2)	42	0
11	1d	2-naph	Me	Mg(ClO ₄) ₂	Bu ₃ SnH (10)	79	84
12	1d	2-naph	Me	Mg(ClO ₄) ₂	Ph ₃ SnH (2)	50	85
13	1d	2-naph	Me	Mg(ClO ₄) ₂	Ph ₃ SnH (5)	77	83
14	1d	2-naph	Me	Mg(ClO ₄) ₂	(TMS) ₃ SiH (2)	6	14

[a] For general reaction conditions see the Supporting Information. Naph = naphthyl. [b] Yields are determined on isolated products and materials purified by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

Table 2 indicate that acetyl (entry 1), α -alkoxyalkyl (entry 2), primary alkyl (entries 3 and 4), secondary alkyl (entry 5), and cycloalkyl (entry 6) all show good selectivity in H-atom transfer. However, the bulky *tert*-butyl radical provided low selectivity (entry 7). The low selectivity for **12** may suggest that the bulky *tert*-butyl group and chiral Lewis acid shield opposite faces and reactions may occur from a monocoordinated or noncomplexed substrate.^[10]

The coordination of the Lewis acid is essential for activating the substrate for conjugate addition (see above). However, the enantioselective H-atom transfer step is subsequent to the radical addition. It is assumed that the structure of the intermediate radical resembles that of the starting complex. The absolute stereochemistry of several products were determined in order to arrive at a working model for the sense of the stereoinduction in the H-atom transfer reactions.^[11] On the basis of these results, a conjugate addition to a seven-membered chelate ternary complex (**13**, starting material+ligand+Lewis acid; Figure 1)^{[12][13]} followed by a H-atom transfer is consistent with the observed stereochemistry.^[14] H-atom transfer to a monodentate complex and/or the flexibility of the seven-membered chelate could lead to the erosion of selectivity. The variation in *ee* values with changes in the *N*-acyl substituent however cannot be readily understood from the proposed model.^[15]

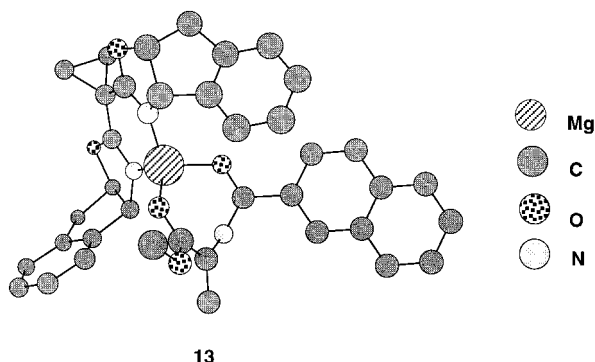
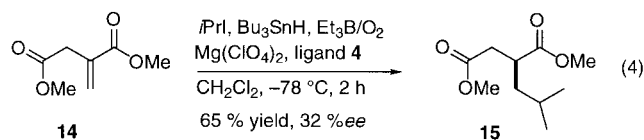


Figure 1. 7-Membered chelate. Shielding of the *Re*-face is observed.

To further corroborate the possibility of a seven-membered chelate, the addition of an isopropyl radical to itaconate **14** under the optimal conditions was investigated [Eq. (4)]. The



product from this experiment shows a moderate *ee* value (32%) with an *S* configuration.^[16] The absolute stereochemistry of **15** is consistent with a model in which H-atom transfer occurs through a seven-membered chelate similar to **13**.

In conclusion, we have shown that chiral Lewis acid mediated conjugate radical addition to dehydroalanines followed by enantioselective H-atom transfer proceeds with moderate to excellent selectivity to provide α -amino acids.

Extension of the methodology to the preparation of C-glycosides and radical addition to β -substituted substrates is underway. The examination of complexes such as **13** as dienophiles in enantioselective Diels–Alder reactions is also underway.

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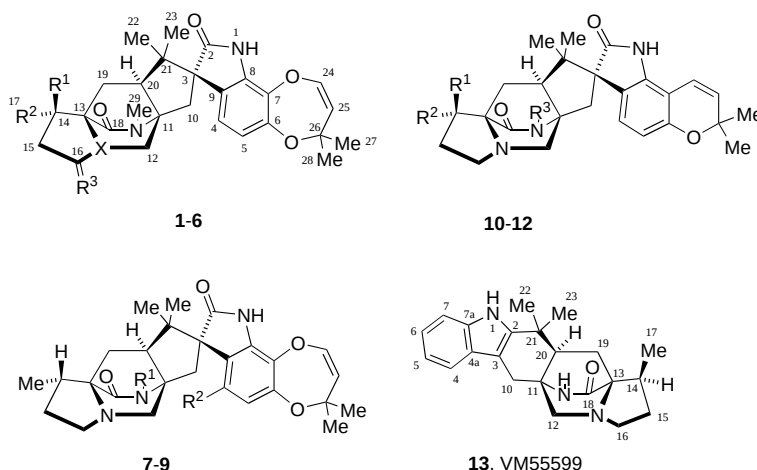


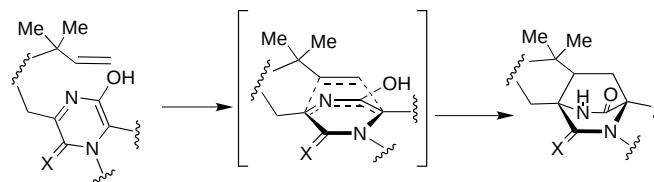
Figure 1. **1**, paraherquamide A: $R^1 = \text{OH}$, $R^2 = \text{Me}$, $R^3 = \text{H}_2$, $X = \text{N}$; **2**, paraherquamide B: $R^1 = \text{H}$, $R^2 = \text{H}$, $R^3 = \text{H}_2$, $X = \text{N}$; **3**, paraherquamide C: $R^1 = R^2 = \text{CH}_2$, $R^3 = \text{H}_2$, $X = \text{N}$; **4**, paraherquamide D: $R^1 = \text{O}$, $R^2 = \text{CH}_2$, $R^3 = \text{H}_2$, $X = \text{N}$; **5**, VM55596: $R^1 = \text{OH}$, $R^2 = \text{Me}$, $R^3 = \text{H}_2$, $X = \text{N}^+ - \text{O}^-$; **6**, VM55597: $R^1 = \text{OH}$, $R^2 = \text{Me}$, $R^3 = \text{O}$, $X = \text{N}$; **7**, paraherquamide E (VM54159): $R^1 = \text{Me}$, $R^2 = \text{H}$; **8**, SB203105: $R^1 = \text{Me}$, $R^2 = \text{OH}$; **9**, SB200437: $R^1 = \text{H}$, $R^2 = \text{H}$; **10**, paraherquamide F (VM55594): $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = \text{Me}$; **11**, paraherquamide G (VM54158): $R^1 = \text{OH}$, $R^2 = \text{Me}$, $R^3 = \text{Me}$; **12**, VM55595: $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = \text{H}$.

Studies on the Biosynthesis of Paraherquamide: Synthesis and Incorporation of a Hexacyclic Indole Derivative as an Advanced Metabolite**

Emily M. Stocking, Juan F. Sanz-Cervera, and Robert M. Williams*

The paraherquamides (Figure 1),^[1] along with the brevianamides,^[2] marcfortines,^[3] and sclerotamides^[4] are indolic fungal metabolites that share the common structural feature of an unusual bicyclo[2.2.2]diazaoctane core. It has been postulated that the bicyclo[2.2.2]diazaoctane ring system arises through an intramolecular hetero Diels–Alder cycloaddition of the isoprene moiety across the α -carbons of the amino acid subunits, as shown in Scheme 1.^[5]

In 1993, Everett and co-workers isolated a very minor metabolite that also possesses the bicyclo[2.2.2]diazaoctane core, VM55599 (**13**, Figure 1), from *Penicillium* sp. (IMI 332995) which produces paraherquamide A.^[6] Based on



Scheme 1. Proposed formation of the bicyclo[2.2.2]diazaoctane ring system in the paraherquamides.

the structural similarities of these co-metabolites, Everett et al. speculated that VM55599 might be a biosynthetic precursor to paraherquamide A.^[6] The relative stereochemistry of VM55599 as shown in Figure 1 was assigned by ¹H NMR spectroscopy with nuclear Overhauser enhancements but the absolute configuration of this substance remains unknown. The stereochemistry of the methyl group in the β -methylproline ring was assigned as being *syn* to the bridging isoprene moiety. In all other known members of the paraherquamide family, the methyl group in the β -methylproline ring is disposed *anti* to the bridging isoprene moiety. If VM55599 was indeed a precursor to paraherquamide A, then oxidation of the β -methylproline ring would have to occur with inversion of stereochemistry at the C-14 center that bears the methyl group.

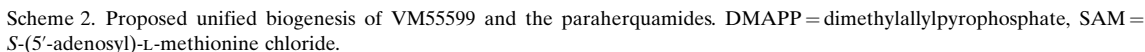
Previous studies from this laboratory on the biosynthesis of paraherquamide A demonstrated that L-isoleucine is the precursor to the β -methyl- β -hydroxy proline ring of paraherquamide A.^[7] The relative disposition of the methyl group in the prolyl ring is retained in the biosynthetic conversion of L-isoleucine into paraherquamide A and, thus, the hydroxylation at C-14 occurs with net retention. These findings bring into question the potential intermediacy of VM55599 in the biosynthesis of the paraherquamides. Furthermore, if L-isoleucine is also the precursor to VM55599, then the absolute stereochemistry of this metabolite must be that depicted in

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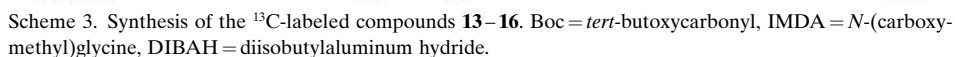
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The proposed ^{13}C -labeled compounds were synthesized according to our previously described synthesis of racemic VM55599 (Scheme 3).^[9c, 10] The advantage of this strategy is that all four candidate precursors are accessible from a single synthesis. In

The racemic cycloadducts (**13–16**) possessed the unfortunate property of being insoluble in water so rendering the planned feeding experiments challenging. To circumvent this problem, the detergent TWEEN 80 was added and was found



to increase the miscibility of these substances in the culture broth without inhibiting production of paraherquamide A. Feeding experiments were performed on *P. fellutanum* (ATCC20841) with all four potential precursors, followed by isolation and purification of paraherquamide A. Within the limits of detection by ^{13}C NMR spectroscopy and mass spectrometry no incorporation was observed for VM55599 (($\pm$)-**13**) or its oxidized counterpart (($\pm$)-**14**). In addition, no incorporation was observed for the diketopiperazine (($\pm$)-**16**). However, for the C-14 epimer of VM55599 (($\pm$)-**15**), significant incorporation was observed by ^{13}C NMR spectroscopy at C-12 and C-18 of paraherquamide A. From analysis of the electrospray mass spectrum, incorporation was determined to be 0.72 % for the intact doubly labeled material.^[11] ^{13}C -Monolabeled paraherquamide A, from catabolism of (($\pm$)-**15**, was not detected in the mass spectrum. The implications of these observations are considerable.

Since the diketopiperazine (($\pm$)-**16**) was not incorporated, this raises interesting questions concerning the timing of the reduction of the prolyl-derived carbonyl group. The incorporation of compound (($\pm$)-**15** in significant isotopic yield, indicates that the formation of the bicyclo[2.2.2]diazaoctane occurs at the stage with the nonoxidized tryptophyl moiety (that is, the indolyl group). This mandates that oxidations of the indole ring to form both the catechol-derived dioxepin and spirooxindole occur *after* the formation of this intermediate. It thus follows that the dioxepin-derived isoprenylation and the *S*-adenosylmethionine-mediated *N*-methylation reactions occur late in the pathway. These results also cast considerable doubt on the intermediacy of VM55599^[6] and its oxidized precursor **14** in the paraherquamide biosynthesis and provide additional circumstantial evidence that VM55599 is a minor shunt metabolite. Finally, the present work documents the intermediacy of an advanced metabolite **15**, which contains the core structural elements of the paraherquamide framework, prior to a series of oxygenation reactions. Efforts to elucidate the exact sequence of biosynthetic reactions immediately preceding and following the formation of **15** are currently under way in these laboratories.

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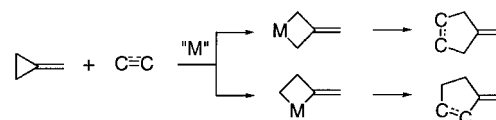
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Novel [3+2] Cycloaddition of Alkylidenecyclopropanes with Aldehydes Catalyzed by Palladium

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A metal-catalyzed cycloaddition between methylenecyclopropane and a carbon–carbon multiple bond can proceed through two different reaction pathways to give regioisomeric [3+2] carbocycles (Scheme 1).^[1–3] The research groups of



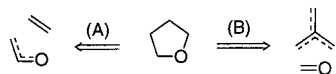
Scheme 1. Metal-catalyzed cycloaddition of methylenecyclopropane and a carbon–carbon multiple bond.

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

Noyori, Binger, and Trost studied primarily the intermolecular [3+2] cycloaddition,^[2] and more recently the research groups of Nakamura, Motherwell, and Lautens investigated the intramolecular version of the carbocycle formation.^[3] However, to the best of our knowledge, there has been no report of the [3+2] cycloaddition between methylenecyclopropane and the carbon–oxygen double bond of aldehydes.^[4]

The synthesis of cyclic ethers by means of transition metal catalyzed [3+2] cycloadditions falls into two categories (Scheme 2). Type A: vinylic oxiranes are used as a “two-



Scheme 2. Construction of tetrahydrofuran rings by transition metal catalyzed [3+2] cycloaddition.

carbon and one-oxygen component” in the palladium-catalyzed cycloaddition with olefins to give 2-vinyltetrahydrofuran derivatives.^[5] The catalytic cycloaddition of metal carbenoids with olefins also falls into this class.^[6] Type B: the reaction of trimethylenemethane (TMM) precursors, which are thought to be “three-carbon components”, with carbonyl compounds in the presence of palladium catalysts gives 3-methylenetetrahydrofurans.^[7]

We now report that the reaction of methylenecyclopropanes **1** with aldehydes **2** in the presence of 2 mol % of [Pd(PPh₃)₄] and 4 mol % of tributylphosphane oxide at 120 °C gives the corresponding [3+2] cycloadducts, the five-membered cyclic ethers **3**, in good to acceptable yields (Table 1).

The reaction of 1-butylpentylidenecyclopropane **1a** (0.5 mmol) with furfural **2a** (1.5 mmol) in the presence of catalytic amounts of [Pd(PPh₃)₄] (2 mol %) and tributylphosphane oxide (4 mol %) but in the absence of solvent at 120 °C for 5 h gave the corresponding cycloadduct **3a** in 75 % yield (Table 1, entry 1). The reaction of **1a** with **2a** did not proceed at all without the palladium catalyst. The use of [Pd(dba)₂]/PPh₃ (dba = *trans,trans*-dibenzylideneacetone) as a catalyst was less effective for producing **3a**, while [Pd₂(dba)₃]·CHCl₃, Pd(OAc)₂, allylpalladium chloride dimer, and [Pt(PPh₃)₄] were totally ineffective as catalysts. The reaction of **1a** with **2a** using traditional phosphane ligands, such as PPh₃, PBu₃, and P(OPh)₃, was slower than the reaction with P(O)Bu₃ and gave **3a** in lower yield. The use of THF as the solvent in the reaction of **1a** and **2a** gave **3a** in lower yield (36 %). The reaction of 1-hexylheptylidenecyclopropane (**1b**), 1-methyl-3-phenylpropylidenecyclopropane (**1c**), and 3-phenylpropylidenecyclopropane (**1d**) with **2a** afforded **3b**, **3c**, and **3d** in yields of 71, 86, and 43 %, respectively (Table 1, entries 2–4). The reaction of **1a** with 5-methylfurfural (**2b**) proceeded smoothly and the corresponding cycloadduct **3e** was produced in 65 % yield (Table 1, entry 5). The spiro compound **3f** was obtained in 77 % yield from the reaction of **2b** and two equivalents of cyclohexylidenecyclopropane (**1e**; Table 1, entry 6). The reactions of **1a** with 3-furaldehyde (**2c**) and with 2-thiophenecarbaldehyde (**2d**) produced **3g** and **3h** in yields of 51 and 64 %, respectively (Table 1, entries 7 and 8). Benzaldehyde derivatives **2e** and **2f** bearing electron-donating groups gave the corresponding 2-aryl-4-methylenetetra-

Table 1. Palladium-catalyzed cycloaddition of alkylidenecyclopropanes **1** with aldehydes **2**.^[a]

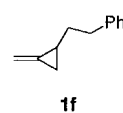
$\begin{array}{c} \text{R}^1 \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{R}^2 \end{array} + \begin{array}{c} \text{R}^3 \\ \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{H} \end{array} \xrightarrow[\text{No solvent}]{\begin{array}{c} 2 \text{ mol \% [Pd(PPh}_3)_4] \\ 4 \text{ mol \% P(O)Bu}_3 \\ 120^\circ\text{C} \end{array}} \begin{array}{c} \text{R}^1 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{R}^3 \\ \diagdown \\ \text{O} \end{array}$					
Entry	1	2	Time [h]	3	Yield [%] ^[b]
1			5	3a	75
2		2a	11	3b	71
3		2a	16	3c	86 (53:47) ^[c]
4		2a	20	3d	42 (54:46) ^[c]
5	1a		6	3e	65
6 ^[d]		2b	20	3f	77
7	1a		12	3g	51
8	1a		19	3h	64
9	1a		19	3i	43
10 ^[d]	1a		32	3j	38

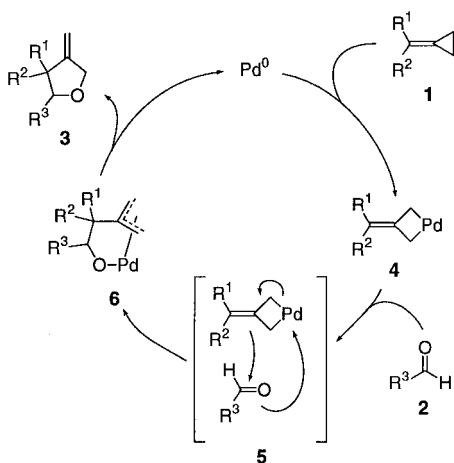
[a] The reaction of **1** (0.5 mmol) with **2** (1.5 mmol) was carried out in the presence of 2 mol % of [Pd(PPh₃)₄] and 4 mol % of tributylphosphane oxide without solvent at 120 °C. [b] Isolated yield based on **1**. [c] The diastereomeric ratio of **3**. [d] Compound **1** (1 mmol) was treated with **2** (0.5 mmol), and the yield is based on **2**.

hydrofuran derivatives **3i** and **3j** in modest yields (Table 1, entries 9 and 10) when treated with **1a**. The reaction of **2a** with methylenecyclopropane **1f**, which has a substituent on the ring, did not afford any cycloadducts at all.

A plausible mechanism is illustrated in Scheme 3. Oxidative addition of palladium(0) to a distal bond of the alkylidenecyclopropane **1** leads to the palladacyclobutane complex **4**.^[8] The pallada-enetype reaction of **4** with the aldehyde **2** may proceed as shown in **5**, to give the π -allylpalladium complex **6**.^[9] Reductive elimination of palladium(0) then gives the [3+2] cycloadduct **3**.

The thermal [3+2] cycloaddition reactions of methylenecyclopropanone ketals with aldehydes^[10] and imines^[11] were reported recently. However, these reactions require the use of highly activated methylenecyclopropanone derivatives.





Scheme 3. A plausible mechanism for the palladium-catalyzed [3+2] cycloaddition of alkylidenecyclopropanes **1** with aldehydes **2**.

In conclusion, we are now in a position to synthesize various types of *exo*-methylene-tetrahydrofuran derivatives through the palladium-catalyzed [3+2] cycloaddition between methylenecyclopropanes and aldehydes. The present atom-economical reaction may be potentially useful for constructing biologically important tetrahydrofuran skeletons.

Experimental Section

3a: Compounds **2a** (1.5 mmol) and **1a** (0.5 mmol) were added to a mixture of [Pd(PPh₃)₄] (11.5 mg, 0.01 mmol) and tributylphosphane oxide (4.4 mg, 0.02 mmol) under argon in a pressure vial. The reaction mixture was heated at 120 °C for 5 h, and then filtered through a silica-gel column using ethyl acetate as an eluent. The product was isolated by passing it through a silica-gel column, and purified by medium-pressure liquid column chromatography (silica gel) to afford the cycloadduct **3a**. IR (neat): $\tilde{\nu}$ = 2957–2870, 1663, 1468, 1379, 1148, 1053, 1011, 980, 885, 733 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ = 0.79 (t, *J* = 7.5 Hz, 3H), 0.89–1.33 (m, 12H), 1.45 (td, *J* = 13.8, 4.0 Hz, 1H), 1.58 (t, *J* = 8.5 Hz, 2H), 4.45 (td, *J* = 13.0, 2.5 Hz, 1H), 4.60 (td, *J* = 13.5, 2.5 Hz, 1H), 4.78–4.79 (m, 2H), 5.02 (t, *J* = 2.0 Hz, 1H), 6.22 (d, *J* = 3.5 Hz, 1H), 6.32 (dd, *J* = 3.2, 2.0 Hz, 1H), 7.35 (dd, *J* = 2.0, 1.0 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ = 13.86, 14.00, 23.28, 23.33, 25.78, 26.06, 32.52, 34.40, 51.79, 71.06, 82.82, 103.97, 107.61, 110.00, 141.56, 152.95, 153.45; HR-MS (EI): calcd for C₁₇H₂₆O₂: [*M*]⁺ 262.1932, found 262.1932.

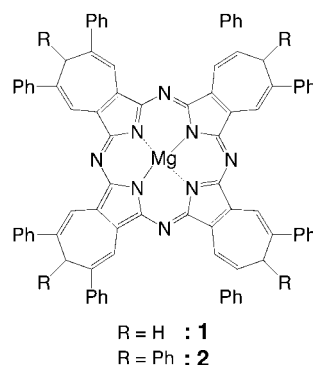
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A Seven-Membered Carbon-Ring-Fused Phthalocyanine Analogue in which the π System Changes during Dehydrogenation/Hydrogenation Cycles**

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Phthalocyanines (Pcs) have been the subject of intensive study in a variety of academic and commercial fields. For example, they have industrial applications as dyes and pigments, photoconducting reagents in photocopiers, catalysts for removing sulfur from crude oil, deodorants, in the photodynamic therapy of cancer, and as germicides.^[1] However, Pc analogues which contain seven-membered carbon rings instead of benzene rings have so far not been reported.^[2] Herein we report the first example of this kind of Pc analogue, namely, compound **1**. This compound contains four fused cycloheptatriene (CHT) rings on the periphery of the parent tetraazaporphyrin skeleton. Cycloheptatriene is well known for being able to convert between nonaromatic CHT and the aromatic tropylium cation through a redox reaction during the elimination/recombination of a hydride ion (H⁻).^[3] Accordingly, we considered that it might be possible to adjust the size of the π -conjugation system in **1** by dehydrogenation/hydrogenation of the CHT



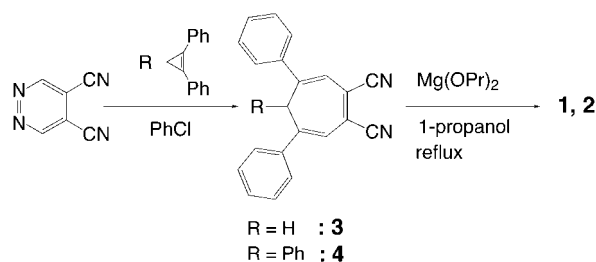
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moiety. Compound **1** is, therefore, not only new but can also vary the size and shape of the π -conjugation system. As will be described below, the addition of dehydrogenation/hydrogenation reagents has succeeded in repeatedly and reversibly producing electronic absorption spectra which are indicative of expansion/reduction of the π system.^[4] Compound **2**, which has a similar structure to **1**, has also been prepared and studied.

The starting aromatic *ortho*-dinitriles for compounds **1** and **2**, namely, 1,6-diphenyl-3,4-dicyanocycloheptatriene (**3**) and 1,6,7-triphenyl-3,4-dicyanocycloheptatriene (**4**), respectively, were synthesized by treating an equimolar amount of 4,5-dicyanopyridazine^[5] and 1,2-diphenylcyclopropene^[6,7] or 1,2,3-triphenylcyclopropene^[6,7] in chlorobenzene at 80 °C for 5 h or at 120 °C overnight, respectively (Scheme 1). Com-



Scheme 1. Synthesis of **1** and **2**.

pounds **3** and **4** were isolated as yellow needles after chromatographic separation on silica gel using a mixture of hexane/ethyl acetate (5/1) as eluent, and recrystallization from mixtures of these two solvents. Compounds **1** and **2** were obtained by tetramerization of **3** and **4** in the presence of magnesium in propanol at 140–150 °C for 12–15 h.^[4] Purification was performed by silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100/1), alumina (Act. V, CHCl_3), and gel-permeation (Bio-beads SX-2, CHCl_3) column chromatography, followed by preparative chromatography on alumina ($\text{CHCl}_3/\text{MeOH}$ 100/1). Satisfactory spectroscopic data were obtained for **1** and **2**,^[8] with the most interesting data being the FAB-MS data of **1** and **2**. Compound **2** showed a parent ion peak [M^+] at the expected m/z 1505, and the isotropic distribution pattern agreed well with the theoretical pattern, while the high-resolution mass spectral pattern of **1** appears to be a superimposition of the species [M^+] and [$M^+ - \text{H}$]. Since compounds having good anionic leaving groups produce cationic fragments after elimination of this kind of group, the above mass spectra of **1** may be an indication that H^- is prone to be liberated from **1**.

Figure 1 shows the electronic absorption and magnetic circular dichroism (MCD) spectra of **1** in CHCl_3 . Although the Q band position is at a relatively long wavelength relative to those of normal Pcs, the absorption spectrum has characteristics of tetraazaporphyrins (TAPs) with approximate D_{4h} symmetry.^[9] The red-shifted Q band arises from the expansion of the π system by the fused CHT units and the substituent effect of the phenyl groups, while the Soret band is sharper than found for Pcs. A broad, weak band lying between the Q and Soret bands is similar to a band often seen in the spectra of TAPs, and may be assigned as a $n(\text{aza or pyrrole nitrogen}) \rightarrow \pi^*$ electronic transition.^[10] One and three Faraday

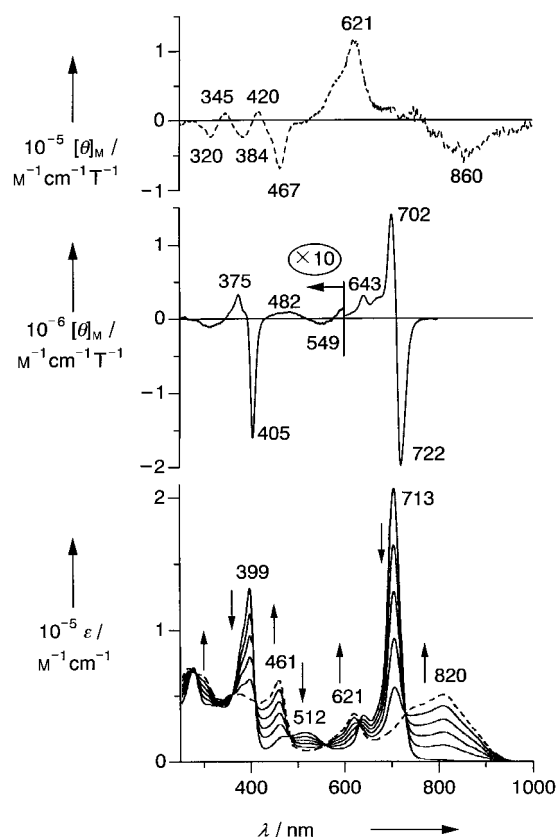


Figure 1. Development of the electronic spectra of **1** by the addition of DDQ (bottom), and its MCD spectra before (middle) and after (top) addition of DDQ in chloroform. The dashed lines denote the spectra at $[\text{DDQ}]:[\mathbf{1}] = 1:1$.

A-term-type curves are observed in the Q and Soret band regions, respectively, in the MCD spectrum, which suggests that there are several orbitally degenerate excited states.^[9]

The redox potentials were measured in *o*-dichlorobenzene containing tetrabutylammonium perchlorate (0.1 mol dm^{-3}). The first oxidation, and first and second reductions of **1** were detected at 0.15, -1.39 , and -1.73 V versus the ferrocenium/ferrocene (Fc^+/Fc) couple, respectively, while those of **2** were found at 0.26, -1.36 , and -1.70 V, respectively; in comparison those for tetra-*tert*-butylated MgPc [$\text{Mg}[(t\text{Bu})_4\text{Pc}]$] appear at -0.02 , -1.64 , and approximately -2.0 V.^[11] The differences in potential between the first oxidation and reduction couples (1.54 and 1.62 V) are similar to those of normal Pcs (approximately 1.5–1.7 V).^[12] In addition, all the couples were reversible one-electron processes and therefore could be assigned to ligand oxidation and reduction not involving hydrogen atoms of the CHT moiety. Accordingly, chemical dehydrogenation/hydrogenation was examined using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the dehydrogenation reagent (Figure 1). The Q band at 713 nm disappeared with an increasing concentration of DDQ at room temperature, and a new peak developed in the red region at 820 nm. The spectral changes became saturated when $[\text{DDQ}]:[\mathbf{1}] = 1:1$. Further addition of DDQ did not cause any spectroscopic change. In addition, many isosbestic points were detected throughout the whole spectral region during this process, which indicate that these changes are

occurring between two distinct systems. We were able to detect the $[M^+ - H]$ peak (that is m/z 1200) in the mass spectrum of the solution containing an equimolar amount of **1** and DDQ. To further confirm that the above spectroscopic change is the result of the expansion of the π system (namely removal of H^- from the CHT moiety), the following experiments were carried out: a) EPR measurements on the solution containing an equimolar amount of **1** and DDQ: DDQ has a highly positive reduction potential (0.51 V^[13] versus Fc^+/Fc). Accordingly, an electron transfer from **1** to DDQ may occur to produce an electron-oxidized, EPR-detectable species. This possibility appears to be ruled out since the solution was EPR-silent.^[14] b) Variation of the quinone molecules: DDQ has cyano groups which can coordinate to the magnesium ions of **1**. In addition, since it is a flat, electron-deficient molecule, it may form a charge-transfer complex with **1** through $\pi-\pi$ interactions. In order to rule out these as possible causes of the spectroscopic changes seen in Figure 1, quinones with different structures and reduction potentials were tried instead of DDQ. These were, in order of decreasing oxidation ability: tetrachloro-1,2-benzoquinone (*o*-chloranil, reduction potential = 0.38 V^[13] versus Fc^+/Fc), tetrachloro-1,4-benzoquinone (*p*-chloranil, 0.22 V^[13]), and 1,4-benzoquinone (−0.05 V^[13]). *o*-Chloranil gave similar spectroscopic changes at room temperature as observed when DDQ was used (Figure 1), while a similar change was only observed for *p*-chloranil when the solution was heated or left for a long period (about 12 hours). The use of 1,4-benzoquinone, which has the weakest oxidation strength, did not yield any spectroscopic changes even after lengthy heating. Thus, these experiments using several types of quinone indicate that the changes in Figure 1 are not caused by coordination of the DDQ molecule to the Mg ion in **1** nor by the quinone structure, but are a result of the hydrogen-extraction power. c) Spectroscopic change on addition of DDQ to the metallotetraazaporphyrin (MtTAP): In order to support the conclusion that the spectroscopic changes depicted in Figure 1 are associated with the CHT moiety, a comparative experiment was performed in which DDQ was added to a solution of $[Mg\{(tBu)_4TAP\}]$ in chloroform. Although TAP is a parent molecule of **1**, the addition of DDQ ([DDQ]:[**1**] = 1:1) did not produce any spectroscopic changes, which implies that the changes shown in Figure 1 on addition of DDQ are associated with the CHT moiety of **1**. d) Comparison of compounds **1** and **2** on addition of DDQ: A similar spectroscopic change occurred very slowly (by about two orders of magnitude) when DDQ was added to **2**. This more-difficult dehydrogenation correlates with the structural change from **3** to **4**,^[3c] that is, from a CHT structure having two hydrogen atoms to one with one hydrogen atom and one phenyl group at the seventh position. It is known that dehydrogenation of an alkane to an alkene becomes more difficult when bulky substituents are linked to the same carbon atom as that of the leaving hydrogen atom.^[3c, 15] Therefore, this experiment further supports the suggestion that the dehydrogenation in **1** occurs at the seventh position of the CHT moiety. e) Determination of the MCD spectra on addition of DDQ: After the addition of DDQ ([DDQ]:[**1**] = 1:1), the MCD spectra changed as shown by the dashed line in

Figure 1, with peaks appearing roughly at the positions of the absorption peaks (Faraday *B* terms). This observation indicates that the symmetry of the π -conjugation system of **1** is lowered from D_{4h} , thus agreeing with a chromophore with C_{2v} symmetry when one CHT ring is oxidized.

The above data indicate that one CHT ring in **1** is aromatized by the action of DDQ (dehydrogenation), which is in agreement with a previous report that DDQ eliminates H^- ions from cycloheptatrienes.^[3a] The reverse spectroscopic change was observed repeatedly when $LiAlH_4$, a hydrogenation reagent, was added, which is also in accord with the previous report that a tropylium cation accepts H^- ions to return to cycloheptatriene.^[3b] Thus, we have succeeded for the first time in reversibly and repeatedly changing the size and symmetry of the π system of Pc derivatives by a new concept using a dehydrogenation/hydrogenation process.

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A Dense and Efficient Clathrate Hydrate Structure with Unusual Cages**

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Clathrate hydrates, hydrogen-bonded networks of water molecules stabilized by the presence of guest molecules, are found in both natural^[1] and industrial settings^[2] and hence have considerable potential to affect human welfare.^[3] As well, they are seen as ideal models for the hydration of hydrophobic bioorganic materials.^[4] The three known hydrate structural families,^[5,6] structure (str.) I, II, and H, have the pentagonal dodecahedron (5^{12} cage) as a common feature. In fact, str. II and str. H are based on the stacking of layers of 5^{12} cages so that other polytypes are likely to exist as well.^[7] Herein we report a new, highly complex hydrate structure that does not have 5^{12} polyhedra and contains two unusual cages, one of which has not been reported before. This new structure is denser than the other hydrate structures because of the low number of empty small cavities, and is likely to be a preferred structure for guests of intermediate dimensions at ambient or somewhat elevated pressures.

Dimethyl ether (DME) is one of a few guests^[8,9] that forms two distinct hydrates.^[10] A phase diagram (not illustrated) shows a hydrate of composition $\text{DME} \cdot 17\text{H}_2\text{O}$ melting incongruently at -20°C (this hydrate was shown to be a str. II hydrate) and a lower hydrate of composition $\text{DME} \cdot 7\text{H}_2\text{O}$ melting incongruently at -28°C . Evidence from dielectric and NMR spectroscopic measurements^[11] suggested a highly anisotropic environment for the DME guest in the lower hydrate and this led to the supposition that the structure might be the same as that of the tetragonal bromine hydrate.^[12] Below, we present the actual structure of the DME hydrate, which although it does have a number of cages in common with bromine hydrate, is unique and has several unusual cages.

The structure^[13] of this hydrate is trigonal, space group $P321$, $a = 34.995$, $c = 12.368 \text{ \AA}$, and can be described as $12\text{P} \cdot 12\text{T} \cdot 24\text{T}' \cdot 12\text{U} \cdot 348\text{H}_2\text{O}$, where P is the $5^{12}6^3$ cage, also

known from bromine hydrate, T is the well-known $5^{12}6^2$ cage from str. I hydrate, T' is a previously unobserved cage designated as $4^15^{10}6^3$, and U is a small cage designated as $4^25^86^1$. The latter has been observed in the structure of one of the hydrates of propylamine.^[5] The DME molecules reside in all three types of large cages in the structure, giving an overall composition of $\text{DME} \cdot 7.25\text{H}_2\text{O}$. There is no interaction between guest and host other than the van der Waals' contacts usual for the true clathrate hydrates. The T' cage has not been recorded in either the hydrate^[5] or clathrasil^[14] literature, and thus this structure represents a new way^[5] of filling three-dimensional space by stacking a novel combination of cages. The new hydrate falls outside the structural numbering scheme proposed by Jeffrey,^[5] and we propose that the structure be known as structure T (from trigonal) hydrate.

The overall structure is shown in Figure 1, the constituent cages in Figure 2. The packing motifs resulting in the trigonal structure derive from several units with three-fold symmetry: clusters of three cages, where pairs of cages share a face so

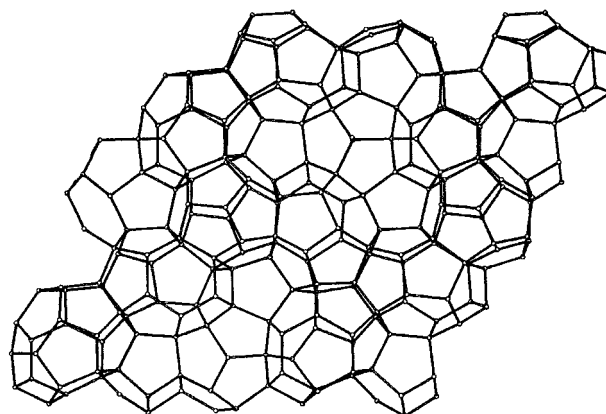


Figure 1. General view of the str. T hydrate as determined by single crystal X-ray diffraction.

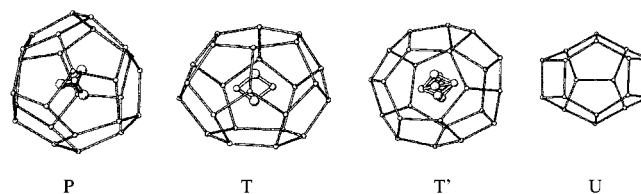


Figure 2. View of the cages in the str. T hydrate; the large cages show the location of the disordered DME guest.

that the three have one common edge, or clusters of four where three cages are attached to a central cage by sharing a face. The guest positions in the three cages are disordered but quite well defined: a single position can be seen for each DME methyl group, whereas multiple positions are observed for the oxygen centers. As in previous work on hydrates,^[15] ^2H NMR spectroscopy has shown the disorder to be dynamic. For samples corresponding to the str. II composition, the line-shape in the ^2H NMR spectrum is isotropic, as expected for DME undergoing rapid reorientation in the large pseudo-spherical $5^{12}6^4$ cage. Str. T shows an anisotropic lineshape

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(Figure 3a) characteristic of an axially symmetric electric-field gradient at the quadrupolar nucleus, which indicates the presence of DME in nonspherical cages. The doublet splitting

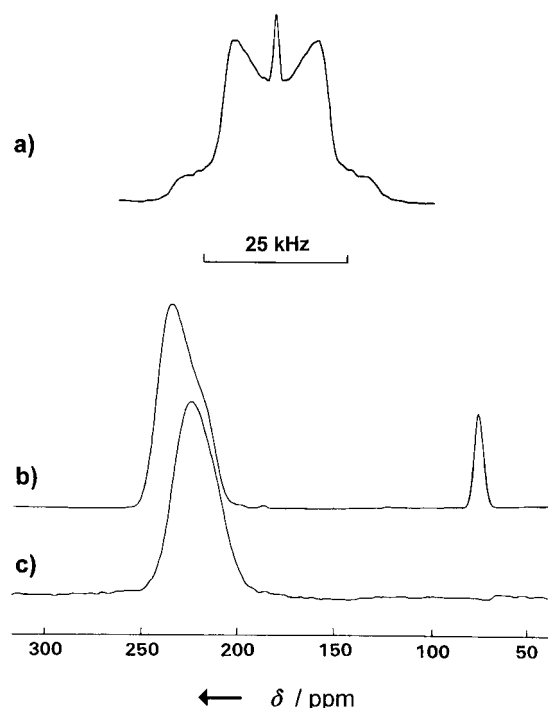


Figure 3. NMR spectra of DME hydrates: a) ^2H NMR spectrum at 152 K of $\text{CD}_3\text{OCH}_3/\text{H}_2\text{O}$, str. T; b) ^{129}Xe NMR spectrum at 77 K, DME:Xe: H_2O ratio 1:2:20, str. II; c) ^{129}Xe NMR spectrum at 77 K, DME:Xe: H_2O ratio 10:1:8.6, str. T.

of 17.5 kHz at 152 K is significantly less than the 38.5 kHz typical for a methyl group reorienting rapidly about its threefold axis. The reduction factor of 0.455 is consistent with further rapid reorientation of the whole molecule about an axis parallel to the C–C direction, as suggested by the disorder in the guest positions, with additional librational dynamics accounting for a further slight reduction.

The ^{129}Xe NMR spectra of mixed Xe/DME hydrates also provide indications of a structure different from those already known. At high water:guest ratios a spectrum (Figure 3b) is observed which is characteristic of str. II hydrates^[16] with a small amount of Xe in the large cages giving the resonance at $\delta = 76$, and a strong signal at $\delta = 232$ for Xe in the small cages. When DME is in excess, however, a quite different spectrum with a signal, arising from a single small cage with a very slight asymmetry, is observed at $\delta = 222$, Figure 3c. This shift is quite different from that of Xe in small cages in other hydrate structures: it falls between the shifts for the 5^{12} cages in str. II and str. H at $\delta = 232$ and the $4^35^66^3$ cage of str. H at $\delta = 212.4$

(Xe in the 5^{12} cages of str. I and the bromine hydrate has larger shifts than str. II). Thus this new signal may be assigned to str. T.

The significance of the structure becomes apparent upon examining some of its properties. One striking feature is the relative number of small cages, the ratio of small to large cages is significantly smaller than for the other known structures. This means that if small-cage guests are absent, this structure is the most efficient in terms of minimizing vacant void space, as also reflected in the density of the hydrate structures (Table 1). The low hydrate is denser than the str. II hydrate, and also the hypothetical str. I hydrate by $\sim 2\%$, with the implication that this structure may be favored over str. I or II for guests of intermediate size at somewhat elevated pressure. It is pertinent to refer to work by Dyadin et al.^[9] on the effect of pressure on the phase structure of a number of hydrates that form str. II at ambient pressure. At a few kbar pressure there is the appearance of a new phase with a hydration number of ~ 7 water molecules per guest. This was interpreted as a transition of str. II to str. I plus ice, as str. II is inherently unstable at high pressure because of the large number of empty small cages. Based on density alone, str. T should be more stable than str. I. However, there are other factors, such as hydrogen-bonded water molecules arranged in squares, that must be energetically unfavorable because of ring strain. Therefore it may be postulated that some or all of the pressure-induced transitions could involve the structure reported here.

Experimental Section

Colorless single crystals ($0.4 \times 0.4 \times 0.5$ mm) of dimethyl ether (DME) hydrate were grown in a sealed tube at -40°C from an aqueous solution containing excess dimethyl ether. Crystal data were collected on a Bruker SMART CCD diffractometer, (graphite monochromator) with $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å, $2\theta_{\text{max}} = < 57.5^\circ$, ω scan mode). The structure proved to be difficult to solve^[17] as the crystal was twinned and the unit cell is large.^[18]

The NMR experiments were performed as described previously.^[15, 16]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151791. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Table 1. The distribution of large and small cages in different hydrate structures and the densities for the corresponding DME hydrates.

Hydrate	Small (S) cages ^[a]	Large (L) cages ^[a]	Ratio (S/L cages)	Density [g cm^{-3}] ^[b]
str. H	3 (5^{12}), 2 ($4^35^66^3$)	1 ($5^{12}6^8$)	5	0.834 ^[c]
str. II	16 (5^{12})	8 ($5^{12}6^4$)	2	0.938
str. I	2 (5^{12})	6 ($5^{12}6^2$)	0.33	1.054 ^[c]
str. T	12 ($4^25^86^1$)	12 ($5^{12}6^3$), 12 ($5^{12}6^2$), 24 ($4^15^{10}6^3$)	0.25	1.074

[a] number per unit cell; [b] calculated for structure with empty small cages and large cages filled with DME; [c] hypothetical structures.

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The Oxidative Power of Protonated Hydrogen Peroxide**

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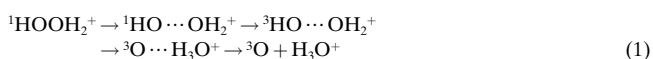
Hydrogen peroxide is an oxidant which receives much attention these days. In order to take full advantage of this

environmentally friendly chemical in a large number of practical applications—for example, for bleaching in the pulp and paper industry—more effective catalysts are required.^[1] Detailed mechanistic studies of simplified model systems are necessary to realize this development.

The compound H_2O_2 is unstable and decomposes into water and dioxygen (O_2) in both acidic and basic solution, as well as in the presence of transition metals.^[2] Good examples of transition metal activation occur with Fenton's reagent (Fe^{2+} and H_2O_2) as well as the enzymes involved in respiration and other oxidative processes.^[3–5] The fine balance between the decomposition chemistry of H_2O_2 and its action as an oxidant is quite clear, both when it is promoted by protonation or by coordination to a transition metal cation. We have recently proposed that $[\text{HOOH}]\text{H}^+$, the species most likely to be formed in acidic hydrogen peroxide solution, is a highly active oxidant in the gas phase; only 150 kJ mol^{-1} are needed to break the O–O bond.^[6]

Hydrogen peroxide demonstrates extraordinary oxidative behavior in superacidic solutions: it inserts an oxygen atom into aliphatic and aromatic C–H bonds to give aldehydes/ketones or alcohols, respectively.^[7–9] Theoretical calculations indicate that the reactive species is protonated hydrogen peroxide, and not free OH^+ .^[10] To date, no experimental evidence has been published that demonstrates the intrinsic chemical properties of HOOH_2^+ , but it is known that this species can be formed by proton transfer in the gas phase (a rough value of $675 \pm 45 \text{ kJ mol}^{-1}$ was reported for the proton affinity (PA) of H_2O_2).^[11] Herein we present the results from an experimental study of the unimolecular and bimolecular gas-phase chemistry of protonated hydrogen peroxide.

We have previously investigated the unimolecular chemistry of the isoelectronic $[\text{H}_2\text{NNH}_2]\text{H}^+$ and $[\text{HONH}_2]\text{H}^+$ systems.^[12, 13] On the basis of the behavior of these ions and from a detailed quantum chemical survey of the singlet and triplet potential energy surfaces of $(\text{H}_3, \text{O}_2)^+$ we recently proposed that protonated hydrogen peroxide in its singlet ground state will preferably lose an oxygen atom according to the spin change mechanism [Eq. (1)].^[6]



We have now conducted experiments on a grand-scale magnetic sector tandem mass spectrometer to verify this prediction. A pure beam of $[\text{HOOH}]\text{H}^+$ ions (m/z 35.01) was selected using the first mass spectrometer of the tandem combination. A small fraction of these ions, with energies close to the threshold value for reaction (the so-called metastable ions), decompose spontaneously during passage through the field-free region preceding the second mass spectrometer, and the fragment ions were registered by scanning the second electric sector. The spectrum obtained is shown in Figure 1. The spectrum contains only one significant peak, namely for H_3O^+ , which corresponds to the loss of one oxygen atom, and is in complete agreement with the theoretical predictions. The maximum amount of energy available to the HOOH_2^+ ions produced in the ion source

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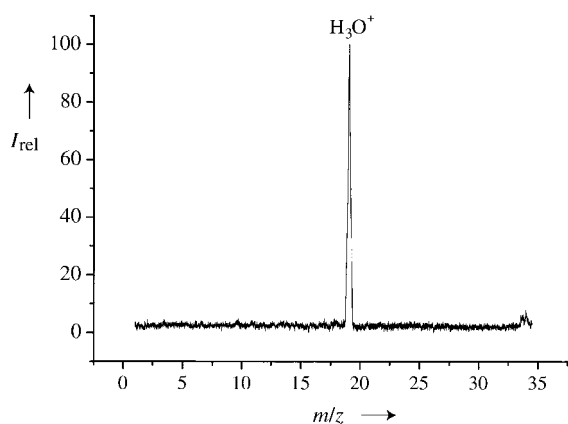


Figure 1. Metastable ion kinetic energy spectrum (see text for explanation) of protonated hydrogen peroxide (m/z 35). Reactant ions were accelerated by an electric potential difference of 6 kV. The translational energy release, which is obtained from the width of the peak at half height, is $T_{0.5} = 8 \text{ kJ mol}^{-1}$. The small peak at m/z 34 arises from collisional activation with residual gas in the analyzer tube (7×10^{-8} mbar). Separate experiments show that the peak at m/z 34 dominates the collisional activation spectrum. The observed peaks are m/z (relative intensity, collision gas He): 34 (100), 33 (8), 32 (9), 19 (27), 18 (25), 17 (10), 16 (2). In addition, there is a narrow signal for m/z 17.5, which corresponds to HOOH_2^{2+} , and is more prominent when O_2 is used as the collision gas.

under the conditions employed is around 150 kJ mol^{-1} . This value corresponds to the difference in proton affinity between methane (the ionizing agent is CH_5^+) and hydrogen peroxide (Table 1^[10, 14, 15]), and includes 20 kJ mol^{-1} as an estimated upper limit to the available thermal energy.

Table 1. Reaction data.

Compound	$PA^{[a]}$ [kJ mol ⁻¹]	ΔH° for H^- transfer ^[b] [kJ mol ⁻¹]	$E_{\text{crit}}^{[c]}$ [kJ mol ⁻¹]	$k^{[d]}$ [cm ³ molecule ⁻¹ s ⁻¹]
CH_4	544	-31	22	$< 7 \times 10^{-13}$
$\text{C}_2\text{H}_6^{[e]}$	596	-214	1	4.9×10^{-11}
C_3H_8	626	-306	-19	3.6×10^{-10}
$i\text{C}_4\text{H}_{10}$	678	-372	-21	1.3×10^{-9}
H_2O_2	675	-	-	-

[a] Proton affinity (data from ref. [14]). [b] Standard enthalpy change for hydride transfer [Eq. (2); data from ref. [15]]. [c] Calculated critical energy (barrier height; data from ref. [10]). [d] Rate coefficient [Eq. (2)] for this work, estimated standard deviations: 20% (absolute). [e] Deuterium-labeling experiments showed that a second reaction channel is operative giving $\text{H}_3\text{O}^+ + \text{C}_2\text{H}_4 + \text{H}_2\text{O}$, with a rate coefficient of less than 3% relative to the dominating C_2H_5^+ -producing reaction.

The O–O bond dissociation energy of neutral HOOH is 214 kJ mol^{-1} .^[15] The present experiment in conjunction with the theoretical model suggests that the effective barrier for bond dissociation of HOOH_2^+ is $\leq 150 \text{ kJ mol}^{-1}$, which shows that protonation activates the hydrogen peroxide molecule considerably. It is noticeable that the neutral product of Equation (1) is oxygen in its triplet electronic state. This atom, and the corresponding isoelectronic triplet NH and CH_2 species, are well known to insert into C–H bonds.

Bimolecular reactions between HOOH_2^+ and alkanes were investigated using a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer using conditions described in detail elsewhere.^[16] Briefly, HOOH_2^+ ions were

produced in an external ion source, transferred to the cell of the instrument, isolated, thermalized, reacted with the alkane, and the reaction rates were determined by recording FT-ICR mass spectra at different reaction times.

The key reaction data are given in Table 1, and a typical mass spectrum is shown in Figure 2. With the exception of

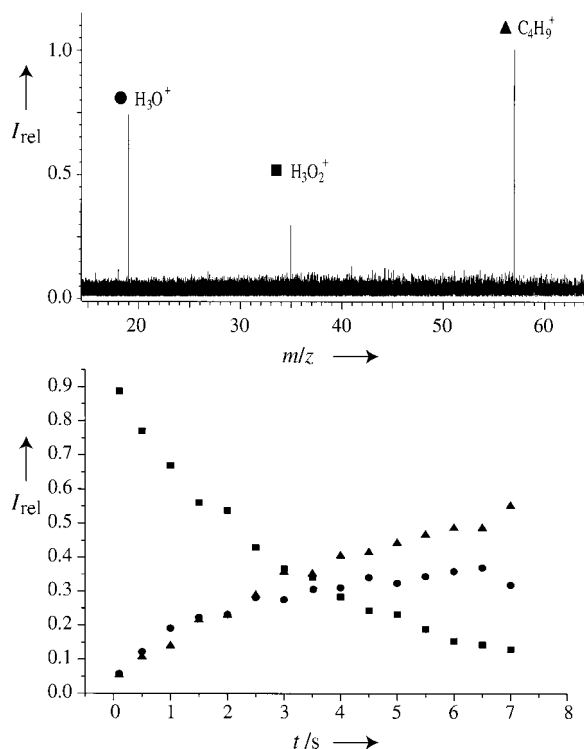


Figure 2. Top: Mass spectrum obtained after 5.5 s reaction between HOOH_2^+ and isobutane at 5×10^{-9} mbar. The signal for H_3O^+ at m/z 19 arises from fast proton transfer with background water. Bottom: The temporal dependence of the reactant ion signal and the two product ions.

methane, all the alkanes investigated underwent reaction according to Equation (2).



There are several noticeable features of these results: Firstly, *n*-butane and isobutane are known to be oxidized to the corresponding alcohols by hydrogen peroxide in superacid,^[8] while in the gas phase even ethane and propane react. Secondly, the reaction product collected in superacid is the alcohol, which means that an O atom has been inserted into the C–H bond. In the gas phase the product is the corresponding alkyl cation, which means that a hydride ion has been abstracted from the alkane. The alternative, namely proton transfer to the alkane followed by dihydrogen loss, is unlikely since Table 1 shows that proton transfer is endothermic, except for isobutane.

Bach and Su have presented a quantum chemical model to account for the observations from the experiments performed in superacid solution.^[10] Interestingly, the properties of the transition state they identified imply that the first stage of the

reaction [Eq. (3)] is hydride abstraction from the alkane by HOOH_2^+ .



The O–O bond breaks simultaneously, and a C–O bond is formed subsequently. Bach and Su took it for granted in their model that the final reaction product is the alcohol plus water, as observed in solution. This may at first glance seem to be inconsistent with the formation of R^+ in the gas phase, but Bach and Su did not take the full gas-phase reaction dynamics into account.

To deal with this problem, we found it pertinent to perform ab initio direct dynamics calculations^[17–20] on the reaction of ethane. Our approach was the following: First, we duplicated the calculations of Bach and Su. As already indicated, the reaction coordinate obtained for the transition structure (TS) corresponds to hydride transfer from ethane to the oxygen atom of the OH part of the molecule in concert with dissociation of the O–O bond (first frame of Figure 3). Secondly, we calculated a series of ab initio direct dynamics trajectories to get an insight into how the liberated energy influences the course of the reaction. In this method Newton's equations are integrated step-by-step along the classical trajectory of a reaction. A total of 25 different trajectories, starting at the TS, were computed using randomly chosen initial conditions. The HF/6-31G(d) wave function was used.^[21] One typical trajectory is presented in Figure 3. The calculations reveal that the water molecule derived from the OH_2 group of the original HOOH_2^+ molecule is already

pushed away from the rest of the product system after passage of the TS. For a short period the remaining $\text{C}_2\text{H}_5\text{OH}_2^+$ unit may be regarded as one entity (a short-lived complex between C_2H_5^+ and H_2O). The large amount of energy deposited in the complex leads in 80 % of the trajectories to dissociation into C_2H_5^+ and H_2O in less than 60 fs after generation of the TS. According to the calculations, all the complexes have dissociated within 400 fs, with the exception of one which dissociates at 900 fs. This behavior of the free gas-phase reaction differs from that in the condensed phase where surrounding molecules confine the products and also act as energy sinks, thereby giving the alcohol as the ultimate product.

When we treated fully deuterated ethane (C_2D_6) with HOOH_2^+ we observed that greater than 97 % of the product mixture is C_2D_5^+ (including secondary products) and less than 3 % HD_2O^+ . The latter product ion is the result of proton transfer from C_2D_5^+ to H_2O during the short lifetime of the initially formed $\text{C}_2\text{D}_5^+ \cdots \text{H}_2\text{O}$ complex. This result is interesting, since it is well known that long-lived $\text{C}_2\text{H}_5^+ \cdots \text{OH}_2$ ions have a strong preference for giving the thermodynamically more-stable product H_3O^+ .^[22–25] In other words, our deuterium-label experiment verifies the outcome of the trajectory calculations, and shows there is an essentially nonstatistical (nonergodic) behavior in the system—at most the complex exists for a couple of vibrational periods. None of the 25 trajectories shows proton transfer to water.

In conclusion, we have found that the oxidation of alkanes by protonated hydrogen peroxide does not occur by insertion of O into C–H, but by a multistep sequence in which a simple hydride transfer is the essential step. There is an ongoing

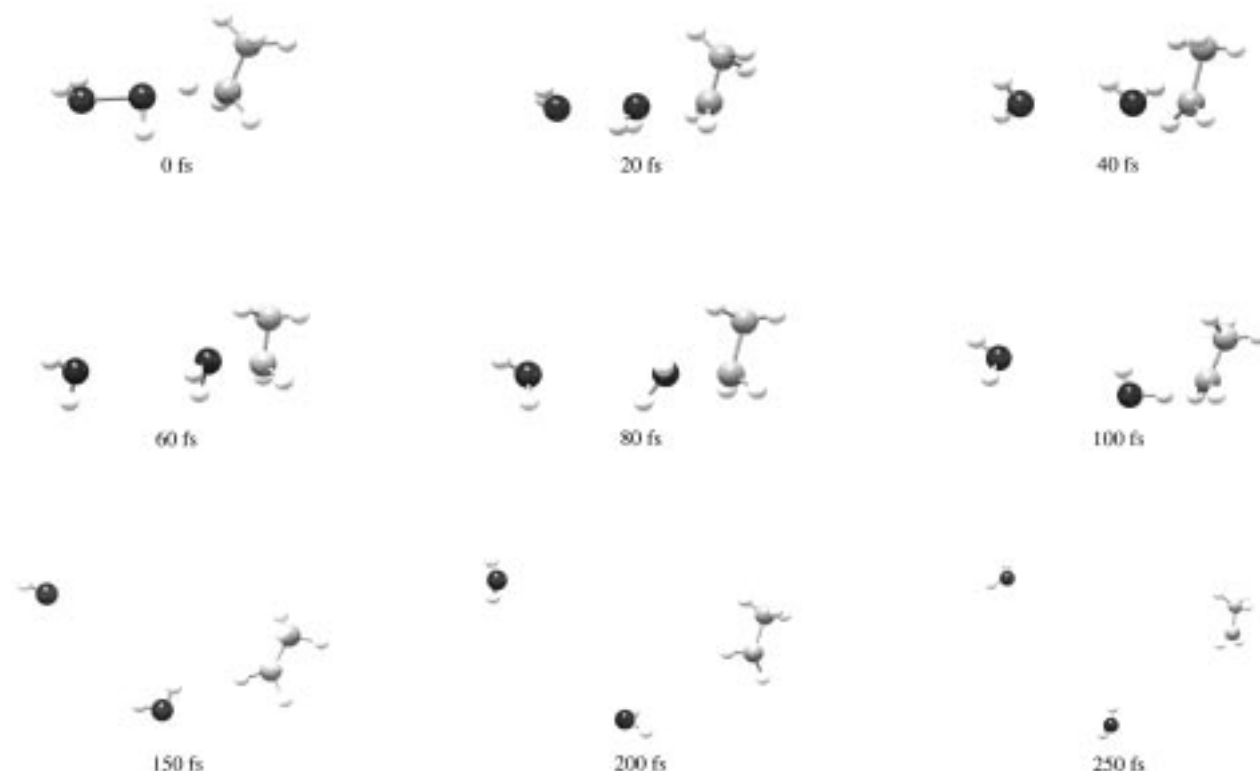
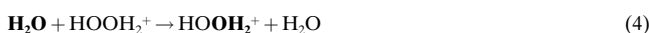


Figure 3. Images of a direct dynamics reaction trajectory (HF/6-31G(d)) for $\text{HOOH}_2^+ + \text{C}_2\text{H}_6 \rightarrow \text{C}_2\text{H}_5^+ + 2\text{H}_2\text{O}$. Images are shown from $t=0$ (transition state) up to 250 fs. The colour codings are H: white, C: light gray, and O: dark gray.

discussion about the mechanism of the activation of iron cations in Fenton chemistry and in related enzymes. We think that the present findings point towards the $\text{Fe}(\text{OH})\text{OH}^+$ structural motif as the active species in these systems.^[3–5]

The above discussion showed that the first stage of Equation (2) corresponds to a concerted hydride abstraction/water loss mechanism. It may be regarded as an $\text{S}_{\text{N}}2$ reaction type and it provides a hint for regarding protonated hydrogen peroxide as a charge-transfer complex formed between OH^+ and H_2O . The analogy to protonated laughing gas (N_2OH^+)^[26] and protonated ozone (O_3H^+)^[27] on one hand, and protonated methanol (CH_3OH_2^+)^[28] on the other is evident. From this point of view it became pertinent to see how easily HOOH_2^+ reacts in more typical $\text{S}_{\text{N}}2$ reactions. The natural prototype would be the identity substitution reaction [Eq. (4)].



In order to check this possibility we performed MP2/6-31G(d,p) ab initio quantum-chemical calculations.^[21] The calculations (Figure 4) revealed that the reaction should have

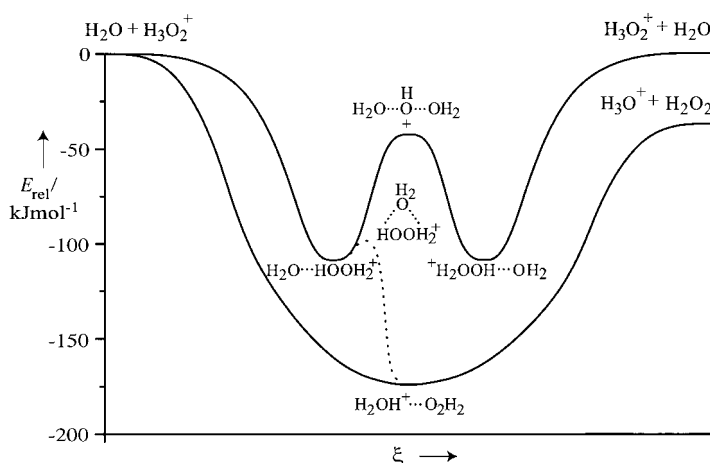
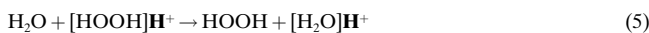


Figure 4. Potential energy diagram for the hypothetical reaction between H_2O and HOOH_2^+ obtained from MP2/6-31G(d,p) calculations. Relative energies are in kJ mol^{-1} and include scaled zero-point vibrational energy corrections.

a potential-energy barrier far below that of the reactants. We also considered an alternative reaction route, the proton-transfer reaction [Eq. (5)].



These theoretical predictions encouraged us to perform an experimental investigation of the outcome of reactions between ^{18}O -labeled water and HOOH_2^+ by using FT-ICR mass spectrometry. Despite the potentially promising $\text{S}_{\text{N}}2$ mechanism, it was not possible to observe any product ion incorporating ^{18}O . Instead proton transfer [Eq. (5)] is dominating as a consequence of its highly favorable entropy factor relative to the tight transition state required for a $\text{S}_{\text{N}}2$

mechanism. Proton transfer occurs efficiently, close to the theoretical collision rate limit. Our results do not rule out the occurrence of Equation (4). If it occurs, the product ion is consumed at an even faster rate through Equation (5). It is possible that HOOH_2^+ will remain unobserved under the conditions of the experiment, even when the rate of Equation (4) is as high as 15 % of that of Equation (5). In any case, it is highly interesting and relevant that our theoretical model indicates that $\text{S}_{\text{N}}2$ reactions are feasible for molecules of this type.

Experimental Section

Protonated hydrogen peroxide was produced in a custom-made chemical ionization ion source in a four-sector (*EBEB* geometry) mass spectrometer (JMS-HX/HX110 A, JEOL Ltd.). Methane was used as the reagent gas. The source of hydrogen peroxide was a 35 wt % H_2O_2 /urea formulation (Acros Chemicals) which permits the use of a direct inlet probe. The ions were accelerated (accelerating voltage 6 kV) and a pure beam of ions with m/z 35.01 at a mass resolution of 2000 was isolated with the first two sectors. A small fraction of the HOOH_2^+ ions selected in this manner—having an energy sufficiently close to the threshold—decompose spontaneously in the field-free region preceding the second *E*-sector. To reach this stage these metastable ions have survived approximately 25 μs after they were formed in the ion source. The product ions formed by this spontaneous unimolecular decomposition were analyzed with the second *E*-sector, and registered by a detector mounted in the field region following that sector.

HOOH_2^+ ions were produced in an external ion source using chemical ionization with methane. The ions formed in the source were transferred to the cell of a Bruker 4.7 T FT-ICR instrument. All ions—except those having m/z 35—were then ejected from the cell. The remaining population of HOOH_2^+ ions (m/z 35.0133) were cooled to ambient temperature upon introducing a short pulse of Ar. The HOOH_2^+ ions were then isolated by single frequency shots that removed ions formed during the cooling period of 4 s. After this process the ions were treated with the respective alkane ($p = 2 \times 10^{-9} - 1.5 \times 10^{-7}$ mbar) for a variable time before a mass spectrum was recorded. In this way the reaction could be followed as a function of time, and rate coefficients obtained by fitting kinetic models to the reactant decay and formation of the product ions.

The direct ab initio approach to trajectory calculations utilizes the first and second derivatives (with respect to atomic displacements) of a general wave function within the framework of the Born–Oppenheimer approximation. Each trajectory $\mathbf{q}(t) = [\mathbf{q}(t_1), \mathbf{q}(t_2), \dots]$ is calculated by a stepwise procedure which requires recalculation of the wavefunction at points $\mathbf{q}_i$ in time steps typically varying between 0.2 and 0.5 fs. This approach is of course very demanding in computer time; one single trajectory requires the calculation of the wave function for a large number of points. For this reason there are limits to the dimension of the wave function which can be used. In this case we were able to calculate 25 different trajectories using HF/6-31G(d), which we think is a reasonable compromise between computer time and chemical accuracy, and is a representative ensemble of the initial conditions taken from a thermal distribution at 298 K.

All quantum chemical calculations were performed using Gaussian 98.^[21] A more comprehensive documentation of the results of the trajectory calculations, including movies, are exclusively available at: <http://www.uio.no/~vebjornb/supmat.html>.

Received: November 24, 2000 [Z16172]

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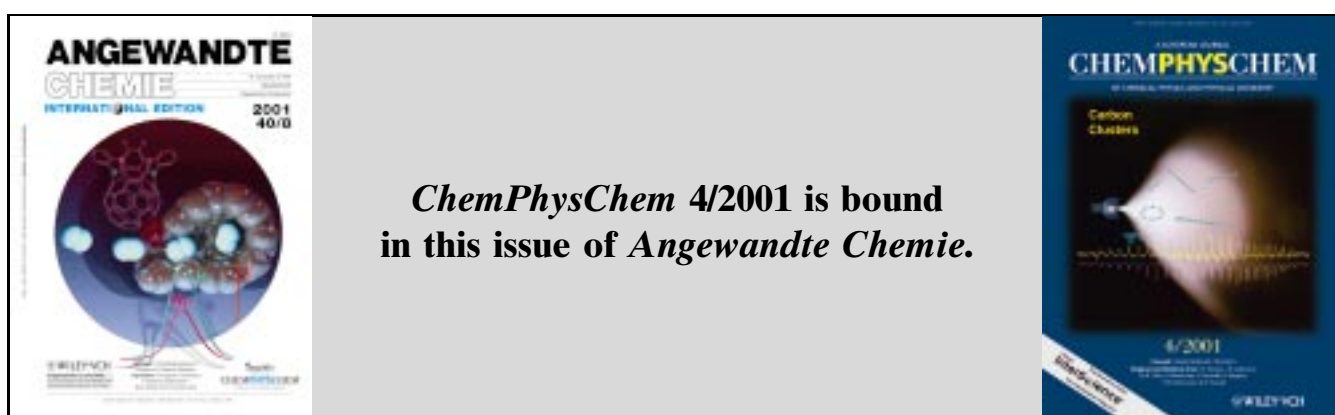
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Cover Picture

**Yves Rubin, Thibaut Jarrosson, Guan-Wu Wang,
Michael D. Bartberger, K. N. Houk, Georg Schick,
Martin Saunders, and R. James Cross**

The cover picture shows the process of hydrogen and helium insertion/expulsion which has been achieved for the first time with an open fullerene derivative (outlined in the background). The experimental activation barrier for helium decomplexation could be obtained and fully agrees with the calculated value (density functional theory). The barrier for H₂ complexation/decomplexation is interestingly almost double that of helium, as illustrated by the energy diagram shown in the foreground. This difference arises from the larger, elongated surface of H₂ undergoing greater van der Waals interaction at the transition state relative to that of helium, even though both atoms have the same radii. More about this process can be found in the article by Rubin, Houk, Saunders, Cross et al. on p. 1543 ff.





COVER PICTURE

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Better prediction of the rate constants of radical addition to alkenes is possible by using new, simpler, physically more sensible, but nonlinear, equations. Starting from representative, experimentally and theoretically obtained data sets and clear state-correlation diagrams for radical addition reactions, the controlling factors have been qualified in a new and rigorous manner. The results of this method lead to a partial revision of the existing qualitative rules and show more clearly how the reaction enthalpy, charge transfer, and the steric effects of substituent groups affect the activation energy barrier.

Angew. Chem. **2001**, *113*, 1380–1414

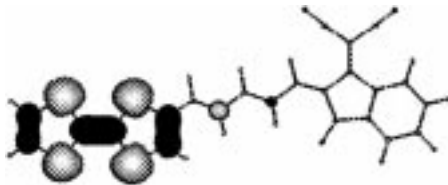
H. Fischer,* L. Radom 1340–1371

Factors Controlling the Addition of Carbon-Centered Radicals to Alkenes—An Experimental and Theoretical Perspective

Keywords: ab initio calculations • additions • kinetics • radical reactions

Modified TTF derivatives display not only electrical conductivity but also nonconventional properties, for example, the TTF derivative shown displays nonlinear optical properties. Recent years have witnessed the development of new possibilities for these compounds.

Angew. Chem. **2001**, *113*, 1416–1455



J. L. Segura, N. Martín* 1372–1409

New Concepts in Tetrathiafulvalene Chemistry

Keywords: donor–acceptor systems • electron transfer • materials science • supramolecular chemistry • tetrathiafulvalene

VIPs

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

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

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



Cyclic Dimers of Metalloporphyrins as Tunable Hosts for Fullerenes: A Remarkable Effect of Rhodium(III)

J.-Y. Zheng, K. Tashiro, Y. Hirabayashi, K. Kinbara, K. Saigo,* T. Aida,* S. Sakamoto, K. Yamaguchi

Direct Observation of Surface-Controlled Self-Assembly of Coordination Cages by using Atomic Force Microscopy as a Molecular Ruler

S. A. Levi, P. Guatterì, F. C. J. M. van Veggel, G. J. Vancso, E. Dalcanele,* D. N. Reinhoudt*

Fluorinated Bis(enyl) Ligands through Metal-Induced Dimerization of Fluorinated Allenes

D. Lentz,* S. Willemsen

Probing Guest Geometry and Dynamics through Host-Guest Interactions

T. Kusukawa, M. Yoshizawa, M. Fujita*

The Natural $^{12}\text{C}/^{13}\text{C}$ Ratio Allows Classification of Terpenoid Biosynthesis According to the Methylerythritolphosphate or the Mevalonate Pathway: Dynamic Allocation of Resources in Induced Plants

A. Jux, G. Gleixner, W. Boland*

Georg Wittig, what is known today about his work? Certainly the Wittig reaction and dehydrobenzene are mentioned when younger chemists refer to Wittig. However, such pioneering discoveries as the halogen/metal exchange reaction and the directed *ortho*-metalation, as well as the key experiments leading to azaenolates or to complex bases, are associated with Wittig only by some old-timers. This is the reason to refer anew to the significance of Wittig's contributions to the chemistry of the 21st century.

Angew. Chem. **2001**, *113*, 1457–1462

R. W. Hoffmann* 1411–1416

Wittig and His Accomplishments:
Still Relevant Beyond His 100th Birthday

Keywords: arenes • biography •
metalation • Wittig reactions • ylides

HIGHLIGHTS

Sulfate-reducing bacteria oxidize phosphite (P^{III}) to phosphate (P^V). This was established for bacteria isolated from marine sediments. The reaction might form part of a hypothetical phosphate cycle. It is possible that the free energy of oxidation is conserved as energy-rich acylphosphate through a primeval stepwise substrate phosphorylation. In anoxic marine sediments of the Pacific near the Oregon coast a syntrophic community of sulfate reducers and methanogens has been identified, which anaerobically oxidizes methane to CO_2 under the formation of sulfide.

Angew. Chem. **2001**, *113*, 1463–1464

W. Buckel* 1417–1418

Inorganic Chemistry in Marine Sediments

Keywords: archaea • bioinorganic
chemistry • phosphite oxidation •
redox chemistry • sulfate reduction

This chapter is not yet closed! The synthesis of a vibrationally stable, neutral, and chemically bound ground-state argon compound, along with recent breakthroughs in xenon chemistry, heralds a renaissance in noble gas chemistry.

Angew. Chem. **2001**, *113*, 1465–1467

K. O. Christe* 1419–1421

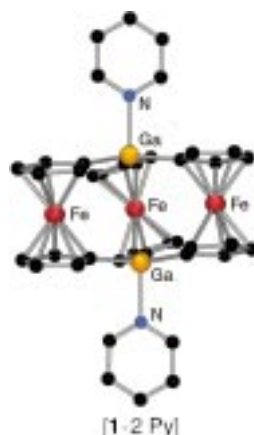
A Renaissance in Noble Gas Chemistry

Keywords: argon • fluorine •
hypervalent compounds • noble gases •
xenon

COMMUNICATIONS

A molecular carousel, that is the appearance of the structure of the title compound [**1**·2py] (see picture), the first complex of a new structure type prepared by a highly selective condensation reaction from the equally new complex $[Fe(C_5H_4-GaMe_2)_2]$. The first gallium bridged [*m,m*]ferrocenophane $[Fe(C_5H_4)_2][GaMe(C_5H_5N)]_2$ is formed as an intermediate; this compound can also be prepared in a planned synthesis and can be converted into [**1**·2py] by warming. The complex [**1**·2py] as well as [**1**·2Et₂O] and [**1**·2DMSO], which were formed by donor exchange, offers various interesting properties, for example, [**1**·2DMSO] can be reversibly oxidized to the mono-, di-, and trication.

Angew. Chem. **2001**, *113*, 1470–1473



P. Jutzi,* N. Lenze, B. Neumann,
H.-G. Stammer 1424–1427

$[Fe(C_5H_4)_2][Ga(C_5H_5N)]_2$:
A Trinuclear Gallium-Bridged
Ferrocenophane with a Carousel
Structure

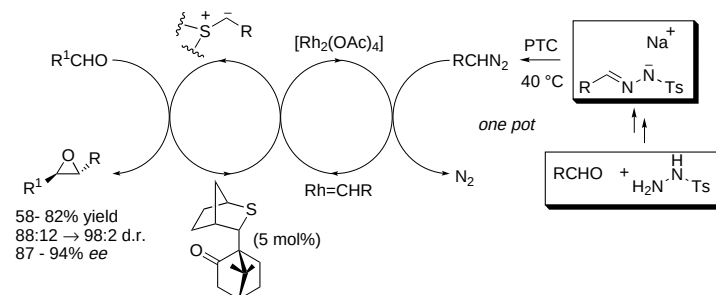
Keywords: carousel structure •
electrochemistry • ferrocenophane •
gallium • mixed-valent compounds

Encouraged by the international race to sequence the human genome, new approaches to decode single copies of DNA have emerged. These could potentially speed up the sequencing process—if all bases in DNA could be tagged with distinct fluorescent labels. Complete labeling of the pyrimidine bases of one strand, as described here, might be a first solution to this problem.

Angew. Chem. **2001**, *113*, 1473–1476



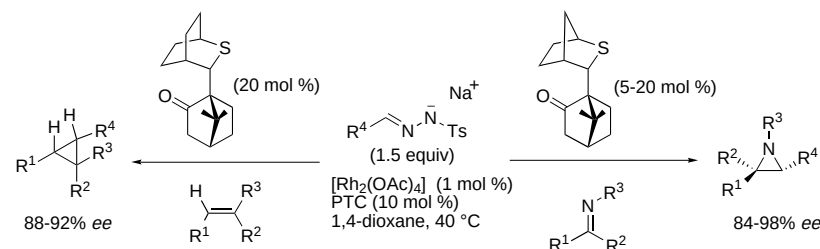
A practical, general, and convergent route to epoxides with control of the relative and absolute stereochemistry has been achieved by generating the reactive intermediate (the diazo compound) in situ from tosylhydrazone salts (see scheme, PTC = phase-transfer catalyst, Ts = toluene-4-sulfonyl). High yields (58–82 %), high d.r. (88:12–98:2), and high *ee* values (87–94 %) have been obtained using a new class of stable chiral sulfides at low catalyst loading (5 mol %) and $[\text{Rh}_2(\text{OAc})_4]$ (0.5 mol %).



Angew. Chem. **2001**, *113*, 1479–1482



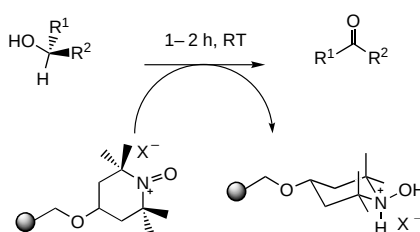
Imines and alkenes can be converted into the corresponding aziridines and cyclopropanes (see scheme, PTC = phase-transfer catalyst, Ts = toluene-4-sulfonyl) in good yield with moderate to high d.r. and high *ee* values using tosylhydrazone salts with catalytic quantities of chiral sulfide (5–20 mol %) and metal catalyst (1 mol %). The process is particularly suited to the synthesis of conformationally locked cyclopropyl amino acids, which can now be prepared in only three steps from commercially available material in 100 % *ee*.



Angew. Chem. **2001**, *113*, 1482–1485

Polymer-supported oxidation of alcohols was conducted very efficiently by employing oxoammonium salts, the reactive intermediates in TEMPO oxidations (TEMPO = 2,2,6,6-tetramethylpiperidinoxyl). These highly reactive salts (see scheme; X = Br, Cl) could be prepared and isolated on the polymeric support, and were used for the conversion of single compounds as well as of complex mixtures of alcohols.

Angew. Chem. **2001**, *113*, 1489–1492



S. Brakmann,*

S. Löbermann 1427–1429

High-Density Labeling of DNA:
Preparation and Characterization of the
Target Material for Single-Molecule
Sequencing

Keywords: fluorescence • nucleotides •
polymerases • sequence analysis

V. K. Aggarwal,* E. Alonso, G. Hynd,
K. M. Lydon, M. J. Palmer, M. Porcelloni,
J. R. Studley 1430–1433

**Catalytic Asymmetric Synthesis of
Epoxides from Aldehydes Using Sulfur
Ylides with In Situ Generation of
Diazocompounds**

Keywords: asymmetric catalysis •
diazo compounds • epoxidation • ylides

V. K. Aggarwal,* E. Alonso, G. Fang,
M. Ferrara, G. Hynd,
M. Porcelloni 1433–1436

**Application of Chiral Sulfides to
Catalytic Asymmetric Aziridination and
Cyclopropanation with In Situ
Generation of the Diazo Compound**

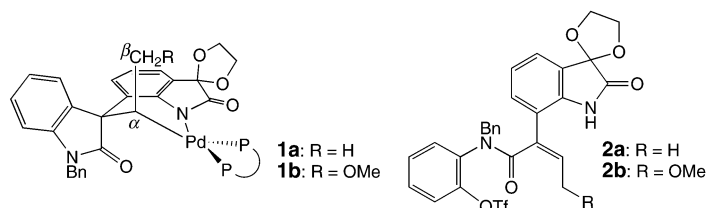
Keywords: asymmetric catalysis •
aziridination • cyclopropanation •
diazo compounds • ylides

S. Weik, G. Nicholson, G. Jung,
J. Rademann* 1436–1439

**Oxoammonium Resins as Metal-Free,
Highly Reactive, Versatile Polymeric
Oxidation Reagents**

Keywords: aldehydes •
combinatorial chemistry • ketones •
oxidations • solid-phase synthesis

 **In spite of containing three conformationally accessible β -H atoms**, palladacycle **1a** is an isolable intermediate in the asymmetric Heck cyclization of **2a**. Although **1a** is stable in the presence of the hydrotriflate salt of 1,2,2,6,6-pentamethylpiperidine, it is converted into the oxindole Heck product when exposed to the more acidic hydrotriflate salt of 2,6-di-*tert*-butylpyridine. Heck cyclization of **2b** is also believed to proceed by way of a palladacyclic intermediate **1b**, which in this case undergoes β -methoxide elimination. Bn = benzyl.



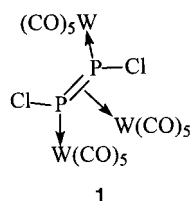
Angew. Chem. **2001**, *113*, 1485–1489

M. Oestreich, P. R. Dennison,
J. J. Kodanko,
L. E. Overman* 1439–1442

Thwarting β -Hydride Elimination:
Capture of the Alkylpalladium
Intermediate of an Asymmetric
Intramolecular Heck Reaction

Keywords: alkaloids •
asymmetric catalysis • cyclization •
Heck reactions • palladium

In contrast to the *cis* configuration of N_2F_2 , the analogous phosphorus subhalogenides, P_2X_2 (X = F, Cl) adopt a *trans* configuration according to density functional theory calculations. Now for the first time dichlorodiphosphene has been stabilized in the coordination sphere of transition metals in the form of complex **1**.



U. Vogel, G. Stößer,
M. Scheer* 1443–1445

Complex Chemical Stabilization of
Dichlorodiphosphene

Keywords: density functional
calculations • P ligands • phosphene •
tungsten

Angew. Chem. **2001**, *113*, 1476–1478

They exist! Boridecarbides of transition metals. A whole series of Nb compounds was prepared from syntheses in Cu/Al melts with Nb_3B_3C , $Nb_4B_3C_2$, $Nb_7B_4C_4$, and $Nb_7B_6C_3$. Their crystal structures can be explained easily with a simple building-set principle based on the binary components NbC, Nb_2B_3 , and Nb_3B_4 .

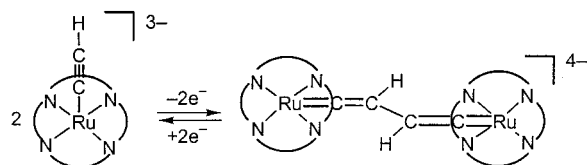
H. Hillebrecht,*
K. Gebhardt 1445–1447

Crystal Structures from a Building Set:
The First Boridecarbides of Niobium

Keywords: boridecarbide • niobium •
solid-state structures •
structure elucidation

Angew. Chem. **2001**, *113*, 1492–1495

 **Through a proton-transfer reaction** a porphyrinogen assists the transformation of terminal acetylenes into Ru–vinylidenes, which are the entry point to a variety of Ru–carbenes and Ru–cumulenes. The scheme (in which the porphyrinogen is stylized) shows the reversible interconversion of an acetylide into a divinylidene unit.



Angew. Chem. **2001**, *113*, 1497–1500

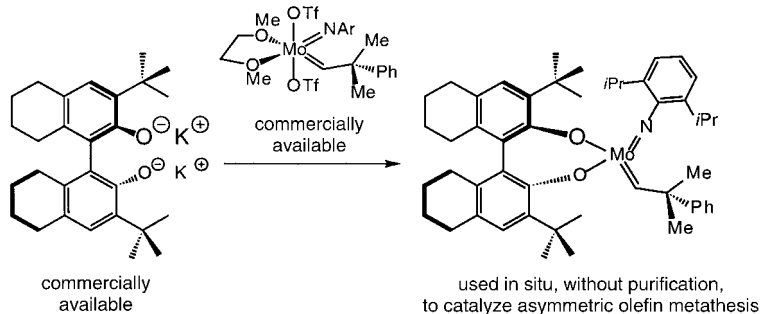
L. Bonomo, C. Stern, E. Solari,
R. Scopelliti, C. Floriani* .. 1449–1452

Acetylenes Rearranging on Ruthenium –
Porphyrinogen and Leading to
Vinylidene and Carbene Functionalities

Keywords: carbenes • cumulenes •
porphyrinogens • ruthenium •
vinylidene complexes



No glove box required! A new chiral catalyst for olefin metathesis is prepared from commercially available materials and is equally or more effective and selective than the previous systems. The new user-friendly catalyst can be prepared in situ (see scheme, Ar = aryl, Tf = trifluoromethanesulfonyl), isolation not needed, outside of a glove box, and delivers reactivity and enantioselectivity levels formerly available only through multiple catalysts.



Angew. Chem. **2001**, *113*, 1500–1504

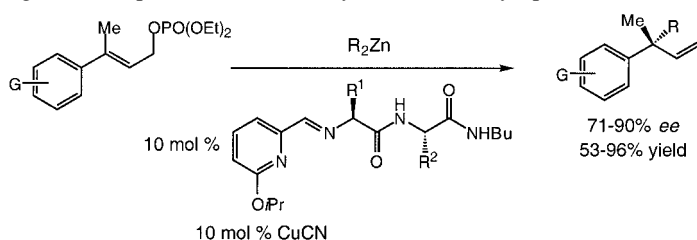
S. L. Aeilts, D. R. Cefalo,
P. J. Bonitatebus, Jr., J. H. Houser,
A. H. Hoveyda,*
R. R. Schrock* 1452–1456

A Readily Available and User-Friendly
Chiral Catalyst for Efficient
Enantioselective Olefin Metathesis

Keywords: asymmetric catalysis •
chiral complexes • enantioselectivity •
metathesis • molybdenum



Highest enantioselectivities so far with dialkylzinc reagents! Quaternary carbon centers are formed enantioselectively through a Cu-catalyzed allylic substitution reaction that is promoted by pyridinyl peptide-based ligands in the presence of dialkylzinc reagents (see scheme). The modularity of this new class of chiral ligands is exploited for reactivity and selectivity optimization.



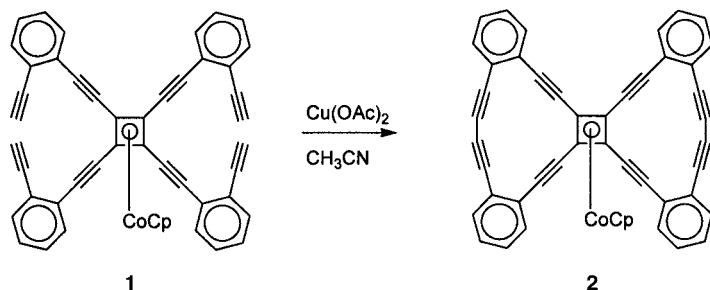
Angew. Chem. **2001**, *113*, 1504–1508

C. A. Luchaco-Cullis, H. Mizutani,
K. E. Murphy,
A. H. Hoveyda* 1456–1460

Modular Pyridinyl Peptide Ligands in
Asymmetric Catalysis: Enantioselective
Synthesis of Quaternary Carbon Atoms
Through Copper-Catalyzed Allylic
Substitutions

Keywords: allylic substitutions •
asymmetric catalysis • chiral ligands •
copper • peptide ligands

A metamorphosis of the tetraethynyl precursor **1** through double Cu-catalyzed ring closure leads to the corresponding butterfly-shaped cyclobutadiene complexes **2** in high yield (94 %). Single-crystal X-ray diffraction shows that the large organic ligand is distinctly nonplanar with a concave topology. Cp = cyclopentadiene.



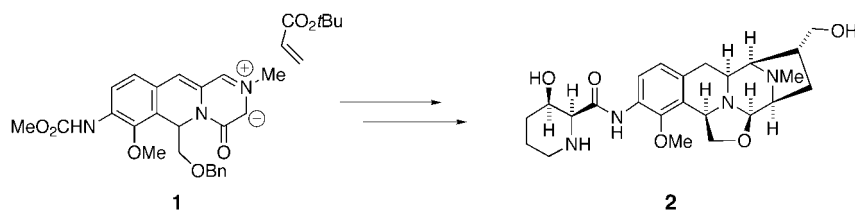
Angew. Chem. **2001**, *113*, 1508–1511

M. Laskoski, G. Roidl, M. D. Smith,
U. H. F. Bunz* 1460–1463

Concave Butterfly-Shaped
Organometallic Hydrocarbons?

Keywords: alkyne complexes • alkynes •
C–C coupling • cobalt • macrocycles

A new method for the formation of the allylic amine precursor to an azomethine ylide **1** has been developed and exploited in an efficient 1,3-dipolar cycloaddition to afford the key tetracyclic intermediate used in the synthesis of (–)-tetrazomine (**2**). Bn = benzyl.



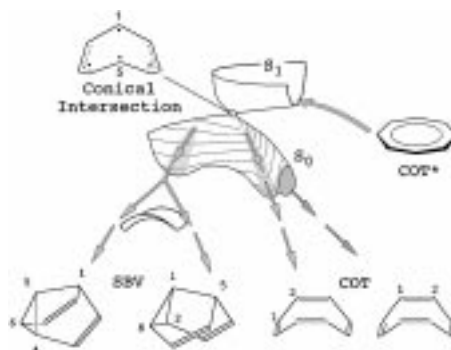
Angew. Chem. **2001**, *113*, 1511–1513

J. D. Scott, R. M. Williams* 1463–1465

Total Synthesis of (–)-Tetrazomine and Determination of Its Stereochemistry

Keywords: alkaloids • antitumor agents • cycloaddition • natural products • total synthesis

A mechanistic view of the deactivation of photoexcited cycloocta-1,3,5,7-tetraene (COT*) through a novel type of conical intersection (see scheme) is provided by ab initio studies. As a consequence of this deactivation, the formation of semi-bullvalene (SBV) and of the double-bond-shifted isomer of COT are intrinsically bound. Both gas-phase and solution-phase experimental data are explained.



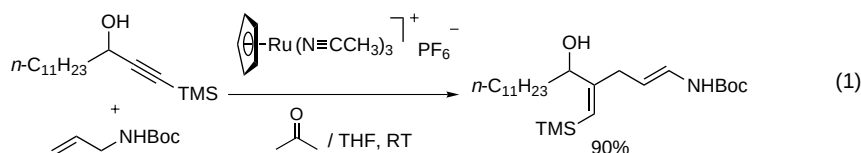
Angew. Chem. **2001**, *113*, 1514–1516

M. Garavelli,* F. Bernardi, V. Moliner, M. Olivucci* 1466–1468

Intrinsically Competitive Photoinduced Polycyclization and Double-Bond Shift through a Boatlike Conical Intersection

Keywords: ab initio calculations • alkenes • computer chemistry • photochemistry • transition states

Di- or trisubstituted alkenes of defined geometry, with terminal enamide groups, are formed in an atom-economic three-carbon chain extension of alkynes with allyl amides catalyzed by ruthenium (see, for example, Equation (1); Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl).



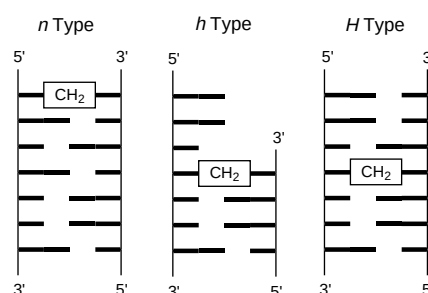
Angew. Chem. **2001**, *113*, 1516–1519

B. M. Trost,* J.-P. Surivet ... 1468–1471

An Atom-Economic Three-Carbon Chain Extension to Give Enamides

Keywords: alkynes • enamides • ene reactions • homogeneous catalysis • synthetic methods

Building bridges: A feasible solid-phase synthesis of antiparallel *n*-, *h*-, and *H*-type DNA oligomers (see picture) has been demonstrated. The oligomers possess a CH₂-bridged base-pair model that should be conformationally flexible, even after base pairing.



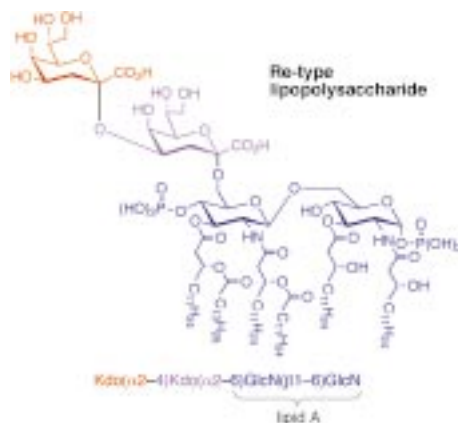
Angew. Chem. **2001**, *113*, 1519–1523

H.-Yu. Li, Y.-L. Qiu, E. Moyroud, Y. Kishi* 1471–1475

Synthesis of DNA Oligomers Possessing a Covalently Cross-Linked Watson–Crick Base Pair Model

Keywords: nucleosides • nucleotides • oligonucleotides • solid-phase synthesis • Watson–Crick base pairs

Three sequential efficient glycosylation reactions starting from D-glucosamine were used in the first total synthesis of *Escherichia coli* Re lipopolysaccharide, which is one of the most simple lipopolysaccharides found on the surface of living bacteria.



Angew. Chem. **2001**, *113*, 1523–1528

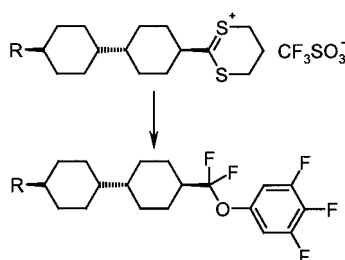
H. Yoshizaki, N. Fukuda, K. Sato,
M. Oikawa,* K. Fukase, Y. Suda,
S. Kusumoto* 1475–1480

First Total Synthesis of the Re-Type
Lipopolysaccharide

Keywords: glycolipids • glycosylations •
lipopolysaccharides • natural products •
total synthesis



Insertion of a difluorooxymethylene bridge into the mesogenic core structure of phenylcyclohexane-based liquid crystals results in a class of materials that exhibits a surprising and unprecedented improvement of essentially all application-relevant properties (see scheme). A novel synthetic procedure allows the convenient large-scale preparation of a variety of compounds based on α,α -difluoroalkyl ether structures.

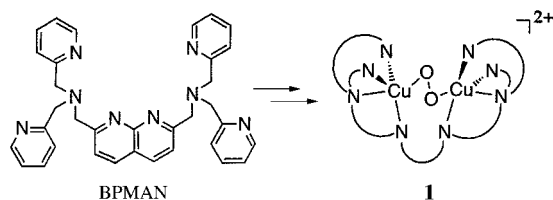


P. Kirsch,* M. Bremer, A. Taugerbeck,
T. Wallmichrath 1480–1484

Difluorooxymethylene-Bridged Liquid
Crystals: A Novel Synthesis Based on the
Oxidative Alkoxydifluorodesulfuration of
Dithianylum Salts

Keywords: desulfuration • fluorine •
liquid crystals • mesogens • sulfur

A copper–copper separation of about 2.84 Å is determined by extended X-ray absorption fine structure studies for the (μ -1,2-peroxo)dicopper(II) species **1**, which has only a 1,8-naphthyridine unit as an additional bridge. Complex **1** was prepared by the reaction of O_2 with a dicopper(I) complex formed from BPMAN (see picture).



Angew. Chem. **2001**, *113*, 1532–1535

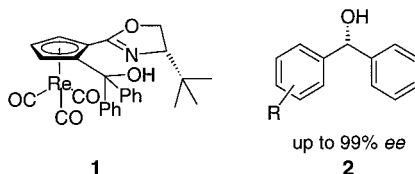
C. He, J. L. DuBois, B. Hedman,*
K. O. Hodgson,*
S. J. Lippard* 1484–1487

A Short Copper–Copper Distance in a
(μ -1,2-Peroxo)dicopper(II) Complex
Having a 1,8-Naphthyridine Unit as an
Additional Bridge

Keywords: copper •
EXAFS spectroscopy •
metal–metal interaction • N ligands •
1,8-naphthyridine • peroxides



A novel planar chiral cyrhetrene 1 has been identified as an efficient catalyst precursor for the asymmetric synthesis of diarylmethanol compounds **2** by phenylation of aldehydes. Compared to the corresponding ferrocene derivative, the performance of the cyrhetrene is superior or at least equally as good and gives excellent enantioselectivities even with catalyst loadings as low as 2 mol %.



Angew. Chem. **2001**, *113*, 1536–1538

C. Bolm,* M. Kesselgruber, N. Hermanns,
J. P. Hildebrand, G. Raabe .. 1488–1490

Application of a Planar Chiral
 η^5 -Cyclopentadienylrhenium(I)tri-
carbonyl Complex in Asymmetric
Catalysis: Highly Enantioselective Phenyl
Transfer to Aldehydes

Keywords: asymmetric catalysis •
diarylmethanols • rhenium • zinc

Anodization of aluminum with H_2SO_4 on an Si substrate results in the formation of individual alumina nanotubes (ANTs). The picture shows an ANT with a length of 650 nm and internal and external diameters of 12 and 35 nm, respectively. Detailed studies by transmission electron microscopy revealed that the ANTs are completely detached cells of the porous anodized aluminum film.



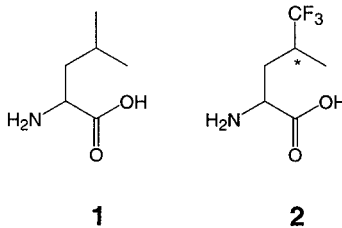
Angew. Chem. **2001**, *113*, 1538–1541

L. Pu,* X. Bao, J. Zou,
D. Feng 1490–1493

Individual Alumina Nanotubes

Keywords: aluminum •
electrochemistry • nanostructures •
oxidations • silicon

Fluorination of the hydrophobic core of a coiled-coil protein significantly improved its stability toward thermal and chemical denaturation. 5',5',5'-Trifluoroleucine (**2**) was efficiently incorporated into a leucine-zipper protein in place of leucine (**1**) during *E. coli* biosynthesis. The fluorinated variant maintained stable secondary and tertiary structures under conditions that caused denaturation of the “wild-type” protein.



Angew. Chem. **2001**, *113*, 1542–1544

Y. Tang, G. Ghirlanda, W. A. Petka,
T. Nakajima, W. F. DeGrado,
D. A. Tirrell* 1494–1496

Fluorinated Coiled-Coil Proteins
Prepared In Vivo Display Enhanced
Thermal and Chemical Stability

Keywords: biosynthesis •
circular dichroism • fluorine •
helical structures • protein structures

Immobile solvated ions such as $\text{NH}_4^+ \cdot \text{NH}_3$ act as kinetic traps that prevent the proton-transfer reaction between H_3O^+ and NH_3 on ice surfaces at 85–140 K reaching thermodynamic equilibrium. A combination of Cs^+ reactive ion scattering and mass spectrometry showed that all species of the reaction (NH_3 , NH_4^+ , H_2O , and H_3O^+) coexist on ice. This result indicates that metastable species can be produced and kinetically stabilized on ice surfaces such that they may contribute to the chemistry of stratospheric and interstellar ice particles.

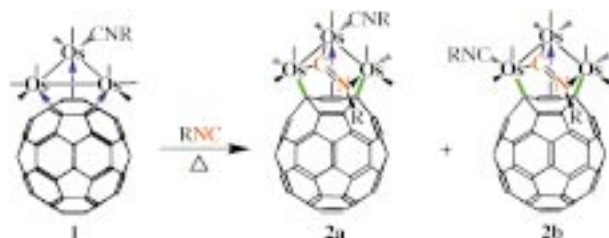
Angew. Chem. **2001**, *113*, 1545–1548

S.-C. Park, K.-W. Maeng, T. Pradeep,*
H. Kang* 1497–1500

Unique Chemistry at Ice Surfaces:
Incomplete Proton Transfer in the
 $\text{H}_3\text{O}^+ - \text{NH}_3$ System

Keywords: ice surface •
ion–molecule reactions •
mass spectrometry • protonations

 **A boat-shaped 1,4-cyclohexadiene-like ring** is present in the C_{60} molecule with a novel σ -type $\mu_3\text{-}\eta^1, \eta^2, \eta^1$ bonding mode in the clusters **2a** and **2b**. The change in coordination mode was induced by insertion of an RNC ligand into an Os–Os bond of the π -type C_{60} complex **1**. $\text{R} = \text{CH}_2\text{C}_6\text{H}_5$.



Angew. Chem. **2001**, *113*, 1548–1550

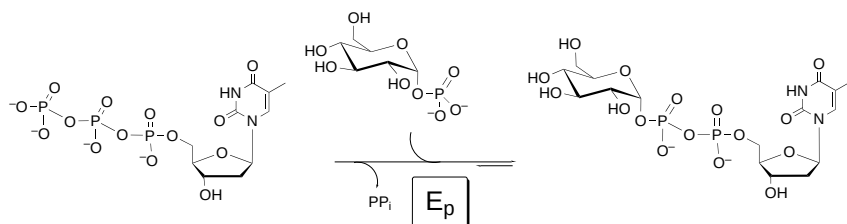
H. Song, K. Lee, C. H. Lee, J. T. Park,*
H. Y. Chang, M.-G. Choi ... 1500–1502

First Example of the $\mu_3\text{-}\eta^1, \eta^2, \eta^1\text{-C}_{60}$
Bonding Mode: Ligand-Induced
Conversion of π to σ C_{60} –Metal
Complexes

Keywords: cluster compounds •
fullerenes • osmium



The exploitation of a unique thymidyltransferase (E_p) allows the rapid syntheses of thymidine and uridine 5'-(aminodeoxy- α -D-hexopyranosyl diphosphates), 5'-(acetamidodeoxy- α -D-hexopyranosyl diphosphates), and even 5'-(aminodideoxy- α -D-hexopyranosyl diphosphates), which are amino analogues of the products from the native reaction of E_p (see scheme).



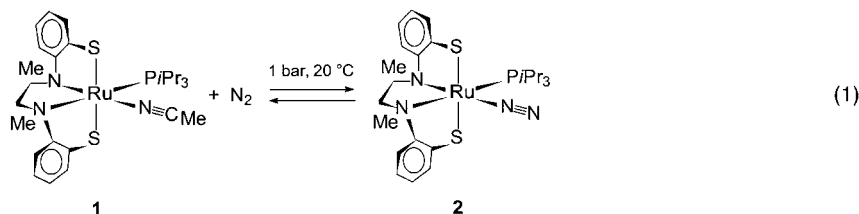
Angew. Chem. **2001**, *113*, 1550–1553

J. Jiang, J. B. Biggins,
J. S. Thorson* 1502–1505

Expanding the Pyrimidine
Diphosphosugar Repertoire: The
Chemoenzymatic Synthesis of Amino-
and Acetamidoglucofuranosyl
Derivatives

Keywords: enzyme catalysis •
glycosyl phosphate • nucleotides •
synthetic methods • transferases

N_2 coordination to the nitrogenase Fe_7MoS_9 cofactor is considered a key step of biological N_2 fixation, however, modeling this step with metal–sulfur complex fragments under mild conditions has remained a long-standing challenge. The title complex **2** represents a first example, forming from N_2 and the precursor CH_3CN complex **1** under standard conditions [Eq. (1)].



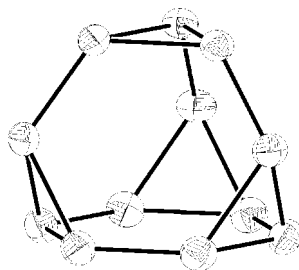
Angew. Chem. **2001**, *113*, 1553–1555

D. Sellmann,* B. Hautsch, A. Rösler,
F. W. Heinemann 1505–1507

$[Ru(N_2)(P/Pr_3)(N_2Me_2S_2)]$:
Coordination of Molecular N_2 to Metal
Thiolate Cores under Mild Conditions

Keywords: dinitrogen complexes •
N ligands • nitrogen fixation •
ruthenium • S ligands

The largest isolated clusters of Group 14 elements, giant truncated tetrahedra of Ge_{12}^{12-} (see picture), are found in the title compound. $RbLi_7Ge_8$, which is an electronically balanced, saltlike Zintl phase, was synthesized by heating the corresponding stoichiometric mixture of elements.



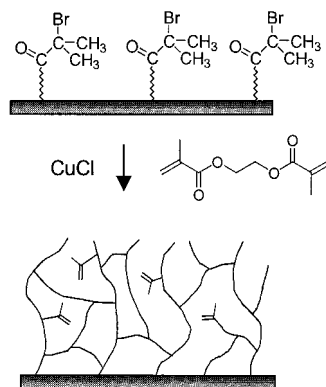
Angew. Chem. **2001**, *113*, 1555–1558

S. Bobev, S. C. Sevov* 1507–1510

Synthesis and Characterization of
 $RbLi_7Ge_8$ with Isolated *closo*- $[Li_4Ge_{12}]^{8-}$
Ions, Lithium-Capped Truncated
Tetrahedra of Ge_{12}^{12-}

Keywords: cluster compounds •
germanium • lithium • solid-state
structures • Zintl phases

Ambient-temperature atom transfer radical polymerization of ethylene-glycol dimethacrylate from a surface yields homogeneous, cross-linked polymer films (see scheme). The absence of polymerization in solution in this “living” procedure avoids physisorption and gives uniform, cross-linked films with controlled thicknesses from 3 to 300 nm.



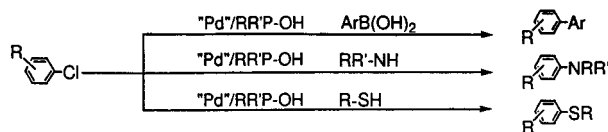
Angew. Chem. **2001**, *113*, 1558–1560

W. Huang, G. L. Baker,*
M. L. Bruening* 1510–1512

Controlled Synthesis of Cross-Linked
Ultrathin Polymer Films by Using
Surface-Initiated Atom Transfer Radical
Polymerization

Keywords: atom transfer radical
polymerization • radicals • surface
chemistry • thin films

Rapid and regioselective oxidative addition of unactivated aryl chlorides in the presence of bases can be achieved by using metal complexes of phosphinous acid ($RR'POH$), for which air-stable phosphine oxides ($RR'P(O)H$) serve as ideal ligand precursors. Such processes can be incorporated into efficient catalytic cycles for a variety of C–C, C–N, and C–S bond-forming processes (see scheme, Ar = aryl).



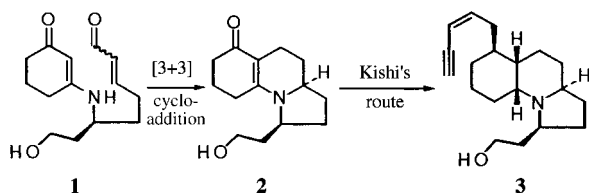
Angew. Chem. **2001**, *113*, 1561–1564

G. Y. Li* 1513–1516

The First Phosphine Oxide Ligand Precursors for Transition Metal Catalyzed Cross-Coupling Reactions: C–C, C–N, and C–S Bond Formation on Unactivated Aryl Chlorides

Keywords: combinatorial chemistry • cross-coupling • homogeneous catalysis • palladium • phosphine oxides

Complex piperidinyl heterocycles (for example, **2**) were accessed by using a novel intramolecular formal [3+3] cycloaddition reaction of vinylogous amides tethered with enals (for example, **1**). This method has been applied to a formal total synthesis of (+)-gephyrotoxin (**3**).



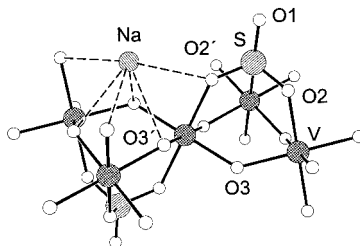
Angew. Chem. **2001**, *113*, 1564–1566

L.-L. Wei, R. P. Hsung,* H. M. Sklenicka, A. I. Gerasyuto 1516–1518

A Novel and Highly Stereoselective Intramolecular Formal [3+3] Cycloaddition Reaction of Vinylogous Amides Tethered with α,β -Unsaturated Aldehydes: A Formal Total Synthesis of (+)-Gephyrotoxin

Keywords: alkaloids • amides • cycloaddition • electrocyclic reactions • synthetic methods

A dominant ferromagnetic exchange interaction propagates about the magnetic sites of the Kagomé lattice of the title compound through the bridging hydroxy groups (see section of the structure). This is at variance with the antiferromagnetic exchange observed for jarosite and its derivatives. The ferromagnetism probably arises from the d^2 electron count of the V^{III} centers.

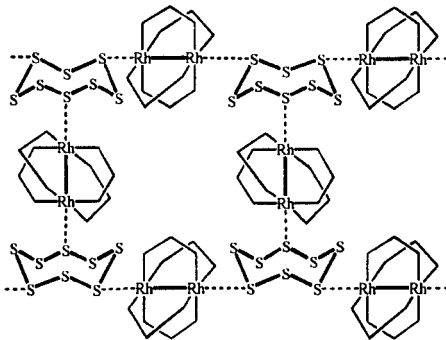


D. Grohol, D. Papoutsakis, D. G. Nocera* 1519–1521

$NaV_3(OH)_6(SO_4)_2$: A Kagomé-Type Vanadium(III) Compound with Strong Intralayer Ferromagnetic Interactions

Keywords: ferromagnetism • hydrothermal synthesis • jarosite • magnetic properties • vanadium

Coordination of neutral S_8 molecules by transition metal centers has been structurally confirmed for the first time. The monoadduct $[Rh_2(O_2CCF_3)_4](S_8)$ is a one-dimensional polymer with an alternating chain of dirhodium(II) tetra(trifluoroacetate) and bidentate S_8 rings, whereas $[Rh_2(O_2CCF_3)_4]_3(S_8)_2$ is a pseudo-two-dimensional ribbon in which all cyclo- S_8 ligands act in a tridentate fashion (see picture).



Angew. Chem. **2001**, *113*, 1569–1571

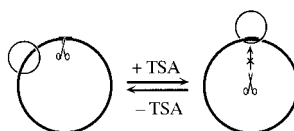
F. A. Cotton,* E. V. Dikarev, M. A. Petrukhina 1521–1523

Neutral Cyclooctasulfur as a Polydentate Ligand: Supramolecular Structures of $[Rh_2(O_2CCF_3)_4]_n(S_8)_m$ ($n:m = 1:1, 3:2$)

Keywords: carboxylato ligands • rhodium • S ligands • structure elucidation • supramolecular chemistry

Catenation of a circular oligonucleotide to a supercoiled plasmid can be achieved in high yields by means of ligand-induced triple-helix formation. The noncovalent interactions in this supramolecular structure can be modulated by a triplex-stabilizing agent (TSA; see picture). The circular oligonucleotide represents a noncovalent anchor for plasmid functionalization.

Angew. Chem. **2001**, *113*, 1571–1574



T. Roulon, C. Hélène,
C. Escudé* 1523–1526

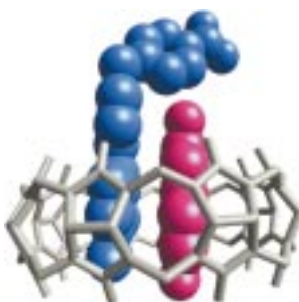
A Ligand-Modulated Padlock
Oligonucleotide for Supercoiled Plasmids

Keywords: catenanes • DNA structures •
helical structures • oligonucleotides •
supramolecular chemistry



Two different molecules are selectively included in cucurbit[8]uril to form a stable 1:1:1 ternary complex, which has been characterized by X-ray crystallography (see picture). The inclusion of a hetero-guest pair (a pyridinium derivative (blue) and 2,6-dihydroxynaphthalene (magenta)) in the molecular host is driven and stabilized by a charge-transfer interaction between the electron-rich and electron-deficient guests.

Angew. Chem. **2001**, *113*, 1574–1577



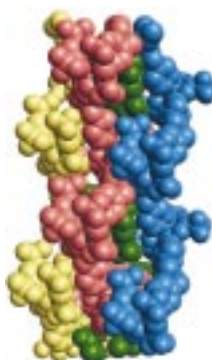
H.-J. Kim, J. Heo, W. S. Jeon, E. Lee,
J. Kim, S. Sakamoto, K. Yamaguchi,
K. Kim* 1526–1529

Selective Inclusion of a Hetero-Guest Pair
in a Molecular Host: Formation of Stable
Charge-Transfer Complexes in
Cucurbit[8]uril

Keywords: charge transfer •
host–guest chemistry •
inclusion compounds •
structure elucidation •
supramolecular chemistry

Coordination-driven assembly based on manganese(II) centers and flexible 1,3-bis(4-pyridyl)propane leads to the solid-state formation of electronically neutral, self-templated homochiral helices (see picture), closed ring structures, and racemic mixtures of helices depending upon the presence or absence of guests such as benzene and 1,2-diphenylethane.

Angew. Chem. **2001**, *113*, 1577–1580



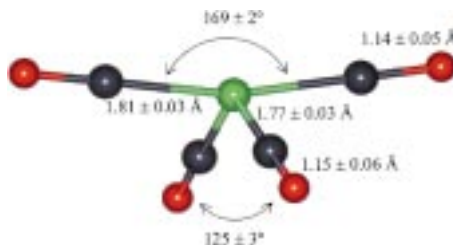
F. M. Tabellion, S. R. Seidel, A. M. Arif,
P. J. Stang* 1529–1532

Template and Guest Effects on the Self-
Assembly of a Neutral and Homochiral
Helix

Keywords: crystal engineering •
helical structures • host–guest chemistry •
manganese • supramolecular chemistry

The temporal diffraction–difference approach of the ultrafast electron diffraction (UED) technique was used to determine the molecular structure of the transient $[\text{Fe}(\text{CO})_4]$ (see picture) formed during the elimination of CO ligands from $[\text{Fe}(\text{CO})_5]$. The results clearly show that the major product, up to 200 ps, is the transient $[\text{Fe}(\text{CO})_4]$ which is formed in the $^1\text{A}_1$ state, rather than the ground $^3\text{B}_2$ state.

Angew. Chem. **2001**, *113*, 1580–1584

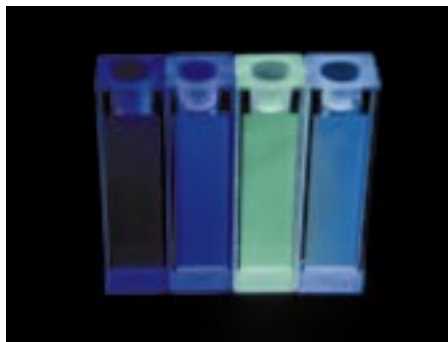


H. Ihee, J. Cao,
A. H. Zewail* 1532–1536

Ultrafast Electron Diffraction of
Transient $[\text{Fe}(\text{CO})_4]$: Determination of
Molecular Structure and Reaction
Pathway

Keywords: carbonyl ligands •
electron diffraction • iron •
laser spectroscopy • intermediates

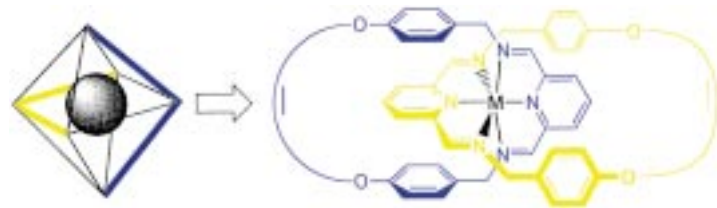
Twist and shout! By restricting conformation, 2,6-biarylpyridines can be induced to “speak” to us through increased fluorescence emission. In combination with induced charge transfer, this allows these simple fluorophores to reveal otherwise silent binding events to alkali metal and alkaline earth cations through brightening and color change (see picture; from left to right: no metal, Li^+ , Mg^{2+} , and Ca^{2+}).



Angew. Chem. **2001**, *113*, 1584–1586

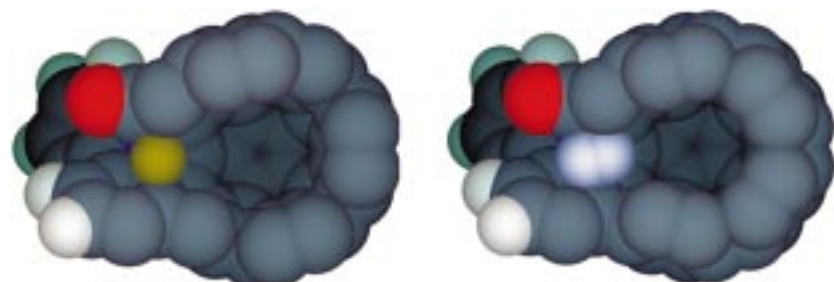


The shape of rings to come: The first members of a new family of simple-to-prepare octahedral analogues of the tetrahedral Sauvage catenates are described (see scheme). $\text{M} = \text{Mn}^{2+}$, Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , Hg^{2+} .



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A “molecular surgery” approach has been used to create an opening within a fullerene cage that is large enough to allow atoms and small molecules to pass through. The thermodynamics for the insertion of He and H_2 into the open fullerene (left and right pictures, respectively) as well as their escape have been studied by NMR spectroscopy and theoretical methods.



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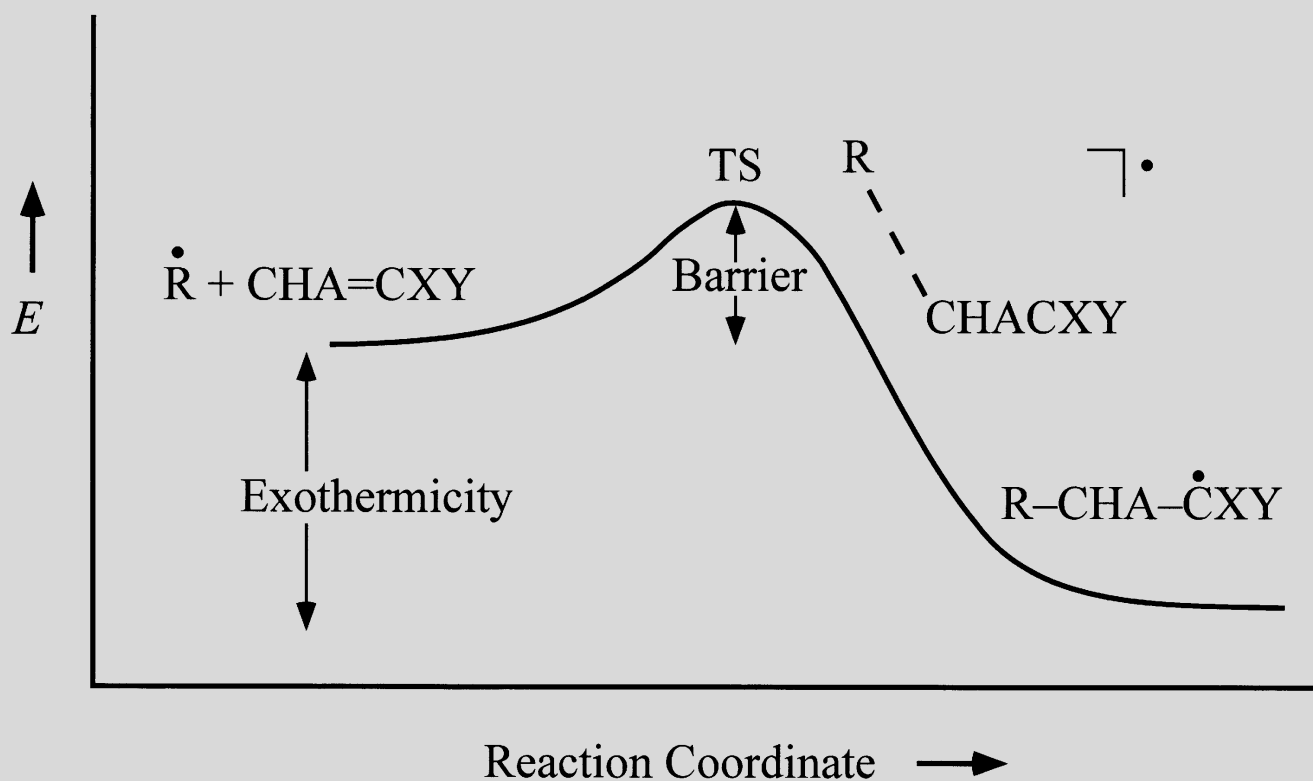
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Kinetic radical additions are apparently controlled by the interplay between the reaction enthalpy and the charge transfer during the course of the reaction, ...



... and the nucleophilic and electrophilic polar effects of the substituents (A, X, Y). This dependency can be described accurately by new nonlinear equations.

Factors Controlling the Addition of Carbon-Centered Radicals to Alkenes—An Experimental and Theoretical Perspective

Hanns Fischer* and Leo Radom

The successful exploitation of syntheses involving the generation of new carbon–carbon bonds by radical reactions rests on some prior knowledge of the rate constants for the addition of carbon-centered radicals to alkenes and other unsaturated molecules, and of the factors controlling them. Two former classical reviews in *Angewandte Chemie* by Tedder (1982) and by Giese (1983) provided mechanistic insight and led to various qualitative rules on the complex interplay of enthalpic, polar, and steric effects. In the meantime, the field has experienced very rapid progress: many more experimental absolute rate constants have become available, and there have been major advances in the efficiency and

reliability of quantum-chemical methods for the accurate calculation of transition structures, reaction barriers, and reaction enthalpies. Herein we review this progress, recommend suitable experimental and theoretical procedures, and display representative data series for radical additions to alkenes. On this basis, and guided by the pictorial tool of the state-correlation diagram for radical additions, we then offer a new and more stringent quantification of the controlling factors. Our analysis leads to a partial revision of the previous qualitative rules, and it more clearly exhibits the interplay of the reaction enthalpy effects, polar charge-transfer contributions, and steric substituent effects on

the reaction energy barrier. The various contributions are cast into the form of new, simple, and physically meaningful but non-linear, predictive equations for the preestimation of rate constants. These equations prove successful in several tests but call for additional theoretical and experimental foundation. The kinetics of related reactions such as polymer propagation, copolymerization, and the addition of radicals to alkynes and aromatic compounds is shown to follow the same principles.

Keywords: ab initio calculations • additions • kinetics • radical reactions

1. Introduction

The addition of carbon-centered radicals to alkenes and other unsaturated compounds leads to the creation of new carbon–carbon σ bonds at the expense of existing π bonds. It is a very important radical reaction and has long been applied in polymer chemistry, but recent years have also seen numerous applications in the synthesis of small molecules.^[1–3] The reaction rates and selectivities vary considerably, and depend on the substitution of both the substrate and the radical. For example, in liquid solution at room temperature

the methyl radical adds to propene with a rate constant of $4300\text{ M}^{-1}\text{ s}^{-1}$, while the reaction is about 100 times faster with styrene ($2.6 \times 10^5\text{ M}^{-1}\text{ s}^{-1}$) and acrylonitrile ($5.4 \times 10^5\text{ M}^{-1}\text{ s}^{-1}$). The addition of a simple derivative, the hydroxymethyl radical, to propene ($270\text{ M}^{-1}\text{ s}^{-1}$) and styrene ($2.3 \times 10^4\text{ M}^{-1}\text{ s}^{-1}$) is more than ten times slower than the addition of the methyl radical, but hydroxymethyl radical reacts markedly faster than the methyl radical with acrylonitrile ($1.1 \times 10^6\text{ M}^{-1}\text{ s}^{-1}$). Such order-of-magnitude rate variations may result in the success or failure of syntheses, and therefore a predictive synthetic strategy relies on some prior knowledge of the rate constants for the addition, and of the factors controlling them.^[2, 4]

These factors have found extensive discussion since the early days of radical chemistry^[5] and were summarized some time ago in this journal, especially for the addition to alkenes, by Tedder^[6] and by Giese.^[7] There is a “complex interplay of polar, steric, and bond-strength effects”,^[6] but Tedder and Giese were able to extract several general but qualitative rules. These were subsequently supported by others,^[2, 8] and have found widespread acceptance.

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In the meantime, considerable progress has been made, both in accurate experimental determinations of absolute rate constants for radical reactions and their activation parameters, and in quantum-chemical calculations of transition state structures and reaction barriers. Moreover, a unifying theoretical model for the interpretation of reaction barriers has become available. Hence, a reconsideration of the controlling factors seems timely. Herein, we first outline the previous interpretations, sketch the refined rationalization concept, and summarize the progress of the experimental and theoretical methods. Then, we present and discuss absolute rate constants and activation parameters for the addition of several prototype carbon-centered radicals to a large variety of typical alkenes, explicitly covering cases mainly from our own work. These form a representative series, allow important and clarifying generalizations, and lead to a general predictive analysis which extends an earlier attempt^[9] and is presented here for the first time. The experimental data have been obtained for reactions in solution, and the theoretical reaction barriers by state-of-the-art *ab initio* calculations. In addition to the main topic of additions to alkenes, related subjects such as additions to alkynes, aromatics, and other unsaturated compounds, as well as polymerizations, are briefly mentioned, but we will not review these fields exhaustively, nor will we cover the stereochemical aspects of additions,^[10] intramolecular cyclizations, and the multitude of known synthetic applications.^[2, 3]

2. Concepts for the Interpretation of Reactivities and Regioselectivities

2.1. Previous Rules for the Addition of Radicals to Alkenes

The addition of a reactive carbon-centered radical to a molecule with a multiple carbon-carbon bond is generally exothermic because a π bond is replaced by a σ bond (Figure 1). Therefore, and according to Hammond's postulate,^[11] the transition state is early, that is, the cleavage of the π bond and the formation of the σ bond are far from being complete in the transition structure. Figure 2 shows the transition structure obtained from recent high-level calcula-

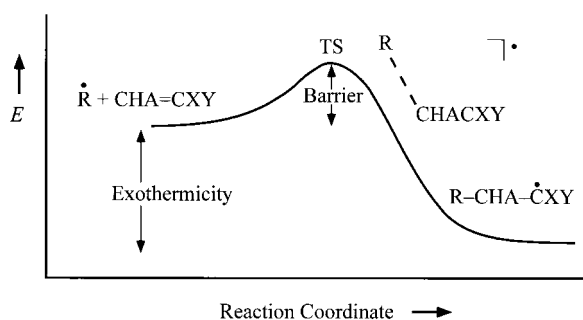


Figure 1. Schematic energy profile showing the reaction of a radical $R^\cdot$ with an alkene $CHA=CXY$.

Hanns Fischer born in 1935 started his academic career at the Technical University Darmstadt, Germany, where he obtained his Diploma (1960), Ph.D. (1963), and Habilitation (1966) all in Physics working at the Deutsches Kunststoff-Institut, mostly studying the structure and reactivity of polymer related transient carbon-centered free radicals by spectroscopic means (ESR, NMR, CIDNP). After leading a physico-chemically oriented division of this Institute, a short period at Carnegie-Mellon University Pittsburgh (USA), and teaching molecular physics at the Technical University Darmstadt he moved in 1969 to his present position as associate, then (1971) full professor for Physical Chemistry of the University of Zürich. There, he continued to work on transient organic free radicals, their structure, reaction mechanisms, and reaction kinetics in liquid solutions employing and developing ESR, CIDNP, optical spectroscopy, and muon spin rotation methods. In this field he has authored more than 200 original publications and several reviews and edited large series of tables on radical properties and kinetics in Landolt-Börnstein. Special honors include the Centenary Medal and Lectureship of the Chemical Society London and the Silver Medal of the International EPR Society.



H. Fischer



L. Radom

*Leo Radom was born in 1944. He studied at the University of Sydney, obtaining a B.Sc. degree and the University Medal in 1965, and a Ph.D. in 1969 in the general area of physical organic chemistry. Following a 3½ year postdoctoral period on a Fulbright Fellowship with John Pople at Carnegie-Mellon University in Pittsburgh (USA), he returned to Australia in 1972 on a Queen Elizabeth II Fellowship at the Research School of Chemistry of the Australian National University where he currently holds the position of Professor. His main research interests are concerned with the study of the structures and stabilities of molecules and the mechanisms of reactions in which they are involved by use of *ab initio* molecular orbital theory. His achievements have been recognized through the award of the Rennie Medal, the H. G. Smith Medal, and the Archibald Olle Prize of the Royal Australian Chemical Institute, the Schrödinger Medal of the World Association of Theoretically Oriented Chemists, and through election to the Australian Academy of Science and the International Academy of Quantum Molecular Science.*

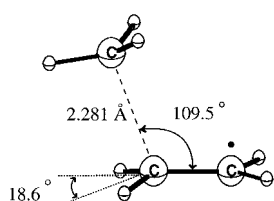


Figure 2. Transition structure for the addition of the methyl radical to ethene (QCISD(T)/6-31GT(d)). From refs. [12, 13].

tions for the addition of the methyl radical to ethene.^[12, 13] As expected, the newly forming bond is still long (2.281 Å), but the angle of attack (109.5°) is already close to the corresponding angle in the product radical. There are appreciable out-of-plane deformations of the hydrogen atoms at both the α carbon atom of ethene (18.6°) and at the radical carbon

(32.4°). These general features have been found for the transition structures for a large variety of addition reactions. The unsymmetrical structure means that additions to the two carbon atoms of an unsymmetrically substituted multiple bond have separate and in general different rate constants. The temperature dependence of the rate constants is well described by the Arrhenius equation $k = A \exp(-E_a/RT)$. Thus, at a given temperature, the rate variations with radical and substrate substitution can be caused by variations in the frequency factor (A) and/or the activation energy (E_a). For polyatomic radicals, the frequency factors span a narrow range of one to two orders of magnitude ($6.5 < \lg(A/\text{M}^{-1}\text{s}^{-1}) < 8.5$).^[6] Hence, the large variation in the rate constants is mainly because of variations in the activation energy.

The major factors influencing the activation energy are a) steric effects of the radical and alkene substituents, b) effects of the overall reaction enthalpy, and c) so-called polar effects. They are covered by the rules of Tedder and Giese.^[6, 7]

a) Steric effects of repulsion between the radical and the alkene substituents X, Y, and A (Figure 1) decrease the rate constants and have been rationalized in terms of steric substituent parameters.^[6, 7] They are thought to decrease the frequency factor and simultaneously increase the activation energy. The steric effects are in accord with the transition structure (Figure 2), in that substituents at the attacked alkene carbon atom (α substituents, A) hinder the reaction much more than substituents at the remote carbon atom (β substituents, X and Y). This explains why the addition to monosubstituted and 1,1-disubstituted alkenes occurs predominantly at the unsubstituted carbon atom, for 1,1,2-trisubstituted alkenes at the carbon with the single substituent, and for 1,2-disubstituted alkenes and alkynes at the carbon atom which carries the “smaller” group.

b) The reaction enthalpies (H_r) range from about -180 kJ mol^{-1} to -20 kJ mol^{-1} (see Sections 4.2, 4.3). The activation energies range from close to zero to about 42 kJ mol^{-1} and show less variation than the reaction enthalpies with alkene or radical substitution, as one would expect for early transition states. Generally, they decrease with increasing exothermicity, as expressed by the Evans–Polanyi–Semenov^[14] relation [Eq. (1)]. For exothermic proc-

$$E_a = \text{const} + \alpha H_r \quad (1)$$

esses, the proportionality constant (α) is thought to be approximately 0.25,^[14b] which means that about one quarter of the variation in H_r is transferred to the transition structure.

H_r includes the stabilizing or destabilizing effects of substituents on the adding radical, the alkene, and the adduct radical, factors which were extensively noted in the earlier work.^[6, 7]

c) Polar substituent effects reveal themselves by particularly fast additions of electron-donor-substituted radicals to electron-acceptor-substituted alkenes and of acceptor-substituted radicals to donor-substituted alkenes. In early work, they were loosely ascribed to contributions of charge-transfer resonance structures to the transition state.^[5a] In the terms of frontier molecular orbital (FMO) theory,^[7] the polar effects are attributed to orbital interactions. The energy of the singly occupied molecular orbital (SOMO) of an electron-donor-substituted radical is relatively high, and the energy of the lowest unoccupied molecular orbital (LUMO) of an acceptor-substituted alkene is low. Interaction of these energetically close orbitals lowers the energy of the transition state and provides a partial electron transfer from the radical to the alkene. Hence, donor-substituted radicals express a nucleophilic character, and this increases with the acceptor strength of the alkene substituent. On the other hand, the low-lying SOMO of an acceptor-substituted radical interacts favorably with the high-lying highest occupied molecular orbital (HOMO) of a donor-substituted alkene. This leads to a partial electron transfer from the alkene to the radical, and such radicals show an electrophilic addition pattern.

Evidence for the polar effects is provided by good correlations of rate data with polar σ -substituent constants, from which a nucleophilic character was deduced for the methyl radical and its alkyl- or other donor-substituted derivatives.^[6, 7] On the other hand, radicals carrying fluoro substituents,^[6, 15] or two cyano,^[16] or two carboxy^[17] groups at the radical center were recognized as electrophilic. Giese, in his review,^[7] thought that the polar effects even override the influence of the enthalpy, the exception being for an attacking radical with phenyl substituents. It has also been stated^[18] that monocyano- and monocarboxy-substituted radicals react fast with alkenes carrying strong electron-acceptor substituents and also with alkenes carrying strong electron-donor substituents, and hence exhibit an ambiphilic addition behavior towards alkene substitution.

Besides the steric, enthalpic (bond strength), and polar effects, other factors have also been suggested. Thus, Szwarc et al.^[19] argued that the activation energy should decrease with decreasing alkene triplet-excitation energy, and this was exemplified by additions to aromatic compounds. In addition, an influence of the hybridization of the radical carbon atom has been proposed. It is known that alkyl radicals with fluoro or other lone-pair-donor substituents are pyramidally hybridized at the radical carbon, whereas methyl, benzyl, and acceptor-substituted radicals are planar or close to planar. In the transition structure, the bonds at the initial radical carbon atom adopt a pyramidal configuration (Figure 2). Intuitively,^[15, 20] this seems easier to reach when it is already present in the radical, and therefore pyramidal radicals such as trifluoromethyl should have an advantage. On the other hand, radicals with extended delocalization such as the benzyl radical and cyano- or carboxy-substituted methyl radicals are expected to resist pyramidalization, which by this argument may lead to higher activation energies.^[21]

2.2. The State Correlation Diagram

In the past 20 years, a more unifying theoretical framework for the discussion of reaction barriers in terms of the correlation and the interaction of reactant and product electronic configurations has been developed by Shaik and Pross.^[22, 23] It extends earlier work^[24] and is based on a valence-bond (VB) description of chemical reactivity. In broad terms, this approach employs qualitative energy diagrams which depict the energies of VB configurations along the reaction coordinate. The curve-crossing model, alternatively referred to as a valence-bond state correlation (VB-SC) model, configuration mixing (VB-CM) model, or state correlation diagram (SCD), has in particular been exploited to help understand the factors influencing the addition reactions of radicals to alkenes^[9, 25–29] and has been theoretically supported by VBCI (CI = configuration interaction) calculations for a model system where zwitterionic states were included and substituent effects were simulated by a variation of nuclear charges.^[30] Its predictive strength is further evaluated in this review.

To construct potential energy profiles for additions, one considers the four lowest doublet configurations of the three-center-three-electron system formed by the initially unpaired electron at the radical carbon atom $R^\bullet$ and the electron pair of the attacked π bond of the alkene $C=C$ bond. These are the reactant ground-state configuration with a singlet electron pair on the alkene ($R^\bullet + C=C^1$), the excited reactant configuration with a triplet electron pair ($R^\bullet + C=C^3$), and two polar charge-transfer (CT) configurations ($R^+ + C=C^-$ and $R^- + C=C^+$). Spin-pairing schemes and VB arguments^[22–24, 30] show that the energies of the diabatic reactant configurations develop along the reaction coordinate as indicated in Figure 3. In the absence of configuration interaction (CI) and upon approach to the product geometry, the energy of the reactant ground-state configuration ($R^\bullet + C=C^1$) increases because the double bond is stretched, and because in this electronic

configuration there is no bonding between the radical center and the attacked carbon atom. Hence, it leads to an excited-state configuration of the product (dotted line). On the other hand, the ground-state configuration of the product with two single bonds approaches an excited configuration of the reactant geometry, the configuration $R^\bullet + C=C^3$. At the transition geometry, the configuration mixing yields an avoided crossing and determines the reaction barrier, as indicated in Figure 3 by the heavy lines.

The polar charge-transfer configurations, $R^+ + C=C^-$ and $R^- + C=C^+$ have high energies at the reactant geometry. They are stabilized as the two reactants approach one another by the Coulomb interaction (C) and can then potentially mix with the other configurations. The degree of mixing will depend on the strength of the interaction (γ) which is related to the FMO coefficients at the interacting centers. However, as long as the energies of the CT configurations remain far above the crossing region, the influence on the barrier is expected to be small. It becomes large when there is sufficient interaction and when the energy of one or both CT configurations, reduced by the Coulomb interaction, falls sufficiently close to the crossing-region of the two lower nonpolar configurations. Then, the adiabatic mixing of the nonpolar configurations with the CT configurations will lower the barrier and cause CT in the transition state.

The SCD predicts the influence of various energy parameters on the reaction barrier. Firstly, when polar effects are small or absent, the barrier should decrease with increasing exothermicity ($-H_r$), as in the Evans–Polanyi–Semenov relation [Eq. (1)]. Secondly, the barrier should decrease with a decreasing singlet–triplet energy gap ΔE_{ST} of the alkene, as suggested by Szwarc.^[19] Also, with increasing exothermicity ($-H_r$) and decreasing ΔE_{ST} , the transition structure will lie earlier on the reaction coordinate, so that the distance between the reactants in the transition structure should increase. If the energies of the CT configurations are low and approach the crossing-region, polar effects will overlay the effects of the reaction enthalpy and of the singlet–triplet energy gap. Hence, the polar effects are expected to increase with decreasing energy of either of the CT configurations, namely $E_i(R) - E_{ea}(A)$ and/or $E_i(A) - E_{ea}(R)$ of the reactants reduced by the Coulomb attraction C (where E_i = ionization energy, E_{ea} = electron affinity, R = radical, A = alkene). Radicals will exhibit a nucleophilic addition pattern if $E_i(R) - E_{ea}(A) - C$ is sufficiently small, and an electrophilic reactivity pattern if $E_i(A) - E_{ea}(R) - C$ is sufficiently small. If both energies are small, the addition pattern becomes ambiphilic. However, in all cases an influence of the exothermicity and of ΔE_{ST} should remain.

A further important point, we wish to note is that the Coulomb interaction C and the interaction strength γ are expected to decrease if the radical electron spin and/or the transferred charges are delocalized over the reactants. Therefore, in comparison with less delocalizing reactants, the polar effects should be smaller in reactions involving highly conjugated radicals or alkenes, such as those carrying phenyl substituents. Also, the parameters C and γ need not be equal for nucleophilic and electrophilic contributions and may differ with radical and alkene. Finally, steric effects and/or a

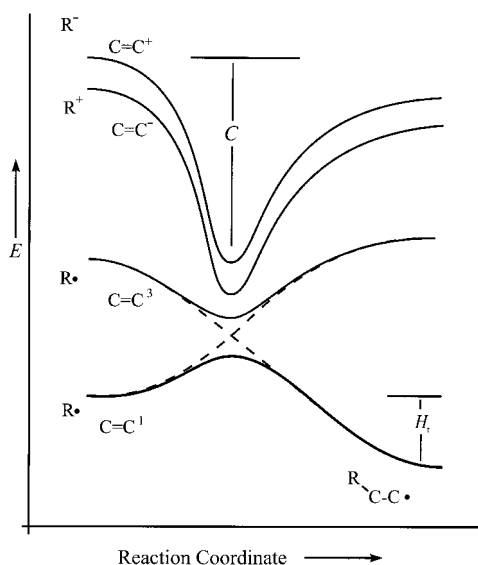


Figure 3. Schematic configuration mixing or state correlation diagram (SCD) for a radical-addition reaction showing the configuration energies as functions of the reaction coordinate.

resistance to pyramidalization of the radical and/or alkene may lead to a steeper increase in the ground-state energy upon approach of the reactants, and may also affect the barrier.

3. Methodology

3.1. Experimental Techniques

Up to about 25 years ago, the knowledge of radical reactivity and selectivity was essentially based only on ratios of rate constants derived from the product distributions of suitably chosen competing reactions. Since then, spectroscopic methods have become available which follow the change in the radical concentrations directly during the reactions in real time and provide absolute data. Most modern techniques employ an intermediate digital sampling and storage of the weak signals, and use digital signal processing and analysis. Hence, the methodology has enormously profited from the rapid developments in computer hardware and software. Even large sets of rate constants can now be measured within reasonable times. The reader is referred to the literature for details,^[31] and we outline only a few important methods here.

Kinetic absorption spectroscopy is probably the most popular technique for determining the rates of radical reactions in solution, and it originates from the flash photolysis studies developed by Porter.^[32] The radicals are generated in a photochemical reaction during a nanosecond laser pulse, and their optical absorption or that of the species formed by the addition is followed in the UV/Vis spectral range. If the reactant and product radicals do not absorb sufficiently, the reaction of interest is run in parallel to another reaction which yields a more easily followed indicator radical. The observation period lasts from about 50 ns to about 100 μ s after the pulse, with the lower limit governed by the laser pulse length and luminescence disturbances. Up to about 50 to 100 μ s there is usually little bimolecular radical termination so that the reactions of interest are followed under kinetic-isolation conditions. This, however, sets a lower limit to the straightforwardly accessible rate constants of about $10^5 \text{ M}^{-1} \text{ s}^{-1}$.

In determinations of lower rate constants, the radical termination can not be avoided. It is often diffusion controlled^[33] and competes with the addition process. In such cases, the rate constants can still be obtained with confidence if the radical signals are observed with sufficiently small noise levels and if all competing reactions are known. This is done by multiparameter fits of theoretical rate laws to the data. Detection by electron spin resonance^[33] is advantageous because of the clear separation of interfering radical signals, and the range of accessible rate constants is about 1 to $10^6 \text{ M}^{-1} \text{ s}^{-1}$.

Apart from these methods, pulse radiolysis initiation,^[34] modulation spectroscopy,^[35] and radical or product detection by muon spin rotation^[35] and electron or nuclear^[36] spin polarization, respectively, have also been used in time-resolving studies of absolute addition rates, and IR or Raman spectroscopy have future potential.^[37] Compilations of most

of the data known for low molecular weight systems are available.^[31]

In the polymer domain, the determination of precise rate constants for the addition of a propagating-chain radical to its monomer has been a long-standing problem. Time-resolved techniques still await application but considerable progress has been made through the invention of laser-pulse polymerization.^[38] In principle, one analyzes the distribution of the molecular weight of the polymer produced by a repetitive pulse initiation and its dependence on the time interval between the pulses. Of the many radicals formed during one pulse only a few survive. They grow by monomer addition until they are effectively scavenged by new radicals formed in the next pulse. Hence, the degree of polymerization shows a peak which depends linearly on the length of the time interval, the monomer concentration, and the propagation constant. Most often, size-exclusion chromatography is used to obtain the molecular-weight distribution, and calibrations and critical evaluations of the data are necessary.^[39]

3.2. Theoretical Procedures

An alternative to experiment as a source of quantitative information about radical-addition reactions is provided by ab initio molecular orbital theory.^[40, 41] Since the time of the Tedder and Giese reviews,^[6, 7] there have been substantial increases in the power of computers and significant advances in the algorithms used to carry out ab initio calculations. As a result, the cost of carrying out such calculations has decreased by a factor of approximately 100 000 during this period, allowing a much greater range of systems to be examined, and providing a greater reliability in the predictions. The theoretical approach consequently represents a useful partner to experiment in the study of radical reactivity.

The ab initio calculations enable the type of information displayed in Figure 1 to be obtained. The schematic potential-energy profile in Figure 1 corresponds to the reaction between a radical $R^\bullet$ and an alkene $CHA=CXY$, proceeding via a transition structure (TS) to give the product radical $RCHA-CXY^\bullet$. Properties that may be calculated include complete geometries (i.e. bond lengths, bond angles, and torsional angles) and vibrational frequencies of all species including the transition structure. The vibrational frequencies rigorously characterize stationary points on the potential energy surface as minima or first-order (or higher) saddle points and they are also useful (after scaling)^[42] in thermochemical and kinetic analyses. Because the determination of experimental geometries and vibrational frequencies is difficult for radicals and virtually impossible for transition structures, theory is playing a particularly useful role here. Theory can also be used to determine thermochemical quantities such as the reaction barrier and exothermicity. It also provides information on the direction and extent of charge transfer. An important feature of the ab initio calculations is that the properties of interest, for example, extent of charge transfer, reaction barrier or reaction enthalpy, can be obtained explicitly and directly.

We note that there are a broad variety of *ab initio* calculations, ranging from cheap and (potentially) nasty to expensive and very accurate. The quality of an *ab initio* calculation depends on two factors, namely the size of the basis set used in the calculation and the extent of incorporation of electron correlation. Better calculations are more expensive. In choosing the level of theory at which the calculations are to be performed, it is necessary to strike a compromise between the accuracy that is required and the computational expense that can be afforded. An important factor is that the computational cost of an *ab initio* calculation increases very rapidly with the size of the system that is being examined, roughly between the 2nd and 7th power of the number of electrons (for a given basis set).

It is beyond the scope of the present article to go into details concerning the theoretical procedures but it is appropriate to comment on various broad features, beginning with basis sets. Among commonly used basis sets developed by Pople and co-workers,^[40] STO-3G is a small basis set, 6-31G(d) (also called 6-31G*) is a medium-sized basis set, while large basis sets have names such as 6-311 + G(3df,2p). For a given system, the cost of the *ab initio* calculation increases rapidly as the basis set size increases.

Theoretical procedures that are in common use, listed in order of increasingly refined treatment of electron correlation (and cost), include Hartree–Fock (HF), Møller–Plesset perturbation theory truncated at second (MP2), third (MP3), or fourth (MP4) order, quadratic configuration interaction including single, double, and (perturbatively calculated) triple excitations (QCISD(T)), and coupled cluster theory (CCSD(T)). Density functional theory (DFT)^[43] is an attractive approach that is often highly cost effective, popular variants being B-LYP and B3-LYP. DFT offers the prospect of applicability to quite large systems because of the recent development of algorithms with so-called linear scaling with respect to the size of system or basis set.^[44]

There is an additional degree of freedom for calculations on open-shell systems such as the radicals involved in radical-addition reactions.^[45] The calculations may be carried out using either a wavefunction restricted, in terms of the electron spins, (restricted HF; RHF) or unrestricted (unrestricted HF; UHF) starting point. In the RHF procedure, the α and β orbitals are constrained to be the same. This has the advantage that the resultant wave function is a pure doublet, characterized by the spin-squared expectation value $\langle S^2 \rangle = 0.75$. On the other hand, if the α and β orbitals are allowed to be different, leading to the UHF procedure, the energy becomes lower. However, the wave function is no longer a pure doublet but is contaminated by states of higher spin multiplicity, as reflected in an $\langle S^2 \rangle$ value greater than 0.75. It is not clear beforehand which out of RHF or UHF is better.

When electron correlation is introduced, the procedures can be based on either UHF or RHF starting points. For example, Møller–Plesset perturbation theory can be based on UHF and is then denoted UMP. If there is severe spin contamination, there can be poor convergence in the Møller–Plesset expansion so that it may be inadvisable to use the UMP procedure (see, for example, references [46, 47]). There is generally a significant improvement with the use of

restricted Møller–Plesset theory (RMP)^[48] or projected Møller–Plesset theory (PMP)^[49] in such circumstances. For more sophisticated procedures, such as quadratic configuration interaction^[50] or coupled cluster,^[51] the difference between the unrestricted (UQCI, UCC) and restricted (RQCI, RCC) approaches is generally much smaller.^[52] DFT calculations also appear to show less spin contamination in the wave function.^[53] It has been argued that calculations using DFT should be carried out in the unrestricted form, for example, UB-LYP and UB3-LYP.^[54]

An *ab initio* calculation requires the specification of a correlation procedure and a basis set, and this defines the level of theory that is being used. For example, HF/STO-3G represents a very low level of theory. B3-LYP/6-31G(d) or MP2/6-31G(d) represent intermediate levels of theory while QCISD(T)/6-311+G(3df,2p) and CCSD(T)/6-311+G(3df,2p) represent high levels of theory. The ultimate level of theory, yielding the exact solution to the nonrelativistic Schrödinger equation, corresponds to full electron correlation with an infinite basis set. Unfortunately, this is not accessible in practice for normal systems, so an appropriate compromise is therefore necessary. In this connection, an essential element in the application of *ab initio* procedures is to assess the performance of a particular method in cases where the answer is known (either from experiment or high-level theory) before using that method to probe the unknown.

A number of theoretical methods attempt to obtain higher quality results from lower quality calculations (and hence to more closely approach the exact solution of the Schrödinger equation at lower cost) by taking advantage of additivity or extrapolation procedures. For example, the assumption of additivity of the basis set and correlation effects often holds reasonably well, and therefore lends itself to such an approach. Composite procedures of this type relevant to the present work include variants of the G2 and G3 procedures of Pople and co-workers,^[55] the CBS (complete basis set) procedures of Petersson and co-workers,^[56] and the extrapolation procedures (e.g. W1) of Martin.^[57]

4. Monosubstituted and 1,1-Disubstituted Alkenes

4.1. Experimental Results

4.1.1. Rate Constants

As described in Section 2.2, the addition of alkyl radicals to monosubstituted and 1,1-disubstituted alkenes is directed by the substituents to occur predominantly at the unsubstituted carbon atom and therefore should not be strongly affected by the individual steric demands of the alkene substituents. Therefore, we first discuss experimental data for this simplest situation and select radicals (Figure 4) which allow a case study for the action of enthalpy and polar effects alone. Besides the methyl radical,^[58] we include the resonance-stabilized benzyl radical,^[21, 59] and three other primary radicals, two with an electron-acceptor substituent (cyanomethyl^[60] and *tert*-butoxycarbonylmethyl^[60]) and one with an electron-donor substituent (hydroxymethyl^[61]), four tertiary

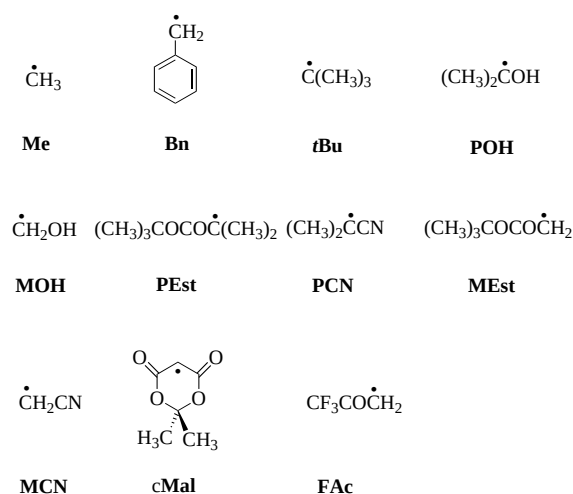


Figure 4. Radicals included in Tables 1 and 2 and in Figures 7, 8, and 12–15.

species, two with only donor substituents (*tert*-butyl^[35, 36a, 62] and 2-hydroxy-2-propyl^[36b, 63]) and two with two donor and one acceptor substituent (2-*tert*-butoxycarbonyl-2-propyl^[64] and 2-cyano-2-propyl^[65]). There are also two radicals with stronger electron-acceptor substitution, namely the cyclic malonyl radical, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl, derived from Meldrum's acid,^[66] and the trifluoroacetyl radical.^[64]

Table 1 gives absolute rate constants measured at or close to room temperature for the addition of these radicals to a variety of monosubstituted and 1,1-disubstituted alkenes in solution. The alkene substituents include electron-donating and electron-accepting groups with a wide range of radical-stabilizing properties, and the rate constants are believed to be accurate to better than a factor of two. For many systems, it was ascertained that the addition occurs, as expected, at the CH_2 group only. Table 1 clearly shows the enormous variability in the rate constants. They range from 14 to $2.7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, that is, they vary by more than seven orders of magnitude. To structure the data, the alkenes are listed according to increasing rate constants for the methyl radical additions, with the exception of the phenyl-substituted alkenes which are placed at the end, and the radicals are ordered according to the different polar effects. Loosely the reactions can be characterized by the following groupings.

Methyl and benzyl radicals do not exhibit strong polar effects. With alkene substitution their rate constants vary by a factor of 200 and in a similar manner. Benzyl reacts 100–1000 times (average 470) more slowly than methyl, and much of this difference may be a result of the radical stabilizing effect of the phenyl group.

tert-Butyl, 2-hydroxy-2-propyl, and hydroxymethyl are the most selective radicals in the series, since their rate constants vary by three to five orders of magnitude. In comparison to methyl, these electron-donor-substituted species react more slowly with electron-rich alkenes but much faster with electron-deficient alkenes. Moreover, their rate constants increase strongly with the electron-accepting power of the alkene substituents. Clearly, these radicals exhibit a strong nucleophilic polar effect, and they react faster with alkenes

bearing strong acceptor groups than with the phenyl-substituted alkenes, despite the exothermicity of addition being larger with the latter systems.

The radicals of the next group carry a carboxy or cyano substituent which should cause an electrophilic rate enhancement. Indeed, with most alkenes the primary species react faster than the methyl radical. Their tertiary counterparts react much more slowly (440 times for the carboxy-substituted and 210 times for the cyano-substituted radical, on average), but the reactivity pattern is similar. All four radicals are about equally selective as the methyl radical. The cyclic malonyl and trifluoroacetyl radicals react much faster than methyl with electron-rich alkenes but slower with alkenes bearing strong electron-acceptor groups, which means that these radicals are certainly electrophilic. However, they are less selective than methyl, because their rate constants for the non-phenyl-substituted alkenes vary only by factors of 10 to 100. For the electrophilic trifluoromethyl and perfluoro-*n*-alkyl radicals, the same trends have been observed.^[20, 67]

4.1.2. Frequency Factors and Activation Energies

For many but not all additions, the activation parameters have been determined from rate constants obtained at several temperatures, and the frequency factors are also presented in Table 1. For a given radical reacting with the various alkenes, these constants and factors center around a mean value. There are large deviations from the averages, but a comparison of all the data appears to show no systematic dependence on the alkene substitution. Instead, the large deviations often occur when the frequency factors and the activation energies are both either exceptionally low or high. This suggests that the scatter is mainly because of the known error correlation of the activation parameters, for which the χ^2 -surface over $\lg(A)$ and E_a has an extended minimum valley. Hence, we believe that the large deviations are accidental.

The frequency factors for the primary radicals center around $\lg(A/\text{M}^{-1} \text{ s}^{-1}) = 8.5$, and for the tertiary radicals they center around $\lg(A/\text{M}^{-1} \text{ s}^{-1}) = 7.5$. The frequency factor for the cyclic malonyl radical is larger, $\lg(A/\text{M}^{-1} \text{ s}^{-1}) = 8.7$, and the corresponding open-chain di-*tert*-butylmalonyl radical (not included in Table 1) has an intermediate value, $\lg(A/\text{M}^{-1} \text{ s}^{-1}) = 8.2$.^[66] Apart from this trend, there appears to be no systematic variation with specific radical substituents. The narrow ranges of the frequency factors are consistent with earlier notions^[6] and with the similar transition structures obtained theoretically for various additions (Figure 2 and Section 4.2.3). Moreover, the differences in $\lg(A)$ appear qualitatively reasonable. Tertiary radicals should show lower values than the primary radicals because they experience increased hindrance of the internal methyl rotations in the transition structure. By the same reasoning, the frequency factor of the open-chain secondary malonyl radical should be intermediate and that of the more rigid cyclic malonyl should be larger. Based on these findings we suggest that average frequency factors can be used to calculate satisfactory activation energies from rate constants observed at a single temperature, though the averages adopted and given below for the different

Table 1. Absolute rate constants [$\text{M}^{-1}\text{s}^{-1}$] and experimental frequency factors ($(\lg(A/\text{M}^{-1}\text{s}^{-1}))$ in parentheses) for the addition of carbon-centered radicals to monosubstituted and 1,1-disubstituted alkenes $\text{CH}_2=\text{CXY}$ in solution at or near room temperature. Radicals: Me = methyl, Bn = benzyl, *t*Bu = *tert*-butyl, POH = 2-hydroxy-2-propyl, MOH = hydroxymethyl, PEst = 2-*tert*-butoxycarbonyl-2-propyl = *iso*-butyryl, PCN = 2-cyano-2-propyl, MEst = *tert*-butoxycarbonylmethyl, MCN = cyanomethyl, cMal = 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl (a cyclic malonyl radical), FAc = trifluoroacetyl (see Figure 4).

$\text{CH}_2=\text{CXY}$ X,Y	Radical					
	nonpolar – nucleophilic Me/ Bn	nucleophilic <i>t</i> Bu	POH/ MOH	ambiphilic – electrophilic PEst/ PCN ^[a]	MEst/ MCN ^[b]	electrophilic cMal/ FAc
H,H ^[c]	3500	1250 (7.9)			1.1×10^4 3.3×10^3	2.0×10^4
H,Me	4300	920 (7.4)	410 (7.9) 270 (7.5)		7.5×10^4 (8.9) 1.2×10^4	1.7×10^5 1.9×10^5
H,Et ^[d]	7600 33	1100 (7.5)	300 (7.5)	34	5.4×10^4 (7.9) 1.1×10^4	2.2×10^5 2.8×10^5
Me,Me	8500	740 (7.7)	240 (8.0)		1.8×10^5 1.1×10^4	3.8×10^5 4.0×10^6
Me,OMe	1.2×10^4 21 (8.9)	220	1080 230 (8.1)	50 82	1.4×10^5 (8.1) 3.5×10^4 (8.9)	4.0×10^5 (8.6)
Me,OAc	1.2×10^4 46 (7.7)	1700	4850 680 (7.4)	58 79	8.8×10^4 (9.1) 1.2×10^4	5.8×10^5 (8.7) 3.0×10^5
H,OEt	1.4×10^4 14 (10.2)	390 (7.7)	320 180 (8.3)	75 108	1.5×10^5 (8.3) 4.3×10^4	3.0×10^5 (8.6)
H,OAc	1.4×10^4 (8.4) 15 (5.9)	4200 (7.2)	7500 590 (7.7)	18 41	6.5×10^4 (8.1) 1.3×10^4	4.0×10^5 (8.8) 2.0×10^5
H,Cl	2.0×10^4	1.6×10^4	5000 (8.3)		7.1×10^4 (8.4) 1.2×10^4	1.1×10^5 9.5×10^4
H,SiMe ₃	2.3×10^4 (8.1) 33 (8.4)	9600 (7.0)	2.5×10^4 2060 (7.8)	75 75	8.9×10^4 (8.3) 1.3×10^4 (8.4)	2.2×10^5 (8.5) 1.0×10^5
Me,Cl	3.5×10^4 43	1.1×10^4	2.2×10^4 2110 (7.9)	150 120	1.6×10^5 (8.4) 1.6×10^4 (8.9)	9.2×10^5 (8.8) 5.0×10^5
Cl,Cl	3.2×10^5 (8.9) 460 (8.5)	3.5×10^5 (8.0)	1.3×10^6 5.3×10^4 (8.1)	1170 (6.9) 603	2.7×10^5 3.3×10^4 (8.8)	3.9×10^5 (8.9) 3.3×10^5
H,CO ₂ Me	3.4×10^5 430 (7.7)	1.1×10^6	3.5×10^7 7.1×10^5 (8.7)	1150 (6.6) 370	4.9×10^5 1.1×10^5	1.1×10^5 (8.7) 1.3×10^5
Me,CO ₂ Me	4.9×10^5 (8.9) 2100 (8.1)	6.6×10^5	1.6×10^7 (9.0) 6.0×10^5 (8.6)	3710 1590	1.3×10^6 2.4×10^5	1.1×10^6 (8.9) 1.2×10^6
H,CN	6.1×10^5 2200 (8.9)	5.2×10^6	1.5×10^8 1.1×10^6 (8.3)	2640 (7.2) 2020	5.4×10^5 1.1×10^5 (8.4)	1.5×10^5 (8.9) 3.5×10^4
H,CHO	7.4×10^5 2500 (8.5)	2.8×10^6	2.7×10^8 2.1×10^6 (8.4)	1810 1200	3.8×10^5 2.5×10^4 (8.5)	1.1×10^5 (8.5) 6.4×10^4
Me,CN	7.9×10^5 (8.9) 6600 (8.4)	1.7×10^6	4.5×10^7 (8.9) 6.7×10^5 (8.2)	4460 1060	9.1×10^5 1.7×10^5	6.0×10^5 (8.7) 1.9×10^5
H,Ph	2.6×10^5 (8.9) 1100 (8.6)	1.3×10^5 (7.6)	7.3×10^5 (7.5) 2.3×10^4 (8.4)	5500 (6.7) 2410 (7.7)	1.9×10^6 3.8×10^5	1.2×10^6 (8.8) 6.3×10^6
Me,Ph	3.1×10^5 (8.8) 850 (9.6)	5.9×10^4	2.0×10^5 (7.5) 2.8×10^4 (8.6)	6030 2310	3.9×10^6 6.6×10^5	1.3×10^6 (8.7) 7.7×10^6
Ph,Ph	7.8×10^5 (7.9) 4100 (8.5)	1.0×10^6	7.1×10^5 (6.9) 1.4×10^5 (8.3)	1.0×10^4 (7.0) 7010	1×10^7 2.4×10^6	2.4×10^6 (8.6) 6.9×10^6
$\lg(A)_{\text{av}}^{\text{[e]}}$	8.6 ± 0.4 8.6 ± 0.3	7.3 ± 0.4	8.0 ± 0.9 8.1 ± 0.1	6.9 ± 0.3 7.7	8.4 ± 0.3 8.7 ± 0.3	8.7 ± 0.1

[a] 315 K. [b] 278 K. [c] Per CH_2 group, that is, the measured rate constants are divided by 2. [d] Also valid for H, *n*-alkyl. [e] Average including data for other alkenes not listed in the Table.

classes of radicals clearly need further experimental and theoretical verification.

Table 2 shows the activation energies for the reactions listed in Table 1, as calculated from the rate constants using the average values of $\lg(A/\text{M}^{-1}\text{s}^{-1}) = 8.5$ for methyl, benzyl, *tert*-butoxycarbonylmethyl, cyanomethyl, and trifluoroacetyl, = 8.2 for hydroxymethyl and di-*tert*-butylmalonyl, = 8.5 for the cyclic malonyl radical, and = 7.5 for all tertiary radicals. The activation energies range from about 42 kJ mol^{-1} down to values close to or set to zero.^[68] For the later analysis and for

comparisons with theoretical data, we also display the ionization energies (E_i) and the electron affinities (E_{ea}) of the radicals and the alkenes, taken from refs. [58, 66], the reaction enthalpy ($H_r(\text{Me})$) for the addition of the methyl radical to each alkene and the differences (ΔH_r) between the reaction enthalpies for the addition of methyl and for the other radicals. The reaction enthalpies $H_r(\text{Me})$ are only available for a very few methyl additions. Hence, the data given in Table 2 were deduced from other known quantities^[69, 70] and have considerable uncertainties^[58] because of the

Table 2. Activation energies E_a [kJ mol⁻¹] for the addition of carbon-centered radicals to monosubstituted and 1,1-disubstituted alkenes CH₂=CXY in solution, ionization energies E_i [eV], and electron affinities E_{ea} [eV] of radicals and alkenes, heats of addition $H_r(\text{Me})$ [kJ mol⁻¹] for the methyl radical, and differences $\Delta H_r = H_r(\text{R}) - H_r(\text{Me})$ for the addition of the other radicals R to ethene. All activation energies were calculated from the rate constants of Table 1 using average frequency factors (see text). For radical abbreviations, see Table 1 and Figure 4.

	Radical							
	nonpolar-nucleophilic Me	Bn ^[a]	nucleophilic tBu	POH/ MOH	ambiphilic-electrophilic PEst/ PCN	MEst/ MCN	electrophilic cMal ^[b]	FAc
$E_i(\text{R})$	9.8	7.2	6.7	6.5/7.6	7.7 ^[c] /8.5	9.8 ^[c] /10.3	11 ^[d]	10.9 ^[c]
$E_{ea}(\text{R})$	0.1	0.9	0.0	0.3/0.1	1.3 ^[c] /1.0	1.7 ^[c] /1.5	1.8 ^[d]	2.63
$\Delta H_r(\text{R})$	0	56	16	18/14	32/55	26/30	42	40
X,Y								
$E_i/E_{ea}/H_r(\text{Me})$								
H,H	28.2		25.3			24.8		24.0
10.5/ - 1.8/ - 99				33.6		26.5		
H,Me	27.7		26.1			20.2	19.8	18.4
9.7/ - 2.0/ - 97				34.6		23.5		
H,Et ^[f]	26.3	39.4	25.6			21.0	19.2	17.4
9.6/ - 1.9/ - 99				34.4	35.2	23.7		
Me,Me	26.0		26.6			18.1	17.8	10.9
9.2/ - 2.2/ - 98				34.9		23.7		
Me,OMe	25.1	40.5	29.6	25.3	33.1	18.7	17.7	
8.6/ - 2.5/ - 94				35.0	33.0	21.1	14.8	
Me,OAc	25.1	38.6	24.5	21.7	32.7	19.8	16.8	15.6
9.1/ - 1.5/ - 109				32.3	33.1	20.1		
H,OEt	24.8	41.5	28.2	28.4	32.1	18.5	18.4	
8.8/ - 2.2/ - 100				35.6	32.3	20.6		
H,OAc	24.8	41.4	22.3	20.6	35.6	20.5	17.7	18.3
9.2/ - 1.2/ - 101				32.7	34.7	23.3		
H,Cl	23.9		18.9			20.3	20.9	20.1
10.0/ - 1.3/ - 106				27.4		23.5		
H,SiMe ₃	23.5	39.4	20.2	17.7	32.1	19.8	19.2	18.1
9.5/ - 1.1/ - 101				29.6	33.2	23.3	16.5	
Me,Cl	22.5	38.8	19.8	17.9	30.4	18.3	15.6	
9.8/ - 1.4/ - 99				29.5	32.0	22.9		
Cl,Cl	17.0	33.0	11.2	9.4	25.3	17.1	17.7	17.0
9.8/ - 0.8/ - 125				21.5	27.9	21.2		
H,CO ₂ Me	16.9	33.1	8.4	0 ^[e]	25.3	15.6	20.9	19.4
9.9/ - 0.5/ - 117		26.0		15.1	29.1	18.4	16.7	
Me,CO ₂ Me	16.0	29.2	9.7	2.6	22.4	13.3	15.2	13.8
9.5/ - 0.4/ - 119		23.0		15.5	25.4	16.6		
H,CN	15.4	29.1	4.5	0 ^[e]	23.3	15.4	20.1	22.6
10.9/ - 0.2/ - 139		23.5		14.0	24.8	18.4	16.3	
H,CHO	15.0	28.8	6.0	0 ^[e]	24.2	16.2	20.9	21.1
10.1/0.0/ - 122				12.4	26.1	21.8	15.3	
Me,CN	14.9	26.4	7.3	0 ^[e]	22.0	14.1	16.7	18.4
10.3/ - 0.2/ - 130				15.3	26.4	17.4		
H,Ph	17.5	30.8	13.7	10.2	21.5	8.3	15.0	9.7
8.4/ - 0.3/ - 150		25.0		23.6	24.3	15.5		
Me,Ph	17.1	31.5	15.7	13.1	21.2	10.6	14.8	9.2
8.2/ - 0.2/ - 144				23.1	24.4	14.3		
Ph,Ph	14.8	28.9	8.6	7.4	20.0	14.5	13.2	9.5
8.0/0.4/ - 153		22.1		19.1	21.6	11.3		

[a] Where two values are given, the second refers to the cumyl radical (rate constants not included in Table 1).^[59] [b] Where two values are given, the second refers to the di-*tert*-butylmalonyl radical (rate constants not included in Table 1).^[66] [c] Calculated values, A. P. Scott, personal communication. References to all other ionization energies and electron affinities are given in ref. [58–66]. [d] Data for the di-*tert*-butylmalonyl radical. [e] The rate constants are higher than the average frequency factor of A ($10^{7.5} \text{ M}^{-1} \text{ s}^{-1}$) for tertiary alkyl radicals. Hence, the activation energy of the addition step was set to zero.^[68] [f] Also valid for H, *n*-alkyl.

imprecision in the available C–H bond dissociation energies. The increments $\Delta H_r^{[71]}$ are also subject to uncertainties, and their use for all alkenes assumes that the effect of γ substituents on the bond dissociation energies is independent of the α substituents.

4.1.3. Phase and Solvent Effects

In the course of this review, we will compare experimental activation energies with theoretical reaction barriers. The experimental data refer to liquid solution at ambient pressure

while the theoretical results are obtained for isolated reaction systems. Hence, a consideration of possible phase and solvent effects is appropriate.

Table 3 shows experimental rate constants and activation parameters for several addition reactions in the liquid and in the gas phase. The gas-phase data were obtained at pressures high enough to disperse the excess heat of reaction very rapidly. At room temperature, all listed gas-phase rate constants are smaller than the liquid-phase values, by an average factor of ten, but the variation with radical and substrate structure are generally rather similar. As in the liquid phase (Table 1), the frequency factors of the gas-phase reactions scatter considerably, which again suggests effects of the error correlation of the activation parameters. Interestingly, for the additions of the methyl radical to monosubstituted and 1,1-disubstituted alkenes, the average gas-phase frequency factor is $\lg(A/\text{M}^{-1}\text{s}^{-1}) = 8.50 \pm 0.75$, and practically identical to the mean reaction-in-solution value. On average, the experimental gas-phase activation energies are higher than their solution counterparts by 2.1 kJ mol^{-1} , however, when considered in detail larger differences are noticed. The close similarity of the mean frequency factors suggests that the average values found above for solutions may be adopted also for the gas phase. Using these, the reported rate constants lead to somewhat more unified gas-phase activation energies which are also shown in Table 3. Their variation with radical and substrate structure closely parallels that established for solutions.

On average, the recalculated activation energies are larger by $6.5 \pm 2.3 \text{ kJ mol}^{-1}$ for the gas than for the liquid phase, and the same trend was previously recognized in the analysis of a larger data set.^[58] However, the straightforward conclusion that there is a significant, general difference, between gas-phase and liquid-phase rate constants caused mainly by different activation energies, not frequency factors, is subject to considerable uncertainty. Firstly, all gas-phase data date back many years and have been determined relative to other rate constants that are not yet firmly established.^[73] Secondly, the difference is also not explained easily because there is no generally accepted theory which relates gas-phase to liquid-phase rate data. A simple explanation of a larger gas-phase activation energy is based on the Eyring equation and the

difference of the thermal expansion coefficients of the two phases.^[74, 75] It leads to the prediction that reaction barriers calculated for isolated systems should be larger than liquid-phase activation energies by $RT = 2.5 \text{ kJ mol}^{-1}$ at room temperature and the frequency factors should also be higher so that the rate constants remain equal. This is not the case in practice. Another possible explanation is suggested by the negative activation volume of the addition reactions ($\Delta V^\ddagger = -11 \text{ to } -17 \text{ cm}^3 \text{ mol}^{-1}$). This is known from polymerizations in solution^[76] and leads to an increase in the rate constants with increasing pressure, as expected from Le Chatelier's principle.^[77] In liquids the molecules are held together by cohesive forces, and these will operate on the reactants and the transition state. These forces are equivalent to considerable internal liquid pressures of many thousand bars, and it has been suggested that this internal pressure influences the reaction rates as an external pressure.^[78b,c] With this assumption, a general difference of the activation energies between the gas and liquid phase can, in fact, be obtained, and it is even of the correct order of magnitude.^[77]

Further evidence for effects of molecular interactions, in the liquid phase, on rate constants of radical addition reactions is given by the small but noticeable dependence of these constants on solvent polarity.^[79] An increase in the rate constant with increasing solvent polarity would generally be expected if the transition structure is more polar than the parent reactants. This pattern is observed for the addition of the hex-5-enyl radical to the electron-deficient alkenes, methylacrylate and acrylonitrile,^[80a] and to nitroso and nitron spin traps,^[80b] and for the addition of the *tert*-butyl radical to acrylonitrile.^[80c] These alkyl radicals exhibit some nucleophilic character in such reactions so that there is charge transfer in the transition state. For the addition of the *tert*-butyl radical to acrylonitrile, the rate constant increases by a factor of 3.6 upon replacement of the nonpolar solvent tetradecane by the much more polar solvent acetonitrile, from this result the transferred charge was estimated as 0.23 elementary charges.^[80c] For the addition of thiyl radicals to alkenes, opposite solvent polarity effects are known, and these are presumably because of the partial loss of the large radical dipole moment during formation of the transition state.^[80d]

Table 3. Rate constants k [$\text{M}^{-1}\text{s}^{-1}$] at 298 K,^[a] frequency factors A [$\text{M}^{-1}\text{s}^{-1}$], and activation energies E_a [kJ mol^{-1}]^[b] for the addition of carbon-centered radicals to unsaturated molecules in the liquid (l) and the medium-pressure gas phase (g).^[c]

Reaction	k^l	k^g	k^l/k^g	$\lg(A^l)$	$\lg(A^g)$	$E_a^{l[b]}$	$E_a^{g[b]}$
$\cdot\text{CH}_3 + \text{CH}_2=\text{CH}_2$	7000 ^[58b]	850 ^[72]	8.2	9.0 ^[d]	8.0 ^[d]	31.4/28.2	30.8/33.5
$\cdot\text{CH}_3 + \text{CH}_2=\text{CHCH}_3$	4300 ^[58b]	500 ^[73]	8.6	9.3	7.9	32.3/27.7	29.7/33.1
$\cdot\text{CH}_3 + \text{CH}_2=\text{CHC}_2\text{H}_5$	7600 ^[58b]	530 ^[73]	14	7.8	8.0	22.5/26.3	30.1/33.0
$\cdot\text{CH}_3 + \text{CH}_2=\text{C}(\text{CH}_3)_2$	8500 ^[58b]	1400 ^[73]	6.1	8.9	8.2	28.1/26.0	28.9/30.5
$\cdot\text{CH}_3 + \text{CH}_2=\text{CHF}$	4600 ^[58b]	560 ^[73]	8.2	–	9.2	–/27.6	36.8/32.8
$\cdot\text{CH}_3 + \text{CH}_2=\text{CHCl}$	20000 ^[58b]	1100 ^[72]	18	–	9.7	–/23.9	38.1/31.1
$\cdot\text{CH}_3 + \text{CH}\equiv\text{CH}$	4800 ^[58b]	1400 ^[72]	3.4	9.4 ^[d]	8.5 ^[d]	34.3/33.2	32.2/36.2
$\cdot\text{CH}_3 + \text{CH}\equiv\text{CCH}_3$	2200 ^[58b]	180 ^[73]	12	8.8	8.7	31.1/33.4	36.8/39.6
$\cdot\text{C}(\text{CH}_3)_3 + \text{CH}_2=\text{CH}_2$	2500 ^[62a]	30 ^[73]	83	7.9 ^[d]	7.0 ^[d]	27.6/25.1	33.4/36.1

[a] Liquid-phase values were taken from Table 1 or calculated from the activation parameters. For vinyl fluoride and vinyl chloride, k_{338} was converted into k_{298} using the recommended frequency factor $\lg(A/[\text{M}^{-1}\text{s}^{-1}]) = 8.5$ for additions of primary alkyl radicals to CH_2 groups (see text). Gas-phase values were calculated from the reported activation parameters. [b] The first entry is the reported experimental activation energy. The second value was calculated from the rate constants of columns 3 and 4 with the frequency factors recommended in this work of $\lg(A/[\text{M}^{-1}\text{s}^{-1}]) = 8.5$ for additions of primary alkyl radicals to individual CH_2 groups, $\lg(A/[\text{M}^{-1}\text{s}^{-1}]) = 9.2$ for additions of primary alkyl radicals to individual $\text{CH}\equiv$ groups, and $\lg(A/[\text{M}^{-1}\text{s}^{-1}]) = 7.5$ for additions of tertiary alkyl radicals to individual CH_2 groups (see text). [c] Where more than one set of gas-phase data are available, the most recent data are used. For vinyl chloride, a second available data set^[73] gives an unreasonably large ratio $k^l/k^g = 1800$. [d] Per CH_2 or $\text{CH}\equiv$ group.

In summary, radical addition rate constants appear to be about one order of magnitude larger in solution than in the gas phase, probably because of a smaller activation energy. However, the rate constants and activation energies in the two phases vary similarly with radical and substrate structure. Changes in solvent polarity cause only small rate variations. Hence, theoretical reaction barriers which are calculated for isolated systems may exceed the barriers of liquid-phase reactions by a few kJ mol^{-1} .

4.2. Theoretical Results

4.2.1. Reaction Barriers

A number of studies have shown that it is not straightforward to obtain a reliable theoretical description of radical addition.^[81] It is important therefore to assess which theoretical methods are suitable for studying such reactions.^[12, 13, 82, 83]

The pattern of results obtained is exemplified by the barriers for methyl radical addition to ethene, calculated with a wide variety of theoretical procedures (Table 4).^[12, 13, 82] The experimental barriers with which to make comparison, obtained from the observed activation energies after back-correcting for temperature and zero-point energy effects,^[82, 84] are either 25.7 kJ mol^{-1} from the gas-phase studies^[72] or 21.3 kJ mol^{-1} from the liquid phase results.^[58] The calculated barriers show a massive dependence on the level of theory used. They range from 7 kJ mol^{-1} for the widely used AM1

semiempirical procedure to nearly 90 kJ mol^{-1} for RHF. The commonly used UMP2 procedure also gives a very high barrier of 60 kJ mol^{-1} . The best levels of theory include variants of the G2(MP2,SVP),^[85] G3,^[86] G3(MP2),^[87, 88] CBS-RAD,^[89] CBS-QB3,^[90] and W1^[57] procedures and give barriers in the range $20.5\text{--}28.6 \text{ kJ mol}^{-1}$, respectably close to the experimental values. The UB3-LYP DFT procedure also gives satisfactory results, including values of 18.3 kJ mol^{-1} (UB3-LYP/6-31G(d)) and 25.0 kJ mol^{-1} (UB3-LYP/6-311+G(d,p)) for small- to moderate-sized basis sets that would be practical to use for calculations on large systems. We note that UB3-LYP and other DFT procedures are found to be less successful in describing hydrogen-addition reactions, significantly underestimating the reaction barriers.^[12, 81o]

The results in Table 4 indicate that the calculated barriers are very sensitive to the choice of theoretical procedure but less sensitive to the choice of basis set. Changes in going from the smallest (6-31G(d)) to the largest (6-311+G(3df,2p)) basis set are typically less than 7 kJ mol^{-1} . Barone and co-workers^[81i] have reported that the B3-LYP results with small basis sets can be further improved by consideration of basis set superposition errors (BSSEs). The effect of the different choice of geometries in the calculations is also relatively small, generally amounting to less than 5 kJ mol^{-1} , though some instances have been encountered where there are larger variations, with UMP2 geometries in particular giving poor results.^[12] Use of the B3-LYP procedure, even with a basis set as small as 6-31G(d), is very cost-effective for geometry and frequency calculations.

The theoretical results do not fully answer the question of whether or not there is a systematic difference between the gas-phase and condensed-phase barriers beyond the correction factor of RT (that has been applied here for back-correction purposes). Some of the high-level theoretical procedures (G2(MP2,SVP), G3(MP2)//B3-LYP, G3(MP2)-RAD, G3//B3-LYP, and W1) give barriers in the range $26.6\text{--}28.6 \text{ kJ mol}^{-1}$, close to the value of 25.7 kJ mol^{-1} derived from older gas-phase experimental data.^[72] On the other hand, other high-level theoretical procedures (CBS-RAD and CBS-QB3) give barriers in the range $20.5\text{--}20.9 \text{ kJ mol}^{-1}$, close to the barrier of 21.3 kJ mol^{-1} derived from recent condensed-phase experimental data.^[58] Although it is not possible to settle on a precise gas-phase barrier at the present time, it is satisfying that all the high-level theoretical barriers and the experimental barriers lie within the relatively narrow range of $20\text{--}29 \text{ kJ mol}^{-1}$.

Because the primary interest in chemical studies is often concerned with trends rather than absolute quantities, it is desirable to examine whether trends are predicted well with the simpler levels of theory. A selection of the results that enable us to examine the performance of theory in predicting relative barriers is shown in Table 5.^[12, 82] The results obtained with the CBS-RAD method are taken to be the most reliable and the substituents are arranged in Table 5 with the CBS-RAD calculated barriers in decreasing order. We can then examine results at the other levels to see how they compare. AM1 is very poor. UMP2 is also very poor. The trend, that is, steadily decreasing barriers, is not reproduced at all. If anything, it goes the other way. The results from UHF

Table 4. Effect of level of theory on calculated barriers E_a [kJ mol^{-1}] for the addition of a methyl radical ($\cdot\text{CH}_3$) to ethene ($\text{CH}_2=\text{CH}_2$).^[a]

Level	E_a	Level	E_a
AM1	7.1	UB3-LYP/6-311+G(d,p) ^[d,e]	25.0
UHF	39.4	UQCISD(T)/6-311+G(d,p) ^[c,d]	30.0
UMP2	60.1	UCCSD(T)/6-311+G(d,p) ^[c,d]	30.8
UMP4	53.7	URCCSD(T)/6-311+G(d,p) ^[c,d]	29.5
PMP2	20.1	UMP2/6-311+G(3df,2p) ^[e,f]	57.5
PMP4	21.5	PMP2/6-311+G(3df,2p) ^[e,f]	20.9
RHF	89.7	RMP2/6-311+G(3df,2p) ^[e,f]	34.4
RMP2	40.3	UB-LYP/6-311+G(3df,2p) ^[b,e]	20.7
RMP4	38.2	UB3-LYP/6-311+G(3df,2p) ^[d,e]	25.6
UB-LYP ^[b]	13.2	G2(MP2,SVP) ^[e,f]	28.6
UB3-LYP ^[c]	14.6	G3(MP2)//B3-LYP ^[c,d]	28.3
UB3-LYP ^[d,e]	18.3	G3(MP2)-RAD ^[c,d]	27.2
UQCISD	35.5	G3//B3-LYP ^[c,d]	26.6
UQCISD(T)	31.7	CBS-RAD ^[c,d]	20.5
UQCISD(T) ^[e,f]	33.8	CBS-RAD ^[e,f]	20.9
UCCSD(T) ^[c,d]	32.7	CBS-QB3 ^[c,g]	20.7
URCCSD(T) ^[c,d]	31.4	W1 ^[c,h]	27.0
URCCSD(T) ^[c,f]	33.7	exp. ^[i]	21.3
		exp. ^[j]	25.7

[a] 6-31G(d) basis set, UHF/6-31G(d) geometries, from ref. [12], unless otherwise specified. Calculated in all cases without the inclusion of zero-point vibrational energies. [b] UB-LYP/6-31G(d) geometry. [c] From ref. [13]. [d] UB3-LYP/6-31G(d) geometry. [e] From ref. [82]. [f] UQCISD/6-31G(d) geometry. [g] UB3-LYP/6-311G(2d,d,p) geometry. [h] UB3-LYP/cc-pVTZ+1 geometry. [i] Solution-phase value at 298 K (28.2 kJ mol^{-1}) from ref. [58], back-corrected to 0 K ($+2.2 \text{ kJ mol}^{-1}$) and for zero-point vibrational energy (ZPVE; 9.1 kJ mol^{-1}). Corrections from ref. [82]. [j] Gas-phase value at 403 K (33.1 kJ mol^{-1}) from ref. [72], back-corrected to 0 K ($+1.7 \text{ kJ mol}^{-1}$) and for ZPVE (9.1 kJ mol^{-1}). Corrections from ref. [82].

Table 5. Effect of level of theory on calculated activation energy barriers [kJ mol⁻¹] for the addition of a methyl radical ($\cdot\text{CH}_3$) to alkenes ($\text{CH}_2=\text{CHX}$).^[a]

X	AM1	UHF	UB-LYP ^[b]	UB3-LYP ^[c,d]	UMP2	PMP2	RMP2	UQCISD	UQCISD(T)	CBS-RAD ^[d,e]
OH	3.3	50.3	13.1	20.0	62.8	24.7	40.4	36.5	32.2	21.7
F	0.3	43.6	13.2	19.1	62.4	22.2	40.8	35.8	31.8	21.4
H	7.1	39.4	13.2	18.3	60.1	20.1	40.3	35.5	31.7	20.9
CH ₃	5.5	42.2	13.4	18.8	60.6	21.0	38.3	34.8	30.7	19.9
NH ₂	0.3	48.2	9.9	16.9	59.4	21.9	37.1	33.7	29.2	19.1
SiH ₃	7.3	36.9	9.6	14.7	55.6	17.2	33.5	29.4	25.6	14.9
Cl	2.9	34.5	9.0	13.9	56.6	15.8	33.3	29.4	25.5	13.8
CHO	2.5	21.6	1.3	6.4	73.8	9.6	23.7	23.3	18.8	7.5
CN	2.1	19.9	1.1	5.4	68.6	6.8	21.3	20.6	16.7	6.6
R^2 ^[f]	0.02	0.89	0.95	0.98	0.35	0.96	0.98	0.99	0.99	1.00

[a] 6-31G(d) basis set, UHF/6-31G(d) geometries, from ref. [12], unless otherwise specified. Calculated without the inclusion of ZPVEs. [b] UB-LYP/6-31G(d) geometries. [c] UB3-LYP/6-31G(d) geometries. [d] From ref. [82]. [e] UQCISD/6-31G(d) geometries. [f] The R^2 values refer to the correlation with CBS-RAD calculated activation energy barriers.

calculations are not particularly good but are much better than those from UMP2. The other procedures—UB-LYP, UB3-LYP, PMP2, RMP2, UQCISD, and UQCISD(T)—are very respectable in reproducing the trends, even though the absolute values are sometimes quite poor. These qualitative observations are mirrored in calculated correlation coefficients, also included in Table 5. The regression factor values (R^2) listed are for correlations of barriers calculated with the simpler methods against barriers calculated by CBS-RAD. QCISD and QCISD(T) are very good with R^2 values above 0.99. RMP2, UB3-LYP, PMP2, and UB-LYP are all reasonably good,^[91] with R^2 values in the 0.95–0.98 range while AM1 is hopeless, with a correlation coefficient of 0.017. UMP2 is also very bad.

The assessment work touched-on here but described in detail elsewhere,^[12, 13, 82] suggests standard levels of theory that might be useful in theoretical studies of radical-addition reactions and it suggests other levels of theory that should be

avoided. For small systems, CBS-RAD and G3(MP2)-RAD are attractive levels of theory, while for larger systems, B3-LYP/6-31G(d), B3-LYP/6-311+G(d,p), or B3-LYP/6-311+G(3df,2p) would all be expected to perform satisfactorily. B3-LYP/6-31G(d) geometries and (scaled) vibrational frequencies (for calculating zero-point energies and thermal enthalpy corrections) are recommended for general use. At the other end of the scale, the UMP2 procedure can be very unreliable because of spin contamination.

The performance of some of the preferred levels of theory can be tested against the experimental results from Table 2 in cases for which both theoretical and experimental data are available (Table 6). The experimental liquid phase barriers at 298 K are back-corrected to 0 K in these comparisons. It can be seen that CBS-RAD and UB3-LYP/6-31G(d) give results in good agreement with experiment barriers, with mean absolute deviations from experiment of 1.7 and 2.6 kJ mol⁻¹, respectively. G3(MP2)-RAD, UB3-LYP/6-311+G(d,p), and

Table 6. Comparison of theoretical^[a] and experimental activation energy barriers [kJ mol⁻¹] at 0 K for the addition of a methyl radical ($\cdot\text{CH}_3$) to alkenes ($\text{CH}_2=\text{CXY}$).

X	Y	UB3-LYP/ 6-31G(d)	UB3-LYP/ 6-311+G(d,p)	UB3-LYP/ 6-311+G(3df,2p)	CBS-RAD	G3(MP2)-RAD	exp. ^[b]
H	H	27.4 ^[c]	34.1 ^[c]	34.7 ^[c]	29.7	36.2	30.4
H	Me	27.0 ^[c]	33.7 ^[c]	34.5 ^[c]	27.6	34.8	29.0
H	Et	26.9	33.6	34.4	26.8	34.5	27.5
Me	Me	26.2	32.3	33.2	25.3	32.8	26.8
Me	OMe	29.5	35.6	36.7		36.8	28.2
H	OEt	30.0	36.5	37.4		38.3	28.3
H	OAc	24.6	30.3	31.3		32.4	29.9
H	Cl	22.2 ^[c]	28.3 ^[c]	29.3 ^[c]	22.2	29.2	25.2
H	SiH ₃	23.1	29.9	30.2	23.1	29.9	24.8 ^[d]
Me	Cl	22.2	28.0	28.7	20.4	27.8	23.1
Cl	Cl	17.3	22.7	23.2	16.7	22.2	17.4
H	CO ₂ Me	14.5	20.5	21.0		21.1	17.6
H	CN	13.1 ^[c]	18.9 ^[c]	19.5 ^[c]	13.8	21.1	16.4
H	CHO	14.3 ^[c]	20.1 ^[c]	20.7 ^[c]	14.6	22.6	16.0
Me	CN	14.2	19.8	20.5		20.7	15.3
MOH ^[e]		25.8 ^[c]	34.2 ^[c]	35.4 ^[c]	27.6	34.1	36.9
MCN ^[f]		32.3 ^[c]	39.6 ^[c]	40.4 ^[c]	28.8	35.7	30.0
MAD ^[g]		2.6	4.7	5.3	1.7	5.4	
R^2 ^[h]		0.77	0.81	0.83	0.87	0.82	

[a] UB3-LYP/6-31G(d) geometries, from ref. [13] unless otherwise specified. [b] Experimental values from Table 2, back-corrected to 0 K using thermal temperature corrections from refs. [13, 82]. [c] From ref. [82]. [d] Experimental barrier is for the SiMe₃ substituent. [e] Barrier for the addition of MOH ($\cdot\text{CH}_2\text{OH}$) to ethene. [f] Barrier for the addition of MCN ($\cdot\text{CH}_2\text{CN}$) to ethene. [g] MAD = mean absolute deviations from experiment. [h] The R^2 value refers to the correlation with experimental barriers.

UB3-LYP/6-311+G(3df,2p), on the other hand, appear to overestimate the liquid-phase barriers but the differences appear to be quite systematic, and the R^2 correlation coefficients when compared with the experimental barriers are 0.82, 0.81, and 0.83, respectively. That the B3-LYP deviations from experiment increase with increasing basis-set size indicates that the very good agreement observed for B3-LYP/6-31G(d) is partly fortuitous. Although the B3-LYP/6-31G(d) method seems to represent a potentially very cost-effective means of obtaining satisfactory barriers for radical-addition reactions, further work is required to see whether the good performance holds more generally.

4.2.2. Reaction Enthalpies

The calculated reaction enthalpies for the addition of methyl radical to ethene are less sensitive than the barriers to the level of theory used (Table 7). The high-level procedures give values from -105.6 to -111.5 kJ mol $^{-1}$, compared with the corrected experimental value of -113.1 kJ mol $^{-1}$. The UB3-LYP/6-311+G(3df,2p) method gives one of the poorest results of -99.0 kJ mol $^{-1}$.

The variation in reaction enthalpy with substitution on the alkene is examined in Table 8. Assuming again that the CBS-RAD results are the most reliable, we can see that AM1 is very poor, UMP2 is also poor in several instances while the other procedures give quite reasonable results. UHF and B3-LYP underestimate the exothermicity while the other methods, particularly RMP2, overestimate the exothermicity. The deviations in the calculated reaction enthalpies from the experimental estimates are, however, quite systematic and the correlation coefficients with CBS-RAD are very reasonable (for methods other than AM1 and UMP2), with R^2 values of 0.93 for UHF and in the range 0.98–0.99 for the other procedures.^[91]

The performance of the standard procedures in calculating reaction enthalpies is compared in Table 9 with the estimates derived from experimental data (taken from Table 2 and back-corrected to 0 K). As has been pointed out above, there are considerable uncertainties in the experimental values because of the imprecision of the C–H bond dissociation energies and possible deviations from additivity assumed in their derivation. We can see that B3-LYP/6-31G(d) system-

Table 7. Effect of level of theory on calculated reaction enthalpies [kJ mol $^{-1}$] for the addition of a methyl radical ($\cdot\text{CH}_3$) to ethene ($\text{CH}_2=\text{CH}_2$).^[a]

Level	Enthalpy	Level	Enthalpy
AM1	–157.5	UB3-LYP/6-311+G(d,p) ^[d,e]	–101.5
UHF	–107.7	UQCISD(T)/6-311+G(d,p) ^[c,d]	–110.5
UMP2	–123.6	UCCSD(T)/6-311+G(d,p) ^[c,d]	–110.4
UMP4	–116.9	URCCSD(T)/6-311+G(d,p) ^[c,d]	–110.5
PMP2	–123.8	UMP2/6-311+G(3df,2p) ^[e,f]	–116.4
PMP4	–117.0	PMP2/6-311+G(3df,2p) ^[e,f]	–116.9
RHF	–107.4	RMP2/6-311+G(3df,2p) ^[e,f]	–117.0
RMP2	–124.2	UB-LYP/6-311+G(3df,2p) ^[b,e]	–85.5
RMP4	–117.0	UB3-LYP/6-311+G(3df,2p) ^[d,e]	–99.0
UB-LYP ^[b]	–107.1	G2(MP2,SVP) ^[e,f]	–106.5
UB3-LYP ^[c]	–120.1	G3(MP2)//B3-LYP ^[c,d]	–105.6
UB3-LYP ^[d,e]	–119.8	G3(MP2)-RAD ^[c,d]	–105.7
UQCISD	–115.6	G3//B3-LYP ^[c,d]	–107.4
UQCISD(T)	–114.4	CBS-RAD ^[c,d]	–111.0
UQCISD(T) ^[e,f]	–112.7	CBS-RAD ^[e,f]	–111.5
UCCSD(T) ^[c,d]	–112.8	CBS-QB3 ^[c,g]	–111.2
URCCSD(T) ^[c,d]	–112.9	exp. ^[h]	–113.1
URCCSD(T) ^[c,f]	–112.7		

[a] 6-31G(d) basis set, UHF/6-31G(d) geometries, from ref. [12], unless otherwise specified. Calculated in all cases without the inclusion of ZPVEs. [b] UB-LYP/6-31G(d) geometry. [c] From ref. [13]. [d] UB3-LYP/6-31G(d) geometry. [e] From ref. [82]. [f] UQCISD/6-31G(d) geometry. [g] B3-LYP/6-311G(2d,d,p) geometry. [h] Gas-phase value at 298 K (-99 kJ mol $^{-1}$) from Table 2, back-corrected to 0 K ($+5.7$ kJ mol $^{-1}$) and for ZPVE (-19.8 kJ mol $^{-1}$). Corrections from ref. [82].

atically overestimates the exothermicity while the larger basis set B3-LYP procedures significantly underestimate the exothermicity. G3(MP2)-RAD generally slightly underestimates the exothermicity while CBS-RAD appears to perform best. The differences between theory and experiment are quite systematic again for all five procedures, with correlation coefficients in the range 0.91–0.93.

4.2.3. Geometries

One of the properties that is not accessible from experiment, at least at the present time, is the geometry of the transition structure for the radical-addition reactions (Figure 2). On the other hand, this can be obtained straightforwardly by ab initio methods and we comment here on some of the more interesting findings.

The first point is that the angle of approach (ϕ) of the radical to the alkene lies within a narrow band of values for a

Table 8. Effect of level of theory on calculated reaction enthalpies [kJ mol $^{-1}$] for the addition of a methyl radical ($\cdot\text{CH}_3$) to alkenes ($\text{CH}_2=\text{CHX}$).^[a]

X	AM1	UHF	UB-LYP ^[b]	UB3-LYP ^[c,d]	UMP2	PMP2	RMP2	UQCISD	UQCISD(T)	CBS-RAD ^[d,e]
OH	–168.5	–101.8	–106.7	–118.0	–122.5	–121.7	–123.7	–118.8	–117.6	–115.2
F	–185.1	–109.9	–111.6	–123.4	–127.6	–126.7	–128.5	–121.7	–120.4	–116.2
H	–157.5	–107.7	–107.1	–119.8	–123.6	–123.8	–124.2	–115.6	–114.4	–111.5
CH ₃	–166.1	–105.6	–106.8	–118.7	–122.0	–122.4	–123.0	–116.7	–115.6	–113.4
NH ₂	–185.1	–107.0	–115.4	–127.1	–129.9	–129.3	–131.4	–126.3	–125.6	–123.6
SiH ₃	–156.5	–113.7	–118.5	–130.1	–130.2	–130.1	–131.4	–126.3	–124.8	–121.8
Cl	–172.0	–118.9	–121.5	–134.2	–135.1	–135.7	–136.7	–130.4	–129.5	–129.9
CHO	–169.1	–144.1	–142.8	–154.2	–123.1	–153.1	–157.5	–152.2	–151.3	–148.4
CN	–172.3	–143.7	–147.6	–158.1	–122.6	–154.8	–160.0	–153.0	–151.4	–150.5
R^2 ^[f]	0.02	0.93	0.98	0.98	0.00	0.98	0.98	0.99	0.99	1.00

[a] 6-31G(d) basis set, UHF/6-31G(d) geometries, from ref. [12], unless otherwise specified. Calculated without the inclusion of ZPVEs. [b] UB-LYP/6-31G(d) geometries. [c] UB3-LYP/6-31G(d) geometries. [d] From ref. [82]. [e] UQCISD/6-31G(d) geometries. [f] The R^2 values refer to the correlation with the calculated CBS-RAD reaction enthalpies.

Table 9. Comparison of theoretical^[a] and experimental reaction enthalpies [kJ mol⁻¹] at 0 K for the addition of a methyl radical ($\cdot\text{CH}_3$) to alkenes ($\text{CH}_2=\text{CXY}$).

X	Y	UB3-LYP/ 6-31G(d)	UB3-LYP/ 6-311+G(d,p)	UB3-LYP/ 6-311+G(3df,2p)	CBS-RAD	G3(MP2)-RAD	exp. ^[b]
H	H	-100.0 ^[c]	-81.7 ^[c]	-79.3 ^[c]	-91.3	-86.3	-93.3
H	Me	-100.8	-82.5	-80.1	-93.6	-86.7	-92.2
H	Et	-100.8	-82.8	-80.4	-94.6	-87.1	-94.2
Me	Me	-96.5	-78.6	-75.7	-91.6	-82.9	-93.6
Me	OMe	-89.6	-72.0	-68.7			-89.2
H	OEt	-99.8	-83.0	-80.0		-86.7	-95.1
H	OAc	-105.7	-89.1	-86.0		-92.7	-95.9
H	Cl	-112.3 ^[c]	-93.9 ^[c]	-92.0 ^[c]	-107.1	-98.8	-100.8
H	SiH ₃	-108.5	-90.6	-88.5	-100.6	-95.0	-95.8 ^[d]
Me	Cl	-110.5	-91.8	-89.7	-108.3	-96.9	-93.6
Cl	Cl	-127.7	-109.0	-107.5	-124.6	-114.1	-119.6
H	CO ₂ Me	-123.7	-105.8	-103.3		-107.4	-111.5
H	CN	-136.3	-117.5	-115.4	-130.4	-118.7	-133.3
H	CHO	-131.1 ^[c]	-112.7 ^[c]	-110.1 ^[c]	-122.9	-112.4	-116.0
Me	CN	-138.1	-120.0	-117.6		-120.7	-125.0
H	Ph	-134.5	-116.4				-144.0
MOH ^[e]		-80.0	-64.7	-61.2	-82.6	-79.6	-81.5
MCN ^[f]		-57.6	-44.4	-41.4	-69.1	-64.7	-65.7
MAD ^[g]		8.0	10.9	12.9	4.3	5.6	
R ² ^[h]		0.91	0.92	0.93	0.93	0.93	

[a] UB3-LYP/6-31G(d) geometries, from ref. [13] unless otherwise specified. [b] Experimental estimates from Table 2, back-corrected to 0 K using thermal temperature corrections from refs. [13, 82]. [c] From ref. [82]. [d] Experimental value is for the SiMe₃ substituent. [e] Reaction enthalpies for the addition of MOH ($\cdot\text{CH}_2\text{OH}$) to ethene. [f] Reaction enthalpies for the addition of MCN ($\cdot\text{CH}_2\text{CN}$) to ethene. [g] MAD = mean average deviation from experimental values. [h] The R^2 value refers to the correlation with experimental reaction enthalpies.

wide variety of radical additions. Thus, for the additions of the methyl, hydroxymethyl, cyanomethyl, and *tert*-butyl radicals to a variety of substituted alkenes, ϕ lies between 106° and 112° (UHF/6-31G(d)).^[26–29] Calculations show that ϕ is not particularly sensitive to the level of theory, with the range of ϕ values for methyl additions changing from 107.5–111.0° (UHF/6-31G(d)) to 109.2–111.0° (UB3-LYP/6-31G(d)) and 108.2–110.6° (QCISD/6-31G(d)).^[82]

The second geometric parameter of particular interest is the length of the partially formed C–C bond. This lies between 2.173 and 2.313 Å (UHF/6-31G(d)) and is found to correlate very nicely with the reaction enthalpy across a wide variety of radical-addition reactions (Figure 5).^[26–29, 81] This result has

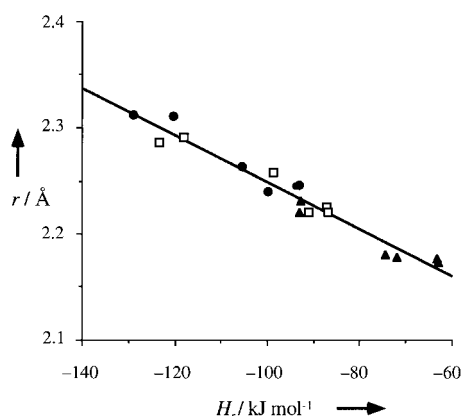


Figure 5. Plot of C–C bond length r [Å] in the transition structure (UHF/6-31G(d)) against reaction enthalpy H_r [kJ mol⁻¹] (QCISD/6-311G(d) + ZPVE.) for the addition of $\cdot\text{CH}_3$ (●), $\cdot\text{CH}_2\text{OH}$ (■), and $\cdot\text{CH}_2\text{CN}$ (▲) radicals to alkenes $\text{CH}_2=\text{CHX}$ ($X = \text{H}, \text{NH}_2, \text{F}, \text{Cl}, \text{CHO}, \text{CN}$). Taken from ref. [28]. The solid regression line is given by $r [\text{Å}] = 2.03 - 2.21 \times 10^{-3} H_r [\text{kJ mol}^{-1}]$ with $R^2 = 0.953$.

been rationalized, using the curve-crossing model, as indicating that the *location* of the transition structure is determined primarily by the intersection of reactant and product configurations while the *energy* of the transition structure may be strongly influenced by contributions from charge-transfer configurations.^[28] This then leads to the observation of a good correlation between $r(\text{C}–\text{C})$ with the reaction enthalpy for a range of radicals and alkenes but not for the barrier with the reaction enthalpy. Calculations at other levels of theory show that there is a small but not negligible dependence on the level of theory for this bond length. Thus for the methyl radical plus ethene reaction, $r(\text{C}–\text{C})$ takes the values 2.246 Å (UHF), 2.261 Å (UMP2), 2.365 Å (UB3-LYP), 2.273 Å (UQCISD), and 2.281 Å (QCISD(T)) (all with the 6-31G(d) basis set).^[12] An even larger variation of $r(\text{C}–\text{C})$ is found for the methyl radical plus acrylonitrile reaction.^[12]

4.2.4. Charge Transfer

Another property that is more directly accessible from theoretical calculations than from experiment is the direction and extent of CT in the transition structure (Table 10).^[26] This is clearly useful in assessing the amount of polar character in a radical-addition reaction. A direct theoretical measure of CT comes from the calculated charges in the transition structures, while a less direct measure, which is also available from experimental data, is the relative energy of the CT states, for example, $\text{CH}_3^+/\text{CH}_2=\text{CHX}^-$ and $\text{CH}_3^-/\text{CH}_2=\text{CHX}^+$. In the case of the addition of the methyl radical to alkenes, it is found that for most substituents (including H) the methyl radical carries a negative charge. It carries a positive charge only for $X = \text{CHO}, \text{NO}_2$, and CN. In addition, in most cases (H again included), the energy of the CT state $\text{CH}_3^-/\text{CH}_2=\text{CHX}^+$ is

Table 10. Energies E_{CT} of CT states and the charge q on CH_3 in the transition state of the reaction of a methyl radical ($\cdot CH_3$) with alkenes ($CH_2=CHX$).^[a]

X	E_{CT} [eV] ^[b]		q ^[c]
	$CH_3^+/CH_2=CHX^-$	$CH_3^-/CH_2=CHX^+$	
F	11.4	10.3	-0.012
H	11.6	10.5	-0.017
OH	11.5	9.2	-0.029
CH ₃	11.6	9.8	-0.024
NH ₂	11.7	8.1	-0.039
SiH ₃	10.7	10.1	-0.009
Cl	11.0	9.9	0.000
CHO	9.7	10.2	+0.006
NO ₂	9.0	11.8	+0.030
CN	10.0	10.9	+0.012

[a] From ref. [26]. [b] G2(MP2) values. [c] Bader charges calculated at the UHF/6-31G(d) level.

lower than the CT state $CH_3^+/CH_2=CHX^-$, once again showing that methyl generally prefers to be an electron acceptor rather than an electron donor. It is an electron donor only when there are strong electron-withdrawing substituents on the alkene. Thus the calculations indicate that methyl radical does not display general nucleophilic behavior, in contrast to previous conventional wisdom. It is nucleophilic only with alkenes such as acrolein and acrylonitrile that bear strong π -electron-withdrawing substituents.

The calculated energies for the possible CT states formed from the radicals (R) $\cdot CH_2OH$ and $\cdot CH_2CN$ with a number of alkenes (A) is shown in Table 11.^[28] It can be seen that the

Table 11. Calculated energies [eV] of CT states related to the addition of $\cdot CH_2OH$ and $\cdot CH_2CN$ to alkenes ($CH_2=CHX$).^[a]

X	$\cdot CH_2OH$		$\cdot CH_2CN$	
	R^+A^-	R^-A^+	R^+A^-	R^-A^+
F	9.1	10.5	11.8	8.8
H	9.3	10.7	12.0	9.0
NH ₂	9.4	8.3	12.1	6.6
Cl	8.7	10.1	11.4	8.4
CHO	7.5	10.4	10.1	8.6
CN	7.7	11.1	10.4	9.4

[a] G2(MP2) values from ref. [28].

$\cdot CH_2CN$ radical is always electrophilic, the R^-A^+ state being low in energy in an absolute sense and always lying below the R^+A^- state. On the other hand, $\cdot CH_2OH$ is generally nucleophilic, the CT R^+A^- state being low in energy in an absolute sense and lying below the R^-A^+ state. The CT states involving the methyl radical (Table 10) are considerably higher in energy. In agreement with experiment, these results suggest that polar effects in the addition reactions of the $\cdot CH_2OH$ and $\cdot CH_2CN$ radicals should be considerably greater than for the methyl radical, where they might generally be expected to be relatively unimportant.

4.2.5. Solvent Effects

Because the ab initio calculations refer to isolated molecules in the gas phase whereas most of the experiments with which comparisons are being made were carried out in

solution, for example 1,1,2-trichloro-1,2,2-trifluoroethane ($\epsilon = 2.4$, $\cdot CH_3$ additions), methanol ($\epsilon = 32.6$, $\cdot CH_2OH$ additions), or acetonitrile ($\epsilon = 37.5$, $\cdot CH_2CN$ additions), it is of interest to examine the effect of solvent.^[81, 82] This has been achieved by using the self-consistent isodensity polarizable continuum model (SCIPCM)^[92] with dielectric constants (ϵ) of 2 (for a nonpolar solvent) and 40 (for a polar solvent) for a selection of radical-addition reactions.^[82]

The predicted effect of solvent is generally not large, leading generally to small increases in the barrier (+0.5 to +1.1 kJ mol⁻¹ for $\epsilon = 2$, +1.1 to +2.8 kJ mol⁻¹ for $\epsilon = 40$) except for the CN and CHO substituents (in the alkene or the radical) for which there are small decreases in the activation energy (-0.2 to -1.1 kJ mol⁻¹ for $\epsilon = 2$, -0.6 to -3.0 kJ mol⁻¹ for $\epsilon = 40$). There predicted lowering of the activation barrier in solvent is a larger (4.7 kJ mol⁻¹; $\epsilon = 40$) for $\cdot CH_2OH + CH_2=CHCN$ relative to $\cdot CH_2OH + CH_2=CH_2$, which is consistent with the significant polar character predicted for the $\cdot CH_2OH + CH_2=CHCN$ reaction (Table 11).

It is found that the effect of solvent (with $\epsilon = 40$) on reaction enthalpy lies between +2.4 and +4.3 kJ mol⁻¹ for methyl radical additions, except for X = NH₂ (+5.9 kJ mol⁻¹).^[82] Larger effects are seen for the $\cdot CH_2OH$ additions. For nonpolar solvents ($\epsilon = 2$) the solvent effect is reduced by about 60%.

4.3. Discussion

4.3.1. General Aspects and Linear Correlations

In general, the trends associated with changing the radical and alkene substitution obtained with the more advanced theoretical procedures agree well with those observed experimentally. Therefore, the two sets of data do not justify separate discussions of the substituent effects, and we base the following analysis of the factors influencing the addition rates on the experimental data only. The possible, but small, phase and solvent effects are ignored. Furthermore, the analysis is restricted to the activation energies because the frequency factors have already been covered in Section 4.1.2.

4.3.1.1. Steric Effects of β and Radical Substitution

The data in tables 1 and 2 nicely confirm the earlier view^[5-7] that bulky alkene β substituents (X, Y, Figure 1) have little effect on the rate constants. In fact, for all the radicals the addition to the very bulky 1,1-diphenylethene is always one of the fastest reactions. Also, depending on the radical and the other β substituent, the replacement of a β -hydrogen atom by a methyl group changes the rate constant in either direction but not greatly, and seldom by more than a factor of two. Primary and tertiary radicals behave similarly, that is, there is also no clear indication of hindering steric interactions between the methyl substituents of the radicals and the alkene β groups. Two methyl groups at the radical center decrease the rate constants markedly if the third radical substituent is a cyano or a carboxy group but lead to an increase for the hydroxy-substituted radical. Furthermore, the *tert*-butyl radical reacts faster than the methyl radical with all

strongly acceptor-substituted alkenes. Clearly, any steric retardation of the rates by β -alkene or radical substituents must be so small that it is completely masked by the other more dominating factors.

4.3.1.2. Characteristic Energy Quantities

Guided by the state correlation diagram (Figure 3) we now seek correlations between the activation energies for the addition with the energy quantities which change with the substitution pattern of the alkenes and the radicals, namely, the reaction enthalpy, the alkene triplet energy, and the relative energies of the CT configurations and the strength of the interactions with these.^[93]

The reaction enthalpy for the addition of a specific radical R to an alkene A follows from the data in Table 2 as $H_r(R,A) = H_r(\text{Me},A) + \Delta H_r(R)$.

Triplet excitation energies ΔE_{ST} are known for only a few monosubstituted and 1,1-disubstituted alkenes.^[94] They range from 2.55 eV for diphenylethene to 3.65 eV for ethene, and correlate very well linearly with the differences in the vertical alkene ionization energies and electron affinities. Since the latter are more widely known (Table 2), this correlation was used to predict ΔE_{ST} for the other alkenes. They fall between $\Delta E_{ST} = 2.55\text{--}2.80$ eV for phenyl-substituted alkenes and $\Delta E_{ST} = 3.10\text{--}3.65$ eV for all other species.^[95]

According to the discussion in Section 2.2, polar effects should become important when the energy of at least one of the CT configurations for the separated reactants is reduced by the Coulomb interaction C in the transition structure, that is, when $E_i(R) - E_{ca}(A) - C$ or $E_i(A) - E_{ca}(R) - C$ lies near or below ΔE_{ST} . For two point charges at the theoretical reaction distance of about 2.2 Å (Figure 5), the Coulomb attraction energy is 6.5 eV. This is an upper limit since in many cases the charges will be delocalized to some extent over both the radical and the alkene substituents. Estimates based on semiempirical calculations lead to values for C between 2.8 eV (for benzyl reacting with phenyl-substituted alkenes, i.e. a system in which a large charge delocalization is expected) and 5.3 eV (for hydroxymethyl with ethene, a system with small charge delocalization).^[62c] Hence, one may expect considerable polar effects if the energy gaps $E_i(R) - E_{ca}(A)$ or $E_i(A) - E_{ca}(R)$ are smaller than about 7–8 eV. However, the interaction parameters γ between the various configurations are also important, and a large γ value will increase the polar effects. Unfortunately, there is presently no means to address this aspect with any confidence.

4.3.1.3. Enthalpic Effects

A natural and frequently used procedure to search for specific correlations is the construction of plots of the activation energies against the characteristic energy quantities. An E_a versus H_r plot is given in Figure 6 for the addition of methyl and benzyl radicals to a variety of alkenes.^[96] For both radicals the data are reasonably well described by one linear Evans–Polanyi–Semenov relation, and this is not unexpected: methyl has a high ionization energy and a low electron affinity, which yields large energy gaps of $E_i(R) - E_{ca}(A) > 9.5$ eV and $E_i(A) - E_{ca}(R) > 8$ eV for all alkenes

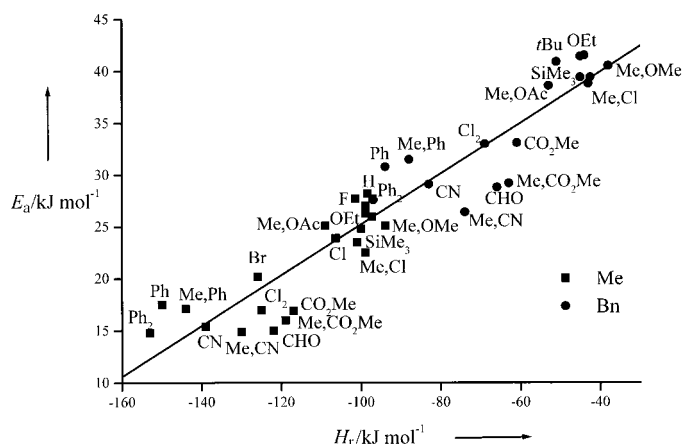


Figure 6. Activation energies for the addition of methyl (■) and benzyl (●) radicals versus the reaction enthalpy. The solid regression line is given by $E_a = 49.7(1.3) + 0.244(0.013) H_r$ with (errors are given in parenthesis, $R^2 = 0.89$).

(Table 10). Therefore, the polar effects should be of minor importance in methyl additions. The benzyl radical has a low ionization energy and a substantial electron affinity. Nucleophilic polar effects could consequently be expected. However, they should be diminished by the lower Coulomb term and the lower interaction strength. Hence, for both radicals a dominant influence of the reaction enthalpy is quite natural. Moreover, the common regression of benzyl and methyl means that the lower reactivity of benzyl is because of the lower exothermicity which is caused by resonance stabilization. Hence, a previous explanation of the low benzyl reactivity^[21] as being the result of a particularly large resistance to pyramidalization is now abandoned.

However, Figure 6 also shows some noticeable deviations from the linear regression: for methyl additions to several electron-deficient alkenes the activation energies lie below the line. In agreement with the direction of the charge transfer given in Table 10, methyl seems to exhibit a noticeable nucleophilic polar effect in these cases, and earlier it was precisely the high reactivity of methyl towards such alkenes which led to its classification as nucleophilic.^[4, 6] For benzyl, small accelerating nucleophilic polar effects towards strongly electron-deficient alkenes are also visible. These are also suggested by the extremely facile addition to the very electron-deficient superalkene C_{60} ($E_{ca} = 2.65$ eV, $k_{298} = 1.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, $E_a = 13.5 \text{ kJ mol}^{-1}$).^[97] Overall, however, the nucleophilicity of benzyl is also rather modest, and this explains why *para* substitution of the benzyl group by electron-donor or -acceptor groups does not change the addition behavior of benzyl markedly, even though these substitutions strongly affect the E_i of the radical.^[21] Hence, one would conclude from Figure 6 that for the additions of methyl and benzyl radicals the reaction enthalpy is the dominating factor, and the slope of the linear regression is also close to the generally accepted $\alpha \approx 0.25$.

Interestingly, but also disturbingly, reasonable linear correlations between the activation energies and the reaction enthalpy are also found for radicals which are thought to have electrophilic or ambiphilic character, such as *tert*-butoxycar-

bonylmethyl ($E_a = 32.4 + 0.17H_r$, $R^2 = 0.67$), cyanomethyl ($E_a = 35.1 + 0.17H_r$, $R^2 = 0.73$), 2-*tert*-butoxycarbonyl-2-propyl ($E_a = 47.9 + 0.24H_r$, $R^2 = 0.80$), and 2-cyano-2-propyl ($E_a = 43.3 + 0.21H_r$, $R^2 = 0.87$). Linear E_a versus H_r relations also hold even for the strongly nucleophilic radicals hydroxymethyl ($E_a = 82.5 + 0.59H_r$, $R^2 = 0.82$), *tert*-butyl ($E_a = 74.5 + 0.60H_r$, $R^2 = 0.77$), and 2-hydroxy-2-propyl ($E_a = 78.0 + 0.69H_r$, $R^2 = 0.72$), but not for the strongly electrophilic radicals cyclic malonyl ($E_a = 18.0 - 0.01H_r$, $R^2 = 0.01$) and trifluoroacetyl ($E_a = 12.0 - 0.07H_r$, $R^2 = 0.02$).

The comparison of all these Evans–Polanyi–Semenov relations reveals remarkable trends. For the donor-substituted hydroxymethyl, *tert*-butyl, and 2-hydroxy-2-propyl radicals, both the intercepts and gradients are much larger than for methyl and benzyl, whereas for the acceptor-substituted *tert*-butoxycarbonylmethyl, cyano-methyl, 2-*tert*-butoxy-carbonyl-2-propyl, and 2-cyano-2-propyl radicals the gradients are smaller. For cyclic malonyl and trifluoro-acetyl they are even negative. Clearly, the correlations found so far point to an influence of the reaction enthalpy on the activation energies but do not allow the specification of a general dependence which could be valid for all radicals and alkenes.

4.3.1.4. Nucleophilic Polar Effects

The nucleophilic polar effect should be large for the *tert*-butyl, hydroxymethyl, and 2-hydroxy-2-propyl radicals which have very small ionization energies (Table 2). For these radicals $\Delta H_i(R)$ is similar, and thus the enthalpic effects should also be similar. For nearly all the alkenes examined, the activation energies decrease in the order hydroxymethyl > *tert*-butyl > hydroxypropyl. This agrees with the order of the radical ionization energies and supports the importance of nucleophilic polar factors. Also, for most of the alkenes the energy $E_i(R) - E_{ca}(A)$ of the CT configuration R^+A^- is smaller than 8 eV. The energy of the second CT configuration R^-A^+ is greater than 8 eV for all the alkenes, and this renders electrophilic polar effects for these radicals unlikely.

Figure 7 shows that the activation energies of the three radicals correlate in a common way with the energy differences $E_i(R) - E_{ca}(A)$, and this correlation is even better than that with the reaction enthalpy. The alkenes form two classes: the activation energies of alkenes without phenyl substituents fall into a rather narrow band (width < 7 kJ mol⁻¹) and decrease from high values when the $E_i(R) - E_{ca}(A)$ energy difference is high (9–10 eV) to values close to zero for $E_i(R) - E_{ca}(A) \approx 6.0$ –6.5 eV. The latter value is close to the Coulomb interaction $C \approx 5$ –6 eV estimated above for non-delocalized systems and, according to Figure 3, $E_i(R) - E_{ca}(A) \approx C$ could mean very low or even vanishing activation energies. For the phenyl-substituted alkenes, the activation energies are higher but they also decrease with decreasing energy gap and tend to zero at $E_i(R) - E_{ca}(A) \approx 5$ eV. This is reasonable, because the Coulomb term should be smaller for the phenyl-substituted alkenes as a result of the delocalization effect. Hence, one can conclude that for the donor-substituted radicals the nucleophilic polar effect is important, at least for

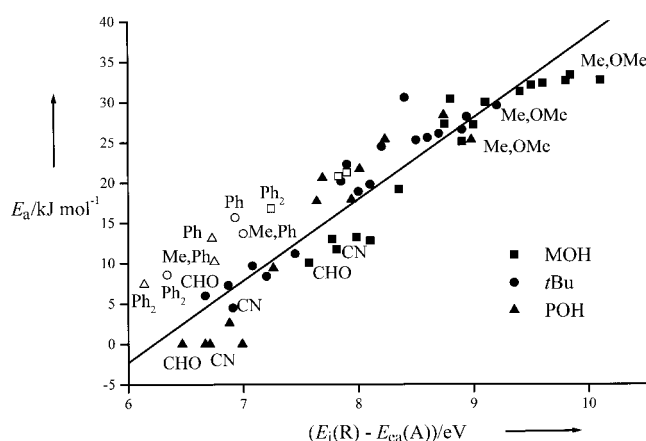


Figure 7. Activation energies for the addition of hydroxymethyl, *tert*-butyl, and 2-hydroxy-2-propyl radicals versus the relative energies of the CT configurations R^+A^- (measured by $E_i(R) - E_{ca}(A)$). Several data points are labeled with the corresponding alkene substituents. The solid regression line is given by $E_a [\text{kJ mol}^{-1}] = -63.0(4.6) + 10.1(0.6)(E_i(R) - E_{ca}(A)) [\text{eV}]$ (errors are given in parenthesis, $R^2 = 0.86$).

energy differences $E_i(R) - E_{ca}(A) < 9$ eV, and that in Figure 7 the influence of the reaction enthalpy is masked.

Surprisingly, however, radicals such as methyl and benzyl with small nucleophilic polar effects also give rise to reasonable correlations of the activation energies with the energy gap $E_i(R) - E_{ca}(A)$ and/or with the alkene electron affinity ($R^2 = 0.86$ and $R^2 = 0.84$, respectively). Even the electron-acceptor-substituted radicals, 2-cyano-2-propyl ($R^2 = 0.76$), 2-*tert*-butoxycarbonyl-2-propyl ($R^2 = 0.75$), *tert*-butoxycarbonylmethyl ($R^2 = 0.51$), and cyanomethyl ($R^2 = 0.52$), behave similarly, only cyclic malonyl and trifluoroacetyl do not. Hence, as noted for the enthalpy effect, linear correlations such as those presented in Figure 7 seem not to be of general and predictive significance.

4.3.1.5. Electrophilic Polar Effects

The trifluoroacetyl and cyclic malonyl radicals have large electron affinities (Table 2). This suggests searching for a correlation of the activation energies with the energy $E_i(A) - E_{ca}(R)$ for the CT configuration R^-A^+ . Figure 8 shows that the $E_i(A) - E_{ca}(R)$ values are indeed low for most alkenes, so that electrophilic polar effects are likely. As expected, the activation energies are lower at lower $E_i(A) - E_{ca}(R)$ energies. However, the gradient of the common correlation is much smaller than that found for the nucleophilic radicals (Figure 7), and very low activation energies are approached only for $E_i(A) - E_{ca}(R) < 6$ eV.

For all the other potentially electrophilic radicals, the plots of the activation energies versus the energy separation $E_i(A) - E_{ca}(R)$ and/or the alkene ionization energies $E_i(A)$ show large scatter and negative gradients. An electrophilic behavior should give a positive slope since the activation energies should decrease with decreasing alkene ionization energy, so that at first sight all four monocyano and monocarboxy substituted radicals appear not to be electrophilic. This is not consistent with intuition and the theoretical results (Table 11) nor with the low activation energies of the primary species, and suggests that other forces are at work.

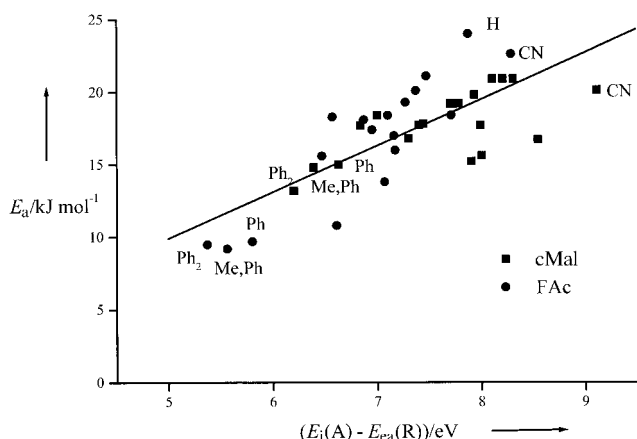


Figure 8. Activation energies for the addition of cyclic malonyl (■) and trifluoroacetyl (●) radicals versus the relative energy of the CT configuration $R^{\cdot-}A^+$ (determined by $E_i(A) - E_{ea}(R)$). The solid regression line is given by $E_a [\text{kJ mol}^{-1}] = -6.1(3.4) + 3.1(0.5)(E_i(A) - E_{ea}(R)) [\text{eV}]$ (errors are given in parenthesis, $R^2 = 0.57$).

4.3.1.6. Correlations With the Alkene Triplet Energy

We have also searched for linear correlations of the activation energies with the alkene triplet energy ΔE_{ST} . Except for the radicals with the strongest polar effects, 2-hydroxy-2-propyl, cyclic malonyl, and trifluoroacetyl, all species give reasonable correlations with the expected positive slopes but the scatter is large.

4.3.1.7. Interrelation of Energy Parameters and Limits of Linear Correlations

As is evident from the discussion above, linear correlations of the activation energies for individual radicals or specific radical groups with the reaction enthalpy, the energies of the CT configurations and the triplet energy appear to point to important factors but do not lead to their specification and straightforward separation. In the course of this analysis, we have recognized that the energy parameters are themselves significantly interrelated, that is, they depend on one another.

Firstly, the reaction enthalpy correlates strongly with the triplet excitation energy: $H_r [\text{kJ mol}^{-1}] = -309 + 0.62\Delta E_{ST} [\text{kJ mol}^{-1}]$, with $R^2 = 0.68$. The large and positive slope means that the effects of H_r and ΔE_{ST} are not separable by linear correlations of the activation energies or of the rate constants with either parameter. In fact, a linear dependence on one parameter will automatically lead to a linear dependence on the other, even if the latter would have no effect if it were operating alone. Despite an extensive search for specific influences of the alkene triplet energy, such influences have not been found. Therefore, we conclude that the correlations with H_r always include the effects of ΔE_{ST} .

Secondly, there is a correlation between H_r and the alkene electron affinity, $H_r [\text{kJ mol}^{-1}] = -136 - 0.20 E_{ea}(A) [\text{kJ mol}^{-1}]$ with $R^2 = 0.77$. The negative slope means that many of the alkene substituents that make the alkene more electron deficient, and hence increase E_{ea} , also stabilize the newly formed radical, and hence decrease H_r . Therefore, for a given radical, the nucleophilic polar effect increases with decreasing

H_r , that is, favorable influences of the enthalpy and the alkene electron affinity reinforce one another.

Thirdly, with the exception of the phenyl-substituted alkenes, the addition exothermicities ($-H_r$) increase with increasing alkene ionization energies, $H_r [\text{kJ mol}^{-1}] = 35 - 0.16 E_i(A) [\text{kJ mol}^{-1}]$ with $R^2 = 0.42$. This correlation is less significant than that of H_r with E_{ea} , but it means that the electrophilic polar substituent effect which increases with decreasing alkene E_i and the enthalpy substituent effect which increases with increasing exothermicity partly cancel one another in the individual plots of the activation energies versus H_r and $E_i(A)$.

In total, these interrelations of the parameters shed considerable doubt on the meaning of the individual correlations and call for a more refined analysis.

4.3.2. Refined Analysis and Predictions

We start with the Evans–Polanyi–Semenov premise, supported by the state correlation diagram, that the reaction barriers should always decrease with decreasing reaction enthalpy (increasing exothermicity). We note in addition that any polar effects that are present can only serve to *decrease the barriers* beyond that indicated by the enthalpy effect. If the dependence of the activation energy on the reaction enthalpy is the same for all radicals and if this is described by a common Evans–Polanyi–Semenov relation, then the interrelations between H_r and the alkene E_{ea} and E_i described in Section 4.3.1.7 suggest alkene specific trends of the data in plots of the activation energies versus the reaction enthalpy if polar effects do operate. These trends are quite different for nucleophilic, electrophilic, and ambiphilic radicals, and this allows a discrimination.

4.1.3.2.1. Nucleophilic Polar Effects

Figure 9 represents in a pictorial way the variation in the activation energy with the reaction enthalpy expected from Equation (1) and from the corresponding changes resulting from accompanying additional nucleophilic polar effects

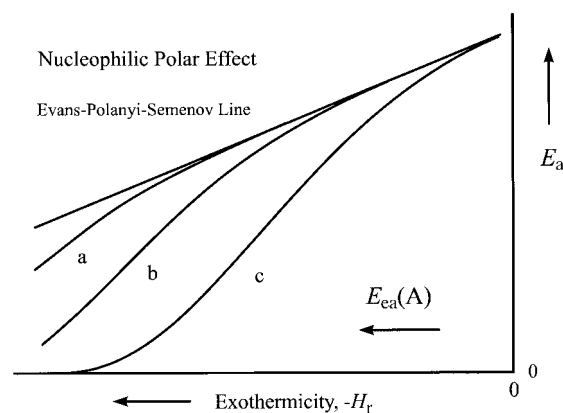


Figure 9. Schematic plot of the activation energy versus reaction exothermicity ($-H_r$) for systems showing negligible polar effects and increasing nucleophilic polar effect (increases from a to b to c).

which increase from curve a to curve c. The lines were drawn with the restriction that activation energies can not become negative but will approach zero if $E_i(R) - E_{ea}(A) - C$ becomes sufficiently small. Because $E_{ea}(A)$ generally increases with decreasing H_r , the deviations from pure enthalpy control will be larger for additions with higher exothermicity. They will set in when $E_i(R) - E_{ea}(A) - C$ falls below a critical value, and they are also influenced by the strength (γ) of the interaction between the CT configurations and the nonpolar configurations. From Figure 9 one predicts that radicals exhibiting both enthalpic effects and nucleophilic polar effects are *generally more selective and more reactive* than radicals lacking the polar effects. Normally, the accessible range of H_r is limited, and, under such circumstances, this will lead to a more or less linear dependence of the activation energies on the reaction enthalpy. Then, as seen in Figure 9, the slopes of the linear correlations are expected to be particularly large for radicals with considerable nucleophilicity. Indeed, this is observed for the nucleophilic hydroxymethyl, *tert*-butyl, and 2-hydroxy-2-propyl radicals.

4.3.2.2. Electrophilic Polar Effects

For electrophilic radicals, the expected variation in the activation energy with the reaction enthalpy is schematically displayed in Figure 10. The deviations from the Evans–Polanyi–Semenov line are largest for small $E_i(A)$, and since

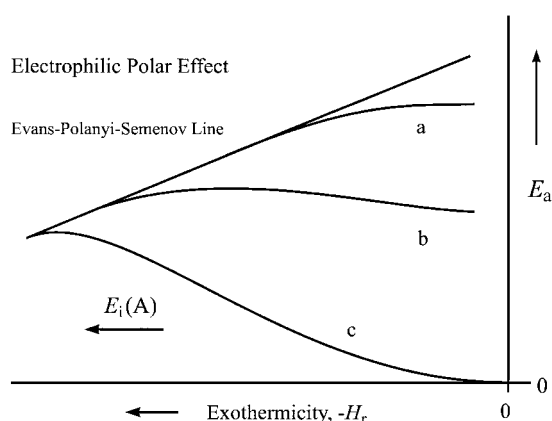


Figure 10. Schematic plot of the activation energy versus reaction exothermicity ($-H_r$) for systems showing negligible polar effects and increasing nucleophilic polar effect (increases from a to b to c).

$E_i(A)$ and the exothermicity are positively correlated, the deviations are largest for additions with low exothermicities. Hence, one predicts from Figure 10 that radicals exhibiting enthalpic and electrophilic effects are *generally more reactive but may be less selective* than radicals without electrophilicity. Again, the limited range of H_r will lead to a more or less linear dependence of the activation energies on the enthalpy, and now the slopes of the correlations will be smaller than that given by the enthalpy effect alone. For very large electrophilicity even a negative slope can result (line c). Small slopes are, in fact, encountered for the acceptor-substituted radicals *tert*-butoxycarbonylmethyl, cyanomethyl, 2-*tert*-butoxycarbonyl-2-propyl, and 2-cyano-2-propyl, and for cyclic malonyl

and trifluoroacetyl the slopes are negative. Hence, all these acceptor-substituted radicals do show an appreciable electrophilicity.

4.3.2.3. Ambiphilic Polar Effects

For radicals with sufficiently low ionization energies and sufficiently large electron affinities, the energy of the CT configuration R^+A^- is small for reactions with strongly electron-deficient alkenes, and the energy of the other CT configuration R^-A^+ is small for additions to electron-rich alkenes. In this case, one expects an ambiphilic reaction behavior. It gives rise to the deviations from the enthalpy correlation shown in Figure 11. One now predicts that

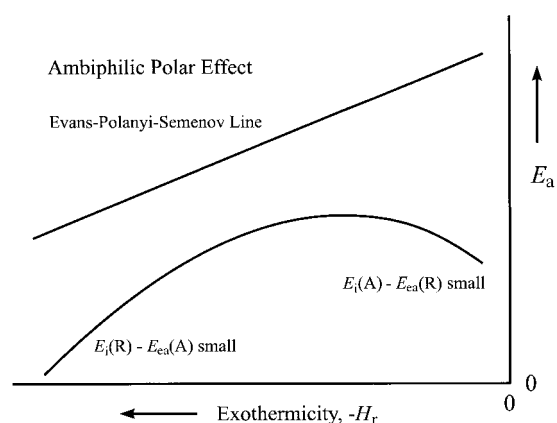


Figure 11. Schematic plot of the activation energy versus reaction exothermicity ($-H_r$) for an ambiphilic reactivity.

ambiphilic radicals will be *rather reactive but not very selective*. In these cases, the linear correlation of the activation energy with the reaction enthalpy may show nearly the correct slope but it gives an intercept that is too low. Hence, the effects of the reaction enthalpy can become more evident for ambiphilic radicals than for purely nucleophilic or electrophilic species, and this was noticed earlier by Giese^[18a]. It will be seen later that several of the radicals we employed are indeed ambiphilic.

4.3.2.4. Consequences

The interrelation of the energy parameters explains the observation of linear correlations of the activation energies with the polar energy quantities for cases where such correlations should not exist, this was noted in Section 4.3.1. If the additions are mainly controlled by the reaction enthalpy, the activation energies will always seemingly decrease with increasing alkene electron affinity as if the radicals were substantially nucleophilic. This deceptive tendency holds for the carboxy- and cyano-substituted species but was not recognized in earlier work. On the other hand, because of the enthalpy effect the slopes of the correlations between E_a and $E_i(A)$ for electrophilic radicals will always appear too small, and they may even become negative. The latter is contrary to intuition, but it is observed for some acceptor-substituted species. However, a correlation of E_a

with $E_i(A)$ with a positive slope always means an electrophilic addition behavior, especially if the radical follows line c in the E_a versus H_r plot of Figure 10.

4.3.2.5 Predictive Equations for the Activation Energy: A Common Evans–Polanyi–Semenov Relation

Our considerations, which, for the first time, include a detailed analysis of the mutual interdependence of the energy parameters, have implicitly assumed the existence of a common dependence of the reaction barriers on the reaction enthalpy. From the sizes of the energy gaps it can be concluded that most of the radicals reported herein should exhibit only weak or negligible polar effects with at least a few alkenes. Therefore, a plot of *all* the activation energy data against the reaction enthalpy should lead to an *upper limiting* line. This line should represent the true enthalpy dependence from which the polar effects are expected to cause only negative deviations. Figure 12 demonstrates that the upper limit does exist. It is even close to linear and thus provides strong support for the Evans–Polanyi–Semenov relation.

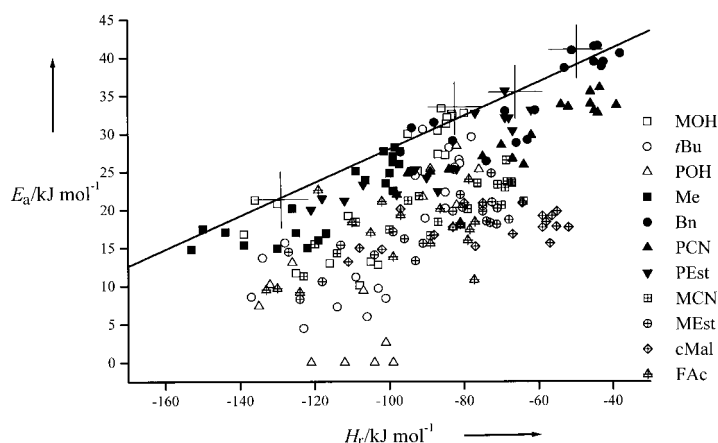


Figure 12. Activation energies for the full set of reactions versus the reaction enthalpy. The solid line is given by $E_a = 50.0 + 0.22 H_r$.

The line is described by Equation (2). With very few exceptions, the activation energies for all radicals approach

$$E_a = 50 + 0.22 H_r \quad (2)$$

the upper limit for specific alkenes, and this further rules out significant steric effects of the radical substituents on the activation energies. The line in Figure 12 [Eq. (2)] accommodates the experimental errors in the activation energies and in the estimated reaction enthalpies, and the resulting parameters are reasonable. Not unexpectedly, they are very similar to those given in Figure 6 for the rather nonpolar methyl and benzyl radicals. A closer inspection of Figure 12 also reveals that the deviations from the upper limiting line for methyl, benzyl, and the strongly donor-substituted radicals increase with increasing exothermicity, as expected from Figure 9, that is, the nucleophilicity of these radicals with electron-deficient alkenes is confirmed. The other radicals conform as expected to Figures 10 and 11, that is, all acceptor-substituted radicals show an electrophilic to ambiphilic behavior.

4.3.2.6 Effects of Polar Interactions on the Activation Energy

The new general Evans–Polanyi–Semenov relation allows a more quantitative analysis of the effects of polar interactions on the activation energies. We propose that the enthalpy effects are covered by Equation (2) and that the polar effects are described by superimposing *multiplicative polar factors* and not additive terms on this equation. Hence, we write the activation energies as Equation (3).^[98, 99] The nucleophilic

$$E_a = (50 + 0.22 H_r) F_n F_e \quad (3)$$

factor F_n depends on $E_i(R) - E_{ca}(A) - C_n$ and an interaction parameter γ_n , and its electrophilic counterpart F_e depends on $E_i(A) - E_{ca}(R) - C_e$ and a corresponding interaction parameter γ_e . Both F_n and F_e are restricted to values between 0 and 1. Figure 13 shows a plot of the activation energies E_a divided by the enthalpic term $(50 + 0.22 H_r)$ for the radicals methyl, hydroxymethyl, *tert*-butyl, and 2-hydroxy-2-propyl versus the energy of the charge-separated configuration R^+A^- , $E_i(R) - E_{ca}(A)$. These radicals should exhibit only nucleophilic polar effects, and hence the ratio $E_a/(50 + 0.22 H_r)$ should represent F_n .

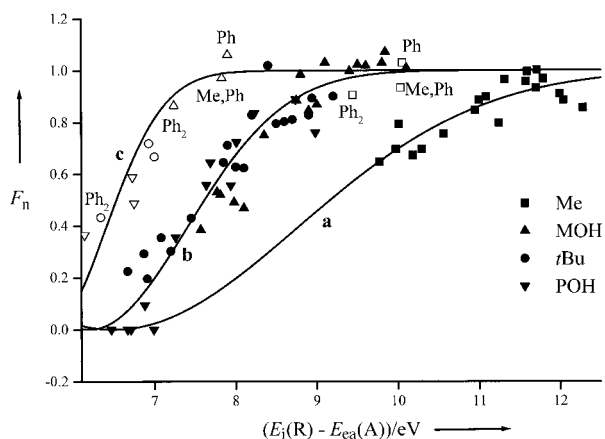


Figure 13. Nucleophilic polar factors for the methyl (■), hydroxymethyl (▲), *tert*-butyl (●), and 2-hydroxy-2-propyl (▼) radicals. Open symbols (□, △, ○, ▽) refer to the same radicals reacting with phenyl-substituted alkenes. The solid lines correspond to a) $F_n = 1 - \exp(-(x - 6.5)/3.2)^2)$, b) $F_n = 1 - \exp(-(x - 6.2)/1.7)^2)$, and c) $F_n = 1 - \exp(-(x - 5.7)/1.0)^2)$.

Also displayed are *heuristic* functions of the type (4) which accommodate the data. The term C_n is the value of $E_i(R) - E_{ca}(A)$ for which the activation energy reaches zero, and γ_n

$$F_n = 1 - \exp(-[(E_i(R) - E_{ca}(A) - C_n)/\gamma_n]^2) \quad (4)$$

denotes the value of $E_i(R) - E_{ca}(A) - C_n$ where the nucleophilic factor F_n reduces the activation energy by a factor of $1 - e^{-1}$, that is, to 63% of the value given by the enthalpy effect alone. As is evident from Figure 13, with the exception of phenyl-substituted alkenes, the polar effects of the strongly nucleophilic radicals can be described by one common F_n with a reasonable Coulomb attraction (6.2 eV) and one interaction term (1.7 eV). The nucleophilic effect of methyl requires the insertion of a larger Coulomb term (6.5 eV) and a larger interaction term (3.2 eV). For the phenyl-substituted alkenes,

the Coulomb and interaction parameters of all four radicals appear to be smaller ($C_n = 5.7$ eV, $\gamma_n = 1.0$ eV), and this also holds for the benzyl radical (not shown, $C_n = 6.0$ eV, $\gamma_n = 1.0$ eV). Clearly and as expected, the parameters C_n and γ_n are related to the charge and spin delocalization in the transition state.

Similar functions F_e accommodate the polar effects of the strongly electrophilic cyclic malonyl and the trifluoroacetyl radical. This is shown in Figure 14 for the non-phenyl-substituted alkenes. Though the variations are less convincing

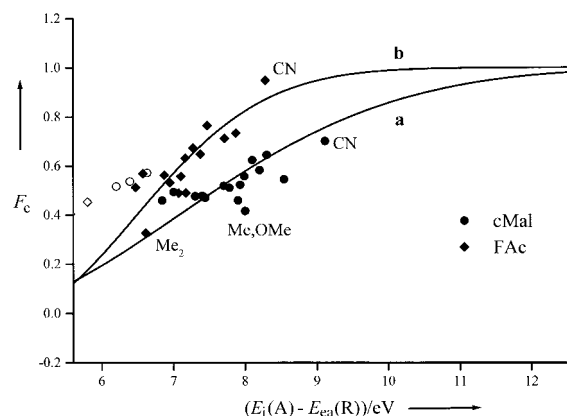


Figure 14. Electrophilic polar factors for the cyclic malonyl (●) and trifluoroacetyl (◆) radicals. Open symbols (○, ◇) refer to the same radicals reacting with phenyl-substituted alkenes. The solid lines correspond to a) $F_e = 1 - \exp(-((x-4)/4.3)^2)$, and b) $F_e = 1 - \exp(-((x-4)/2)^2)$.

than those in Figure 13, the phenyl-substituted species are again the exceptions and call for weaker polar effects. In comparison to the values given above for the nucleophilic radicals, the Coulomb terms in Figure 14 are smaller, possibly because the carboxy- and cyano-acceptor substituents delocalize charge more easily than methyl or hydroxy groups, yet the interaction parameters of these strongly electrophilic radicals appear to be relatively large.

The activation energies of the remaining *tert*-butoxycarbonylmethyl, cyanomethyl, 2-*tert*-butoxycarbonyl-2-propyl, and 2-cyano-2-propyl radicals are smaller than those given by the general Evans–Polanyi–Semenov relation, and this holds both for the electron-deficient and for the electron-rich alkenes. This suggests an ambiphilic reaction behavior, that is, both polar factors are important. A detailed analysis shows similar parameters to those found for the purely nucleophilic and purely electrophilic radicals, and again smaller values for C and γ are needed for the phenyl-substituted alkenes.

To provide an overview of the results of our approach, in Figure 15 we compare the experimental activation energies (Table 2) with values calculated from Equations (3) and (4) and with a unified set of polar Coulomb and interaction parameters.^[100] The agreement is very satisfying and lends support to the interpretation and to Equation (3). The deviations between experimental and calculated data obey the most probable Gaussian distribution, and the largest deviations of 7 kJ mol^{-1} may even be a result of the experimental errors. Of course, the polar parameters and Equation (4), especially the interactions γ and their variation with radical structure, call for theoretical explanations.

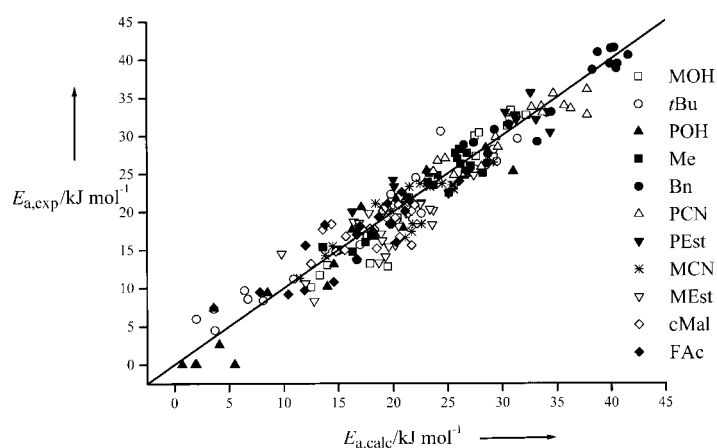


Figure 15. Experimental versus calculated activation energies for the addition reactions covered in Table 2, except cumyl and di-*tert*-butylmalonyl additions, with different symbols for different radicals. The solid line corresponds to $E_{a,\text{exp}} = E_{a,\text{calc}}$ and describes the 206 data points with the standard deviation of 2.4 kJ mol^{-1} .

4.3.2.7. Tests of the Predictions

The polar parameters used for Figure 15 depend on the structures of the radicals and on the alkenes but do not vary extensively.^[100] Therefore, they should allow the prediction of unknown activation energies for additions of similar species. Unfortunately, there are not many absolute rate constants against which such predictions can be checked. However, amongst some other scattered single values, the absolute rate constants are available for the addition of trifluoromethyl and perfluoro-*n*-alkyl radicals,^[20, 67] the *n*-hexenyl and *n*-heptyl radicals,^[101] the cumyl radical,^[59] and various *p*-substituted benzyl radicals^[21] to several alkenes at room temperature. These serve as test cases here. Using the general Evans–Polanyi–Semenov relation with estimated reaction enthalpies, and the average frequency factors and polar parameters which are close to or equal to those found for the related radicals from our series,^[102–106] we arrive at the comparison of experimental and predicted rate constants shown in Figure 16.

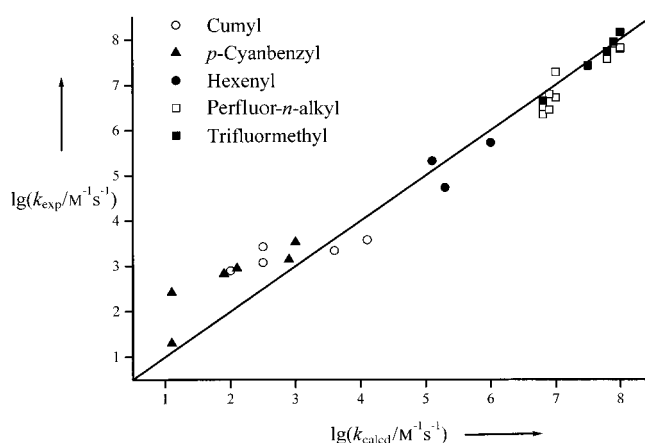


Figure 16. Experimental versus predicted rate constants for the addition of several radicals to alkenes in solution at room temperature with different symbols for different radicals. The solid line corresponds to $\lg(k_{\text{exp}}) = \lg(k_{\text{calcd}})$ and describes the 29 data points with the standard deviation of 0.54.

The data cover about seven orders of magnitude. There are a few deviations of about one order of magnitude, but the average standard deviation between the experimental and the predicted rate constants is only 0.54 units of $\lg(kM^{-1}s^{-1})$, which means a factor of 3.5 for the rate constants. Hence, our refined analysis of the experimental data has not only provided additional insight on the action of the enthalpic and polar factors but also appears to allow predictions of rate constants for the addition of carbon-centered radicals to monosubstituted and 1,1-disubstituted alkenes to within one order of magnitude. We show in Section 5 that the operating principles also hold for related addition reactions. The most serious limitation to a widespread application of our predictive equations is currently the restricted availability of reliable reaction enthalpies.

5. Related Addition Reactions

5.1. 1,2-Disubstituted and 1,1,2-Trisubstituted Alkenes—The Steric Factor

5.1.1. General Observations

It is well established^[3–9] that substitution of one or both methylene hydrogen atoms of a monosubstituted or 1,1-disubstituted alkene $CH_2=CXY$ by other atoms or groups changes the overall rate constant of a radical addition considerably and can also change the regioselectivity of the attack. In most cases, substitution at the attacked site (named C_a) lowers the rate constants. This is commonly attributed to a steric substituent effect which hinders the approach of the radical. As a rule, the effect increases with the steric demand of the substituent and of the attacking radical but it depends also on the size of the substituents at the nonattacked carbon. It may be diminished by favorable polar α -substituent effects.

In terms of activation parameters, a pure steric substituent effect should diminish the frequency factor because it means additional motional constraints on the transition structure. Further, both for bulky radicals $R^\bullet$ and bulky α -substituents A, the newly formed C–C bond of the adduct radical $R-CHA-CXY^\bullet$ will be strained, that is, upon substitution of H by A the reaction should generally become less exothermic and have a higher activation energy. There are not enough experimental data currently available for a large-scale analysis. Therefore, we address here only some of the more important points for a representative reaction series.

Table 12 allows a comparison of the absolute rate constants and the activation parameters for the addition to alkenes $CHA=CXY$ and $CH_2=CXY$. In the chosen examples, the attack at the less-substituted carbon atom is always strongly preferred. As expected, α substitution lowers the rate constants for most additions, and the decrease is larger for bulkier vicinal substituents (A and X,Y) and it is larger for the bulkier *tert*-butyl radical than for the smaller methyl radical. Moreover, the frequency factors for addition to the 1,2-disubstituted and 1,1,2-trisubstituted alkenes are lower than the average frequency factors established in Section 4.1.2 for

Table 12. Rate effects of α -alkene substituents. Ratios of absolute rate constants per CH_2 group of monosubstituted and 1,1-disubstituted alkenes $CH_2=CXY$, or per CH group of 1,2-disubstituted and 1,1,2-trisubstituted alkenes $CHA=CXY$ at 298 K, frequency factors $A^A [M^{-1}s^{-1}]$ for the addition to $CHA=CXY$ per CH group and differences in activation energies $E_a^A - E_a^H [kJ mol^{-1}]$ for the addition of methyl (Me) and *tert*-butyl (*t*Bu) radicals.

Radical	X	Y	A	k^A/k^H	$\lg(A^A)$	$E_a^A - E_a^H$
Me ^[58]	H	Me	(<i>E</i>)-Me ^[a]	0.21	7.4	– 2.4
	H	Me	(<i>Z</i>)-Me ^[a]	0.11	7.1	– 2.6
	Me	Me	Me	0.29 ^[b]		
	H	Ph	(<i>E</i>)-Me	0.12 ^[b]		
	H	Ph	(<i>Z</i>)-Me	0.055 ^[b]		
	H	Ph	(<i>E</i>)-Ph	0.069	8.0	3.9
	H	Ph	(<i>Z</i>)-Ph	0.018	7.9	6.6
	Ph	Ph	Ph	46	7.4	3.3
	H	CO ₂ Me	(<i>E</i>)-Me	0.022 ^[b]		
	H	CO ₂ Et	(<i>E</i>)-CO ₂ Et	2.2 ^[c]	6.6	– 12.8
	H	CO ₂ Et	(<i>Z</i>)-CO ₂ Et	0.22 ^[c]	7.4	– 2.5
	H	CO ₂ Me	(<i>Z</i>)-CO ₂ Me	0.070		
<i>t</i> Bu ^[36c, 62]	H	Me	(<i>Z</i>)-Me	0.033	6.1	– 5.3
	Me	Me	Me	0.11	7.1	2.8
	H	Cl	(<i>E</i>)-Cl	0.23	7.0	0.6
	H	Cl	(<i>Z</i>)-Cl	0.085	7.4	5.3
	Cl	Cl	Me	0.005	6.0	5.1
	Cl	Cl	Cl	0.048	7.3	6.6
	H	Ph	(<i>E</i>)-Me	0.014		
	H	Ph	(<i>E</i>)-CO ₂ Me	1.1		
	H	Ph	(<i>E</i>)-CN	2.8		
	H	CO ₂ Me	(<i>E</i>)-CO ₂ Me	0.18		
	H	CO ₂ Me	(<i>Z</i>)-CO ₂ Me	0.070		

[a] *E* and *Z* isomers. [b] 338 K. [c] Calculated using $k(CH_2=CHCO_2Me)$.

$CH_2=CXY$, namely $\lg(A/M^{-1}s^{-1}) = 8.5$ for methyl and $\lg(A/M^{-1}s^{-1}) = 7.5$ for *tert*-butyl additions, and this decreases the rate constants by a factor of about 5 to 15. With few exceptions, the activation energies are larger for the α -substituted alkenes than for the unsubstituted alkenes, and this suggests a lower exothermicity for the former reaction.^[107] As is evident from the Table 12 this effect of the steric strain on the activation energy may lead to an additional rate decrease by a factor similar to that originating from the frequency factor difference.^[108]

Polar effects of α -substituents are also noticed. Firstly, in comparison the addition to methylacrylate, the additions of the methyl radical to diethylfumarate and to diethylmaleate are considerably faster than expected from the rate-diminishing steric substituent effect, and have lower activation energies. As shown before (Figure 6), the addition of the methyl radical to strongly acceptor-substituted alkenes such as methylacrylate is facilitated by the nucleophilic polar effect, and for diethylfumarate and diethylmaleate this appears to be enhanced by the second ester group. Secondly, the *tert*-butyl radical adds faster to 2-carboxystyrene and 2-cyanostyrene than to styrene, thus, in these cases the polar effect of the α substituent even overrides the steric substituent effect. In this context, it has to be mentioned that the somewhat lower activation energies for additions to 2-butene, when compared with propene, may not be significant and may be a result of error compensation effects in the activation parameters. For methyl additions the difference is small, and for *tert*-butyl the experimental frequency factor is suspiciously low.

5.1.2. The Isomer Effect

Generally, *Z*-1,2-disubstituted alkenes react considerably more slowly than *E*-1,2-disubstituted alkenes (Table 12). The different reactivity of isomers was noticed long ago,^[109] and constituted very early evidence for the now established transition structure in which the alkene moiety in the transition state resembles the parent alkene (Figure 2). However, the direction of the effect is not easily explained. One contribution to different reactivities is likely to come from enthalpy effects because the different isomers have different enthalpies of formation whereas the product radicals that result from additions are energetically identical. However, the direction of the effect is often contra to thermodynamics. In the case of the stilbenes, the relative reactivities were attributed to the *E* isomer having a structure closer to planarity than the *Z* isomer, and it was suggested that these arrangements could be retained in the transition structure. Hence, the newly-formed benzyl-type radical could gain some of its resonance stabilization for the *E* but not for the *Z* isomer already at an early stage of the reaction, and this would lower the barrier for the former compound.^[109] The same reasoning may also explain the higher reactivity of fumarates compared with maleates. An additional possibility is that, because the isomers have different ionization energies and electron affinities, different polar effects may operate. In fact, this isomer effect has been found to explain the addition of the strongly nucleophilic *tert*-butyl radical to the 1,2-dichloroethenes.^[62a,b] It seems that the isomer effect may have different origins for different cases, and the very limited amount of data currently available precludes a closer analysis.

5.1.3. Regioselectivity

For a multiply substituted alkene $C(1)AB=C(2)XY$, the regioselectivity of addition is given by the ratio of the rate constants for addition to $C(1)$ and $C(2)$, k_1/k_2 , and this is strongly dependent on all the factors mentioned before. Firstly, for different motional constraints on the different transition structures, the frequency factors of k_1 and k_2 will be different, and addition to the less-crowded carbon atom should be favored. Secondly, the reaction enthalpies of the two additions differ by the difference in the enthalpies of formation of the adduct radicals $R-CAB-CXY\cdot$ and $R-CXY-CAB\cdot$. Therefore, from the enthalpy effect one expects the lower activation energy and a higher rate constant for the addition leading to a new $R-C$ bond that is stronger or less strained, and to a more stabilized radical. Thirdly, it has been argued that radical attack is directed towards the alkene carbon which possesses the highest spin population in the alkene triplet state.^[25] This effect normally favors attack at the less substituted carbon, and thus coincides with predictions from steric considerations. Finally, for reactions with polar effects, the correction factors F_n and F_e of the activation energies involve the same energy gaps to the CT configurations $E_i(R) - E_{ea}(A)$ and $E_i(A) - E_{ea}(R)$ for both pathways. However, the Coulomb and the interaction terms may differ, that is, the polar effects may also not be equal for the additions to $C(1)$ and $C(2)$. When the enthalpy and spin population or

steric effects reinforce one another, addition at the less substituted carbon ensues. However, when they oppose one another, a regioselectivity crossover, as in the case of methyl radical addition to $CHF=CF_2$, may be observed.^[25]

The experimental data indicate that the decrease in the frequency factor caused by increasing steric substituent effects often goes in parallel with an increase in the activation energy but there are noteworthy exceptions. Tedder et al.^[6, 110] have shown that a variety of fluorine-substituted methyl radicals add preferentially to the less-substituted carbon atom of fluoroethenes. The frequency factors are larger and the activation energies are smaller than for the addition to the more-substituted site, and from the above arguments this is as expected. In contrast, the methyl radical adds preferentially at the disubstituted carbon atom of trifluoroethene, and this reaction has a lower activation energy than the addition to the monosubstituted site. For 1,1-difluoroethene, the regioselectivity of methyl addition is also relatively low. The seemingly anomalous behavior of the methyl radical towards these compounds can simply be explained in terms of the enthalpic effect. It is known that CH_n-CF_m bonds are unusually strong ($n, m \geq 2$),^[20] and this facilitates the addition of methyl to the substituted carbon of $CH_2=CF_2$ ^[81b, 111] whereas for trifluoromethyl and other fluorine-substituted radicals it facilitates the addition to the less-substituted site.^[112] The same should also hold for trifluoroethene and would lead to the anomalous regioselectivity for methyl and the lower activation energy for addition to the more-substituted site. This explanation has also been offered by others and is supported by ab initio calculations.^[25, 81b, 112]

5.2. Homopolymerization Rate Constants, Copolymerization Parameters, and the Penultimate Unit Effect

In radical polymerizations, the repeated addition of alkyl radicals to alkene monomers gives rise to the polymer chains. Hence, one might expect that the rate constants of chain propagation should be subject to the same factors that control the rates of addition of small radicals to alkenes.^[7] This is supported by the following comparisons.

5.2.1. Homopolymerization

Table 13 lists recent homopolymerization rate constants and their activation parameters, together with the corresponding rate data for reactions of structurally related small radicals as taken from Tables 1 and 2. With the exception of ethene propagation, for which the addition of the methyl radical to ethene may not be an adequate model, the propagation constants are about 10- to 60-fold smaller than the rate constants for the model systems. Both sets of constants vary with radical and alkene substitution by nearly three orders of magnitude and in a similar way. The activation energies of the propagations are generally slightly higher. This may be a result of a slightly larger steric effect for the polymeric species which should decrease the reaction enthalpy and increase the activation energy (see Section 5.1.1).

Table 13. Rate data for the homopolymerization of vinyl monomers and for the corresponding addition of small alkyl radicals. For radical notation, see Table 1 and Figure 4.

Homopolymerization monomer model Reaction	k_{300} [M ⁻¹ s ⁻¹]	$\lg(A/M^{-1}s^{-1})$	E_a [kJ mol ⁻¹]
ethene ^[113a]	20	7.27	34.3
Me + ethene	7000	8.5 ^[a]	28.2
methacrylonitrile ^[113b]	18	6.43	29.7
PCN + methacrylonitrile	1060	7.5 ^[a]	26.4
styrene ^[39a]	93	7.63	32.5
Bn + styrene	1100	8.5 ^[a,b]	30.8
methylmethacrylate ^[39b]	345	6.43	22.4
PEst + methylmethacrylate	3710	7.5 ^[a]	22.4
methylacrylate ^[113c]	19000	7.3	17.0
MEst + methylacrylate	490000	8.5 ^[a,b]	15.6

[a] Average frequency factors, see text. [b] For a secondary radical, $\lg(A/M^{-1}s^{-1}) = 8.0$ is expected, see text.

However, the similarity in the activation energies strongly suggests that the major influences of the enthalpic and polar substituent effects on the addition rates are similar for long- and short-chain carbon-centered radicals. On the other hand, the frequency factors of the propagation constants are considerably smaller than those established for the model systems. In view of the larger conformational and motional complexity of the propagating species and the constraints on the transition structure, this is not surprising. In total, the lower frequency factor lowers the rate constant by a factor of about ten for polymeric radicals in comparison with related small-radical additions, and an additional smaller decrease may be a result of the increased activation energy. Probably the same factors explain why propagation rate constants tend to decrease with the increasing chain length of the polymeric radicals.^[114–116]

5.2.2. Copolymerization

As a further test for the similarity of the dominant factors, we compare copolymerisation parameters with ratios of rate constants of model systems. For a propagating radical R adding to its parent monomer M and a second monomer M', the copolymerization parameter r_1 is defined as $r_1 = k_{RM}/k_{RM'}$, and for a given monomer feed such ratios determine the copolymer composition. Figure 17 shows experimental copolymerization parameters for styrene^[117] and ratios of rate constants, $r_{1(\text{calc})}$, of the model benzyl radical adding to styrene relative to the addition to other alkenes calculated from our absolute data.^[59] The frequency factor difference between the secondary polystyryl and the primary benzyl radical should not affect the ratios, and therefore one expects a good correlation between the observed copolymerization parameters and those calculated from rate constants for the small radical if the additions of polymeric and small radicals experience similar enthalpic and polar factors. Figure 17 shows an excellent linear correlation, with a slope close to one and a small intercept value, and this confirms the similarity of the operating factors. Excellent correlations were also found for the cyanomethyl radical as a model for the propagation radical of acrylonitrile,^[60] for the *tert*-butoxycarbonyl methyl radical as a model for methylacrylate,^[60] and for

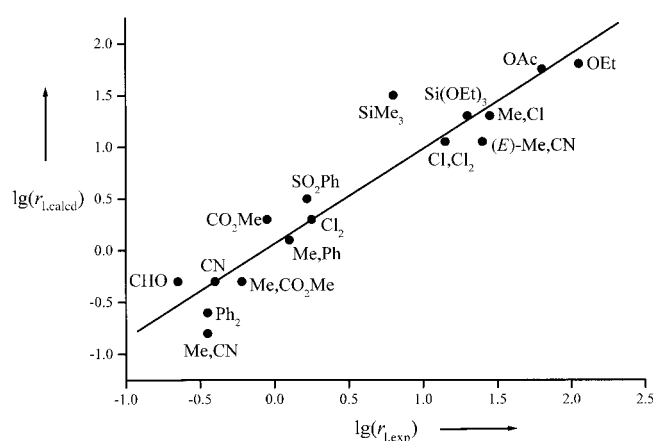


Figure 17. Experimental and predicted copolymerization parameters for styrene. The solid regression line corresponds to $\lg(r_{1,\text{calc}}) = 0.07 + 0.92 \times \lg(r_{1,\text{exp}})$ and describes the 16 data points with $R^2 = 0.90$.

the methoxycarbonyl-2-propyl radical as a model for methylmethacrylate.^[65]

5.2.3. The Penultimate Unit Effect

Studies of copolymerization rates have recently revealed that the rate constant for the addition of a polymeric radical to a monomer does not only depend on the monomer and on the terminal structure of the radical but also to some extent on its penultimate unit^[118] and possibly on even more remote groups. That is, the rate constants k_{iii} for the addition of a radical of type P-M_i-M_i·, where P is a polymer chain, to the monomer M_i is different from the rate constant k_{jii} for the addition of the radical P-M_j-M_i· to the same monomer. The selectivity ratio $s_i = k_{iii}/k_{jii}$ is difficult to determine from the polymerization rates and depends on the analysis method. Values ranging from about 0.2 to about 5 have been extracted, and they agree with the results of selectivities obtained for small model systems.^[119] Hence, the penultimate unit effect is small, and this complicates its explanation. Ab initio studies indicate^[120] that modest changes in the reaction enthalpy and in polar effects may be involved and affect the activation barriers, but changes in the frequency factors could also play a role.^[116c, 121]

A recent detailed analysis has compared alternative models for free-radical copolymerization kinetics.^[122] The simplest “terminal” model assumes that the reactivity is determined entirely by the nature of the monomer and the terminal unit of the polymeric radical. In the “implicit penultimate” model, it is assumed that the penultimate unit of the polymeric radical also plays a role but that it affects the composition but not the rate of the copolymerization processes. The most general “explicit penultimate” model assumes that both the composition and the rate of copolymerization are affected by the penultimate unit. The recent theoretical study concludes that the explicit penultimate model should be adopted as the basis for analyzing free-radical polymerization kinetics.^[122]

Table 14 shows experimental absolute rate constants^[123a] for the addition of radicals R-CH₂-CXY·, derived by reaction of small radicals R· with methylmethacrylate and methylacry-

Table 14. Absolute rate constants for the addition to monomers $\text{CH}_2=\text{CXY}$ and ESR hyperfine coupling constants (± 0.05 G) of radicals $\text{R}-\text{CH}_2-\text{CXY}^\bullet$ at 295 K. MA = methylacrylate, MMA = methylmethacrylate, *t*Bu = *tert*-butyl, POH = 2-hydroxy-2-propyl, Ph = phenyl, MOH = hydroxymethyl.

Reaction	k [$\text{M}^{-1}\text{s}^{-1}$]	$3H_\beta, H_\alpha$ [G]	$2H_\beta$ [G]	$3H_\gamma(\text{CO}_2\text{Me})$ [G]
<i>t</i> Bu-MMA $^\bullet$ + MMA ^[a]	600	21.88	11.71	1.32
POH-MMA $^\bullet$ + MMA ^[a]	1205	22.09	11.93	1.35
Ph-MMA $^\bullet$ + MMA ^[b]	2640	22.05	14.03	1.29
MOH-MMA $^\bullet$ + MMA ^[c]	3290	22.17	14.43	1.36
<i>t</i> Bu-MA $^\bullet$ + MA ^[c]	6120	19.83	21.09	1.50
POH-MA $^\bullet$ + MA ^[a]	3290	20.03	21.28	1.55
Ph-MA $^\bullet$ + MA ^[b]	22400	20.34	21.44	1.40
MOH-MA $^\bullet$ + MA ^[c]	18110	20.41	22.32	1.50

[a] Solvent: 2-propanol. [b] Solvent: 1,1,2-trifluoro-1,2,2-trichloroethane. [c] Solvent: methanol.

late, to their monomers, that is, for the second step in a polymerization. The rate constants do depend on the penultimate unit (R), that is, there is a significant γ -substituent effect. They represent the first direct kinetic data providing evidence for the penultimate effect, and they support the explicit penultimate model. In particular, for methylmethacrylate, the second-step additions are faster than the homopropagation ($345\text{ M}^{-1}\text{s}^{-1}$), and they decrease with the increasing steric demand of R (primary alkyl < phenyl < tertiary alkyl) by a factor of about five. The adducts of tertiary radicals $\text{R}^\bullet$ also add to methylacrylate more slowly, by up to a factor of seven, than the adducts of the sterically less-demanding hydroxymethyl and phenyl radicals. However, adducts of tertiary radicals add more slowly to this monomer than its homopropagation radical ($19000\text{ M}^{-1}\text{s}^{-1}$). Thus, in these cases, the propagation constant does not decrease but increases with increasing chain length. For both monomers, the reactivity ratios s_i are in the usual range.

Table 14 also presents hyperfine coupling constants for the adduct radicals. In accord with abundant ESR studies^[124] on radicals of the type $\text{R}-\text{CH}_2-\text{CXY}^\bullet$ with polyatomic groups R, they indicate planar radical centers with very similar spin populations and two equivalent equilibrium conformations with non-zero dihedral angles $\phi < 45^\circ$ between the $\text{C}_\beta\text{-R}$ bond and the $2p_z$ axis of the radical center (Figure 18). The equilibrium angle ϕ is smaller for the methacrylate than for the acrylate-derived radicals and decreases with the increasing size of R. There is an exchange between the equilibrium conformations, and line-broadening effects point to a faster exchange for the acrylate than for the methacrylate radicals and a slower exchange for bulkier groups R. This all means that the radicals with smaller groups R have more rotational freedom about the $\text{C}_\beta\text{-R}$ bond, and that this motion is less hindered for acrylate than for methacrylate radicals, as might have been expected from simple steric considerations.^[125]

These structural features provide some indications as to the origin of the penultimate unit effect.^[126] We first note that, according to the theoretical calculations, the dihedral angle must be close to zero in the transition structure (Figure 2); for the radicals presented here this is not the case. Hence, upon

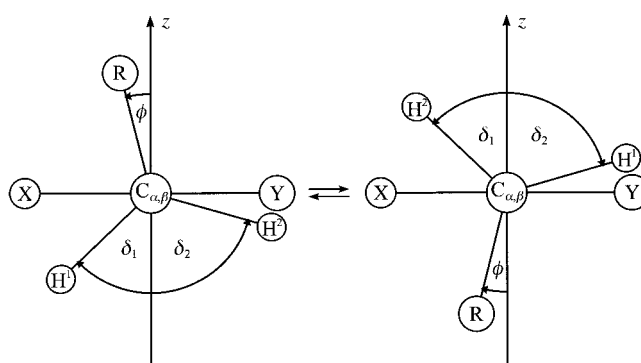


Figure 18. Equilibrium conformations of adduct radicals $\text{R}-\text{CH}_2-\text{CXY}^\bullet$.

approach to the transition structure for the next addition they have to reach higher energy conformations and will lose motional freedom. This will be energetically and entropically more costly for the radicals with bulkier groups R, and will increase the activation energy and lower the frequency factor of the addition. Both effects lead to a decrease in the rate constants with increasing size of R, as is observed. They also explain why the methacrylate radicals with tertiary penultimate groups R add more slowly to their monomer than the homopropagation radical for which R is a less sterically demanding secondary group. Moreover, the attacking radical, as suggested by the theoretical findings, is bent considerably in the transition structure (Figure 2). For the radicals $\text{R}-\text{CH}_2-\text{CXY}^\bullet$, this bending requires an approach of the α -substituents X and Y to the β -substituent R which will again be more costly for the larger groups R. Calculations are under way which should allow the importance of these effects to be addressed.^[123b]

5.3. Other Unsaturated Compounds

In addition to the rate data discussed so far, there are numerous individual absolute and relative rate constants and activation parameters for additions of carbon-centered radicals to other molecules with unsaturated carbon-carbon bonds such as polyenes, allenes, alkynes, aromatic compounds, and heteroaromatic compounds, both for the liquid and for the gas phase.^[31, 72, 73, 127] Of particular diagnostic value are the large series of so-called radical affinities reported by Szwarc and others.^[127] These are ratios of the addition constants versus the rate constants for hydrogen abstraction by the same radical from suitable solvents. The methyl affinities were recently converted into absolute constants.^[58b] A complete analysis is not yet possible because the heats of reaction and the energies of the CT configurations which determine the enthalpic and polar factors can not be reliably estimated for most cases. However, for a few examples predictions are possible.

Table 15 lists experimental rate parameters^[58b] for the addition of the methyl radical to 1,3-butadiene, 1,2-butadiene (i.e. an allene), benzene, and ethyne in solution. They should not be subject to strong polar effects, and hence the activation

Table 15. Experimental and predicted rate constants at room temperature, frequency factors, and activation energies for the addition of the methyl radical to several unsaturated molecules. Predicted rate data are given in italics.

Compound	k_{300} [M ⁻¹ s ⁻¹]	$\lg(A/M^{-1}s^{-1})$	E_a [kJ mol ⁻¹]
1,3-butadiene	$6.4 \times 10^5/1.1 \times 10^5$	9.6/8.5 ^[a]	21.8/20.0 ^[b]
1,2-butadiene	$4.3 \times 10^3/2.8 \times 10^3$	8.3/8.5 ^[a]	26.8/29.0 ^[b]
benzene	46/34	8.2/8.5 ^[c]	37.2/40.0 ^[b]
ethyne	$5.3 \times 10^3/1.1 \times 10^5$	9.7/9.4 ^[d]	34.3/25.0 ^[b]

[a] As for the addition of the methyl radical to monosubstituted and 1,1-disubstituted alkenes. [b] Estimated as described^[69] from reaction enthalpies derived from available heats of formation and bond dissociation energies and using Equation (3). [c] Estimated from $\lg(A/M^{-1}s^{-1}) = 8.5$ for the addition of the methyl radical to monosubstituted and 1,1-disubstituted alkenes with a downward correction of about 0.5 for the steric effect of α substitution and an upward correction for the increased number of addition sites. [d] As for the addition of various radicals to other alkynes, see text.

energies should follow an Evans – Polanyi – Semenov relation. Using the best available enthalpies of formation and bond-dissociation energies to estimate the reaction enthalpies as before,^[69] and applying Equation (2), we arrive at the predicted activation energies which are also listed in Table 15. The frequency factors should not vary grossly, and therefore they can be estimated from the values observed for other reactions presented above. The activation energies and frequency factors then yield the predicted rate constants. As is evident from Table 15, the agreement between the experimental and predicted rate parameters is very satisfactory for the first three cases, where the observed and predicted rate constants agree within one order of magnitude. This indicates that the basic Evans – Polanyi – Semenov relation is also valid for more than just the monosubstituted and 1,1-disubstituted alkenes, at least approximately, and it supports the general and strong influence of the reaction enthalpy on the activation energies. A consideration of the terms leading to the reaction enthalpy reveals that, in comparison with ethene, the methyl radical adds faster to 1,3-butadiene because a more stabilized radical is formed. It adds faster to allene because the parent compound is less stabilized than the products, and to benzene it adds more slowly because the aromatic resonance stabilization is lost. Data for additions to electron-acceptor-substituted polyenes, benzenes, condensed aromatic compounds, and heterocycles also clearly confirm the weak nucleophilicity of the methyl radical.^[58b]

For ethyne, the prediction is not satisfactory because the estimated activation energy is too low by nearly 10 kJ mol⁻¹, and the estimated rate constant exceeds the experimental value by more than one order of magnitude. Of course, this may be because of a failure in our enthalpy estimation procedure. However, methyl adds more slowly to ethyne than to ethene (Table 16), even though the reaction is more exothermic by an estimated 15 kJ mol⁻¹, an ab initio calculation gave an increased exothermicity of 34 kJ mol⁻¹.^[128] Hence, additions to alkynes deserve special discussion. In fact, the slower addition of carbon-centered radicals to alkynes in comparison with similarly substituted alkenes is a

Table 16. Rate constants at room temperature, frequency factors, and activation energies for the addition of methyl (Me),^[58b] *tert*-butyl (*t*Bu),^[62d] and *tert*-butoxycarbonyl methyl^[62d] (MEst) radicals to alkynes and alkenes.

Reaction	k_{300} [M ⁻¹ s ⁻¹]	$\lg(A/M^{-1}s^{-1})$	E_a [kJ mol ⁻¹]
Me + HC≡CH	5.3×10^3	9.7	34.3
Me + H ₂ C=CH ₂	7.0×10^3	8.5	28.2
Me + HC≡CCH ₃	2.4×10^3	8.8	31.1
Me + CH ₂ =CHCH ₃	4.3×10^3	8.5	27.7
Me + HC≡CPh	4.9×10^4	9.2	25.9
Me + CH ₂ =CHPh	2.6×10^5	8.5	17.5
Me + PhC≡CPh	1.5×10^3	10.5	42.1
Me + (<i>E</i>)-PhCH=CHPh	9.7×10^3	8.2	24.2
<i>t</i> Bu + HC≡CSiMe ₃	2.4×10^3	8.9	30.8
<i>t</i> Bu + CH ₂ =CHSiMe ₃	9.6×10^3	7.5	20.2
<i>t</i> Bu + HC≡CPh	2.1×10^4	8.7	23.8
<i>t</i> Bu + CH ₂ =CHPh	1.3×10^5	7.5	13.7
<i>t</i> Bu + HC≡CCO ₂ Me	1.8×10^5		
<i>t</i> Bu + CH ₂ =CHCO ₂ Me	1.1×10^6		
MEst + HC≡CSiMe ₃	2.2×10^4	9.4	31.7
MEst + CH ₂ =CHSiMe ₃	8.9×10^4	8.5	19.8
MEst + HC≡CCO ₂ Et	5.1×10^4	8.5	21.6
MEst + CH ₂ =CHSiMe ₃	4.9×10^5	8.5	15.6

general feature,^[2-4, 127] and it is again demonstrated by the results given in Table 16. The rate constants for the addition of the three radicals to alkynes are all lower than for the addition to the corresponding alkenes. Also, the substituent effects appear to be less pronounced, that is, the enthalpic and the polar substituent effects are smaller though they show the same direction for alkenes and alkynes. For the alkynes the frequency factors are higher, and from a larger series an average $\lg(A/M^{-1}s^{-1}) = 9.2 \pm 0.4$ was deduced.^[62d] Presumably, this is because of the linear alkyne structure and the correspondingly missing degree of freedom of rotation about the alkyne triple bond. The lower alkyne entropy suggests a smaller entropy loss upon formation of the transition structure for the alkynes than for the alkenes, and this is confirmed by calculations.^[128] Since the frequency factors are higher, the lower rate constants are caused by the considerably higher activation energies. The additions to alkynes are more exothermic than the additions to alkenes, thus the higher activation energies are contra thermodynamics. A consideration of the state correlation diagram points to possible reasons. Firstly, for alkynes the electron affinities are smaller and the ionization energies are larger than for the corresponding alkenes. This diminishes the polar effects, and makes the alkyne reactions less selective and increases the activation energies. Secondly, the triplet energies are higher for alkynes than for alkenes, and this should also increase the barriers. In Sections 4.3.1.6 and 4.3.1.7 for the additions to alkenes we did not find a clear influence of the location of the triplet state, and thought it was incorporated in the enthalpic effect. However, in principle, variations of the triplet energy should cause changes in the activation energy independent of the reaction enthalpy, and we suggest that the slower additions to alkynes are partly a manifestation of this effect. It implies that the parameters in the Evans – Polanyi – Semenov relation [Eq. (2)] are smaller for alkyne additions than for alkene and other closely related additions.

6. Synopsis and Perspective

Rate constants for the addition of carbon-centered radicals to alkenes and other compounds with unsaturated carbon–carbon bonds can presently be measured to rather high precision, that is, with errors < 50 %. They vary with radical and substrate substitution by many orders of magnitude from values close to zero to the upper diffusion- or collision-controlled limit of about 10^9 – 10^{10} M^{−1} s^{−1}. Because of error correlation, the frequency factors are usually precise only within a factor of two and the activation energies to ± 4 – 6 kJ mol^{−1}.

The frequency factors for additions to structurally related systems span a limited range, and the often much larger rate variations are primarily because of variations in the activation energy associated with radical and substrate substitution. Excursions of the frequency factors from the established ranges often go parallel with unusual activation energies. This deviation points to error compensation effects of the Arrhenius parameters and calls for advanced error analyses.^[129] Both for the gas and the liquid phase, the frequency factors of radical addition to monosubstituted and 1,1-disubstituted alkenes CH₂=CXY are insensitive to the β -alkene substituents X and Y, are in the range $6.5 < \lg(A\text{M}^{-1}\text{s}^{-1}) < 9.0$ and decrease with the increasing steric demand of the attacking radical. As a rule, one has $\lg(A\text{M}^{-1}\text{s}^{-1}) = 7.0 \pm 0.5$ for polymeric, 7.5 ± 0.5 for tertiary, 8.0 ± 0.5 for secondary and 8.5 ± 0.5 for primary small alkyl radicals. Because of steric effects, alkene substitution at the attacked carbon atom lowers the frequency factor by about one order of magnitude. For the addition to polyenes, allenes, and aromatic compounds, similar frequency factor ranges and steric substituent effects apply but for alkynes a larger frequency factor of $\lg(A\text{M}^{-1}\text{s}^{-1}) = 9.2 \pm 0.5$ is recommended. If the reaction rate approaches that for diffusion-controlled reactions, the frequency factor increases to $\lg(A\text{M}^{-1}\text{s}^{-1}) = 9$ – 10 . Enthalpic, polar, and solvent effects appear to have only a minor influence on the frequency factors.

The activation energies of additions follow the same pattern for gas and liquid phase systems but, in general, the gas-phase activation energies seem to be higher by several kJ mol^{−1} which leads to rate constants that are about ten times lower. *High-level ab initio calculations* can provide barriers and reaction enthalpies within the experimental precision, if the phase effect is taken into account. Suitable high-level theoretical methods include CBS-RAD and G3(MP2)-RAD, while less costly techniques like B3-LYP/6-31G(d) can still be usefully employed for larger systems. The popular UMP2 procedure often gives quite unreliable results.

The state correlation diagram provides an excellent basis for the discussion of the activation energies which, depending on the reaction, are dominated by enthalpic and polar substituent effects. *Steric effects on the activation energies* should generally be considered as part of the enthalpic effect, and it should be noticed that diffusion sets a lower limit to the activation energy of about 10 kJ mol^{−1}.

The reaction enthalpy H_r has a general and often dominating influence on the activation energy which for many alkyl radical additions to monosubstituted and 1,1-disubstituted

alkenes is well described by a linear Evans–Polanyi–Semenov relation, specifically $E_a[\text{kJ mol}^{-1}] = 50 + 0.22 H_r[\text{kJ mol}^{-1}]$. This relation is also approximately valid for other additions. The enthalpy contribution seems to incorporate an expected effect from the location of the excited triplet state of the reactants, with the possible exception of additions to alkynes where a higher constant term in the Evans–Polanyi–Semenov relation may apply. Hence, the reactivities of alkynes are remarkably low.

Polar substituent effects reflect contributions of the CT configurations to the transition state. They become noticeable when the energies of the CT configurations are less than about 10 eV higher than the reactant ground-state energy. For nucleophilic radicals with low ionization energies ($E_i < 8$ – 9 eV) this is the case for additions to electron-deficient alkenes, while for electrophilic radicals with high electron affinities ($E_{\text{ea}} > 2$ eV) it holds for additions to electron-rich alkenes. Radicals with borderline ionization energies and electron affinities often show an ambiphilic behavior.

The polar substituent effects decrease the activation energies below the enthalpy contribution by *multiplicative factors* ($0 < F_p < 1$). Besides depending on the energy location of the CT configurations, these depend also on the Coulomb attraction and the strength of the interaction between the polar and nonpolar configurations at the transition structure. The polar factors can not be separated into radical and alkene contributions.^[130] As a rule, substituents which are capable of strongly delocalizing the transferred charges lead to smaller decreases in the activation energies by polar effects. Because of the combination of enthalpy and polar effects, nucleophilic radicals are usually more selective and more reactive in reactions with different substrates than non-nucleophilic radicals, electrophilic radicals are less selective but more reactive, and ambiphilic radicals are as selective as radicals without polar effects but more reactive. Recommended ranges for the Coulomb and the interaction parameters are given in the text and footnotes for the additions to monosubstituted and 1,1-disubstituted alkenes. For other additions, the same principles operate but accurate parameters can not yet be given.

To predict the magnitude of the enthalpy contribution to the activation energies, one needs to know the reaction enthalpy H_r . This can either be calculated by quantum chemical methods or estimated. The latter procedure requires the knowledge of the enthalpies of formation and bond dissociation energies for the molecule and radical. To predict the size of the polar factors one needs CT energies and a reliable estimate of the Coulomb and interaction energies.

Linear correlations of rate constants or activation energies with energy parameters such as the reaction enthalpy and the electron affinities and ionization energies of the reactants are of limited value because these parameters are mutually interrelated, and such an approach may even lead to wrong conclusions.^[132] The analysis presented herein avoids this difficulty and takes the nonadditive operation of the various effects into proper account. For a variety of cases, it has allowed the prediction of addition constants correct to within one order of magnitude of the experimental data. The predictive power of the present analysis greatly exceeds that

of the previous qualitative rules. In contrast to these, we conclude that the reaction enthalpy has a large influence in all cases. We believe that our rationalization of addition rates and the factors controlling them can be extended to many more reactions than covered so far, with the increasing availability of more reliable radical heats of formation, bond dissociation energies, molecular electron affinities and ionization energies and with a better understanding of the Coulomb and interaction terms from either experiment or theory.

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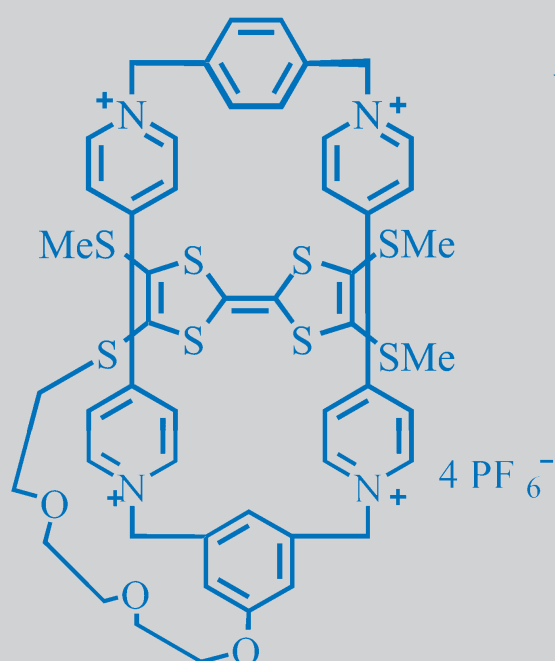
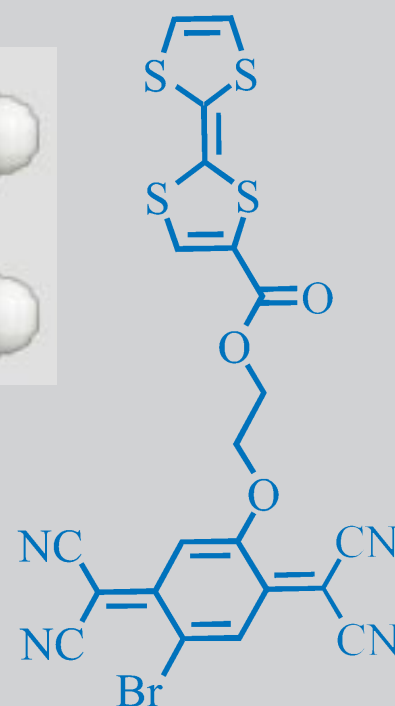
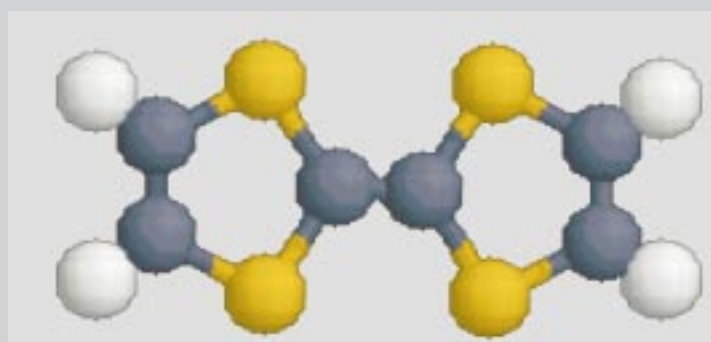
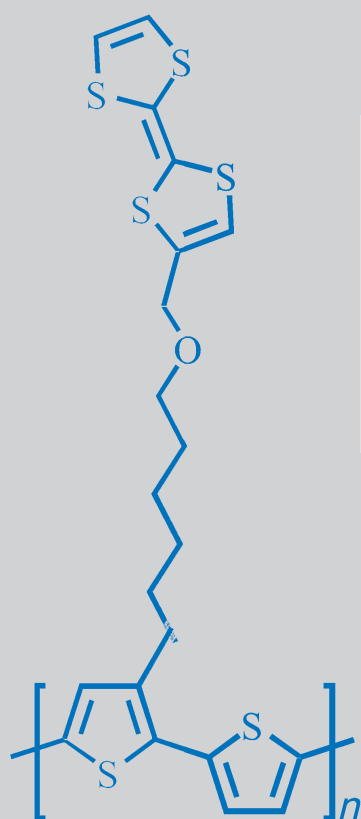
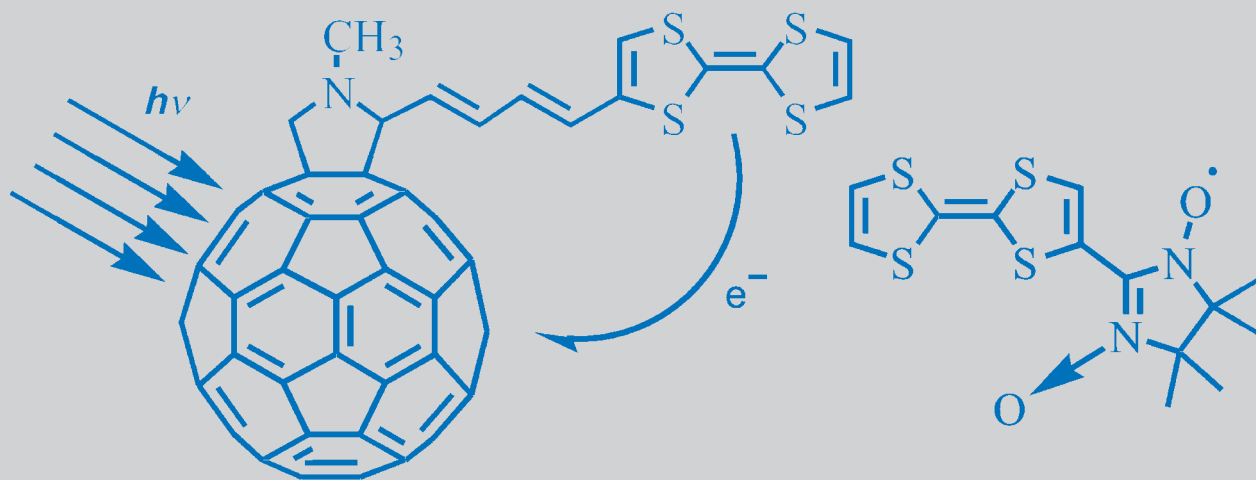
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Tetrathiafulvalene and its derivatives offer new possibilities at the molecular to the supramolecular levels, as well as in macromolecular aspects.

New Concepts in Tetrathiafulvalene Chemistry

José L. Segura and Nazario Martín*

*Dedicated to Professor Michael Hanack
on the occasion of his retirement*

Tetrathiafulvalene (TTF) and its derivatives were originally prepared as strong electron-donor molecules for the development of electrically conducting materials. This Review emphasizes how TTF and its derivatives offer new and in some cases little-exploited possibilities at the molecular to the supramolecular levels, as well as in macromolecular aspects. TTF is a well-established molecule whose interest goes beyond the field of materials chemistry to be considered an important building block in supramolecular chemistry, crystal engineering, and in systems able to operate as machines. At the molecular level, TTF is a readily available molecule which displays a strong electron-donor ability. However, its use as a catalyst for radical-polar crossover reactions, thus mimicking samarium iodide chemistry, has only recently been addressed. Important goals have been achieved in the

use of TTF at the macromolecular level where TTF-containing oligomers, polymers, and dendrimers have allowed the preparation of new materials that integrate the unique properties of TTF with the processability and stability that macromolecules display. The TTF molecule has also been successfully used in the construction of redox-active supramolecular systems. Thus, chemical sensors and redox-switchable ligands have been prepared from TTF while molecular shuttles and molecular switches have been prepared from TTF-containing rotaxanes and catenanes. A large synthetic effort has been devoted to the preparation of the so-called organic ferromagnets, many of which are derived from TTF. The main task in these systems is the introduction of ferromagnetic coupling between the conduction electrons and localized electrons. TTF has also played a prominent role in molecular

electronics where TTF-containing D- σ -A molecules have allowed the preparation of the first confirmed unimolecular rectifier. Recently, it has been confirmed that TTF can display efficient nonlinear optic (NLO) responses in the second and third harmonic generation as well as a good thermal stability. These findings can be combined with the redox ability of TTF as an external stimuli to provide a promising strategy for the molecular engineering of switchable NLO materials. Fullerenes endowed with TTF exhibit outstanding photophysical properties leading to charge-separated (CS) states that show remarkable lifetimes.

Keywords: donor-acceptor systems • electron transfer • materials science • supramolecular chemistry • tetrathiafulvalene

1. Introduction

Shortly after Wudl reported the synthesis of tetrathiafulvalene (TTF, **1**) in 1970,^[1] the first "organic metal" tetrathiafulvalene-tetracyano-*p*-quinodimethane (TTF-TCNQ) was discovered.^[2,3] In 1979, the first molecule-based superconductor based on the Bechgaard salts [TMTSF]₂X (X = PF₆⁻, AsF₆⁻)^[4,5] was prepared by using a selenium-

containing TTF analogue, namely tetramethyltetraselenafulvalene (TMTSF). Since then, and during almost two decades, a huge amount of work has been carried out to enhance the electron-donating power of TTF analogues in order to improve the conductivities of salts and charge-transfer (CT) complexes derived from them. However, during the last few years, the utility of TTF derivatives as building blocks in macromolecular and supramolecular structures, as molecule-based ferromagnetic compounds, as synthetic intermediates in organic chemistry, as a donor moiety in intramolecular donor-acceptor (D-A) systems in nonlinear optic (NLO) materials and in association with the fullerene core, as well as in the preparation of liquid crystalline materials and Langmuir-Blodgett (LB) films has made TTF one of the most extensively studied molecules. Thus, during the last few years,

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partial aspects of the synthesis and properties of tetrathiafulvalenes have been reviewed (Table 1).^[6–24]

Table 1. Recent reviews on specific aspects of TTF.

Main author	Title
M. R. Bryce	Recent progress on conducting CT salts ^[6]
V. Khodorkovsky	Molecular design of organic conductors ^[7]
M. R. Bryce	Increasing dimensionality in the solid state ^[8]
G. Schukat	TTF chemistry ^[9]
J. Garín	Reactivity of TTF and TSeF ^[10]
K. B. Simonsen	Functionalization of TTF ^[11]
T. Otsubo	TTF dimers ^[12]
M. Adam	TTF oligomers ^[13]
J. Becher	TTF oligomers ^[14]
M. R. Bryce	Macromolecular TTF chemistry ^[15]
T. Jørgensen	Supramolecular TTF chemistry ^[16]
K. B. Simonsen	Macrocyclic and Supramolecular TTF chemistry ^[17]
M. B. Nielsen	Two- and three-dimensional TTF macrocycles ^[18]
E. Coronado	Hybrid polyoxometalates-TTF materials ^[19]
J. Roncali	Linearly π -extended TTF derivatives ^[20]
P. Day	Molecular magnetic semiconductors, metals and superconductors ^[21]
M. R. Bryce	TTF as π -donors in intramolecular CT-materials ^[22]
M. B. Nielsen	Tetrathiafulvalenes as building blocks in supramolecular chemistry ^[23]
M. R. Bryce	Functionalised tetrathiafulvalenes: new applications as versatile π -electron systems in materials chemistry ^[24]

The purpose of this account is not to duplicate those aspects previously reviewed in the different fields but to give an overview of recently synthesized TTF-containing systems and to summarize their new applications which are different from the extensively studied electrical conductivity. Thus, we will briefly mention the most recent developments on the chemical modifications of TTF-containing materials and concentrate on the new applications of this unique molecule.

2. Current Trends in the Development of New TTF-Containing Materials

Tetrathiafulvalene is a nonaromatic 14- π -electron system in which oxidation to the cation radical and dication occurs sequentially and reversibly at relatively low potentials ($E_{1/2}^1 = 0.37$ V and $E_{1/2}^2 = 0.67$ V in dichloromethane versus the saturated calomel electrode). In contrast to the neutral TTF molecule, both the cation radical and dication are aromatic in the Hückel sense as a result of the 6 π -electron heteroaromaticity of the 1,3-dithiolium cation, and, therefore, while TTF^{•+} and TTF²⁺ have a planar *D*_{2h} symmetry, neutral TTF has a boatlike equilibrium structure with *C*_{2v} symmetry.^[25] However, because of the small difference between planar and boatlike conformations, TTF (**1**) is very flexible and can

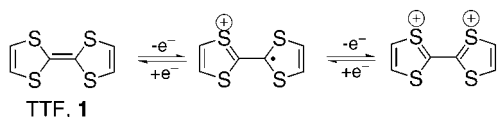
Nazario Martín studied chemistry at the Universidad Complutense de Madrid (UCM), where he obtained his Doctorate at the Department of Organic Chemistry under Professor C. Seoane in 1984. After spending a year working on X-ray contrast agents in a pharmaceutical company, he worked as a postdoctoral fellow (1987–1988) at the Institut für Organische Chemie der Universität Tübingen under Professor M. Hanack on electrically conducting organic materials. In 1994, he was a visiting Professor at the Institut for Polymers and Organic Solids (IPOS) at the University of California, Santa Barbara (UCSB) working with Professor F. Wudl on modified fullerenes. Since 1989, he has been Associate Professor of Organic Chemistry at the University Complutense (UCM). His research interests range over electroactive molecules with emphasis on the optoelectronic properties of electron-donor tetrathiafulvalene (TTF) derivatives and electron acceptors, the chemistry of fullerenes, and, in particular, the design and synthesis of electroactive organofullerenes. He is also active in the asymmetric synthesis of heterocyclic systems and reactive intermediates. He has published around two hundred papers, and he is currently a member of the International Advisory Editorial Board of *The Journal of Materials Chemistry* and Editor of the Spanish journal *Anales de la Real Sociedad Española de Química*.



N. Martín

J. L. Segura

José L. Segura studied chemistry at the Universidad Complutense de Madrid, where he obtained his diploma in 1989 and his Ph.D. in 1994 under Professor N. Martín and Professor C. Seoane working on the synthesis of inter- and intramolecular charge transfer complexes derived from TTF, TCNQ, and DCNQI. In 1993 he visited the group of Professor W. Daily (University of Pennsylvania) where he worked in the area of strained-ring organic syntheses. After post-doctoral stays in the group of Prof. M. Hanack (University of Tübingen) working on the syntheses of electroluminescent conjugated polymers and in the group of Professor F. Wudl (University of California at Santa Barbara) working on the functionalization of *C*₆₀ fullerene, he joined the faculty in the Department of Organic Chemistry at the Universidad Complutense de Madrid in 1995.



appear in various conformations depending on the donor–donor and donor–acceptor interactions in the crystals.

In the following sections we will outline the main research lines towards the development of new TTF-containing systems at the molecular, macromolecular, and supramolecular level.

2.1. Molecular Level

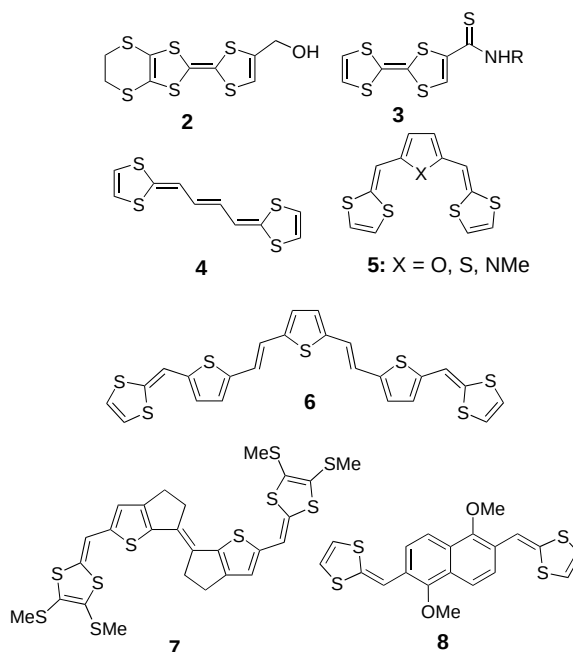
As Bryce has pointed out,^[22] recent progress in the syntheses of TTF-containing systems can be divided into the four following points:

- The possibility of synthesizing TTF in multigram quantities.^[26]
- The availability of a great amount of monosubstituted TTF derivatives by electrophilic substitution of lithiated TTF.^[10]
- The new selective protection/deprotection chemistry of the thiolate groups of the 1,3-dithiole-2-thione-4,5-dithiolate (DMIT) system which provides a number of versatile TTF building blocks.^[27]
- The discovery of the cyanomethyl protecting group.^[11]

The reading of the comprehensive review articles by Schukat et al.^[9] and Garín^[10] is highly recommended to get insight into the rich chemistry of tetrathiafulvalene.

Although in recent years different chemical modifications have been carried out on the TTF unit to prepare building blocks for macro- and supramolecular chemistry at the molecular level, the “classical” chemical modifications carried out on the TTF skeleton are aimed at increasing the electrical conductivity^[6] and are related to the above outlined properties: on the one hand by the fine tuning of the donor ability by changing the substitution pattern and, on the other hand, by changing sulfur to other chalcogens or by introducing chalcogens in a peripheral position on the TTF moiety. These modifications increase the overlap between the chalcogen atoms and result in the formation of dimers, highly ordered stacks, or two-dimensional sheets.

The increase in the dimensionality of the charge-transfer materials has been identified as a priority provided that low-dimensional conductors are unstable and a suppression of the metallic state is produced as the temperature decreases. Thus, during the last few years, the large development in the chemistry of TTF^[9–11, 28] has been taken advantage of to develop different alternative routes for the replacement of sulfur by other chalcogen atoms so as to increase the dimensionality in tetrathiafulvalene chemistry. In 1995, Bryce reviewed some of these strategies^[8] including hydrogen bonding in functionalized TTF derivatives (**2**, **3**) and the syntheses of TTF analogues with extended π conjugation (**4**–**8**).^[29] The syntheses and properties of TTF analogues with polyalkenic (**4**), heterocyclic (**5**), π -conjugated heterocycles such as oligoheteroarylenevinylene (**6**), and other rigid π -conjugated spacers (**7**) have been reviewed in more detail by



Roncali.^[20] More recently, conjugated carbocyclic spacers (**8**) have also been used. Roncali points out that by precise control of the spacer length it should be possible to tune the conduction mechanism between the “vertical” mixed-valence conduction of TTF charge-transfer salts to the “horizontal” polaron/bipolaron conduction of linear systems.^[20]

Otsubo et al.,^[12] and more recently Becher et al.,^[14] reviewed the different TTF dimers.^[30] As a result of the intramolecular through-bond or through-space interactions between the TTF units, these kinds of TTF derivatives display multi-stage redox behavior which might provide the possibility of controlling the stoichiometry, band filling, and molecular assembly in desired conductive complexes.^[12] The intramolecular interaction between the two redox moieties, and hence between the stacks or slabs, can be modified in a controlled way by changing the nature of the bridging group between the TTF units. Figure 1 shows the different types of bis-TTF derivatives.

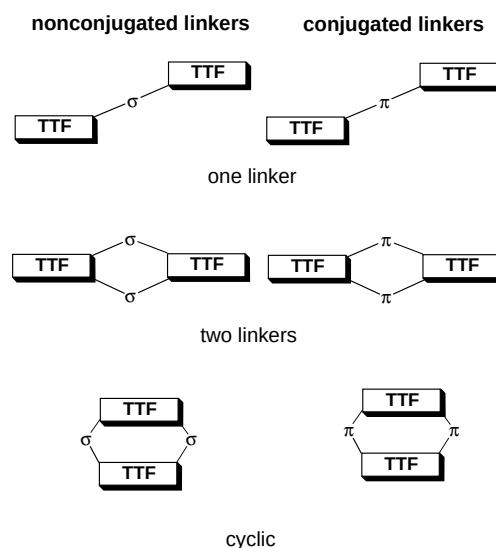
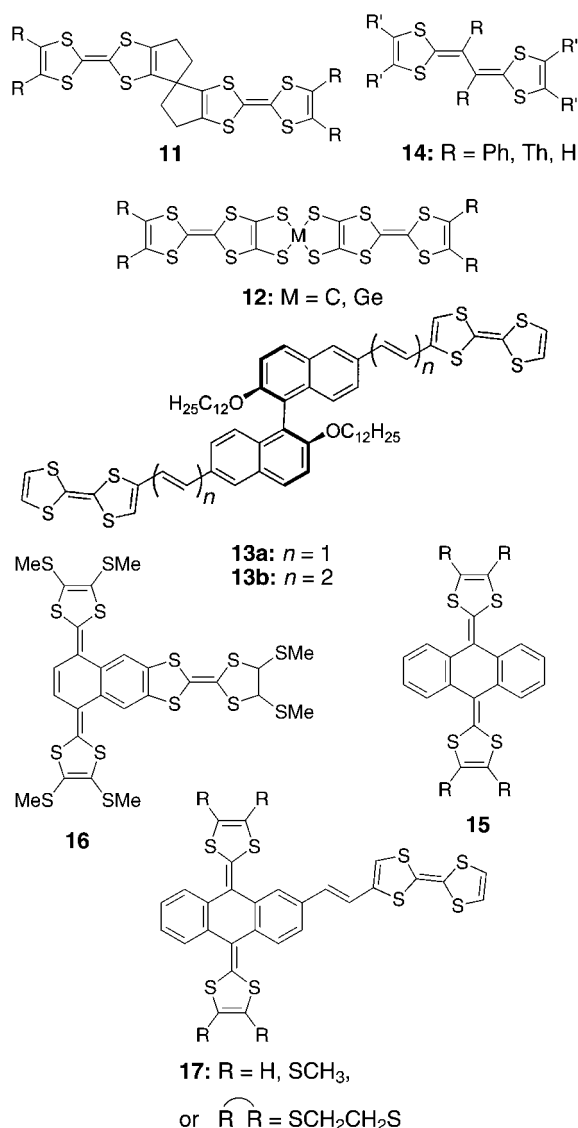


Figure 1. Different types of bis-TTF derivatives.^[14]

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Contrary to the unsubstituted vinylogues **14** ($R = H$), derivatives containing bulky substituents, such as phenyl (Ph) or thienyl (Th) groups, exhibit a highly twisted structure.^[37] These types of compounds can be synthesized electrochemically by using 1,4-dithiafulvenes as starting materials. As a result of this lack of planarity, neither the formation of radical cation^[38a] and dication salts^[38b] of these compounds nor their use as components for organic conductors had been reported until recently. Yamashita et al. reported in 1998 the first examples of cation radical salts of TTF vinylogues containing substituents at the vinyl positions (**14**, $R = Ph$, $R' = (CH=CH)_2$).^[38a] Interestingly, although the X-ray data observed for this phenyl-substituted vinylogue show a highly distorted structure, the molecular structure is drastically changed upon oxidation. Thus, the cation radical salt **14**·PF₆ has a planar TTF vinylogue skeleton with the aryl groups



The incorporation of cyclic “spacer” groups between two 1,3-dithiafulvenyl rings has also been used to extend π conjugation in TTF-based systems. Similarly to the previously studied TTF vinyllogues **14**, derivatives **15** exhibit highly distorted geometries with the central quinoid ring bent into a boat conformation. This distortion allows the relief of the steric congestion between the *peri*-hydrogens and the sulfur atoms.^[39] Upon oxidation, donors **15** adopt an almost planar conformation with the two dithiolium cation rings nearly orthogonal to the anthracene moiety, thereby preventing conjugation between the two heterocyclic rings.^[8] We have recently reported the preparation and redox properties of more π -extended TTF analogues of **15**^[40] as well as of related dimeric compounds.^[41] These compounds exhibit a first oxidation wave involving two electrons, and lead directly to the formation of the dication as a result of the corresponding radical cation having a high instability because of the above-mentioned steric interactions. Hudhomme, Gorgues, et al.

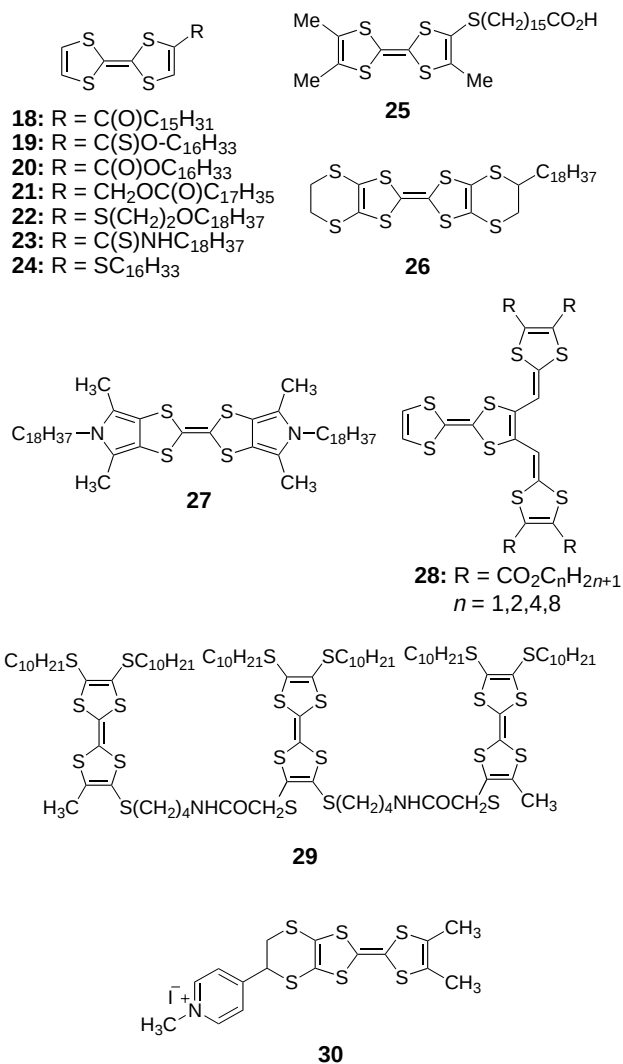
have reported the synthesis of **16**, which contains a TTF unit fused to a π -extended TTF system.^[42] Cyclic voltammetry (CV) investigations on **16** showed three reversible oxidation peaks, the first one corresponding to a $2e^-$ process arising from the π -extended *p*-quinodimethane analogue of TTF, while the following two correspond to $1e^-$ oxidation peaks related to the TTF moiety. These are of interest for studying the possible formation of radical cation salts.

New hybrid TTF dimers (**17**) formed by the parent TTF molecule in conjugation with the π -extended TTF **15** have recently been reported. Electrochemical studies show that these compounds mainly retain the electrochemical properties of both the TTF and the π -extended TTF components. Interestingly, the CV studies reveal an intramolecular electronic interaction between the two moieties. These strong electron donors were able to form CT complexes with dichlorodicyano-*p*-benzoquinone (DDQ), with a donor:acceptor stoichiometry of 1:3.^[43]

Yamashita et al. have reported heterocyclic analogues of **15** in which heterocyclic rings are fused to the central quinonic core.^[44] Substitution of the fused benzene rings by the less sterically demanding thiadiazole rings results in planar π -extended TTF derivatives. Yamashita et al. have also prepared derivatives containing a fused benzene ring and a thiadiazole ring; these molecules have a nonplanar structure and form metallic radical cation salts.^[45] The cyclic voltammetric measurements on these compounds show one reversible oxidation wave involving two electrons, which indicates that the cation radical states are thermodynamically unstable. However, their radical cation salts were isolated as single crystals when they were electrochemically oxidized in the presence of Bu_4NPF_6 in tetrahydrofuran. These radical cation salts show electrical conductivity, and the solvent molecules seem to play an important role in the construction of the crystal structure.^[46]

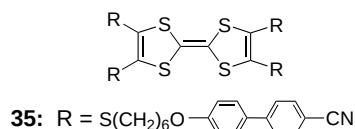
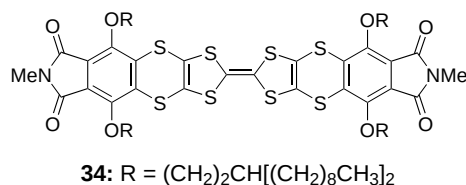
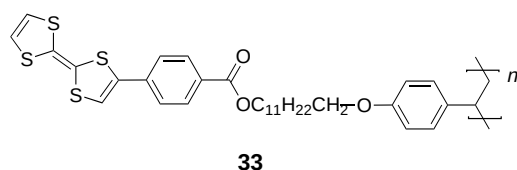
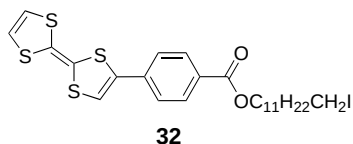
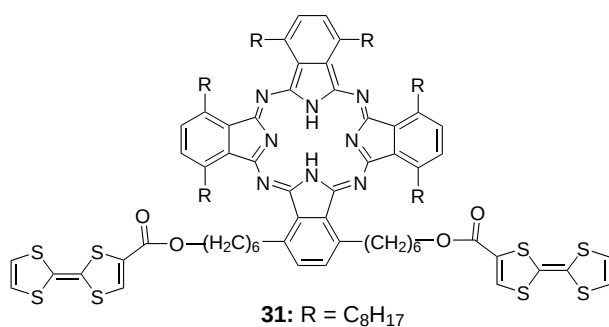
To finish with this short resume of the latest trends in the development of new TTF derivatives as electrically conducting materials, it is worth mentioning that in spite of the fact that studies of conducting charge-transfer complexes have concentrated almost exclusively on single crystals, other alternatives have appeared during the last few years. The Langmuir–Blodgett (LB) technique offers the possibility of assembling organic molecules with a greater level of structural control than in the corresponding crystalline material, and makes it possible to incorporate conducting CT salts into practical devices.^[47] With this aim, amphiphilic TTF derivatives have been prepared by attaching hydrophobic tails (**18–29**) or charged aromatic substituents (**30**) to the TTF core and used to make LB films of CT complexes and CT salts.^[48]

Organic chemical vapour deposition has been used to grow TTF–TCNQ layers.^[49] The stoichiometry of the deposits can be controlled by varying the evaporation temperature of the precursors. While the use of amorphous substrates does not induce in-plane textures and the microcrystals are randomly distributed, the use of substrates such as KCl or KBr induce in-plane orientations. Therefore, the influence of the substrate on the in-plane texture of the film is very important in providing a way to control the growth of films of charge-transfer complexes.^[50]



An alternative to the above methods for obtaining an assembly of ordered arrays of TTF-containing molecules is based on the preparation of mesogenic derivatives by either attaching a TTF unit to a mesogenic liquid crystalline center or by incorporating substituents which show mesomorphic behavior with the TTF moiety.^[51–55] Some of the early citations^[51] presented poorly characterized liquid crystal behavior. In contrast, **31–35** are representative recent examples of TTF derivatives exhibiting “proper” liquid crystal behavior.

Cook et al. attached the TTF unit to a discotic phthalocyanine liquid crystalline center to obtain the first discotic liquid crystalline tetrathiafulvalenylphthalocyanine derivative (**31**). They observed by UV/Vis spectroscopy of spin-coated films that the molecular architecture of this material can be changed by oxidation with iodine vapor and heating to within the mesophase region.^[54] In 1995 Müllen et al. reported the synthesis of the TTF derivative **32**. Although the available data could not distinguish between a nematic or smectic phase, the mesogenic behavior of **32** was used by incorporating it as a side chain into a polymer, thus enabling the electron-donating properties of TTF systems to be combined with the general characteristics of high molecular weight



polymers, such as film forming and processability.^[53] Unfortunately, polymer **33** exhibited no liquid crystalline phase after polymerization, which indicated that the TTF moieties act as separate and independent molecules.

In 1998 Bushby et al. reported on the enantiotropic liquid crystalline behaviour of TTF derivative **34**.^[55] However, upon p-doping with 2 mol % of antimony pentachloride to give a radical cation concentration of about 10²⁰ cm⁻³ (EPR), the conductivity of the alternating current was lower than is normally found in doped discotic liquid crystals. This result probably indicates that the radical cations formed are highly localized and/or fixed by the counterions.

Compound **35** is a thermotropic liquid crystal which displays monotropic behavior and gives the complex **35**·I₁₀ on mixing solutions of **35** and I₂ in CH₂Cl₂.^[52] The results of microscopy observations and X-ray data unambiguously indicate a nematic phase for the iodine-doped compound. The fact that this compound shows mesomorphic behavior after doping with iodine is a very promising result for the use of liquid crystalline TTF derivatives in forming highly ordered supramolecules and new multiproperty materials.

This section should not conclude without mentioning the great amount of work devoted to the obtention of tetrathia-

fulvalenes as π -electron donors for intramolecular donor-acceptor materials. However, this topic was thoroughly reviewed by Bryce in 1999,^[22, 24] and the reader is referred to these excellent review articles for complete coverage of the field. Some of the most interesting applications of this type of material will be presented in Section 3.2.

2.2. Macromolecular Systems

In this section we will consider dendrimers, polymers, as well as macrocyclic systems containing one or more TTF units.

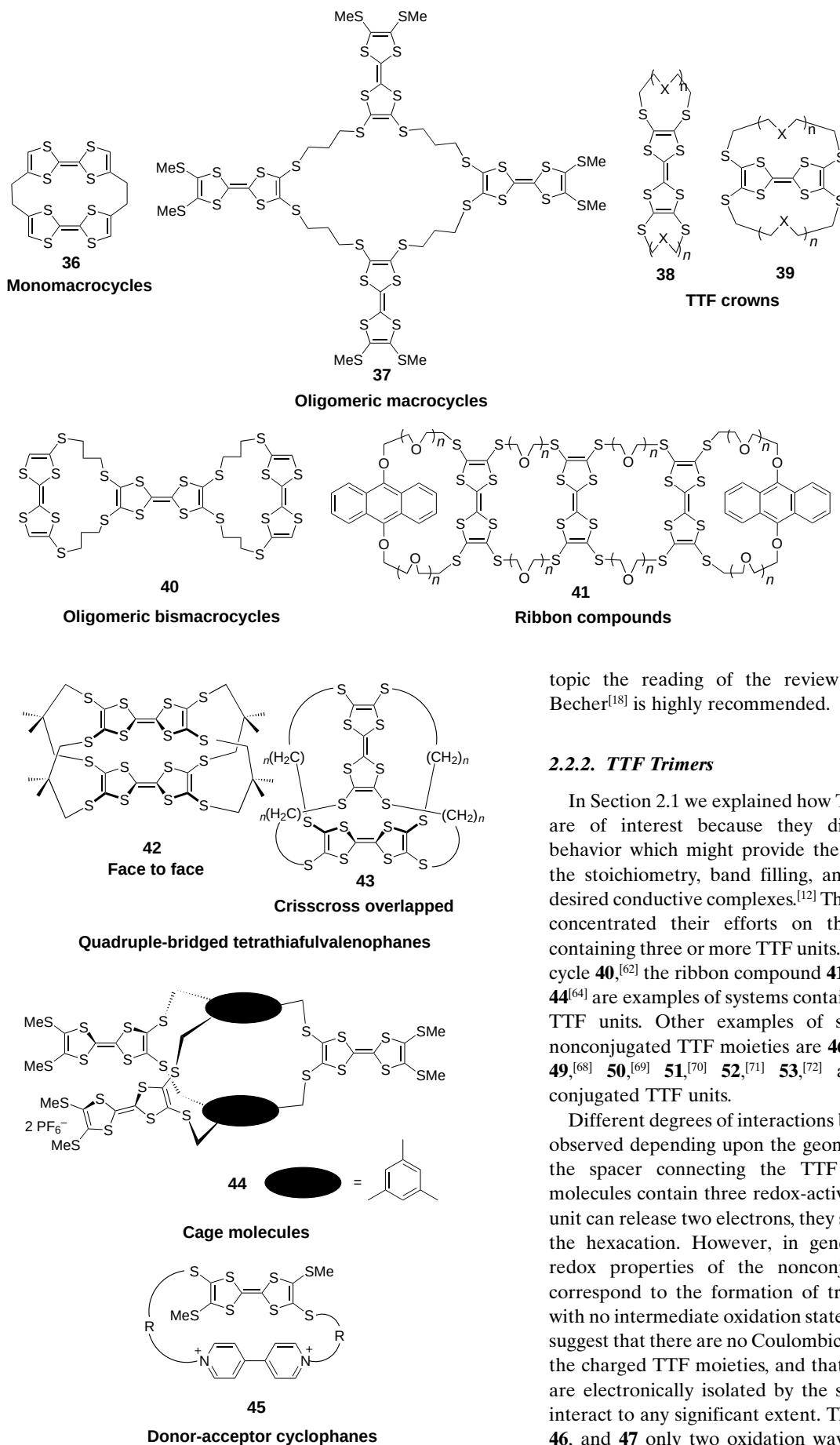
2.2.1. TTF-Containing Macrocycles

Tetrathiafulvalenophanes (cyclophanes containing one or more TTF units) have been extensively studied. These types of compounds could have been included in the previous section devoted to the nonplanar TTF derivatives. However, the interest in these compounds arises not only for the increased dimensionality of their charge-transfer salts but mainly because of their implications in macro- and supramolecular chemistry where they might act as receptors for electron-deficient compounds and, therefore, might be used for electroactive recognition.

In 1997 Nielsen and Becher reviewed^[18] the two- and three-dimensional TTF macrocycles and classified them into seven classes:

1. Monomacrocycles, such as **36**, which include macrocycles containing one or two TTF units with different spacers.
2. Oligomeric monomacrocycles including tris-, tetra- (**37**), and pentameric TTF monomacrocycles.
3. Bismacrocycles where the central TTF unit can be cyclized either in the peripheral or the lateral positions and which include TTF crowns, such as **38** and **39**, which contain two crown ether moieties annelated to the central TTF unit, and oligomeric bismacrocycles, such as **40**, which are similar to the previous ones but contain more than one TTF unit.
4. Ribbon compounds, such as **41**, in which the tetravalency of the TTF unit is used to prepare ribbon-type systems.
5. Quadruple-bridged tetrathiafulvalenophanes in which the TTF units can be either stacked in a face-to-face arrangement (**42**) or crisscross overlapped (**43**).
6. Cage molecules, such as **44**, which are macrobicyclic tetrathiafulvalenophanes with three bridges.
7. Donor-acceptor cyclophanes, such as **45**, in which the TTF moiety and an acceptor unit are incorporated into the same cyclophane.^[23]

Recent research into these types of compounds includes the syntheses of new bis(tetrathiafulvalene)cyclophanes^[56] and crisscross-overlapped tetrathiafulvalenophanes,^[57, 58] the synthesis and characterization of the first double-bridged tetrathiafulvalenophanes synthesized by Otsubo et al.,^[59] the convergent synthesis of rigid macrocycles containing one or two TTF units,^[60] and the synthesis and characterization of geometrically constrained tetrathiafulvalenophanes^[61] by Becher et al. For a comprehensive treatment of this specific

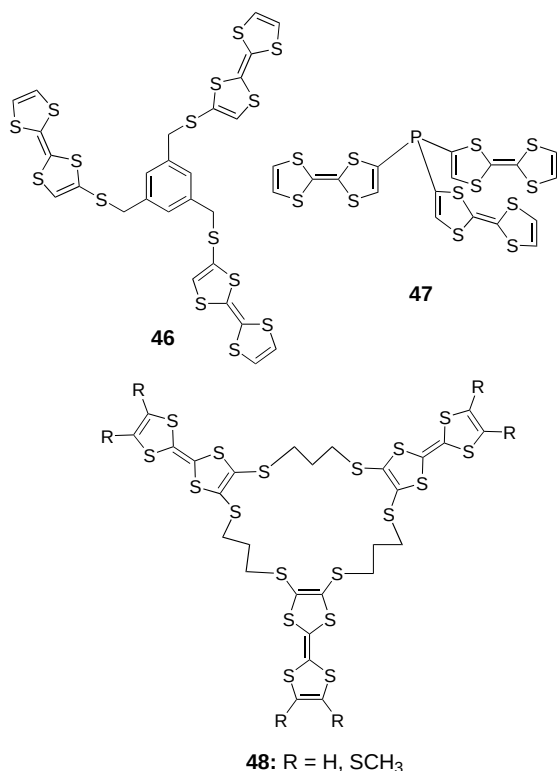


topic the reading of the review article by Nielsen and Becher^[18] is highly recommended.

2.2.2. TTF Trimers

In Section 2.1 we explained how TTF dimers and oligomers are of interest because they display multi-stage redox behavior which might provide the possibility of controlling the stoichiometry, band filling, and molecular assembly in desired conductive complexes.^[12] Thus, other researchers have concentrated their efforts on the syntheses of systems containing three or more TTF units. The oligomeric bismacrocyclic **40**,^[62] the ribbon compound **41**^[63] and the cage molecule **44**^[64] are examples of systems containing three nonconjugated TTF units. Other examples of systems containing three nonconjugated TTF moieties are **46**,^[65] **47**,^[66] and **48**,^[67] while **49**,^[68] **50**,^[69] **51**,^[70] **52**,^[71] **53**,^[72] and **54**^[73] contain three conjugated TTF units.

Different degrees of interactions between the TTF units are observed depending upon the geometry of the molecule and the spacer connecting the TTF units. As these donor molecules contain three redox-active moieties and each TTF unit can release two electrons, they should be oxidizable up to the hexacation. However, in general, the electrochemical redox properties of the nonconjugated TTF derivatives correspond to the formation of trications and hexacations, with no intermediate oxidation states detected. These findings suggest that there are no Coulombic repulsion effects between the charged TTF moieties, and that the individual TTF units are electronically isolated by the spacer groups and do not interact to any significant extent. Thus, for derivatives **40**, **44**, **46**, and **47** only two oxidation waves were observed, which

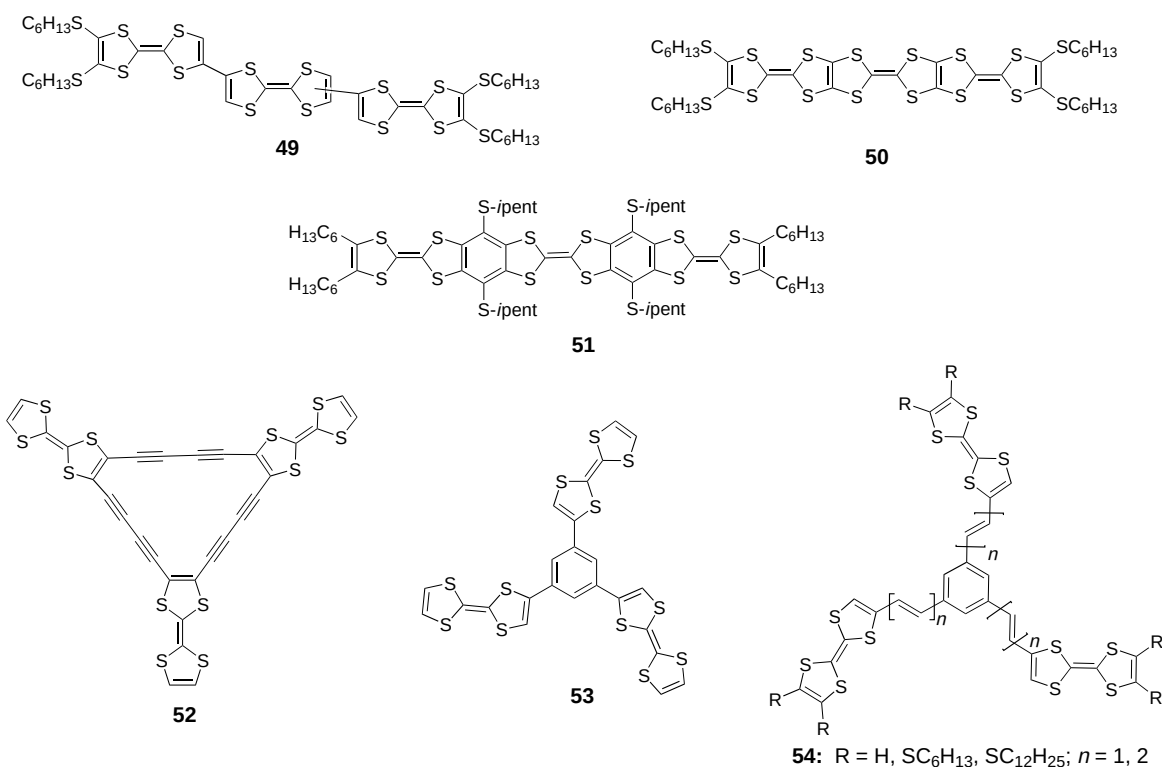


correspond to the oxidation to the trications and hexacations. However, it is worth mentioning the impact that the molecular geometry has on the electrochemical behavior. The cyclic voltammogram of the triple-layered TTF-phane **40** in which the central TTF unit is perpendicular to the peripheral ones shows two redox waves: the first process

involves a two-electron process and the second one involves a four-electron process. It is reasonable to assign the first two-electron process to the oxidation of the two outer TTF units while the second wave remains unresolved and appears as a coalescence of the remaining oxidations.^[62] On the other hand, the cyclic voltammetric measurements of an isomeric compound of **40** in which the three TTF units are not perpendicular but parallel show three waves: the first two-electron wave corresponds to the oxidation of the outer TTF units, the second one-electron wave to the oxidation of the inner TTF unit, and the third three-electron wave to the simultaneous oxidation of all the TTF units.^[62] The different electrochemical behavior of these two isomeric compounds indicates that the columbic repulsion between the TTF units is less important in the perpendicularly oriented TTF-phane and gives an idea of the importance of the molecular structure on the electrochemical behavior.

Another example showing the influence that the molecular geometry has on its redox properties can be seen with the cage molecule **44**. It is a rigid molecule in which the TTF moieties are linked to the spacer through the 2,3 positions, with the three TTF groups pointing out of the cavity. Only one broad first redox wave is visible, which indicates there are weak interactions between the redox centers.^[64] An isomeric cage compound in which the TTF groups are linked through the 2,7 or 6 positions exhibits three redox waves for the generation of the radical cation state. This result indicates that there are strong through-space Coulombic interactions as a result of the close proximity of the three redox moieties.^[64]

In the case of some conjugated systems containing three TTF moieties, six possible electrochemical processes have been observed which indicate the strong interaction between the conjugated TTF units. This is the case for trimer **51**, for



which six oxidation waves can be observed in the cyclic voltammogram. This compound represents the first example of a fully reversible stepwise oxidation of a donor containing three redox-active TTF subunits up to a hexacation.^[70]

Single-bonded TTF trimers **49** show five reversible waves in their cyclic voltammograms, while in the double-bonded analogue **50**, the redox process is composed of three stages of two-electron transfer to form the hexacation. In this last case, it is worth mentioning how the electron-donating ability of this type of fused-TTF system decreases as the number of fused TTF moieties increases. Thus, under the same conditions, the first oxidation wave was observed at +0.62 V for the tetrahexylthio-substituted TTF, at +0.67 V for **50**, and at +0.65 V for the analogue containing only two fused TTF units. Moreover, while one-electron processes were observed for the first oxidation wave in the case of the substituted TTF molecule and the analogue containing two fused TTF units, a two-electron process was observed for **50**. This result occurs because of the small orbital energy difference between HOMO and HOMO-1 in **50** which may cause HOMO–HOMO-1 mixing in the dicationic state. As a result, on-site coulombic repulsion in **50**²⁺ should considerably decrease because they are mainly located on the outer TTF moieties as a consequence of the participation of HOMO-1 (which is mainly localized in the outer TTF units, Figure 2). As a consequence, the dicationic state of **48** is largely stabilized, which justifies the double-electron transfer observed for the first redox stage in the cyclic voltammogram.^[67]

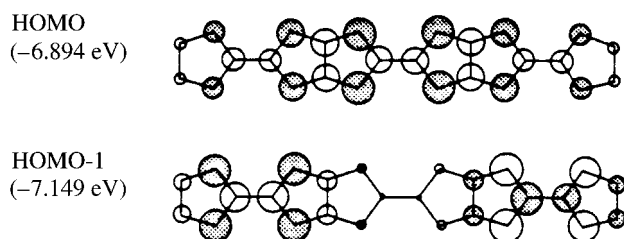


Figure 2. HOMO and HOMO-1 (HF/6-31G* level) of **50**. The radii of the circles are approximately proportional to the LCAO coefficients. (Reprinted with permission from ref. [69].)

Rubin et al. have recently reported the synthesis of tetraethynyltetrathiafulvalenes as precursors to the highly unsaturated tetrathiafulvalene trimer **52**. This compound will have the potential to form CT salts with enhanced dimensionality provided that the overall π -rich surface can enhance the lateral and π -stacking interactions between the individual units.^[71] However, to the best of our knowledge, the synthesis of **52** has not yet been reported.

TTF trimers in which the TTF units are located at the 1,3,5-positions of a benzene ring have also been synthesized to examine the interactions of the TTF radical cations in the triradical trication states. If a ferromagnetic interaction between TTF units could occur in the CT complex or radical–cation salts of molecules such as **53**, a quartet ground state would be expected and a ferromagnetic CT complex might be generated.^[72] Compound **53** possess oxidation potentials similar to that of TTF: it is oxidized by two three-

electron steps, which indicate that small interactions occur between the TTF units as a consequence of the lack of conjugation through the *meta* positions of the benzene ring. This compound forms a conducting CT complex with TCNQ ($\sigma_{RT} = 30 \text{ S cm}^{-1}$, compressed pellet, 4 samples).^[72] To the best of our knowledge, no report about the interactions of TTF units in the radical cation species have yet been published.

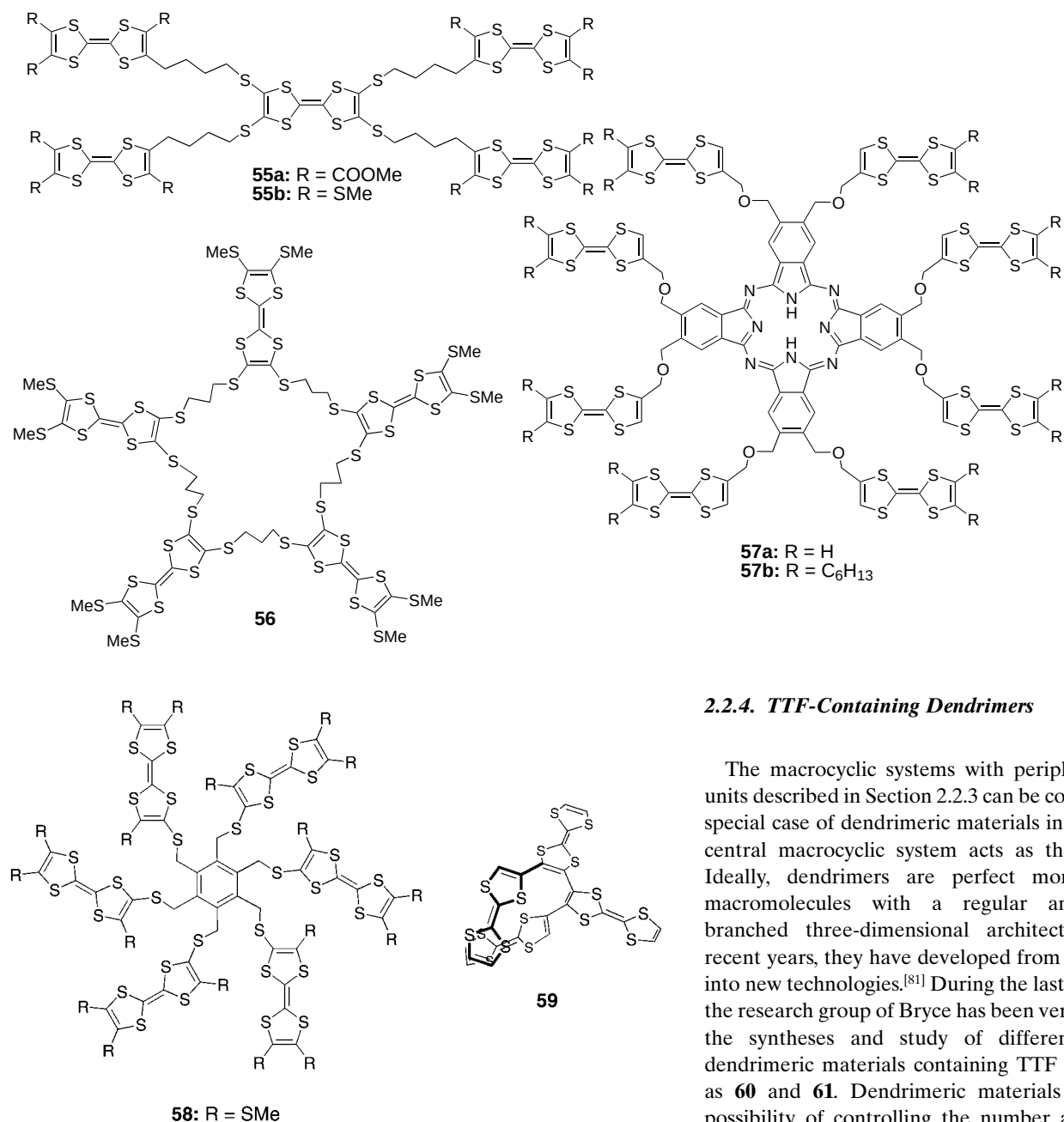
Syntheses of the trimeric system **54** ($R = H, n = 1$) have also been attempted. However, the product obtained was highly insoluble, which prevented its characterization.^[73a] We have recently synthesized soluble derivatives of **54** and its magnetic and liquid crystalline properties are currently under investigation.^[73b]

2.2.3. Donor Systems With a High Number of TTF Units

The trends outlined above for systems containing three TTF units are also followed by systems containing more TTF moieties. Thus, in pentakis(TTF) compounds **55**, in which the TTF units are linked through nonconjugated spacers, no interaction between the TTF units is observed by cyclic voltammetry and hence **55a** ($R = \text{CO}_2\text{Me}$) exhibits four reversible redox couples.^[74] The first one corresponds to the formation of the radical cation of the central TTF unit. The second redox wave can be assigned to the formation of the penta radical cation by the loss of one electron from each of the four peripheral TTF units. The third redox couple corresponds to the formation of the dication of the central TTF unit, and the fourth redox couple arises from the second oxidation of the peripheral TTF units. Only two reversible redox couples are observed in the case of **55b** ($R = \text{SMe}$), probably because the central and the peripheral TTF units are almost equivalent in regard to their redox behavior.

Further multi-TTF systems reported in the literature are **56**^[67] and **57**.^[75] In 1996 Bryce et al. reported on the synthesis of **57a**, which was the first phthalocyanine bearing TTF substituents to be prepared in the search for novel optoelectronic materials. Although this compound was extremely insoluble in most organic solvents, a combination of UV/Vis and CV studies allowed the conclusion to be drawn that the molecular design of this system does not prevent the strong tendency of phthalocyanine units to assemble in solution and does not inhibit the redox behavior of the appended TTF units. Thus, this work paved the way for the study of other systems with phthalocyanine and TTF units^[76] which combine the versatile electrochemical, optical, and coordination properties of phthalocyanines with the redox properties of many TTF units.^[15] Bryce et al. have reviewed some of the most interesting results in an article concentrating on multi-TTF systems^[15] in which different phthalocyanine-TTF systems are studied and the results compared with that for a pyrazinoporphyrazine system endowed with eight appended TTF groups.^[77]

Two recent and outstanding examples of multiple TTF containing molecules are the hexakis(TTF) derivative **58** and the TTF tetramer **59**. Compound **58** was prepared by the groups of Bryce and Becher in an efficient one-pot synthesis in which a sixfold reaction occurs to open the way to the



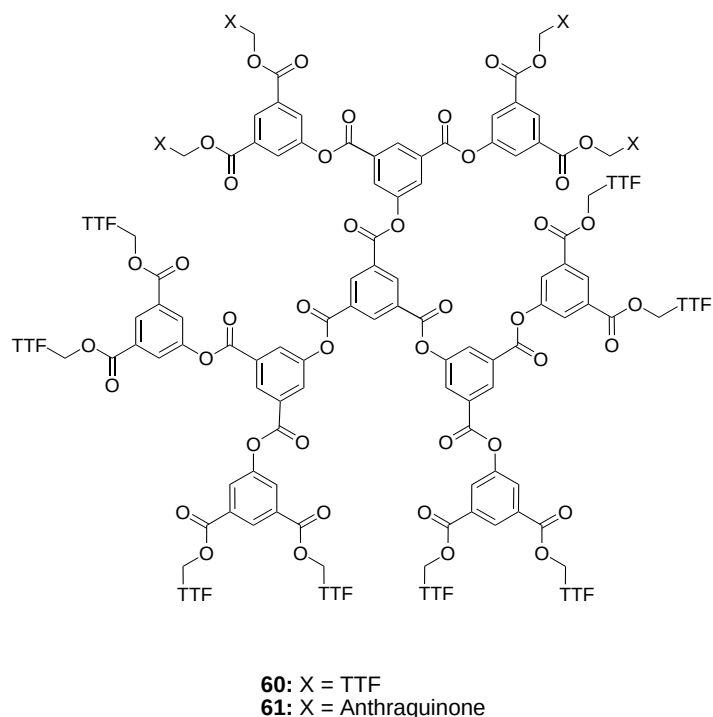
convergent construction of higher TTF oligomers and dendrimers.^[78] Compound **59** is the first example of a helical tetrathiafulvalene tetramer and was prepared by Iyoda et al.^[79] Both compounds were synthesized by using cross- and homocoupling reactions of tetrathiafulvalenylzinc derivatives, and in their neutral state have a tight helical conformation with closely situated terminal TTF rings. Interestingly, the cationic charges in the dication are mainly localized on the inside TTF rings and are stabilized by the face-to-face intramolecular stacking of the two terminal TTF rings. The same situation is observed for the tetracation. On the contrary, the third and fourth oxidations are restrained by the repulsion of positive charges on the terminal TTF units, which makes it more difficult to form the hexa- and octacations.

2.2.4. TTF-Containing Dendrimers

The macrocyclic systems with peripheral TTF units described in Section 2.2.3 can be considered a special case of dendrimeric materials in which the central macrocyclic system acts as the nucleus. Ideally, dendrimers are perfect monodisperse macromolecules with a regular and highly branched three-dimensional architecture.^[80] In recent years, they have developed from curiosities into new technologies.^[81] During the last few years, the research group of Bryce has been very active in the syntheses and study of different soluble dendrimeric materials containing TTF units such as **60** and **61**. Dendrimeric materials offer the possibility of controlling the number and placement of TTF groups with well-behaved solubility features that facilitate characterization, as well as

to integrate the unique properties of the TTF molecules with the characteristic properties of polymers, such as film formation and processability.

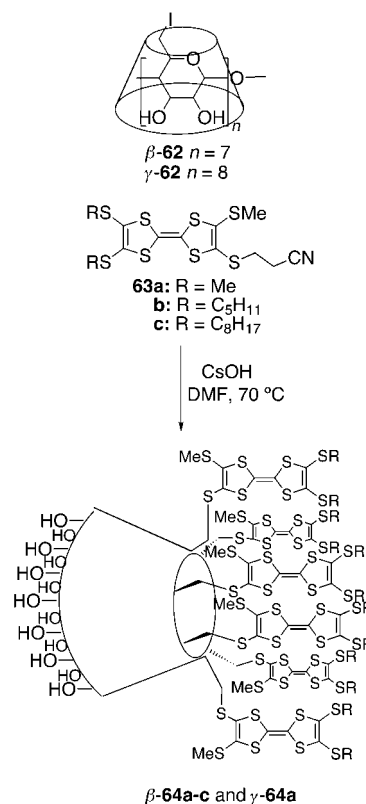
Compound **60** is a dendrimer containing a benzene 1,3,5-triester core and a surface functionalized with twelve TTF units. It is an oil which is readily soluble in polar organic solvents and stable when stored below 0 °C. Dendrimer **60** was synthesized by using a convergent strategy based on a repetitive coupling/deprotection sequence with 4-(hydroxymethyl)-TTF as the starting monomer.^[82] The stability of this type of macromolecule decreases with increasing molecular weight as a result, at least in part, of the steric crowding imposed by the trifunctionalized core. Thus, more “open” bifunctional cores (terephthaloyl chloride, biphenyl-4,4'-dicarbonyl dichloride, 4,4'-oxydibenzoyl dichloride) have been



used to synthesize hyper-branched multi-TTF derivatives that have good shelf stability, display reversible redox activity in solution, and form semiconducting CT complexes with TCNQ.^[83] More recently, a (TTF)₂₁ dendrimer has been synthesized which contains TTF units not only at peripheral sites but also within the branches of the structure.^[84] Glycol chains were incorporated into the branches to impart solubility in organic solvents, to give air stability, and to provide a flexible structure to facilitate interactions between the TTF units.^[84] TTF itself has been used as the nucleus in a different approach towards TTF-containing dendrimers in which the TTF units are placed at all layers of the structural hierarchy.^[85] More recently, the convergent synthesis of (TTF)_x(AQ)_y (AQ = anthraquinone), polyester dendrimer **61**, has been reported.^[86] This molecule undergoes amphoteric redox behavior as a consequence of the presence of the electron-donating TTF moiety and the electron-accepting anthraquinone system. These types of donor–acceptor systems are specially attractive since the incorporation of stronger π -acceptor groups^[87] will enable the study of intramolecular charge-transfer interactions within a dendritic microenvironment.^[86] A more in-depth study of dendrimers containing TTF units can be found in the recent feature articles of Bryce et al.^[15, 24]

Cyclodextrins (CDs) have been also used as platforms to carry TTF units.^[88] Cyclodextrins are cyclic oligosaccharides consisting of six, seven, or eight (α -CD, β -CD, γ -CD, respectively) α -1,4-linked D-glucopyranose units forming a truncated cone. They were used as platforms to carry TTF units, and were shown to form LB films when various amphiphilic β - and γ -cyclodextrins functionalized with alkyl chains at the primary hydroxy positions or modified on the secondary face were used. Thus, Sallé and co-workers carried out the synthesis and electrochemical characterization of

molecular blocks, Langmuir monolayers, and LB films built from the association of CD and TTF moieties.^[88] The target compounds **64** were achieved according to a convergent synthesis involving nucleophilic persubstitution of the 6-deoxy-6-iodocyclomaltooligosaccharides **62** with the free thiolate derivative **63** (Scheme 1). These systems are interesting



Scheme 1. Convergent synthesis of **64** by a complete nucleophilic substitution of **62** with the TTF derivative **63**.

since they are designed to combine the complexing ability of the CD cavity with the redox properties of the TTF core. Furthermore, the ability of the CD fragment to promote film transfer has been successfully transposed to produce good quality LB films incorporating electroactive TTF units. Thus, the covalent grafting of appropriate electroactive units onto the CD entity can be envisaged as a good way to produce LB films with physical properties that require a high degree of molecular organization in the material, such as electroconductivity or second-order nonlinear optics.^[88]

2.2.5. TTF-Containing Polymers

In the last part of this section dedicated to the macromolecular chemistry of tetrathiafulvalene we will focus on the most recent developments of polymers containing TTF units both as side chains or as a part of the main chain (Figure 3).

The incorporation of TTF into polymeric matrices for improving the processability of TTF-based conductors was investigated several years ago, and different research groups developed the synthesis of polymers **65** with spacers such as polyamide, polyurethane, polyphenylene, polystyrene or

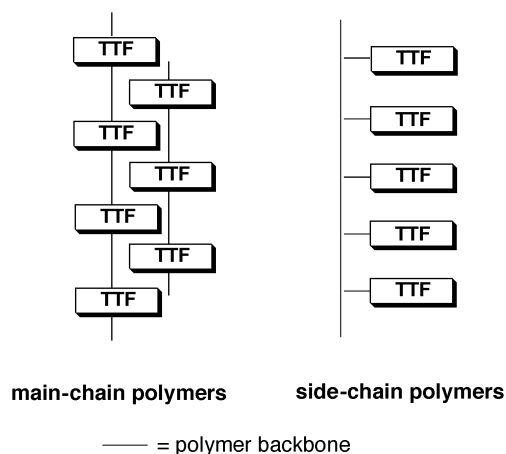
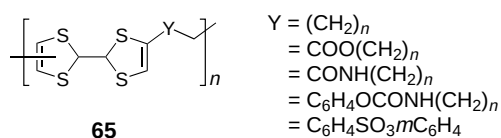


Figure 3. Different types of TTF-containing polymers (redrawn from ref. [53]).



polyesters.^[89] However, it was generally accepted that although such linkages do provide spatial proximity of the redox centers, they cannot ensure a well-defined orientation of the TTF groups relative to one another because the torsion around the bridging bonds allows a great number of different conformations. Thus, these polymers are deficient both in the order of the TTF subunits and in the dimensionality of the conduction process in the doped state.^[53] Polymers **65** were poorly characterized and, as a consequence of the above drawbacks, they have attracted little attention for further studies.

One way to reduce the conformational freedom would be to bridge the TTF units on each side with two σ bonds. Röhrig and Müllen have used dithiones such as **66** as precursors to σ -bonded tetrathiafulvalene oligomers and polymers. When dithione **66** was subjected to a phosphite-induced^[90] coupling reaction, polymer **67** was obtained in yields of less than 15 %; instead, the formation of a macrocycle by the self-coupling of both thione groups took place.^[91] However, the synthesis of **67** can be achieved starting from dithione **66** by using a four-step

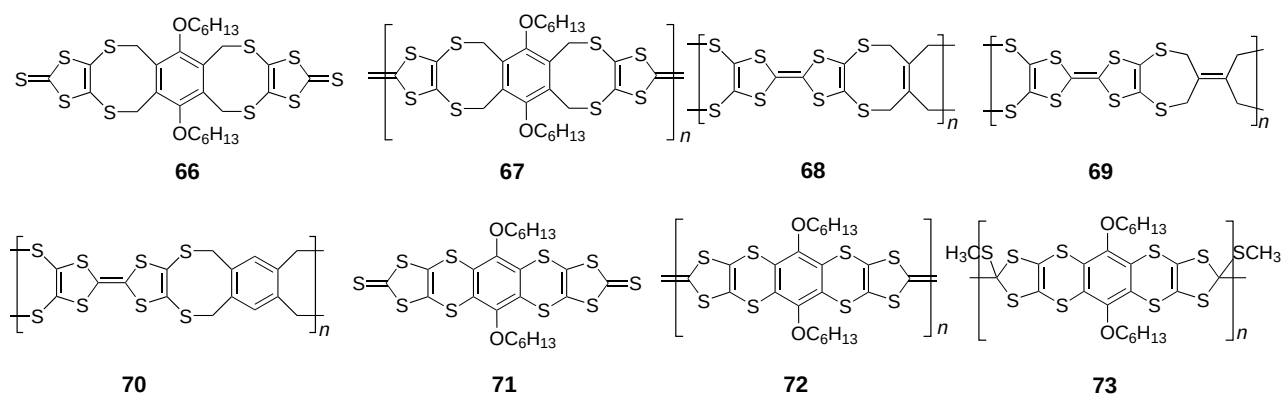
reaction sequence. By changing the concentrations in the four-step sequence, the formation of the macrocycle can be inhibited and the polymer is obtained as the main reaction product.^[53]

Elsenbaumer and co-workers have developed a different and recommended strategy for producing ladder-type polymers based on TTF that circumvents the generation of the TTF system in the last step.^[92] They used a tetraanion of tetrathia-TTF derived from tetrakis(cyanoethylthio)tetrathiafulvalene and the two different building blocks tetrakis(bromomethyl)benzene and 2,3-bis(bromomethyl)-1,4-dibromo-2-butene to generate polymers **68–70**. The overall yield of these new organic metals is very high (>90 %), which means that this kind of coupling is applicable to the synthesis of high molecular weight bulk materials. Polymers **68** and **70** can be doped with $FeCl_3$ to give blue/black CT materials with pressed pellet conductivities of 6×10^{-4} and $2 \times 10^{-4} \text{ S cm}^{-1}$, respectively.

A different way of inducing some order into TTF-containing polymeric materials would be to induce a regular arrangement of the TTF subunits in an eventual liquid crystalline phase of the polymers in order to achieve π -stacking interactions in the polymer matrix. Thus, Müllen and co-workers have reported on the syntheses of a variety of polymeric materials, such as **33**, with TTF units either taking part of the main chain or as side chains.^[53] TTF was incorporated quantitatively into the polymer chain by reaction of the precursor TTF-containing molecule **32** with poly(*p*-hydroxystyrene). Unfortunately, they have not been able to induce a liquid crystalline phase in this type of polymer. However, it may not be necessary to achieve a liquid crystalline phase with the undoped TTF-containing polymer and the possibility has to be considered that smectic phases can be induced by introducing complex formation between donor and acceptor pairs in separate mesogenic units. Thus, undoped TTF-containing polymers should be potentially liquid crystalline and may exhibit mesogenic behavior when doped with an acceptor.^[53]

In recent years the major interest has focused on the association of TTF-based conductors with linear π -conjugated structures.^[13, 20, 93] There are different reasons for this interest:^[20]

1. The possibility of combining the outstanding electron-donating properties of TTF systems with the general characteristics of high molecular weight polymers, such as



film formation and processability, to obtain polymers that could be doped with strong acceptors.^[53]

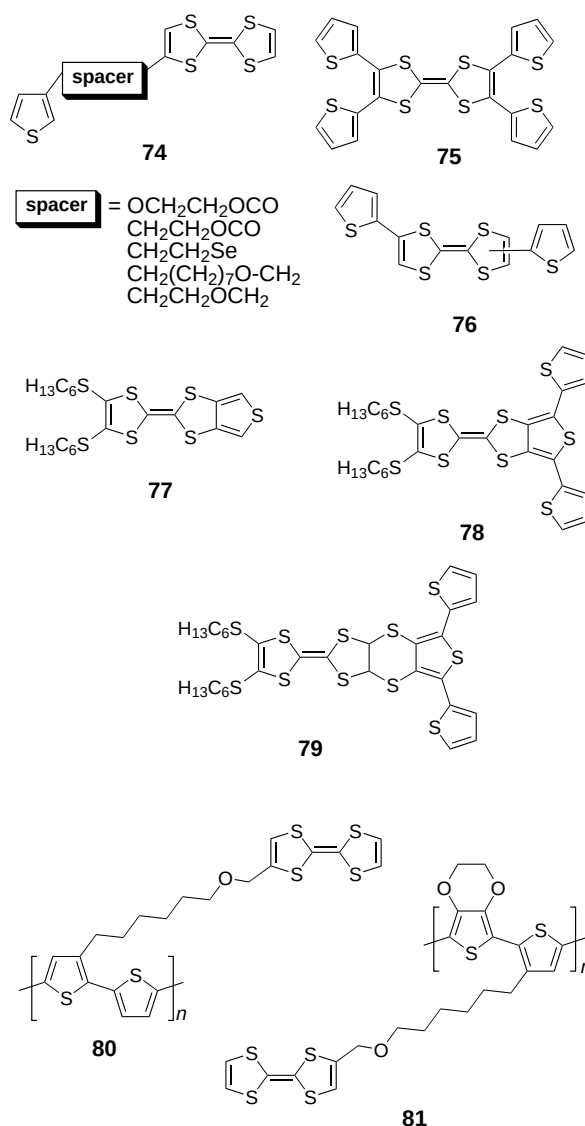
- The propensity of TTF to form ordered stacks can represent an interesting tool for controlling the long-range order of a conjugated backbone.
- The combination of TTF with a conjugated polymer chain can contribute to an increase in the dimensionality of the conduction process and might eventually lead to materials presenting hybrid conduction. In this regard, two parallel charge-transport mechanisms might be possible: the intrastack transfer of aromaticity associated with the mixed-valence interactions in TTF stacks^[94] and the polaron/bipolaron conduction in the π -conjugated chain.^[95]

72 is a fully conjugated ribbon-structure polymer in which conductivity along the polymer chain through π -conjugation as well as along the stacking direction through π -orbital overlap might be expected. Compound **72** can be obtained starting from dithione **71** using a four-step synthetic route similar to that used for the synthesis of **67**.^[53] Polymer **72** is an orange TTF material that can be doped with iodine to give a black material. However, characterization methods are very limited because of its poor solubility. A new route involving the film-forming precursor polymer **73** has been proposed as an alternative route for casting a thin self-supporting film that could generate a thin film of the conjugated polymer **72** after thermal extrusion.^[53] This type of conjugated polymer can be used as an electroactive conducting rod in which the TTF group permits the rods to bend easily in the direction perpendicular to the ring plane.^[31]

Other attempts have been made to incorporate TTF moieties on a conjugated polymer backbone. One approach in this direction involves the grafting of a TTF moiety onto an electropolymerizable monomer to yield conjugated polymers with pendant TTF groups. This strategy was originally developed by Bryce et al. as a possible way to indirectly control the long-range order of electrogenerated poly(thiophene) (PT) by using the strong propensity of TTF to self-assemble into regular π stacks.^[96] After the seminal work of Bryce et al. reported in 1991, other thiophenic precursors **74**–**79** have been synthesized.^[97, 98, 99]

Unequivocal evidence for electropolymerization was reported in one case^[97] although the large potential difference between the first TTF oxidation (ca. 0.40 V/SCE) and the potential needed to polymerize the substituted thiophene (1.80 V) has been identified as a serious problem.^[97] The cyclic voltammogram of the resulting polymer exhibits a splitting of the first TTF reduction wave typical of the occurrence of the mixed-valence dimer (TTF)²⁺,^[100] which indicates that self-assembly of the oxidized TTF moieties already takes place in the material.^[97] Roncali and co-workers have recently shown that as a consequence of a much lower electropolymerization potential,^[101] TTF-substituted bithiophenic precursors are readily converted into extensively π -conjugated TTF-derivatized poly(thiophenes) **80** and **81** with interesting electrochemical properties.^[102]

The cyclic voltammogram of these polymers have revealed a hitherto unknown additional oxidation wave at a potential intermediate between those corresponding to the generation



of the TTF radical cation and the dication.^[100] This electrochemical behavior has been studied in more depth on equilibrated films and in dynamic conditions by Roncali and co-workers using classical and time-resolved spectroelectrochemical techniques.^[93] The results obtained provide evidence for the occurrence of large amounts of mixed-valence dimers and π dimers in these polymers. At the potential needed to electropolymerize the attached bithiophene precursor, initially formed mixed-valence dimers are successively converted into π dimers and dications. Therefore, mixed valence interactions must be reconstructed by subsequent undoping and controlled reoxidation of the polymer. This process will probably result in a partial loss of the initial order.^[93] Thus, different strategies have been proposed by Roncali and co-workers^[93] to design more appropriate precursors:

- a further increase of the electropolymerization potential,
- an increase in the first oxidation potential of the attached TTF by electron-withdrawing substituents, and
- an increase in the TTF concentration within the polymer by grafting more than one TTF unit onto the precursor structure.

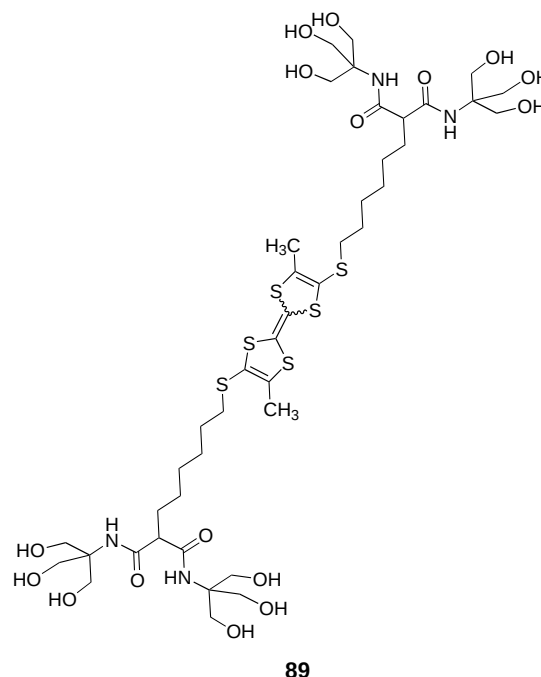
- Functionalizing the TTF ring with OH^[118] and/or NRH^[119] groups that would enable intermolecular hydrogen bonding to occur.

Together with these strategies, other less conventional methods such as supramolecular arrangements have been attempted. Thus, incorporation of TTF species in calix[4]arenes, which are well known in supramolecular chemistry for acting as organizing platforms for various kinds of substituents, has also been carried out.^[120] A more recent approach which is also related to “crystal engineering” has been developed by Yamamoto et al. which utilizes Lewis acid/base interactions between anions and iodine-containing neutral molecules to accomplish multicomponent molecular conductors with supramolecular assemblies.^[121] By using this strategy they obtained radical–cation salts with new types of donor arrangements. The authors claim that examination of many cases of different arrangements will allow the design of “tailor-made” anion networks to accomplish desired donor arrangements.

The use of the old, but elegant, Langmuir–Blodgett technique is another way of arranging molecules into organized assemblies. For example, the possibility offered by the LB technique to build noncentrosymmetric architectures has been widely used to achieve nonlinear optical properties in these materials.^[47, 122]

It is also worth mentioning how the preparation of mesogenic derivatives by either attaching a TTF unit to a mesogenic liquid crystalline center or by incorporating substituents which show mesomorphic behavior onto the TTF moiety have been used as an alternative to the above procedures to obtain an assembly of ordered arrays of TTF-containing molecules.^[51–55]

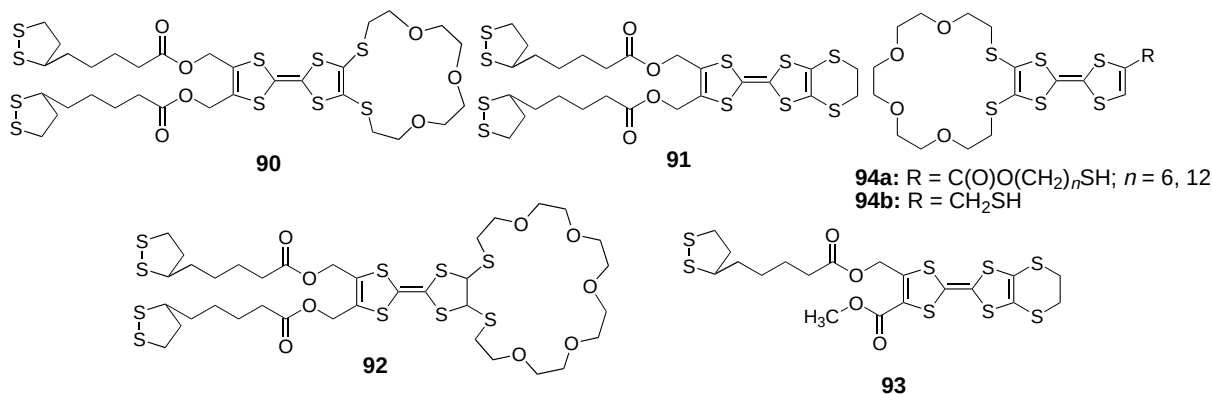
In 1994 Jørgensen et al. utilized self-assembly principles and gel-formation techniques to manufacture a prototype “molecular” wire.^[123] Gel formation can usually be best understood as resulting from a competition between the tendencies of the gelator to dissolve in the solvent or to self-assemble and crystallize.^[124] Thus, by taking advantage of the work of Newkome et al., who prepared the so-called bis-arborols that readily form gels consisting of stringlike assemblies in water,^[125] Jørgensen et al. synthesized the bis-arborol-tetrathiafulvalene **89**, which forms a gel, which consists of string- or bandlike structures with a length of tens of micrometers and diameters in the 300–1000 Å range.

**89**

UV/Vis-NIR spectroscopy on the oxidized gel revealed a CT band typical of stacked TTF molecules.

One of the most challenging projects in the field of molecular optoelectronics involves the self-assembly of monolayers of electroactive molecular systems on solid supports.^[126] The monolayer represents a two-dimensional array on the solid support. TTF compounds containing four thiol groups have been reported to form very robust self-assembled monolayers (SAM) on gold which were stable after repeated voltammetric cycling.^[127] Echegoyen and co-workers took advantage of the good results obtained by anchoring SAMs on metal surfaces by using thioctic acid derivatives^[128] to synthesize bis-thioctic ester derivatives of TTF units annealed with crown ethers (**90–93**) that form stable self-assembled monolayers on gold electrodes (Figure 4).^[129] Thus, they have prepared electrochemically active SAMs which are almost indefinitely stable and that show promise as potential thin-film sensors for electrochemically inactive metal ions.^[129]

Prior to this work, Bryce and co-workers reported crown-annulated TTF derivatives **94** which also contained single alkyl chains terminated in thiol groups.^[130] Monolayers of



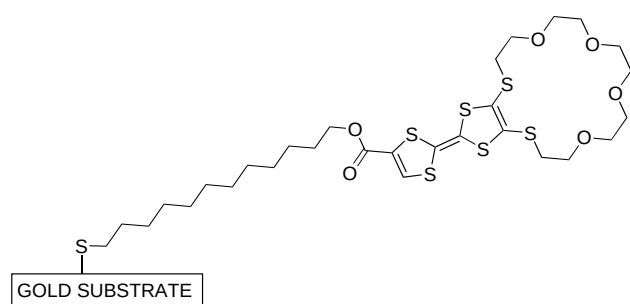


Figure 4. Probable disposition of the SAM of **94a** on a gold surface.

compounds **94** were assembled onto gold or platinum surfaces from saturated acetonitrile or acetonitrile/benzene solutions. Figure 4 shows the probable orientation of a SAM of compound **94a** ($n = 12$). Similar CV responses to metal cations were obtained for SAMs and acetonitrile solutions (electrochemical recognition of Na^+ , Ba^{2+} , and Ag^+ , with the largest response for Ag^+), which represents an important step forward in the design of thin-layer molecular devices that function as electrochemically responsive detectors for metal cations.^[130] Bryce has recently reviewed these SAMs within the context of materials chemistry.^[24]

The construction of redox-active supramolecular systems with applications in different areas and the construction of supramolecular assemblies in the solid state has been another important overlap-zone between TTF and supramolecular chemistry. Becher and co-workers have reviewed most of the work in this area. They focused on cation-sensitive TTF systems including TTF-crown ether derivatives, TTF-thia-crown ether derivatives, macrocyclic and bis-macrocyclic TTF units, all of which are molecular systems containing the redox-active TTF functionality together with a host unit capable of cation binding. These types of TTF derivatives as well as those that incorporate the TTF moiety in supramolecular systems, such as rotaxanes or catenanes, have been the origin of some of the most interesting recent applications found for TTF-containing molecules.^[23] With the purpose of taking a systematic approach, we will study this type of TTF derivatives within the next section dedicated to the nonconventional application of TTF derivatives.

3. Nonconventional Applications of TTF Derivatives

Although thirty years have passed since the synthesis of TTF was firstly reported by Wudl et al.,^[1] an explosive growth of activity in the area of tetrathiafulvalene chemistry has arisen during the last decade. Interest has arisen in a variety of new fields by taking advantage of its unique solid-state as well as its solution properties.

The main emphasis of the investigation during almost twenty years was on the solid-state properties of the TTF charge-transfer (CT) complexes and CT salts. It is still a very active field of research and new TTF salts with improved solid-state properties are being reported week by week. However, since there is a great deal of excellent litera-

ture^[131, 132] dedicated to the study of CT salts, their study will not be included in the present review article, which instead will be more concerned with the less-well known but very promising “nonconventional” applications of TTF derivatives.

3.1. TTF as an Electroactive Unit in Chemical Sensors and Redox-Switchable Ligands

As discussed previously, the construction of macrocycles containing TTF units has received considerable attention since such molecules may act as a host in host–guest chemistry.^[133] Figure 5 shows schematically a) a redox-detected sensor molecule and b) a redox-controlled ligand system.

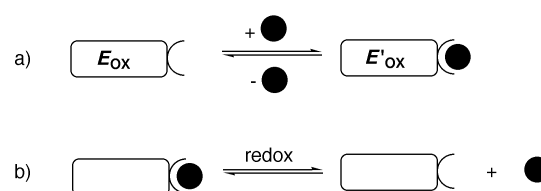
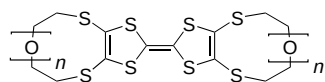
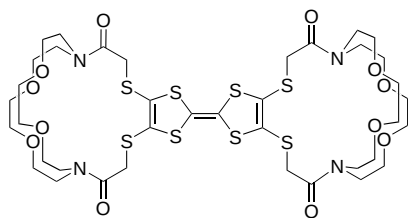


Figure 5. a) Redox-detected sensor molecule and b) redox-controlled ligand system (redrawn from ref. [16]).

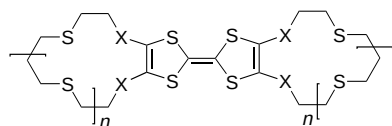
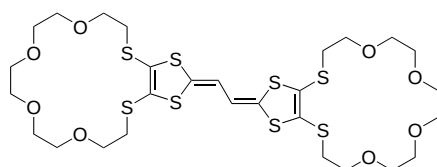
In the first case, a “transducer” built into the molecule responds to complexation in the host by a change in physical properties. In the redox controlled/switchable ligand system the roles of the two parts are reversed so that a physical change of the transducer units is imposed by an external stimulus. A positive charge is created after oxidation of systems containing a TTF unit which inductively decreases the binding ability of the attached host unit towards cations.^[16] Although the voltammetric response upon metal binding in this system is quite small (< 100 mV), an advantage of the TTF moiety is that only the first oxidation potential is affected, and the second (unchanged) oxidation potential serves as an internal reference.^[134] In addition, both TTF redox steps occur in a convenient potential window.

Since Jørgensen et al. reviewed^[16] the literature related to cation-sensitive TTFs prior to 1994 thoroughly, we will only give a brief account of recent examples in order to update the improvements reported in recent years. By using the same classification method used by Jørgensen et al.^[16] in their review, cation-sensitive TTFs can be divided into planar TTF derivatives with annelated macrocyclic moieties and distorted macrocyclic TTF systems. Planar derivatives include TTF-crown ether (**95**) and TTF thiacycrown ether (**97**) derivatives as well as a TTF-cryptand (**96**). These compounds have been investigated for their potential use as electroactive cation sensors.^[16, 23] The ring size of the macrocycle and the extension of the π system of the TTF unit (**98**)^[16] have also been the subject of study.

Changes in the ^1H NMR spectrum of the macrocyclic ligand, and the changes in the redox properties of the TTF system as determined by cyclic voltammetry, have been used to monitor metal binding within the crown rings. A shift in the value of the first oxidation potential to more anodic (positive) potentials was observed upon addition of metal salts ($M = \text{Li}$,

95: $n = 1-5$ 

96

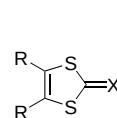
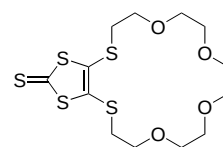
97: $X = S, Se; n = 1-3$ 

98

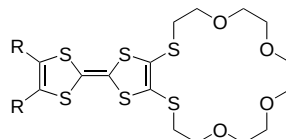
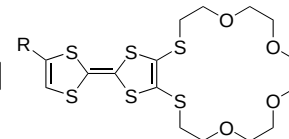
Na, K, Ba, Ag) to a solution of the TTF-crown molecules. This observation indicates that metal complexation has occurred. The scope of this application for TTF-containing systems has been explored by using synthetic approaches previously used in TTF chemistry^[10]:

1. cross-coupling reactions to produce functionalized TTF-crown systems, such as the amphiphilic TTF-crown **103** and the diester **104**,
2. electrophilic substitution of TTF-crown compounds, via a lithiated intermediate, to provide derivative **106**, and
3. functional group removal and interconversion to give **107–109** as well as **106** again, these derivatives are suitably functionalized for further chemical transformations.^[16, 23]

However, a very large proportion of these types of TTF derivatives have been synthesized from macrocycle-fused 1,3-dithiole-2-thione-4,5-dithiolate (DMIT, **111**; Scheme 2).^[26] The readily available compound **111** can be treated with a variety of chain-containing electrophiles **112** to generate a variety of monomeric (**114**) or dimeric

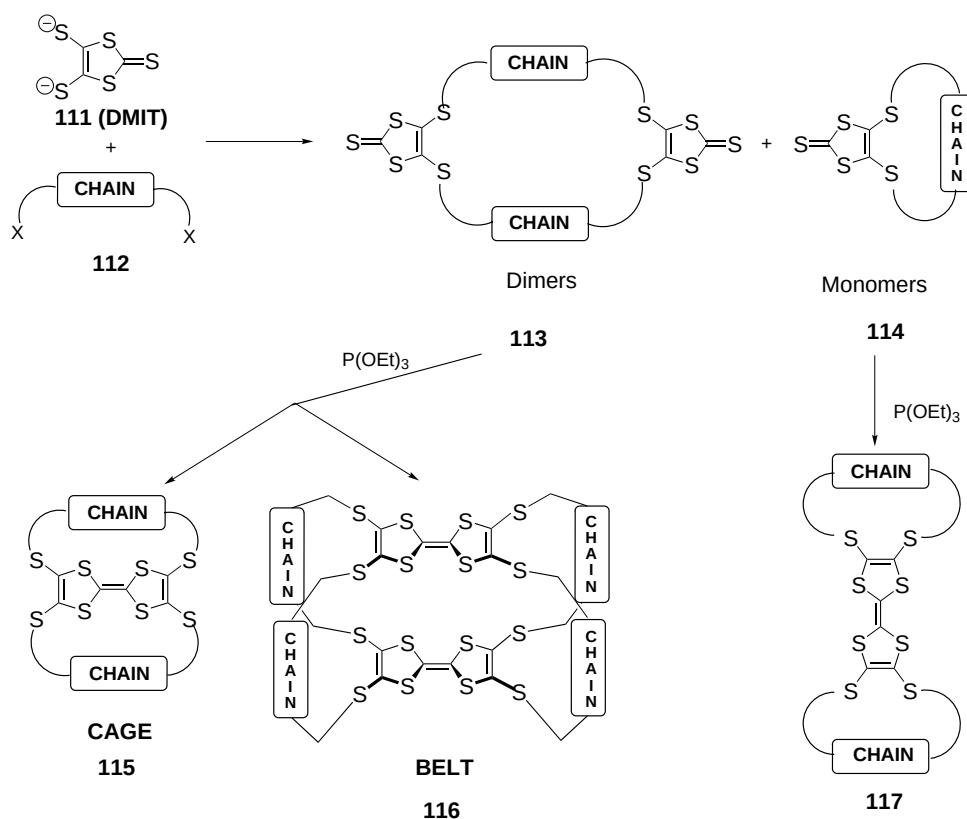
99: $R = SC_{18}H_{37}; X = S$ 100: $R = H; X = S$ 101: $R = CO_2Me; X = O$ 

102

103: $R = SC_{18}H_{37}$ 104: $R = CO_2CH_3$ 105: $R = H$ 106: $R = CHO$ 107: $R = CO_2Me$ 108: $R = CH_2OH$ 109: $R = CO_2H$ 110: $R = CH_2OC(O)C_{17}H_{35}$

(**113**) thiones. The coupling of monomeric thiones with themselves or with other thiones by using the standard coupling reaction with trialkyl phosphites yields the corresponding symmetric (**95–97**, **117**) and unsymmetric (**103–110**) TTF derivatives with annelated macrocyclic moieties.

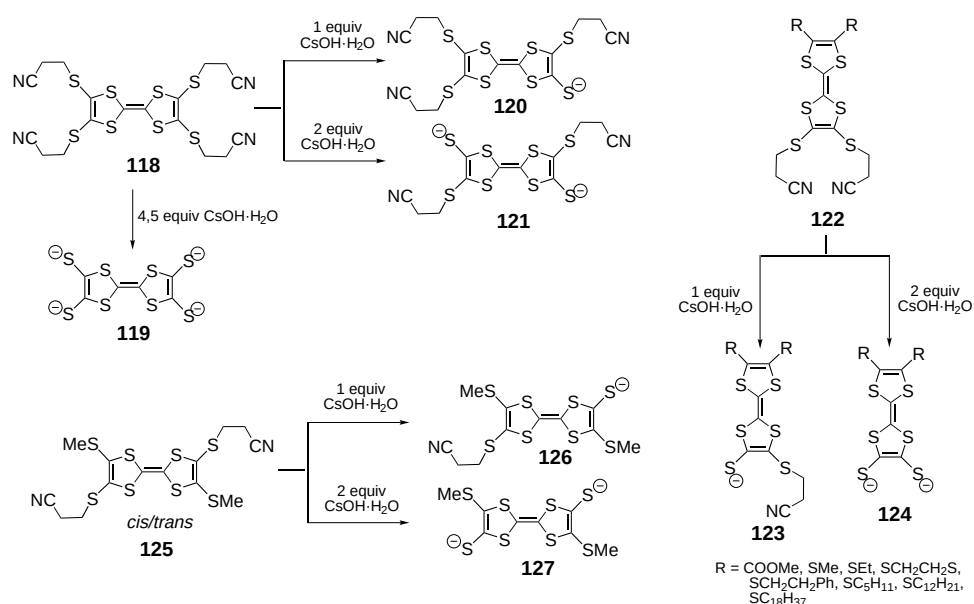
DMIT (**111**) derivatives have also been directly involved in the second type of TTF-containing systems capable of binding cations; these are the distorted macrocyclic derivatives.^[28] By using high-dilution techniques it is possible to maximize the yield of dimeric thione derivative **113** in the reaction of DMIT with chain-containing electrophiles. Subsequent phosphite

Scheme 2. Synthesis of the macrocyclic TTF derivatives from DMIT **111**.

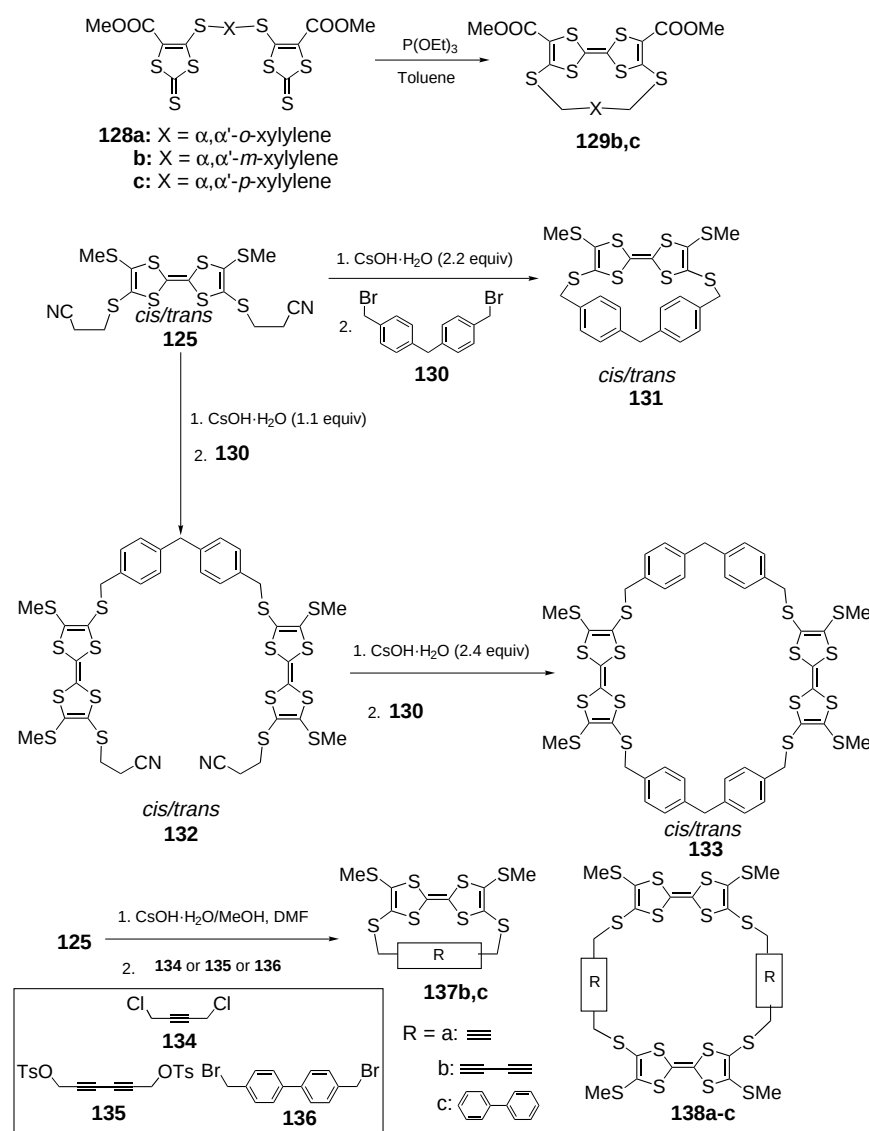
coupling normally proceeds in an intramolecular fashion, to give rise to monomeric cage molecules **115**. Occasionally, intermolecular coupling which produces low yields of larger “belt-type” macrocycles has also been observed.^[16] Whether these reactions give inter- or intramolecular cyclization seems to be controlled solely by the length of the linker between the two dithiol units. Very short linkers, namely two,^[135] three,^[135] four,^[136] or five^[137] atoms gives intermolecular coupling, whereas longer spacers tend to result in intramolecular reactions.

Special credit has to be given to the effective protection/deprotection methodology for the preparation of tetrathiafulvalene thiolates (TTFTT) developed by Becher and co-workers that use the cyanoethyl group as a versatile protecting group for TTF thiolate groups and which allows the incorporation of preformed TTF derivatives in macrocyclic compounds.^[11, 17, 18, 23] Selective monodeprotection makes it possible to carry out stepwise deprotection of TTF with several cyanoethylthio groups by using caesium hydroxide in the cleavage step. Thus, from only three different TTF units (**118**, **122**, **125**) it is possible to prepare a variety of TTF thiolates bearing one to four thiolate moieties (Scheme 3).^[17] By taking advantage of the above reactions, a variety of TTF-containing macrocyclic systems with specific physical and chemical properties have been prepared.

Becher and co-workers have recently revisited the triethyl phosphite coupling of some bis-trithiocarbonates in order to study the influence of the linkers on the course of the reaction.^[61] By using triethyl phosphite mediated coupling of the corresponding bis-1,3-dithiole-2-thiones **128b,c**, the *m*- and *p*-cyclotetrathiafulvalenophanes **129b** and **129c** could be isolated (Scheme 4). Treatment of **128a** with triethyl phosphite gave an intractable solid. The $\lambda_{\max}$ value for **129b** is 414 nm whereas that for **129c** is 424 nm, which indicates



Scheme 3. Preparation of different TTF thiolates with one, two, or four thiolate groups.

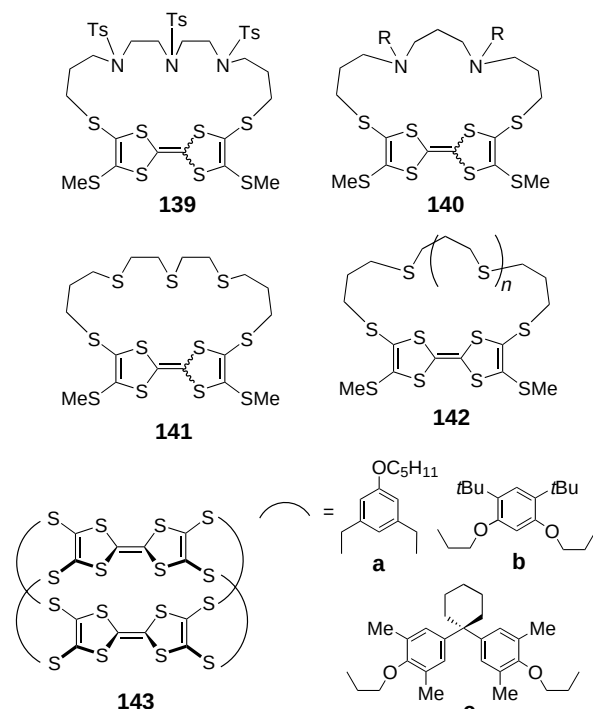


Scheme 4. Synthesis of macrocycles with TTF units.

that the *m*-cyclophane has a more distorted TTF group that allows for less π delocalization. The protection/deprotection methodology using the cyanoethyl group was used to generate a TTF bis-thiolate starting from **125** which upon reaction with the bis-bromo reagent **130** yielded the tetrathiafulvalenophane **131** as an orange powder. No trace of dimeric product **133** was detected by plasma desorption mass spectrometry (PD-MS).

The addition of 1,4-dichlorobut-2-yne (**134**) to deprotected **125** under high-dilution conditions gave only the [2+2] addition product **138a**. This occurs because in this case the length of the spacer group is considerably shorter than the thiolate–thiolate distance in the TTF unit.^[60] When the length of the spacer group, for example, 4,4'-bis(bromomethyl)biphenyl (**136**) and hexa-2,4-diyne-1,6-diol ditosylate (**135**), is comparable to the thiolate–thiolate distance in the TTF system, the two reaction products **137b,c** and **138b,c** could be isolated after chromatography.^[60] Therefore, it can be concluded that 1) the length of the linker as well as its geometry have a profound influence on the course of the coupling reaction of bis-1,3-dithiole-2-thione and 2) that a general method for preparing tetrathiafulvalenophanes with more than one TTF moiety requires strategies involving a preformed TTF building block.^[61]

Macrocycles **139** and **140** are cage compounds (Ts = toluene-4-sulfonyl) that have been designed to have the crown complexing part in close proximity to the TTF core and to have a sufficiently large cavity so as to minimize the structural



distortions of the TTF moiety previously observed in cage compounds with small crown systems.^[138] In comparison with the shorter crown-annelated TTF derivatives for which the first oxidation step is either irreversible or is found at much more anodic E_{pa} values, because of distortion of the central TTF core, derivatives **139** and **140** exhibit two reversible

oxidation processes similar to that observed for planar substituted TTF derivatives. The addition of a solution of Ag^+ ions to **139** results in the formation of a 1:1 complex, which can be observed in the FAB mass spectrum. Interestingly, only 70% of **139** is complexed. This observation, together with the fact that a 70:30 *Z:E* ratio was determined from NMR experiments performed on **139**, indicate that Ag^+ is only complexed by the *Z* isomer.^[138]

Other crown-TTF derivatives with increased chain length relative to the previously described thiacycrown TTF derivatives are compounds **141** and **142**.^[139] Two reversible one-electron redox processes were observed upon oxidation which is consistent with the quasi-planar character of the TTF skeleton in these systems. No change was observed in the cyclic voltammograms of compound **142** upon addition of Ag^+ . In contrast, the addition of controlled amounts of silver triflate to **141** results in a positive shift of E_{ox}^1 . No shift of E_{ox}^1 was observed upon addition of a wide variety of Group 1 and 2 or transition metal ions (Na^+ , K^+ , Cs^+ , Mg^{2+} , Ba^{2+} , Cr^{3+} , Ni^{2+} , Zn^{2+} , Cd^{2+}), which illustrates the good selectivity of ligand **141** for Ag^+ ions.

As discussed in previous sections, bistetrathiafulvalenophanes (TTF-phanes) such as **42** and **43** have been studied because the two TTF units can adopt a sandwich structure, which enables intermolecular interactions between the two redox units to occur and increases the likelihood of strong noncovalent inter- and intramolecular interactions occurring.^[12, 13, 14] Most of the TTF belts reported by the research group of Otsubo^[12, 58, 137b] are based on the coupling of bis-2,3-dithiole precursors to give the TTF core in the final step of the synthesis, while the above studied deprotection/realkylation protocol involving tetrathiafulvalene thiolates developed by the research group of Becher have also been recently applied to the synthesis of belt compounds. Thus, in 1999, the stepwise synthesis of the new TTF belts **143** with well-defined large cavities have been reported.^[140] The spacers used were chosen to confer rigidity as well as solubility to the belt molecules. They are stable and isolable compounds which show some promise as host molecules: the solid-state structure of **143c** shows that it crystallizes with two molecules of chloroform inside its spacious cavity (Figure 6). However, no complexation studies have been reported for these interesting systems so far.

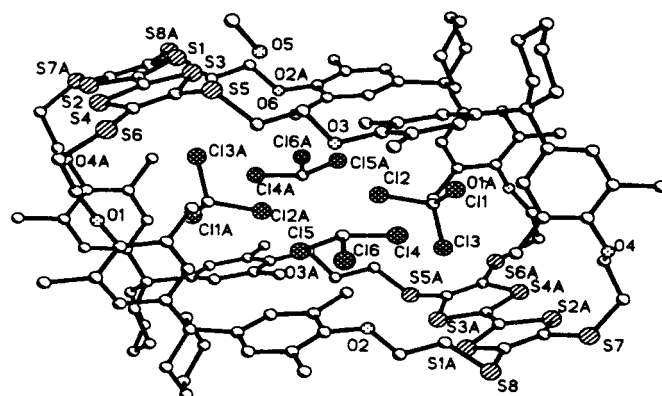


Figure 6. View of the molecular structure of **143c** including solvent molecules. (Reprinted with permission from ref. [140].)

3.2. Molecular Shuttles and Molecular Switches Containing TTF Units

TTF is an ideal building block for the construction of supramolecular systems which can be controlled by external stimuli because its reversible oxidation to its radical cation that can be realized chemically and electrochemically.^[141] This type of compound can be used as molecular devices which can operate as machines upon external energy transfer since they may be able to store and process information at the molecular level.^[108, 142] Rotaxanes, catenanes, and other intertwined structures and superstructures (Figure 7)^[143, 144] are ideally suited for building integrated, multicomponent modular systems.^[145]

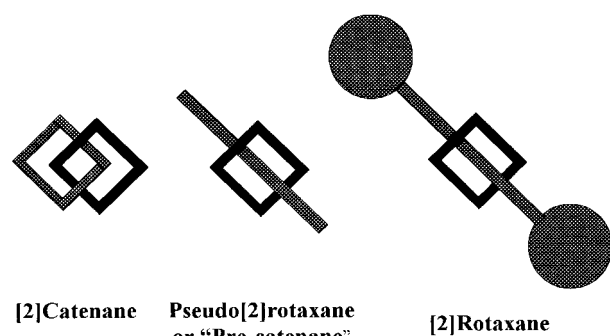
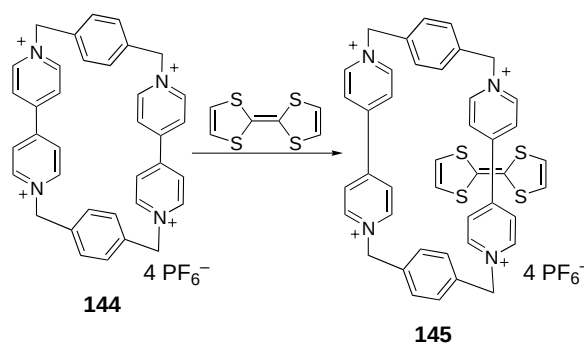


Figure 7. Schematic representation of a [2]catenane, a pseudo[2]rotaxane, and a rotaxane.

Some of these supramolecular systems have been prepared by taking advantage of the experience gained in the syntheses of macrocyclic systems containing TTF units as well as of the self-assembly strategy developed by Stoddart and co-workers which uses the ability of the bis(benzyl)-4,4'-bipyridinium dication to self-assemble with a variety of electron-rich systems.^[143] This field has been excellently reviewed by Becher and co-workers in a very recent paper devoted to the use of TTF as a building block in supramolecular chemistry.^[23] Different TTF derivatives have been prepared in which the TTF unit is covalently attached to pyridinium and bipyridinium acceptors. The literature related to these systems containing TTF and σ acceptors of pyridinium and bipyridinium cations are studied in detail in the 1999 review by Bryce on the use of TTF derivatives as donors in intramolecular charge-transfer materials.^[22]

In 1991, Stoddart and co-workers reported that the receptor cyclobis(paraquat-*p*-phenylene) (**144**) forms a complex^[146] with TTF which crystallizes with a pseudorotaxane-like geometry (**145**, Scheme 5). Further studies on this complex carried out by Bryce and co-workers show that the electrochemical oxidation of TTF to the radical cation results in decomplexation, which is accompanied by a visible change in the color of the solution.^[147] Moreover, this process is highly reversible over many redox cycles. It therefore seemed that the combination of the TTF residue and the cyclobis(paraquat-*p*-phenylene) moiety is an ideal choice for incorporating into "molecular shuttles" with potential application as electrochemically controlled molecular switches.^[143a]



Scheme 5. Formation of a pseudorotaxane-like structure through complexation of TTF with cyclobis(paraquat-*p*-phenylene) (**144**).

When two different π -electron-rich residues ("stations") are connected in a dumbbell-shaped chain structure and encircled by an electron-deficient ring (shuttle) to form a [2]rotaxane, a chemical, electrochemical, or photochemical stimulus can disturb the equilibrium position of translational isomers and the [2]rotaxane can behave as a molecular shuttle (Figure 8). Although other rotaxane-based switches^[148] and gates^[149] have been previously demonstrated in solution, the TTF moiety is especially interesting for constructing new types of catenanes provided that it is, in principle, tetravalent. Most building blocks hitherto used to construct catenane systems, for example, hydroquinone, phenylene-1,4-diamine, benzidine, and bipyridine, are divalent species.

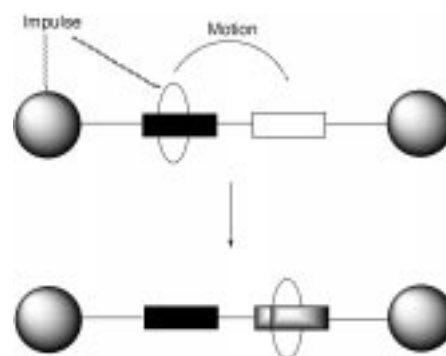
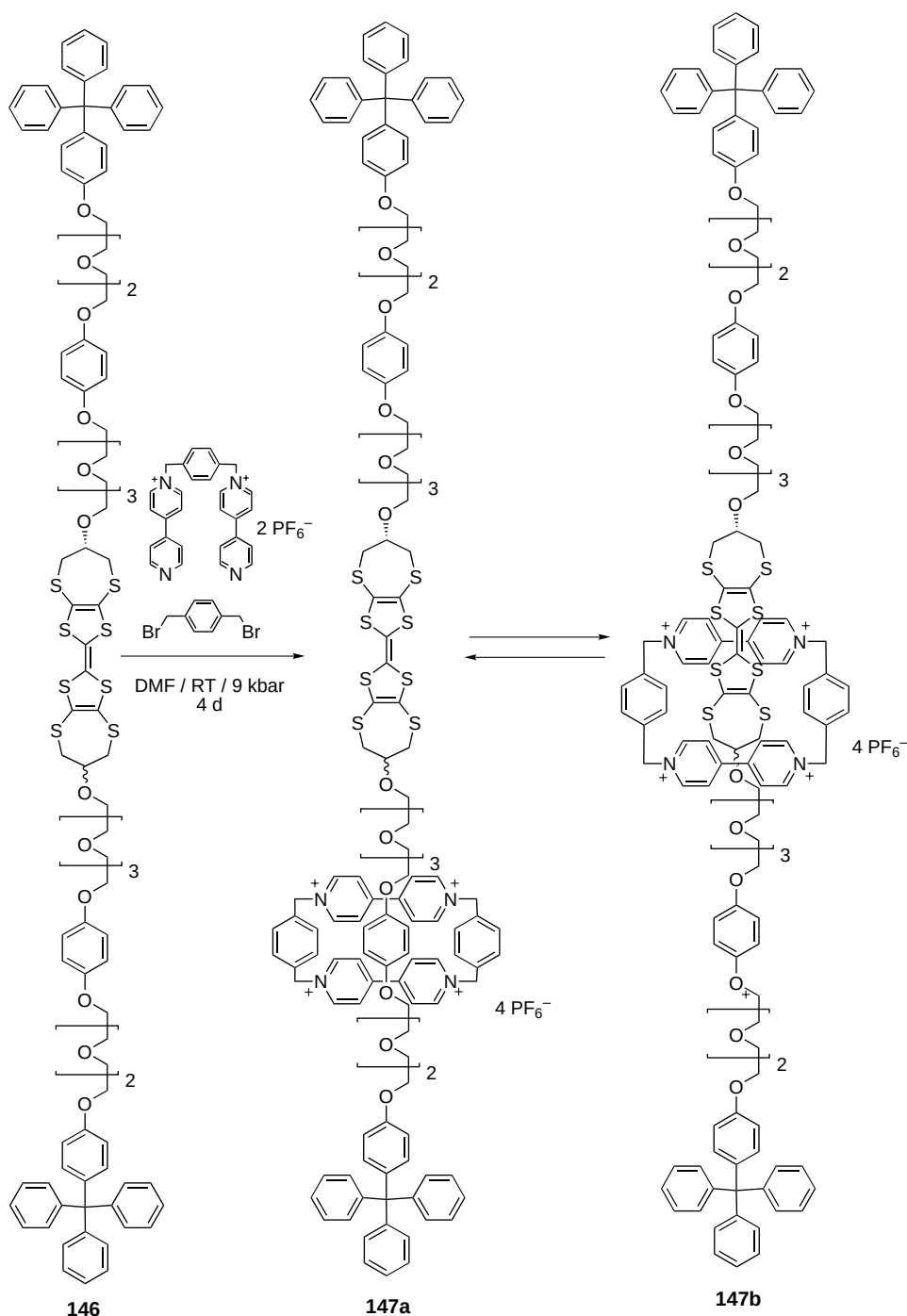


Figure 8. Molecular shuttle obtained from a [2]rotaxane comprised of two different electron-rich units (stations) connected in a dumbbell-shaped chain and encircled by an electron-deficient ring (shuttle).

With the aim of preparing a molecular shuttle, Stoddart and co-workers carried out the self-assembly of the [2]rotaxane **147** with two degenerate stations located on either side of a TTF residue.^[146] The two hydroquinone rings are positioned on each side of the TTF residue to ensure that it is the most thermodynamically favorable position for occupation by the π -electron-deficient cyclophane. Two 4-tritylphenyl ether units were used as "stoppers". The TTF residue is the site which is occupied predominantly by the cyclophane. Upon selective oxidation of the TTF unit, the positive charge on TTF⁺ (**147b**) repels the tetracationic acceptor macrocycle by coulombic forces, forcing the "shuttle" away from the TTF unit to one of the hydroquinol units (**147a**; Scheme 6).



Scheme 6. A molecular shuttle bearing a central TTF unit and two hydroquinone rings as electron-rich residues.

Other interlocking molecular systems containing the TTF unit and the π -electron-accepting cyclophane cyclobis(paraquat-*p*-phenylene) have been synthesized by using the self-assembly strategy developed by Stoddart and co-workers.^[23, 59, 63] Some recent examples of these types of materials (**148**–**151**) are depicted in Scheme 7. Since these systems have been very recently reviewed by Becher and co-workers, we refer the reader to this timely and outstanding paper.^[23]

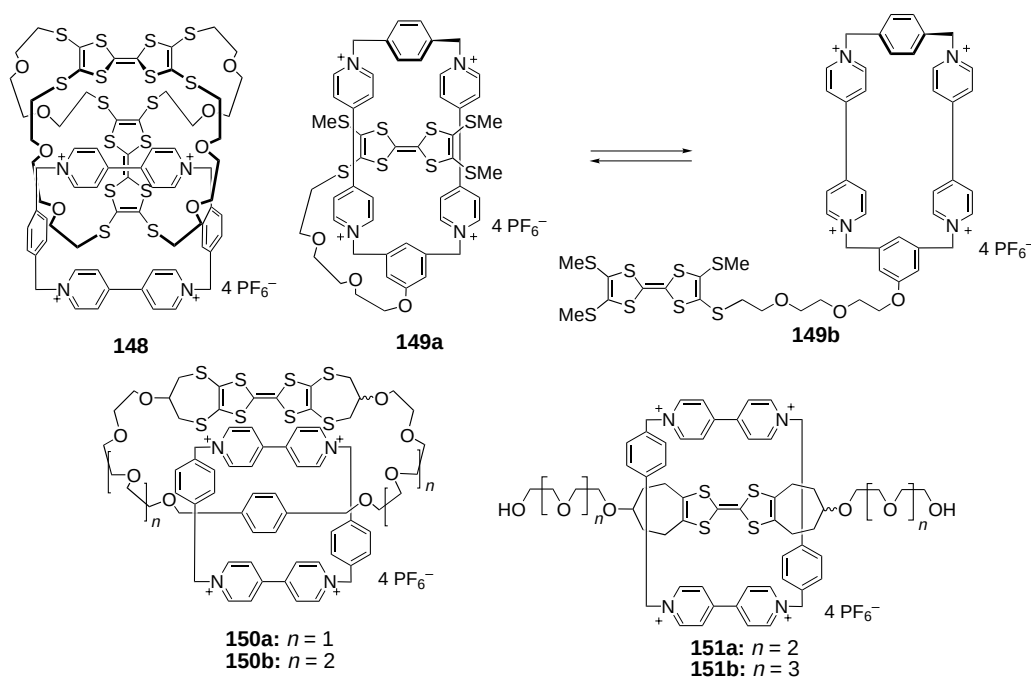
We will briefly discuss pseudorotaxane **151**. Thus, a complex having a [2]pseudorotaxane geometry (**151**) was formed by

mixing a polyether containing a (2-oxy-1,3-propylenedithio)TTF unit with the cyclobis(paraquat-*p*-phenylene) π acceptor.^[141] The TTF unit is oxidized to the radical monocation upon addition of three molar equivalents of I_2 and dissociation of the complex occurs as a result of the disruption of the CT interaction and the presence of electrostatic repulsion between the tetracationic host and the monocationic guest. Reduction of the monocationic species to their neutral states is accompanied by the insertion of the regenerated neutral guests into the cavity of the host. Therefore, this is a new example of prototypical molecular-sized machines which can be controlled by external redox stimuli.^[141]

Ashton et al. also reported in 1999 a supramolecular system that can be switched between three distinct states through electrochemical manipulation of a guest's redox properties in the presence of two hosts with different π -donor/ π -acceptor capabilities.^[150] Together with the π acceptor cyclobis(paraquat-*p*-phenylene) (CBPQT) acting as the guest, the π -electron-donating macrocyclic polyether 1,5-dinaphtho[38]-crown-10 (1/5DN38C10) and TTF were used as the hosts in this new supramolecular system (Figure 9).

A new concept was introduced in this study: the reverse role of the TTF moiety. The TTF²⁺ ion generated upon oxidation could play the role of an electron-acceptor (EA) guest in complexes with electron-donor (ED) hosts. Then it should be possible to use TTF as a switchable ED/EA guest, so that its association with EA/ED hosts can be controlled electrochemically. In this supramolecular

system, depending on the potential range, TTF can 1) be free when present as the radical cation TTF^{•+}, 2) form a complex with CBPQT⁴⁺ in its TTF(0) state, or 3) be complexed by 1/5DN38C10 when it exists as TTF²⁺. The authors claim that second-generation three-pole systems can be conceived wherein the occurrence of, in addition to the choice of the partner in, energy- or electron-transfer processes can be coordinated by electrochemically driven molecular motions. Such a system may lead to its application as molecular-level signal processors.^[150]



Scheme 7. **148**: a catenane with a *cis/cis*-configured tetrathiafulvalenophane; **149**: a macrocycle bearing a pendant TTF unit that exhibits "anchimeric complexation"; **150**: a [2]catenane with a TTF unit; **151**: a [2]pseudorotaxane as a prototype for molecular-sized machines.

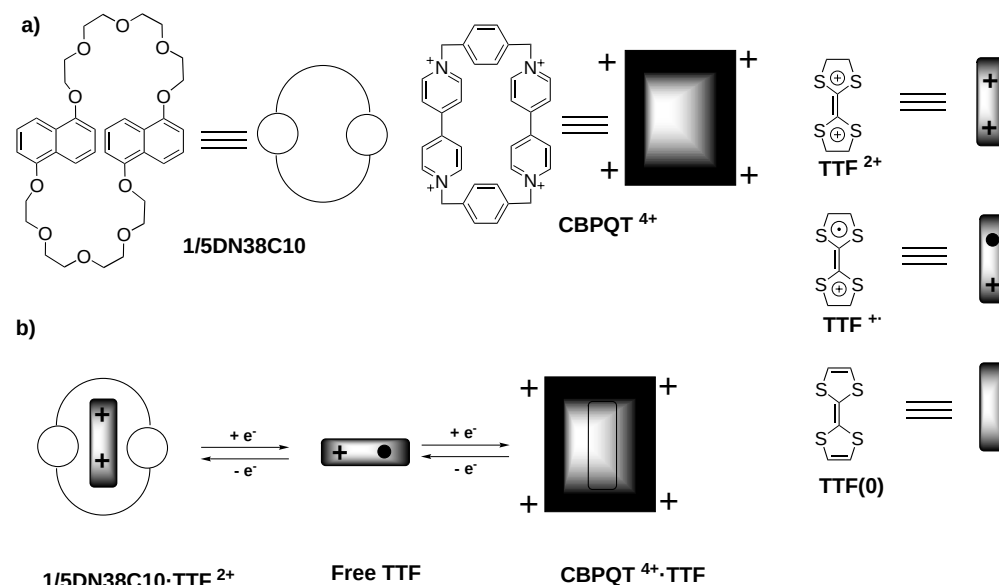


Figure 9. a) Structural formulas and schematic representations of the components of the three-pole supramolecular switch described in ref. [150]. b) Schematic representation of the electrochemically reversible three-pole supramolecular switch based on the three-component mixture CBPQT⁴⁺-1/5DN38C10-TTF (redrawn from ref. [150a]).

A research group led by Heath at the University of California and Williams at the Hewlett–Packard Laboratories in Palo Alto have described new electronically configurable molecular-based logic gates consisting of a monolayer of redox-active rotaxanes sandwiched between metal electrodes.^[151] The switches were read by monitoring the current flow at reducing voltages. The demonstration circuit is not very flexible, because the rotaxanes cannot be restored to their original state once oxidized. Hence turning off any given switch is irreversible. This facility is sufficient for read-only

memory and certain kinds of logic circuits.^[152] Considering the particular redox behavior of the TTF moiety and the extensive knowledge obtained in recent years on its supramolecular chemistry, TTF-based rotaxanes might be good candidates to be investigated in this type of device in the hope of finding a system that may switch back and forth and create a novel version of computer memory that could be written and erased many times over.^[152]

3.3. TTF Derivatives Exhibiting Magnetic Properties

One of current trends in molecular science deals with the investigation of compounds that exhibit, if possible in a synergistic way, multiple physical properties such as electrical conductivity and magnetic interactions, spin crossover and magnetism, optical and magnetic properties.^[153] Thus, a contemporary challenge in this field is that of designing, by the wise choice of constituent molecules, new materials that combine properties not normally associated with a single material.^[154, 155] It has long been thought that conductivity and magnetism were inimical to one another.^[156] However, several attempts have been made to couple interesting conducting and magnetic behaviors

in molecule-based compounds.^[157] With this aim, different approaches have been followed to design and synthesize new TTF-containing organic conductors exhibiting localized magnetic moments. Since Day et al. reported the first observation of the coexistence of localized and conducting electrons in a metallic charge-transfer salt in 1992,^[158] different types of TTF-containing metallic radical cation salts with paramagnetic anions have been prepared to study the possibility of new physical phenomena resulting from the mutual interaction between delocalized conduction electrons and localized

magnetic moments.^[157, 159] Comprehensive review articles have recently been published that focus on the different magnetic molecular materials based on CT complexes and CT salts of tetrathiafulvalene in which magnetism arises from the presence of magnetic ions. In 1997 Day and Kurmoo reviewed the different molecular magnetic semiconductors, metals, and superconductors based on bis(ethylenedithio)(BEDT)-TTF salts with magnetic anions.^[21] In a comprehensive review article Coronado and Gómez-García collected recent results of organic/inorganic hybrid salts in which the electron donors are organic molecules of the TTF type and the electron acceptors are polyoxometalates that can also act as ligands that incorporate one or more magnetically active transition metal ion.^[19] Ouahab has also recently reviewed the use of organic/inorganic molecular materials in which the inorganic components are coordination complexes (tetracyanometalates, hexacyanometalates, metal bis(dithiolates), metal bis(dithiolenes), metallocenium complexes, and polyoxometalates) and the organic part is concerned with TTF and BEDT-TTF derivatives.^[153] In these kinds of materials it is possible to couple ferromagnetically isolated and localized spins on transition metals in the inorganic network, as a consequence of the π electrons of the organic network. Rovira has recently reviewed the structural and magnetic characteristics of the recently discovered quantum – spin ladders.^[160] In this regard, molecular spin ladders involving some TTF derivatives have been prepared from dithiophenetetrathiafulvalene (DT-TTF) and BEDT-TTF salts. The reading of the above mentioned review articles^[19, 21, 153, 160] is highly recommended for a comprehensive coverage of the field.

The second type of TTF derivatives that exhibit magnetic behavior are those which include only organic species, the so-called organic ferromagnets.^[161, 162] Enormous efforts have been devoted in recent years towards the obtention of organic magnetic materials composed of molecular species or polymers. This research has been stimulated by the promise of applications in future generations of electronic, magnetic, and/or photonic/photronic devices ranging from information storage and magnetic imaging to static and low-frequency magnetic shielding.^[163, 164] The target of this research is the obtention of organic compounds that combine the inherent properties of organic compounds with a usable magnetic property. Some of the foreseeable advantages of the organic and polymeric over the traditional materials have been recently pointed out by Veciana:^[165]

1. Their transparency in many spectral regions and the possibility of being obtained in optically active chiral forms might enable them to be used as magneto-optical switches and for the manipulation of polarized light in optical devices.
2. The flexibility and solubility of organic/polymeric compounds makes them easily processable, and they are therefore good candidates for obtaining magnetically active thin films and colloidal dispersions with ferrofluid properties.
3. The possible biocompatibility of organic magnetic compounds allows applications such as selective contrasting agents in nuclear magnetic resonance imaging to be envisaged.

4. The enormous versatility of organic chemistry allows small structural modifications to be performed to obtain desired materials properties which are not usual in most traditional inorganic materials.

Although a number of organic ferromagnets have been reported,^[166] the transition temperatures of genuine organic ferromagnets are still extremely low. One promising approach to raise transition temperatures is the above-mentioned strategy of using conduction electrons which itinerate along a stack of organic donor radicals.^[167] The main point in this methodology is the introduction of ferromagnetic coupling between the conduction electrons and localized spins. Thus, in order to introduce a ferromagnetic exchange interaction between a localized spin on the radical unit and a π spin generated on the donor unit, Sugawara and co-workers proposed an open-shell donor, where the π -donor and π -radical units are connected through cross-conjugation.^[168] They prepared nitronyl nitroxide (NN) derivative **152** bearing a TTF unit at the nodal carbon atom of NN (Figure 10). When **152** was oxidized by excess I_2 in 2-methyltetrahydrofuran (MTHF), the ESR spectrum of the oxidized species in a frozen matrix of MTHF at 100 K showed a set of fine structure signals corresponding to the triplet species along with a signal ($g = 4.030$) of $\Delta m_s = 2$ in a half-field region (Figure 10). The temperature dependence of the signal intensity in the THF glass was measured in the temperature range 50–150 K.

The results show that the ground-state spin multiplicity of the cation radical of **152** is a singlet and the observed triplet signal is derived from a thermally populated species and that two spins interact antiferromagnetically.^[168a] In 1999, the research groups of Sugawara and Fujiwara reported on the synthesis of new TTF-based donor radicals **153** and **154** (Figure 10).^[169] These radicals were also oxidized with excess iodine in THF solution and the ESR spectra showed a set of fine structured signals corresponding to a triplet species. The results obtained suggest that the triplet is the ground state of these cation diradicals. This result is in sharp contrast with that obtained for **152**. This difference is probably because although the TTF and NN groups in **152** are connected through cross-conjugation, they are considered to be severely twisted as a result of steric repulsion. The delocalization of the HOMO or SOMO to the radical site is therefore suppressed, which leads to a breakdown of the electronic feature of a spin-polarized donor. This unfavorable steric hindrance is released by inserting a *p*-phenylene or *p*-thiophenylene group (**153**) as seen from the ESR measurements. If a columnar stacking of these TTF-based donor radicals that afford the ground-state triplet cation radicals upon one-electron oxidation can be realized, an organic conducting ferromagnet is expected to form.^[169a]

The cross-conjugated dimeric TTF units **155**^[170] and **156**^[171] also provide the possibility of a stable triplet ground state, and they can be regarded as simple model compounds for the high-spin system **157**. Mizouchi et al. predicted theoretically that the radical cations of **157** should show a high-spin ground state.^[172] The dication radical of **155a** possesses a singlet ground state, which is not in agreement with the prediction of a triplet state from theoretical calculations, presumably because it is fairly well stabilized. The calculations do predict

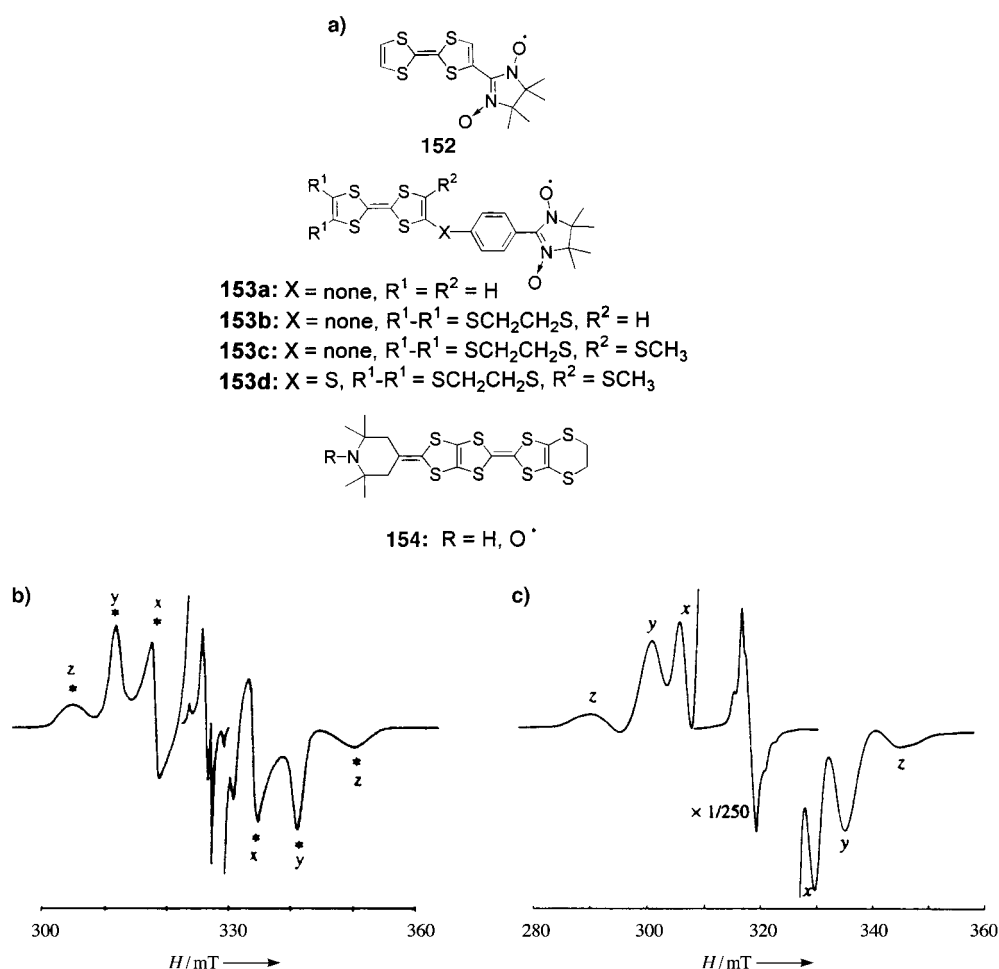
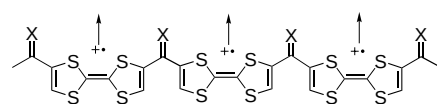
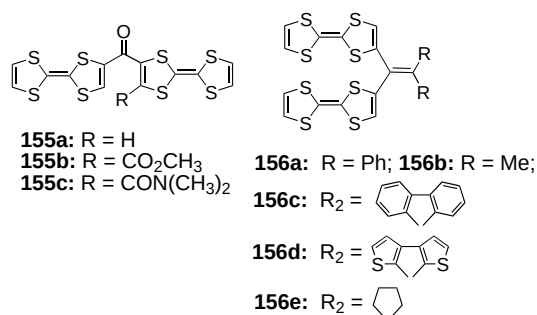


Figure 10. a) TTF-based donor radicals (**152**–**154**); b) ESR spectra of iodine-doped **152** $^{+\bullet}$ (reprinted with permission from ref. [168a]) and c) ESR spectrum of iodine-doped **153c** (reprinted with permission from ref. [169a]).



the observed smaller singlet–triplet difference in **155a** $^{2+}$ compared with those in other bis(tetrathiafulvalenyl)vinylene and bis(tetrathiafulvalenyl)thioetone dication. Furthermore, the polarization of a carbonyl group might contribute to the stabilization of the singlet species.^[170] Therefore, Iyoda

et al. have carried out the synthesis of derivatives **156a–e** in order to examine the spin–spin interaction in their oxidized state.^[171] The redox processes of these dimeric TTF compounds display no separation in either of the two-electron transfers in their cyclic voltammograms, presumably as a consequence of the weak interaction between the two TTF moieties in these molecules. This weak interaction reflects the twisted structure, which could be elucidated by the X-ray analysis of **156a**. Treatment of **156a** with iodine yielded the corresponding radical cation salt which shows interesting magnetic and electrical behavior. The ESR spectrum of the powdered sample of the radical cation salt of **156a** consists of a broad signal at the center and a fine structure ($g = 2.0074$, $D = 108$ G at 163 K) together with signals with $\Delta m_s = 2$ corresponding to a triplet species. The distance between the two spins, as estimated from the D value by the point–dipole approximation (6.36 Å), seems

to be comparable to the distance between the two TTF units in the CT salt. This interesting result paves the way towards the synthesis of polymeric analogues exhibiting the more preferential triplet ground state.

A third type of TTF-containing magnetic materials lies at the frontier between the two previous types. They consist of TTF derivatives that incorporate magnetic ions in their structure.

In 1994, McCullough et al. reported on the first synthesis and characterization of metal coordination complexes of TTF as new building blocks (**158**–**161**, Figure 11a) for new electronic, optical, and magnetic materials.^[173] They consist of early and late transition metal homobimetallic coordination complexes of tetrathiafulvalene tetrathiolate (TTFS₄); the TTFS₄ framework allows spin interaction between the two metal centers by superexchange (Figure 11b).^[174] In addition, a one-electron oxidation should produce a spin ordering of the molecule through an intramolecular antiferromagnetic coupling of the spins (Figure 11c). The electrochemical characterization of **158** shows two reversible oxidations corresponding to the TTF moiety together with a reduction process at -0.85 V corresponding to the Ti^{IV}/Ti^{III} couple. Compound **158** forms charge-transfer complexes with tetracyano-*p*-quinodimethane (TCNQ) which is important for

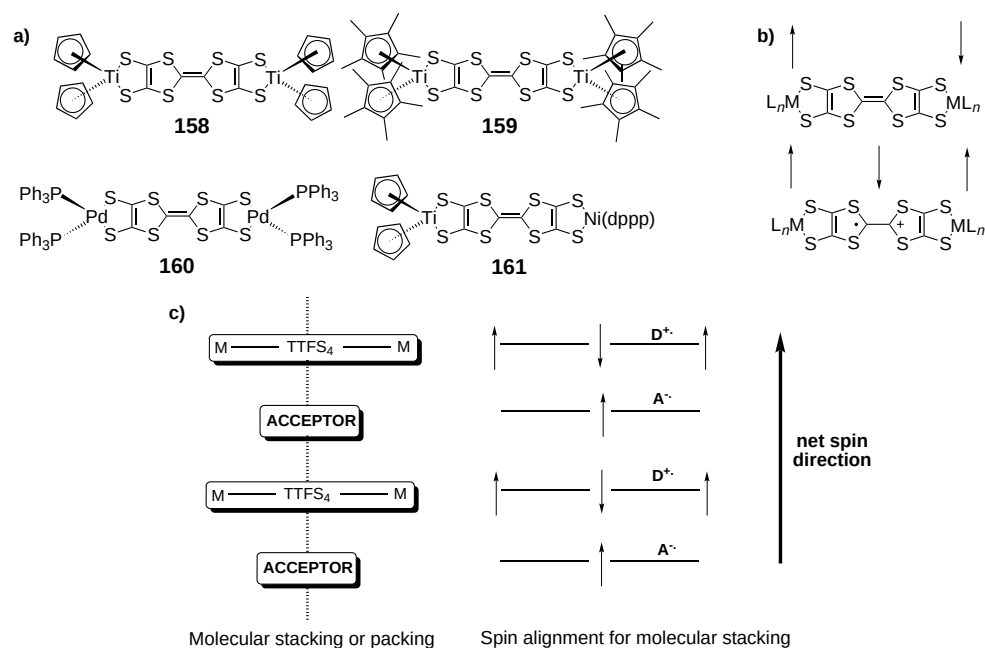
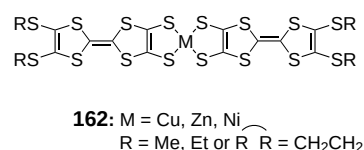


Figure 11. a) New metal coordination complex of tetrathiafulvalene thiolates **158**–**160**. b) Spin interaction in bimetallic TTF₄ complexes. The complexes shown are based on the metal M having a $S = 1/2$ ground state. c) Proposal for molecular ferrimagnets based on mixed-stack, charge-transfer complexes. (Redrawn from ref. [173a].) dppp = bis(diphenylphosphanyl)propane.

achieving the mixed-stack complexes required for magnetic materials.^[175] However, although the main target in the syntheses of these compounds was the preparation of ferrimagnetic materials based on the use of mixed-stack charge-transfer complexes of the bimetallic TTF₄ complexes, to the best of our knowledge, no report on their magnetic properties have so far been reported.

A similar approach has been more recently followed by Sugimoto and co-workers.^[176] They synthesized a new type of TTF-containing organic complex (**162**) with magnetic metal ions incorporated through covalent bonds into the two- or three-dimensional π -conducting network provided by the TTF moiety.



It was expected that unique solid organic systems involving both conducting π electrons and localized d electrons in interaction with each other would be formed. In contrast to this expectation, a large degree of intramolecular electron transfer from the Cu^{II} ion to the TTF radical cation ligands occurs to give rise to almost no spin on the resultant Cu^{III} atom. Interestingly, as the one electron transferred from the Cu^{II} atom can be equally accepted by the two TTF radical cation ligands, a 50% radical cation resides on each TTF ligands; hence a mixed-valence state can be achieved. In fact, the present neutral copper complexes exhibited comparatively high electrical conductivities (single crystal $\sigma_{RT} = 10^{-4}$ – 10^{-1} S cm⁻¹) without any doping. The authors suggest that

magnetic metal ions other than Cu^{II}, for example, Cr^{III} ($S = 3/2$), Mn^{II} ($S = 5/2$ or $1/2$), Co^{II} ($S = 1/2$), and Fe^{III} ($S = 5/2$ or $1/2$) could also be used in the preparation of similar neutral complexes. Different electrical conducting and magnetic properties might be observed with these new complexes.

3.4. Molecular Rectification in TTF- σ -Acceptor Materials

In 1974 Aviram and Ratner proposed rectification of electrical current through a single D- σ -A molecule, in which a strong donor moiety is covalently attached to a strong acceptor moiety through a covalent, saturated σ bridge.^[177]

Molecule **163** was chosen as a prototype material because of the excellent donor and acceptor properties of TTF and TCNQ, respectively. In order to achieve molecular rectification the molecule should exhibit anisotropic electrical properties. Thus, these materials should be aligned uniformly between two electrodes (M_1 and M_2) so that they would allow electron flow from the cathode M_2 to the acceptor end, from there to the donor by electron tunneling through the σ bridge, and then from the donor terminus to the anode M_1 . Figure 12b shows how such a device is asymmetric because the HOMO of D is relatively low while the LUMO of A is relatively high. The device will work if the inelastic through-bond tunneling is more likely than the elastic through-space tunneling, which is unaffected by molecular orbitals.^[178]

Although the research groups of Panetta and Metzger have performed a great deal of work during the last two decades to bring this theoretical project into reality,^[179–181] to the best of our knowledge, the D- σ -A structure **163** has not yet been synthesized. However, they have developed a systematic synthetic plan aimed at the obtention of a series of model compounds in which different donor and acceptor moieties as well as σ bridges are incorporated.^[179b, 180] This effort has allowed different D- σ -A molecules and several ground-state zwitterions D⁺- π -A⁻ to be obtained, one of which became the first confirmed unimolecular rectifier.^[182] **164**–**170** are selected examples of TTF-containing D- σ -A molecules proposed as molecular rectifiers.

The first two D- σ -A products prepared (**164**, **165**) containing the strong donor TTF and the strong acceptor TCNQ were metastable materials; they were amorphous, difficult to purify, and readily decomposed. The ¹H NMR studies of these products resulted in spectra in which many of the resonances were extremely broad: perhaps indicative of

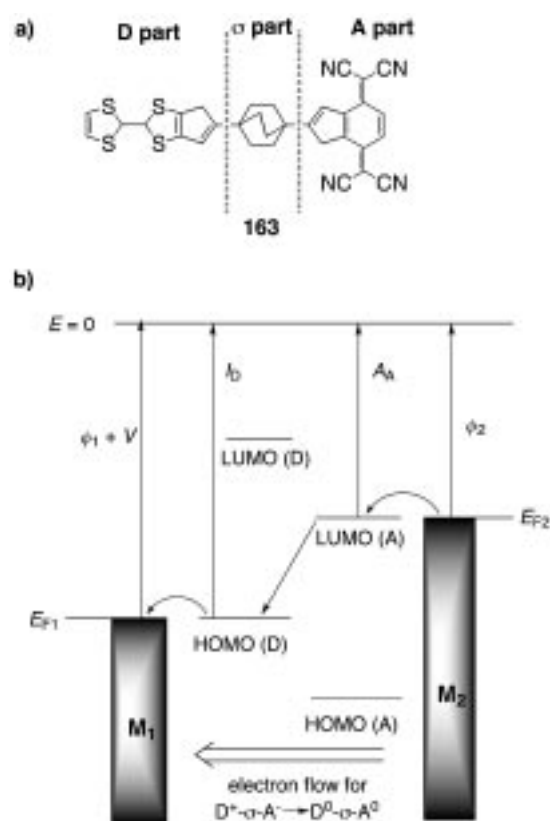


Figure 12. a) Original D-σ-A structure **163** proposed by Aviram and Ratner for a molecular rectifier. b) The Aviram-Ratner mechanism, showing the through-molecule electron flow from the excited zwitterion state $D^+-\sigma-A^-$ to the ground state $D^0-\sigma-A^0$.^[180]

exhibiting rectification.^[180] On the other hand, TTF has been incorporated in stable D-σ-A systems by replacing the strong TCNQ acceptor moiety by other moderate acceptors such as the triptycenequinone system (**166**, **167**).^[183] Further conversion of the triptycenequinone derivatives **166** and **167** into the triptycene-dicyanoquinonediimines (stronger acceptors) failed.^[87, 180, 184] The presence of long alkyl chains in **166** and **167** allows these compounds to form Pockels-Langmuir (PL) films at the air-water interface and can be mostly transferred as LB films onto solid substrates. No charge-transfer band was however observed in the LB films.

In 1998, Bryce and co-workers reported on the synthesis and study of **168** and a related TTF-σ-TCAQ-σ-TTF triad in which the strong donor TTF is covalently attached to the moderate acceptor TCAQ moiety.^[185] These are the first readily available, analytically pure, stable TTF-spacer-TCNQ derivatives. In contrast with compound **165**, ESR (no signal) and IR data on powdered samples of **168** suggested a neutral ground state. Simultaneous electrochemistry and ESR experiments provide evidence that the spin-density distribution in the radical cation of **168** was modulated intramolecularly by the adjacent TCAQ moiety. This behavior was significantly different to that observed in a mixture of model TTF and TCAQ derivatives which did not interact in solution when mixed under the same experimental conditions. Derivatives of **168** would therefore be good candidates for preparing macroscopic films to study their potential behavior as bulk rectifiers in suitable devices.

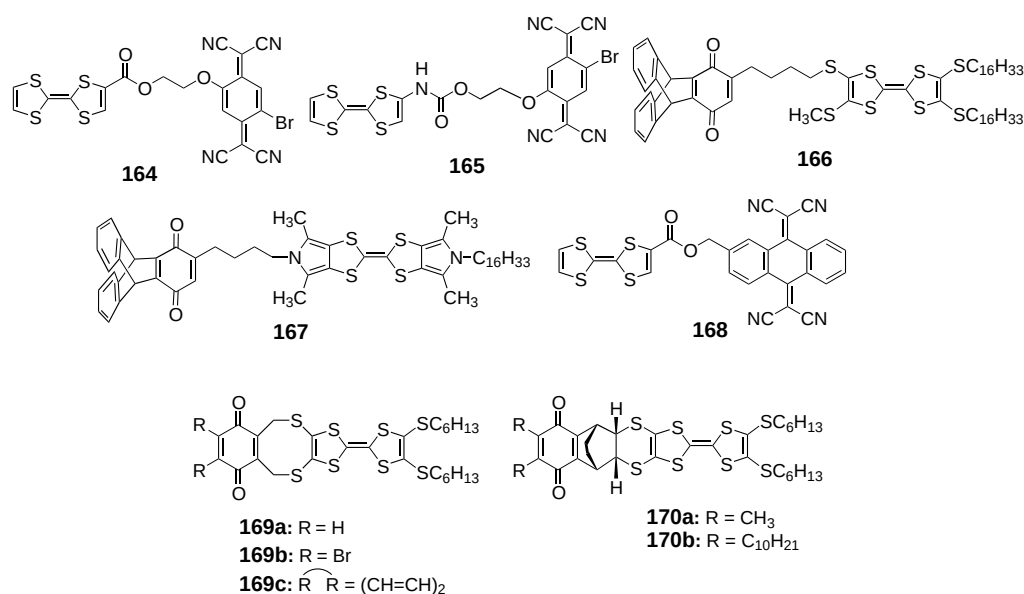
We have also reported on the synthesis of novel single-component donor-acceptor compounds (**169**) containing *p*-benzoquinone-TTF units.^[186-187]

Since the substitution on the *p*-benzoquinone ring has a striking influence on the acceptor ability of this moiety, we have introduced different substituents to tune the acceptor ability of the quinone moiety. The presence of the long alkyl chains attached to the TTF moiety led to compounds that were highly soluble in common organic solvents, which is very important for obtaining easily characterizable and processable materials. The CV data reveal the presence of both donor and acceptor moieties which behave independently and preserve their own redox character. Work is in progress

to improve the acceptor ability of the quinone moiety by replacing the *p*-benzoquinone unit with the stronger acceptors TCNQ and DCNQI. The preparation of LB films of **169** and other bisdodecyl-substituted derivatives as well as their possible rectifying behavior is also under study.

Khodorkovsky and co-workers have recently reported on a similar TTF-*p*-benzoquinone system (**170**).^[188] The X-ray structure of **170** shows the molecule has a bent configuration

to improve the acceptor ability of the quinone moiety by replacing the *p*-benzoquinone unit with the stronger acceptors TCNQ and DCNQI. The preparation of LB films of **169** and other bisdodecyl-substituted derivatives as well as their possible rectifying behavior is also under study.



paramagnetic species or charge-transfer complexes.^[179a] A ground-state biradical character for these compounds is also suggested by the intense broad signal observed in the ESR spectrum of a powdered sample of **165** recorded at 300 K. In order to avoid these problems, other weaker donor moieties (dialkylamine, pyrene, anthracene) were covalently attached through different bridges (ester, carbamate) to the TCNQ moiety to yield stable D-σ-A systems, with some of them

with the acceptor *p*-benzoquinone moiety spatially located above the donor dimethylthio-TTF unit. A low charge transfer can be observed in the ground state of **170** because of the short intramolecular face-to-face distances between the planes of donor and acceptor molecules. A photoinduced intramolecular electron transfer takes place after irradiation with sunlight which results in the appearance of broad signals in the EPR measurements. This is one of the first examples of systems with inherent intramolecular through-space charge-transfer properties.^[188]

3.5. TTF Derivatives as New Organic Electrooptic Materials

3.5.1. TTF Derivatives as NLO Materials

Recent advances in polymeric electrooptic materials and fabrication techniques for devices have significantly increased the potential incorporation of these materials and devices into modern high-bandwidth (fiber and wireless) telecommunication, information processing, and radar systems.^[189] Push–pull systems of general structure D- π -A are being actively studied as NLO chromophores,^[190] since they can exhibit large quadratic molecular hyperpolarizabilities (β). These are electrooptic materials whose refraction index can be changed by the application of an electric field and are of interest as a result of their potential use in areas such as optical modulation, molecular switching, optical memory, and frequency doubling.^[191]

In this context, we reported in 1998 the first NLO materials containing the TTF unit as the donor moiety in D- π -A systems (**171**, **172**, Table 2).^[192] We have studied the influence of different acceptors and spacers in order to optimize the nonlinear optical response of these materials.^[193–196] Table 2 shows the $\mu\beta$ values of selected TTF-containing NLO materi-

als (**171–177**). The $\mu\beta$ values were measured using the electric-field-induced second harmonic generation (EFISH) technique at 1907 nm.

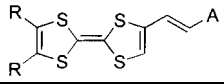
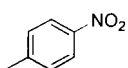
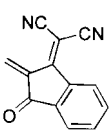
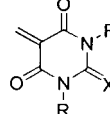
An increase in the NLO properties of these materials has been observed by using stronger electron acceptors attached to the TTF moiety. Low $\mu\beta$ values were obtained for derivative **171** bearing the weak formyl electron acceptor.^[192] An improvement in the $\mu\beta$ values was observed when the formyl group was replaced by stronger electron acceptors such as dicyanomethylene (**172**),^[192, 193] nitrobenzene (**173**)^[194] and (thio)barbituric acid (**175–177**),^[195] with the best results ($\mu\beta = 1350.10^{-48}$ esu) being observed when the strong acceptor 3-(dicyanomethylidene)indan-1-one was used in combination with the TTF unit.^[196]

As in other NLO materials, the $\mu\beta$ values increase in the series **a** < **b** < **c**, which shows the beneficial effects of the extended conjugated chain on the molecular first hyperpolarizability (Table 2).^[190c]

The UV/Vis absorptions of the novel compounds were measured in the same solvent used for the EFISH measurements. In all of them, a low-intensity charge-transfer band is observed in the visible region. A bathochromic shift is observed when increasing the acceptor ability of the acceptor moiety. A most interesting observation of these compounds is that they present an increase in their $\mu\beta$ values with substitution on the TTF skeleton and, in spite of their larger π extension, a hypsochromic shift is observed when going from the **a** to the **c** member of a series. Thus the well-known trade-off in the efficiency of the NLO transparency is overcome.

The charge-transfer nature of this band, which is a prerequisite for the attainment of high β values,^[197, 198] has been studied by quantum-chemical methods. Figure 13 depicts the molecular orbital topologies calculated by using the PM3 semiempirical method for the HOMO and LUMO orbitals of compound **174c**. This topology is representative of

Table 2. UV/Vis absorption [nm] and $\mu\beta$ values [10^{-48} esu] of selected TTF-containing NLO materials.

			$\lambda_{\text{max}}^{[\text{a}]}$	$\mu\beta^{[\text{b}]}$	$\mu\beta_0^{[\text{b}]}$	Ref.	
171	A = CHO	<i>n</i> = 1	486	80	35	[192]	
172	A = 	a : <i>n</i> = 1 b : <i>n</i> = 2	636 628	470 630	190 320	[192] [193]	
173	A = 	a : <i>n</i> = 1 b : <i>n</i> = 2 c : <i>n</i> = 3	512 500 500	135 270 315	135 180 205	[194]	
174	A = 	a : <i>n</i> = 0 b : <i>n</i> = 1 c : <i>n</i> = 2	798 726 690	– 700 1350	– 259 570	[196]	
175	A = 	R = H, X = O	a : <i>n</i> = 0 b : <i>n</i> = 1	641 597	80 190	39 104	[195]
176		R = CH ₃ , X = O	a : <i>n</i> = 0 b : <i>n</i> = 1	650 609	142 290	67 154	
177		R = CH ₃ -CH ₂ , X = S	a : <i>n</i> = 0 b : <i>n</i> = 1 c : <i>n</i> = 2	716 661 646	480 760 960	180 347 455	

[a] Recorded in CH₂Cl₂. [b] Measured by the EFISH technique at 1907 nm; R = H, SCH₃, or $\widehat{\text{R}}\text{R} = \text{S}(\text{CH}_2)_2\text{S}$.

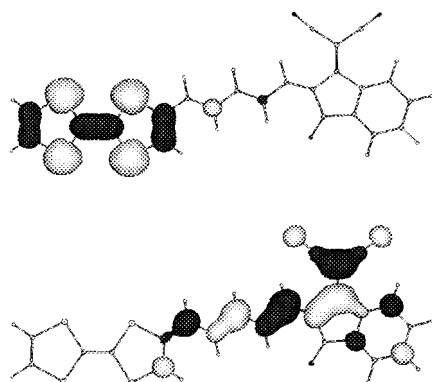


Figure 13. Molecular orbitals (PM3) of **174c**.

that calculated for the other TTF-containing NLO materials. It can be seen how the HOMO is mainly located on the TTF unit while the LUMO extends along the acceptor moiety and the ethylenic spacer. The different location of these orbitals indicate the charge-transfer character of the HOMO–LUMO transition and shows the HOMO–LUMO overlap necessary for obtaining good NLO responses.^[197]

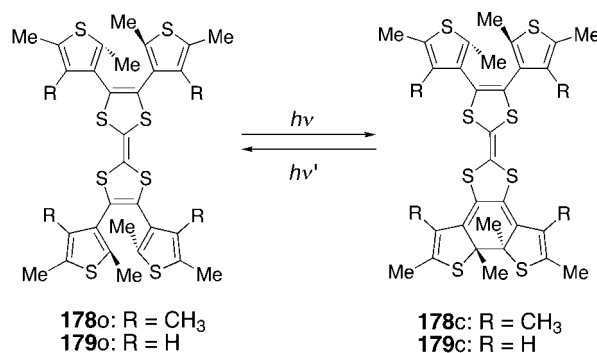
With these promising results in hand, better $\mu\beta$ values may be expected for TTF-containing materials in which more polarizable spacers and stronger acceptor units are included. In addition, TTF-based NLO chromophores display good thermal stabilities which make them potential candidates for incorporation in poled polymers.

The NLO behavior of TTF derivatives seems not to be limited to second-order effects. In 1999, Nakano et al.^[199] reported that the radical cation of TTF provides unique third-order optical nonlinearity, that is, a large negative γ value (second hyperpolarizability) according to a structure–property correlation rule developed by their research group.^[200] The sign of γ is important in quantum optics:^[201] the positive values cause the self-focusing effect of an incident beam, while the negative one causes the self-defocusing effects. Thus, since systems with negative values of γ are in general rare and are also expected to be candidates for fundamental systems of “controllable NLO materials”, the finding that the radical cation of TTF exhibits large negative values of γ paves the way for further studies on this specific property. Furthermore, as the radical cation of TTF is present in the segregated stacks of several electrically conducting charge-transfer complexes in combination with acceptor counterparts, this type of material may constitute a new possibility for multiproperty systems combining high electrical conductivity and unique third-order nonlinearity ($\gamma < 0$).

3.5.2. TTF Derivatives as Photochromic Materials

Organic photochromic compounds that allow reversible modulation of a given electronic property, such as conjugation, by an external trigger, such as light, are attractive for different applications^[202] including optical information storage systems.^[203] One important class of these compounds are those bearing the diarylethene moiety because of their fatigue resistance and thermally irreversible reactivity.^[204] Compounds of this type undergo a reversible electrocyclic

interconversion (Scheme 8) between a colorless, unconjugated open state (o) and a colored, conjugated state (c) on irradiation.



Scheme 8. Photochemical interconversion of compounds **178** and **179** between their open (o) and closed (c) forms.

Uchida et al. have recently synthesized 4,4',5,5'-tetrakis(2,4,5-trimethyl-3-thienyl)tetrathiafulvalene (**178**) and 4,4',5,5'-tetrakis(2,5-dimethyl-3-thienyl)tetrathiafulvalene (**179**) bearing the dithienylethene units.^[205] Upon irradiation with UV light, the colorless solution of **178** changed to yellow. The yellow color was bleached by irradiation with visible light ($\lambda > 450$ nm). In contrast to **178** which underwent reversible photochromic reactions, the related analogue **179** did not show any color change by irradiation with UV light. This remarkably different behavior has been accounted for by the lack of steric repulsion which takes place between the methyl groups in **178** and results in an inactive photochromic conformation.

Interestingly, light-triggered electrochemistry of **178** was examined by cyclic voltammetry and revealed that this TTF derivative undergoes a direct electron-transfer reaction with the electrode on irradiation with UV light, whereas irradiation with visible light decreased the Faradaic current. Therefore, an electrochemical switching function was also observed to accompany the photochromism. This first example of photochromism in TTF derivatives paves the way for the very appealing field of multiproperty materials and, therefore, more effort should be paid to this type of TTF-based photochromic system.

3.5.3. Photovoltaic Applications of TTF-Containing Fullerenes

The design and synthesis of organic molecules with two chromophores, namely an electroactive donor and an acceptor fragment connected through a spacer, that display charge separation is an important topic in chemistry since they can be used as artificial photosynthetic systems to transform sunlight into chemical energy.^[206]

During the last few years fullerenes, and particularly [60]fullerene, have been shown to have unique photophysical properties that are promising features for the preparation of photovoltaic devices.^[207] Thus, one of the most outstanding properties of [60]fullerene in electron-transfer processes is that it accelerates the photoinduced charge separation and

retards the charge recombination in the absence of light.^[208] These findings suggest that C₆₀ and its derivatives are promising candidates for the preparation of artificial photosynthetic systems and photovoltaic devices, which constitutes one of the most realistic and outstanding applications of fullerenes.

Since the preparation of C₆₀ on a multigram scale in 1990^[209] a huge amount of work has been devoted to the chemistry of C₆₀ and it is already well-established. Therefore, during the last few years many C₆₀-donor systems have been prepared in the search for electron-transfer properties. We have recently reviewed this topic and a wide variety of C₆₀-based intermolecular as well as intramolecular complexes have been synthesized.^[210]

It is worth mentioning that most of the donor molecules used in the preparation of C₆₀-σ-donor systems have an aromatic character in the ground state which is partially or totally lost upon oxidation to form the radical cation species.^[210] In contrast, TTF and its derivatives are non-aromatic molecules which upon oxidation form the 1,3-dithiolium cation which possesses aromatic character (Scheme 1). This gain of aromaticity in forming the radical cation and dication species of TTF in the oxidation process is an important improvement for increasing the stabilization of the charge-separated state (Figure 14).

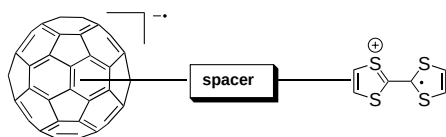


Figure 14. Approach for the design of molecules showing remarkably long-lived CS states: the TTF unit gains aromaticity upon oxidation.

The first C₆₀-TTF dyad (**180**) was simultaneously and independently reported by Prato et al.^[211] and Martín et al.^[212] in 1996. Since then, other C₆₀-TTF derivatives, such as **181**,^[213] **182**,^[214] **183**,^[215] **184**,^[216] **185**,^[217] and **186**,^[218] have been published in the search of photoinduced electron-transfer processes.

The C₆₀-TTF dyad **183** was prepared by a Diels–Alder cycloaddition of the *o*-quinodimethane analogue of TTF to C₆₀.^[215] These systems undergo a rapid quenching of the triplet excited states, as observed by nanosecond-resolved flash photolysis, to generate transient charge-separated open-shell species with lifetimes typically around 75 μs.^[219] These lifetimes

are, however, far away from those measured for dyads such as **180** and **185–187**.

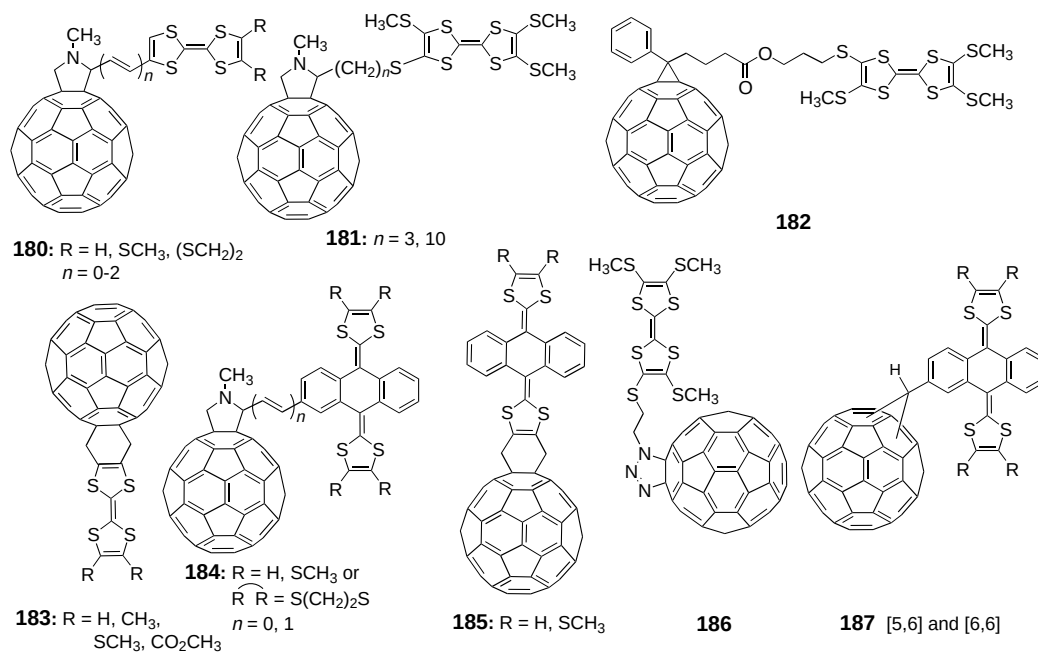
The nature and length of the spacer linking the two electroactive moieties have a profound impact on the rate and efficiency of intramolecular electron-transfer processes.^[220] Thus, we have prepared dyads (**180**) in which the TTF donor unit is attached to the C₆₀ core through a single σ bond and one (*n* = 1) or two (*n* = 2) vinyl spacers. We have recently reported the photophysics of the TTF-containing dyads **180**^[221] and **186**.^[218] Absorption of light by these dyads leads to the formation of the excited singlet state of fullerene, which undergoes an intramolecular electron transfer to form the charge-separated (CS) state (Figure 14). Evidence for the electron transfer comes from steady-state and time-resolved photolysis.^[221, 222] It is worth mentioning that an increase in the stabilization of the CS state takes place by gaining aromaticity upon oxidation of the TTF moiety.

Charge recombination proceeds mainly through formation of the triplet excited state of fullerene as a result of the strong second-order vibronic spin–orbit coupling induced by the presence of the sulfur atoms of the TTF unit. This charge-recombination behavior forming a fullerene triplet excited state is different to most of the previously reported C₆₀-based dyads that bear donor moieties other than TTF (Figure 15).^[221]

The lifetimes of the charge-separated states in all these C₆₀-TTF dyads are in the range of 1–2 ns, which is similar to that found in other C₆₀-based tetraphenylporphyrin dyads (ca. 0.5 ns) endowed with similar spacers.^[223]

More recently, we have found that C₆₀-based dyads bearing a π-extended TTF fragment (**187**) that forms very stable cationic species upon oxidation exhibit a CS state with a highly remarkable stability, being improved by about two orders of magnitude relative to other C₆₀-TTF dyads.^[224]

Systems **188**^[225] and **189**^[226] are other more complex electroactive systems involving C₆₀ and TTF moieties. These



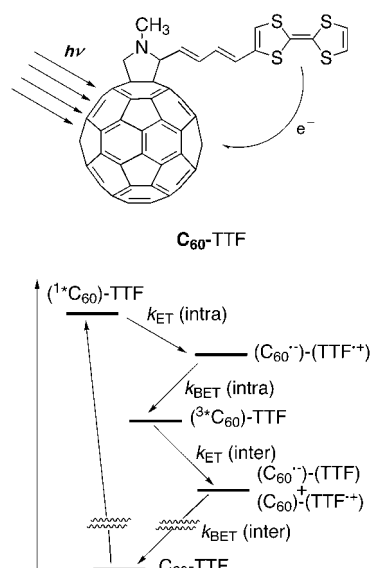
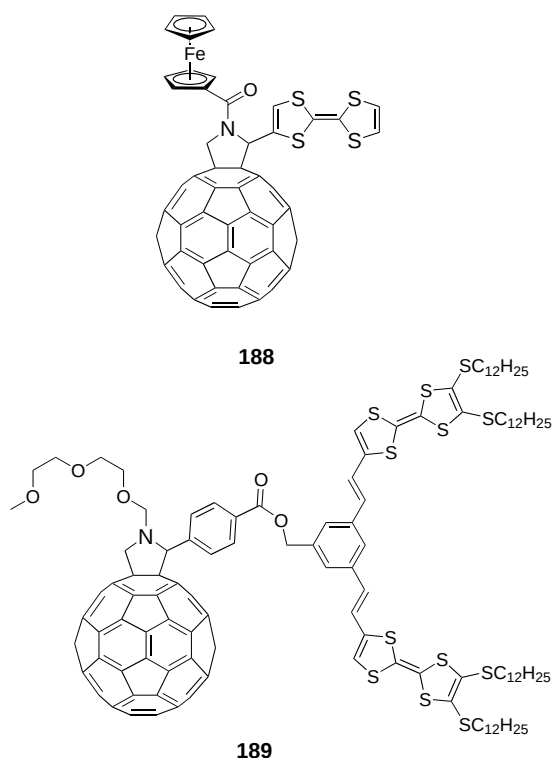


Figure 15. Deactivation process of the singlet excited state of fullerene in C_{60} -TTF dyads.

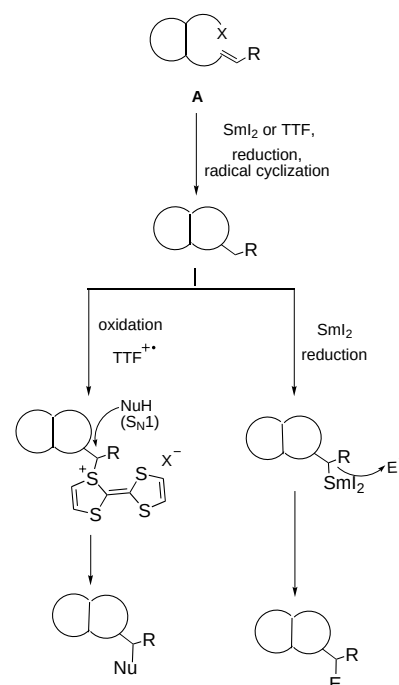


have been recently prepared in the search for a range of redox centers which could stabilize the formed CS state. Work is currently in progress to determine this behavior.

These findings suggest that C_{60} -TTF dyads are promising candidates for the preparation of devices for the conversion of solar energy. The search for novel photovoltaic devices and artificial photosynthetic systems is currently a major task in chemistry and the photophysical properties shown by dyads involving TTF and π -extended TTFs are among the most outstanding found for these purposes. In fact, we are currently working on the preparation of photovoltaic cells using TTF derivatives as donor moieties in C_{60} -based dyads.

3.6. Tetrathiafulvalene as a Catalyst for Radical–Polar Crossover Reactions

In spite of the extensive studies on the chemistry of TTF as a precursor of new conductors and semiconductors, it has been little exploited in synthesis. Given that it is an excellent donor, Murphy and co-workers anticipated that it could be used as a single-electron-donating catalyst in new sequential reactions.^[227] Tietze and Beifuss^[228] reviewed the advantages of using sequential reactions in organic synthesis in 1993 and, more recently, Skrydstrup has studied new examples of these types of reactions that rely on single-electron-donating agents to provide an effective means to synthesize a series of polycyclic compounds.^[229] In contrast to the traditional radical/polar reactions induced by SmI_2 ,^[230] Murphy and co-workers have shown that radical cyclizations promoted by TTF may be terminated by S_N1 -type nucleophilic substitution at the new exocyclic center (Scheme 9). Single-electron

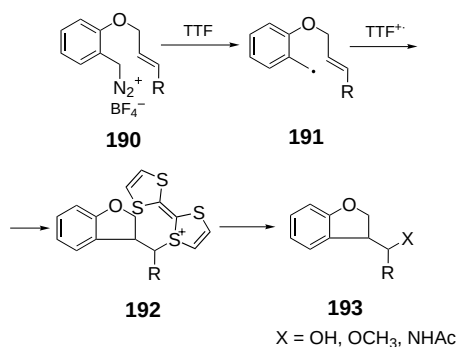


Scheme 9. Comparison of the SmI_2 -induced radical/polar reaction with the radical route involving a TTF-mediated cyclization, which can proceed through a S_N1 -type nucleophilic substitution to form an exocyclic center.

reduction of a suitable substrate **A** by TTF and subsequent radical cyclization in analogy to the SmI_2 -promoted reactions yields a carbon radical which can be oxidized by combination with the TTF radical cation. While the carbon radical is further reduced by a second SmI_2 molecule in the SmI_2 -mediated reactions, a sulfonium ion is formed in the TTF-mediated reaction sequence. Substitution at the sulfonium ion containing a carbon center by external nucleophiles (for example, solvents such as H_2O , $MeOH$, CH_3CN) were found to follow S_N1 -type kinetics.

These reactions have so far been mostly applied to aryldiazonium salts and therefore are restricted to cyclizations of aryl radicals. In the original paper of Murphy and co-

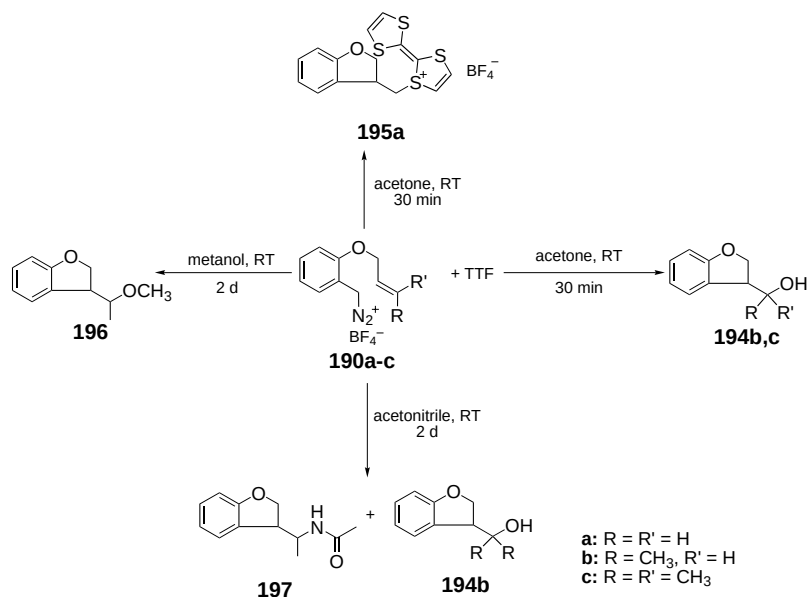
workers^[227a] they reported how aryldiazonium salts (**190**) could be converted into aryl radicals (**191**) which then underwent a further cyclization. The alkyl radicals produced then underwent C–S bond formation with the tetrathiafulvalene radical cation. Such salts underwent a rapid unimolecular substitution in moist acetone, methanol, or acetonitrile to afford alcohols, ethers, and amides, respectively (Scheme 10, **193**). Solvolysis was so retarded for TTF salts **192**^[231] (where R = H) that it was not observed under the reaction conditions.



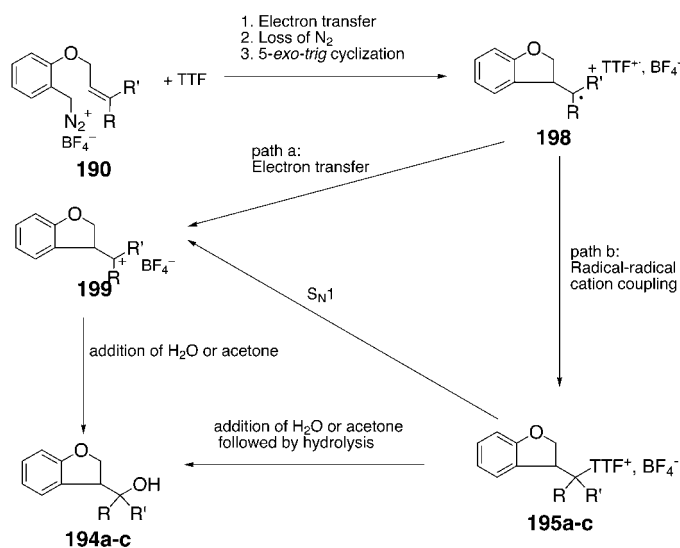
Scheme 10. Reaction of aryldiazonium salts **190** to form the radical intermediate **191** and subsequent reaction with the TTF radical cation.

The 2-allyloxybenzenediazonium salts **190b,c** react with TTF in acetone at room temperature to furnish the alcohols **194b,c**. The arenediazonium salt **190b** reacts with TTF in methanol to give the methyl ether **196**, and in acetonitrile to give the amide **197**. The diazonium salt **190a** reacts with TTF in acetone to give the sulfonium salt **195a** as a mixture of two diastereoisomers. It was not possible to effect conversion of this compound into the alcohol **194a** (Scheme 11).^[232]

Although different mechanisms have been proposed for these reactions,^[233] the most likely mechanism is that proposed by Murphy and co-workers^[232] which is outlined in Scheme 12. The reaction starts with a single-electron transfer (SET)



Scheme 11. Reactions of the 2-allyloxybenzenediazonium salts **190a–c**.

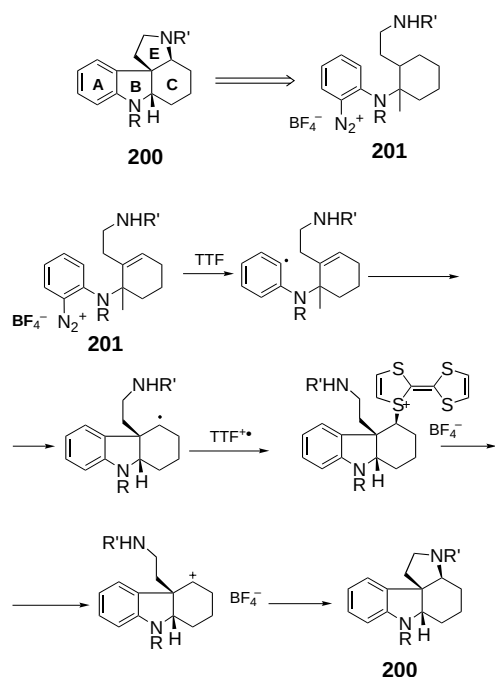


Scheme 12. Reaction mechanism for the conversion of the 2-allyloxybenzenediazonium salts **190a** by Murphy and co-workers.^[232]

followed by nitrogen expulsion and 5-*exo-trig* cyclization to afford the intermediate alkyl radical **198** and the tetrathiafulvalenium radical cation. The reaction can follow two alternative pathways: in path a, the oxidation occurs by SET to another molecule of the diazonium salt or, less likely to the TTF radical cation. The observed alcohols can then be formed upon reaction of the so-formed carbocation **199** with residual moisture in the acetone. In path b, the alkyl radical and the TTF radical cation couples to give the intermediate salt **195**, which upon substitution would yield alcohols **194**.

As the stereocontrolled construction of complex polycyclic systems is a challenging goal in synthetic organic chemistry, Murphy and co-workers explored whether these TTF-mediated radical–polar crossover reactions could afford a direct, novel, and stereoselective route to alkaloids^[234] by using intramolecular nucleophiles.^[235] Many members of the *Aspidosperma* alkaloids (aspidospermidine and strychnine) contain the ABCE tetracyclic substructure **200** which features defined stereochemistry at three contiguous centers. Murphy and co-workers proposed that the diazonium salt **201** should afford **200** with complete stereoselectivity (Scheme 13). Thus, by using this synthetic strategy, a family of tetracyclic synthetic precursors of complex alkaloids have been synthesized^[234a–c] and, in 1999, a novel route to (±)-aspidospermidine was reported as the first application of the TTF-mediated radical–polar crossover reactions to total synthesis.^[234d]

In a recent study by Bashir and Murphy on the role of neighboring group participation in the TTF-mediated radical–polar crossover reactions, secondary alkyl radicals have been trapped for the first time, thus confirming the proposed mechanism. In addition, it has also been observed that groups other than arenes can participate in the solvolysis, thus extending the scope of the radical–polar crossover reaction.^[236]



Scheme 13. Stereospecific synthesis of the tetracyclic ABCE substructure **200** from the diazonium salt **201**.^[234a-c]

4. Summary and Outlook

The first two decades after the first synthesis of tetrathiafulvalene (TTF) in 1970 have witnessed an impressive development of TTF chemistry in the search for improved electrically conducting materials. However, during the 1990s a renewed interest was devoted to the use of the TTF molecule as a new building block able to exhibit other different nonconventional properties. In this review on the new concepts in TTF chemistry, we have classified the latest advances in this field in three structurally different levels, namely at the molecular level, the macromolecular level, and the supramolecular level.

Although the chemistry of TTF can be considered well-established at the molecular level, important advances in the synthesis of the parent TTF molecule in multigram quantities and, particularly, on the discovery of the cyanomethyl protecting group for the selective protection/deprotection chemistry of thiolate groups have occurred.

In regard to the development of new TTF derivatives in the search of electrically conducting materials, some alternatives to the study of single crystals have been used to grow layers of charge-transfer complexes, such as the formation of LB films or chemical vapor (CV) deposition. Preparation of mesogenic derivatives in which the TTF molecule is linked to a mesogenic liquid crystalline center has also been used as an alternative to form ordered arrays of TTF units. Although these strategies are not comparable to the single crystals in terms of conductivity, they present better opportunities for incorporation into optoelectronic devices for practical applications.

At the macromolecular level, a systematic study of molecules containing TTF units has been undertaken and mole-

cules running from dimers, trimers, and oligomers to polymers have been prepared. In addition, dendrimers comprised of TTF or TTF and acceptors have been prepared, thus forming giant molecules that show only electron-donor or amphoteric redox behavior. These dendrimeric materials offer the possibility of combining the control over the number and localization of TTF units with well-behaved solubility features, thus integrating the redox properties of TTF with the film-formation and processability of polymers. In the same way, cyclodextrins have also been used as platforms to carry TTF units.

The incorporation of TTF into polymeric matrices is well documented from several years ago. However, there is no control over the orientation of the TTF groups relative to one another as a consequence of the great number of different conformations of the polymer. Therefore, during the last few years, efforts have been directed towards the reduction of the conformational freedom by using ladder-type polymers containing TTF as part of the main chain. When doped, these polymers showed reasonable electrical conductivity values.

In recent years, interest has mainly focused on the association of TTF-based conductors with linear π -conjugated structures since better processability and conductivity are expected. In these materials two parallel charge-transport mechanisms might be possible: through intrastack interactions of the TTF units and the polaron/bipolaron conduction in the π -conjugated chain.

Although multi-TTF macromolecules can not compete with other typical conducting polymers, they can be envisaged as promising electroactive systems for multiple applications which deserve to be studied in more depth.

At the supramolecular level, different types of intermolecular interactions have been used to build novel supramolecular assemblies. Thus, incorporation of TTF units into calix[4]arenes, the use of crystal engineering, and gel formation have been used successfully to achieve ordered arrays of TTF-containing molecules. However, one of the most challenging projects in the field of molecular optoelectronics involves the assembly of monolayers (SAM) of electroactive molecular systems on solid supports. Some TTF-containing SAMs have been reported which are almost indefinitely stable and which can be used to prepare thin-film sensors.

During the last decade, the study of TTF derivatives has undergone an explosive growth of activity in the search for nonconventional applications. Thus, macrocycles and supramolecular systems endowed with TTF units have allowed the preparation of chemical sensors, molecular shuttles, and new molecular switches.

The intriguing concept of molecular switches has recently attracted great interest from a variety of perspectives.^[237] In this regard, TTF-based NLO chromophores can act as a molecular-scale switch. The preparation of materials exhibiting electronic/photonic properties that can be switched by stimulating changes at the molecular and/or macroscopic levels still represents a challenge in TTF chemistry.

To achieve a switching effect, the D- π -A molecules must be stable in two states that show very different NLO properties. Complete reversibility and a high speed of response are also important for practical applications.^[238] Tetrathiafulvalene

fulfills the above requirements as a result of its unique redox properties. Consequently, TTF-based D- π -A systems are suited for redox-switching NLO responses since changes in the β values will occur upon oxidation of the TTF moiety.

The switching of NLO responses which utilize redox reactions as stimuli is currently a less-well studied strategy for the molecular engineering of switchable NLO materials in which TTF deserves to be explored in depth.

Although important advances have been carried out in the search for magnetic properties and a number of organic ferromagnets have been recently reported, the transition temperatures exhibited are still extremely low. The versatility of organic chemistry to tailor desired materials properties represents an advantage over the traditional inorganic materials. However, to raise the transition temperature for applications in devices is far from reality at the moment.

Pico- and nanosecond-resolved transient absorption measurements of dyads comprised of TTF and C₆₀ have shown rapid transformations of the initially formed singlet excited fullerene states into the charge-separated (CS) radical pairs. The lifetime (several hundreds of nanoseconds) of the CS radical pair has been accounted for by the gain of aromaticity, which occurs upon oxidation of the TTF moiety. This feature is an important property of TTF which makes it a very attractive candidate for the development of further devices for electron/energy storage. In this regard, a large effort is currently being devoted to the study of multichromophoric redox systems which resemble the primary photosynthetic process. The TTF molecule, and particularly the π -extended derivatives, fulfill most of the requirements necessary to improve some of the artificial photosynthetic systems prepared so far.

In summary, tetrathiafulvalene (TTF) is a molecule with unique electronic properties that challenges the creativity and inventiveness of chemists in areas such as organic chemistry, polymer and materials chemistry, and supramolecular chemistry. The knowledge obtained during its thirty years of existence paves the way for the development of the outstanding properties that TTF derivatives display. Thus, TTF faces the new century as one of the target molecules to be exploited in depth.

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Wittig and His Accomplishments: Still Relevant Beyond His 100th Birthday**

Reinhard W. Hoffmann*

Prof. Georg Wittig

1897	Born in Berlin (Germany)
1916	Enrollment for chemistry at the university of Tübingen
1916–1919	Lieutenant and prisoner of war in World War I
1919–1923	Studied chemistry in Marburg
1923–1926	Habilitation in Marburg
1926–1932	Privatdozent in Marburg
1932–1937	Junior Professor in Braunschweig
1937–1944	Associate Professor in Freiburg
1944–1956	Professor in Tübingen
1956–1967	Professor in Heidelberg
1979	Award of the Nobel prize for chemistry
1987	Died in Heidelberg

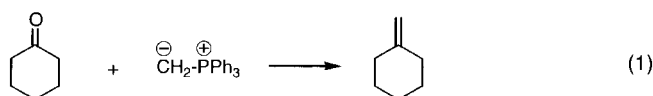


To understand the developments in chemistry at the turn of the 20th into the 21st century, one has to recognize the guidelines laid down at the beginning and in the middle of the last century. Georg Wittig was one of the scientists who, in the middle of the last century, founded such guiding principles. The 100th anniversary of Wittig's birth was in 1997. By virtue of this, Wittig has become a historical person, a subject for the history of chemistry.

Perspectives tend to be shortened when looking at the past, developments are seen in a compression of time and some aspects, which are considered not to be of relevance, are discarded. To evaluate the importance of Wittig's contributions in such a manner one should simply ask which of Wittig's accomplishments are known to the young generation of

chemists today. Of course, the Wittig reaction and the Wittig ether rearrangement would be at the top of the list. For many, the name of Wittig is also attached to the chemistry of dehydrobenzene (benzyne). If, however, today's younger chemists do not know more about Wittig's accomplishments, this has to be blamed primarily on those currently in their sixties, for not handing down more information on Wittig to the next generation.

Is the carbonyl olefination of ketones or aldehydes by phosphorous ylids, that is, the Wittig reaction, his most important contribution? The initial investigations by Wittig and Schöllkopf^[1] revealed that this reaction allows the conversion of cyclohexanone into methylenecyclohexane [Eq. (1)], a compound with a semicyclic double bond. Structures of this kind could previously only be obtained by circuitous routes and with low selectivity.



From today's point of view, it is quite normal that this very aspect of Wittig's chemistry found an immediate application

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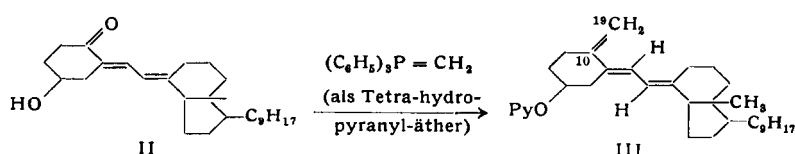
[**] A condensed version of a lecture given on the occasion of the inauguration of the Georg Wittig Lectureship at the Universität Heidelberg (27.10.1999)

in natural product synthesis. As the synthesis of vitamin D required the construction of such a moiety, Inhoffen et al. utilized the Wittig reaction in this context immediately following Wittig and Schöllkopf's first publication on the subject (Figure 1).^[2]

Partialsynthese einer „trans“-Vitamin D₂-Verbindung mit Hilfe der Reaktion von Wittig

Von Prof. Dr. H. H. INHOFFEN, Dr. J. F. KATH
und Dr. K. BRÜCKNER

Aus dem Organisch-Chemischen Institut der T. H. Braunschweig

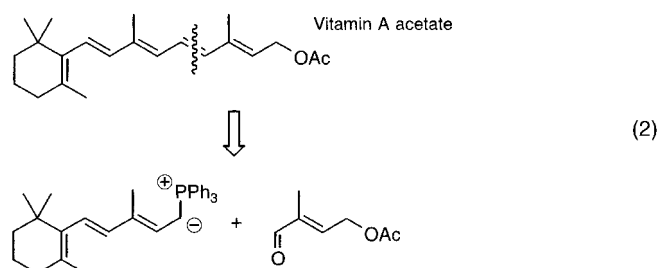


Wittig und Schöllkopf^[1a] haben nun eine Reaktion beschrieben, durch die ein Ring-Keton mit Triphenylphosphin-methylid in eine entspr. Methylen-Verbindung umzuwandeln ist. Mit Einverständnis von Prof. Wittig haben wir die Reaktion auf unser C₂₇-Keton übertragen, um die für das antirachitische Vitamin charakteristische Methylen-Gruppe zu erzeugen.

Figure 1. Reproduction of the publication by H. H. Inhoffen on the application of the Wittig reaction, *Angew. Chem.* **1955**, 67, 276 (English translation given in ref. [40]).

This fact, however, is remarkable considering the context of natural product synthesis in those days: in the first half of the twentieth century and even far into the sixties, the onus of natural product synthesis was to provide proof for the proposed structure of a natural product by synthesis.^[3] This restricted natural product synthesis to the use of only such reactions, the reliability of which was beyond doubt. It attests to the uniqueness of the Wittig reaction that it was applied in natural product synthesis (Figure 1) within one year of first being reported, despite not being an “established” reaction.

The Wittig reaction was unique in yet another aspect: it was applied just as rapidly in industrial synthesis as in natural product synthesis. Since the fifties vitamin A and other carotenoids had been produced by Hoffmann LaRoche in Basel. Horst Pommer at BASF was studying alternative routes to this class of compounds and he immediately recognized the potential of the Wittig reaction for the synthesis of vitamin A [Eq. (2)].^[4]



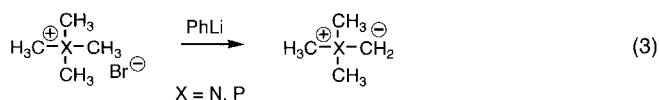
A collaboration between Wittig and Pommer soon led to a landmark patent.^[5] It was an outstanding achievement both scientifically and economically to bring a vitamin A synthesis

from the first experiments in the laboratory to large-scale commercial production within five years, an accomplishment, of which BASF can be proud. Ever since, the Wittig reaction has been used like no other as one of the standard reactions to assemble molecules by C=C bond formation.

It should be stressed that Wittig did not conceive the Wittig reaction, he discovered it. People today tend to forget that truly innovative research cannot be planned. It is foremost the ability of the scientists to properly comprehend unexpected observations and to recognize their potential. Wittig possessed this ability second to none. In part, this was related to Wittig's tendency to frown upon trendy topics of his time. The choice of his research projects rested completely within his own thinking. For a scientist in an academic institution this is a risky predisposition, that can lead to a loss in standing amongst peers, but this is also a predisposition which is the seedbed of truly novel insights.

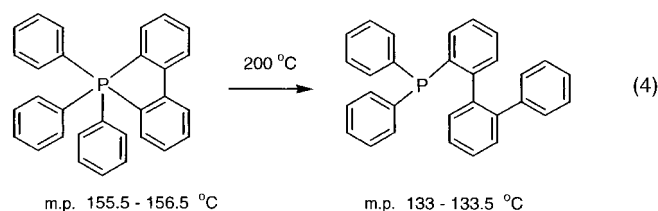
Wittig was impressed by the daring concepts of Meerwein's carbocation chemistry. He was directly exposed to it as a Privatdozent at the Marburg chemical institute (1929–1932) headed by Meerwein. Wittig envisioned carbanion chemistry becoming the counterpart of Meerwein's carbocation chemistry. For this reason, Wittig investigated in breadth reactions that

might lead to carbanionic species. This approach led him to ylids such as the simplest nitrogen ylid formed on deprotonation of the tetramethyl ammonium ion [Eq. (3)].

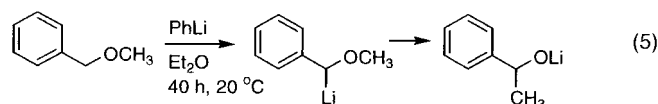


However, in truth, the experiments shown were carried out for a different purpose: Wittig always felt challenged by dogmas. He wanted to prove them wrong or at least define the limits of their validity. One dogma prevalent at Wittig's time was that elements of the first period of the periodic table could only form tetravalent compounds. Pentavalent carbon was considered, if at all, only as a transition state in an S_N2 reaction. Wittig nevertheless wanted to see whether phenyllithium might be added to the tetramethylammonium ion to form a compound with a pentavalent nitrogen atom. He did not succeed, because deprotonation of the ammonium ion led to a nitrogen ylid.^[6] As a control, he reacted phenyllithium with the tetramethylphosphonium ion; this constituted the entry to phosphorus ylids and their chemistry.^[7] To obtain compounds with pentavalent phosphorous, Wittig turned to phosphonium salts which cannot be deprotonated. Following this line of thought, Wittig generated the first pentarylphosphorane starting from the tetraphenylphosphonium ion.^[8] This compound has not reached a similar level of importance as the phosphorus ylids, but these studies exemplify some aspects of Wittig's thinking and work. We tend to forget how important the determination of melting points was to the

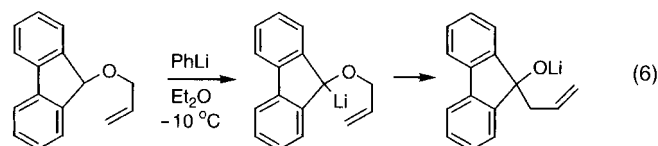
chemists of the first half of the twentieth century. Melting points provided the only means to prove the identity or nonidentity of two compounds. Accordingly, the process of crystal growing was central to the activities of chemists of those days. In many cases, the “boss” did it himself—at the very least, he reproduced the crystallization process with his own hands. Next, he had to find out whether the “melting point” was a true melting point, or whether it was merely a decomposition point, or caused by a chemical transition or a crystal modification. To clarify those matters, the melt was resolidified in the melting point tube (after taking the melting point) by scratching with a thin wire, and then the melting point was determined a second time. A difference in the melting behavior was a clear indication of an unexpected process. It was this “standard procedure” that brought to light the rearrangement of pentaarylphosphoranes to triarylphosphines [Eq. (4)].^[9] I doubt whether present day chemists take advantage of these simple techniques to unveil unprecedented thermal transformations.



Another reaction named after Wittig is the anionic ether rearrangement [Eq. (5)]. This reaction was discovered upon



attempting to generate carbanions by deprotonation of benzyl alkyl ethers.^[10] The resulting ether rearrangement forms a new carbon–carbon bond. Such bond-forming reactions are of interest today, as they permit the generation of stereogenic centers in a predefined configuration. Thus, the Wittig rearrangement of benzyl allyl ethers^[11] [Eq. (6)] has become an important tool for the stereoselective synthesis of alcohols.^[12]

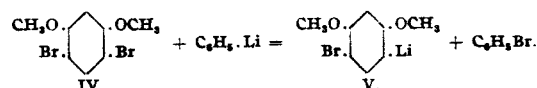


A reaction of even broader importance is the halogen/metal-exchange reaction, which few chemists today associate with the name of Wittig. The bromine/lithium-exchange reaction was described simultaneously (the manuscripts were received within three months of each other) and independent from one another by Wittig^[13] and by Gilman;^[14] thus Wittig's

contribution is clear! This reaction was so fundamentally novel and paradoxical that Wittig characterized it as shown in Figure 2 (a translation of the original German text is given in

**316. Georg Wittig, Utta Pockels und Hermann Dröge:
Über die Austauschbarkeit von aromatisch gebundenem Wasserstoff
gegen Lithium mittels Phenyl-lithiums.**

[Aus d. Chem. Instituten d. Techn. Hochschule Braunschweig u. d. Universität Freiburg i. Br.]
(Eingegangen am 26. Juli 1938.)

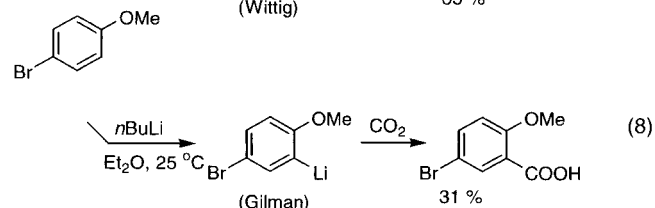
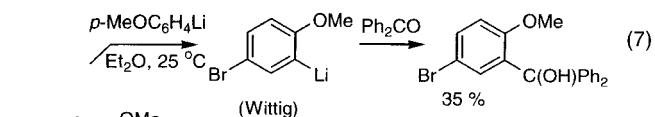


... Es hat sich also die folgende jedem chemischen Gefühl widerstrebende Reaktion abgespielt: Daß Brom und das Alkalimetallatom statt der Vereinigung einen Austausch von Molekül zu Molekül vorziehen, ist u. W. bisher noch nicht beobachtet worden; aber das Ergebnis ist gesichert, da die Reaktion, die wiederholt angesetzt wurde, rasch und ohne nennenswerte Nebenproduktbildung erfolgt.

Figure 2. Reproduction of the publication by Wittig on the halogen/metal-exchange reaction, *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1903 (English translation given in ref. [41]).

ref. [41]). To publish these findings and concepts required courage. If the interpretation had been found to be wrong, the professional career of the young assistant professor at Braunschweig would have been jeopardized. The observations on the halogen/metal-exchange reaction however, turned out to be correct. This reaction has since grown into one of the most widely used procedures for the generation of vinyl- and aryllithium compounds.

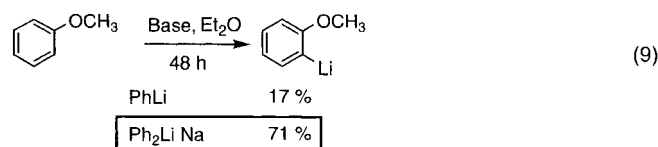
In this key paper by Wittig,^[13] another important observation is documented (again parallel to Gilman's paper^[14]), this is the directed metalation of aromatic compounds in the position *ortho* to a methoxy group [Eqs. (7, 8)].



Today, it is common knowledge that electronegative substituents which may coordinate a lithium cation can induce a directed *ortho*-metalation by alkyl- or aryllithium reagents.^[15] Following the first record of this reaction by Wittig and Gilman, the method has since been developed into a general tool in the chemistry of aromatic compounds.^[16] Wittig could not have foreseen that some of today's big-selling drugs such as Losartan^[17] or Efavirenz^[18] would be produced utilizing a directed *ortho*-metalation. Over the whole breadth of Wittig's research, phenyllithium was the key reagent, he himself described it as his “divining rod”. But how did Wittig come to use phenyllithium? The preparation of phenyllithium was

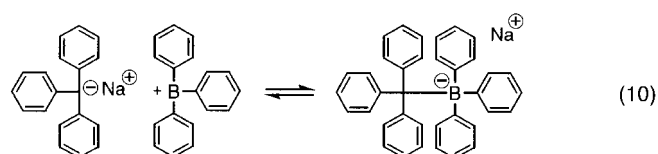
pioneered 1930 by Karl Ziegler,^[19] a close friend of Wittig's; both started their academic career at Marburg and overlapped there for many years.

For *ortho*-metalation and complexation assisted metalation Wittig continually tested more and more reactive bases. He was the first to have used complex bases, such as a 1:1 mixture of phenyllithium and phenylsodium. This complex base deprotonated anisole more rapidly than either of its constituents [Eq. (9)].^[20]

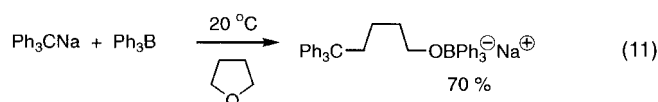


With this finding, Wittig described and studied the forerunner of the complex bases presently in use, such as the Lochmann–Schlosser base (potassium *tert*-butoxide + *n*-butyllithium^[21]) or Caubère's system (sodium *tert*-butoxide + sodium amide).^[22] The chemistry of these complex bases is still in its infancy.

Another concept of Wittig was quickly accepted by the scientific community: neutral Lewis base plus positively charged electrophile forms an onium-complex. An anionic Lewis base plus a neutral electrophile forms an ate complex, a term coined by Wittig.^[23] In studying ate complexes, Wittig hit upon the fascinating combination of triphenylmethylsodium and triphenylboron. In this system the equilibrium for forming an ate complex is not completely on the side of the complex because of steric hindrance in the latter. As a consequence, the Lewis base triphenylmethylsodium and the Lewis acid triphenylboron coexist in substantial concentrations in solution [Eq. (10)].



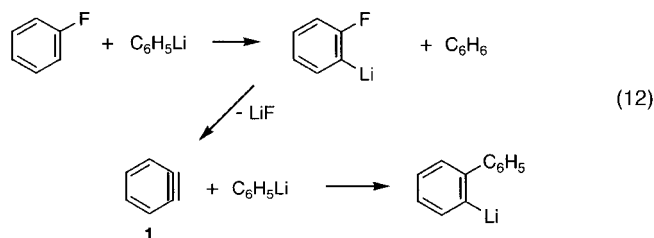
This allowed, for the first time, a Lewis acid catalysis of Lewis base induced reactions,^[24] as shown in the following example: triphenylmethylsodium by itself is stable in THF solution, so is triphenylboron. In combination they induce a rapid polymerization of THF [Eq. (11)] the first step being ring opening of the THF.



Wittig had no doubts about the mechanism of these “triphenylmethylsodium-initiated and triphenylboron-assisted reactions” as he termed them. Subsequent to Wittig's seminal studies, numerous examples of this type of Lewis acid

catalyzed reaction of organometallic compounds have been described^[25] and the principle rediscovered many times!

The directed *ortho*-metalation was the godfather to another completely unexpected finding by Wittig: 2-biphenyllithium was formed on reaction of fluorobenzene with phenyllithium [Eq. (12)].



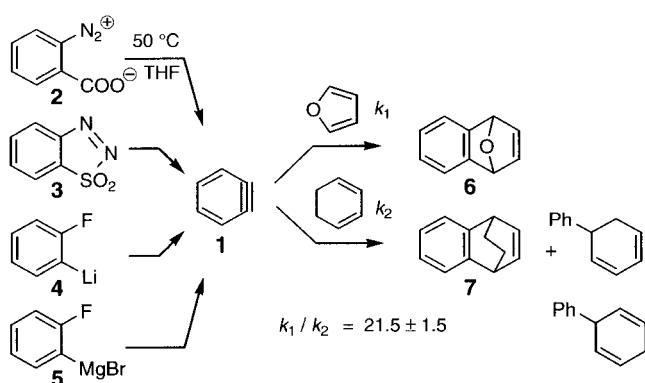
Wittig's interpretation of this transformation envisioned an *ortho*-lithiation of fluorobenzene as the first step. The resulting *ortho*-fluorophenyllithium was then postulated to lose lithium fluoride forming dehydrobenzene (benzyne; **1**) as a reactive intermediate which was then trapped by phenyllithium forming the 2-biphenyllithium end product.^[26]

This may seem reasonable for a chemist of today but, to a chemist before 1950, this was a dare-devil proposition. We should recognize that during the forties there was no perception of reactive intermediates in the mind of most German chemists. The only thing that mattered in a reaction was the starting material and the product. In line with this, the carbocation concept of Meerwein had not yet found general acceptance. To postulate such a novel reactive intermediate back in those days could easily have put an academic career at risk. This may explain why Wittig hesitated for years before publishing his hypothesis. He always was (and remained) skeptical about hypotheses, especially his own. Hence, he referred for decades to “dehydrobenzene” as being a “chemistry as if”.^[27] To Wittig, all the results obtained were consistent with the dehydrobenzene hypothesis, nevertheless they failed to prove the existence and structure of this reactive intermediate. This skepticism remained even after J. D. Roberts proved the symmetrical nature of this intermediate by brilliant isotope labeling experiments,^[28] and after Wittig himself provided the most convincing evidence in trapping dehydrobenzene in Diels–Alder reactions.^[29]

It was finally in 1964 that Wittig accepted dehydrobenzene as a reality, after Huisgen showed through his elegant determination of competition constants^[30] (cf. Scheme 1) that a common intermediate is generated from the different precursors **2–5**, an intermediate that selects between furan and cyclohexadiene in an identical manner.

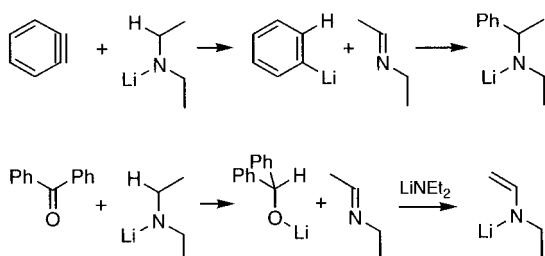
It follows that the same intermediate is generated in all these reactions. Simple comparison of the structures of the precursor compounds on the one side and of the trapping products **6** and **7** on the other leaves no doubt that the reactive intermediate has to be dehydrobenzene **1** with the shown connectivity of atoms.

Wittig was the first to note that lithium dialkylamides may transfer hydride to acceptor molecules, a reaction which Wittig had neither planned nor sought. It was again seren-



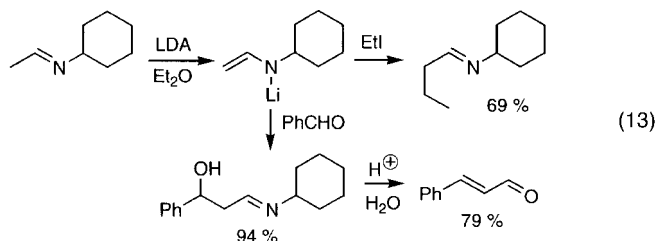
Scheme 1. Huisgen's confirmation, by using various precursors, of the identity of the intermediate dehydrobenzene.

dipity, but Wittig recognized right away the importance of this finding. The plan had been to generate dehydrobenzene from fluorobenzene using lithium diethylamide as base. Wittig noted that the dehydrobenzene generated was transformed under these conditions into phenyllithium in a process in which lithium diethylamide served as a hydride source (Scheme 2),^[31] much akin to the Meerwein–Verley–Ponndorf reduction.



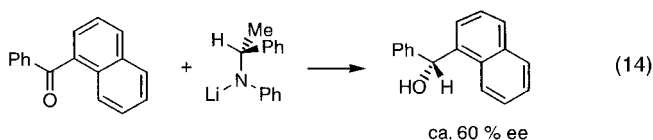
Scheme 2. Lithium diethylamide as a hydride donor.

As a corollary lithium diethylamide was also dehydrogenated by benzophenone to a Schiff base which underwent deprotonation to furnish an azaenolate. This very experiment provided the first access route to azaenolates, which are now standard reagents in organic synthesis. Wittig himself demonstrated the potential of azaenolates to effect directed aldol additions [Eq. (13)].^[32]



However, let us rather focus on the first step of the above reaction sequence of Equation (13) the ability of lithium diethylamide to serve as a hydride donor. Wittig demonstrated the possibility to reduce non-enolizable ketones by lithium diethylamide (see Scheme 2). Thus, it should be

possible to reduce prochiral ketones by application of a chiral “lithium diethylamide”. This can indeed be accomplished as Wittig showed in 1969 [Eq. (14)].^[33]

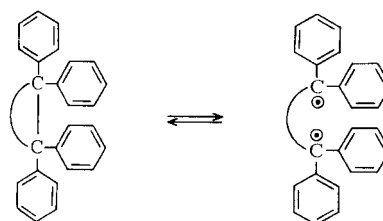


Wittig reached an asymmetric induction of 60 % *ee*, a value, which was surely a highlight at the end of the sixties. With more elaborate chiral derivatives of lithium diethylamide, enantioselectivities of >95 % *ee* were recorded in 1999.^[34] Wittig was therefore one of the forerunners in the development of chiral reducing agents for prochiral ketones.

When Wittig received the Nobel price in 1979, he was at an age which permitted only a retrospective. In his Nobel lecture “From diyls to ylides to my idyll”, he reviewed the leading themes of his oeuvre (Figure 3).^[35] The chemistry of free radicals marked the outset. He tried to generate kinetically persistent diradicals = diyls; he modeled his target compounds on the persistent triphenylmethyl radical of M. Gomberg.^[36]

Von Diylen über Ylide zu meinem Idyll (Nobel-Vortrag)^[*]

Von Georg Wittig^[*]

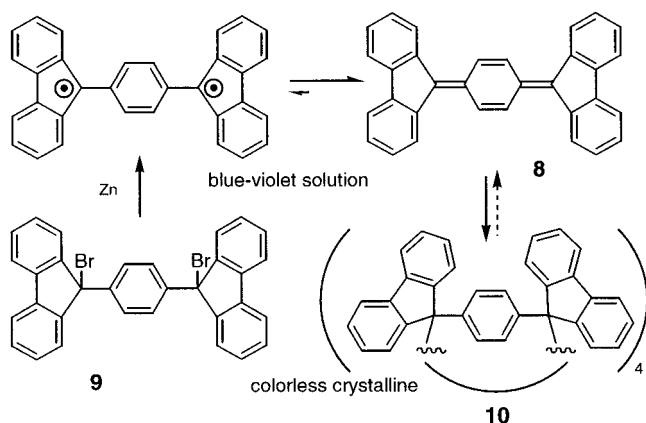


... Das Fazit der Untersuchungen über Radikalbildung und Ringspannung scheint demnach zu sein, daß der Ringschluß eher zu einer Stabilisierung als zu einer Lockerung der Ethan-Bindung beiträgt.

Figure 3. Reproduction of Wittig's retrospective on the chemistry of diyls (Nobel Lecture), *Angew. Chem.* **1980**, 92, 671 (English translation given in ref. [42]).

Wittig hoped to arrive at persistent diradicals by stabilization of the radical centers by π delocalization and by destabilization of the dimerization products by ring strain. Out of this context the experiment shown in Scheme 3 was performed.

The reduction of the dibromo compound **9** furnished a $C_{32}H_{20}$ hydrocarbon, a stable diradical? Careful determination of the molecular weight indicated the hydrocarbon **10** to be a “tetramer” $C_{128}H_{80}$,^[37] its constitution was revealed years



Scheme 3. Tetramerization of a stabilized diyl to the hydrocarbon ($C_{32}H_{40}$)₄.

later by X-ray crystal structure analysis.^[38] This compound held an additional fascination for Wittig, it was piezochromic and thermochromic. We should remember that Wittig is a representative of a generation of chemists, for whom the elucidation of the relationship between color and constitution was a life task. Every graduate student in Wittig's group knew how much Wittig insisted on finding explanations for each color phenomenon observed. As we know today, the color generated on heating **10** is caused by the appearance of the desired diradical in conjunction with the dissociation of the "tetramer" into the monomer **8**.

These studies rested unnoticed for decades. Today, they have become important in quite a different context: on tetramerization of the diradical **8**, four readily accessible building blocks are joined in a single operation to give a spherical molecular object. Thus, in 1999 a 32-armed dendrimer with a compact core was assembled in one stroke based on Wittig's studies.^[39]

The many examples provided in this essay show that Wittig's accomplishments become and remain important to chemists in changing contexts far beyond his hundredth birthday. The next generation of chemists has only to realize that Wittig's oeuvre is still a gold mine of facts and concepts to be exploited.

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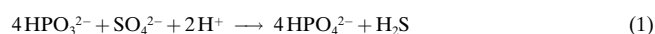
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- [41] Title: "On the Exchange of Aromatic-Bound Hydrogen for Lithium by Phenyllithium". The following reaction that runs contrary to all chemical intuition has been observed: that bromine and alkali metal atoms exchange between molecules rather than unite was not been observed before; however, the result is fully secured, the reaction has been tested repeatedly and occurs rapidly and without the formation of any significant by-products.
- [42] ...The conclusion of the investigations of radical formation and ring strain seems to be that the ring closure tends to cause a stabilization, rather than a weakening of the ethane bond.

Inorganic Chemistry in Marine Sediments

Wolfgang Buckel*

Several anaerobic microorganisms exploit inorganic energy sources and are collectively termed lithotrophs. The best known organisms of this type are acetogenic bacteria and methanogenic archaea, which are able to reduce CO_2 with molecular hydrogen to acetate or methane, respectively.^[1] Instead of CO_2 , marine organisms usually use sulfate (S^{VI}) as an electron acceptor, which is reduced by eight electrons to sulfide ($\text{S}^{-\text{II}}$). These sulfate reducers are able to grow at partial hydrogen pressures lower than that required by methanogens and acetogens. In sea water with 20 mM sulfate, the sulfate reducers are superior to the methanogens, which predominate in sulfate-deficient freshwater swamps and sediments. Sulfate reducers are metabolically much more versatile than methanogens. Besides hydrogen they are able to oxidize various organic acids such as lactate, fatty acids, dicarboxylic acids, and benzoate either to acetate or completely to CO_2 .^[2]

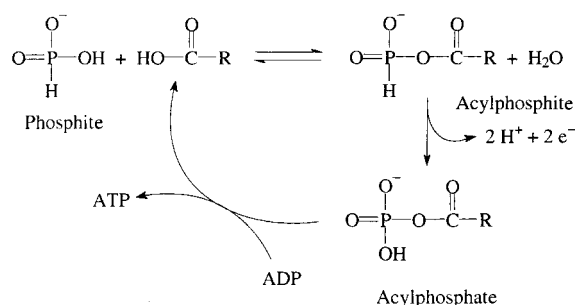
Recently, phosphite, a new inorganic electron donor was introduced into microbiology. Bernhard Schink, Universität Konstanz, Germany, and Michael Friedrich, Max-Planck-Institut für terrestrische Mikrobiologie in Marburg, Germany, isolated sulfate-reducing bacteria from sediments of the Canale Grande in Venice that are capable of oxidizing phosphite (P^{III}) to phosphate (P^{V}) [Eq. (1)].^[3] The strictly



anaerobic organisms (strains FiPS3 and FiPS5), which perform this purely inorganic fermentation or sulfate respiration, grow with a doubling time of three days and require no organic compounds for the synthesis of cellular material. They are able to assimilate CO_2 and are therefore called lithoautotrophs. According to the sequence of their 16S ribosomal RNA, these organisms are classified as members of the δ -group of the Gram-negative proteobacteria; most sulfate reducers belong to this group. Only a few sulfate reducers are found among the archaea and the Gram-positive bacteria.

The smooth microbial oxidation of phosphite by the unusual oxidant sulfate is surprising because the nonenzymatic oxidation of phosphite to phosphate with various agents

only occurs slowly and exhibits complex kinetics.^[4] The considerably high free energy of phosphite oxidation of $-364 \text{ kJ per mol sulfate}$ is sufficient to yield 5 mol ATP from ADP and inorganic phosphate. Under the irreversible conditions of the living cell about -70 kJ mol^{-1} of metabolic energy are generally required for the synthesis of 1 mol ATP.^[5] Whereas sulfate reduction itself leads to a maximum of 1 mol ATP, it is doubtful, however, whether the extremely low redox potential of the $\text{HPO}_4^{2-}/\text{HPO}_3^{2-}$ pair ($E'_0 = -690 \text{ mV}$) can be used for the formation of electrochemical proton gradients ($\Delta\mu(\text{H}^+)$) to generate additional ATP through the standard mechanisms. The oxidative formation of ATP seduces me to propose a novel type of stepwise substrate phosphorylation. Reaction of phosphite with a carboxylate of an enzyme could yield an acylphosphite, consecutive oxidation of which might afford an acylphosphate, whose energy-rich phosphate residue ($\Delta G_{\text{hydrolysis}}^{\ominus'} \approx -50 \text{ kJ mol}^{-1}$) is readily transferred to ADP thus generating ATP (Scheme 1).^{[5][**]} The thermodynamically unfavorable formation of acylphosphite can be “pulled



Scheme 1. Novel stepwise substrate phosphorylation by oxidation of acylphosphite to acylphosphate.

over” by the strongly exergonic oxidation with sulfate ($\Delta E'_0 = 470 \text{ mV}$ or $\Delta G^{\ominus'} = -91 \text{ kJ per mol phosphite}$). In glycolysis (Embden–Meyerhof pathway) the energy-poor thiosemiacetal, formed by addition of glyceraldehyde-3-phosphate to a specific cysteine residue of the enzyme glyceraldehyde-3-phosphate dehydrogenase, is oxidized to an energy-rich thiol ester in an analogous fashion. Phosphorolysis leads to 3-phosphoglyceroyl-1-phosphate, whose energy rich 1-phos-

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[**] In biochemistry an energy-rich compound is defined as: $\Delta G_{\text{hydrolysis}}^{\ominus'} \leq -30 \text{ kJ mol}^{-1}$.

phate is transferred to ADP in a reaction catalyzed by 3-phosphoglycerate kinase. Whether the oxidation of phosphite is linked to the formation of ATP [Eq. (1)], could be investigated by measuring the cell yield (cell mass per mol sulfate reduced). Under autotrophic (CO_2 -assimilating) growth conditions, 2–3 g dry cells are produced per mol of ATP. A preliminary estimation of the cell yield indeed suggests an involvement of phosphite oxidation in the synthesis of ATP (B. Schink, M. Friedrich, personal communication).

In nature, phosphorus almost exclusively occurs in the oxidation state +v, whereas all the oxidation states of nitrogen from +v to –III are known in biology. The discovery of the biological phosphite oxidation raises the question of whether there is a phosphorus cycle analogous to the nitrogen cycle. One can find almost nothing in the literature on the reduction of phosphate to phosphane (PH_3), which has been detected in trace amounts in anoxic sediments and even in human faeces.^[6] St. Elmo's fire is caused by self-igniting diphosphane, though the origin of this phosphane remains enigmatic. The lower oxidation states of phosphorus formally occur in biological molecules with C–P and C–P–C bonds, which are synthesized from phosphoenolpyruvate. Phosphinotricin [2-amino-4-(hydroxymethylphosphinoyl)butyric acid], a herbicide that inhibits glutamine synthetase, contains a phosphorus atom, which is directly connected to two carbon atoms. Hydrolysis of phosphinotricin could yield phosphinic acid (phosphinate, +I), which at 140°C under acidic conditions disproportionates to phosphonic acid (phosphite, +III) and phosphane (–III).^[7] An organism containing enzymes, which catalyse this disproportionation at lower temperatures and at neutral pH, is certainly present in nature. If one put these reactions together, a biological phosphorus cycle is formed: Phosphoenolpyruvate (+v) → phosphinotricin (+I) → phosphinate (+I) → phosphane (–III) + phosphite (+III) → phosphate (+v). The phosphane is also oxidized by air to phosphate.

At the time of the origin of life, about 3.8 billion years ago, phosphites could have been more important than today. Phosphites could have originated from volcanoes or may have been introduced to earth by meteorites. At this time anaerobic inorganic fermenters, such as the phosphite-oxidizing sulfate reducers, could have formed the predominating class of organisms. Perhaps in an iron–sulfur world,^[8] the first energy-rich acylphosphates for ATP synthesis were generated by the oxidation of acylphosphites.

In October 2000, only four months after the publication of the paper describing phosphite oxidation, the sulfate reducers

again attracted attention. Antje Boetius et al.^[9] from the Max-Planck-Institut für marine Mikrobiologie, Bremen, Germany, and the GEOMAR Forschungszentrum für marine Geowissenschaften, Kiel, Germany, reported very large sulfate reduction rates where methane hydrate enters upper anoxic levels of the sea floor, for example in the Pacific Ocean at depths of 600–800 m near the Oregon coast. Analysis of the microbial population with DNA-probes showed that methanogenic archaea were surrounded by sulfate reducers of the δ -subgroup of proteobacteria. Although biochemical data are lacking, there is evidence that the methanogens catalyze the oxidation of methane to H_2 and CO_2 or acetate by reversion of their “normal” methane-forming pathway. The thermodynamically very unfavorable anaerobic methane oxidation is only made possible by the presence of sulfate reducers, which keep the partial pressure of H_2 and, if applicable, the acetate concentration at extremely low values. Under standard conditions the oxidation of methane by sulfate yields only small amounts of free energy ($\Delta G^\circ = -30 \text{ kJ mol}^{-1}$, [Eq. (2)]), from which two organisms have to thrive. In



reality the free energy ΔG certainly is higher, because dissolved methane hydrate leads to locally high methane concentrations, and the H_2S generated will be rapidly consumed by sulfate-oxidizing bacteria sitting on the oxic top of the sea floor. The importance of the work of Boetius et al. lies in that it provides the first concrete indications of the organisms, which participate in anaerobic methane oxidation.

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A Renaissance in Noble Gas Chemistry

Karl O. Christe*

In spite of the predictions of stable noble gas compounds since at least 1902, unsuccessful attempts at their synthesis gave rise to the widely held opinion that noble gases are not only noble but also inert.^[1] Thus, dogma-type statements to this effect could be found in practically every chemistry textbook and for a long time discouraged experimentalists from working in this area. It was not until 1962 that this dogma was shattered when Bartlett in Canada^[2] published the first stable noble gas compound XePtF₆. This discovery triggered a worldwide frenzy in this area, and within a short time span many new xenon, radon, and krypton compounds were prepared and characterized. About 30 years and many publications later, new results in this area had slowed down to a trickle, and in the minds of most chemists the chapter on noble gas chemistry had been completed. A recent burst of startling discoveries, however, shows that noble gas chemistry is still full of surprises and may signal the beginning of a renaissance in this field.

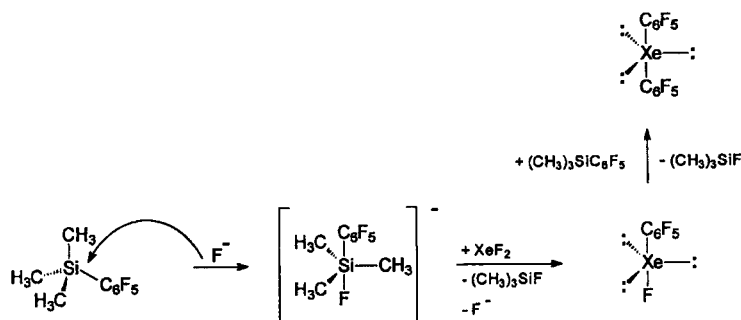
The recent discoveries fall into four categories, and selected examples are given in the following paragraphs for recently published or ongoing research in these areas:

- 1) The formation of either new xenon(II)–heteroatom linkages or known xenon–heteroatom connectivities that involve higher oxidation states of xenon
- 2) The ability of XeF₂ to act as a ligand for numerous “naked” metal ions
- 3) The ability of xenon to act as a ligand
- 4) The observation of the first ground state argon compound containing covalent argon–heteroatom bonds

Formation of New Xe^{II}–Heteroatom Bonds

In the area of new Xe^{II}–heteroatom linkages the first examples of a C–Xe–C group have been prepared independently by two groups. Frohn's group at the University of Duisburg, Germany, synthesized first C₆F₅XeF from [C₆F₅Xe]⁺ salts and N(CH₃)₄F by metathesis and then converted it into C₆F₅XeC₆F₅ and C₆F₅XeCN by treating it with [Cd(C₆F₅)₂] and (CH₃)₃SiCN, respectively.^[3] In a different approach, Naumann's group at the University of Cologne, Germany, found that C₆F₅XeC₆F₅ and C₆F₅XeF are directly

accessible from XeF₂ and (CH₃)₃SiC₆F₅ (Scheme 1).^[4] Furthermore, Frohn and Schroer have recently obtained C₆F₅XeCl and [C₆F₅XeClXeC₆F₅]⁺ (see Figure 1), two



Scheme 1. Synthesis of C₆F₅XeC₆F₅ and C₆F₅XeF from ref. [4].

other interesting new compounds containing both Xe–C and Xe–Cl bonds.^[5] These compounds are remarkable because, analogous to XeF₂, they have semi-ionic 3-center-4-electron bonds^[6–8] that are only half as strong as the previously known, predominantly covalent, Xe–C and Xe–Cl bonds in the ions [XeC₆F₅]⁺^[9, 10] and [XeCl]⁺,^[5] respectively. Although the synthesis of CF₃XeCF₃ was already claimed in 1979,^[11] all attempts to verify this claim have so far failed.^[4]

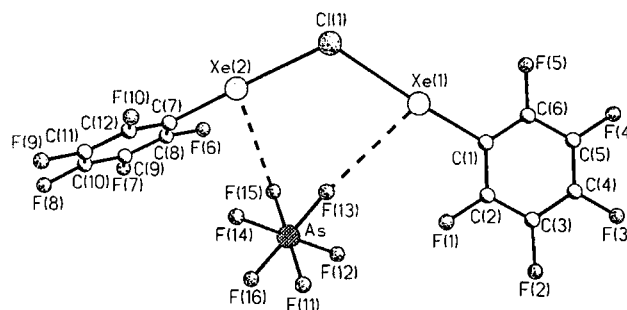


Figure 1. Molecular structure of [C₆F₅XeClXeC₆F₅][AsF₆] from ref. [5].

A second example of a novel linkage involving Xe^{II} is the Xe–O–Xe bridge in the [FXeOXeFXeF]⁺ ion discovered by Gerken and Schrobilgen at McMaster University^[12] in part of a joint study with our group of the XeF⁺/H₂O reaction system.^[13]

Another first are the compounds involving Xe^{IV}–C bonds. From the reaction of XeF₄ with C₆F₅BF₂ the groups of Frohn and Zemva have successfully prepared and characterized the [C₆F₅XeF₂]⁺ ion^[14] that was also observed by Schrobilgen's group in the XeF₆/C₆F₅BF₂ reaction system.^[15] Maggiora and Naumann have demonstrated a different approach toward the synthesis of a Xe^{IV}–C bond. By treating XeF₄ with the [CN][−] ion they prepared the interesting [XeF₄CN][−]

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ion.^[16] This anion is noteworthy because it is only the third example, after $[\text{XeF}_5]^-$ ^[17] and $[\text{IF}_5]^{2-}$,^[18] of a pentagonal planar AX_5 -type species. Examples for $\text{Xe}^{\text{VI}}-\text{C}$ bonds are still missing. This is not surprising, as the compatibility problems between a strongly oxidizing xenon fragment and a potential “fuel” ligand increase with increasing oxidation state and fluorine content of the xenon unit. Two promising approaches to overcome this problem involve the synthesis of anions rather than cations, because for a given oxidation state anions are weaker oxidizers than the corresponding cations, and the replacement of fluorine ligand pairs by doubly bonded oxygen atoms. The latter approach has been elegantly demonstrated by Schrobilgen’s group for the synthesis of the first examples of the amazing $\text{Xe}^{\text{VI}}-\text{N}$ and $\text{Xe}^{\text{VIII}}-\text{N}$ bonds in the form of $\text{O}_3\text{Xe}-\text{NCCH}_3$, $\text{F}_4\text{OXe}-\text{NCCH}_3$, and $\text{O}_4\text{Xe}-\text{NCCH}_3$, respectively.^[19]

In addition to the synthesis and characterization of the above compounds containing novel xenon connectivities, impressive progress was recently made in the characterization, by crystal structure determinations, of many previously known but poorly characterized noble gas compounds. Typical examples are $[\text{KrF}]^+$, $[\text{Kr}_2\text{F}_3]^+$, $[\text{XeNHTeF}_5]^+$, $[\text{O}_2\text{XeF}]^+$, $[\text{F}(\text{XeO}_2\text{F})_2]^+$, and $[\text{RCNXeF}]^+$ salts by Schrobilgen et al.^[20] and $[\text{Xe}_2]^+$ (Figure 2) by Seppelt’s group from the Freie Universität in Berlin^[21] that provided an opportunity to obtain an experimental bond length for the only known noble gas–noble gas bond. These studies provide much needed structural information, which helps us to understand the nature of these compounds.

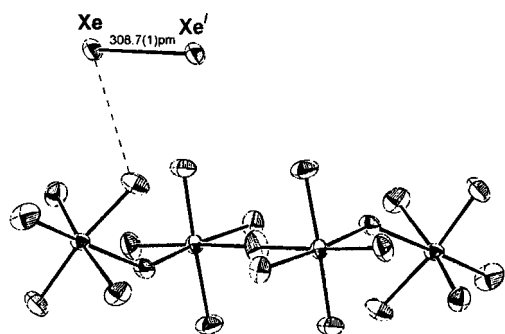
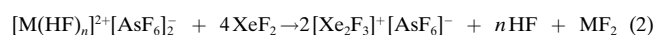
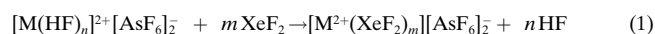


Figure 2. Molecular structure of $[\text{Xe}_2]^+[\text{Sb}_4\text{F}_{21}]^-$ from ref. [21].

XeF₂ as a Ligand for “Naked” Metal Ions

The second area of interest involves the recent exploitation by Zemva’s group at the Jozef Stefan Institute in Ljubljana of a previous discovery in Bartlett’s laboratory that XeF_2 can act as a fluorine-bridged ligand for Ag^{I} .^[22] This discovery has been extended to numerous “naked” metal ions.^[23] It is based on the reaction of metal $[\text{AsF}_6]^-$ salts in anhydrous HF solution with XeF_2 . If the basicity of XeF_2 is intermediate between those of HF and the parent metal fluoride, XeF_2 can displace HF from the solvation sphere around the metal cation [Eq. (1)] without displacing the metal cation itself under formation of $[\text{Xe}_2\text{F}_3]^+$ salts [Eq. (2)]. In this manner, $[\text{M}(\text{XeF}_2)_m][\text{AsF}_6]_n$ salts have been isolated in which M can



be Ag^{I} , Pb^{II} , Mg^{II} , Ca^{II} , Sr^{II} , Ba^{II} , or lanthanide(III); $m = 2-6$; for clarity the solvation of the other species by HF has been omitted from [Eqs. (1) and (2)]. A very interesting feature of these salts is the coordination around the metal ions. In the crystal structures determined so far, the metal ions coordinate to fluorine ligands from both XeF_2 and $[\text{AsF}_6]^-$ and exhibit high coordination numbers, typically 8 or 9, resulting in body-centered square antiprisms or trigonal prisms. Clearly, a systematic study of these types of adducts can provide a wealth of information on high coordination number chemistry.

Xenon as a Ligand

The third area of interest results from the discovery by Seppelt’s group that more than one xenon atom can attach itself to a metal center which in the case of gold leads to surprisingly stable $\text{Au}-\text{Xe}$ bonds. Although weakly covalent bonding of a single noble gas atom to a metal center, such as Cu or Ag in their monohalides or Mn, Fe, Cr, Mo, or W in their pentacarbonyls, had been known, the bonding in $[\text{AuXe}_4]^{2+}$ involves 4(!) Xe ligands attached by relatively strong bonds to a single Au^{II} center in a square planar arrangement with a $\text{Xe}-\text{Au}$ bond length of about 274 pm.^[24] This discovery provides not only the first example of multiple xenon ligands but also represents the first strong metal–xenon bond. In view of the generally weak donor abilities of the noble gases, it remains to be seen if this type of coordination can be extended to other suitable transition metals.

The First Ground State Argon Compound with Covalent Argon–Heteroatom Bonds

The last subject of this highlight involves the work of Räsänen and co-workers at the University of Helsinki in Finland. By using low-temperature matrix-isolation spectroscopy, they have demonstrated not only the existence of numerous novel xenon- or krypton-heteroatom bonds, such as $\text{Xe}-\text{H}$, $\text{Xe}-\text{I}$, $\text{Xe}-\text{Br}$, $\text{Xe}-\text{S}$, $\text{Kr}-\text{H}$, $\text{Kr}-\text{C}$, and $\text{Kr}-\text{Cl}$,^[25] but most significantly have provided experimental evidence for the first predominantly covalent, ground state argon-heteroatom bonds, $\text{Ar}-\text{H}$ and $\text{Ar}-\text{F}$ in the neutral $\text{H}-\text{Ar}-\text{F}$ molecule.^[26] Whereas weak van der Waals or excited state argon-heteroatom bonds had previously been known, vibrationally stable bonds in neutral ground state argon compounds were unknown. The HArF molecule appears to be stable only at very low temperatures in a matrix, and the energy barrier toward the 135 kcal mol⁻¹ exothermic intramolecular elimination of HF was calculated to be only 8 kcal mol⁻¹. As pointed out by Frenking in a recent commentary,^[27] the noble gas hydrogenfluoride molecules are only kinetically stable; their stability depends on the energy barriers toward decomposition which can be quite low, particularly in the condensed neat phase. Therefore, HArF is quite different from the many known Xe, Kr, and Rn compounds. Also, it should be kept in mind that there are no sharp boundaries between chemical bonds, charge transfer compounds,^[28] and van der Waals complexes. In HArF , for example, the $\text{H}-\text{Ar}$ bond has strong covalent contributions while the $\text{Ar}-\text{F}$ bond is highly ionic. It is a human trait to put

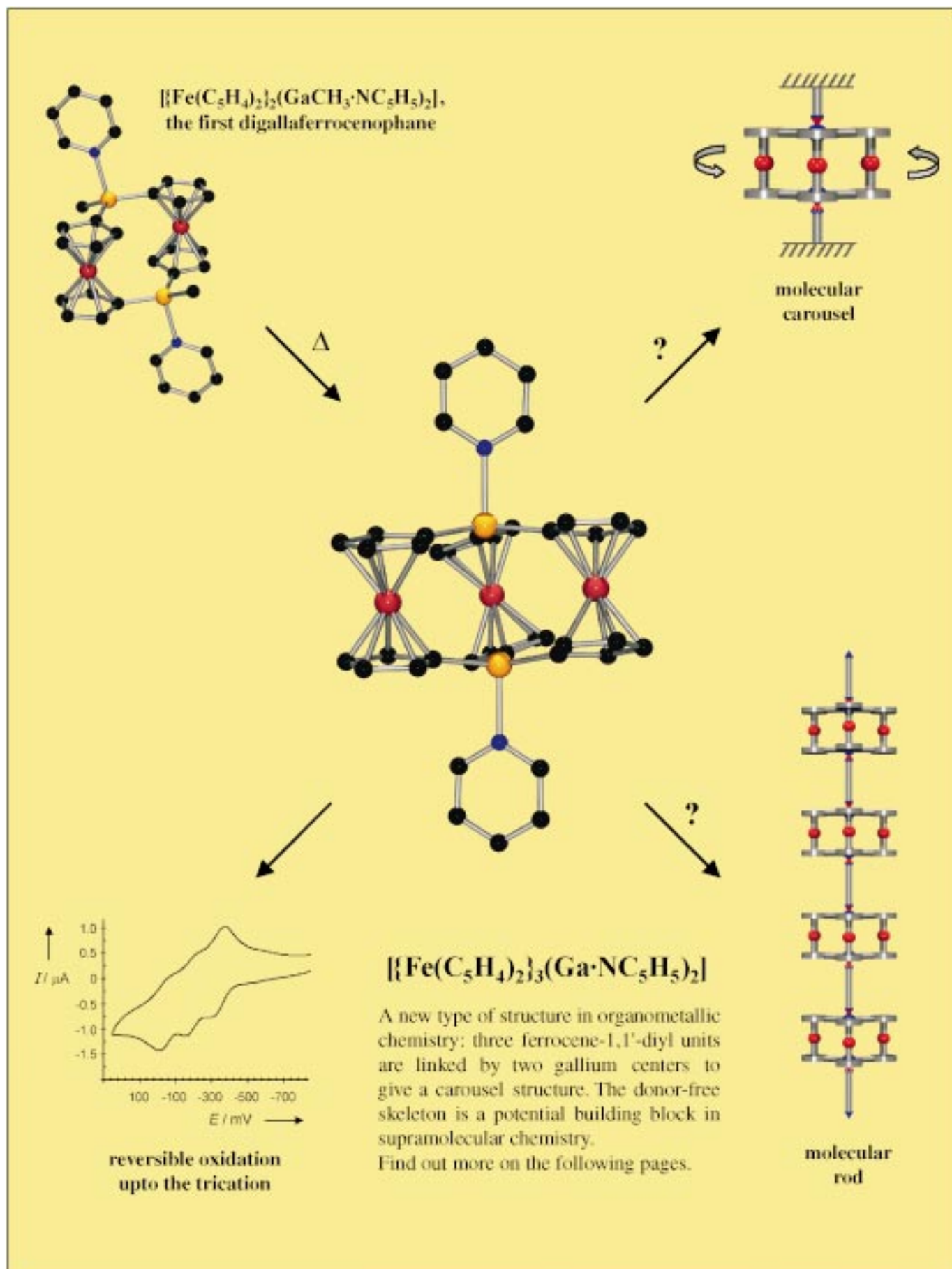
black-and-white labels on an universe consisting mainly of different shades of gray.

Does Räsänen's pioneering work suggest that we can expect to see in the near future the synthesis of marginally stable $[\text{ArH}]^+$, $[\text{XeH}]^+$ or $[\text{ArF}]^+$ salts as pure solids? Born–Haber cycle estimates show that solid $[\text{ArH}]^+[\text{F}]^-$ is about $130 \text{ kcal mol}^{-1}$ endothermic with respect to Ar and HF. Using the very strong Lewis acid SbF_5 to stabilize the ion as $[\text{SbF}_6]^-$, one can reduce the exothermicity of the decomposition reaction to about 70 kcal mol^{-1} . This value implies that a Lewis acid with an $[\text{F}]^-$ affinity that exceeds that of SbF_5 by at least 70 kcal mol^{-1} would be required to render this reaction thermally neutral. This is beyond the current capabilities of Lewis acid chemistry.^[29] The corresponding $[\text{XeH}]^+$ salt would be somewhat more favorable, but previous experiments from our laboratory to protonate Xe in HF/SbF_5 solution at -78°C were unsuccessful,^[30] indicating that a Lewis acid stronger than SbF_5 is also required in this case. However, the bulk synthesis of marginally stable $[\text{ArF}]^+[\text{XF}]^-$ salts looks more promising, as was also concluded in a previous study.^[31] Our Born–Haber cycle estimates indicate that $[\text{ArF}]^+[\text{SbF}_6]^-$ would be unstable by only 25 kcal mol^{-1} relative to Ar, F_2 , and SbF_5 , and one can envision Lewis acids of a high enough $[\text{F}]^-$ affinity to achieve the goal of a marginally stable $[\text{ArF}]^+$ salt. However, even with a Lewis acid stronger than SbF_5 the synthesis would still present a major challenge because the ArF_2 parent molecule is vibrationally unstable. Therefore, any synthesis of $[\text{ArF}]^+$ salts will require synthetic methods analogous to those previously used for the syntheses of cations derived from nonexistent parent molecules, such as $[\text{NF}_4]^+$,^[32, 33] which involve the use of elemental fluorine in combination with suitable activation energy sources.

This highlight shows that in spite of the relatively small number of laboratories involved in the ongoing efforts, significant breakthroughs have recently been achieved in noble gas chemistry, which heralds a renaissance in this field. In addition to the areas discussed above, one could envision the syntheses of compounds such as $[\text{XeF}_7]^+$, XeF_8 , $[\text{XeOF}_5]^+$, XeOF_6 , or KrF_4 . With today's computational capabilities, the possible existence of these targets molecules should be reexamined and, if warranted, experimentally pursued.

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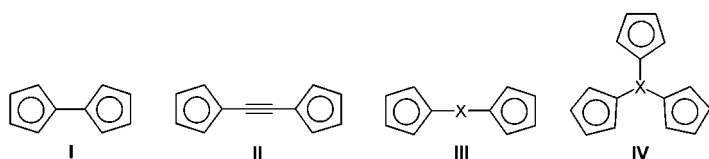


[[Fe(C₅H₄)₂]₃{Ga(C₅H₅N)}₂]: A Trinuclear Gallium-Bridged Ferrocenophane with a Carousel Structure**

Peter Jutzi,* Norman Lenze, Beate Neumann, and Hans-Georg Stammler

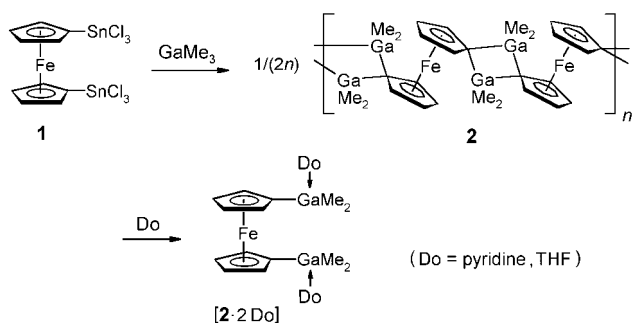
Dedicated to Professor Hansgeorg Schnöckel on the occasion of his 60th birthday

Multinuclear ferrocene systems are important model substances in the study of Fe–Fe interactions, such interactions can result in very different electronic and magnetic effects.^[1] Particularly interesting are those compounds in which the ferrocene units are fixed in a mutually coplanar geometry. This criterion is met ideally by the dinuclear [*m,m*]ferrocenophanes that are derived from the dicyclopentadienyl units of type I and II, and to a lesser extent by the compounds derived from type III.^[1, 2] Until now no trinuclear ferrocenophane



complexes based on the tricyclopentadienyl system IV were known.^[3] Herein we report this new type of linking for the first time and describe a complex in which the three ferrocene-1,1'-diyl units are held together by gallium centers.

The complex 1,1'-bis(dimethylgallyl)ferrocene (**2**), reported here for the first time, is prepared in good yield from 1,1'-bis(trichlorostannyl)ferrocene (**1**)^[5] with an excess of trimethylgallium (Scheme 1) and serves as the starting material. This orange compound, which is sparingly soluble in non-donating solvents and extremely air sensitive, is presumably a



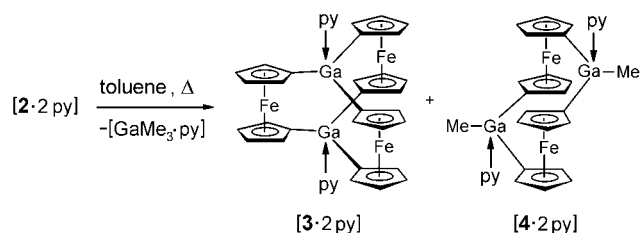
Scheme 1. Synthesis of the coordination polymer 1,1'-bis(dimethylgallyl)ferrocene **2** and the formation of the monomeric adduct in donor solvents.

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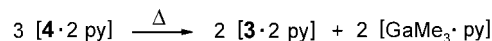
coordination polymer made up of [$\{\text{Fe}(\text{C}_5\text{H}_4)(\mu_2\text{-GaMe}_2)_2(\text{C}_5\text{H}_4)\}_n$] units with bridging GaMe_2 units which form four-membered Ga_2C_2 rings (for comparison: dimethylgallylferrocene has a dimeric structure with GaMe_2 bridges^[6]). The solubility of **2** in donor solvents (Do), for example pyridine and THF, results from the formation of monomeric adducts [**2**·2Do].

If a solution of **2**, in a mixture of pyridine (py) and, for example, toluene is heated for a short time to a temperature over 100 °C, then, on cooling, the title complex [**3**·2py] is formed in good yield as an orange microcrystalline solid (Scheme 2). This product can also include a relatively small amount of the [1.1]digallaferrocenophane [**4**·2py]^[7]. A further product, the pyridine adduct of trimethylgallium, can be identified in the NMR spectra of the reaction solution.



Scheme 2. Preparation of the ferrocenophanes [**3**·2py] and [**4**·2py].

Dissolving the product mixture in a high-boiling solvent (e.g. toluene or *p*-xylene) and subsequent cooling affords [**3**·2py] in a pure crystalline form. During this process some of the [**4**·2py] is converted into [**3**·2py]. This proposal is confirmed by the conversion of pure [**4**·2py]^[7] into [**3**·2py] in boiling toluene (Scheme 3). Consequently the prolonged heating of **2** in toluene/pyridine affords exclusively [**3**·2py].



Scheme 3. The formation of [**3**·2py] from [**4**·2py].

Clearly [**4**·2py] and [**3**·2py] must be formed by highly selective condensation reactions. In understanding the formation of [**3**·2py] it is important to know that the complex [**4**·2py], which in the solid state is found in the *anti*-conformation, is highly dynamic in solution where the *anti*- and *syn*-conformations are in equilibrium. This behavior is demonstrated by NMR spectroscopy which shows only one set of signals arising from the α -CH and one set from the β -CH groups of both ferrocene-1,1'-diyl units.^[8]

As a result of their poor solubility analytical data for the compounds [**3**·2py] and [**4**·2py] could only be obtained in [D₆]DMSO. This treatment leads to the complete exchange of the pyridine donors by DMSO donors, as confirmed by a ¹H NMR spectrum of a solid which precipitated from a solution of [**3**·2py] in [D₆]DMSO and which no longer displays any signals arising from pyridine. Similar behavior is expected for the compounds [**4**·2py] and [GaMe₃·py]. Compound [**3**·2Do] (Do = py or [D₆]DMSO) is fully characterized by NMR spectroscopy, mass spectrometry, crystal-

structure and elemental analysis, and electrochemical methods.

The crystal structure of $[3 \cdot 2\text{py}]^{[9]}$ shows that three ferrocene-1,1'-diyl units are linked together by two pyridine-stabilized gallium(III) centers to form a "carousel structure" $^{[2]}$ (Figure 1; the disordered toluene molecules found in the

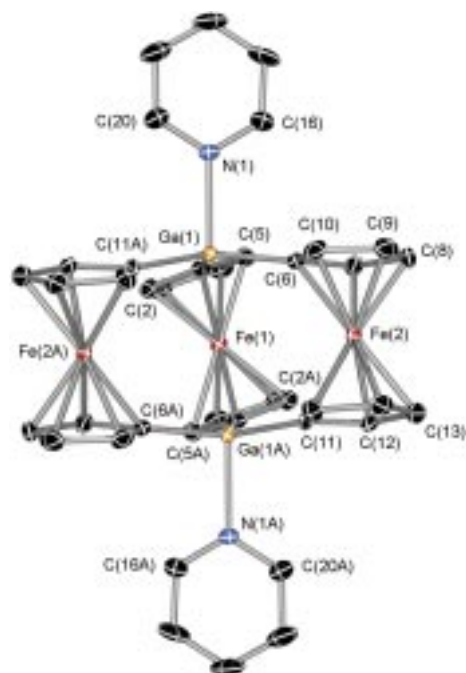


Figure 1. The molecular structure of $[3 \cdot 2\text{py}]$. Selected distances [Å] and angles [°]: Ga(1)-C(1) 1.968(19), Ga(1)-C(6) 1.965(17), Ga(1)-C(11A) 1.973(17), Ga(1)-N(1) 2.143(14), Fe-C(Cp) 2.034–2.101, C(Cp)-C(Cp) 1.41–1.44, Ga...Ga 3.87, Fe(1)...Fe(2) 5.40, Fe(2)...Fe(2A) 5.58; C(1)-Ga(1)-C(6) 117.9(8), C(1)-Ga(1)-C(11A) 116.8(7), C(6)-Ga(1)-C(11A) 120.6(8), C(2)-C(1)-Ga(1) 128.3(14), C(5)-C(1)-Ga(1) 126.9(13), C(7)-C(6)-Ga(1) 127.1(14), C(10)-C(6)-Ga(1) 126.4(13), C(12A)-C(11A)-Ga(1) 124.8(14), C(15A)-C(11A)-Ga(1) 129.3(14), C(1)-Ga(1)-N(1) 98.1(7), C(6)-Ga(1)-N(1) 95.0(6), C(11A)-Ga(1)-N(1) 98.8(7).

crystal lattice are not shown). The Ga–Ga separation is 3.87 Å which is roughly double the van der Waals radius of gallium (1.87 Å $^{[10]}$); the average nonbonding distance between the Fe centers is 5.46 Å. The gallium center has a slightly distorted trigonal pyramidal coordination geometry (C–Ga–C angle sum: 355°; C–Ga–N angles: 95.0(6), 98.1(7), 98.8(7)°; Ga–C bond (average): 1.97 Å; Ga–N bond: 2.143(14) Å). $^{[11]}$ The pyramidalization of the gallium centers twists the complex and results in a deviation of the Cp(centroid)–C–Ga units from linearity and a distortion of the ferrocene-1,1'-diyl units. The six cyclopentadienyl ligands of the three ferrocene-1,1'-diyl units deviate from a mutually coplanar arrangement in that they are tilted in the same direction relative to the Ga–Ga axis. This results in the complex having a slightly twisted and thus chiral structure; the torsion angles α_T , taken from the Ga–Ga axis and the individual Cp(centroid)–Cp(centroid) axes of the ferrocene-1,1'-diyl units can be used as a measure of the amount of twist ($\alpha_T = 11.3^\circ$ (average)). $^{[12]}$ The C(Cp)–Ga bonds, with reference

to the Cp ring plane, are bent away from the iron centers by 4.4° (average). The deviation of the Cp ligands within the ferrocene-1,1'-diyl units from a mutually parallel arrangement is slight (Cp–Cp angle: 3.7° (average)), the average distance between the centers of the Cp rings is 3.3 Å which corresponds to that in ferrocene. A result of the chiral structure is that in the layerlike structure of the crystal lattice two enantiomeric forms, **A** and **B**, of complex $[3 \cdot 2\text{py}]$ are found. Each layer is made up of only one enantiomer and the layers alternate through the lattice in an AB pattern (Figure 2). The poor solubility of the complex probably arises from π – π interactions between the pair wise, mutually parallel arranged pyridine groups on each pair of molecules (py–py separation: 3.45 Å).

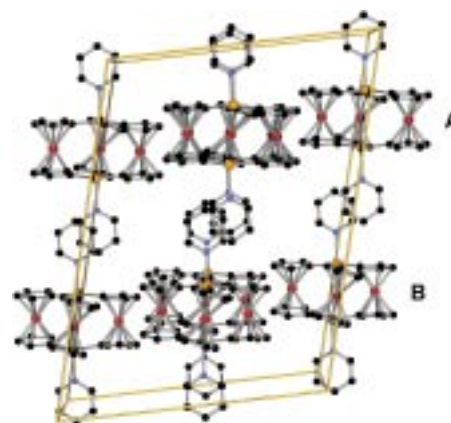


Figure 2. Layered packing of the enantiomers **A** and **B** of $[3 \cdot 2\text{py}]$ in the crystal lattice (the disordered toluene molecules between the layers are not shown).

Both the ^1H and ^{13}C NMR spectra of $[3 \cdot 2\text{Do}]$ display only one set of signals for the α -CH and one set for the β -CH units of the three ferrocene-1,1'-diyl fragments. This result indicates an averaged, highly symmetrical structure in solution. One can assume that a rapid interconversion of the enantiomers **A** and **B** into their respective mirror-image structures, as well as rapid motion of the donor molecules and the fc_3Ga_2 fragment (fc = ferrocene-1,1'-diyl) around the Ga–Ga axis occurs.

Figure 3 shows the cyclic and the square-wave voltammogram $^{[13]}$ of $[3 \cdot 2\text{py}]$ dissolved in DMSO. The voltammograms show three reversible oxidation steps in which the waves corresponding to the oxidation and reduction process are

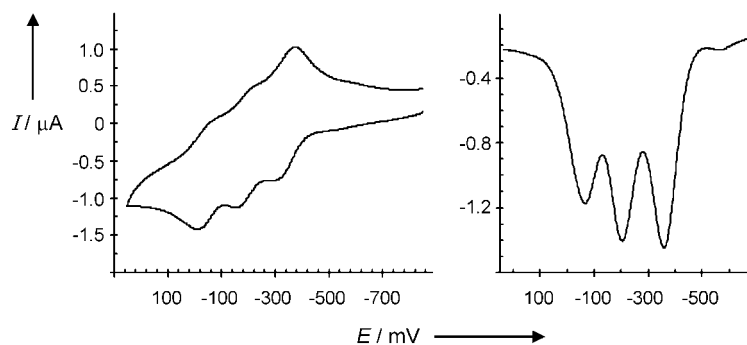


Figure 3. Cyclic and square-wave voltammograms of $[3 \cdot 2\text{py}]$ dissolved in DMSO (0.1M NBu_4PF_6). $^{[13]}$

separated by 70 mV in each case. The corresponding half-wave potentials are $E_1 = -360$, $E_2 = -205$, and $E_3 = -65$ mV (vs. the ferrocene/ferrocenium ion couple); thus the complex $[3 \cdot 2\text{DMSO}]$ is more easily oxidized than ferrocene. The observed differences in the half-wave potentials of $\Delta E_{2-1} = 155$ mV ($3^+/3^{2+}$) and $\Delta E_{3-2} = 140$ mV ($3^{2+}/3^{3+}$) indicate only a partial delocalization of the unpaired electron(s) in the cationic species (presumably, class II in the Robin and Day classification^[14]). To obtain a more detailed description of the electronic properties of $[3 \cdot 2\text{Do}]$ further physical measurements are required.

The donor-stabilized ferrocenophanes of the form $[3 \cdot 2\text{Do}]$ are the first compounds of a new structural class, they suggest many new avenues of further study. Spectroelectrochemical and magnetic measurements of the cationic species should provide detailed information on the Fe–Fe interactions.^[1] The donor-free species **3** has potential as a building block in supramolecular chemistry; through the incorporation of different polyfunctional donor groups the design of oligomeric and polymeric coordination compounds should be possible.^[15, 16] The reaction of $[3 \cdot 2\text{Do}]$ with electron acceptors should enable the preparation of new charge-transfer complexes.^[17] If it were possible to fix the donor molecules then the rotation of the fc_3Ga_2 fragment about the donor–Ga–Ga–donor axis, as in a molecular-level carousel, could be expected; in which case it would be worth investigating whether the rotation of such a molecule or one with a derivatized fc_3Ga_2 fragment could be controlled in a planned way.^[18]

Experimental Section

2: Trimethylgallium ((pyrophoric!)) 4.17 g, 36.3 mmol) was added to a suspension of 1,1'-bis(trichlorostannyl)ferrocene **1** (2.30 g, 3.63 mmol) in toluene (5 mL) in a 25 mL Schlenk flask. The reaction mixture was heated to 60 °C in the tightly closed flask until everything had dissolved. On cooling to room temperature **2** formed as an orange, microcrystalline solid. The supernatant solution was decanted and the solid residue was washed with hexane (or toluene) and dried in vacuum, yield 1.20 g (3.13 mmol; 86%). ¹H NMR (500.1 MHz, $[\text{D}_5]\text{pyridine}$): $\delta = 0.19$ (12 H; CH_3), 4.38 (4 H; ring C2/5-H or C3/4-H), 4.58 (4 H; ring C2/5-H or C3/4-H); ¹H NMR (500.1 MHz, $[\text{D}_8]\text{THF}$): $\delta = -0.27$ (12 H; CH_3), 3.86 (4 H; ring C2/5-H or C3/4-H), 4.08 (4 H; ring C2/5-H or C3/4-H); ¹³C NMR (125.8 MHz, $[\text{D}_5]\text{pyridine}$): $\delta = -6.6$ (CH_3), 70.8 (ring C2/5 or C3/4), 75.3 (ring C2/5 or C3/4), 70.8 (C1–GaMe₂). Compound **2** is very air sensitive.

$[3 \cdot 2\text{py}]$: **2** (0.30 g, 0.78 mmol) was dissolved in pyridine (0.5 mL) and together with toluene (5 mL) heated to boiling point for 5 min in a closed Schlenk flask. After cooling and decantation of the supernatant reaction solution the residue was washed with hexane to give an orange, microcrystalline solid containing $[3 \cdot 2\text{py}]$ and a small amount of $[4 \cdot 2\text{py}]$ ^[7]. The product mixture was dissolved in hot toluene and then cooled affording $[3 \cdot 2\text{py}]$ as orange, toluene-containing crystals; removal of the toluene under vacuum left $[3 \cdot 2\text{py}]$ as a powder which was characterized by NMR spectroscopy and elemental analysis, yield 76 mg (0.11 mmol; 42%). ¹H NMR (500.1 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 4.20$ (12 H; ring C2/5-H or C3/4-H), 4.30 (12 H; ring C2/5-H or C3/4-H), 7.38/7.78/8.55 (free pyridine); ¹³C NMR (125.8 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 69.2$ (ring C2/5 or C3/4), 74.9 (ring C2/5 or C3/4), 123.9/125.3/150.3 (free pyridine); EI-MS: m/z (%): 692 (29) [$M^+ - 2\text{py}$]; elemental analysis (%) calcd for $\text{C}_{40}\text{H}_{34}\text{Fe}_3\text{Ga}_2\text{N}_2$ (849.71): C 56.54, H 4.03, N 3.30; found: C 56.17, H 3.93, N 3.27. $[\text{GaMe}_3 \cdot \text{py}]$ can be identified in the reaction solution by NMR spectroscopy: ¹H NMR (500.1 MHz, CDCl_3): $\delta = -0.33$ (CH_3).

$[3 \cdot 2\text{py}]$ from $[4 \cdot 2\text{py}]$: Several milligrams of $[4 \cdot 2\text{py}]$ ^[7] were dissolved in toluene (1 mL) in a tightly closed NMR tube and heated to boiling point for

10 min. On cooling the probe orange crystals formed which, after removal of the solvent, were identified as $[3 \cdot 2\text{py}]$ by NMR spectroscopy.

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- [12] An indication that the pyramidalization of the gallium center is the cause of the twisting and other distortions of the Fc_3Ga_2 fragment is that in the complex $[\mathbf{3} \cdot 2\text{Et}_2\text{O}]$, which we could prepare from **2** and Et_2O , the gallium center is less pyramidalized (C–Ga–C angle sum 357°) and less twisted ($\alpha_T = 4.7^\circ$ (average)). In addition the Ga–Ga separation is shorter (3.73 Å), so it can be assumed that in the donor-free compound **3** there is an even shorter Ga–Ga separation. Because of the poor *R* value of the structure determination the values given should be treated with caution. Whether the $\text{Ga}(\text{C}_5\text{H}_4)_3$ units of this compound are planar and mutually parallel with a Ga–Ga separation of under 3.4 Å (the Cp–Cp separation in ferrocene) should be shown by theoretical calculations (W. W. Schoeller, unpublished results).
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High-Density Labeling of DNA: Preparation and Characterization of the Target Material for Single-Molecule Sequencing**

Susanne Brakmann* and Sylvia Löbermann

Single-molecule detection has emerged as the ultimate analytical tool and requires concentrations as low as femto- to zeptomolar (10^{-15} to 10^{-21}). In extreme cases the sensitivity of single-molecule techniques can even reach the yoctomole limit (10^{-24}),^[1–5] and, thereby, offer insights into the chemical behavior and fate of individual molecules, as well as reflect

subtle changes at the molecular level that might influence chemical reactivities.^[6–10] With classic methods these effects have as yet been hidden by ensemble averaging.

Further impetus for research into this field came when it was suggested that sequencing of DNA and RNA might be accelerated by using single-molecule detection and analysis.^[3, 11, 12] The sequencing attempts are based on the fact that single fluorescent molecules can be identified within milliseconds,^[13] and they combine sequential enzymatic hydrolysis of individual DNA molecules with subsequent identification of released monomers by their fluorescence characteristics, either wavelengths, fluorescence lifetimes, or both.^[14, 15] As natural nucleotides exhibit only marginal fluorescence at room temperature, the idea requires complete and faithful labeling of single DNA or RNA molecules with fluorescent dyes, whereby each dye distinctly codes one of the four bases (A, G, C, or T/U). Modification of DNA with fluorophores may be achieved either by enzymatic, or by postsynthetic labeling. As the chemical attachment of even a single dye molecule to oligomeric DNA does not yield 100 % modified product, synthetic introduction of dyes would result in unreliable sequencing templates. Instead, fluorophore-labeled DNA may be synthesized enzymatically using polymerase-mediated incorporation of fluorescently tagged nucleotide analogues. Nucleic acid polymerases from a variety of organisms may be used for the synthesis of complementary, fluorescently labeled DNA through nick translation, primer extension, reverse transcription, or a polymerase chain reaction (PCR). However, preliminary experiments performed by us suggested that most natural and commercially available DNA polymerases failed to accept substrates that are heavily modified with fluorescent dyes (unpublished results). Experiments by other groups,^[16, 17] as well as suggestions by suppliers of dye-labeled nucleotides,^[18] confirmed that a maximum 28 % of possible substitution sites could be labeled by PCR, whereas only about 18 % exchange were achieved by nick translation.^[19]

Using an assay for screening polymerase activity with dye-labeled nucleotides, which was based on fluorescence correlation spectroscopy (FCS),^[3] we then observed that the wild-type, as well as the exonuclease-deficient Klenow fragment, of *Escherichia coli* DNA polymerase I is capable of incorporating 55 subsequent, fluorophore-labeled deoxyribonucleotides by extension of a synthetic primer-template (100 % incorporation).^[20] Although this finding was surprising, it did not contradict the previous results cited above because labeling was achieved by replication in a single round, that is, in the absence of amplification, with an artificial poly(dA) template, and the polymeric product could be detected by the highly sensitive FCS technique. FCS also provided a closer view of the enzymatic fluorophore incorporation because fluorescence intensity and diffusion time of individual molecular species were determined in parallel: Under optimal conditions, that is, in the absence of quenching phenomena and with molecular species of comparable linear shape, FCS yields data on the amount of fluorophores incorporated into a specific molecule, as well as information on the relative length of the polymeric product, which can be clearly distinguished from the length of the respective primer-template.

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In pursuance of the labeling of long fragments for single-molecule sequencing, we applied the primer extension by Klenow polymerase to a natural DNA fragment with a length of 2.7 kilo base pairs (kb), which originated from the bacteriophage T7 genome. We started our experiments by completely substituting the dTTP^[21] by its fluorescent analogue tetramethylrhodamine-4-dUTP (TMR-dUTP, Fluoro-Red; Amersham Pharmacia) and obtained a nonfluorescent reaction product with the expected electrophoretic mobility and an absorbance spectrum (in 10 mM tris(hydroxymethyl)-aminomethane-HCl (tris-HCl) buffer at pH 7.5) resembling that of natural DNA, except that its maximum was shifted from 260 nm to approximately 275 nm (Figure 1).

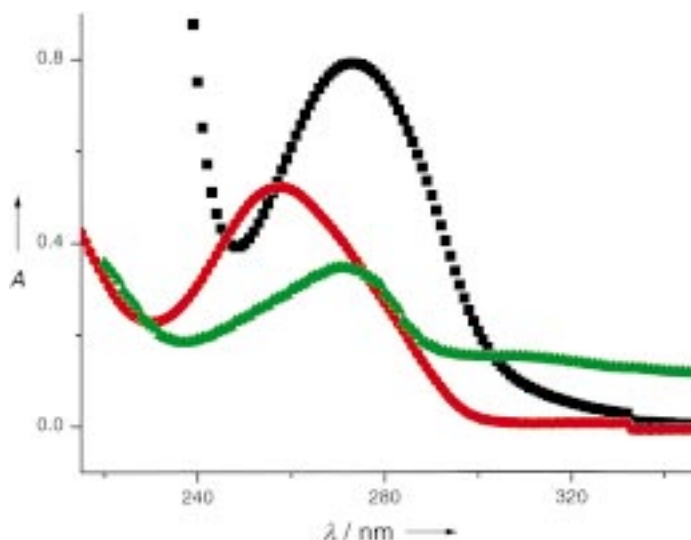


Figure 1. Comparison of the absorption spectra of natural and fluorescently labeled DNA. The spectra of nonlabeled DNA (red) and DNA labeled with TMR-dUTP (black) were determined from aqueous solutions (10 mM tris-HCl, pH 7.5); DNA labeled with TMR-dUTP and R110-dCTP (green) was dissolved in aqueous solutions of 10 mM tris-HCl buffer (pH 7.5) containing 50% dioxane.

Complete incorporation of a second fluorescence label was achieved by replacing dCTP with its analogue rhodamine-110-dCTP (R110-dCTP, Applied Biosystems), in addition to the substitution of dTTP with TMR-dUTP. Again, the primer-extension reaction of the same template yielded a product with the expected electrophoretic mobility that did not fluoresce. Optical absorbance measurements in aqueous solution (10 mM tris-HCl at pH 7.5) showed strong light scattering due to aggregation of the product molecules. However, the product was fully soluble in H₂O/dioxane (50/50) and gave an absorbance spectrum resembling that of the TMR-labeled DNA derivative with a maximum at about 275 nm (Figure 1).

DNA labeled either with TMR-dUTP or both TMR-dUTP and R110-dCTP exhibited an increasing tendency to form aggregates upon solution in aqueous solvents. This was first observed by monitoring the absorbance spectra and also became apparent with experiments to visualize the product of dye incorporation: Atomic force microscopy revealed very large aggregates (approximately 400 nm diameter and 50 nm height) of labeled DNA on the polar surface of the mica that

prevented the optical differentiation of single-molecule shapes (T. Schäffer, Göttingen, personal communication). On the other hand, transmission electron microscopy (TEM) on the nonpolar graphite surface allowed the visualization of TMR-dUTP/R110-dCTP-labeled DNA (Figure 2; in cooperation with D. Czerny, Göttingen). The reaction product

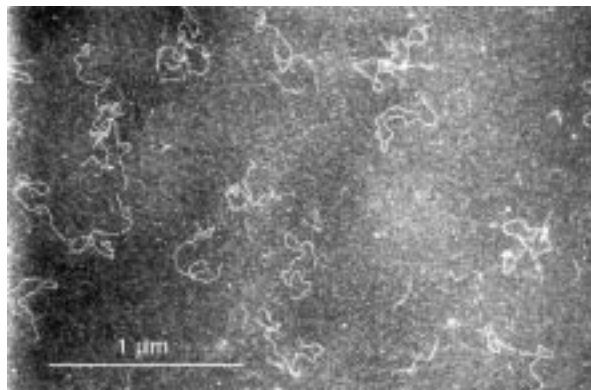


Figure 2. Transmission electron micrograph of dsDNA labeled with TMR-dUTP and R110-dCTP (graphite surface; staining with uranyl acetate). The lengths of DNA structures were determined using analySIS software (Soft Imaging System GmbH, Münster).

formed an even distribution of individual molecules, which exhibited a shape similar to that of natural double-stranded DNA, and a length of approximately 1 μm, which was expected for the 2.7 kb fragment. Although information on structural details, such as the helix characteristics, of the dye-labeled product is limited using electron microscopy, it can be concluded that full-length dsDNA represented the main product ($\geq 90\%$) because almost no single-stranded DNA was observed.

Furthermore, fluorescently labeled DNA did not show the cooperative melting behavior that is observed with natural DNA (D. Pörschke, Göttingen, personal communication). However, 30 min heating of a solution of dry, double-labeled DNA in 100% DMSO at 50 °C converted about 90% into single-stranded DNA (observation after medium pressure liquid chromatography (MPLC) on sepharose). We applied this finding to double-labeled DNA which was generated using a biotinylated primer, and tested whether the modified strand served as a template for further polymerase reactions: Immobilization of the biotinylated, dye-labeled dsDNA, separation of the nonlabeled strand, and subsequent PCR amplification (using natural nucleotides and proof-reading *Pfu* DNA polymerase) revealed that the labeled strand served as a template for PCR. Subcloning of the PCR product, sequence determination (*Taq* DyeDeoxy Terminator method; Applied Biosystems), and interpretation of the sequence data (approximately 10000 base pairs sequenced) revealed no alteration of the original T7 sequence. Thus, the overall error rate of label incorporation using primer-extension by exonuclease-deficient Klenow polymerase did not exceed a maximum of 10^{-4} .

The complete fluorescent labeling of the pyrimidines of one strand of dsDNA with dyes of the rhodamine type seems to

induce a drastic conformational transition: Comparison of the circular dichroism spectra of the natural 2.7 kb fragment with either TMR-dUTP-modified, or TMR-dUTP- and R110-dCTP-modified DNA showed curves that represent curves that have the opposite sign to the spectrum exhibited by the natural DNA (Figure 3). This fact might indicate that the double helix, upon high-density incorporation of rhodamine dyes, undergoes a transition from the right-handed B form (natural DNA) to the left-handed Z form (labeled DNA). Inversion of the circular dichroism spectrum had originally been observed with the detection of Z-form DNA.^[22]

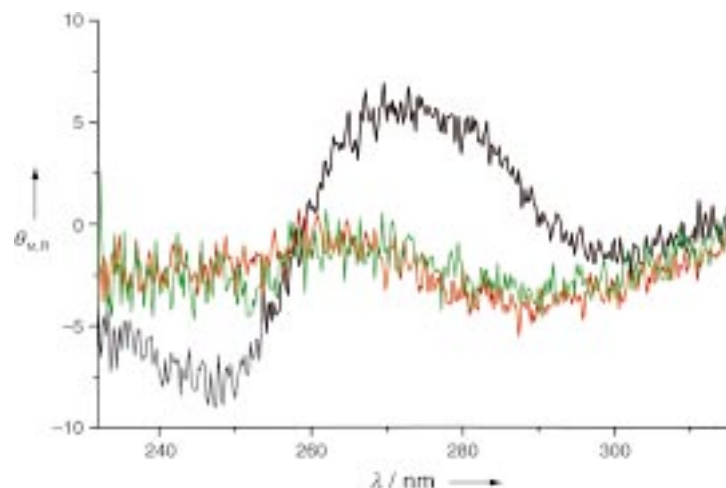


Figure 3. Comparison of the circular dichroism spectra of natural and fluorescently labeled DNA ($\theta_{M,R}$ is in $\text{deg cm}^2 \text{dmol}^{-1}$ and is the ellipticity per mole and residue). Black: nonlabeled DNA; red: DNA labeled with TMR-dUTP; green: DNA labeled with TMR-dUTP and R110-dCTP.

Although it has not yet been proven whether the sequence of single, completely labeled DNA molecules can be resolved using successive degradation by an exonuclease, preliminary results suggest that double-labeled DNA serves as a template, for example, for exonuclease III of *Escherichia coli* (unpublished results). Regarding single-molecule sequencing, it can be concluded that distinct fluorescent tagging at each base pair is sufficient if both complementary strands of dsDNA can be labeled crosswise and degraded with time-resolved detection (two-color concept):^[14] As in conventional, automated sequencing, both strands of a certain fragment could be copied into dye-labeled DNA using a set of two flanking primers and separate primer-extension reactions. This procedure does not require labeling of the second strand to start from the first labeled strand. Using both dye-labeled daughter strands in separate degradation experiments, the sequence of basepairs could, in principle, be determined provided that the exonucleolytic degradation is both highly processive and reproducible. In conclusion, the double-labeling of the A:T base pair with tetramethylrhodamine, and the tagging of G:C with rhodamine-110 might present a first solution for the complete labeling of DNA for single-molecule sequencing.

Experimental Section

A solution of dsDNA template (2.5 pmol; 2.7 kb; gene 1 fragment of bacteriophage T7 encoding T7 RNA polymerase^[23]) and primer 5'-GGCGTTAGTGATGGTGATGGTGATGCGCGAACGCGAAGTCCGACTCTAAG-3' (10 pmol) in 50 mM tris-HCl (80 μL , pH 7.5) was heated to 100 °C for 5 min and then cooled to 25 °C within 30 min (annealing). Primer extension and double-labeling was achieved by addition of dATP, dGTP, TMR-dUTP, and R110-dCTP (5 nmol each), as well as Klenow Exo⁻ polymerase (50 U, New England Biolabs) in a buffer (420 μL) containing 10 mM tris-HCl (pH 7.5), 5 mM MgCl_2 , 7.5 mM dithiothreitol, and 10% DMSO. After 1 h incubation at 37 °C the reaction was stopped with 0.5 M EDTA (20 μL), and the product was purified using agarose gel electrophoresis (1.2% agarose). Labeled DNA was recovered by electroelution and ethanol precipitation, and was routinely dissolved in aqueous solutions containing 10% DMSO.

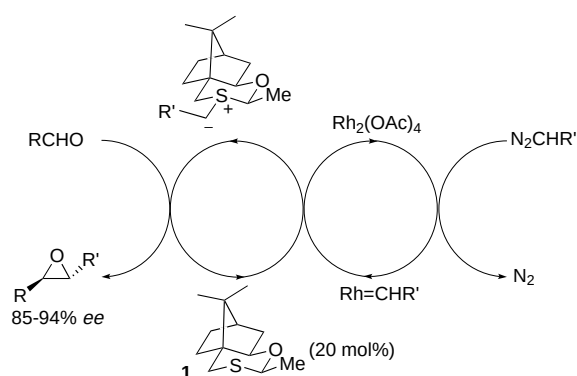
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Catalytic Asymmetric Synthesis of Epoxides from Aldehydes Using Sulfur Ylides with In Situ Generation of Diazocompounds**

Varinder K. Aggarwal,* Emma Alonso, George Hynd, Kevin M. Lydon, Matthew J. Palmer, Marina Porcelloni, and John R. Studley

The development of new methods for catalytic epoxidation continues to attract considerable attention. Whilst most methods have concentrated on alkene oxidation,^[1] we have focused our efforts on the epoxidation of carbonyl compounds.^[2] Recently, we reported a catalytic and asymmetric process for converting carbonyl compounds directly into epoxides which operated under neutral conditions and employed sub-stoichiometric amounts of sulfide **1** and metal catalyst (Scheme 1).^[3]



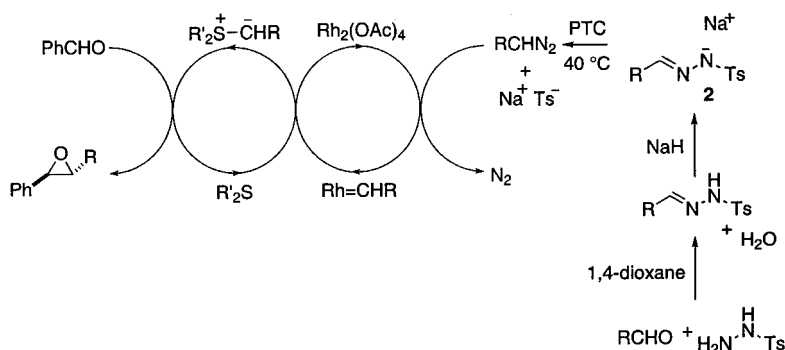
Scheme 1. Catalytic cycle for epoxidation.

However, a limitation of the original protocol was the need to synthesize and handle diazocompounds, which, since they are potentially explosive,^[4] severely limits the practicality of the process. We therefore considered the possibility of generating the diazo compound in situ and coupling this reaction to our established epoxidation process. Herein we describe our success in achieving this aim and beyond—to the development of a unique process for the direct

coupling of two different aldehydes to form epoxides with control over the relative and absolute stereochemistry.

We focused our efforts on the use of the Bamford–Stevens reaction for generating the diazo compound,^[5] and after some experimentation found that warming a suspension of the tosylhydrazone salt **2** (tosyl = Ts = toluene-4-sulfonyl) in the presence of a phase-transfer catalyst^[6] (PTC; to aid the passage from the solid to the liquid phase), allowed the generation of the diazo compound at moderate temperature.^[7] This modified protocol was also compatible with our established epoxidation process and was remarkably efficient (Scheme 2, Table 1, entry 1). Furthermore, these new conditions were found to be general (Table 1). All the aromatic, heteroaromatic, and unsaturated aldehydes investigated furnished the corresponding epoxide in high yields and with high *trans* selectivities (entries 1–7). Aliphatic aldehydes also worked well, although they gave lower yields and selectivities (entries 8 and 9).

Following this success we decided to investigate a more diverse range of tosylhydrazone salts in the epoxidation process. Initially, we utilized a variety of substituted aryl tosylhydrazone salts (**2a–g**, Table 2). The yields of the epoxides obtained were excellent, except where a sterically hindered reagent was employed (Table 2, entry 6). In general *trans* epoxides were obtained exclusively, but tosylhydrazone



Scheme 2. One-pot coupling of a carbonyl compound with either a tosylhydrazone salt or a second carbonyl compound. Ts = toluene-4-sulfonyl.

Table 1. Yields and ratios of epoxides formed from aldehydes and tosylhydrazone salt **2** using 0.2 equivalents of tetrahydrothiophene.

Entry	Aldehyde	Yield [%] ^[a]	<i>trans</i> : <i>cis</i> ^[b]
1	benzaldehyde	95	> 98:2
2	<i>p</i> -nitrobenzaldehyde	94	> 98:2
3	<i>p</i> -chlorobenzaldehyde	86	> 98:2
4	<i>p</i> -methoxybenzaldehyde	98	> 98:2
5	3-pyridinecarboxaldehyde	71	> 98:2
6	<i>trans</i> -cinnamaldehyde	97 ^[c]	> 98:2
7	<i>trans</i> -crotonaldehyde	78 ^[c]	91:9
8	cyclohexanecarboxaldehyde	69	65:35
9	valeraldehyde	59	70:30

[a] Yield of isolated product. [b] Determined by ¹H NMR spectroscopy. [c] Crude yield determined by ¹H NMR spectroscopy (epoxides are unstable to silica gel). Bn = benzyl.

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Table 2. Yields and ratios of epoxides formed from benzaldehyde and tosylhydrazone salts using 0.2 equivalents of tetrahydrothiophene.

Entry	Ar	R'	Salt	Yield [%] ^[a]	<i>trans</i> : <i>cis</i> ^[b]
1	<i>p</i> -ClC ₆ H ₄	H	2a	95	> 98:2
2	<i>p</i> -MeOC ₆ H ₄	H	2b	96	67:33
3	<i>p</i> -MeC ₆ H ₄	H	2c	73	80:20
4	<i>o</i> -MeC ₆ H ₄	H	2d	86	> 98:2
5	<i>p</i> -CNC ₆ H ₄	H	2e	89	> 98:2
6	2,4,6-Me ₃ C ₆ H ₂	H	2f	17	> 98:2
7	C ₆ H ₅	Me	2g ^[c]	86	> 98:2

[a] Yield of isolated product. [b] Determined by ¹H NMR spectroscopy. [c] In situ salt formation from 2,4,6-triisopropylbenzenesulfonyl hydrazone using NaHMDS (HMDS = 1,1,1,3,3,3-hexamethyldisilazane) as the base.

salts bearing electron-donating substituents led to lower diastereoselectivity (Table 2, entries 2 and 3). Tosylhydrazone salts derived from aryl ketones were also successfully employed in the process (Table 2, entry 7). We were also able to couple alkenylhydrazones **3–5** with benzaldehyde to furnish vinyl epoxides (Table 3). Although high yields were obtained, the diastereoselectivity was poor and this problem is currently being addressed.

Table 3. Yields and ratios of epoxides formed from benzaldehyde and alkenyl-substituted sulfonylhydrazones using 1.0 equivalents of tetrahydrothiophene.

Entry	R	R'	Hydrazone	Yield [%] ^[a]	<i>trans</i> : <i>cis</i> ^[b]
1	CH ₃	CH ₃	3	> 90	50:50
2 ^[c]	Ph	Ph	4	> 90	67:33
3	H	SiMe ₃	5	76 ^[d]	50:50

[a] Crude yield determined by ¹H NMR spectroscopy (epoxides are unstable to silica gel). [b] Determined by ¹H NMR spectroscopy. [c] Using 0.2 equiv of tetrahydrothiophene. [d] Yield of isolated pure epoxide (stable to silica gel).

Having demonstrated that we could generate a diazo compound in situ, we considered the possibility of generating the hydrazone itself in situ. Remarkably, this worked (Table 4) and provided a one-pot, atom-economical method for coupling two different aldehydes to give epoxides. Thus, we have developed a general, user-friendly catalytic process for preparing epoxides by coupling together a carbonyl compound with either a tosylhydrazone salt or a second carbonyl compound (Scheme 2).

Our efforts to render these processes asymmetric using thioacetal **1**, which had worked well in the epoxidation process when preformed phenyldiazomethane was used,^[3] were not successful: only low yields of the corresponding

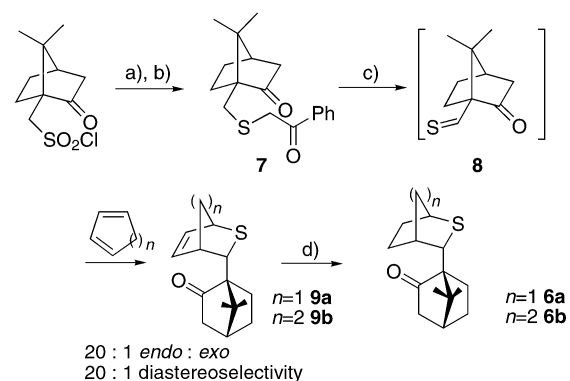
Table 4. Yields and ratios of epoxides formed from aldehydes and tosylhydrazone salt **2** (generated in situ) using 0.2 equivalents of tetrahydrothiophene.

Entry	Aldehyde (RCHO)	Yield [%] ^[a]	<i>trans</i> : <i>cis</i> ^[b]
1	benzaldehyde	70	> 98:2
2	<i>p</i> -nitrobenzaldehyde	81	> 98:2
3	<i>p</i> -methoxybenzaldehyde	70	> 98:2
4	pyridine 3-carboxaldehyde	40	> 98:2
5	cyclohexanecarboxaldehyde	30	70:30
6	valeraldehyde	43	80:20

[a] Yield of isolated product. [b] Determined by ¹H NMR spectroscopy.

epoxides were obtained. We therefore embarked on the synthesis of a range of stable, mono and bicyclic chiral sulfides based on thiolanes, thianes, and 1,4-oxathianes, and from this extensive study we found that the bridged bicyclic sulfides **6a, b** performed exceptionally well.

The [2.2.1] bicyclic sulfide **6a** was prepared in four steps from camphorsulfonyl chloride in 48% overall yield (Scheme 3). The key step in the synthesis was the cyclo-



Scheme 3. Reagents and conditions: a) PPh₃, 1,4-dioxane:H₂O (4:1), 1 h, reflux, 92%; b) PhCOCH₂Cl, K₂CO₃, THF, RT, 20 h, 82%; c) sun lamp (hν), CH₂Cl₂, 20°C, 6 h, cyclopentadiene → **9a**, 76% or cyclohexadiene → **9b**, 40%; d) H₂, Pd-S/C EtOH, RT, 3 h, **6a**, 84%; **6b**, 82%.

addition of thioaldehyde **8** (generated photochemically from phenacyl sulfide **7**) with cyclopentadiene.^[8] This reaction was not only highly *endo* selective, but also showed very high levels of diastereoselectivity. A single diastereomeric cycloadduct was obtained in 76% yield. Hydrogenation and recrystallization gave analytically pure sulfide **6a** whose structure was confirmed by X-ray analysis. The [2.2.2] bicyclic sulfide **6b** was prepared in an analogous manner (Scheme 3).

The conditions for epoxidation were optimized with sulfide **6a** and it was found that the sulfide loading could be reduced from 20 mol % to just 5 mol % without significantly affecting the yield or *ee* value (Table 5, entry 1). Furthermore we were also able to recover and reuse the sulfide without any loss of

Table 5. Yields, enantioselectivities, and diastereoselectivities of epoxides formed from aldehydes and tosylhydrazone salt **2** using 0.05 equivalents of sulfide **6a**.^[a]

Entry	Aldehyde	Yield [%] ^[b]	d.r. ^[c]	ee [%]
1	benzaldehyde	82	> 98:2	94
2	benzaldehyde ^[d]	82	> 98:2	92
3	<i>p</i> -nitrobenzaldehyde	75	> 98:2	92
4	<i>p</i> -chlorobenzaldehyde	80	> 98:2	91
5	<i>p</i> -methoxybenzaldehyde	68	> 98:2	92
6	<i>p</i> -tolualdehyde	84	> 98:2	90
7	<i>o</i> -tolualdehyde	68	> 98:2	90
8	<i>trans</i> -cinnamaldehyde	70 ^[c]	98:2	87
9	cyclohexanecarboxaldehyde	58	88:12	90
10	2-furylaldehyde	60 ^[c]	98:2	91
11	3-furylaldehyde	77	98:2	92

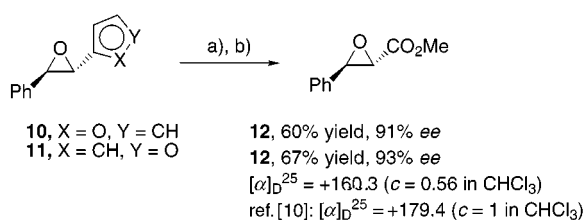
[a] Aldehyde (1.0 mmol), tosylhydrazone sodium salt **2** (2.0 mmol), sulfide **6a** (0.05 mmol), phase-transfer catalyst (0.05 mmol), Rh₂(OAc)₄ (0.01 mmol), and CH₃CN (0.8 mL). [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy (epoxides are unstable to silica gel). [d] Using **6b** in place of **6a**.

asymmetric induction. Sulfide **6b** gave a similarly high yield and enantioselectivity (Table 5, entry 2), but as its synthesis was lower yielding further studies were conducted with **6a**.

The new procedure was applied to a range of aromatic, heteroaromatic, unsaturated, and aliphatic aldehydes and was found to be general (Table 5) and gave high yields, high diastereoselectivities, and high enantioselectivities in all cases.

The process shown in Table 5, entry 1 has been scaled up to a 50-mmol scale and found to give similar yields and enantioselectivities (78 and 92 %, respectively). Further reductions in catalyst loading of Rh₂(OAc)₄ and the phase-transfer catalyst have been achieved upon scale-up. Conducting work on this scale would not have been contemplated using the *ex situ* process.^[4]

Finally, the synthetic utility of the process is demonstrated by the conversion of the furaldehyde-derived epoxides into glycidic esters with high enantiomeric excess values (Scheme 4). Glycidic esters are versatile intermediates and

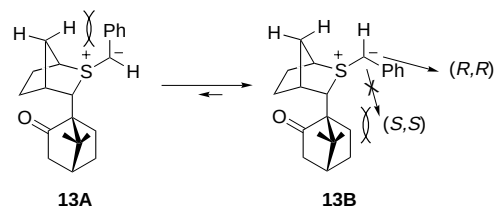


Scheme 4. Reagents and conditions: a) RuCl₃ (2 mol %), NaIO₄ (4 equiv), MeCN:CCl₄:H₂O, RT, 3 h; b) CH₂N₂, Et₂O, RT.

have found widespread use in synthesis. Thus, oxidation of **10**/**11** with RuCl₃/NaIO₄ followed by esterification^[9] furnished the glycidic esters in good yields. The absolute stereochemistry of the glycidic ester was determined by comparison of the [α]_D value with the literature value,^[10] and this provided additional proof of the stereochemical assignment of the furaldehyde-derived epoxides.

The following model is proposed to account for the high enantioselectivity.^[11] Of the two lone pairs only the *exo* lone

pair reacts to form a single sulfonium ylide **13**.^[12] The ylide can adopt conformations **13A** or **13B**, but **13B** should be strongly favored because of the 1,4-steric interactions present in **13A** (Scheme 5). The face selectivity of the ylide is then controlled



Scheme 5. Model to account for the enantioselectivity.

by the bulky camphor group which blocks attack from the *Si* face, thus leading to the *R,R* epoxide. To achieve *high* enantioselectivity requires control of the conformation and high face selectivity of the ylide. The control in the ylide conformation arises from the conformational rigidity of sulfides **6a, b**, which means that ylide conformer **13A** cannot be easily accommodated through small changes in bond angles around the sulfur atom. This effect leads to a significant difference in the energy between the two ylide conformers **13A, B**, which in conjunction with the high face selectivity imposed by the bulky camphor moiety results in the high enantioselectivity observed.

In summary, we have developed a new class of sulfides which, at 5 mol % loading, gives high diastereoselectivities, high enantioselectivities, and high yields in the coupling of a range of different aldehydes with tosylhydrazone salts. The process has been scaled up and now represents a practical way of converting carbonyl compounds directly into epoxides with control of relative and absolute stereochemistry.

Experimental Section

Epoxidation of benzaldehyde (50-mmol scale): Compound **6a** (62.5 mg, 2.5 mmol), anhydrous acetonitrile (50 mL), rhodium(II) acetate dimer (110 mg, 0.25 mmol), benzyl triethylammonium chloride (228 mg, 1.0 mmol), benzaldehyde (5.1 mL, 50 mmol), and tosylhydrazone sodium salt **2** (22.3 g, 75 mmol) were added sequentially to a 100-mL 2-neck flask. The reaction mixture was stirred at 40 °C under a static nitrogen pressure for 2 d using an overhead stirrer. The reaction was quenched by the addition of water (25 mL) and ethyl acetate (25 mL), and the phases were separated. The aqueous layer was washed with ethyl acetate (2 × 25 mL) and the combined organic phases dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product was analyzed by ¹H NMR spectroscopy to determine the diastereomeric ratio and then purified by flash column chromatography to afford stilbene oxide (7.6 g, 78 %).

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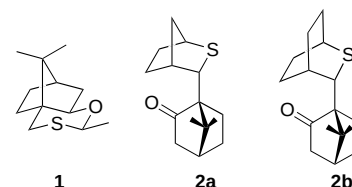
Application of Chiral Sulfides to Catalytic Asymmetric Aziridination and Cyclopropanation with In Situ Generation of the Diazo Compound**

Varinder K. Aggarwal,* Emma Alonso, Guangyu Fang, Marco Ferrara, George Hynd, and Marina Porcelloni

In the preceding paper we described a highly efficient catalytic process for converting carbonyl compounds into

epoxides with high enantioselectivity. Herein we describe the extension of this work to the asymmetric aziridination of imines^[1] and to the asymmetric cyclopropanation of electron-deficient alkenes.^[2]

We previously reported that 1,3-oxathiane **1** gave good yields and high enantioselectivity in aziridination^[3] and cyclopropanation^[4] reactions. However, these processes are



potentially hazardous, cannot be easily scaled up, and the sulfide cannot be fully recovered. We successfully solved these problems in the epoxidation reaction by generating the diazo compound in situ and by developing a new class of chiral sulfides **2**,^[5] which were completely stable to the reaction conditions. We were keen to examine whether these new conditions and new sulfides were compatible with the aziridination and cyclopropanation processes.

Optimization of the conditions for aziridination of the *N*-SES-activated imine derived from benzaldehyde^[6] (this imine is easily prepared and provides a readily cleavable group) with sulfide **2a** revealed that 1,4-dioxane was the best solvent. A broad study of different activating groups on the nitrogen atom showed that sulfonylimines^[7] led to aziridines in good yield, high enantioselectivities, but low diastereoselectivities (Table 1, entries 1–3). A notable example is the naphthylsulfonylimine, which gave excellent results and this group is considerably easier to deprotect^[8] than the toluene-4-sulfonyl (tosyl) group. Improved diastereoselectivity was observed

Table 1. Effect of the nitrogen substituent on the yield, diastereoselectivity, and enantioselectivity.^[a]

$\text{Ph}-\text{C}(=\text{O})-\text{N}^+\text{R} + \text{Ph}-\text{C}(\text{N}^+\text{R})=\text{N}^-\text{Ts} \xrightarrow[\text{sulfide } \mathbf{2a} \text{ (20 mol\%)}]{\text{Rh}_2(\text{OAc})_4 \text{ (1 mol\%)}, \text{BnEt}_3\text{N}^+\text{Cl}^- \text{ (10 mol\%)}, \text{1,4-dioxane, 40 }^\circ\text{C}}$				
Entry	R	Yield [%] ^[b]	d.r. ^[c] (<i>trans</i> : <i>cis</i>)	ee [%] ^[d]
1	SES	75	2.5:1	94
2	Ts	68	2.5:1	98
3	SO ₂ C ₁₀ H ₇	70	3:1	97
4	Boc	33 ^[e,f]	8:1	89
5	TcBoc	71	6:1	90
6 ^[g]	SES	66	2.5:1	95

[a] Tosylhydrazone salt (1.5 equiv), imine (1.0 equiv), phase-transfer catalyst (PTC, 0.1 equiv), Rh₂(OAc)₄ (0.01 equiv), 1,4-dioxane (0.33 M), chiral sulfide **2a** (0.2 equiv), 40 °C. [b] Yield of isolated product. [c] The *trans*:*cis* ratio was determined by ¹H NMR spectroscopy. [d] Enantiomeric excess values were determined on a Chiralcel OD column; the absolute configuration was 1*R*,2*R*. [e] 0.05 equiv of PTC were used. [f] *trans*-stilbene oxide was obtained as the main side product. [g] 5 mol % of sulfide was used. Ts = tosyl = toluene-sulfonyl.

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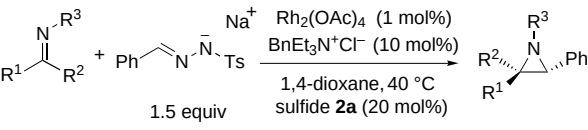
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

with carbamoylimines (entries 4 and 5),^[9] and of the two tested the TcBoc-protected^[9] imine gave the higher yield (the Boc-protected imine partially hydrolyzed during the course of the reaction). The sulfide loading could be reduced to just 5 mol % without a significant reduction in the yield, and the aziridine was obtained with the same enantioselectivity (entry 6).

This study of activating groups on the nitrogen atom revealed that sulfonyl- or TcBoc-activated imines provided the best combination of yield, enantioselectivity, and diastereoselectivity to date in a practical, user-friendly catalytic process.^[10] These groups were therefore tested with a range of imines derived from aromatic, heteroaromatic, unsaturated, and even aliphatic aldehydes and ketones^[11] (Table 2). As sulfonyl-substituted imines were easier to prepare than

Table 2. Asymmetric aziridination of a range of imines.^[a]

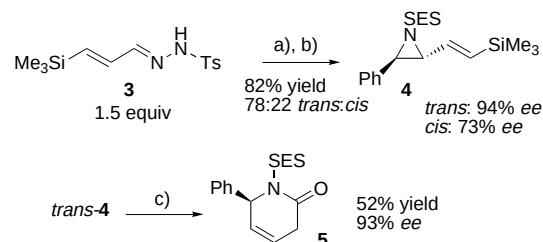
						
Entry	R ¹	R ²	R ³	Yield [%] ^[b]	d.r. ^[c]	ee [%] (<i>trans</i> : <i>cis</i>) ^[d]
1	<i>p</i> -ClC ₆ H ₄	H	TcBoc	56	6:1	94:90
2	<i>p</i> -ClC ₆ H ₄	H	SES	82	2:1	98:81
3	C ₆ H ₁₁	H	SES	50	2.5:1	98:89
4	<i>t</i> Bu	H	Ts	53	2:1	73:95
5	<i>trans</i> -PhCH=CH	H	SES	59	8:1	94
6	<i>p</i> -MeOC ₆ H ₄	H	SES	60	2.5:1	92:78
7	3-furfuryl	H	Ts	72	8:1	95
8	Ph	Ph	SO ₂ C ₈ H ₇	50	–	84

[a] Tosylhydrazone salt (1.5 equiv), imine (1.0 equiv), PTC (0.1 equiv), Rh₂(OAc)₄ (0.01 equiv), 1,4-dioxane (0.33 M), chiral sulfide **2a** (0.2 equiv), 40 °C. Bn = benzyl. [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy. [d] Enantiomeric excess values were determined on a Chiralcel OD column. See the Supporting Information.

TcBoc-substituted ones, most studies were conducted with the former group. In all cases good yields and high enantioselectivities were observed, although the diastereoselectivity was found to be dependent on both the nature of the nitrogen activating group and on the imine substituent. Most encouragingly was the observation that good diastereoselectivity could be achieved with sulfonyl activating groups on the imines derived from cinnamaldehyde (Table 2, entry 5) and 3-furfural (Table 2, entry 7). High enantioselectivity was obtained from imines derived from aliphatic aldehydes (Table 2, entry 3), although curiously the *tert*-butyl imine only gave high enantioselectivity in the formation of the *cis*-aziridine (Table 2, entry 4). The origin of this unusual selectivity is not known at present and is currently under investigation. The imine derived from benzophenone could also be employed and allowed access to trisubstituted aziridines (Table 2, entry 8).

The process could also be extended to alkenyldiazomethanes and again good yields, high enantioselectivities, and good diastereoselectivities were obtained with the *N*-SES-activated imine derived from benzaldehyde (Scheme 1). The

synthetic utility of the process was demonstrated by further manipulation of the unsaturated aziridine. Unsaturated aziridines are very useful intermediates which are known to undergo ring expansion under a variety of conditions to give



Scheme 1. Reagents and conditions: a) LiHMDS (1.5 equiv), THF, –78 °C, 1 h; b) PhCHNSES (1 equiv), Rh₂(OAc)₄ (1 mol %), phase-transfer catalyst (PTC, 10 mol %), sulfide **2a** (20 mol %), 1,4-dioxane, 40 °C, 12 h; c) [Pd₂(dba)₃ · CHCl₃] (15 mol %), PPh₃ (1.3 equiv), PhH, CO (1 atm), 50 °C, 12 h. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, SES = 2-(trimethylsilyl)ethanesulfonyl, dba = *trans,trans*-dibenzylideneacetone.

either β -^[12] or δ -lactams.^[13] Treatment of *trans*-aziridine **4** with Pd and CO led cleanly to the δ -lactam **5** in good yield and with the same high enantiomeric excess. This selectivity for the formation of the δ -lactam must be a consequence of a directing effect of the silyl group since a similar compound without the silyl group gave the β -lactam under the same conditions.^[12b] The origin of this selectivity is the subject of further investigations.

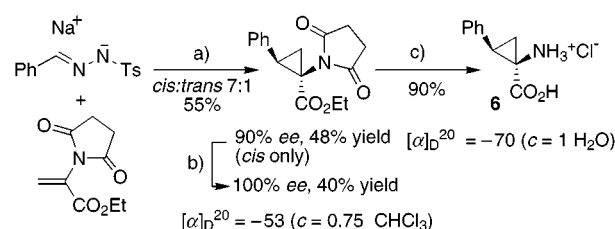
Having developed a highly efficient, practical process for asymmetric aziridination, we focused our attention to the cyclopropanation of electron-deficient alkenes. The reaction of chalcone with sulfide **2a** was initially chosen, and once again 1,4-dioxane emerged as the optimal solvent (Table 3, entry 1). However, although high enantioselectivity was obtained, the yield was rather poor. Since six membered ring sulfides were found to be superior to five membered ring sulfides in cyclopropanation reactions,^[4] we decided to test the novel [2.2.2] bicyclic sulfide **2b**. Sulfide **2b** did indeed give improved yields in the cyclopropanation of chalcone (Table 3, entry 2)^[14] and so studies were extended to a range of Michael acceptors. It was found that phenyl ketones were excellent substrates (Table 3, entries 2 and 3), whilst methyl ketones were less good (Table 3, entries 4 and 5). Although unsubstituted acrylates (Table 3, entry 6) were not very effective substrates, we found that α -amino-substituted acrylates performed extremely well to give cyclopropanes in high yields, high enantioselectivities, and high diastereoselectivities (Table 3, entries 7 and 8). In all cases, high enantioselectivity was obtained and the sulfide could be recovered in quantitative yield.

The cyclopropanes derived from the amino acrylates could be converted in one step into the corresponding amino acids (Scheme 2) or the Boc-protected amino esters (Scheme 3). Furthermore, a single recrystallization either before or after deprotection led to enantiomerically pure material (Schemes 2 and 3). The acrylates are made in one step^[15, 16] and thus provides the most efficient route to this important class of conformationally locked amino acids. This cyclo-

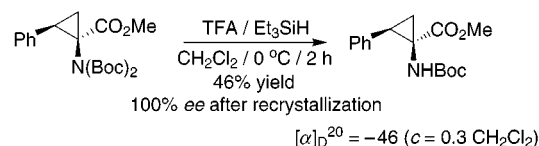
Table 3. Catalytic asymmetric cyclopropanation of electron-deficient alkenes.^[a]

Entry	R ¹	R ²	R ³	Sulfide	Yield [%] ^[b]	d.r. (<i>trans</i> : <i>cis</i>)	ee [%] ^[d]	Absolute config.
1	Ph	H	COPh	2a	30 ^[e]	5:1 ^[c]	89	1 <i>R</i> ,1 <i>R</i>
2	Ph	H	COPh	2b	73	4:1 ^[c]	91	1 <i>R</i> ,1 <i>R</i>
3	CH ₃	H	COPh	2b	50	4:1 ^[c]	90	1 <i>R</i> ,1 <i>R</i>
4	Ph	H	COCH ₃	2b	5	—	—	—
5	CH ₃	H	COCH ₃	2b	12	1:1:1 ^[f]	—	—
6	H	H	CO ₂ Et	2b	10	7:1 ^[c]	—	—
7	H	<i>N</i> -succinimide	CO ₂ Et	2b	55	1:7 ^[c]	91	1 <i>S</i> ,1 <i>S</i>
8	H	N(Boc) ₂	CO ₂ Me	2b	72	1:6 ^[c]	92	1 <i>S</i> ,1 <i>S</i>

[a] Tosylhydrazone salt (1.5 equiv), alkene (1.0 equiv), sulfide **2a/2b** (0.2 equiv), PTC (0.2 equiv), Rh₂(OAc)₄ (0.01 equiv), in dioxane (0.13 M) at 40 °C. Bn = benzyl. [b] Combined yield of all isomers. These can be separated except in those cases indicated. [c] Ratio of *trans*:*cis* isomers was determined by ¹H NMR spectroscopy. [d] Enantiomeric excess values were determined on a Chiralcel OD column. See the Supporting Information. [e] 50 % of enone was recovered.

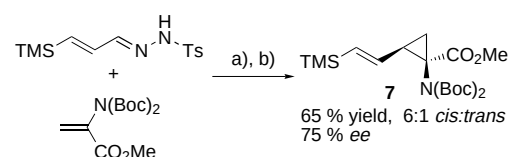


Scheme 2. Reagents and conditions: a) Sulfide **2b** (20 mol %), Rh₂(OAc)₄ (1 mol %), PTC (20 mol %), 1,4-dioxane, 40 °C, 24 h; b) Recrystallization. c) 6 N HCl, reflux, 4 h. Ts = tosyl = toluene-4-sulfonyl.



Scheme 3. Partial hydrolysis of the protected amino acid. TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl.

propanation methodology was further illustrated in the synthesis of protected vinylcyclopropyl amino acid **7** (Scheme 4). In this scheme an unsaturated diazocompound was prepared in situ using our modified Bamford–Stevens reaction.^[5] The vinylsilane moiety provides a very useful handle for the incorporation of alternative functional groups^[17] onto the cyclopropane ring and so will allow access to a much broader range of conformationally locked amino acids.



Scheme 4. Reagents and conditions: a) LiHMDS (1.2 equiv), THF, -78 °C; b) Rh₂(OAc)₄ (1 mol %), sulfide **2b** (100 mol %), BnEt₃N⁺Cl⁻ (20 mol %), 1,4-dioxane, 40 °C, 16 h. Ts = toluene-4-sulfonyl.

The absolute stereochemistries of the cyclopropanes derived from chalcone^[4b] and α-succinimidy acrylate^[18] were determined by comparison of the [α]_D values with those reported in the literature. All other absolute stereochemistries are given by analogy with the above and are in keeping with the absolute stereochemistries obtained in the related epoxidation and aziridination reactions.

The high enantioselectivity in the aziridination and cyclopropanation reactions can be readily accounted for by using the same model as described for epoxidation.^[5] Further work is needed to understand the diastereoselectivity, and studies in this area are ongoing.^[19]

In summary, we have developed a highly effective, user-friendly, catalytic asymmetric process for the aziridination of imines and the cyclopropanation of electron-deficient alkenes. The process is general and can be applied to a broad range of electrophiles and diazo precursors. Further applications of these new processes in asymmetric synthesis are ongoing.

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- [10] Compare entry 1 or entry 6 with our previous best results with sulfide **1**, which was 55 % yield, 97 % *ee*, and 3:1 d.r.^[3] Note this result used stoichiometric amounts of **1** and cannot be easily scaled up (see citation [3] in ref. [5]). Antilla and Wulff's process (ref. [1d]) is complementary to ours as it uses preformed diazoesters and gives *cis* aziridines (ours uses diazoalkanes/diazoalkenes and gives *trans*-aziridines).
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- [14] Compare entry 2 with our previous best result with sulfide **1**, which gave 38 % yield, 4:1 d.r., and 97 % *ee*.
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- [16] 2-Propenoic acid 2-bis[(1,1-dimethylethoxy)carbonyl]amino-methyl ester was prepared from serine and Boc-ON by the method described by: P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, *Tetrahedron Lett.* **1998**, 39, 9575–9578. We have found that this acrylate can be prepared in one step from serine methyl ester and (Boc)₂O.
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- [19] We have found from crossover experiments relating to aziridination that betaine formation is irreversible. Thus, the diastereoselectivity is controlled by nonbonding interactions that lead to the betaine.

Oxoammonium Resins as Metal-Free, Highly Reactive, Versatile Polymeric Oxidation Reagents**

Steffen Weik, Graeme Nicholson, Günther Jung, and Jörg Rademann*

Complex organic molecules can be constructed either in solution or attached to an insoluble polymeric support. Polymer-assisted solution-phase (PASP) synthesis^[1–3] offers a highly attractive supplement to these concepts by exploiting the virtues of both traditional approaches. Polymeric reagents^[4, 5] can be used in high excess and are removed by filtration, the products can be easily analyzed and further transformed in solution. They are especially suitable for parallel combinatorial synthesis.^[6, 7] They allow preparation of complex libraries by multistep syntheses in solution, they can be utilized in automated and in flow-through systems, and finally they can be employed—as will be demonstrated herein—to transform single compounds as well as complex mixtures.^[8]

The oxidation of alcohols to carbonyl compounds is one of the most relevant transformations in organic synthesis, owing to the large diversity of products that can be obtained from aldehyde and ketone precursors.^[9] Common oxidative agents for this transformation include dimethyl sulfoxide (DMSO),^[10] periodinanes^[11] as well as various heavy-metal reagents, the latter usually based on either chromium^[12] or ruthenium oxides.^[13] There are several examples of polymer-supported oxidation reagents,^[14] including heavy-metal oxides bound to ion-exchange resins.^[15, 16] One resin of this type has been recently employed in a reaction sequence leading to heterocyclic compounds.^[17] However, low reactivity with non-benzylic alcohols, potential persistence of highly toxic heavy metals in the products as well as overoxidation of aldehydes limits the use of solid-supported metal oxides in parallel syntheses.

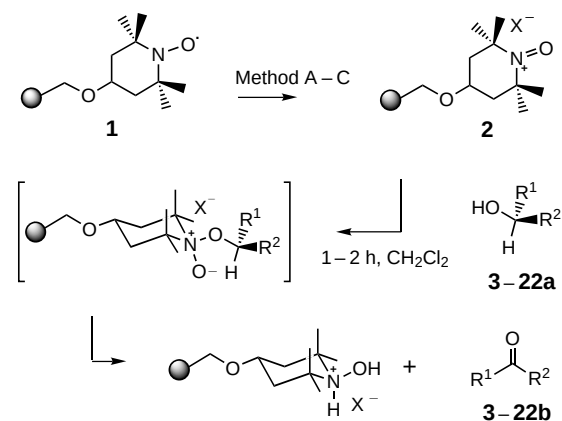
Herein we report on the generation of oxoammonium halides as oxidizing reactive species on a solid support and on the use of this reagent in the oxidation of single alcohols and of complex compound collections. Oxoammonium salts have been postulated as reactive intermediates in oxidations employing the 2,2,6,6-tetramethylpiperidine 1-oxyl radical (TEMPO), which is commonly employed under phase-transfer conditions with, for example, sodium hypochlorite as activating oxidant in the aqueous phase.^[18, 19] Recently TEMPO has been used in solution together with a polymer-attached oxidizing agent^[20] and as a catalyst on silica.^[21] No reports were found about using oxoammonium salts on insoluble, crosslinked polymers, which would allow the

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integration in common polymer-assisted solution-phase synthesis operations.^[22] We decided to synthesize and employ reactive oxoammonium salts in a water-free system with the intention of generating a highly reactive oxidation agent that avoids over-oxidation to the acid due to the absence of oxygen donors.^[23]

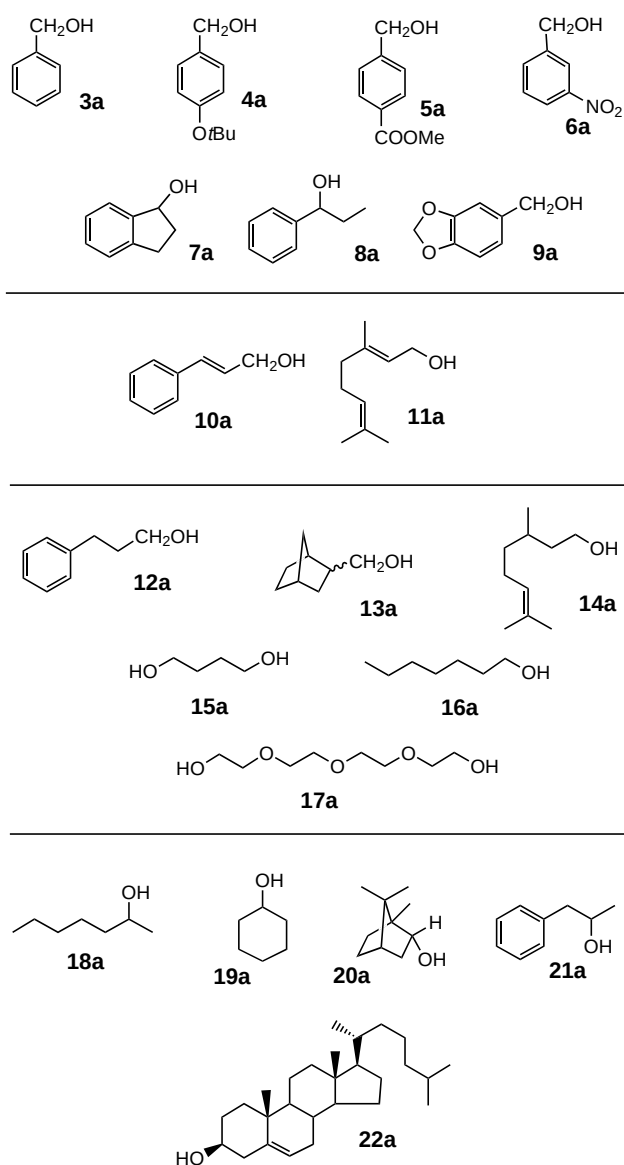
The 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl radical was coupled to 1% divinylbenzene polystyrene resin by employing sodium hydride as base (Scheme 1). Elemental analysis of



Scheme 1. Oxoammonium resin **2** was prepared in a three-step procedure from chloromethylated polystyrene resin and was employed in the oxidation of alcohols **3a–22a**. Oxidation of resin **1** was effected by Br₂, Cl₂, or NCS/HCl (Methods A–C).

the resulting resin **1** revealed a loading of 0.93 mmol g^{−1} of the radical; the presence of the free radical electron was proved by ESR spectroscopy, which displayed the characteristic triplet signal due to coupling with the ¹⁴N nucleus. Likewise, the high-resolution magic angle spinning (HR-MAS) NMR spectrum displayed significant line broadening, which can be attributed to enhanced relaxation of the nuclear magnetization through interaction with the persistent electron spins. Oxidation of the radical was performed with elemental bromine, chlorine, and *N*-chlorosuccinimide/HCl (Methods A–C; Scheme 1). Following oxidation, the resulting resin **2** displays a strong absorption at 1700 cm^{−1} in the attenuated total reflection IR spectrum (FT-ATR-IR), presumably characteristic for the N=O double bond of the reactive intermediate. The oxidation is accompanied by a distinct color change from colorless to a bright orange-red in case of chloride as counterion and brown-red in case of bromide.

We investigated the reactivity of reagent **2** towards a selection of 20 different alcohols **3a–22a**, representing the categories of benzylic, allylic, primary as well as secondary aliphatic alcohols. Comparing the different counterions, chloride was more reactive than bromide and led to fewer side products, presumably due to the presence of the Br₃[−] ion in the case of bromine oxidation. Various temperatures were tested; all comparative reactions were conducted at room temperature (Table 1). Analysis and quantification of all reactions were conducted by GC either with a flame-ionization detector (FID) or a mass-sensitive detector (EI-MS, 70 eV). Compounds were identified by comparison with pure samples, by software-based structure assignment using the



mass spectra and the NIST spectral library, or by NMR analysis.

First, alcohol **9a** was treated with various amounts of **2**. Complete conversion within 1 h was achieved with three equivalents of **2** (Figure 1). Results of the oxidation (Table 1) can be summarized as follows: Clean and fast quantitative conversion of the starting alcohols was observed in general, only in the case of alcohol **17a** was the starting material detected after the reaction. All benzylic or allylic alcohols yielded aldehyde or ketone products in very good purities. The same was found for open-chain primary and secondary alcohols. Representative yields for less volatile products such as aldehydes **9b**, **10b**, or **20b** were determined by weight and were around 90%; the identity of the products was confirmed by NMR analysis (250 MHz, CDCl₃).^[24]

Very easily enolizable primary ketones obtained from cyclohexanol (**19a**), 1-phenylpropan-2-ol (**21a**), and cholesterol (**22a**) could be further converted to the diones, **19c**, **21c**, and **22c**, respectively (Scheme 2). In this reaction the primary

Table 1. Results of the oxidation of the alcohols **3a–22a**.

Starting alcohol	Main product ^[a]	Product purity [%]	GC-EI-MS-analysis (characteristic signals ^[b] [<i>m/z</i>])
3a	3b	> 95	106 [<i>M</i> ⁺], 105, 77, 51
4a	4b	> 95	178 [<i>M</i> ⁺], 163, 121, 93, 77, 65, 57, 41
5a	5b	> 95	164 [<i>M</i> ⁺], 133, 119, 105, 77, 51
6a	6b	> 95	151 [<i>M</i> ⁺], 150, 105, 77, 51
7a	7b	85	132 [<i>M</i> ⁺], 104, 78, 63, 51
8a	8b	> 95	134 [<i>M</i> ⁺], 105, 77, 51
9a	9b	> 95	150 [<i>M</i> ⁺], 149, 121, 91, 63
10a	10b	> 95	132 [<i>M</i> ⁺], 131, 103, 77, 51
11a	11d	83	150 [<i>M</i> ⁺], 135, 122, 107, 95, 91, 82, 77, 54, 39
12a	12b	90	134 [<i>M</i> ⁺], 105, 91, 78, 65, 51, 39
13a	13b	72 ^[c]	124 [<i>M</i> ⁺], 106, 95, 91, 80, 67, 55
14a	14c	60 ^[d]	154 [<i>M</i> ⁺], 139, 136, 121, 111, 95, 84, 81, 71, 55, 41
15a	15c	65	86 [<i>M</i> ⁺], 56, 42, 41, 39
16a	16b	> 95	96, 86, 81, 70, 57, 55, 44, 41
17a	17c	30 ^[e]	146, 102, 86, 73, 58, 45, 43, 32
18a	18b	90	114 [<i>M</i> ⁺], 99, 85, 71, 58, 43, 39
19a	19c	85	112 [<i>M</i> ⁺], 97, 83, 70, 55, 51, 43, 39
20a	20b	> 95	152 [<i>M</i> ⁺], 137, 108, 95, 81, 69, 55, 41
21a	21c	76	148 [<i>M</i> ⁺], 105, 77, 51, 43
22a	22c	79	398 [<i>M</i> ⁺], 383, 370, 356, 285, 243, 137

[a] Ketones or aldehydes obtained in the primary oxidation are designated as compounds **3b–22b**. [b] In accordance with EI mass spectra from the NIST spectral library. Further products see Scheme 2. [c] Decarbonylated by-product. [d] 20% **14b**. [e] Mainly recovered diol.

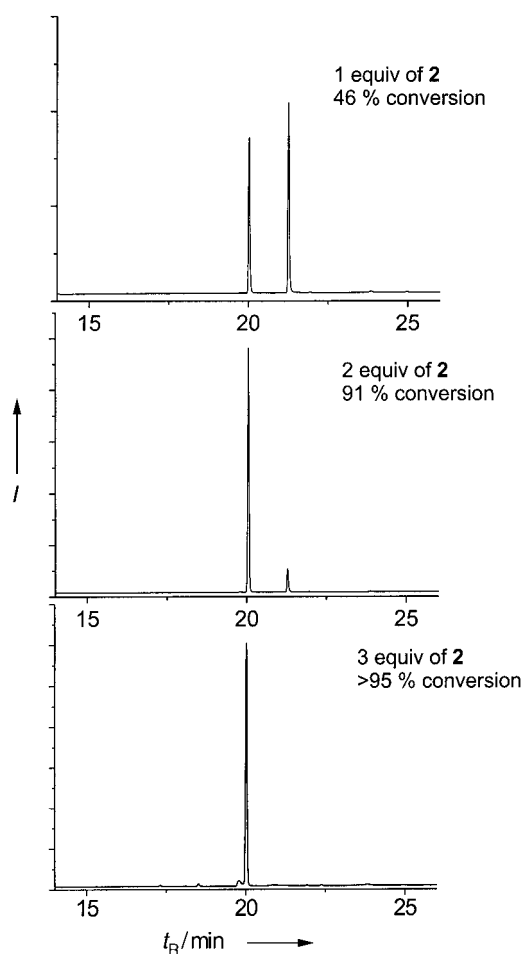
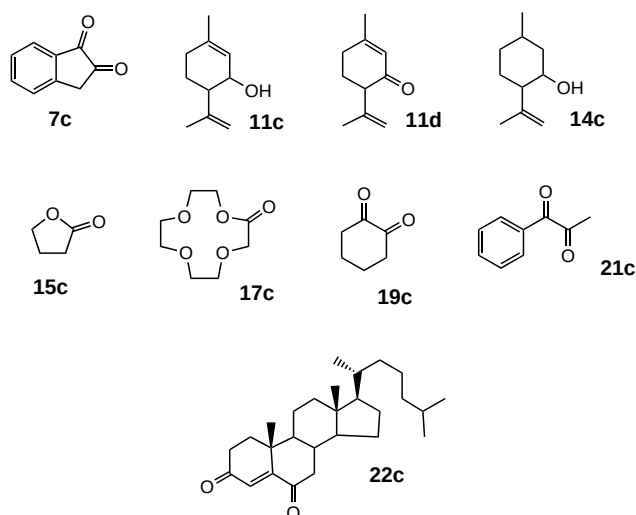


Figure 1. GC analysis (FID) of the reaction of **9a** in CH_2Cl_2 (1 mg mL^{-1}) for 1 h with one, two, and three equivalents of the polymeric oxoammonium salt **2**.



Scheme 2. Secondary oxidation products obtained from alcohols by treatment with resin **2**.

oxidation product, for example, cyclohexanone is transformed to the final diketone product via an enolized intermediate.^[25] In contrast, diols (**15a**, **17a**) are converted to lactones (**15c**, **17c**) in the secondary oxidation step. Interestingly, cascade-like reactions were observed with terpene alcohols such as geraniol (**11a**) and citronellol (**14a**). Monitoring by GC-MS revealed that with an excess of reagent **2**, the primary oxidation products, the open-chain terpene aldehydes (**11b**, **14b**) were cyclized in an ene-type reaction to furnish the secondary alcohols (**11c**, **14c**).^[26] For the geraniol system the secondary product could be further oxidized to yield the terpene ketone **11d** in good purity.

Finally, a compound collection consisting of 15 alcohols (**3a–10a**, **12a**, **13a**, **15a**, **16a**, **18a–20a**) was employed to investigate the feasibility of converting complex mixtures

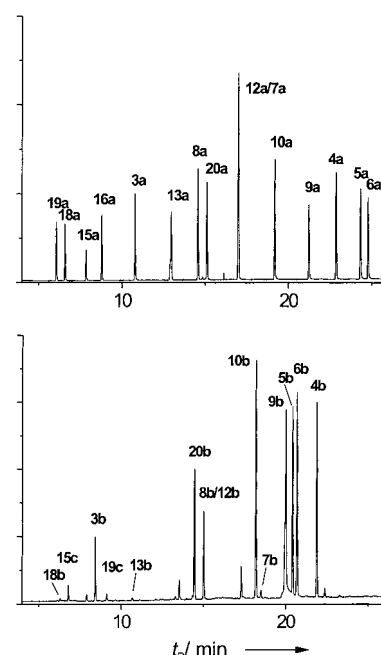


Figure 2. GC analysis (FID) of a mixture of 15 alcohols (top) and the product mixture obtained following oxidation with resin **2** (bottom).

of chemically diverse alcohols (Figure 2). The mixture (1 mg mL⁻¹ per alcohol) was analyzed by GC-FID as well as GC-MS. In the starting mixture all alcohols could be separated and identified by their mass spectra. Following treatment with resin **2** for 2 h, GC analysis revealed the complete disappearance of all of the alcohol precursors. All but one of the expected aldehyde, ketone, lactone, or dione products could be separated and identified; **8b** and **12b** co-eluted, whereas **16b** was not detected at all. The concentration of products with a low-boiling point eluting early in the GC was reduced, whereas the concentration of the high-boiling aldehydes and ketones remained stable in the complex mixture.

In summary, the reported polymer-bound oxoammonium reagent should be of great value in polymer-supported transformations in solution, in automated parallel synthesis operations, and in flow-through reactors in up-scaled production processes. Herein we have only considered the preformed oxoammonium salts as reactive species. The potential of the TEMPO–resin should, however, be exploitable as well as in situ generated oxoammonium salt, obtained by one of the available regeneration systems (e.g. Cu^{II}/O₂), in multiple phases, or by electrochemical means.

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- [24] Experimental details: a) Preparation of TEMPO resin **1**. Sodium hydride (1.28 g, stabilized with paraffin oil, 60%, 32.1 mmol) was

suspended in dry DMF (40 mL) in a 100 mL round-bottom flask. 2,2,6,6-Tetramethylpiperidine 1-oxyl (3.57 g, 20.7 mmol) was added slowly, the flask was sealed with a drying tube, and stirred for 3 h. Chloromethylated divinylbenzene (1%)/polystyrene (loading 1.07 mmol g⁻¹, 100–200 mesh, 2 g, 2.14 mmol) was added and the reaction was agitated for three days at room temperature. The resin was filtered and thoroughly washed with water, water/DMF (1/1), DMF, THF, CH₂Cl₂, and MeOH and dried in vacuo. Loading: 0.93 mmol g⁻¹. Chlorine content: 0.07%. b) Oxidation to oxoammonium resin **2** (Method C; Scheme 1). *N*-Chlorosuccinimide (6 equiv) was dissolved in CH₂Cl₂, 4 M HCl in dioxane was added (5 equiv). After 5 min the solution was added to resin **1** (1 equiv) swollen in dry CH₂Cl₂. Agitation for 15 min was followed by filtration of the resin and washing with dry CH₂Cl₂. Half-life time (*t*_{1/2}) of the activated form was about one week when stored in vacuo at 4 °C. c) Oxidation of alcohols. Alcohols **3a–22a** (1 equiv) were dissolved in dry CH₂Cl₂. Freshly prepared oxoammonium resin **2** (5 equiv as calculated from the loading of resin **1**) was added and agitated at room temperature for 1 h for the primary alcohols and 2 h for the secondary alcohols. The resin was filtered and washed with CH₂Cl₂, the washings were employed for analysis by GC, using a 25 m × 0.32 mm Permaabond SE 54 (*d*_f = 1.0 μ) fused silica capillary. Temperature program: 50 °C, 2 min isotherm, 5 °C min⁻¹ to 200 °C. H₂ was used as carrier gas (*p*_i = 50 kPa) for FI detection and He for GC-MS in the EI-mode (70 eV). Purities are reported in Table 1. Exemplified yields for 10 mg alcohol, after reaction for 1 h, washing with CH₂Cl₂ (4 × 3 mL), and evaporation of the solvent at room temperature: **9b**: 8.9 mg, 90%; **10b**: 8.7 mg, 88%; **20b**: 9.2 mg, 91%. The identity of the isolated products was confirmed by NMR analysis (250 MHz, CDCl₃).

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Thwarting β-Hydride Elimination: Capture of the Alkylpalladium Intermediate of an Asymmetric Intramolecular Heck Reaction**

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

The asymmetric intramolecular Heck reaction^[1,2] has proven to be one of the most efficient methods for enantioselective construction of quaternary carbon centers.^[3] We

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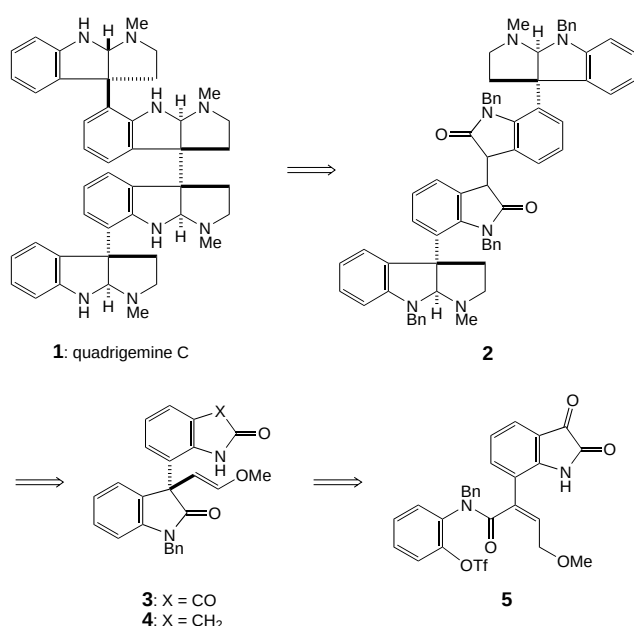
[†] NMR analyses

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

have been engaged for some time in the development of catalytic asymmetric Heck cyclizations, with particular focus on enantioselective synthesis of oxindoles containing quaternary stereocenters.^[4] Chiral oxindoles of this type have numerous applications in synthesis and are key intermediates in our approach to the synthesis of pyrrolidinoindoline alkaloids,^[5] having recently been employed in enantioselective total syntheses of monomeric^[6] and dimeric^[7] members of this large family of natural products.

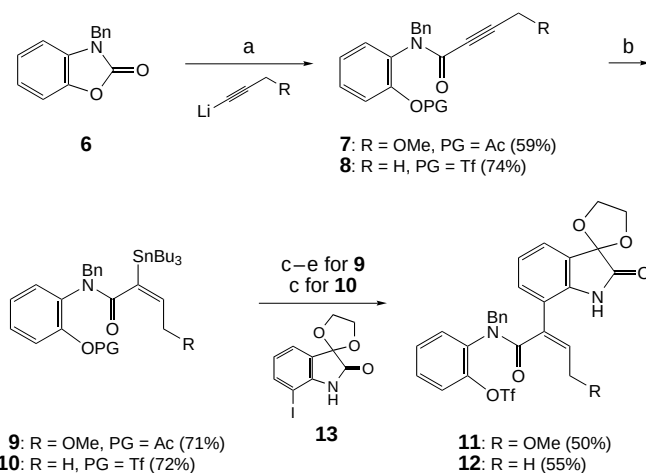
One focus of our current efforts is the enantioselective total synthesis of a tetrameric member of the polypyrrolidinoindoline alkaloid family, quadrigemine C (**1**),^[8] which is proposed to have a *meso* bis(pyrrolidinoindoline) core decorated with two pyrrolidinoindolines of identical absolute configuration. This uncommon stereochemistry led us to consider a convergent dimerization strategy for synthesis of **1** (Scheme 1).



Scheme 1. Retrosynthetic analysis of quadrigemine C (**1**).

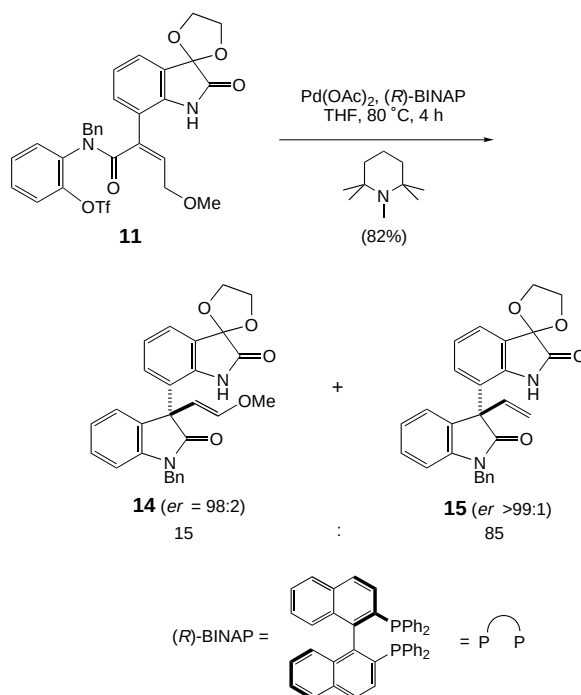
We envisioned dihydroisoindigo intermediate **2**, having both *outer* pyrrolidinoindoline units installed, a suitable substrate for our dialkylation method of constructing the vicinal stereogenic quaternary carbon centers of the central six rings.^[9] Intermediate **2** should be accessible by aldol condensation of an isatin (**3**, X = CO) and a cognate oxindole (**4**, X = CH₂) followed by reduction. Enantioenriched isatin **3** and oxindole **4** in turn would derive from asymmetric Heck cyclization of triflate **5**.^[10] Herein we report highly enantioselective Heck reactions of substrates of type **5** and the isolation of a σ -alkylpalladium intermediate having stereo-electronically accessible β -hydrogen atoms of this Heck sequence.^[11]

Cyclization precursors **11** and **12** were each prepared from 3-benzyl-3*H*-benzooxazol-2-one (**6**)^[12] in short routes analogous to those previously described (Scheme 2).^[10] Stille coupling^[13] of vinylstannane **9** or **10** with ketal-protected 7-iodoisatin **13**^[14] and further functional group manipulation provided **11** and **12**.



Scheme 2. a) 1) lithium acetylide, THF, **6**, –78 °C to –25 °C, 5 h, 2) AcCl or PhNTf₂, THF, –25 °C to RT, 12 h; b) Bu₃SnH, [Pd(PPh₃)₄], THF (BHT-inhibited), 0 °C to RT; c) [Pd₂(dba)₃] · CHCl₃, P(2-furyl)₃, CuI, NMP, RT, 12 h; d) K₂CO₃, THF/MeOH (1:1), RT, 2 h; e) PhNTf₂, Cs₂CO₃, DMF, RT, 12 h. Ac = acetyl, BHT = 2,6-di-*tert*-butyl-4-methylphenol, Bn = benzyl, dba = *trans,trans*-dibenzylideneacetone, DMF = *N,N*-dimethylformamide, NMP = 1-methyl-2-pyrrolidinone, PG = protective group, Tf = trifluoromethanesulfonyl.

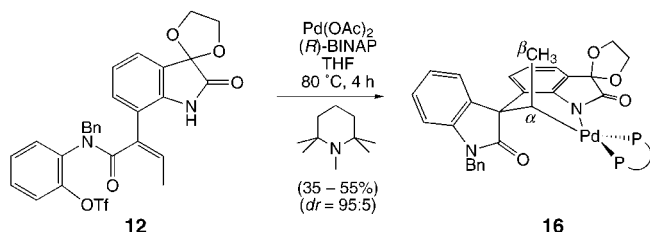
When triflate **11** was cyclized under conditions optimized in our earlier model study (40 mol % Pd(OAc)₂, 60 mol % (*R*)-BINAP, 1,2,2,6,6-pentamethylpiperidine (PMP), THF, 80 °C, 4 h),^[10] two products were formed in an 85:15 ratio and 82 % overall yield (Scheme 3). Only minor amounts of the expected Heck product **14** were isolated; the major product was **15**, a compound resulting from a β -methoxide, rather than β -hydride elimination. The structure of **15** was unambiguously secured by X-ray crystallography.^[15] The quaternary carbon centers of both oxindoles **14** and **15** were formed in high



Scheme 3. Asymmetric Heck reaction of **11**.

enantiomeric ratios ($er=98:2$ and $>99:1$, respectively).^[16] O-Tosylation of the protected isatin fragment and X-ray analysis of the resulting O-tosylimidate derivative established the absolute configuration of **15**.^[15, 17]

In an attempt to access **15** from a simpler precursor, we investigated the Heck cyclization of (*Z*)-butenanilide **12** (Scheme 4). To our surprise, the asymmetric Heck reaction



Scheme 4. Asymmetric Heck reaction of **12**. $P^*P = (R)$ -BINAP.

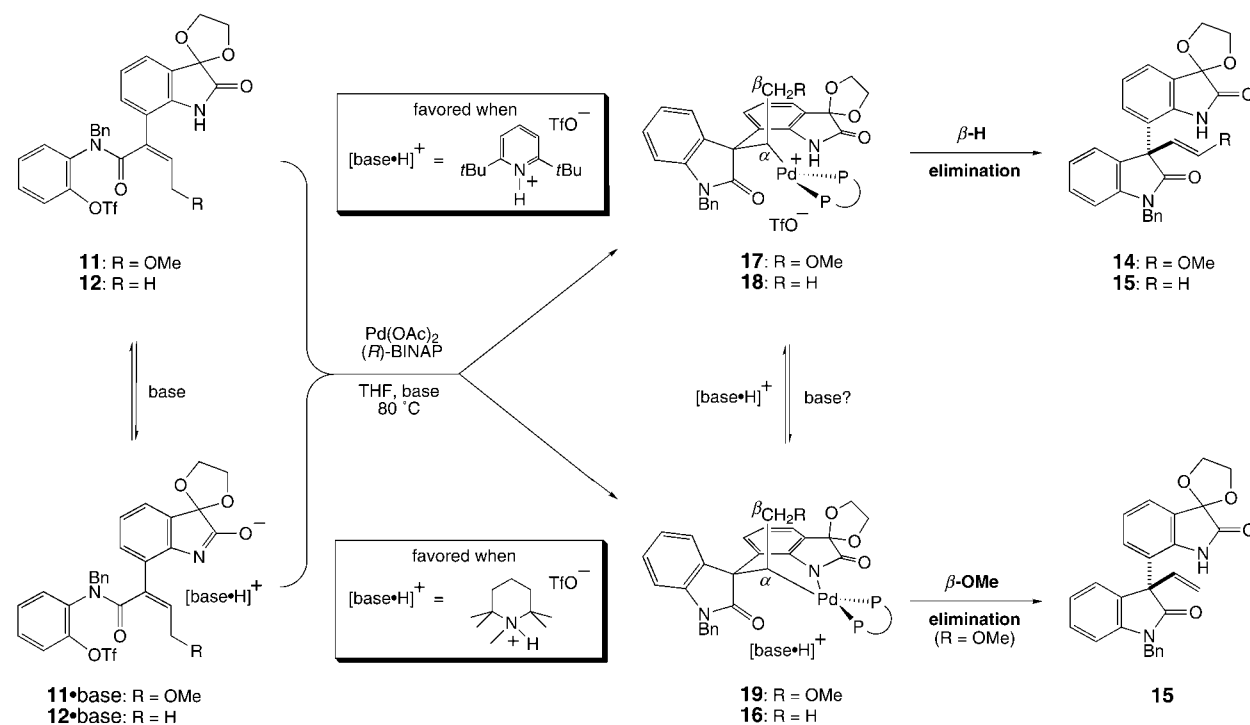
of **12** under identical conditions provided only traces of **15**, together with unreacted starting material and uncharacterized by-products. When **12** was cyclized in the presence of 100 mol % $Pd(OAc)_2$ and 150 mol % (*R*)-BINAP, substantial amounts (~ 35 –55% based on **12**) of a stable, palladium-containing compound **16** were isolated after workup and flash chromatography.

Careful mass spectrometric analysis and NMR studies support the structure depicted for **16** [$C_{27}H_{22}N_2O_4Pd \cdot (R)$ -BINAP] in Scheme 4. In particular, a ^{31}P – ^1H correlation proves the existence of the relevant fragment of palladacycle **16**: both phosphorus atoms, P_{cis} and P_{trans} , couple with the hydrogen atoms attached to C_α and C_β ; the individual coupling constants were resolved by decoupling experiments.^[18a] The

α -carbon has a diagnostic chemical shift of $\delta = 43.7$ in the ^{13}C NMR spectrum, which compares well with literature precedent for sp^3 -hybridized alkylpalladium compounds.^[19] The ^{31}P NMR spectrum with ^1H decoupling shows two sets of signals in a ratio of 95:5, which we assign as two epimeric palladacycles **16** and *epi*-**16**, indicating high stereoselection in forming the oxindole quaternary carbon center.^[18b]

To provide further evidence for the structure of **16**, a pure sample of this product was heated in THF at 80 °C for 4 h in the presence of an excess of PMP, 2,6-di-*tert*-butylpyridine (TBP), or PMP hydrotriflate. Palladium complex **16** proved to be stable under these conditions, suffering only minor decomposition. In dramatic contrast, addition of an equimolar amount of the stronger acid, TBP hydrotriflate^[20] to the bright yellow solution of **16** and THF at room temperature occasioned an instantaneous color change from yellow to red, indicating the generation of a Pd^0 –BINAP complex. After this solution had been heated at 80 °C for 4 h, the product of β -hydride elimination **15** was isolated in 48% yield ($er = 95:5$). As suggested by this observation, replacing PMP with TBP in Heck reactions of **11** and **12** had a profound effect on the product distribution. Carrying out these reactions in the presence of TBP provided conventional Heck products arising from β -hydride elimination (**11** $\rightarrow$ **14** and **12** $\rightarrow$ **15**, Scheme 5) in good yield (Scheme 5), in contrast to related cyclizations employing PMP as a base (Scheme 3 and 4).^[21]

Based on these observations, we propose that the reaction pathway of the Heck reactions of **11** and **12** is governed by the acidity of the conjugate acid of the trifluoromethanesulfonic acid scavenger employed. Although direct estimates do not exist for THF as solvent, TBP hydrotriflate should be a stronger acid than PMP hydrotriflate by about 7 pK_a units.^[22, 23] When the Heck cyclizations are carried out in the



Scheme 5. Postulated mechanism for the formation of **14** and **15**.

presence of the strong base PMP, palladacycles **16** and **19** are generated. Although **16** and **19** possess three and two β -hydrogen atoms, respectively, these intermediates do not undergo β -hydride elimination since a tightly bound ligand (BINAP or the conjugate base of the protected isatin) would have to dissociate to generate a vacant coordination site.^[24, 25] Therefore, palladacycle **16** is stable, while **19** undergoes β -methoxide elimination to generate **15**.^[26] In contrast, when the Heck reactions are carried out in the presence of the weaker base TBP, TBP hydrotriflate is acidic enough to shift the equilibrium from the palladacyclic intermediates toward the cationic palladium(II) species **17** and **18**, which undergo facile β -hydride elimination to generate conventional Heck products **14** and **15**.

In summary, an asymmetric Heck reaction has been successfully employed for the enantioselective construction (*er* > 99:1) of the quaternary stereocenter of an advanced intermediate en route to quadrigemine C (**1**). The unusual outcome of the Pd⁰–BINAP-catalyzed cyclization of **11** is rationalized by the intermediacy of palladacycle **19**, which preferentially suffers β -methoxide elimination. The corresponding palladacyclic intermediate **16** lacking a methoxy group on the β -carbon atom is a stable compound. Palladacycle **16** is a rare example of a stable σ -alkylpalladium complex that has β -hydrogen atoms residing on a freely rotating β -carbon atom.^[11] To the best of our knowledge, this is the first example of the isolation of an intermediate of this type in a Heck reaction.

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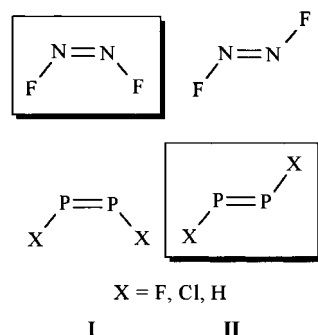
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Complex Chemical Stabilization of Dichlorodiphosphene**

Ulf Vogel, Gregor Stöber, and Manfred Scheer*

Dedicated to Professor Hansgeorg Schnöckel on occasion of his 60th birthday

Small molecules with multiple bonds between main group elements have always been a fascinating field. For example, N_2F_2 , the *cis* configuration **I** of which is 12.6 kJ mol⁻¹ more stable than the *trans* configuration **II**, has been known for a long time (Scheme 1).^[1] Although the phosphorus analogues

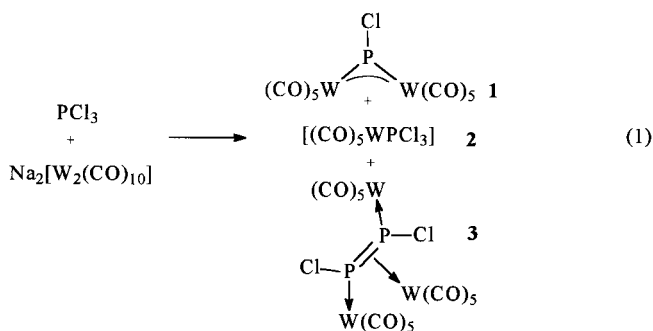


Scheme 1. *cis* and *trans* isomers of N_2F_2 and P_2X_2 (the thermodynamically favored configuration is marked by a frame).

P_2X_2 have not yet been obtained experimentally, ab initio-SCF calculations for $X = F$ show that the *trans* configuration **II** is 5.9 kJ mol⁻¹ more stable than the *cis* configuration **I** as the ground state for such a singlet molecule.^[2] For diphosphene, P_2H_2 , which was detected during the pyrolysis of diphosphane, P_2H_4 ,^[3] the *trans* configuration **II** is 15 kJ mol⁻¹ more stable than the corresponding *cis* configuration **I**.

Our CCSD(T) calculations^[4] regarding the stability of dichlorodiphosphene, P_2Cl_2 , show a similar result: here, the *trans* arrangement (C_{2h} symmetry, $d(P-P) = 2.066$ Å, $d(P-Cl) = 2.100$ Å, $\angle(Cl-P-P) = 97.5^\circ$) is more stable than the *cis* arrangement (C_{2v} symmetry, $d(P-P) = 2.072$ Å, $d(P-Cl) = 2.073$ Å, $\angle(Cl-P-P) = 108.7^\circ$) by 7 kJ mol⁻¹. As there has been no experimental proof for the existence of the dihalogenodiphosphenes until now, we report herein on the stabilization of dichlorodiphosphene in the coordination sphere of tungsten carbonyl complexes.

The extraction of the solid product from the reaction between $Na_2[W_2(CO)_{10}]$ and PCl_3 in THF with *n*-pentane/ CH_2Cl_2 yields a deep purple colored solution. According to its ³¹P NMR spectrum, this solution contains the chlorophosphinidene complex **1** as the main component, along with some **2**^[5] and the dichlorodiphosphene complex **3** [Eq. (1)].^[6] Whereas **1** and **2** decompose upon column chromatographic workup on silica gel, **3** can be isolated as a red solid in 17 % yield.



The ³¹P NMR spectrum of **1** shows a singlet at $\delta = 868$ with a ¹⁸³W,³¹P coupling constant of 200 Hz, which is in accordance with the NMR data of phosphinidene complexes with organic substituents. The ³¹P NMR shifts of these compounds are generally found at very low field (e.g. [MesP{W(CO)₅]₂]: $\delta = 961$, $^1J_{W,P} = 176$ Hz;^[7] Mes = 2,4,6-Me₃C₆H₂). This feature along with the $\pi-\pi^*$ transitions at long wavelengths in the visible spectra of these compounds are interpreted as an electron delocalization in a $3c-4\pi e^-$ system (structure **III**).^[8] This is supported by the crystal structure of [MesP{Cr(CO)₅]₂, which shows equidistant P–Cr bonds (2.263(1) Å).^[7] Our CCSD(T) calculations^[4] of **1** show also that the symmetric structure **III** represents an energy minimum (C_s symmetry, $d(P-Cl) = 2.120$ Å, $d(P-W1) = 2.449$ Å, $d(P-W2) = 2.442$ Å, $\angle(Cl-P-W1) = 109.9^\circ$, $\angle(Cl-P-W2) = 112.0^\circ$, $\angle(W-P-W) = 138.1^\circ$).

The red dichlorodiphosphene complex **3** is insoluble in *n*-hexane, slightly soluble in toluene, and readily soluble in CH_2Cl_2 . In the IR spectrum, CO stretching frequencies are found for terminal CO ligands.

The mass spectrum of **3** shows the molecular ion peak, as well as characteristic fragment ion peaks.

The ³¹P NMR spectrum of **3** shows a singlet at $\delta = 39.9$ with three tungsten satellites of similar intensity (¹⁸³W,³¹P coupling constants 26.0, 121.2, and 166.1 Hz, respectively). The ³¹P NMR signal of the structurally related phenyl-substituted diphosphene complex **4a** ($\delta(^{31}P) = -16.6$,^[9] -20.6 ^[10]), which



was synthesized by Huttner et al. as well as by Mathey et al., is found in a comparable chemical shift region. In contrast, however, signals of uncoordinated diphosphenes are shifted strongly downfield (e.g. $RP=PR$, $\delta(^{31}P) = 492.2$ (R = 2,4,6-*t*Bu₃C₆H₂)^[11]), and the resonance is shifted to high field if the molecule is side-on coordinated to a transition metal fragment (cf. $[\eta^1:\eta^1-P_2Ph_2\{Cr(CO)_5\}_2]$ ($\delta(^{31}P) = 927$ ^[12]) and **4b** ($\delta(^{31}P) = 97$ ^[9])). The largest $J_{W,P}$ coupling of **3** can be assigned to the coupling of the phosphorus atoms to the terminal penta-carbonyl tungsten units. Thus, for the complex $[R^1P=PR^2\{W(CO)_5\}]$ (R¹ = 2,4,6-*t*Bu₃C₆H₂, R² = 2,4,6-Me₃C₆H₂), in which the $[W(CO)_5]$ fragment is coordinated through only one lone pair of electrons on phosphorus, a $^1J_{W,P}$ value of 238 Hz is found,^[13] which is slightly larger than that in **3**. The two other ¹⁸³W,³¹P coupling constants of **3** should be

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assigned to $^2J_{\text{W,P}}$ coupling to the terminal $[\text{W}(\text{CO})_5]$ group and to the coupling to the tungsten atom that bridges the P–P double bond.^[14]

Compound **3** crystallizes from dichloromethane as red platelets. The central structural feature of **3**^[15] (Figure 1) is a P_2Cl_2 unit which is coordinated side-on to a $[\text{W}(\text{CO})_5]$ fragment. The two phosphorus atoms coordinate through

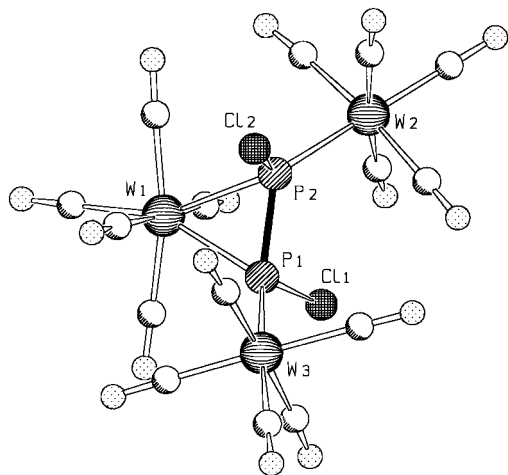
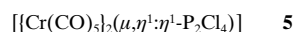


Figure 1. Molecular structure of $[\text{W}(\text{CO})_5(\mu, \eta^2: \eta^1: \eta^1\text{-P}_2\text{Cl}_2[\text{W}(\text{CO})_5]_2)]$ (**3**). Selected bond lengths [Å] and angles [°]: P1–P2 2.140(6), P1–Cl1 2.089(6), P2–Cl2 2.079(6), W1–P1 2.582(4), W1–P2 2.573(4), W2–P2 2.484(5), W3–P1 2.479(4); P1–W1–P2 49.1(1), P1–P2–W1 65.7(2), P2–P1–W1 65.2(2), Cl1–P1–P2 98.7(3), Cl2–P2–P1 98.9(3), W3–P1–P2 132.3(2), W2–P2–P1 126.7(2), Cl1–P1–W3 115.7(2), Cl2–P2–W2 117.1(2); torsion angles Cl1–P1–P2–Cl2 155.92, W2–P2–P1–W3 115.04.

their lone pairs additionally to two $[\text{W}(\text{CO})_5]$ moieties. The two phosphorus atoms are disordered (ratio 80:20). The bonding features of the molecule with the major occupancy are hereafter discussed. The P–P bond length (2.140(6) Å) is significantly shorter than the single bond in white phosphorus (2.21 Å)^[16] or in the tetrachlorodiphosphane complex **5**



(2.268(3) Å);^[17] however, it is significantly longer than the P–P bond in the free diphosphene $\text{RP}=\text{PR}$ ($\text{R} = 2,4,6\text{-}i\text{Bu}_3\text{C}_6\text{H}_2$, 2.034(6) Å).^[11] For the structurally similar complex **4a**, Huttner et al. and Mathey et al. reported P–P lengths of 2.14(1)^[9] and 2.162(3) Å,^[10] respectively; these values correspond well to the distance observed in **3**. The lengthening of the formal P–P double bond in **3** can be accounted for in terms of the electronic effects of η^2 -coordination to the $[\text{W}(\text{CO})_5]$ fragment.^[18] All P–W bonds in **3** are found to be slightly shorter (bridging, 2.582(4) and 2.573(5) Å; terminal, 2.484(5) and 2.479(4) Å) than those in **4a** (2.604 Å (av) and 2.535 Å (av),^[9]), which can be attributed to the more electronegative chlorine atoms as well as to the larger steric demand of the phenyl groups in **4a**. The difference in the torsion angle W2–P2–P1–W1 between **3** (115.04°) and **4a** (123.6°) also supports this explanation. The P–Cl bonds in **3** (2.084 Å (av)) are slightly longer than those in PCl_3 (2.030 Å)^[19] as well as those in the tetrachlorodiphosphane complex **5** (2.0435 Å (av)).^[17]

Good agreement was found between the X-ray structural data of **3** and values calculated for a C_2 -symmetric structure.^[14, 20] For example, a P–P of 2.175 Å (exp. 2.140(6) Å) and a P–Cl distance of 2.119 Å (exp. 2.089(6) and 2.079(6) Å) were obtained. The calculated vibrational spectrum of **3** also shows good agreement with the experimentally obtained IR and Raman spectra in the solid state, in which, for example, the symmetrical P–P stretching frequency is found at 434 cm^{-1} .^[21]

Experimental Section

PCl_3 (0.33 mL, 3.8 mmol) was added dropwise at ambient temperature to a solution of $\text{Na}_2[\text{W}_2(\text{CO})_{10}]$ (2.63 g, 3.8 mmol) in THF (25 mL). The color changed from yellow to reddish violet. All volatiles were immediately removed at reduced pressure, and the residue was extracted with a mixture of *n*-pentane/ CH_2Cl_2 (100 mL; 1/1). This solution was filtered over celite and washed twice with the same mixture ($2 \times 25\text{ mL}$). After removal of the solvent, the residue was separated by chromatography on a silica gel column (Merck 60, $2 \times 20\text{ cm}$). A red fraction, containing **3**, was eluted with *n*-hexane/toluene (5/1). Recrystallization from CH_2Cl_2 yielded **3** (150 mg; 17%) as red crystals.

1: $^{31}\text{P}\{^1\text{H}\}$ NMR (101.256 MHz, $[\text{D}_6]$ benzene, 298 K, 85% H_3PO_4 ext.): $\delta = 868.2$ ($J(\text{W,P}) = 200\text{ Hz}$); EI-MS (70 eV; 50°C): m/z (%): 713.8 (4) $[\text{M}^+]$, 657.8 (2) $[\text{M}^+ - 2\text{CO}]$, 629.8 (1) $[\text{M}^+ - 3\text{CO}]$.

2: $^{31}\text{P}\{^1\text{H}\}$ NMR (101.256 MHz, $[\text{D}_6]$ benzene, 298 K, 85% H_3PO_4 ext.): $\delta = 98.4$ ($J(\text{W,P}) = 427.2\text{ Hz}$); EI-MS (70 eV; 50°C): m/z (%): 461.8 (23) $[\text{M}^+]$, 433.8 (4) $[\text{M}^+ - \text{CO}]$, 426.8 (22) $[\text{M}^+ - \text{Cl}]$.

3: $^{31}\text{P}\{^1\text{H}\}$ NMR (101.256 MHz, $[\text{D}_6]$ benzene, 298 K, 85% H_3PO_4 ext.): $\delta = 39.3$ ($J(\text{W,P}) = 166.3, 121.2, 26.0\text{ Hz}$); IR (KBr): $\tilde{\nu}(\text{CO}) = 2114$ (m), 2076 (vs), 2041 (m), 2018 (s), 2003 (s), 1950 (sh), 1932 (vs, br); Raman (solid state): $\tilde{\nu} = 2112$ (s), 2078 (s), 2065 (m), 2042 (m), 2003 (s), 1991 (m), 1969 (w), 1942 (m), 1929 (m), 569 (w), 539 (w), 468 (w), 434 (s), 372 (w), 313 (m), 269 (m), 220 (w), 120 (m, br); EI-MS (70 eV; 70°C): m/z (%): 1103.6 (4) $[\text{M}^+]$, 1007.6 (0.2) $[\text{M}^+ - 2\text{Cl}]$, 1004.7 (1) $[\text{M}^+ - 2\text{Cl} - \text{CO}]$, 920.6 (0.5) $[\text{M}^+ - 2\text{Cl} - 4\text{CO}]$, 851.7 (10) $[\text{M}^+ - 9\text{CO}]$, 779.6 (2) $[\text{M}^+ - \text{W}(\text{CO})_5]$, 767.6 (13) $[\text{M}^+ - 12\text{CO}]$, 744.7 (34) $[\text{M}^+ - \text{W}(\text{CO})_5 - \text{Cl}]$, 35.5 (16) $[\text{Cl}^+]$, 28.0 (100) $[\text{CO}^+]$.

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column chromatographic workup on silica gel. The NMR data might correspond to $[\{W(CO)_5\}_2(\mu, \eta^1\text{-P}_2\text{Cl}_4)]$, for which a molecular ion peak at m/z (%) 851.7 (3) was found in the mass spectrum (EI-MS (70 eV, 50 °C)) of the crude reaction mixture. The analogous Cr derivative $[\{Cr(CO)_5\}_2(\mu, \eta^1\text{-P}_2\text{Cl}_4)]$ (**5**) has been synthesized and structurally characterized in reference [17].

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Crystal Structures from a Building Set: The First Boridecarbides of Niobium**

Harald Hillebrecht* and Knuth Gebhardt

*Dedicated to Professor Gerhard Thiele
on the occasion of his 65th birthday*

Borides and carbides of the “early” transition metals are distinguished by high chemical stability and unique physical properties such as high melting points (NbB₂: 3036 °C, NbC_{1-x}: 3600 °C), great hardness (NbB₂: 33 GPa, TiC: 27 GPa), and metallic conductivity. The development of methods to generate high temperatures^[1] has enabled the syntheses of these compounds. Structure analyses revealed that carbides can be described as interstitial compounds with carbon atoms in the octahedral holes of a close-packed array of metal atoms.^[2] NaCl-type structures prevail, frequently combined with a significant variation in the carbon content and a number of stacking and ordering variants have been described.^[3] In contrast, in borides the boron atoms usually prefer a trigonal prismatic coordination. Different compositions are given by connecting the prisms in different manners through the rectangular faces. According to the degree of condensation zigzag chains result (monoborides MB), single (M₃B₄) or double chains (M₂B₃) of boron hexagons, or graphite-like layers of hexagons (diborides MB₂, AlB₂-type). Without exception the boron–boron separations at around 1.8 Å are in the region of single bonds (e.g. V₃B₄, Nb₃B₄, CoB).^[4, 5]

An increase of these unique properties, or their modification, may be possible in ternary compounds M/B/C (M = metal atom). Numerous investigations by conventional means (direct reaction of the elements at high temperatures, melting in an arc furnace followed by annealing) only gave Mo₂BC, which is known since 1963.^[6, 7]

We suppose the main reason for the unsuccessful syntheses of further transition metal boridecarbides is that in the temperature region in which the desired compounds are thermodynamically stable product formation is impossible because of kinetic reasons. Our earlier investigations have shown that the use of molten metals as a reaction medium, as in an “auxiliary bath technique” (Lebeau^[8]), leads to single crystals of new compounds, which are not accessible by other means.^[9]

For transition metal borides the use of aluminum as an auxiliary metal is well established.^[10] But aluminum is not suitable for the synthesis of analogous carbides because the formation of Al₄C₃ dominates. The same is true in attempts to prepare boridecarbides as carbon again reacts to give Al₄C₃.^[5] With copper, which forms neither borides (exception CuB_{~24}) nor carbides,^[11] as an auxiliary metal single crystals of boron

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carbide B_4C ^[5, 12] are formed but no boridecarbides are produced. The starting point of our experiments was to try and vary the ratio of Al:Cu to assure a sufficient high reactivity of the transition metal towards boron and carbon on the one hand and to avoid the formation of Al_4C_3 and B_4C on the other.^[5] In the system Nb/B/C this concept led, for the first time, to the successful synthesis of a series of boridecarbides (see Experimental Section). The compounds Nb_3B_3C , $Nb_4B_3C_2$, $Nb_7B_4C_4$, and $Nb_7B_6C_3$ were yielded as single crystals and their structures determined.^[13]

All the four crystal structures (see Figure 1) are characterized by a separation into two partial structures with a layerlike arrangement. In the boride partial structure, boron

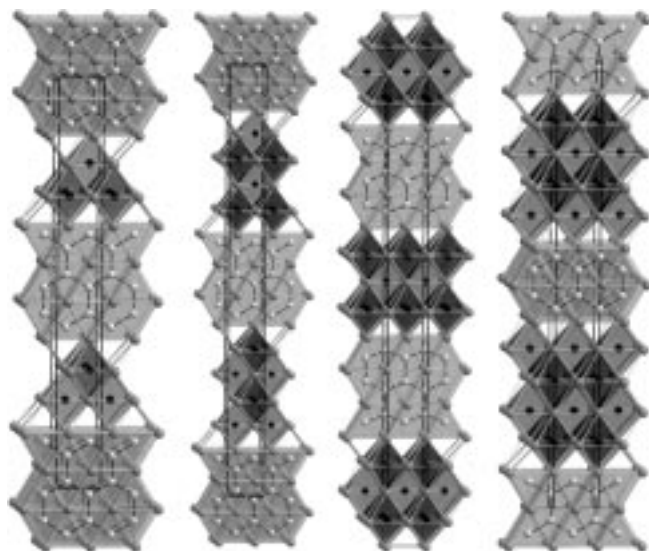


Figure 1. Crystal structure of (from left to right) Nb_3B_3C (view in $[100]$), $Nb_4B_3C_2$ (view in $[100]$), $Nb_7B_6C_3$ (view in $[010]$), and $Nb_7B_4C_4$ (view in $[001]$). Atoms: Nb grey, B white, C black; polyhedra: Nb_6C octahedra dark, Nb_6B trigonal prisms light.

atoms are trigonal prismatically coordinated by niobium. These trigonal prisms are interconnected by the rectangular faces forming boron–boron bonds. Thus the boron atoms build up hexagons which are connected to chains ($Nb_7B_4C_4$) or double chains (Nb_3B_3C , $Nb_4B_3C_2$, $Nb_7B_6C_3$). A junction to layers is made by joining the trigonal faces; the same structural motif is found in Nb_3B_4 and Nb_2B_3 . The carbide partial structure represents a fragment of an NaCl-type (100)-layer, that is, a cubic close packing of Nb atoms with carbon atoms in octahedral holes. The thickness of these layers varies, resulting in different compositions: $(NbC)_2$ in Nb_3B_3C ; $(NbC)_3$ in $Nb_7B_6C_3$; $(NbC)_4$ in $Nb_4B_3C_2$ and $Nb_7B_4C_4$.

Therefore the crystal structures of the four ternary compounds can be reduced to well-known fragments of binary phases by a combination of layers with different thickness: $Nb_3B_3C = (Nb_2B_3)_2(NbC)_2$, $Nb_4B_3C_2 = (Nb_2B_3)_2(NbC)_4$, $Nb_7B_6C_3 = (Nb_2B_3)_2(NbC)_3$, $Nb_7B_4C_4 = Nb_3B_4(NbC)_4$. Because of this close relationship the distances between the atoms are comparable to those in the binary compounds (Nb–Nb: 3.05–3.17 Å, Nb–C: 2.11–2.27 Å, Nb–B: 2.34–2.50 Å, B–B: 1.80–1.85 Å). The separation into two partial structures avoids boron–carbon bonds, which are known

from the boridecarbides of alkali earth metals,^[14] rare earth metals,^[15] and aluminum.^[9c] A significant substitution, that of boron for carbon, which is discussed in literature,^[3, 4] seems to be impossible because of the fundamentally different coordination spheres.

The free combination of boride and carbide layers is possible because both partial structures are based on a quadratic net of Nb atoms (4^4 net according to Schläfli). The different coordination polyhedra result from different ways of stacking the layers. For the carbide partial structure the next layer of Nb atoms is placed above and below the center of the square forming an octahedral hole. In the boride partial structure subsequent layers are placed identically above and below an edge of the square. Boron atoms are in trigonal prismatic holes above and below the square planes. Because there are twice as many boron atoms as Nb atoms in the 4^4 nets an NbB_2 composition results. The partial structures are linked because they share the “outer” 4^4 net of the layers. The different sizes of partial structures are described by the general formula $(NbB)_2(NbB_2)_n(NbC)_m$: Nb_3B_3C ($n=2$, $m=2$), $Nb_4B_3C_2$ ($n=2$, $m=4$), $Nb_7B_4C_4$ ($n=1$, $m=4$), and $Nb_7B_6C_3$ ($n=2$, $m=3$). The example of Nb_3B_3C and $Nb_4B_3C_2$ shows the space group remains unchanged if the value of n is changed by two (or any other even number). Independent of the n value the same is true for the values of m . So all members of the series $Nb_xB_yC_z$ can be reduced to one of four basic types, depending on whether m and n have odd or even values (see Table 1). Three of the four different combinations, leading to four different space groups, could be identified experimentally by us. Only for the case where n and m are odd (space group $Pmmm$) have we been unable to find a niobium boridecarbide.

Table 1. Classification of phases $Nb_xB_yC_z$ and related compounds according to a building-set principle $[(NbB)_2(NbB_2)_n](NbC)_m$.

m even n even	m even n odd	m odd n even	m odd n odd
<i>Cmcm</i>	<i>Immm</i>	<i>Cmmm</i>	<i>Pmmm</i>
Nb_3B_3C $n=2$, $m=2$	$Nb_7B_4C_4$ $n=1$, $m=4$	$Nb_7B_6C_3$ $n=2$, $m=3$	–
$Nb_4B_3C_2$ $n=2$, $m=4$			
Mo_2BC/Nb_2BN $n=0$, $m=2$	Nb_3B_4 $n=1$, $m=0$	Cr_2AlB_2 ^[a] $n=0$, $m=1$	Cr_3AlB_4 ^[a] $n=1$, $m=1$

[a] Ordering and defect variant, because C positions are empty and there are two kinds of metal atoms.

On the basis of this building-set principle it is not only possible to specify the different space groups for the four different variants but one can also predict lattice constants and positional parameters of each atom. Furthermore several other compounds with close structural relationships can be arranged into this scheme. Binary borides can be included by setting $m=0$ ($n=0$: NbB ; $n=1$: Nb_3B_4 ; $n=2$: Nb_2B_3 ; $n \rightarrow \infty$: NbB_2). The structure of Mo_2BC can also be classified ($n=0$ and $m=2$), where the boride fragment (zigzag chain) corresponds to the monoboride MoB . Crystal structure arrangements of ternary borides are yielded if the carbon

positions are empty and the metal positions were occupied in an ordered way by two different metals (see Table 1).

In general it should be possible to synthesize boridecarbides of other transition metals by following the modified auxiliary metal bath technique. Their crystal structures should fit the building-set principle outlined above. The fact that despite many attempts the synthesis of compounds analogous to Mo_2BC failed^[16] shows that besides geometrical reasons electronic factors also determine the field of stability and existence of transition metal boridecarbides. The existence of Nb_2BN ,^[17] which is isotypical to Mo_2BC , suggests that the same considerations are valid for M/B/N systems too. Experimental work in this field has been started. Further investigations on physical properties (electrical conductivity, magnetic properties) and band-structure calculations on niobium boridecarbides are in progress.

Experimental Section

Syntheses were carried out in corundum crucibles with argon as the inert atmosphere. The temperature program for a horizontal tube furnace was: RT to 1600 °C with 400 °C h⁻¹, 24 h holding, cooling to 1500 °C with 100 °C h⁻¹, cooling to 1100 °C with 1 °C h⁻¹, cooling to RT with 150 °C. Molar ratios Cu:Al:B:C:Nb were chosen as: $\text{Nb}_3\text{B}_3\text{C}$: 20:5:2:1:4, $\text{Nb}_4\text{B}_3\text{C}_2$: 20:5:0.2:0.1:0.2, $\text{Nb}_7\text{B}_6\text{C}_3$: 20:5:2:1:2, $\text{Nb}_7\text{B}_4\text{C}_4$: 20:5:0.1:0.1:0.2. Single crystals were yielded as irregularly shaped polyhedra after dissolving the metal excess in half conc. HNO_3 . A comparison of calculated and observed X-ray powder diagrams revealed that in all cases only one ternary compound was the main product with, in each case, microcrystalline NbC as a by-product. By means of energy dispersive X-ray spectroscopy (EDX) Nb was detected as the only metal, that is, the auxiliary metals Cu and Al were not incorporated significantly.

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Unlike in the reactions reported for the conventional Ru–organometallic fragments,^[2, 6, 8] the reaction discussed here, possibly, proceeds by a different pathway, which does not involve in a preliminary stage any η^2 complexation of the alkyne.^[11] Diphenylacetylene or other internal alkynes do not react with **1**. For **1**, we propose the preliminary protonation of the porphyrinogen skeleton^[12] followed by the binding of the acetylide anion to the metal (see intermediate **A** in Scheme 1), then rearrangement to the vinylidene functionality^[2, 6, 8] upon proton transfer from the porphyrinogen ligand. The protonation of Ni–porphyrinogen by $\text{PhC}\equiv\text{CH}$ ^[13] gave strong support to the hypothesis that the porphyrinogen ligand assists the proton transfer reaction; the reaction of **1** with $\text{CH}\equiv\text{CNa}$ in THF also supports this hypothesis. The reaction gave a compound which displays different structures in the solid state, depending on the crystallization solvent. The crystallization from dimethoxyethane (DME) led to **4a**, while the crystallization from THF gave the **4b** form. Both of these compounds contain the same core $[\{\text{Ru}(\text{Me}_8\text{N}_4)\}_2(\mu\text{-N}_2)(\mu\text{-Na})_4]^{2-}$, where the two Ru–porphyrinogen moieties are bridged by four sodium cations and a dinitrogen molecule.^[13] Although structural details are only given for **4b**, it is useful to stress the structural differences between **4a** and **4b**. The form **4a** contains the acetylide functionalities (Ru–C 1.875(3); C $\equiv$ C 1.185(4) Å) with two noninteracting sodium counteranions $[\text{Na}(\text{dme})_3]^+$, while in **4b** (see Figure 1),^[14] the terminal functionalities have the anionic vinylidene form, with the $[\text{Na}(\text{thf})_5]^+$ cations associated with them. In the latter case, the solvated sodium cation plays the role of an incoming electrophile (Ru=C 1.807(9), C=C 1.314(12) Å). Both forms **4a** and **4b**, when dissolved in $[\text{D}_8]\text{THF}$ ($\text{C}_4\text{D}_8\text{O}$), gave a ^1H NMR spectrum consistent with the **4b** structure. Complex **4b** in solution is easily protonated to **2**.

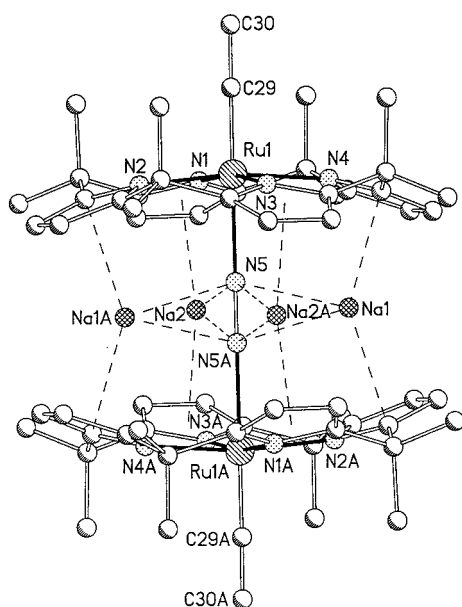


Figure 1. Molecular structure of **4b** (hydrogen atoms and $[\text{Na}(\text{thf})_5]^+$ ions are omitted for clarity). Selected distances [Å] and angles [°]: Ru1–N1– $\text{N}_{\text{average}}$ 2.119(8), Ru1–C29 1.807(9), Ru1–N5 2.251(8), C29–C30 1.314(12), N5–N5A 1.284(15), Na1...N5 2.573(10), Na1...N5A 2.609(9), Na2...N5 2.542(9), Na2...N5A 2.631(9); C29–Ru1–N5 179.2(4), N5A–N5–Ru1 177.4(10), C30–C29–Ru1 177.9(9). The A indicates the following symmetry operation: $-x+1, -y+1, -z+1$.

The vinylidene unit in **2** and **3** offers the synthetic entry to heterocarbenes and cumulenes otherwise inaccessible with macrocyclic ligands. Such synthetic versatility has been demonstrated in the reaction of **2** with methanol and thiophenol, leading to **5** and **6**, respectively.^[10] The reaction proceeds according to the vinylidene polarization with the proton reacting at the β carbon, followed by the nucleophile attacking the α carbon.^[2, 6] Unlike for many organometallic counterparts, the reaction occurs with a very high degree of selectivity and high yield. The characterization of **5** (Ru–C 1.80(1), C–OMe 1.38(1) Å) and **6** is given in the Supporting Information. The reaction of **2** with H_2O follows the pathway shown for the other protic substrates (Scheme 1, intermediates **B** and **C**),^[2, 6c] except that the final compound (**7**) has an acyl functionality which has been formed in conjunction with the oxidation of Ru^{II} to Ru^{III} , as depicted in Scheme 1. The complex is paramagnetic ($\mu_{\text{eff}} = 1.85$ BM at 293 K, $\tilde{\nu}_{\text{CO}} = 1577$ cm^{-1}), and has been characterized in the solid state by X-ray analysis (Ru–C 1.91(1), C=O 1.24(1) Å).

The vinylidene functionality in **2** allows a versatile derivatization of the Ru–porphyrinogen, thus providing an easy way to produce a dimetallabisvinylidene. The oxidation of **2** has been carried out using PhN_3 , which was reduced to aniline. The reaction led to **8**^[10] (Scheme 1; Ru–C 1.735(14), C–C 1.338(16), C–C 1.473(17) Å) by the oxidative coupling of the vinylidene functionality. The oxidation of **4b** using the oxidizing agent $[\text{Cp}_2\text{Fe}]^+$ gave **8** equally effectively (in solution **4a** converts into **4b**, see above). The latter reaction is reversible, since the reduction of **8** with Na–naphthalene gave back **4b** with the cleavage of a C–C single bond. The analytical and spectroscopic characterization of **8** is given in the Experimental Section while the X-ray structure, showing one out of the four sodium cations sandwiched between two porphyrinogen units, is displayed in Figure 2,^[14] the other

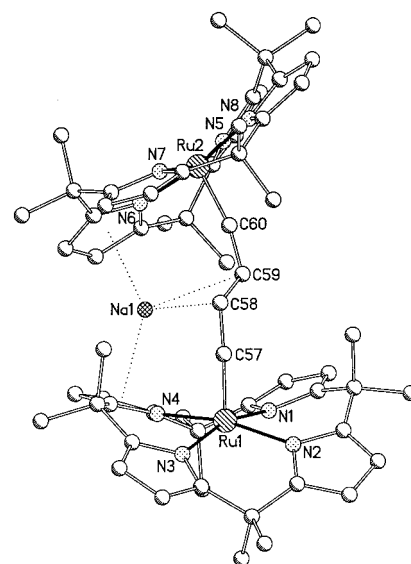


Figure 2. Molecular structure of compound **8** (hydrogen atoms, solvated sodium atoms, and solvent molecules are omitted for clarity). Selected distances [Å] and angles [°]: Ru1– $\text{N}_{\text{average}}$ 2.047(10), Ru1–C57 1.735(14), Ru2– N_{av} 2.033(12), Ru2–C60 1.734(14), C57–C58 1.338(16), C58–C59 1.473(17), C59–C60 1.326(17), Na1...C58 2.762(13), Na1...C59 2.796(14); C59–C60–Ru2 166.2(12), C58–C57–Ru1 164.6(11).

three sodium cations being present as solvent-separated cations. Complex **8** can provide an entry to dimetallacumulene and dimetallacarbene compounds.

Experimental Section

1: [RuCl₂(cod)] (6.19 g, 22.0 mmol; COD = 1.5 cyclooctadiene) was added to a solution of [Me₈N₄Na₄(thf)₄] (17.8 g, 22.0 mmol) in dimethoxyethane (DME; 300 mL). The reaction mixture was heated to reflux for 24 h and the NaCl was filtered off. The resulting solution was allowed to stand at –20 °C giving an orange crystalline product which was collected and dried in vacuo (11 g, 45 %). Crystals suitable for X-ray diffraction were grown in DME. ¹H NMR (400 MHz, [D₆]DMSO, 25 °C, TMS): δ = 5.74 (s, 8H; C₄H₂N), 3.41 (s, 24H; DME), 3.23 (s, 36H; DME), 1.43 (s, 24H; CH₃); ¹³C NMR (400 MHz, [D₆]DMSO, 25 °C): δ = 146.1, 100.1, 71.0, 58.0, 39.1, 36.9; elemental analysis calcd (%) for 1·6(C₄H₁₀O₂), C₅₂H₉₂N₄Na₂O₁₂Ru (1112.4): C 56.15, H 8.34, N 5.04; found: C 55.91, H 8.40, N 4.96.

2: A solution of 1·6(C₄H₁₀O₂) (1.50 g, 1.35 mmol) in THF (100 mL) was stirred under an acetylene atmosphere at room temperature for 24 h and then the solvent was removed in vacuo. The residue was treated with *n*-hexane (50 mL) giving an amber solid which was collected and dried in vacuo (0.93 g, yield 88 %). Crystals suitable for X-ray diffraction were grown in a mixture of THF/*n*-hexane. ¹H NMR (400 MHz, [D₆]benzene/[D₈]THF, 25 °C, TMS): δ = 6.46 (s, 8H; C₄H₂N), 3.06 (s, 8H; dimethoxyethane (DME)), 2.98 (s, 12H; DME), 2.78 (s, 2H; CH₂), 1.91 (s, 12H; CH₃), 1.81 (s, 12H; CH₃); ¹³C NMR (400 MHz, [D₆]benzene/[D₈]THF, 25 °C): δ = 300.28, 145.07, 102.44, 94.44, 71.51, 58.84, 39.49, 38.18, 33.21; IR (nujol, $\tilde{\nu}_{\text{max}}$): 1557.6 cm^{–1}; elemental analysis calcd (%) for 2·2(C₄H₁₀O₂), C₃₈H₅₄N₄Na₂O₄Ru (777.9): C 58.67, H 7.00, N 7.20; found: C 59.0, H 6.92, N 7.28.

4a:^[10] HC₂Na (86 mg, 1.8 mmol) was added to a solution of **1** (1.0 g, 0.9 mmol) in THF (100 mL) at room temperature. The reaction mixture immediately became light yellow. After 1 h of stirring, the solution was evaporated to dryness and the residue was washed with Et₂O (50 mL) to give a white solid which was collected and dried in vacuo (0.59 g, 77 %) (IR; $\tilde{\nu}_{\text{C}\equiv\text{C}}$, 2000 cm^{–1}). Crystals suitable for X-ray diffraction were grown in DME and have a different degree of solvation by THF than the noncrystalline product. ¹H NMR (400 MHz, [D₈]THF, 25 °C, TMS): δ = 5.76 (s, 8H; C₄H₂N), 5.68 (s, 8H; C₄H₂N), 3.47 (s, 24H; DME), 3.31 (s, 36H; DME), 2.19 (s, 2H; CH), 1.63 (s, 12H; CH₃), 1.58 (s, 12H; CH₃), 1.24 (s, 12H; CH₃), 1.18 (s, 12H; CH₃); elemental analysis calcd (%) for 4·6(C₄H₁₀O₂), C₆₄H₁₂₆N₁₀Na₆O₁₂Ru₂ (1808.0): C 55.80, H 7.02, N 7.75; found: C 55.85, H 7.05, N 7.67.

8: Method A: PhN₃ (0.61 mg, 5.14 mmol) was added to a solution of 2·2(C₄H₁₀O₂) (4.0 g, 5.14 mmol) in THF (100 mL). The reaction mixture was stirred at room temperature overnight, then evaporated to dryness and the solid residue triturated with *n*-hexane (100 mL) to give a brown solid which was collected and dried in vacuo (1.26 g, 85 %). Crystals suitable for X-ray diffraction were grown in a mixture of THF/dioxane. ¹H NMR (400 MHz, [D₅]pyridine, 25 °C, TMS): δ = 6.54 (s, 16H; C₄H₂N), 3.66 (s, 2H; CH), 3.48 (s, 16H; DME), 3.25 (s, 24H; DME), 1.90 (s, 24H; CH₃), 1.46 (s, 24H; CH₃); elemental analysis calcd (%) for 8·4(C₄H₁₀O₂), C₇₆H₁₀₆N₈Na₄O₈Ru₂ (1553.8): C 58.75, H 6.88, N 7.21; found: C 58.61, H 6.24, N 7.15. Method B: [Cp₂Fe]⁺BPh₄[–] (1.9 g, 3.38 mmol) was added to a solution of 4·4(C₄H₁₀O₂)·2(C₄H₈O) (2.8 g, 1.69 mmol) in THF (150 mL). The reaction mixture was stirred at room temperature overnight, then was evaporated to dryness and the solid residue triturated with *n*-hexane (100 mL) to give a brown solid which was collected and dried in vacuo (1.73 g, 76 %). ¹H NMR (400 MHz, [D₅]pyridine, 15 °C, TMS): δ = 6.54 (s, 16H; C₄H₂N), 3.66 (s, 2H; CH), 3.48 (s, 16H; DME), 3.25 (s, 24H; DME), 1.90 (s, 24H; CH₃), 1.46 (s, 24H; CH₃); elemental analysis calcd (%) for 8·4(C₄H₁₀O₂), C₇₆H₁₀₆N₈Na₄O₈Ru₂: C 58.75, H 6.88, N 7.21; found: C 58.73, H 6.21, N 7.09.

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direct methods and refined using the full-matrix least-squares on F^2 with all non-H atoms anisotropically defined (except the external sodium atom and the solvent molecules). For 4426 observed reflections ($I > 2\sigma(I)$) and 921 parameters, the conventional R is 0.0879 ($wR2 = 0.2670$ for 10835 independent reflections). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-154158 (**4**) and CCDC-154159 (**8**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

A Readily Available and User-Friendly Chiral Catalyst for Efficient Enantioselective Olefin Metathesis**

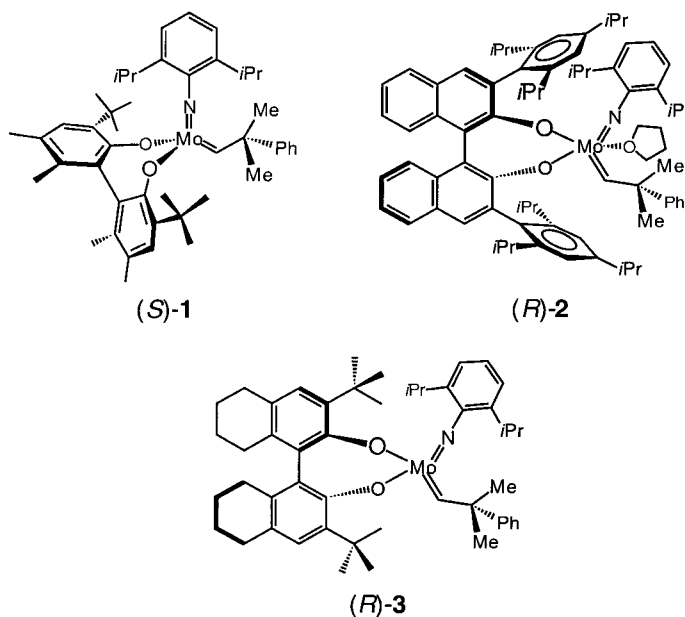
Sarah L. Aeilts, Dustin R. Cefalo,
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Amir H. Hoveyda,* and Richard R. Schrock*

We recently reported the synthesis and utility of various Mo-based chiral catalysts that promote enantioselective olefin metathesis.^[1] These complexes, represented by (*S*)-**1**^[2] and (*R*)-**2**^[3], are the only existing class of chiral catalysts that efficiently and selectively promote the formation of optically pure or enriched carbo- and heterocycles through asymmetric ring-closing^[4] and ring-opening metathesis (ARCM and AROM, respectively).^[5] One notable difference between **1** and **2** is that biphenolate **1** initiates selective ARCM of five-membered rings and binaphtholate **2** is often the catalyst of choice for the enantioselective synthesis of six-membered analogues.^[3]

From a practical point of view, binaphthol-based systems (e.g., **2**) have a significant advantage: the synthesis of the optically pure diolate begins from the inexpensive and commercially available (*R*)- or (*S*)-binaphthol.^[6] In contrast, access to the optically pure biphenol ligand in **1** and its derivatives requires resolution of the racemic samples by

fractional crystallization of the derived phosphorus(v) mentholates.^[2] We therefore judged that a chiral Mo complex that bears a “biphenol-type” ligand, but is synthesized from the readily available optically pure binaphthol, would be an important and valuable addition to this unique class of chiral catalysts. We also suspected that such a catalyst could exhibit greater generality: its reactivity and selectivity trends may overlap those exhibited by the biphenol- (e.g., **1**) and binaphthol-based complexes (e.g., **2**).

Herein, we report the synthesis, structure, and synthetic utility of chiral complex **3**, a Mo catalyst that resembles a



biphenol-based catalyst (**1**) but, similar to **2**, is easily prepared from optically pure binaphthol. We demonstrate that complex **3** offers a solution to the important problem of practicality in Mo-catalyzed asymmetric olefin metathesis. The new catalyst may be prepared from commercially available starting materials and can be used in situ, without isolation, to effect enantioselective olefin metathesis.

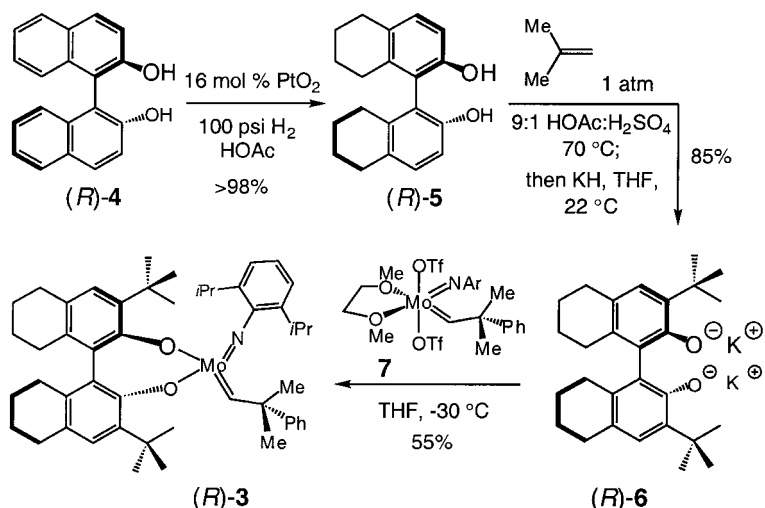
Preparation of chiral catalyst **3** (Scheme 1) begins with catalytic hydrogenation of commercially available, optically pure (*R*)-**4** in the presence of PtO_2 ^[7] under 100 psi (6.9 atm, 690 KPa) H_2 in glacial acetic acid (HOAc).^[8] In a 20 g (69.9 mmol) scale reaction, the desired octahydrobinaphthol **5** is formed in > 98 % yield (cream-colored powder).^[9] Installation of *t*Bu groups at the C2 and C2' sites is carried out by acid-catalyzed alkylation with isobutylene, a procedure that involves the difficult separation of the desired functionalized binaphthol from adventitious oligoisobutylenes; pure dialkylated product is obtained after chromatography on silica gel in 40 % yield. However, when the unpurified mixture is directly treated with 2 equivalents of KH, the derived dipotassium salt (*R*)-**6** is isolated in 85 % yield. Through this procedure, oligoisobutylene impurities are removed by washing with pentane. The resulting dipotassium salt (*R*)-**6** (soon to be commercially available through Strem) does not need further purification before it is employed in the synthesis of **3**.^[10]

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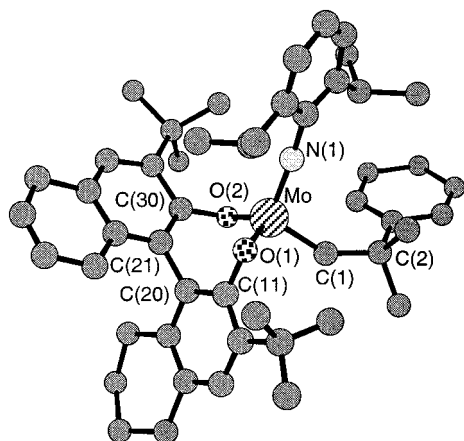
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

Scheme 1. Synthesis of chiral catalyst **3**.

Complex (*R*)-**3** is synthesized by treatment of (*R*)-**6** with bis(triflate) **7** at -30°C in THF in 55% yield as an orange solid after recrystallization from MeCN to afford (*R*)-**3**·MeCN, a complex that releases the bound solvent in vacuo, yielding analytically pure (*R*)-**3**.^[11] The (*R*)-**3**·MeCN complex allows for facile isolation of the chiral catalyst, since solvent free **3** is soluble in hydrocarbons (e.g., pentane and toluene) and Et₂O and is recrystallized with difficulty even from these relatively nonpolar media. We have prepared *rac*-**3** in an analogous manner and find that it can be recrystallized far more readily (vs. (*R*)-**3**) to deliver red needles from *n*-octane.

Crystals of *rac*-**3** were suitable for X-ray crystallography (Figure 1).^[12] Distances and bond angles in **1**^[4b] and **3**, listed in Table 1 for comparison, indicate that the geometry of the

Figure 1. X-ray structure of **3**.

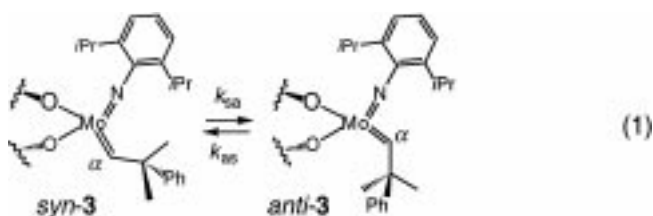
chiral diolate in **3** deviates significantly from that of the biphenolate in **1**. In particular, the dihedral angle C(30)–C(21)–C(20)–C(11) is smaller in **3** than in **1** (88.6° vs. 102.2°). Other structural differences between **1** and **3** include: a smaller O–Mo–O angle in **3** ($119.9(5)^{\circ}$ vs. $127.0(2)^{\circ}$), and larger Mo–O–C bond angles in **3** ($102.8(7)^{\circ}$ and $102.0(8)^{\circ}$ vs. $97.1(4)^{\circ}$ and $96.8(4)^{\circ}$). The above features are consistent

Table 1. Selected bond lengths [Å] and angles [$^{\circ}$] in chiral Mo complexes **1** and **3**.

	Complex 1	Complex 3
Mo–N(1)	1.738(6)	1.761(11)
Mo–C(1)	1.885(10)	1.919(13)
Mo–O(1)	1.999(5)	1.949(8)
Mo–O(2)	2.006(5)	1.980(9)
N(1)–Mo–C(1)	105.2(3)	106.0(6)
N(1)–Mo–O(1)	110.2(2)	105.9(5)
N(1)–Mo–O(2)	107.9(3)	115.0(5)
C(11)–O(1)–Mo	97.1(4)	102.8(7)
C(30)–O(2)–Mo	96.8(4)	102.0(8)
O(1)–Mo–O(2)	127.0(2)	119.9(5)
C(2)–C(1)–Mo	143.8(7)	146.4(11)
C(30)–C(21)–C(20)–C(11)	102.2(8)	88.6(15)

with a greater steric repulsion between the cyclohexyl rings of the chiral diolate and the imido and alkylidene groups, as compared to the smaller Me substituents in **1**.

Crystals of *rac*-**3** exist as *syn*-alkylidene isomers [Eq. (1)]. Nonetheless, in the ^1H NMR spectrum of **3** (C₆D₆, 22°C), in



addition to a resonance at $\delta = 10.97$ assigned to the alkylidene CH in the *syn* isomer (determined by ^{13}C satellite resonances), there is another resonance at $\delta = 12.76$, assigned to the alkylidene CH in the *anti* isomer. At 22°C , the *syn/anti* equilibrium constant is ~ 13 , and the *syn* and *anti* CH resonance signals sharpen when the sample is cooled to 0°C and broaden when it is heated to 70°C . The latter observation is consistent with interconversion of the two isomers on the NMR time scale. We have calculated a rate constant (k_{sa} , [Eq. (1)]) for *syn* to *anti* conversion by spin-saturation transfer experiments. At 20°C , $k_{sa} = 0.21(1) \text{ s}^{-1}$, a value that is similar in magnitude to that measured for **1** (0.50 s^{-1}).^[13, 14] These findings suggest that both *syn* and *anti* alkylidenes are probably accessible in solution. Therefore, it may well be the relative rates of the subsequent steps (e.g., metallacyclobutane formation) that determine the identity of the faster reacting (kinetic resolution) or major enantiomer (asymmetric synthesis).

The data summarized in Table 2 illustrate some of the unique attributes of chiral complex **3** in connection with its ability to catalyze the kinetic resolution^[15] of polyenes. Catalytic ARCM in entries 1–3 indicate that **3**, similar to the biphen-based catalyst **1** but in contrast to binaphtholate **2**, efficiently promotes the kinetic resolution of **11**.^[16] There is no significant difference in the activity of **3** versus **1**, and the amount of dimeric side product^[17] generated by **3** remains relatively small. Another example is the catalytic resolution of diene **13** in entries 4–6; although more dimer is generated than

Table 2. Mo-catalyzed kinetic resolutions through ARCM.^[a]

Entry	Substrate	Product ^[b]	Catalyst	Time	Conv [%] ^[c]	Dimer [%]	<i>k</i> _{rel} ^[d]
1	 (±)- 11	 (<i>S</i>)- 12	1	2 min	52	< 2	> 25
2			2	5 min	63	< 2	3.0
3			3	2 min	58	7	> 25
4	 (±)- 13	 (<i>S</i>)- 14	1	1 h	54	47	< 2.0
5			2	1 h	60	8	> 25
6			3	1 h	65	45	> 25
7	 (±)- 15	 (<i>R</i>)- 16	1	5 min	51	< 2	2.0
8			2	30 min	41	< 2	5.0
9			3	5 min	42	18	20
10	 (±)- 17	 (<i>S</i>)- 18	1	5 min	59	< 2	11
11			2	6 h	44	< 2	< 2.0
12			3	1 h	58	< 2	23

[a] Conditions: 5 mol % catalyst, Ar atmosphere, C₆H₆. [b] Identity of products shown is for reactions promoted with catalysts **2** and **3** ((*R*)-binaphtholates); the opposite isomer is generated with **1** ((*S*)-biphenolate). [c] Conversion determined by analysis of the 400 MHz ¹H NMR spectrum of the unpurified mixture. [d] Enantioselectivity determined by gas-liquid chromatography (GLC) analysis (CHIRALDEX-GTA by Alltech) in comparison with authentic racemic material. Relative rate determined based on the recovered substrate (see ref. [16]).

in reactions involving diene **11**, complex **3** provides similar levels of selectivity observed with binaphthol **2** but not **1**. In the catalytic resolution of **15** (entries 7–9), **3** affords larger amounts of the dimeric product. It is however only catalyst **3** that initiates a resolution with *k*_{rel} = 20 (entry 9); biphenolate **1** or binaphtholate **2** fail to deliver substantial levels of enantioselection (entries 7 and 8). Entries 10–12 provide an example of a catalytic kinetic resolution of a 1,6-diene, a class of substrates for which complex **1** is particularly well suited.^[4a] Complex **3** catalyzes ARCM even more efficiently and enantioselectively than **1**. The above data collectively illustrate that the more readily available **3** promotes catalytic ARCM with similar or higher levels of selectivity than **1**.

The data in Table 3 showcase representative catalytic asymmetric desymmetrization processes involving catalysts **1**–**3**. With triene **19** as the substrate, catalyst **3** is more efficient than **1** and affords the desired compound **20** with similar levels of selectivity as with **1** and **2**. In the case of the catalytic ARCM of silyl triene **21**, another representative of a class of substrates for which **2** is most suitable,^[3] catalyst **3** not only performs far more efficiently and selectively than **1**, it delivers (*R*)-**22** in 96 % *ee* and 54 % isolated yield. The catalytic ARCM effected by **3** (entry 6) remains synthetically useful, but is less efficient and selective than that effected with **2** as the catalyst (entry 5). Nevertheless, the outcome shown in entry 6 of Table 3 is delivered by a catalytic system (**3**) that

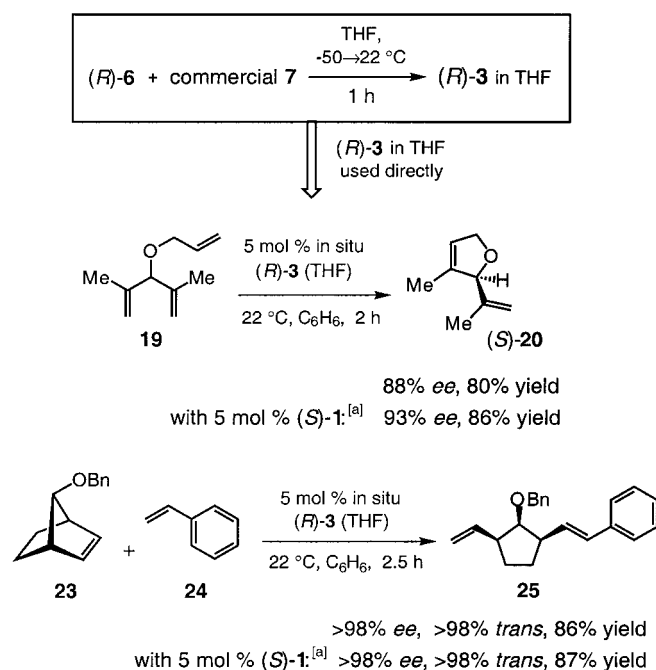
Table 3. Enantioselective desymmetrization through Mo-catalyzed ARCM.^[a]

Entry	Substrate	Product ^[b]	Catalyst	Time [h]	<i>T</i> [°C]	Conv [%] ^[c]	Dimer [%]	Yield [%] ^[d]	<i>ee</i> [%] ^[e]
1	 19	 (<i>S</i>)- 20	1	6	22	52	< 2	86	93
2			2	1	22	63	< 2	72	90
3			3	1	22	58	7	81	92
4	 21	 (<i>S</i>)- 22	1	24	22	50	32	17	65
5			2	3	60	> 98	< 2	98	> 98
6			3	3	80	69	11	54	96

[a]–[c] See Table 1. [d] Yields of isolated products after silica gel chromatography. [e] Enantioselectivity determined by GLC analysis (CHIRALDEX-GTA by Alltech) in comparison with authentic racemic material.

can perform as well or better in cases where catalyst **2** is entirely ineffective (see entries 1–3 and 10–12, Table 2).

Not only is catalyst **3** more easily prepared than **1**, more importantly, as illustrated in Scheme 2, a solution of this chiral complex, obtained by the reaction of commercially available



Scheme 2. In situ preparation and utility of chiral metathesis catalyst **3**. [a] Reactions were promoted by (S)-**1** to afford the enantiomers of the products shown.

reagents bis(potassium salt) **6** (Strem) and Mo triflate **7** (Strem), can be directly used to promote enantioselective metathesis (see the Experimental Section for procedure). Regarding the in situ catalyst preparation and use, it must be noted that: 1) similar levels of reactivity and selectivity are obtained with in situ **3** as with isolated and purified **1** or **3** (see Scheme 2),^[18] 2) asymmetric olefin metatheses proceed with equal efficiency and selectivity with the same stock solutions of (R)-**6** and **7** after two weeks, 3) the use of a glove box, Schlenck equipment, or vacuum lines is not necessary (even with the two-week old solutions). These findings demonstrate that chiral catalyst **3** is highly user-friendly. An efficient and active catalyst solution can be accessed by the pre-mixing of a readily available salt ((R)-**6**) and a commercially available Mo triflate (**7**); this active catalyst can be used directly, without further purification, in a typical fume hood (under N₂). Noteworthy is that the formation of **25** (Scheme 2) cannot be effected by the new generation of imidazolium-based Ru catalysts (5 mol % or one equivalent catalyst at 22 or 75 °C).^[19] That is, in addition to being easy to use (commonly a Ru catalyst trademark), chiral Mo-based complexes disclosed herein offer reactivity and selectivity levels that remain unavailable with Ru-based complexes.

In summary, we disclose the synthesis, structure, and synthetic utility of a Mo-based chiral metathesis catalyst that is prepared more easily and efficiently than **1**, can be used in situ in a regular fume hood (vs. a dry box), and without the

need for Schlenck or other specialty glassware. Catalyst **3** promotes ARCM reactions with equal or higher levels of efficiency and selectivity than **1**. Moreover, since **3** shares certain structural features with binaphtholate **2**, it may also be employed to effect asymmetric olefin metatheses that are typically best performed by the latter complex. The advent of chiral catalyst **3** elevates the status of Mo-catalyzed asymmetric olefin metathesis to a practical as well as efficient and unique method for the synthesis of optically enriched or pure organic molecules.

Experimental Section

(R)-**6**:^[20] Diol (R)-**5** (7.0 g, 23.8 mmol) was placed in a 88 mL pressure vessel and sulfuric acid (7 mL) and glacial acetic acid (63 mL) were added. The vessel was flushed with isobutylene and pressurized to 1 atm. The mixture is heated to 70 °C and allowed to stir for 14 h, at which time pressure was released, water (35 mL) added, and the biphasic mixture washed with Et₂O (2 × 20 mL). Organic layers were washed with a saturated solution of NaHCO₃ (2 × 20 mL), and dried over MgSO₄. Solvent removal in vacuo left behind a tan liquid; subsequent vacuum distillation (85 °C, 0.03 mm Hg) partially removed adventitious isobutylenes to afford impure (R)-**5** as a brown solid. The solid was dissolved in THF (20 mL) and KH (1.91 g, 47.6 mmol) added slowly in portions (22 °C, within 20 min). The resulting mixture was stirred for 1 h at 22 °C, then diluted with Et₂O (10 mL) and THF (5 mL), and filtered through Celite. Removal of the volatiles in vacuo produced a brown solid, which was washed with pentane (4 × 10 mL) and dried in vacuo to yield 9.80 g of (R)-**6** as cream-colored powder (20.3 mmol, 85 % yield). This material was used directly in the synthesis of **3**, described below.

(R)-**3**: Diolate (R)-**6** (500 mg, 1.04 mmol) was dissolved in cold (−30 °C) THF (10 mL at −30 °C) and added to a stirred solution of **7** (820 mg, 1.04 mmol) in cold THF (25 mL at −30 °C). The solution was warmed to 22 °C and the mixture stirred for 0.5 h. Volatiles were removed in vacuo to afford a brown solid. The product was taken up in pentane (20 mL) and filtered. The pentane was subsequently removed in vacuo to give the unpurified product as a dark orange powder. Precipitation from MeCN delivered **3**·MeCN as an orange solid (1.67 g, 55 % yield), which was later freed of acetonitrile in vacuo. ¹H NMR (C₆D₆): δ = 12.76 (s, 0.08 H, MoCH anti), 10.97 (s, 0.92 H, ¹J_{C,H} = 120, MoCH syn), 7.46 (d, ³J_{H,H} = 7.0, 2 H, neophyl o-H), 7.39 (s, 1 H, aromatic H), 7.20 (t, ³J_{H,H} = 7.5, 2 H, neophyl H), 7.12 (s, 1 H, aromatic H), 7.04 (t, ³J_{H,H} = 7.5, 1 H, neophyl p-H), 6.93 (s, 3 H, imido aromatic H), 3.67 (sept, ³J_{H,H} = 6.6, 2 H, CH(CH₃)₂), 2.69 (t, ³J_{H,H} = 5.5, 2 H, cyclohexyl H), 2.60 (qt, ³J_{H,H} = 2.3, 3 H, cyclohexyl H), 2.50 (dt, ³J_{H,H} = 1.8, 1 H, cyclohexyl H), 2.30 (dt, ³J_{H,H} = 1.8, 1 H, cyclohexyl H), 2.00 (m, 2 H, cyclohexyl H), 1.87 (s, 3 H, C(CH₃)₂Ph), 1.62 (s, 9 H, *t*Bu), 1.55 (s, 9 H, *t*Bu), 1.53 (m, 8 H, cyclohexyl H), 1.15 (d, ³J_{H,H} = 6.5, 6 H, CH(CH₃)₂), 1.11 (s, 3 H, C(CH₃)₂Ph), 0.93 (d, ³J_{H,H} = 7.0, 6 H, CH(CH₃)₂); ¹³C NMR (C₆D₆): δ = 275.9, 155.1, 154.4, 153.8, 151.5, 146.6, 140.2, 138.3, 136.5, 135.8, 132.2, 131.7, 131.6, 130.5, 128.8, 128.6, 128.6, 127.8, 127.8, 126.3, 123.7, 53.5, 36.0, 35.7, 30.7, 30.5, 29.2, 28.1, 27.8, 23.9, 23.8, 23.6, 33.4, 33.0, 30.8, 30.4, 24.7, 24.6, 23.5; elemental analysis calcd (%) for C₃₀H₆₅MoNO₂: C 74.32, H 8.11, N 1.73; found: C 74.22, H 8.04, N 1.70.

Representative procedure for in situ use of catalyst **3**: Solutions of (R)-**6** (48.3 mg, 0.100 mmol, 1 mL THF) and **7** (79.2 mg, 0.100 mmol, 1 mL THF) were prepared and cooled to −50 °C (under N₂). Subsequently, 100 μL (0.01 mmol) of each solution was withdrawn, mixed in a flask cooled to −50 °C, and then warmed to 22 °C (1 h). At this point, a solution of **19** (34.4 mg, 0.2 mmol, corresponding to 5 mol % loading of in situ **3**) in C₆H₆ (2 mL) was added and the mixture stirred for 2 h at 22 °C (95 % conv). Typical work up,^[3] followed by chromatography on silica gel affords (S)-**20** in 88 % ee and 80 % yield.

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- [8] Catalytic hydrogenation under lower pressures of H₂ are significantly slower (e.g., consumption of **4** after one week at 45 psi (310 kPa, 3 atm)) and some partially hydrogenated product is often present.
- [9] Optically pure **5** is available from Kankyo Kagaku Center, but at nearly ten times the cost of (*R*)- or (*S*)-**4**.
- [10] To establish the enantiopurity of dialkylation product (*R*)-**6** and its corresponding diol, the derived mentholate phosphate was prepared and its ³¹P NMR spectrum was compared to that of a sample of *rac*-phosphate. The spectrum of a racemic sample exhibits two resonances at $\delta = 144.4$ and 139.2 (1:1 ratio); that of (*R*)-phosphate contains a single resonance at $\delta = 144.9$. Oxidation to the corresponding phosphonate and comparison of its ³¹P NMR spectrum to that of the corresponding racemic mixture was carried out as well ($\delta = -4.9$ and -3.3 for the *rac* sample and -4.9 for the (*R*)-isomer).
- [11] Protonated (*R*)-**6** may also be treated with two equivalents of benzyl potassium and one equivalent of Mo triflate **7** (22 °C, THF) to afford optically pure (*R*)-**3** in 41 % isolated yield after purification.
- [12] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155703. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [13] Values for *k_{sa}* (determined at 10 °C intervals from 0 to 30 °C) were used to establish the activation parameters for **3** from an Eyring plot (*R*² = 0.994); these calculations give $\Delta H^\ddagger = 15.7(0.9)$ kcal mol⁻¹ and $\Delta S^\ddagger = -8(3)$ kcal K⁻¹ mol⁻¹.
- [14] The variable temperature ¹H NMR spectra of **3** with one equivalent of MeCN indicates the presence of all four possible **3**·MeCN diastereomers (–60 °C). There is a notable downfield shift of the alkylidene H resonance of the less Lewis acidic *syn* isomer as the temperature is lowered, indicating the weaker association of *syn* **3** with MeCN. The more Lewis acidic *anti* isomers require a higher temperature (~0 °C) for the same process to occur.
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- [17] By dimeric product we mean the material obtained by catalytic intermolecular cross-coupling of two substrate molecules through their terminal alkenes.
- [18] The reaction times with in situ **3** are longer (e.g., 2 h vs. 1 h for formation of (*R*)-**20**) because of the presence of the Lewis basic solvent THF. Typically the final ratio of THF:C₆H₆ is ~1:10.
- [19] Treatment of **23** and the derived methoxymethyl (MOM) ether of **23** with styrene in the presence of 5–100 mol % of imidazolium-containing Ru catalysts of Grubbs or Hoveyda at 22 or 75 °C (CH₂Cl₂

and CHCl₃) results in <5 % conversion after 12 h. See: a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956; b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

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Modular Pyridinyl Peptide Ligands in Asymmetric Catalysis: Enantioselective Synthesis of Quaternary Carbon Atoms Through Copper-Catalyzed Allylic Substitutions**

Courtney A. Luchaco-Cullis, Hirotake Mizutani, Kerry E. Murphy, and Amir H. Hoveyda*

Dedicated to Professor David A. Evans on the occasion of his 60th birthday

To develop a new transformation and achieve maximum levels of reactivity and selectivity, myriad reaction parameters must be explored and adjusted. In the context of establishing an effective catalytic enantioselective process,^[1] the choice of an appropriate chiral ligand and metal salt is perhaps most crucial: a blend of mechanistic knowledge (e.g., details of coordination chemistry) and human intuition are typically used to identify a desirable metal–ligand combination. Such a task becomes significantly more facile if readily modifiable chiral ligands are at hand; depending on the nature of the metal salts involved and the type of transformation that is being developed, ligand structures may be altered so that reactivity and selectivity levels are improved. The latter approach is particularly attractive if identification of the lead candidates is accomplished through screening of ligand libraries.^[2]

In the past few years we have studied and developed various peptide-based ligands that promote a range of catalytic asymmetric C–C bond-forming reactions. In all instances, optimal catalysts have been identified through examination of collections of peptide–metal complexes.^[3–6] Peptidic structures represented by **I** (Figure 1) have been developed to initiate efficient and asymmetric Ti-catalyzed CN addition to epoxides^[3] and imines.^[4] Zr-catalyzed alkylation of imines has been demonstrated to proceed efficiently and with high asymmetric induction in the presence of ligands

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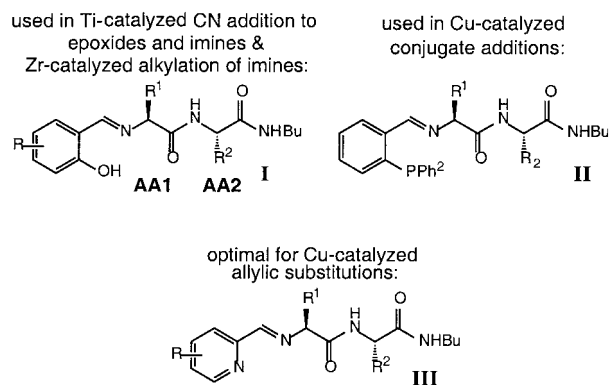


Figure 1. Various peptide-based chiral ligands used in catalytic asymmetric reactions involving early and late transition metals.

I or the corresponding peptidic amines.^[5] Chiral phosphines **II** effect catalytic asymmetric conjugate additions to cyclic enones, where both the catalyst (CuOTf; OTf = trifluoromethanesulfonate) and the reagent (dialkylzinc reagents) are late transition metal complexes.^[6] In every instance, readily modular and non-*C2*-symmetric^[7] peptide-based chiral ligands have played a central role in establishing optimal reactivity and selectivity.

More recently, we set out to investigate the possibility of using peptidic ligands to promote enantioselective allylic substitutions. Largely because of the scarcity of related protocols, we are particularly interested in transformations that utilize the less explored “hard” alkylating agents^[8] which enantioselectively deliver the problematic quaternary carbon centers.^[9] Herein, we report the results of our studies regarding the development of Cu-catalyzed allylic substitutions, in which pyridinyl peptidic structures represented by **III** (Figure 1) emerge for the first time as the chiral ligands of choice. The catalytic enantioselective method described allows for the efficient, regio- and enantioselective formation of quaternary carbon centers from readily available substrates, catalysts, and alkylating agents.

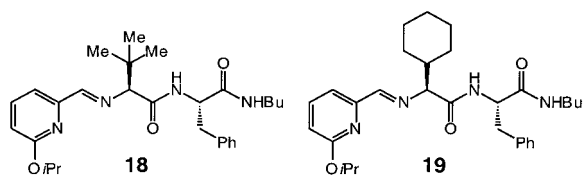
We initiated our search for the optimal conditions by using the more reactive and readily accessible disubstituted olefins (vs. trisubstituted alkenes described below). Since CuCN exhibits a preference for the *S_N2'* mode of addition in related processes with Grignard reagents, it was selected for the preliminary optimization studies (in preference to copper halides or acetate).^[10] Examination of potential substrates indicated that allylic phosphates are the most suitable starting materials (see Scheme 1).^[11, 12] These electrophiles are inert to Et₂Zn but undergo alkylation in the presence of Cu salts in CH₂Cl₂, toluene, Et₂O, and THF. The corresponding chlorides react smoothly with Et₂Zn in CH₂Cl₂, toluene, or Et₂O (−30 °C, 18 h, without ligand and Cu salt) and the derived acetates, phenyl ethers, and phenyl carbamates afford <10% conversion, even in the presence of Cu salts (e.g., CuCN and CuCl). With the above parameters clarified, we turned our attention to the identification of optimal ligands. Related mechanistic work suggest that the Schiff base portion of the peptidic ligands is likely to be a metal-ligation site and is critical to reactivity and selectivity.^[13] We therefore decided to perform catalyst optimization in the following order: 1) iden-

tify the optimal Schiff base type, 2) ascertain the identity of the most desirable Cu salt, 3) determine the optimal peptidic construct (e.g., di- or tripeptide), 4) further enhance the enantioselectivity through identification of the optimal Schiff base and amino acid moieties.

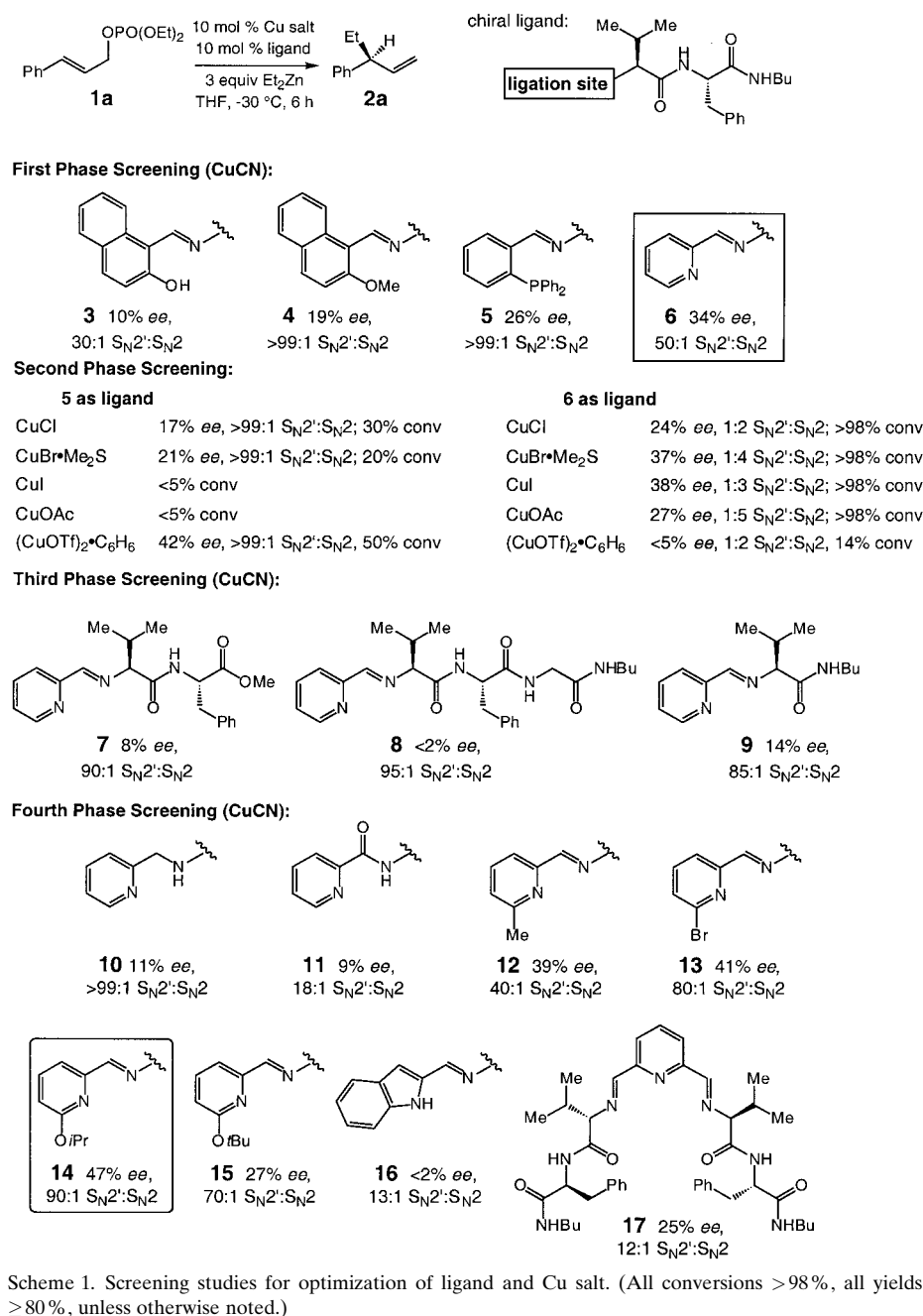
Chiral ligands **3–6** (Scheme 1) were prepared. Readily available L-Val and L-Phe served as the AA1 and AA2 and the Schiff base structure was altered. As shown in Scheme 1 (First Phase Screening), treatment of phosphate **1a** with Et₂Zn in the presence of 10 mol% CuCN and chiral ligands **3–6** in THF at −30 °C leads to >98% conversion within 6 h. Pyridine dipeptide **6** delivers the highest level of enantioselectivity (34% *ee*), followed by phosphine **5** (26% *ee*). To ascertain the identity of the most efficient and selective ligand/Cu salt combination, formation of **2a** was examined in two sets of experiments involving ligands **5** and **6** and a collection of Cu salts (see Scheme 1, Second Phase Screening). This study established that **6** and CuCN, overall, provide the most efficient, regio- and enantioselective process.^[14]

Next, we secured the following additional ligand attributes (Third Phase Screening, Scheme 1): 1) an amide terminus is critical to the enantioselectivity; replacement of the NHBu in **6** with an OMe group (**7**, Scheme 1) leads to a significant reduction of *ee*, 2) incorporation of a third amino acid (**8**, Scheme 1) or removal of one (**9**, Scheme 1) is detrimental to the enantioselectivity.^[15] The stereochemical outcome from the reaction with **9** (14% *ee*) underlines the importance of the AA2 moiety and indicates that simple attachment of a chiral group to the pyridine ligation site is alone not sufficient for high asymmetric induction.

With the pyridinyl dipeptide framework emerging as the optimal construct, we prepared chiral ligands **10–17** (Scheme 1, Fourth Phase Screening) and examined their ability to initiate the enantioselective alkylation of **1a** under the same conditions mentioned above. Thus, the catalytic ability of the derived amine **10**, amide **11**, and various α -substituted pyridyl systems (**12–15**) were investigated; in addition, the related indole-based **16** and *C2*-symmetric **17** were probed. All reactions proceed to >98% conversion and exhibit high degrees of *S_N2'*:*S_N2* selectivity, but it is the α -substituted ligands **12–14** that generate the highest *ee*.



We thus selected *o*-OiPr pyridine as the Schiff base moiety, and continued with the optimization of the AA1 and AA2 segments (see Figure 1) according to methods reported previously.^[3] These studies uniformly suggest that L-Phe is the AA2 of choice, and that ligands that bear L-Val (**14**), L-Leu (**18**), and L-Chg (**19**) at the AA1 position offer similarly superior enantioselection.^[16] Chiral ligands **14**, **18**, and **19** (10 mol%) were subsequently used in catalytic alkylation of aryl olefins **1a–c** in the presence of Et₂Zn and 10 mol% CuCN in THF. The results shown in Table 1 indicate the ligands that provide the highest selectivity for a particular



substrate. Thus, when alkylation is performed at -78 °C, **2a–c** are generated efficiently in 66%, 87%, and 75% ee, respectively (< 2% S_N2 product).^[17, 18] The selectivity and reactivity levels (Table 1) are competitive with the recently reported catalytic alkylations of allylic chlorides,^[19] where sterically demanding dialkylzinc reagents (e.g., dineopentylzinc) are required for high enantioselectivity (≤ 50% ee with *n*-alkylzinc reagents).

At this point, we began to investigate Cu-catalyzed reactions of trisubstituted olefin substrates and the catalytic enantioselective synthesis of quaternary carbon centers. Catalytic alkylation of allylic phosphates **20a–e** (Table 2) in the presence of 10 mol % of chiral ligands **14**, **18**, and **19** and 10 mol % CuCN (Et₂Zn, -78 °C, THF) was investigated; all C–C bond-forming reactions occur efficiently and with excellent regiocontrol (< 2% S_N2 product formed). Importantly, alkylation products **21a–e** are formed in 78–90% ee (Table 2);^[20] the highest enantioselectivities are observed with substrates that bear electron-withdrawing aryl substituents (**20c–e**). The optimal chiral ligand varies depending on the starting material: Reaction of **20b** (entry 2, Table 2) in the presence of **14** and **18** affords **21b** in 72% and 69% ee, respectively (vs. 78% ee with **19**); catalytic alkylation of **20d** (entry 4, Table 2) with ligands **14** and **19** leads to the formation of **21d** in 83% and 81% ee, respec-

Table 1. Cu-catalyzed asymmetric allylic substitution of disubstituted alkenes.^[a]

Entry	Aryl group	Ligand	Conv [%] ^[b]	Yield [%] ^[c]	ee ^[d] (config.)
1	Ph	2a 19	> 98	34 ^[e]	66 (+)
2	<i>o</i> NO ₂ Ph	2b 18	> 98	85	87 (–)
3	<i>p</i> NO ₂ Ph	2c 19	> 98	73	75 (+)

[a] Conditions: 10 mol % ligand, 10 mol % CuCN, 3.0 equivalents Et₂Zn, THF, -78 °C, 12 h. [b] Determined by analysis of the 400 MHz ¹H NMR spectrum. [c] Yields of isolated products after silica gel chromatography. [d] Determined by chiral gas–liquid chromatography (GLC) analysis (Chiraldex GTA for entries 1 and 2, Betadex 120 for entry 3). [e] Low yield is because of the volatility of product.

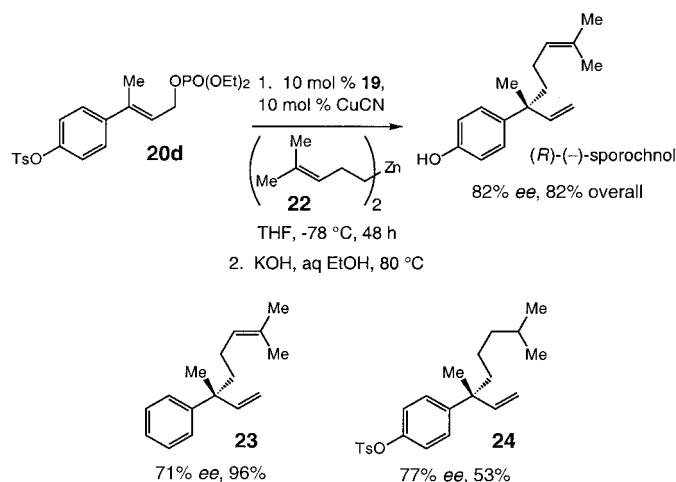
Table 2. Cu-catalyzed asymmetric allylic substitution of trisubstituted alkenes.^[a]

Entry	Aryl group	Ligand	Conv [%] ^[b]	Yield [%] ^[c]	ee ^[d] (config.)
1	Ph	20a 14	> 98	80	78 (+)
2	<i>o</i> OMePh	20b 19	> 98	70	78 (+)
3	<i>p</i> NO ₂ Ph	20c 18	> 98	80	86 (+)
4	<i>p</i> OTsPh	20d 18	> 98	83	90 (+)
5	<i>p</i> CF ₃ Ph	20e 14	> 98	59	81 (+)

[a] Conditions: Same as in Table 1, except 24 h. [b] Determined by analysis of the 400 MHz ¹H NMR spectrum. [c] Yields of isolated products after silica gel chromatography. [d] Determined by chiral GLC analysis (Chiraldex GTA for entry 1, Betadex 120 for entries 2, 3 and 5) and chiral high-performance liquid chromatography (HPLC; chiralcel OD for entry 4).

tively (vs. 90% *ee* with **18**). These results highlight the practical advantages of a readily modular class of chiral catalysts.

The method presented herein should prove to be of notable utility in natural product synthesis. The example shown in Scheme 2 is illustrative. The fish deterrent, sporochinol, has



Scheme 2. Cu-catalyzed asymmetric allylic substitution with longer-chain alkylzinc reagents and the total synthesis of sporochinol.

been prepared enantioselectively by the use of the Cu-catalyzed asymmetric process through a route that is significantly shorter than outlined previously.^[21] This asymmetric synthesis demonstrates that the present method can be readily extended to other functionalized organozinc reagents (82% *ee* and 82% yield). There is another noteworthy feature of the catalytic alkylations in Scheme 2: the reaction of **20d** with alkylzinc **22** proceeds in the opposite stereochemical sense to the reaction with Et₂Zn (see entry 4, Table 2). The catalytic alkylation of **20a** with **22** leads to preferential formation of the *R* isomer of the desired product as well (*(R)*-**23** in 71% *ee*, 96% yield; compare to entry 1 in Table 2). Catalytic alkylation of **20d** with the corresponding saturated alkylzinc reagent also leads to preferential formation of *(R)*-**24** (77% *ee*, 53% yield; Scheme 2). The reversal of enantioselectivity is therefore not because of the electron-withdrawing OTs (Ts = 4-methylphenylsulfonyl) group and/or the alkene in **22**. Mechanistic studies to address whether the above selectivity trend is a result of the steric difference between the alkylzinc reagents (e.g., Et₂Zn vs. **22**) or other factors is in progress.^[22]

In summary, we disclose a new class of peptide-based chiral ligands bearing a pyridinyl residue that is suitable for late transition metal binding and catalysis. Through synthesis and analysis of libraries, the modularity of these ligands can be exploited for the improvement of reaction efficiency as well as regio- and enantioselectivity. These attributes have been used in the development of a new class of catalytic asymmetric alkylation reactions that deliver quaternary carbon centers with high levels of site and enantiofacial control. Study of the mechanism, extension to reactions of aliphatic substrates, and further exploration of this and related classes of peptidic ligands in catalytic asymmetric synthesis are in progress.

Experimental Section

2-(6-Isopropoxy)-pyridine carboxaldehyde-*L*-Val-*L*-Phe-Bu (**14**). 2-(6-isopropoxy)-pyridine carboxaldehyde (0.10 g, 0.61 mmol) and anhydrous MgSO₄ (0.10 g) were added to a solution of H₂N-*L*-Val-*L*-Phe-Bu (0.19 g, 0.61 mmol) in CH₂Cl₂ (3.0 mL). The resulting mixture was stirred for 12 h at 22 °C. Filtration of solids and removal of volatiles in vacuo, followed by recrystallization from hot Et₂O delivered the pure product as a white solid (0.20 g, 0.43 mmol, 70%). IR (KBr): $\tilde{\nu}$ = 3298 (br), 2963 (m), 2932 (m), 2872 (w), 1646 (s), 1598 (m), 1567 (m), 1451 (s), 1323 (m), 1262 (m), 1116 (m), 1000 (m), 811 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.06 (1H, s, pyrCHNR), 7.64 (1H, t, ³J_{H,H} = 7.6 Hz, pyrH), 7.53 (1H, d, ³J_{H,H} = 7.2 Hz, pyrH), 7.33–7.22 (6H, m, ArH and NH), 6.75 (1H, d, *J* = 8.0 Hz, pyrH), 5.87 (1H, br s, NH), 5.38–5.31 (1H, m, OCH(CH₃)₂), 4.64 (1H, dd, ³J_{H,H} = 15.2, 7.6 Hz, CHCH₂Ph), 3.65 (1H, d, ³J_{H,H} = 4.0 Hz, CH₂Pr), 3.22–3.02 (4H, m, CHCH₂Ph and NHCH₂(CH₂)₂CH₃), 2.28–2.20 (1H, m, CHCH(CH₃)₂), 1.35 (6H, dd, ³J_{H,H} = 6.0 Hz, OCH(CH₃)₂), 1.32–1.09 (4H, m, NHCH₂(CH₂)₂CH₃), 0.90–0.75 (9H, m, CHCH(CH₃)₂ and NHCH₂(CH₂)₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 173.1, 170.9, 164.3, 151.7, 139.4, 137.5, 129.9, 129.3, 127.5, 114.2, 114.0, 79.1, 68.8, 55.1, 39.9, 38.7, 33.8, 32.1, 22.9, 22.8, 20.7, 20.2, 18.0, 14.5; high resolution MS calcd for C₂₇H₃₈N₄O₃ [*M*+1]: 467.3022; found: 467.3023; elemental analysis calcd (%) for C₂₇H₃₈N₄O₃: C 69.50, H 8.21, N 12.01; found: C 69.22, H 7.93, N 11.91. [α]_D²⁰ +1.77° (c 5.59, CHCl₃).

(+)-(*S*)-3-methyl-3-phenyl-1-pentene (**21a**). (CAUTION: Et₂Zn IS PYROPHORIC! USE EXTREME CAUTION!) A flame-dried 13 × 100 test tube was charged with CuCN (1.4 mg, 1.6 × 10⁻³ mmol), and **14** (7.6 mg, 1.6 × 10⁻³ mmol); the mixture was cooled to -78 °C and of a solution of 2-phenyl-4-(diethyl-phosphoryloxy)-2-butene (5.0 × 10⁻² g, 0.16 mmol; 1.0 mL) in THF was then added. After equilibration of the reaction to -78 °C for 15 min, Et₂Zn (5.0 × 10⁻² mL, 0.49 mmol) was added dropwise, at which point the solution turned bright red. The mixture was allowed to stir at -78 °C for 12 h, after which time the reaction was quenched through addition of a solution of HCl (1.0 mL, 10% by volume). Extraction with Et₂O (3 × 2.0 mL), removal of volatiles in vacuo, and purification of the resulting yellow oil through chromatography on silica gel (100% pentanes to 20:1 pentanes:Et₂O) afforded (*S*)-**21a** (20.5 mg, 80%). GLC analysis indicates that the enantiomeric ratio of the product is 89:11. IR (KBr): $\tilde{\nu}$ = 3089 (w), 3058 (w), 2976 (s), 2932 (m), 2882 (m), 1719 (w), 1638 (w), 1600 (w), 1499 (m), 1456 (m), 1380 (w), 1273 (w), 1003 (w), 921 (m), 771 (s), 708 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.32–7.15 (5H, m, ArH), 6.03 (1H, dd, ³J_{H,H} = 17.7, 10.8 Hz, CCHCH₂), 5.10 (1H, dd, ³J_{H,H} = 10.8, 1.2 Hz, CCHCH₂), 5.04 (1H, dd, ³J_{H,H} = 17.4, 1.2 Hz, CCHCH₂), 1.80 (2H, dq, ³J_{H,H} = 14.1, 7.8 Hz, CCH₂CH₃), 1.35 (3H, s, CCH₃), 0.77 (3H, t, ³J_{H,H} = 7.2 Hz, CCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 173.4, 148.0, 147.4, 128.6, 127.3, 126.2, 112.4, 45.3, 34.2, 25.2, 9.8; high resolution MS calcd for C₁₂H₁₆: 160.1252; found: 160.1250; elemental analysis calcd (%) for C₁₂H₁₆: C 89.94, H 10.06; found: C 89.74, H 9.99. [α]_D²⁰ +4.53° (c 10.43, CHCl₃) for 78% *ee* sample.

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- [16] When D-Val is used as AA1, the sense of enantioselection is reversed, indicating that the stereochemical identity of AA1 is critical to the sense of stereochemical induction and that the D,L-ligand may deliver lower levels of enantioselectivity than the L,L isomer.
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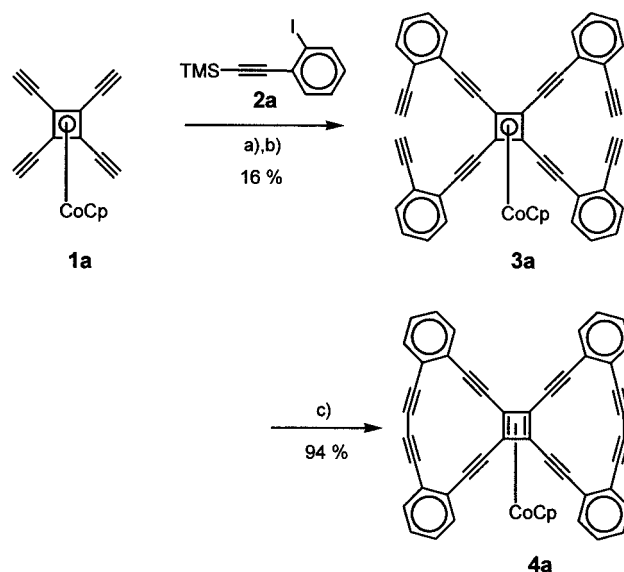
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Concave Butterfly-Shaped Organometallic Hydrocarbons?*

Matthew Laskoski, Gaby Roidl, Mark D. Smith, and Uwe H. F. Bunz*

Carbon-rich organometallic materials are of special interest because their structures display topologies, such as tetragonal or pentagonal, unattainable by their hydrocarbon counterparts.^[1–3] In the realm of organic structures, Haley et al. made a series of large polycyclic hydrocarbons of hexagonal topology, in which benzene rings are separated by alkyne units.^[4] We are interested in the chemistry and materials science of tetragonal cyclobutadiene complexes,^[5] and herein we present the synthesis (**4a–c**, see Scheme 1 and 2) and single-



Scheme 1. Synthesis of the unsubstituted bow-tie complex **4a**. a) [(PPh₃)₂PdCl₂], CuI, piperidine, 18 h, 25 °C; aqueous workup and chromatography. b) K₂CO₃, THF, methanol, 16 h, 25 °C. c) Cu(OAc)₂, CH₃CN (20 mL), 18 h, 80 °C; aqueous workup and chromatography.

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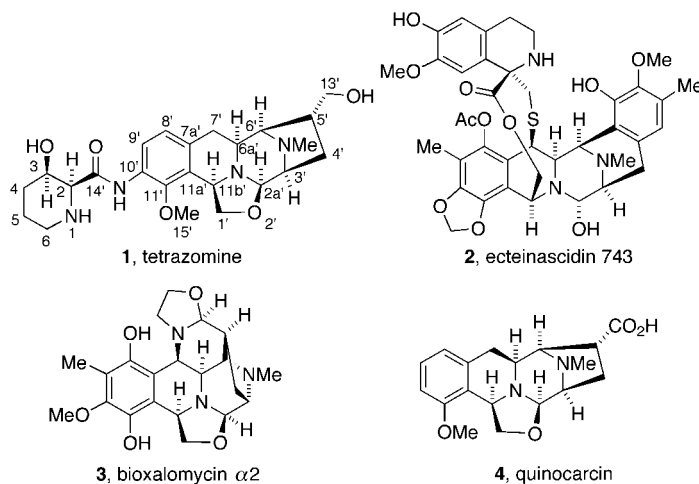
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Total Synthesis of (–)-Tetrazomine and Determination of Its Stereochemistry**

Jack D. Scott and Robert M. Williams*

Dedicated to Professor K. Barry Sharpless on the occasion of his 60th birthday

The antitumor antibiotic tetrazomine **1** was isolated from *Saccharothrix mutabilis* at the Yamanouchi Pharmaceutical company by Suzuki et al.^[1] Tetrazomine is a member of the tetrahydroisoquinoline family of antitumor antibiotics that



includes ecteinascidin 743 (**2**),^[2] bioxalomycin α₂ (**3**),^[3] and quinocarcin (**4**).^[4] Tetrazomine most closely resembles quinocarcin, except for the amino functionality at C10', the unusual β-hydroxy pipecolic acid moiety, and the oxidation state of C13'. Neither the relative nor the absolute stereochemistry of tetrazomine were determined when the structure was initially reported.^[1b] We have since determined that the absolute stereochemistry of the pipecolic acid moiety is 2*S*,3*R*.^[5]

Preliminary antitumor/antimicrobial assays of tetrazomine revealed that this substance possesses activity against P388 leukemia in vivo and good antimicrobial activity against both Gram-negative and Gram-positive bacteria.^[1a] Tetrazomine exerts its cytotoxic activity through oxidative damage to DNA by the superoxides formed in the auto-redox disproportionation of the fused oxazolidine, and possibly through DNA alkylation.^[6]

The total synthesis of tetrazomine has not been reported in the literature,^[7] although the synthesis of the AB-ring system of tetrazomine has been discussed by Ponzo and Kaufman.^[8] Herein, we describe the first total synthesis of (–)-tetra-

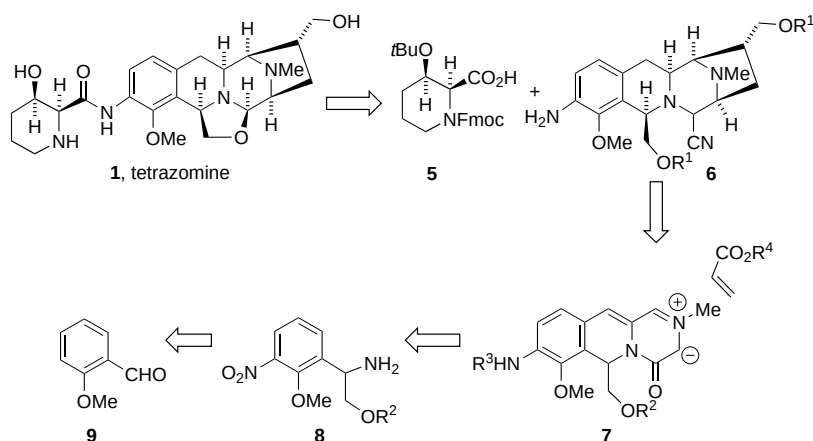
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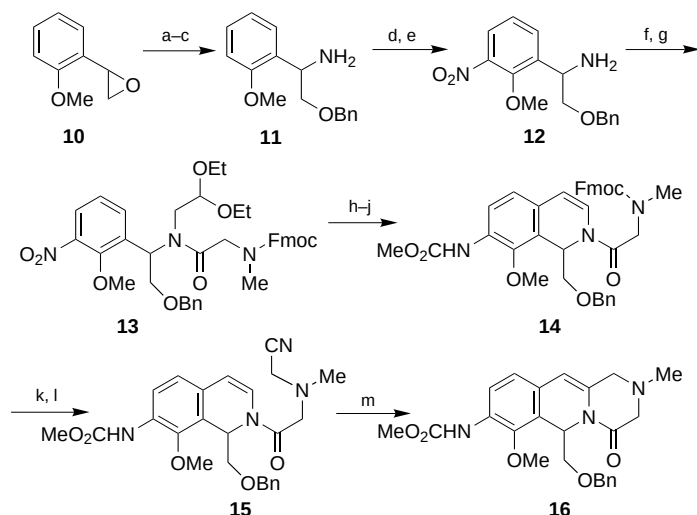
mine and the determination of its relative and absolute stereochemistry.

A retrosynthetic disconnection of tetrazomine included the late-stage coupling of the protected β -hydroxypipicolinic acid **5**^[9] to the aniline **6** (Scheme 1). The aniline was to be derived from a 1,3-dipolar cycloaddition to the azomethine ylide of tricycle **7** using a methodology developed in our laboratories.^[7e] Substance **7** could in turn be obtained from the trisubstituted nitroaromatic **8**, which would ultimately be derived from *ortho*-anisaldehyde (**9**).



Scheme 1. Retrosynthesis of tetrazomine (**1**). Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl.

The synthesis began with the regioselective opening of the previously described^[10] epoxide **10** with sodium azide (Scheme 2). The resulting primary alcohol was protected as the benzyl ether, and the azide was hydrogenated to afford amine **11**. Selective nitration *ortho* to the methoxy group was



Scheme 2. Synthesis of tricyclic precursor **16**. Reagents and conditions: a) NaN₃, acetone/H₂O, Δ ; b) NaH, THF; BnBr, KI (94%, two steps); c) H₂, Pd/C, EtOH (87%); d) KNO₃, TFAA, CH₂Cl₂, -20 °C; e) LiOH (2M), EtOH, (56%, two steps); f) bromoacetaldehyde diethylacetal, K₂CO₃, MeCN, Δ (74%); g) *N*-Fmoc-sarcosine-Cl, DMAP, pyridine, CH₂Cl₂ (82%); h) H₂ (60 psi (414 kPa)), PtO₂, EtOH/THF; i) HCl (6M), dioxane, 90 °C; j) MeOCOCl, pyridine, CH₂Cl₂, 4 °C (92%, three steps); k) pyrrolidine, MeCN (94%); l) ICH₂CN, *i*Pr₂NEt (99%); m) AgO-COCF₃, TFA, TFAA, ClCH₂CH₂Cl, Δ (93%).

accomplished at low temperature by using potassium nitrate and trifluoroacetic anhydride (TFAA).^[8] Hydrolysis of the trifluoroacetamide afforded amine **12**. Alkylation of the primary amine with bromoacetaldehyde diethylacetal was followed by coupling with *N*-Fmoc-sarcosine acid chloride to yield amide **13** in 82% yield. The nitro group was hydrogenated by using platinum oxide to afford the aniline derivative necessary for acid-promoted cyclization onto the acetal.^[7a, 8] The aniline was then protected as the methyl carbamate to afford **14** in 92% yield from **13**. Removal of the

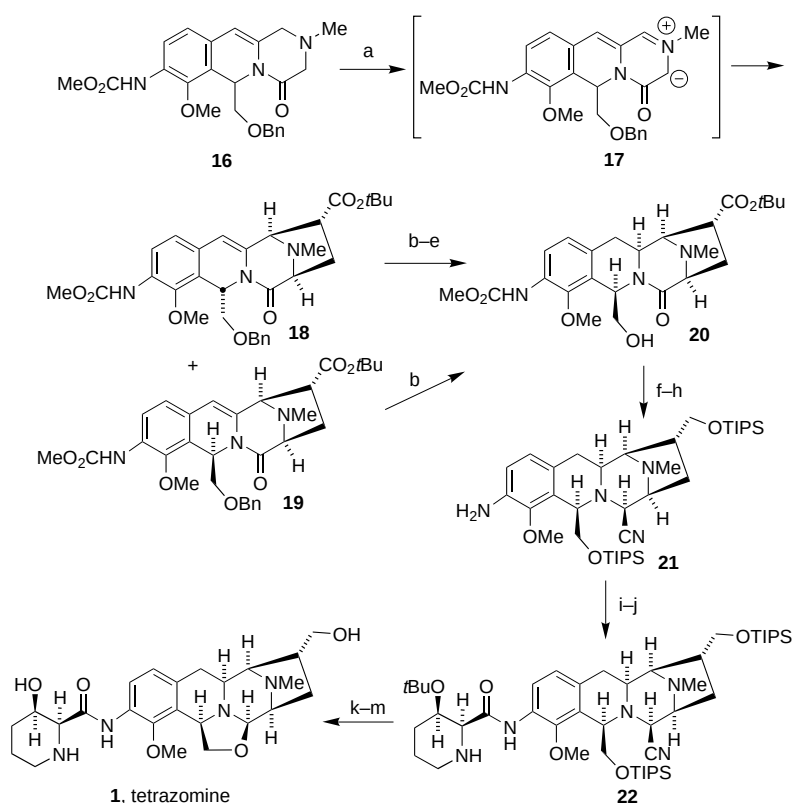
Fmoc group was followed by amine alkylation with iodoacetone nitrile to yield aminonitrile **15** in 93% yield over the two steps. Attempted iminium cyclization to form tricyclic **16** by using AgNO₃^[11] or AgBF₄^[12] afforded no desired product. After extensive experimentation, it was found that treatment of **15** with silver(I) trifluoroacetate in the presence of trifluoroacetic acid (TFA) and trifluoroacetic anhydride afforded the tricycle **16** in 93% yield.

Treatment of allylic amine **16** with *N*-bromosuccinimide (NBS) in refluxing chloroform^[7e] yielded the corresponding iminium ion species that upon deprotonation with triethylamine afforded the azomethine ylide **17** (see **7**, Scheme 1), which was trapped by *tert*-butyl acrylate to afford

a 3.9:1 mixture of separable cycloadducts **18** and **19**, respectively (Scheme 3).

Tetracycle **19** was hydrogenated in the presence of Raney-nickel at a moderate pressure, which resulted in the removal of the benzyl group and reduction of the benzylic olefin from the least hindered face to afford **20**. The major product from the cycloaddition, **18**, possessed the undesired configuration at C11b', thus an epimerization at C11b' was executed. After hydrogenation, the resulting alcohol was oxidized to the aldehyde. Treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded a 1.4:1 mixture of epimers at C-11b' with the desired isomer as the predominant product. These aldehydes were easily separated by column chromatography, thus allowing the undesired epimer to be recycled. Sodium borohydride reduction of the desired epimer afforded alcohol **20**.

The simultaneous reduction of the *tert*-butyl ester group and partial reduction of the lactam were fortuitously accomplished in a single step by using LiAlH₃OEt in THF at 0 °C. The resulting methanolamine was trapped with potassium cyanide under acidic conditions^[13] to afford the corresponding stable aminonitrile. The relative stereochemistry of this product was determined by extensive 2D NMR studies. The two primary alcohols were protected as their triisopropylsilyl (TIPS) ethers, and the methyl carbamate was hydrolyzed to afford aniline **21**. The optically active acid chloride of **5**^[9] was prepared by using oxalyl chloride, and was coupled to **21** in the presence of 4-dimethylaminopyridine to afford the corresponding pipecolamide (plus a separable diastereomer, which was identified as the *ent*-tetrahydroisoquinoline portion; obtained as a 1:1 mixture of optically active diaster-



Scheme 3. Synthesis of tetrazomine (**1**). Reagents and conditions: a) NBS, CHCl_3 , Δ ; *tert*-butyl acrylate, Et_3N , 0°C to room temperature, **18** (35%), **19** (9%); b) H_2 (100 psi (689 kPa)), Raney-Ni, EtOH (90%); c) Swern oxidation (98%); d) DBU, THF, (55% + 38% starting material); e) NaBH_4 , EtOH (89%); f) LiAlH_4OEt , THF, 0°C ; KCN, AcOH, 0°C to room temperature (69%); g) TIPSCl, imidazole, DMF (92%); h) 2 M LiOH, EtOH, Δ , (63%); i) **5**, oxalyl chloride, DMF, CH_2Cl_2 ; **21**, DMAP, CH_2Cl_2 ; j) DBU, CH_2Cl_2 (72%, two steps); k) TFA, 4°C , (53%); l) HF, MeCN (82%); m) AgOCOCF_3 , TFA, MeOH/ H_2O ; Dowex (Cl^-) (61%).

omers). The intermediate pipecolamide was treated with DBU to cleave the Fmoc group, thus furnishing **22**.

To determine which diastereomer would lead to tetrazomine, natural tetrazomine was treated with sodium cyanide to afford 2a'- α -cyanotetrazominol, which was compared to the synthetic diastereomeric products of the cleavage of the *tert*-butyl ether and silyl ethers of **22** and its diastereomer. As expected, one diastereomer afforded a product that had identical spectral data to the naturally derived substance. With this comparison, the relative stereochemistry of the pentacyclic core of tetrazomine was established. Based on biosynthetic considerations, the absolute configuration of the tetrahydroisoquinoline core is assumed to be that depicted in structure **1**, since quinocarcin, bioxalomycin, and ecteinascidin possess the same absolute configuration of the tetrahydroisoquinoline moiety.

After removal of the protecting groups, precursor **22** was treated with silver(I) trifluoroacetate in the presence of TFA for four hours to furnish the intact oxazolidine ring. The addition of Dowex (Cl^-), followed by filtration and lyophilization afforded (–)-tetrazomine $\cdot 2\text{HCl}$, which after purification by HPLC exhibited identical spectral characteristics to those of the natural product. The chemistry described herein is currently being extended to the preparation of several

mechanistically inspired analogues for biochemical and biological evaluation, and will be reported in due course.

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Intrinsically Competitive Photoinduced Polycyclization and Double-Bond Shift through a Boatlike Conical Intersection**

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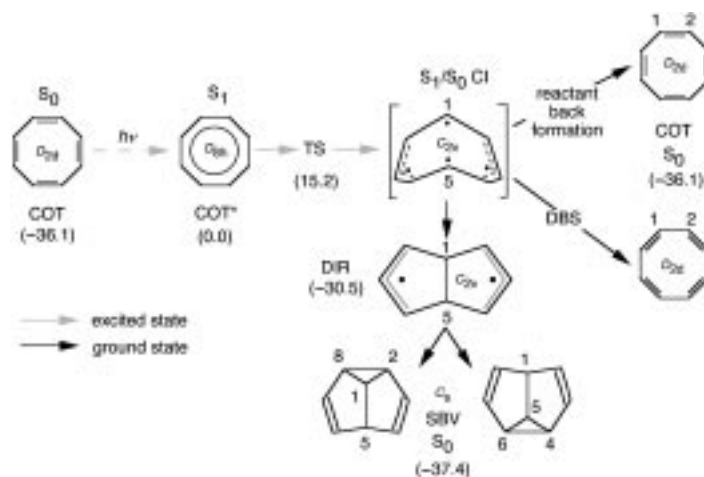
The production of polycyclic carbon backbones through the direct irradiation of simple conjugated hydrocarbons is a remarkably simple way of forming complex molecular architectures.^[1] Examples of these processes are the production of bicyclobutanes from butadienes,^[2] tetrahydronaphthalenes from cyclobutadienes,^[3] benzvalenes from benzenes,^[4] and semibullvalenes from cyclooctatetraenes.^[5] We have demonstrated^[6] that the photogeneration of 1,2-di-*tert*-butylbicyclobutane and benzvalene involves the deactivation at different types of S_1/S_0 conical intersections, which prompts a concerted (simultaneous formation of two new σ bonds)^[6a] or stepwise (initial formation of the prefulvene diradical)^[6b] mechanism, respectively. Herein, we discuss our investigations into the mechanisms of the photochemical production of polycyclic hydrocarbons, specifically the conversion of cycloocta-1,3,5,7-tetraene (COT) into semibullvalene (SBV). We show that a novel type of conical intersection is involved in this process.

Although SBV was first isolated after the sensitized irradiation of barrelene,^[5a] it can also be synthesized by the direct irradiation of COT.^[5b,c] In particular, direct irradiation in solution^[5b] affords SBV and benzene (as a by-product), whereas vapor-phase UV irradiation is of preparative value.^[5c] Experimental evidence was obtained for the direct formation of SBV,^[5b] and a two-photon mechanism for SBV photogeneration was proposed.^[5b] According to this model, the first photon is absorbed by the stable (*cis,cis,cis,cis*) configuration of COT, thus leading to the production of the strained *trans,cis,cis,cis* isomer, which then absorbs a second photon to produce SBV. The SBV is produced more rapidly than the strained isomer.

Double-bond shifting (DBS) is an alternative process that occurs in antiaromatic $[4n]$ systems such as COT. It has been established that the reversible interconversion between DBS isomers (a π -skeletal rearrangement) may be induced either thermally or photochemically.^[7–9] Although DBS is of no practical interest for the parent COT, it may be used to turn on and off the conjugation between π substituents located at

the vicinal position. The DBS reaction may thus be exploited to design photochemically driven switches.^[9]

We have found computational evidence that SBV and DBS originate from the same (excited-state) reaction path. In particular, the calculated S_1 path^[10] (Scheme 1; light lines) goes through a novel type of boatlike S_1/S_0 conical intersection (CI), which provides the locus for decay and branching^[11] by means of three independent S_0 paths (dark lines).



Scheme 1. Schematic representation of the reaction paths of COT*. Symmetry labels and relative CASPT2 energies (kcal mol⁻¹ in parenthesis) are also reported for each calculated structure.

S_1 COT is a planar D_{8h} -symmetric minimum (COT*). This structure (Figure 1) corresponds to the expected (aromatic) geometry, which characterizes the S_1 state of an antiaromatic system.^[7] The S_1-S_0 energy gap in COT* is relatively large (20 kcal mol⁻¹), and deformation towards a C_{2v} boat conformation causes a progressive decrease in the gap. This change leads to the C_{2v} S_1/S_0 conical intersection point (CI; see structure in Figure 1). Access to the CI is controlled by a C_{2v} transition structure (TS) that is located 15.2 kcal mol⁻¹ above COT* (CASPT2 and ZPE-corrected value)^[12] and is structurally close to CI. The reactive mode (i.e. the transition vector) is shown on the CI structure. Although higher energy conical intersections exist on the S_1 surface, these do not provide competitive reaction channels and are not discussed herein.^[12]

The analysis of the molecular and electronic structure shows that the CI has tetradical character, with two unpaired electrons located at opposite centers (atoms C1 and C5) and another two electrons residing on the allyl moieties C2-C3-C4 and C6-C7-C8. S_1 motion towards the CI promotes the approach of the unpaired electrons (the C1-C5 distance decreases from 3.68 Å in COT* to 2.89 Å in CI), to form a diradical intermediate with a C1-C5 transannular bond. The S_0 path that corresponds to this process has been located at a distance of 5 au from the conical intersection (see Figure 1). The calculated C_{2v} bicyclo[3.3.0]octadienyl diradical (DIR) corresponds to the structure suggested by Iwamura and Morio^[13] and by Martin et al.^[14] as an intermediate in the thermal valence tautomerization of COT to SBV. Although DIR is a flat S_0 energy minimum at the CASSCF level, the inclusion of dynamic correlation energy (CASPT2 level)

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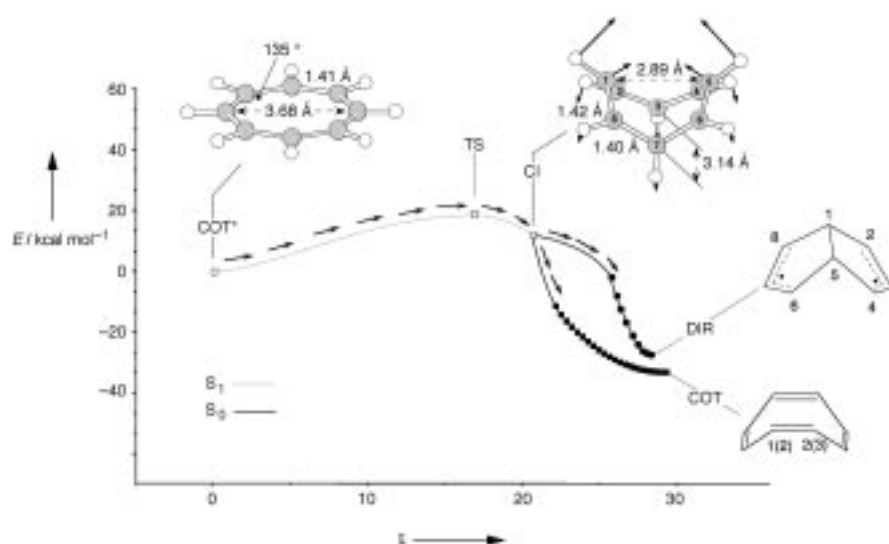


Figure 1. CASPT2-scaled energy profiles along the reaction coordinate ξ [bohr(amu)^{1/2}] describing the evolution of COT*. The geometries of COT* and of the conical intersection (CI) document the progression along the path (open squares). The arrows illustrate the S_1 reactive mode. The two S_0 relaxation paths (full squares and full circles) terminate at COT (or its DBS isomer), or at the DIR transition state. The inclusion of ZPE correction lowers the excited-state barrier from 18 to 15.2 kcal mol⁻¹.

shows that this structure is unstable along the symmetry-breaking deformation that leads to SBV (see Scheme 1). Thus, DIR is the transition state in the Cope rearrangement of SBV, as previously proposed by Jiao et al.^[15b] and more recently by Castano et al.^[16]

The SBV relaxation path discussed above is a continuation of the S_1 path, through the CI and DIR structures. We have been able to locate two additional (degenerate) relaxation paths (Scheme 1 and Figure 1), which start closer (1.5 au distance) to the CI and develop along a steeper region of the S_0 energy surface (Figure 1). One path leads back to the reactant, whereas the other leads to its DBS isomer. The associated relaxation coordinates indicate that a drastic change in direction of “motion” from the S_1 path is needed to access these channels.

The above results do not provide evidence for the formation of the previously proposed^[5b] *trans,cis,cis,cis*-COT as an intermediate in the two-photon formation of SBV.^[17] On the other hand, the documented paths provide a computational model for predicting the products of “vibrationally hot” or “vibrationally cold” photochemistry.^[5b,c] When the S_1 vibrational excess energy is low, COT* would either decay radiatively/non-radiatively at its equilibrium structure, or be displaced towards the CI with a small momentum along the reactive mode, thus populating only the closer and steeper S_0 relaxation paths.^[18] In both cases, the decay would yield COT together with its DBS isomer only. On the other hand, in the presence of a vibrationally excited reactant, part of the S_1 population would be channeled along the transition vector, with enough momentum to be displaced towards the SBV path. As a consequence, the photolysis of COT would yield a mixture of SBV and double-bond shifted COT photoproducts. This model provides an explanation for the fact that SBV can be produced efficiently by the gas-phase (vibrationally hot) photolysis of COT,^[5c] as well as for the low reactivity of

1,3,5,7-tetramethyl-COT,^[5b] which does not lead to a detectable production of 1,3,5,7-tetramethyl-SBV (i.e. inertia and steric effects imposed by the substituents restrain DIR formation). Finally, the production of bicyclo[4.2.0]octa-2,4,6-triene, as a precursor of benzene (and acetylene),^[5b] may occur from the CI through an additional relaxation path, which leads to C2–C7 transannular bond formation (currently under investigation).^[12]

In conclusion, we have investigated the S_1 potential-energy surface of the prototype antiaromatic hydrocarbon COT. The results show that the photochemical behavior of COT is controlled by the conical intersection, which features a tetradical structure that has never been found in aromatic (e.g. benzene) or open-chain (e.g. butadiene) conjugated hydrocarbons. In Figure 2a we show that in the CI, the weak interactions of the four singly occupied

orbitals adopt a tetrahedral pattern (see dashed lines). In the previously reported bicyclobutane^[6a] and benzvalene^[6b] conical intersection structures (Figures 2b and 2c, respectively), the interactions of the four singly occupied orbitals adopt different patterns (rhomboid (Figure 2b) and triangular (Figure 2c)). In the past, the same interaction patterns have been documented for the conical intersections of H_4 clusters.^[19] Thus our results support the conjecture by Michl and co-workers^[19] that the structure of the conical intersections of conjugated hydrocarbons conforms to the conical intersections of elementary systems.

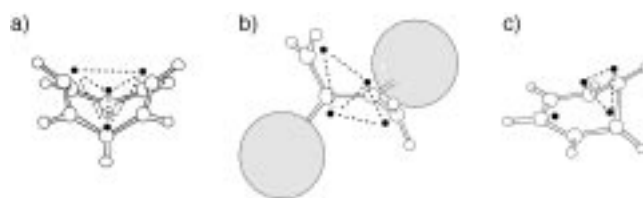


Figure 2. Prototype tetradical conical intersections found in conjugated hydrocarbons: a) SBV; b) bicyclobutane; c) benzvalene photogeneration.

The main “chemical” result reported above is that the production of SBV and DBS are bound processes. However DBS dominates only under conditions of low vibrational excess energy (for instance in solution or in a matrix). This feature should be considered when designing DBS-based molecular switches.

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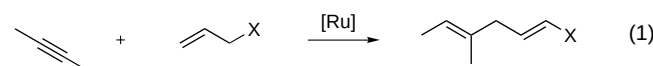
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An Atom-Economic Three-Carbon Chain Extension to Give Enamides**

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Enamides represent a significant class of compounds because of their versatility as building blocks—a result of the enhanced nucleophilicity of the double bond—and as precursors to saturated amines.^[1–3] Normally, such compounds are prepared by additions to aldehydes via imines or other equivalent intermediates.^[2] As a continuation of our development of metal-catalyzed additions of alkenes and alkynes,^[4] we have been interested in chain-extension reactions by means of additions catalyzed by ruthenium complexes [Eq. (1)]. Our recent discovery of the effectiveness of $[(\eta^5\text{-C}_5\text{H}_5)\text{Ru}(\text{N}=\text{CCH}_3)_3]\text{PF}_6$ (**1**)^[5,6] suggested the prospect of



expanding the scope of such additions. If X was an amide function, this chain-extension method would directly create an enamide. A significant issue in such a reaction is the

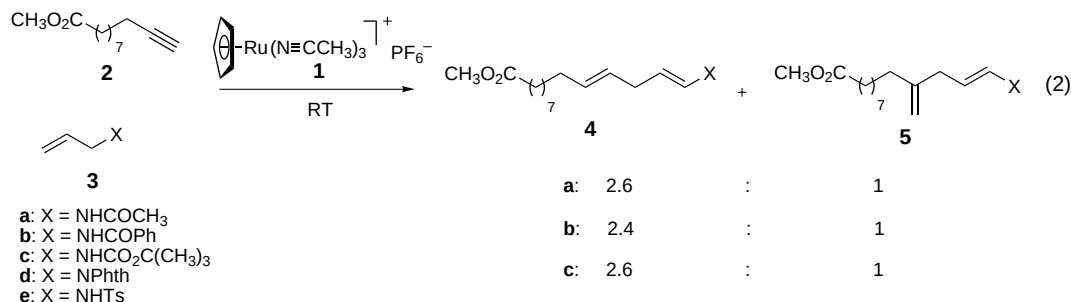
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possibility of a low-valent ruthenium complex promoting ionization of the allylic leaving groups.^[7] The ability of the Ru complex to function as a Lewis acid also raises the question of the compatibility of an amide substrate owing to its Lewis basicity, as well as the question of the stability of the enamide product under the reaction conditions.

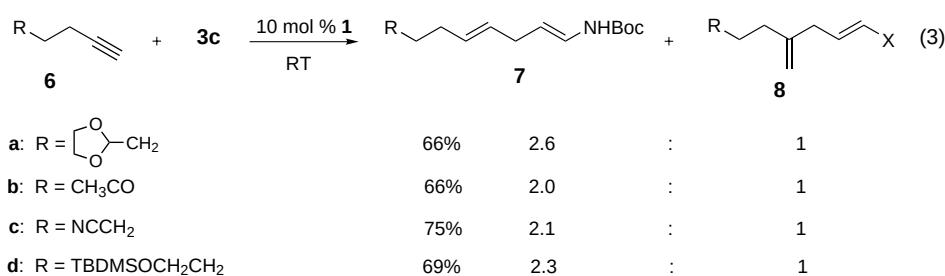
We chose a terminal alkyne with a series of allylic amides [Eq. (2)] to examine the feasibility simultaneously with the



regioselectivity of this ruthenium-catalyzed chain-extension reaction. The initial experimental protocol involved the treatment of alkyne **2** and allyl amide **3** (1:1) with 10 mol % of complex **1** in acetone at room temperature [Eq. (2)].

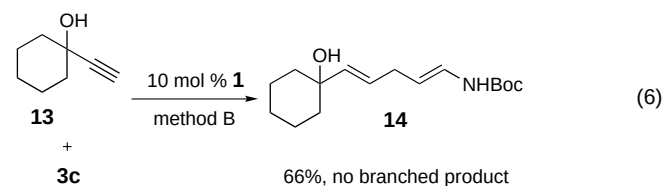
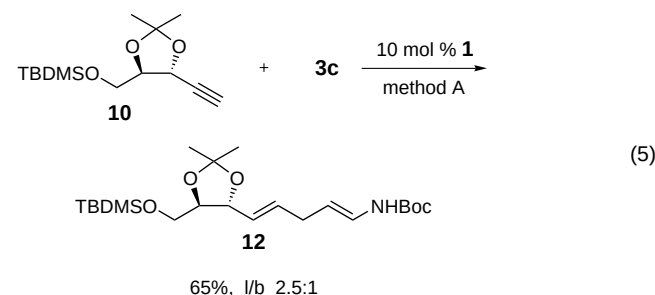
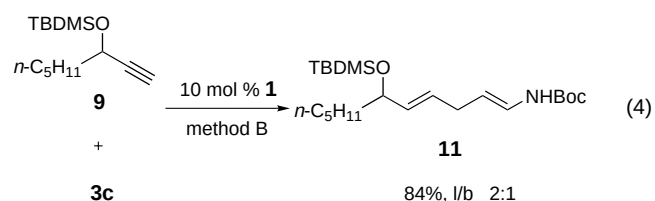
We used the phthalimide **3d** and sulfonamide **3e** to minimize the Lewis basicity of the allyl amide; however, the reactions gave low conversions even after prolonged reaction times. On the other hand, the acetamide **3a** gave a 62 % yield of the adducts **4a** and **5a**^[8] after only 1 h. When the amount of catalyst was decreased to 5 or even 3 mol %, yields of 66 and 55 %, respectively, were obtained in the same time period. Surprisingly, the linear product **4a** dominated over the branched isomer **5a**, in contrast to alkenes (X = alkyl chain).^[6, 9] However, our earlier studies with [CpRu(cod)Cl] (cod = 1,5-cyclooctadiene) as a catalyst in reactions with allyl alcohol did show a similar regioselectivity.^[10] The benzamide **3b** showed virtually identical behavior, and gave the adducts **4b** and **5b**^[8] within 1.5–2 h in combined yields of 72 or 76 % when 5 or 3 mol %, respectively, of complex **1** was used. The *tert*-butoxycarbonyl (Boc) derivative **3c** gave a 63 % yield of adducts **4c** and **5c**^[8] within 2 h. In this last case, the choice of solvent had an effect on the yield. When a THF/acetone ratio of 5:1 was used, the yield increased to 81 % with a 5 mol % catalyst load, but dropped to 67 % with a 3 mol % load. Remarkably, the choice of amide had virtually no effect on the ratio of branched to linear products [Eq. (2)].

Using either acetone (method A) or THF/acetone 5:1 (method B) as the solvent, we explored a range of alkynes, [Eq. (3)]. Excellent chemoselectivity was observed in the addition of an acetal **6a**, a ketone **6b**, a cyano **6c**, and a silyl ether **6d** (TBDMS = *tert*-butyldimethylsilyl) to the carbamate ester **3c**. Evidently, all the enamide functional groups were

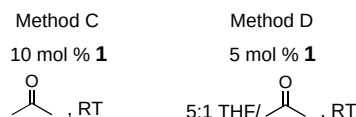
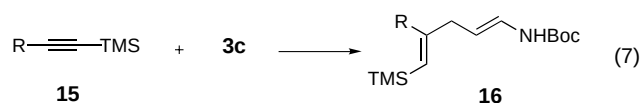


stable under the reaction conditions, and gave the linear adducts **7**^[8] as the major products. Generally, method B was preferred except for ketone **6b**.

The introduction of a propargylic oxygen substituent was of interest to us because of the possibility of forming allenylidene complexes.^[11] Nevertheless, as shown in Equations (4)–(6), no problems were encountered. A single branch at the propargylic position (e.g. **9** [Eq. (4)] and **10** [Eq. (5)]) had no effect on the regioselectivity, and resulted predominantly in the linear products **11**^[8] and **12**^[8] respectively, but with significant amounts of branched products. When a substrate with a quaternary propargylic position (**13**) was used [Eq. (6)], only the linear regioisomer **14** was obtained.^[8]



We used a trimethylsilyl group (e.g. **15**; TMS = trimethylsilyl) to examine the possibility of reversing the regioselectivity and thus favor the branched product [Eq. (7)].^[12] These



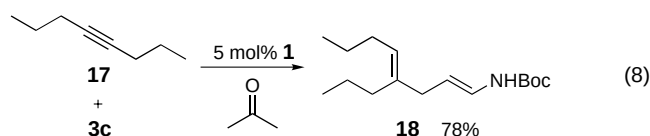
reactions proceeded very smoothly and in high yield, in contrast to our experience with the [CpRu(cod)Cl] catalyst. This reaction produced a single regioisomer **16**^[8] in every case [Eq. (7), Table 1]. An advantage of the vinylsilanes is their use

Table 1. Three-carbon chain extension of silylalkynes [Eq. (7)].^[a]

R	Method	Time [h]	Product	Yield [%]
TBDMSO(CH ₂) ₅ -	D	1	16a	95
Boc(Ts)NCH ₂ CH ₂ -	C	3	16b	94
 -(CH ₂) ₃ -	D	0.67	16c	81
HO(CH ₂) ₅ -	C	1	16d	97
HO(CH ₂) ₃ -	D	9	16e	91
<i>n</i> -C ₁₁ H ₂₃ CH(OH)-	D	2	16f	90

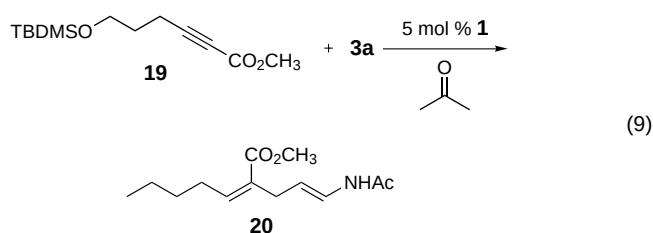
[a] All reactions were performed as in Equation (2). Ts = tosyl = *para*-toluenesulfonyl, NPhT = phthalimide.

in further elaborations—the silyl group can be replaced by electrophiles, including a proton, with control of the alkene geometry. The use of such processes allows trisubstituted alkenes of defined geometry and regioselectivity to be constructed. A simple internal alkyne **17** also served as an excellent partner; product **18**^[8] was obtained in 78% yield, after a reaction time of 0.67 h at room temperature [Eq. (8)].

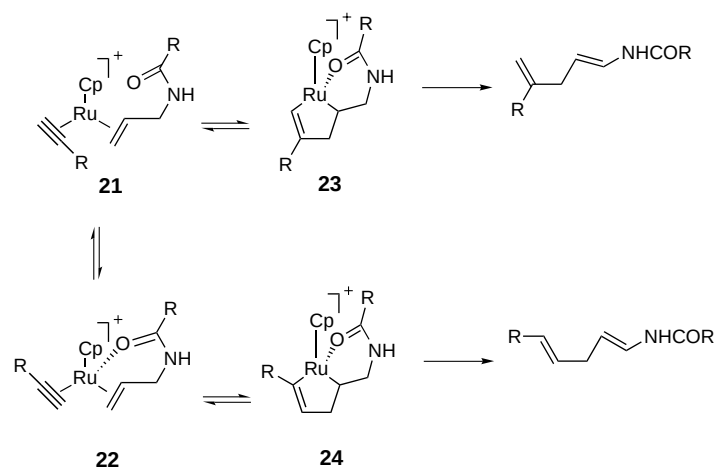


Alkynoates such as **19** also served as suitable substrates, although the reactions were slower; the adduct **20**^[8] was isolated in 50% yield (82% based on recovered starting material) after 1.5 h [Eq. (9)]. As observed in other cases,^[13] the major regioisomer (7:1) arose from the formation of the new C–C bond at the α -carbon atom of the α,β -alkynoate.

This atom-economic^[14] three-carbon chain extension is a simple and mild approach for the simultaneous formation of enamides and di- or trisubstituted alkenes of defined geometry. This process demonstrates excellent chemoselectivity. The issue of regioselectivity is quite intriguing, and excellent regioselectivity was observed with a variety of disubstituted



alkynes. In the case of silylalkynes, a subsequent protodesilylation of the products provided a clear access to “branched”-type products like **8**. Interestingly, terminal alkynes led mainly to linear products, in contrast to the additions to alkenes bearing no heteroatoms at the allylic position. A reasonable rationale invokes metallacycle intermediates **23** and **24** (Scheme 1), which derive from the coordination complexes



Scheme 1. Rationale of regioselectivity.

21 and **22**, respectively. Because of the steric interactions between R and the bulky ligands around the ruthenium center in **22**, the formation of metallacycle **23** from complex **21** is kinetically favored. If β -hydrogen insertion and reductive elimination occurs more rapidly than metallacycle formation, the branched isomer dominates. On the other hand, the presence of electronegative substituents at the allylic position may slow down the rate of the β -hydrogen insertion.^[15] In the latter scenario, the higher stability of **24** than **23** may be reflected in the product distribution, since there is no evident reason why the rate of this insertion should be noticeably different in these two metallacycles. Clearly, further work is required to probe these complex issues. Nevertheless, the current method constitutes a useful synthetic protocol.

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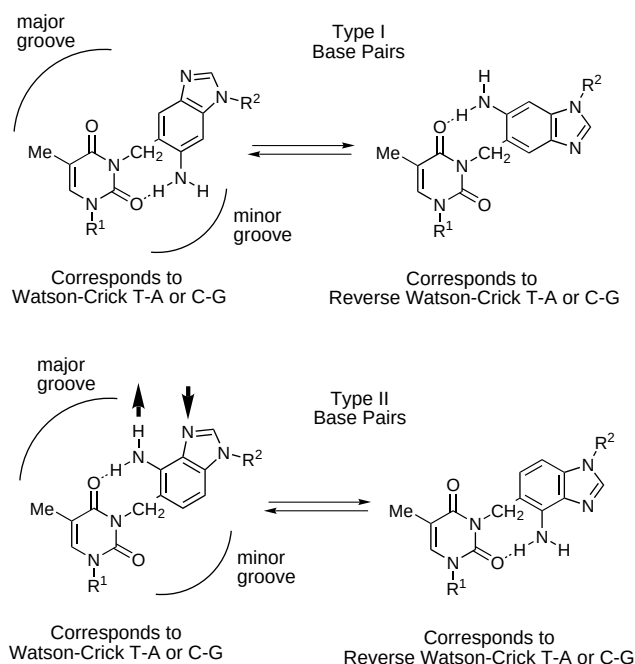
Synthesis of DNA Oligomers Possessing a Covalently Cross-Linked Watson–Crick Base Pair Model**

Hong-Yu Li, Yao-Ling Qiu, Elisabeth Moyroud, and Yoshito Kishi*

The concept of covalently cross-linked sections with molecular architecture similar to Watson–Crick hydrogen-bonded base pairs was introduced by Devadas and Leonard in the mid-1980's.^[1] Since then, several types of covalently linked systems have been developed. However, these systems^[2, 3] were generated from preformed double helices, as seen in the seminal work of Ferentz and Verdine. The Leonard system may offer unique opportunities to address questions regarding the chemistry of DNA and RNA, but this system has several drawbacks, including difficulty in attempted duplex formation

and lack of conformational flexibility between the base pairs.^[1]

We have recognized the possibility that CH₂-bridged base pair models may be uniquely suited to the chemical exploration of covalently cross-linked nucleosides/nucleotides. In addition to their increased chemical stability, these base pair models are expected to adopt only Watson–Crick or reverse Watson–Crick base pairings while maintaining conformational flexibility along the CH₂ bridge. We have focused on two specific types (types I and II) of base pair models (Scheme 1), with the anticipation that they might exhibit



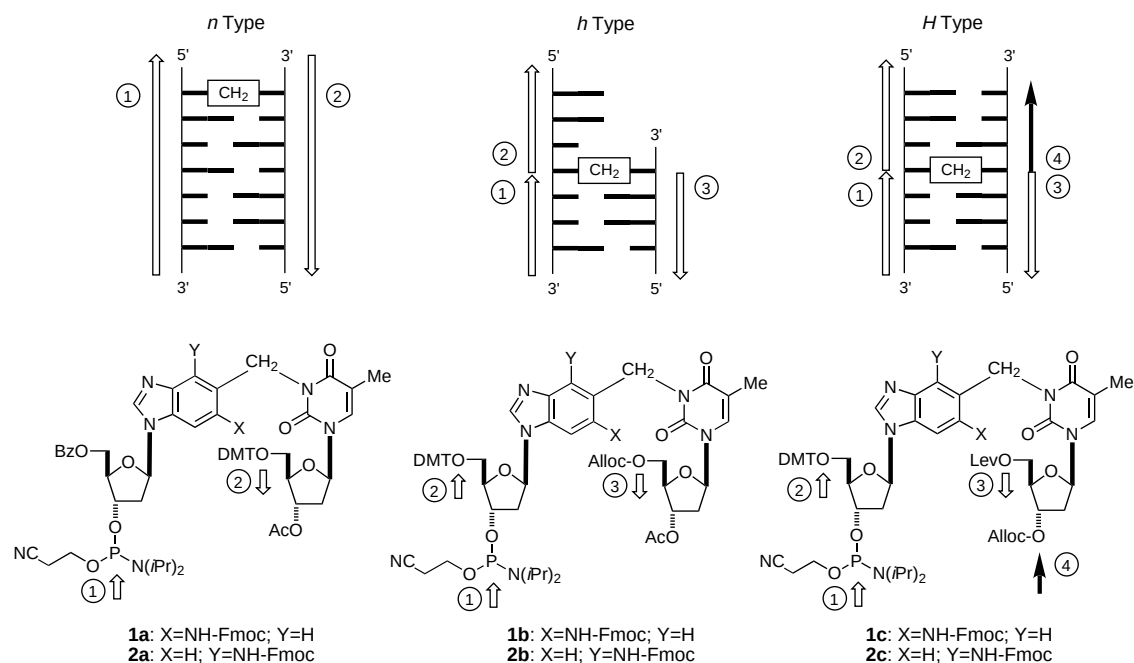
Scheme 1. Covalently cross-linked Watson–Crick base pair models. A = 2'-deoxyadenosine, C = 2'-deoxycytidine, G = 2'-deoxyguanosine, T = 2'-deoxythymidine.

differing structural characteristics. Although both the type I and type II models adopt only Watson–Crick or reverse Watson–Crick base pairings in the sense of primary hydrogen-bonded base pairing, only the type II model provides a structural motif for formation of Hoogsteen triplets such as T–AT and C–GC: see the two bold arrows in Scheme 1 which indicate possible hydrogen-bonding sites in a major groove. We recently reported the synthesis and structural properties of type I and II base pairs.^[4] In this paper, we present a method for incorporating these base pair models into DNA oligomers.

A priori, we considered that phosphoramidite-based solid-phase synthesis^[3, 5] would best meet with our future needs, and we studied its applicability to three types of oligomers incorporating a covalently cross-linked base pair, the *n*, *h*, and *H* types. Our synthetic plan is schematically depicted in Scheme 2, with the order of chain elongation being indicated by a circled number. First, all of the proposed chain elongations take place in the 3' → 5' direction for *n*- and *h*-type oligomers, but the last chain elongation takes place in the 5' → 3' direction for *H*-type oligomers. Second, the order of the

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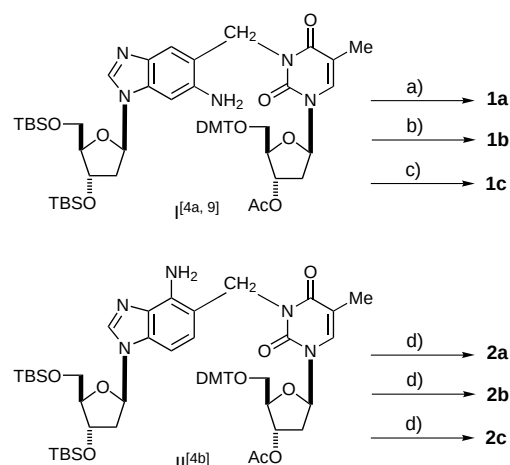
[**] Financial support from the National Institutes of Health (Grant: NS 12108) is gratefully acknowledged.



Scheme 2. Synthetic plan for *n*-, *h*-, and *H*-type oligomers. Ac = acetyl, Alloc = allyloxycarbonyl, Bz = benzoyl, DMT = 4,4'-dimethoxytrityl, Fmoc = 9-fluorenylmethoxycarbonyl, Lev = levulinoyl.

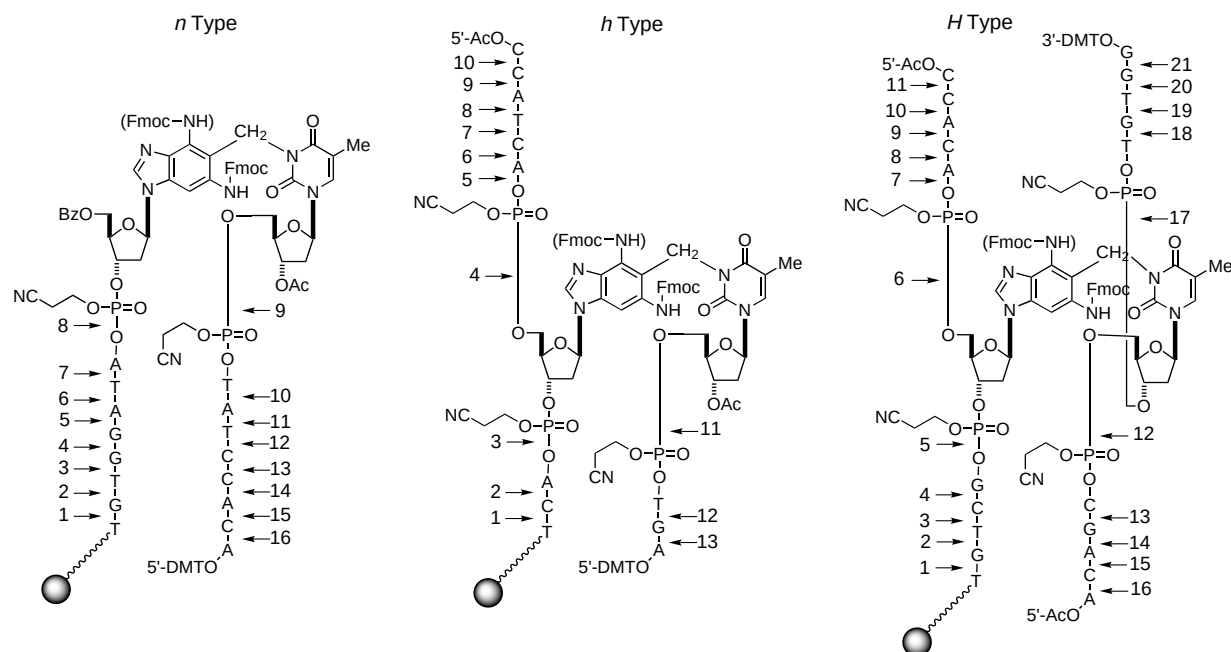
second and third chain elongations for the *h* and *H* types can be inverted simply by switching the DMT group with the Alloc or the Lev group in **1b** and **2b** or **1c** and **2c**, respectively. Third, an Fmoc group is chosen for protection of the amino group; this allows for simultaneous removal, along with deprotection of the protecting groups on the A, T, G, and C nucleotides, upon detachment of the oligomers from the solid support. Fourth, we plan to employ solid-phase synthesis with controlled-pore glass (CPG) supports.^[6] Thus, alcoholic protecting groups compatible with this solid support are required; Alloc and Lev protecting groups are known to meet with this requirement.^[7, 8]

To put this plan in practice, we first required base pairs **1a–c**^[9] and **2a–c**, which were efficiently synthesized as summarized in Scheme 3. With the arbitrarily chosen base sequences shown in Scheme 4, the feasibility of this plan was then tested. Clearly, the crucial step in these syntheses entails adding a CH₂-bridged base pair model onto an elongating oligonucleotide chain, that is, step 8 for *n*-type oligomer syntheses, step 3 for *h*-type, and step 5 for *H*-type. The base pairs **1a–c** and **2a–c** could be incorporated into these oligomers approximately as efficiently as the nonmodified nucleotides (see Experimental Section for more details).^[10] However, to achieve this efficiency, longer coupling times and higher concentrations of the modified bases were required.^[11] Under these conditions, approximately 10–15 equivalents of a modified base were delivered to a DNA synthesizer. However, the unused modified base could be recovered almost quantitatively by employing the method recently reported.^[12] In the case of *h*-type oligomer syntheses, the solid support was removed from the synthesizer after completion of the second chain elongation, subjected to Alloc deprotection on the solid support,^[7] and reintroduced into the synthesizer to complete the third chain elongation, step 11. In the case of *H*-type



Scheme 3. Reagents and conditions. a) 1. FmocCl, DMAP, Pyr, RT, 92 %; 2. *n*Bu₄NF, AcOH, THF, RT, 93 %; 3. BzCl, Pyr, CH₂Cl₂, 0 °C, 63 % of the product, along with 33 % of starting material; 4. (*i*Pr)₂NP(Cl)O(CH₂)₂CN, Et(*i*Pr)₂N, CH₂Cl₂, RT, 93 %; b) 1. FmocCl, DMAP, Pyr, RT, 92 %; 2. TCA, CH₂Cl₂, RT, 96 %; 3. Alloc-OBt, DMAP, Pyr, THF, RT, 95 %; 4. *n*Bu₄NF, AcOH, THF, RT, 89 %; 5. DMTCl, DMAP, CH₂Cl₂, RT, 92 %; 6. (*i*Pr)₂NP(Cl)O(CH₂)₂CN, Et(*i*Pr)₂N, CH₂Cl₂, RT, 95 %; c) 1. NH₃, MeOH, RT, 100 %; 2. FmocCl, DMAP, Pyr, RT, 95 %; 3. Alloc-OBt, Pyr, DMAP, THF, RT, 96 %; 4. TCA, CH₂Cl₂, RT, 90 %; 5. (Lev)₂O, Pyr, RT, 92 %; 6. *n*Bu₄NF, AcOH, THF, RT, 87 %; 7. DMTCl, Pyr, CH₂Cl₂, RT, 93 %; 8. (*i*Pr)₂NP(Cl)O(CH₂)₂CN, Et(*i*Pr)₂N, CH₂Cl₂, RT, 100 %; d) steps (h) 1–3, (h) 1–5, or (h) 1–7 of Scheme 1 in ref. [4b] as appropriate, followed by (*i*Pr)₂NP(Cl)O(CH₂)₂CN, Et(*i*Pr)₂N, CH₂Cl₂, RT, 94 % for **2a**, 95 % for **2b**, 97 % for **2c**. Abbreviations: Bt = benzotriazol-1-yl, *n*Bu = normal butyl, DMAP = 4-dimethylaminopyridine, Et = ethyl, *i*Pr = isopropyl, Pyr = pyridine, TBS = *tert*-butyldimethylsilyl, TCA = trichloroacetic acid, THF = tetrahydrofuran.

oligomer syntheses, the column containing the solid support was removed from the synthesizer twice (after completion of the second and third chain elongations), subjected to Lev and



Scheme 4. Synthesis of *n*-, *h*-, and *H*-type oligomers. The order in which the chains were elongated is indicated. For synthetic details and yields, see the Experimental Section.

Alloc deprotections on the solid support,^[7, 8] and reintroduced into the synthesizer to complete the third and fourth chain elongations, steps 12 and 17. The overall efficiencies of these syntheses are summarized in the Experimental Section and demonstrate that the CH₂-bridged base pair models **1a–c** and **2a–c** could be efficiently incorporated into *n*-, *h*-, and *H*-type oligomers.^[13]

After completion of the chain elongations, the oligomers were detached from the solid support, isolated, and purified under the conditions specified in the Experimental Section. The syntheses were carried out on 1-μmol scale and furnished approximately 0.45 μmol, 0.35 μmol, and 0.15 μmol of HPLC-purified *n*-, *h*-, and *H*-type oligomers, respectively (Figure 1).^[14]

The molecular weight of each synthetic oligomer was established by mass spectrometry. In the early phase of these studies, we relied on electrospray ionization (ESI) mass spectrometry, but in later phases, we used the matrix-assisted laser desorption/ionization (MALDI) mass spectrometry for technical reasons.^[15] By knowing both the order of nucleotides introduced on an elongating chain and the molecular weight of the products, we could secure the structure of the synthetic oligomers.

In conclusion, we have demonstrated the synthetic feasibility of *n*-, *h*-, and *H*-type DNA oligomers possessing a covalently cross-linked Watson–Crick base pair model. It should be noted that the current study is focused on the synthesis of *anti-parallel* DNA duplexes. However, with adjustments of the protecting groups in **1a–c** and **2a–c**, the plan depicted in Scheme 2 can be extended to the synthesis of *parallel* DNA duplexes. Circular dichroism and NMR spectroscopic studies, which demonstrate that the structural properties of DNA oligomers containing a covalently cross-linked Watson–Crick base pair model resemble those of the corresponding native duplex DNA, will be reported elsewhere.^[16]

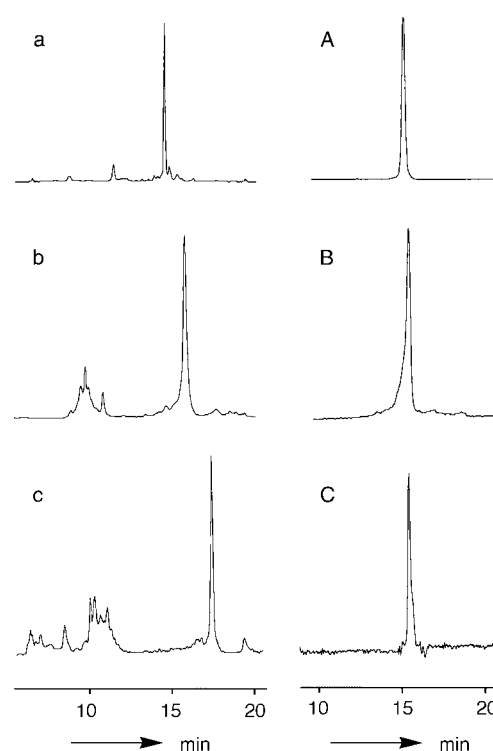


Figure 1. HPLC chromatograms of crude and purified DNA oligomers. Traces a)–c) indicate the purity of the crude products obtained after the detachment/deprotection step: a) type II, *n* type; b) type II, *h* type; c) type II, *H* type. Traces A)–C) indicate the purity of the isolated products after the final purification step: A) type II, *n* type; B) type II, *h* type; C) type II, *H* type. For further details, see the Experimental Section.

Experimental Section

Synthesis of *n*-, *h*-, or *H*-type DNA oligomers was carried out on 1-μmol scale with an Applied Biosystems 392 DNA/RNA synthesizer (coupling time: 25 seconds for 3'-CE phosphoramidites; 10 minutes for the modified

dinucleoside phosphoramidites and for 5'-CE phosphoramidites) or with a PerSeptive Expedite 8909 (coupling time: 90 seconds for 3'-CE phosphoramidites; 15 minutes for the modified dinucleoside phosphoramidites and for 5'-CE phosphoramidites). CE = β -cyanoethyl.

The following reagents were used: deblocking mix: TCA/CH₂Cl₂; activator: 1*H*-tetrazole/MeCN; cap mix A: Ac₂O/THF; cap mix B: 1-methylimidazole/Pyr/THF; oxidizing solution: I₂/H₂O/Pyr/THF. All the reagents and the dA-, dT-, dC-, or dG-3'/5'-CE phosphoramidites were purchased from Glen Research, Virginia. A 0.1M solution of dA-, dT-, dC-, or dG-3'/5'-CE phosphoramidites was used with the Applied Biosystems 392 DNA/RNA synthesizer, whereas a 0.06M solution was used with PerSeptive Biosystems Expedite 8909 DNA/RNA synthesizer. A 0.08–0.1M solution was used for coupling **1a**–**c** or **2a**–**c** onto a chain. Removal of the Alloc protecting group was performed with [Pd(PPh₃)₄] and HCO₂NH₄ in THF at RT over 24 h and removal of the Lev protecting group was required NH₂NH₂·H₂O (0.5M) in Pyr/HOAc at RT for 10 min.

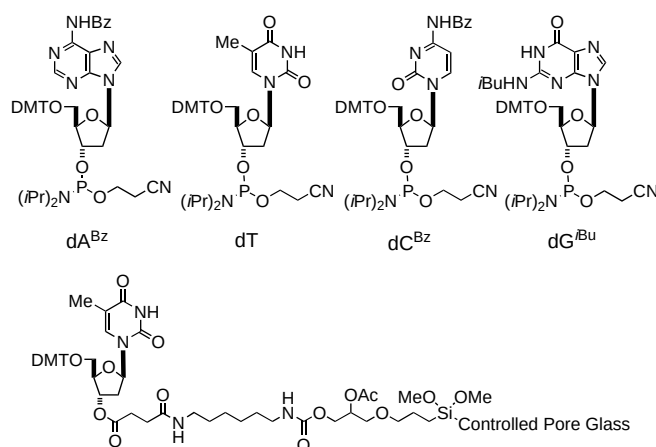
Based on the amount of DMT released in a coupling cycle over that in the preceding coupling cycle, the coupling yield was estimated to be 97–100% for step 8 of the *n*-type, steps 3 and 11 of the *h*-type, and steps 5, 12, and 17 of the *H*-type oligomer syntheses, and 98–100% for all the other steps. The overall yields, estimated from the amount of DMT released in the second-to-last coupling cycle over that in the first coupling cycle, were 70–80%, 60–70%, and 50–60% for the *n*-, *h*-, or *H*-type oligomers, respectively.

Purification/isolation of an oligomer was achieved through a five-step procedure: 1) 28% NH₄OH, 55°C, 24 h (detachment/deprotection of an oligomer from solid support); 2) HPLC purification under the conditions indicated below; 3) 10% AcOH (deprotection of DMT); 4) C18 cartridge filtration; 5) lyophilization. The HPLC chromatograms (Figure 1) were recorded on a Vydac C4 column (10 × 250 mm); solvent system: MeCN/100 mM AcONH₄, 3%–50% over 20 min for a)–c) and 2%–15% over 20 min for A)–C); flow rate: 3 mL min^{−1}. Traces a–c indicate the purity of the crude products obtained after step 1 of the purification. Retention times: a) type II, *n* type: 15.0 min; b) type II, *h* type: 16.1 min; c) type II, *H* type: 17.2 min. Traces A–C indicate the purity of the products after step 5 of the purification. Retention times: A) type II, *n* type: 15.4 min; B) type II, *h* type: 15.9 min; C) type II, *H* type: 16.1 min.

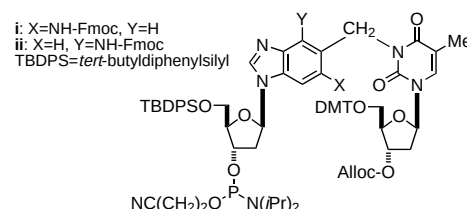
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Revised: January 18, 2001 [Z16143]

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- [10] At an earlier stage of this study, the solid-phase synthesis was carried out on an Applied Biosystems 392 DNA/RNA Synthesizer in the Verdine group. We thank Professor G. Verdine for his generosity and help. In later stages, the synthesis was performed on a PerSeptive Biosystems Expedite 8909. No obvious difference in synthetic efficiency was noticed between the two instruments.
- [11] Using a PerSeptive Biosystems Expedite 8909, optimal conditions were briefly studied for the case of **1a** and **2a**. To achieve the efficient attachment of **1a** and **2a** onto the elongating chain, their concentration should be at least 0.08M and the coupling time for attaching them on the elongating chain should be longer than the coupling time (90 seconds) for the nonmodified nucleotides.
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- [14] The low yields of *H*-type oligomers, relative to the estimated overall yields (see the Experimental Section), were largely due to the difficulties encountered during HPLC purification.

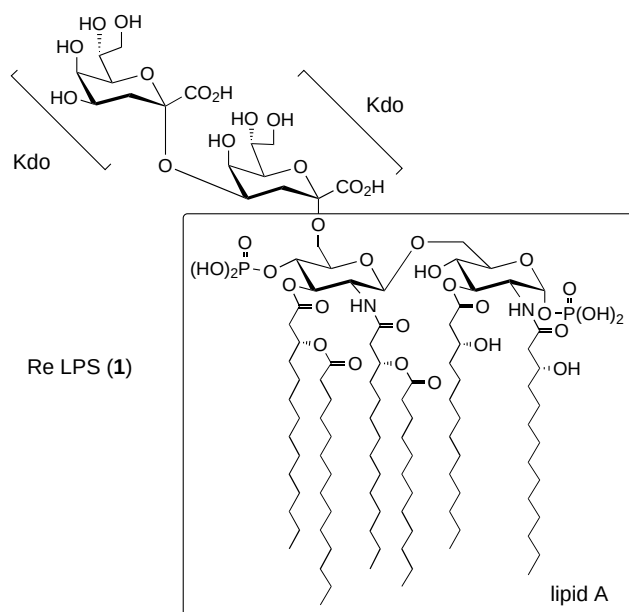
[15] *n* Type: *m/z* calcd: 5445; type I found: 5444 (negative ion ESI-MS); type II found: 5440 (MALDI-MS, matrix: 3-hydroxypicolinic acid/ammonium citrate). *h* Type: *m/z* calcd: 4154; type I found: 4151 (MALDI-MS, matrix: 2,6-dihydroxyacetophenone/ammonium citrate); type II found: 4127 (MALDI-MS, matrix: 2,6-dihydroxyacetophenone/ammonium citrate). *H* Type: *m/z* calcd: 6683; type I found: 6669 (MALDI-MS, matrix: 2,6-dihydroxyacetophenone/ammonium citrate); type II found: 6671 (MALDI-MS, matrix: 3-hydroxypicolinic acid/ammonium citrate).

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First Total Synthesis of the Re-Type Lipopolysaccharide**

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Lipopolysaccharides (LPS) are ubiquitous glycoconjugates located on the surface of Gram-negative bacteria such as *Escherichia coli*, and exhibit multiple and potent biological activity, both toxic and beneficial, towards higher animals.^[1] LPS consist of a phosphorylated acyl glucosamine disaccharide covalently bonded to a polysaccharide. The former glycolipid, lipid A, is the entity responsible for most of the biological activity of LPS.^[2, 3] Lipid A is therefore never present on living bacterial cells in the free form; it is an artificial product obtained only by the acid hydrolysis of LPS. The simplest LPS molecule that is known to be present on bacterial cells and that comes into contact with animal cells is the so-called Re-type LPS produced by the *Escherichia coli* Re mutant (Re LPS, **1**).^[4] This LPS derivative is composed of lipid A and two molar equivalents of 3-deoxy-D-manno-2-octurosonic acid (formerly called 2-keto-3-deoxy-D-manno-octonic acid (Kdo)). The chemical synthesis of Re LPS is not only a highly challenging goal, but would also contribute towards the elucidation of the biological and physicochemical role of the sugar moieties linked to lipid A. It has often been implied that the polysaccharide portion enhances or modifies the activity of Re LPS.^[5] In fact, Re LPS that only has two units of Kdo was reported to exhibit more potent antitumor and cytokine-inducing activity than lipid A.^[6, 7] However, these observations have never been confirmed owing to the



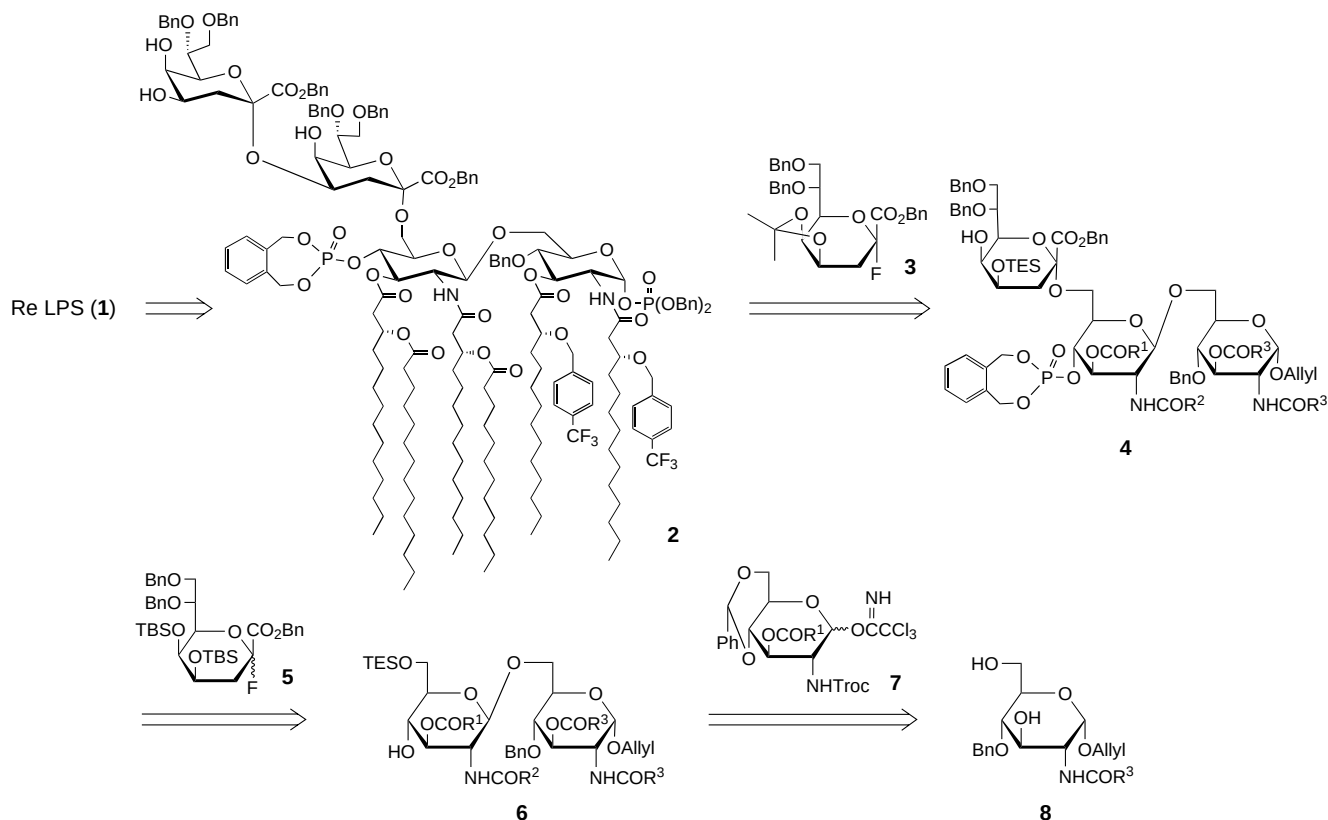
inherent heterogeneity and the difficult purification of natural specimens. An efficient synthesis of Re LPS would also provide easy access to various structural congeners required for the study of structure–activity relationships. Such a strategy based on chemical synthesis has been effective in our studies of the role of acyl and phosphoryl moieties in the bioactivity of lipid A.^[8]

Until now, only partial syntheses of Re LPS have been reported, for example, our synthesis of the 1-*O*-dephospho analogue.^[9] The total synthesis of Re LPS has not yet been accomplished because of the difficulty in synthesizing the complex structure, which contains highly acid-labile glycosyl phosphate, as well as base-labile ester functional groups in the amphiphilic structure. A high-yielding and stereoselective formation of α -Kdo glycosides^[10–13] is a key step towards the synthesis of Re LPS. We have recently completed an efficient synthesis of lipid A^[8c, 14] and its labeled analogues^[15] by means of an optimized synthetic pathway coupled with a high-yielding efficient purification method for the final products based on liquid–liquid partition.^[16] These achievements prompted us to undertake the synthesis of Re LPS (Scheme 1). Herein we describe an efficient stereoselective glycosylation method with Kdo donors, and the first total synthesis of Re LPS. A direct comparison of the biological activities of synthetic and natural specimens is also reported.

Based on our experience with the synthesis of lipid A and its analogues,^[8, 9, 15, 16] we employed benzyl-type groups that are removable by neutral hydrogenolysis, as they are resilient protecting groups for the hydroxy, carboxy, and phosphate groups in **2**. The 4-(trifluoromethyl)benzyl group, which was found to be resistant to oxidation but readily removable by hydrogenolysis,^[17] was used especially for the protection of the hydroxy groups on the 3-hydroxyacyl residues. Unsubstituted benzyl groups at these positions are prone to air-oxidation and gradually are transformed into the corresponding benzoyl groups during storage, even at -5°C .^[17, 18] The tetrasaccharide backbone of **2** was formed by the successive coupling of two

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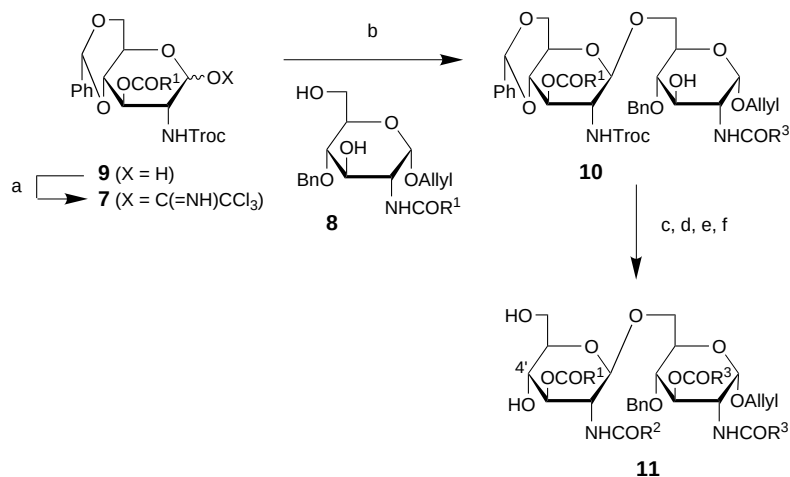
Scheme 1. Retrosynthesis of Re LPS (**1**). The tetrasaccharide backbone was constructed by sequential glycosylation reactions starting from terminal glucosamine **8**. Bn = benzyl, R¹COOH = (*R*)-3-(tetradecanoyloxy)tetradecanoic acid, R²COOH = (*R*)-3-(dodecanoyloxy)tetradecanoic acid, R³COOH = (*R*)-3-(4-(trifluoromethyl)benzyloxy)tetradecanoic acid.

different, suitably protected Kdo donors (**3** and **5**) to the β -D-glucosamine disaccharide derivative **6**, which was prepared by starting from the glycosylation of **8** with **7**, using polymer-supported reagents (Scheme 1).

Disaccharide **11**, a precursor of **6**, was synthesized as shown in Scheme 2. The 3-*O*-acylated glucosamine derivative **9**^[8] was

readily prepared in six steps from D-glucosamine, and transformed into glycosyl trichloroacetimidate **7** by using trichloroacetonitrile and Dowex 1-X8 (OH⁻ form) as a polymer-supported basic catalyst. The resin was packed in a MicroKan, so that the work-up was easier than that in conventional methods using either inorganic (e.g. Cs₂CO₃) or organic (e.g.

1,8-diazabicyclo[5,4,0]undec-7-ene) bases.^[19] The desired trichloroacetimidate **7** was obtained quantitatively by simply removing the resin-filled MicroKan from the mixture after the reaction had gone to completion, and evaporating the solvent. Glucosamine derivative **8**^[8b] was coupled with saccharide **7** by using another polymer-supported catalyst, Nafion-TMS, as a Lewis acid.^[20] This reaction did not proceed well in either CH₂Cl₂ or perfluorohexane, but occurred smoothly in a 3:1 mixture of the two solvents at room temperature over 24 h to give the desired β(1→6)-disaccharide **10** in 73% yield. This glycosylation is a new method for activating a glycosyl donor.^[21] The hydroxy group of **10** was then acylated with a (trifluoromethyl)benzyl-protected 3-hydroxy fatty acid in 85% yield. Cleavage of the (2,2,2-trichloroethoxy)carbonyl (Troc) group at the 2'-position, followed by N-acylation with (*R*)-3-(dodecanoyloxy)tetradecanoic acid^[22] and removal of the benzylidene group, gave the tetraacylated disaccharide **11** in



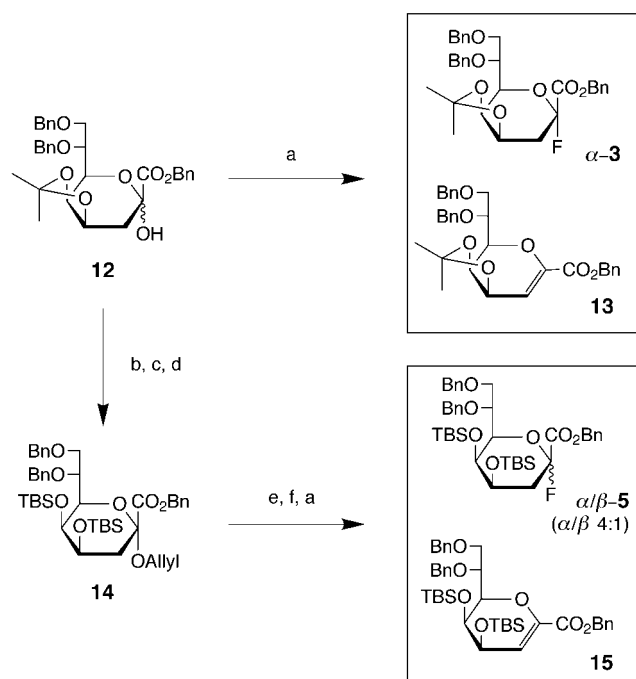
Scheme 2. Synthesis of lipid A moiety **11**. a) Dowex 1-X8 (OH⁻ form) in MicroKan, CCl₃CN, CH₂Cl₂, 3 h (100 %); b) Nafion-TMS, MS4A, CH₂Cl₂/perfluorohexane (3/1), 24 h (73 %); c) (R)-3-(4-(trifluoromethyl)benzyloxy)tetradecanoic acid, DCC, DMAP, CH₂Cl₂, 22 h (85 %); d) Zn–Cu, AcOH, 1.5 h; e) (R)-3-(dodecanoxy)tetradecanoic acid, DCC, CH₂Cl₂, 18 h (85 % over two steps); f) TFA, H₂O, CH₂Cl₂, 2 h (90 %). DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, MS4A = molecular sieves (4 Å), TFA = trifluoroacetic acid.

77% yield. The reaction of Kdo donors at the 6'-hydroxy group of the lipid A moiety is sluggish in the presence of the 4'-*O*-phosphono group (data not shown), and hence coupling with Kdo was examined prior to 4'-*O*-phosphorylation.

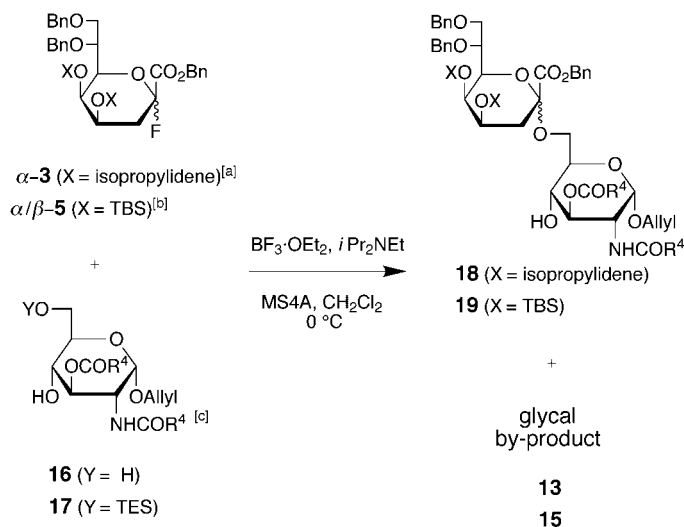
The key α -selective glycosylation step with a Kdo donor is not a well-established reaction and thus was intensively investigated in the present work. The major problem of this glycosylation is the lack of a functional group that controls the anomeric stereoselectivity at the neighboring C3 position of Kdo. We previously obtained a high α -selectivity by using 4,5-*O*-isopropylidene-protected Kdo fluoride as a donor. With this Kdo donor, the undesirable β -side attack by a glycosyl acceptor is prevented by the presence of the bulky isopropylidene group.^[12a] This approach was successfully extended in the present work. Another problem encountered during the glycosylation was the formation of considerable amounts of glycals in side reactions. The undesirable formation of glycals^[23] was drastically suppressed without the loss of α -stereoselectivity by replacing the 4,5-*O*-isopropylidene group with other bulky protecting groups, as described below.

The two Kdo fluorides **3** and **5**, which are protected with isopropylidene and *tert*-butyldimethylsilyl (TBS) groups, respectively, were synthesized from a common precursor **12** (Scheme 3). Compound **12** was prepared from D-mannose in nine steps.^[24] The reaction of **12** with (diethylamino)sulfur trifluoride (DAST) gave an inseparable mixture of α -glycosyl fluoride (α -**3**) and glycal **13** (ca. 3:1 ratio, 88%) which was used directly in the subsequent glycosylation.^[25] For the synthesis of TBS-protected Kdo fluoride **5**, the anomeric position of **12** was temporarily protected as the allyl glycoside in 89% yield.^[26, 27] Replacement of the isopropylidene group with a TBS group, followed by deallylation and fluorination afforded α/β -**5**. Only trace amounts of glycal by-product **15** were formed in the fluorination of the hemiacetal derived from **14**. This suggests that the oxocarbenium ionic intermediate generated from **14** is more stable than the one generated from **12**.

Glycosylations with the Kdo donors α -**3** and α/β -**5** were carried out with 6-hydroxy and 6-*O*-silylated model glucosamine acceptors **16** and **17**^[3] (Scheme 4, Table 1).^[12a, 28] The reactions were carried out with excess $\text{BF}_3 \cdot \text{OEt}_2$ ^[29] in the presence (Table 1, entries 1 and 2) or absence (Table 1, entries 3 and 4) of ethyldiisopropylamine.^[30] When the strain on the pyranose ring was released by changing the 4,5-*O*-protecting groups from a cyclic (isopropylidene) to an acyclic (TBS) group, we observed a decrease in the yields of the coupling products, but also a significant suppression of the formation of the undesired glycals (Table 1, entries 1,2 and 3,4). These protecting groups apparently control the conformation of the pyranose ring and affect the stability of the



Scheme 3. Synthesis of Kdo donors α -**3** and α/β -**5**. a) DAST, CH_2Cl_2 , MS4A, $-78 \rightarrow 25^\circ\text{C}$, 30 min (66% for α -**3**, 95% for α/β -**5**); b) $[\text{Pd}_2(\text{dba})_3]$, $\text{AllylOCO}_2\text{Et}$, dppb, THF, 65°C , 2 h (89%); c) aqueous AcOH (90%), reflux, 1 h (92%); d) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 15 h (96%); e) $[\text{Ir}(\text{H}_2)(\text{cod})(\text{MePh}_2\text{P})_2]\text{PF}_6$, THF, 1 h; f) I_2 , H_2O , 20 min (85%). dba = dibenzylideneacetone, dppb = 1,4-bis(diphenylphosphanyl)butane, Tf = trifluoromethanesulfonyl, cod = 1,5-cyclooctadiene.



Scheme 4. Glycosylation of glucosamine acceptors **16** and **17** with Kdo donors α -**3** and α/β -**5**. [a] Contaminated by the glycal **13** which is, however, inert during the reaction. [b] Used as a mixture of anomers (α/β = 4:1). [c] R^4COOH = (*R*)-3-(benzyloxy)tetradecanoic acid.

Table 1. Glycosylation of glucosamine acceptors **16** and **17** with Kdo donors α -**3** and α/β -**5** (see Scheme 4).^[a]

Entry	Donor (equiv)	Acceptor	$\text{BF}_3 \cdot \text{OEt}_2$ [equiv]	$i\text{Pr}_2\text{NEt}$ [equiv]	Disaccharide (yield [%], α/β)	Glycal (yield [%])
1	α - 3 (4.0)	16	2.5	2.0	18 (72, 90:10)	13 (61)
2	α/β - 5 (4.0)	16	2.5	2.0	19 (45, 94:6)	15 (10)
3	α - 3 (2.0)	17	1.1	–	18 (83, 87:13)	13 (42)
4	α/β - 5 (2.0)	17	1.5	–	19 (81, 93:7)	15 (5)

[a] Yields of disaccharides and glycals are based on glycosyl acceptors and glycosyl donors, respectively.

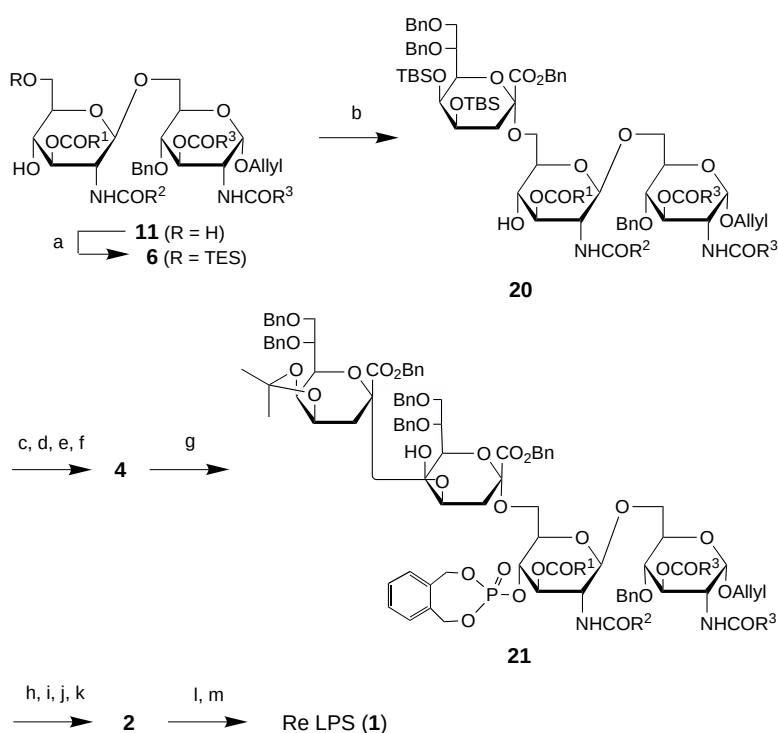
oxocarbenium ionic intermediates generated from the corresponding Kdo fluorides. Indeed, the glycosylation of **16** with 2.5 equivalents of a 4,5-*O*-tetraisopropylidisiloxanylidene-(TIPDS)-protected Kdo fluoride (data and structure not shown) afforded the corresponding disaccharide and the glycal in yields of 50% (based on **16**) and 42% (based on the fluoride), respectively. Both values lie between the respective values of the isopropylidene- and TBS-protected derivatives (Table 1, entries 1 and 2), and correspond to the order of the conformational flexibility of the pyranose ring: isopropylidene < TIPDS < TBS. All the reactions in Table 1 were highly α -selective, irrespective of the anomeric stereochemistry of the donors employed. Higher α -stereoselectivities were observed in the glycosylation with the TBS-protected Kdo fluoride **5** (Table 1, entries 2 and 4). Triethylsilylation of the acceptor greatly improved the yields, even when fewer equivalents of the Kdo donors were used (Table 1, entries 3 and 4). Based on these results, the TBS-protected Kdo fluoride α/β -**5** and the triethylsilyl(TES)-protected glycosyl acceptor are the best coupling partners that provide Kdo glycosides in high yields and with high stereoselectivity.

The final stages that lead to the completion of our synthesis of Re LPS are shown in Scheme 5. TES ether **6** was prepared by the selective protection of diol **11**, and then coupled with the TBS-protected Kdo fluoride α/β -**5**. The desired $\alpha(2 \rightarrow 6)$ -

glycoside **20** was obtained with complete regio- and stereoselectivity, which was unambiguously confirmed by ^1H NMR spectroscopy (Table 2). The free 4'-hydroxy group of **20** was phosphorylated to give the protected 4'-phosphate,^[31] which was then subjected to desilylation followed by regioselective triethylsilylation to give **4**, ready for the incorporation of the second Kdo residue. The use of α/β -**5** also as the second Kdo source gave the desired tetrasaccharide in a disappointingly low yield of 26%, probably due to the steric repulsion between both coupling components. In fact, when the less bulky isopropylidene-protected Kdo fluoride α -**3** was employed—an excess (4 equiv) was used to compensate for possible side reactions resulting from its higher activity—the desired tetrasaccharide **21** was obtained in 75% yield with complete regio- and stereoselectivity, which was confirmed by detailed ^1H NMR spectroscopic analysis (Table 2). After the removal of the isopropylidene and allyl groups, the resulting anomeric hydroxy group was selectively phosphorylated^[32] to give the protected Re LPS derivative **2**. The removal of the isopropylidene group of **21** by aqueous acetic acid at 80 °C unexpectedly also resulted in interresidual lactonization of Kdo (26%). This side reaction was almost completely diminished by the use of aqueous trifluoroacetic acid (TFA) in CH_2Cl_2 at 0 °C for the deisopropylidenation. Finally, all the benzyl-type protecting groups were removed by hydrogenolysis. The lactone and/or 1-*O*-dephosphorylated derivatives

formed during this reaction were effectively removed by liquid–liquid partition column chromatography using a two-layered solvent system (*n*BuOH/THF/H₂O/MeOH 16/7/1/20) on Sephadex LH-20 gel to give the first synthetic, highly pure Re LPS.^[33] The product was identical to natural Re LPS (NMR spectroscopy,^[34] MS, and behavior on TLC (Table 2)), except for the presence of several minor peaks or spots (data not shown) that were present in the natural specimen, even after purification (see below).

The synthetic Re LPS exhibited the same level of cytokine(TNF- α and IL-6)-inducing activity in heparinized human peripheral whole blood cells^[35] as did natural Re LPS that had been purified by liquid–liquid partition column chromatography in the same manner as described above. The amounts of TNF- α induced by synthetic and natural specimens (100 ng mL⁻¹) were found to be 871 and 1047 ng mL⁻¹, respectively. The level of IL-6 (4760 ng mL⁻¹) induced by the same natural Re LPS (10 ng mL⁻¹) was also higher than that (3331 ng mL⁻¹) induced by the same dose of the synthetic Re LPS. The slightly higher activity of natural Re LPS can be explained by the presence of more highly active contaminants, most likely those containing longer saccharide chains. These minor contaminants are still detectable by spectroscopic and TLC analyses, even after extensive purification. This result clearly demonstrates the obvious merit of chemical synthesis, which completely excludes the influences of other bacterial components. Only by this



Scheme 5. Final steps leading to Re LPS (**1**). a) TESCl, imidazole, CH_2Cl_2 , 0 °C, 1 h (85%); b) α/β -**5**, $\text{BF}_3 \cdot \text{OEt}_2$, MS4A, CH_2Cl_2 , 0 °C, 1 h (89%); c) *N,N*-diethyl-1,5-dihydro-3*H*-2,3,4-benzodioxaphosphepin-3-amine, 1*H*-tetrazole, MS4A, CH_2Cl_2 , 40 min; d) MCPBA, -20 °C, 1 h (96% over two steps); e) HF (47%)/ CH_2Cl_2 /MeCN (1/5/5), 5 h (89%); f) TESCl, imidazole, MS4A, CH_2Cl_2 , 2 h (85%); g) α -**3**, $\text{BF}_3 \cdot \text{OEt}_2$, MS4A, CH_2Cl_2 , 0 °C, 1 h (75%); h) TFA, H_2O , CH_2Cl_2 , 0 °C, 4 h (82%); i) $[\text{Ir}(\text{H}_2)\text{-(cod)}(\text{MePh}_2\text{P})_2]\text{PF}_6$, THF, 1 h; j) I_2 , H_2O (82%); k) tetrabenzyl diphosphate, $\text{LiN}(\text{TMS})_2$, THF, -78 $\rightarrow$ 20 °C, 2.5 h; l) **1** (10–20 kg cm⁻²), Pd (black), THF, 1 d; m) liquid–liquid partition column chromatography (see text) (22% over three steps). MCPBA = *meta*-chloroperoxybenzoic acid.

Table 2. Selected data for **20**, **21**, and synthetic **1**.

20: R_f = 0.50 (silica gel, $\text{CHCl}_3/\text{acetone}$ 20/1); ^1H NMR (500 MHz, CDCl_3 , 30 °C, TMS): δ = 7.57 (d, J = 8.2 Hz, 2H; CF_3Ph), 7.48 (d, J = 8.2 Hz, 2H; CF_3Ph), 7.42 (d, J = 8.0 Hz, 2H; CF_3Ph), 7.35–7.16 (m, 22H; CF_3Ph , Ph), 6.09 (d, J = 9.4 Hz, 1H; NH), 5.87 (d, J = 8.2 Hz, 1H; NH'), 5.55 (m, 1H; allyl), 5.28 and 5.14 (AB, J = 12.2 Hz, 2H; ArCH_2), 5.27 (t, J = 9.8 Hz, 1H; H-3), 5.20 (m, 1H; acyl), 5.06–4.99 (m, 3H; H-3', allyl, acyl), 4.97 (dd, J = 10.5, 1.4 Hz, 1H; allyl), 4.63 (d, J = 3.5 Hz, 1H; H-1), 4.60–4.52 (m, 7H; H-1', ArCH_2), 4.45 and 4.43 (AB, J = 11.4 Hz, 2H; ArCH_2), 4.45 (AB, J = 11.4 Hz, 1H; ArCH_2), 4.42 (AB, J = 12.4 Hz, 1H; ArCH_2), 4.22 (ddd, J = 12.9, 10.6, 3.5 Hz, 1H; H-2), 4.12 (brs, 1H; H-5''), 4.06 (m, 1H; H-4''), 3.97–3.79 (m, 8H; H-6a, H-6a', H-6'', H-7'', H-8a'', allyl, acyl), 3.76–3.59 (m, 5H; H-4, H-5, H-6b, H-2', H-8b''), 3.55 (dd, J = 10.3, 6.4 Hz, 1H; H-6b'), 3.49–3.39 (m, 3H; H-4', H-5', allyl), 2.62 (dd, J = 15.6, 7.8 Hz, 1H; acyl), 2.57–2.50 (m, 2H; acyl), 2.39 (dd, J = 16.3, 4.8 Hz, 1H; acyl), 2.34–2.22 (m, 7H; acyl), 2.28–2.11 (m, 2H; H-3a'', acyl), 1.76 (dd, J = 12.4, 4.3 Hz, 1H; H-3b''), 1.59–1.23 (m, 120H; acyl), 0.89–0.82 (m, 36H; acyl, $t\text{BuSi}$), 0.07 (s, 3H; MeSi), 0.06 (s, 3H; MeSi), 0.04 (s, 3H; MeSi), 0.02 (s, 3H; MeSi); ESI-MS (positive-ion mode): m/z : calcd for $\text{C}_{161}\text{H}_{254}\text{F}_6\text{N}_2\text{O}_{26}\text{Si}_2\text{Na}$ [$M+\text{Na}$] $^+$: 2824.8, found 2824.9

21: R_f = 0.54 (silica gel, toluene/EtOAc 4/1); ^1H NMR (500 MHz, CDCl_3 , 30 °C, TMS): δ = 7.55 (d, J = 8.1 Hz, 2H; CF_3Ph), 7.48 (d, J = 8.0 Hz, 2H; CF_3Ph), 7.49 (d, J = 8.0 Hz, 2H; CF_3Ph), 7.34–7.11 (m, 40H; CF_3Ph , Ph, $o\text{-C}_6\text{H}_4(\text{CH}_2\text{O})_2\text{P}$), 6.86 (d, J = 7.2 Hz, 1H; $o\text{-C}_6\text{H}_4(\text{CH}_2\text{O})_2\text{P}$), 6.12 (d, J = 9.3 Hz, 1H; NH), 6.10 (d, J = 9.4 Hz, 1H; NH'), 5.57 (m, 1H; allyl), 5.50 (dd, J = 10.2, 10.0 Hz, 1H; H-3'), 5.31 (dd, J = 10.8, 9.3 Hz, 1H; H-3), 5.26 (m, 1H; acyl), 5.12–4.82 (m, 13H; H-1', allyl, acyl, ArCH_2 , $o\text{-C}_6\text{H}_4(\text{CH}_2\text{O})_2\text{P}$), 4.70 and 4.65 (AB, J = 11.4 Hz, 2H; ArCH_2), 4.66 (d, J = 3.5 Hz, 1H; H-1), 4.59–4.34 (m, 16H; H-4', H-4'', H-4''', H-5'', ArCH_2), 4.22 (ddd, J = 10.8, 9.3, 3.5 Hz, 1H; H-2), 4.12 (d, J = 9.0 Hz, 1H; H-6a), 4.01 (m, 1H; H-7''), 3.96–3.90 (m, 3H; H-5'', H-6'', allyl), 3.86–3.84 (m, 2H; H-6'', H-8a''), 3.81–3.74 (m, 7H; H-6a', H-8a'', H-8b'', H-7'', H-8b''', acyl), 3.72–3.61 (m, 6H; H-4, H-5, H-6b, H-5', H-6b', allyl), 3.34 (ddd, J = 10.1, 8.0, 7.0 Hz, 1H; H-2'), 2.88 (dd, J = 15.3, 3.4 Hz, 1H; H-3a''), 2.61 (d, J = 6.6 Hz, 2H; acyl), 2.54 (brs, 1H; 5'-OH), 2.47 (dd, J = 16.3, 7.1 Hz, 1H; acyl), 2.37–2.22 (m, 9H; H-3a'', acyl), 2.17 (dd, J = 15.2, 5.3 Hz, 1H; acyl), 2.07 (dd, J = 12.7, 12.0 Hz, 1H; H-3b''), 1.92 (dd, J = 15.3, 2.6 Hz, 1H; H-3b'''), 1.63–1.19 (m, 126H; isopropylidene, acyl), 0.89–0.85 (m, 18H; acyl); ESI-MS (positive-ion mode): m/z : calcd for $\text{C}_{189}\text{H}_{267}\text{F}_6\text{N}_2\text{O}_{36}\text{PNa}$ [$M+\text{Na}$] $^+$: 3308.9, found 3308.8

Synthetic Re LPS (**1**): R_f = 0.29 (silica gel, $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}/\text{Et}_3\text{N}$ 60/40/10/0.02); ^1H NMR (500 MHz, Triton X-100/ D_2O , 30 °C, $\delta(\text{HDO})$ as reference): δ = 5.29 (m, 1H; H-1), 5.15 (m, 1H; acyl), 5.13 (m, 1H; H-3), 5.06 (m, 1H; acyl), 5.06 (m, 1H; H-3'), 4.53 (m, 1H; H-4'), 4.52 (m, 1H; H-1'), 4.03–3.32 (m, 16H; H-4, H-5, H-6a, H-6b, H-5', H-6a', H-6b', H-5'', H-6'', H-7'', H-8a'', H-8b'', H-6'', H-7'', H-8a'', H-8b'', 4.01 (m, 1H; H-2), 3.98 (m, 1H; H-4'''), 3.90 (m, 1H; H-4''), 3.87 (m, 1H; acyl), 3.80 (m, 1H; acyl), 3.76 (m, 1H; H-2'), 3.73 (m, 1H; H-5''), 2.56 (m, 2H; acyl), 2.44 (m, 2H; acyl), 2.33 (m, 3H; acyl), 2.22 (m, 5H; acyl), 1.99 (m, 1H; H-3a''), 1.84 (m, 1H; H-3a'''), 1.79 (m, 1H; H-3b'''), 1.63 (m, 1H; H-3b''), 1.60–1.20 (m, 120H; acyl), 0.71 (m, 18H; acyl); ESI-MS (negative-ion mode): m/z : calcd for $\text{C}_{110}\text{H}_{200}\text{N}_2\text{O}_{39}\text{P}_2$ [$M-2\text{H}$] $^{2-}$: 1117.7, found 1117.8

approach can the true biological activity be discussed precisely in relation to chemical structures.

In summary, we have accomplished the first total synthesis of Re LPS starting from D-glucosamine hydrochloride with an overall yield of 0.9% over 23 steps. In combination with an efficient purification method based on liquid–liquid partition, structural congeners such as the one lacking the terminal Kdo residue (Kdo-lipid A) and its 4'-O-dephosphorylated analogue have also been successfully synthesized by using a similar synthetic pathway.^[36] The present work has opened a new stage of research into bacterial LPS at precise molecular levels, for example, its recognition by receptors and detailed analyses of the relationships between bioactivity and three-

dimensional molecular structures, which are currently under intensive investigation in our laboratory.

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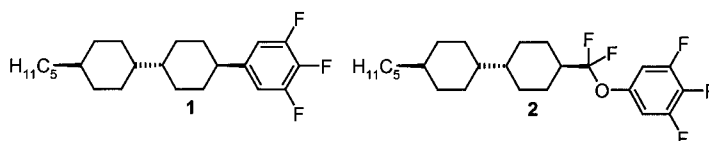
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Diffuorooxymethylene-Bridged Liquid Crystals: A Novel Synthesis Based on the Oxidative Alkoxydifluorodesulfuration of Dithianylum Salts**

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Dedicated to Professor Heinz A. Staab on the occasion of his 75th birthday

In our search for new, superior liquid crystals^[1] for use in active-matrix liquid crystal displays^[2] (AM-LCD or thin film transistor LCD, TFT-LCD) it was found that the insertion of a difluorooxymethylene bridge into a specific location of the mesogenic core structure of phenylbicyclohexyl-type liquid crystals (**1**)^[3] results in a class of materials (**2**; Scheme 1)^[4] that



Scheme 1. The liquid crystalline basic structure **1** and its analogue **2** which is extended by a difluorooxymethylene bridge.

exhibits a surprising improvement of essentially all application-relevant properties (see Table 1). These include a broader nematic phase range, a higher dielectric anisotropy ($\Delta\epsilon$), a lower rotational viscosity (γ_1)^[5] but also a higher specific resistivity and voltage holding ratio.^[6] Since the liquid crystals **1** are currently the most commonly used type of materials for all kinds of AM-LCDs, this fundamental improvement represents significant progress for LCD technology as a whole with regard to faster switching times and a broader operating temperature range.

Whilst there is a variety of methods reported for the preparation of aryl α,α -difluorobenzyl ethers,^[7] the efficient synthesis of aryl and alkyl α,α -difluoroalkyl ethers has been an unsolved problem so far. The first small amounts of **2**^[4b, 8] and its analogues were synthesized by the general methods depicted in Scheme 2. But both synthetic routes suffer from serious drawbacks, such as low yields and difficult purification of the intermediates **7**^[4b, 8] and **8**,^[9–11] and of the target compounds **9**. Therefore, it was our aim to develop a new,

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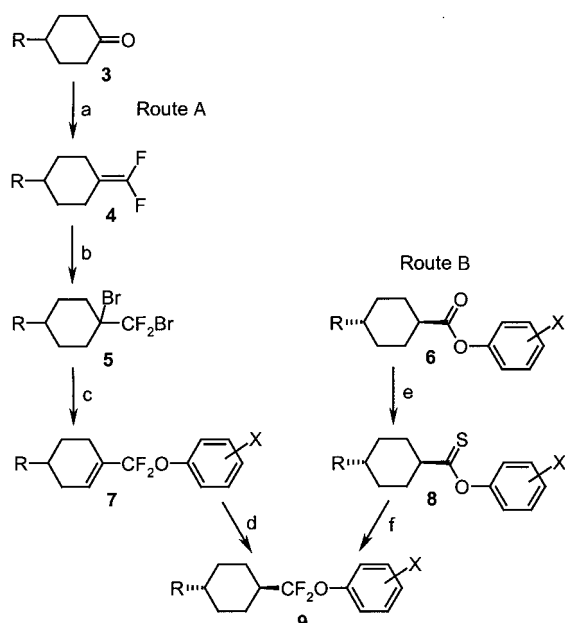
[**] We thank A. Hahn and R. Sander for experimental assistance, and Dr. J. Krause, J. Haas, and H. Heldmann for the physical evaluation of the new substances. A part of the work presented in this article was performed under the management of the Association of Super-Advanced Electronics Industries (ASET) in the R&D program of the Japanese Ministry of International Trade and Industry (MITI) supported by the New Energy and Industrial Development Organization (NEDO). Another part was supported by the German Bundesministerium für Bildung und Forschung (01 BM 904).

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

Table 1. Physical properties of liquid crystals (**1**, **2**, **26–32**) and chiral dopants (**33**, **34**)^[19, 20] containing an α,α -difluoroalkyl ether bridge.^[a]

Compound	Phase sequence	T_{NI}	$\Delta\epsilon$	Δn	γ_1
1	C 88 N 102.4 I	82.8	8.4	0.0720	233
2	C 59 N 112.1 I	99.3	9.5	0.0688	184
26	C 67 N 116.5 I	108.2	11.8	0.0800	488
27	C 41 I	–31.7	19.0	0.1025	116
28	C 81 S _B 169 N 285.7 I	296.7	–0.2	0.0695	796
29	C 140 S ₂ 150 S _B 169 N > 325 I	333.2	–2.1	0.0626	2935
30	C 45 N (28.8) I	–8.4	17.0	0.1115	123
31	C 19 S _B 72 I	4.3	0.7	0.0500	93
32	C 47 I	–39.0	1.2	0.0488	–
33	T _g –76 I	–	–	–	–
34	T _g 27 I	–	–	–	–

[a] “Virtual” clearing points (T_{NI}), dielectric anisotropies ($\Delta\epsilon$), birefringences (Δn), and rotational viscosities (γ_1) are extrapolated from the Merck liquid crystal mixture ZLI-4792.^[21] The temperatures are given in °C, the γ_1 values in mPas. C = crystalline, S_x = smectic X, N = nematic, I = isotropic, T_g = glass transition. Numbers in parentheses denote monotropic phase transitions.

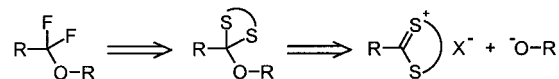


Scheme 2. Previously reported general synthetic routes to cyclohexyl- α,α -difluoromethyl phenyl ethers **9**.^[4] The yields vary strongly depending on the phenol component: Route A: a) CF_2Br_2 , $\text{P}(\text{NMe}_2)_3$, THF/dioxane 10/1; 0 °C → room temperature (RT), 18 h (80–90%); b) Br_2 , Et_2O ; 0 °C, 1 h (85–95%); c) 2.6 equiv XPhONa , DMF; 60 °C, 18 h (35–70%); d) 1. H_2 , 5% Pd-C, THF; 60 °C, 60 bar; 2. preparative HPLC; 3. crystallization from *n*-pentane (25–35%). Route B: e) 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent),^[9] chlorobenzene; reflux, 18 h (5–30%); f) DBH (1,3-dibromo-5,5-dimethylhydanthoin), 70% HF-pyridine, CH_2Cl_2 ; –70 °C → RT (5–40%).

universally applicable large-scale synthesis for α,α -difluoroalkyl ethers such as **2**, which does not require sophisticated purification steps and which is based on inexpensive and readily available precursors.

Oxidative fluorodesulfuration^[11, 12] is one of the most versatile synthetic tools for the selective introduction of fluorine into complex organic molecules, which is also compatible with other sensitive function-

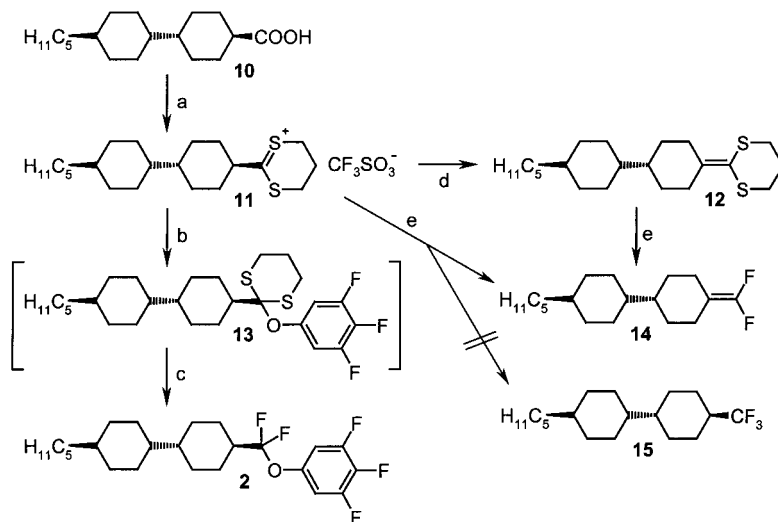
alities. Since cycloaliphatic thionoesters (such as **8**) often suffer from poor stability, in this case a cyclic dithioorthoester seemed a more suitable alternative substrate for the fluoro-desulfuration (Scheme 3). The results reported by Klaveness et al.^[13] indicated that these dithioorthoesters might be obtained by reaction of a dithianylum salt^[14] with a hydroxy compound in the presence of an auxiliary base.



Scheme 3. Retrosynthetic analysis of the formation of the difluoroalkoxy-methylene link.

Putting these considerations into practice, we were able to convert the carboxylic acid **10** into the corresponding dithianylum triflate (**11**⁺ CF_3SO_3^-) by condensation with 1,3-propanedithiol and trifluoromethanesulfonic acid under azeotropic water removal (Scheme 4; for details see Experimental Section). The same procedure can also be applied for the conversion of aromatic carboxylic acids. The resulting dithianylum salt **11**⁺ CF_3SO_3^- and its aromatic analogues are non-hygroscopic solids which can be stored for months at ambient temperature without special precautions. Some dithianylum salts with a shorter alkyl or 4-alkylcyclohexyl group are semi-solids at ambient temperature, without clearly defined melting points. These noncrystalline salts are best stored at –20 °C as a solution in dichloromethane to avoid their slow decomposition by elimination of trifluoromethanesulfonic acid.

First attempts to synthesize and purify the dithioorthoester **13** according to the procedure described in reference [13] only resulted in the exclusive isolation of the ketenedithioketal **12** (Scheme 4). However, conducting the whole reaction se-



Scheme 4. Synthesis of the liquid crystal **2** and conditions leading to the formation of **12** and **14**: a) 1. $\text{HS}(\text{CH}_2)_3\text{SH}$, $\text{CF}_3\text{SO}_3\text{H}$, toluene/isooctane 1/1; azeotropic removal of water; 2. crystallization by addition of methyl *tert*-butyl ether at 0 °C (90%); b) 3,4,5-trifluorophenol, NEt_3 , CH_2Cl_2 ; –70 °C, 10 min; c) 1. $\text{NEt}_3 \cdot 3\text{HF}$; –70 °C, 5 min; 2. Br_2 ; –70 °C → 0 °C (84%); d) NEt_3 , CH_2Cl_2 ; RT, 1 h (39%); e) 1. $\text{NEt}_3 \cdot 3\text{HF}$; –70 °C, 5 min; 2. *N*-bromosuccinimide; –70 °C → 0 °C (from **11**⁺ CF_3SO_3^- and **12**: complex mixture with **14** as main identifiable product, yield not determined).

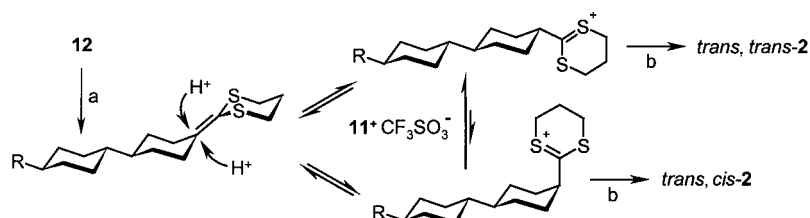
quence—formation of the dithioorthoester and subsequent halonium-mediated fluorodesulfuration^[11, 12] (triethylamine tris(hydrofluoride) ($\text{NEt}_3 \cdot 3\text{HF}$); 1,3-dibromo-5,5-dimethylhydanthoin (DBH), *N*-bromosuccinimide (NBS) or bromine)—as a one-pot procedure at -70°C furnished the desired product **2** in good to excellent yields. The highest yields are obtained by using the phenol in an excess of about 0.5 equivalents with regard to the dithianylum salt.

Treatment of the dithianylum salt **11**⁺ CF_3SO_3^- with base (triethylamine) results in quantitative deprotonation of the cation to the ketenedithio-ketal **12**. Contrary to our expectations, direct fluorodesulfuration of **11**⁺ CF_3SO_3^- , without prior addition of the phenoxide, does not lead to the trifluoromethylbicyclohexyl **15** but to a complex mixture containing **14** as the major identifiable component. A mixture of a similar composition is obtained by the fluorodesulfuration of **12** (Scheme 4).

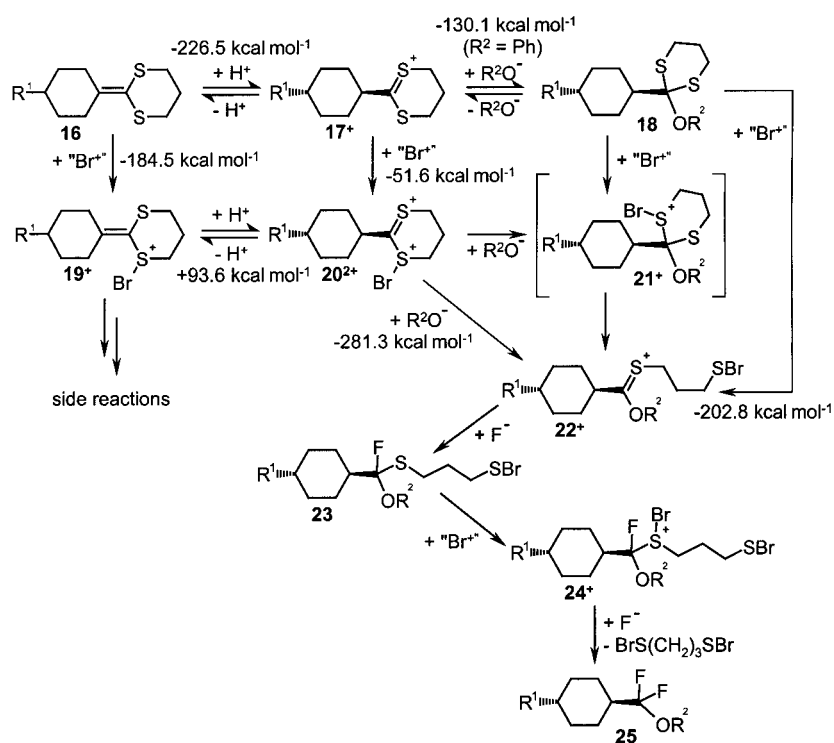
The alkoxydifluorodesulfuration works not only in the presence of phenols but also with acidic alcohols such as trifluoroethanol, trichloroethanol, or even *S*-1,1,1-trifluorooctan-2-ol.^[15] For aromatic dithianylum salts the use of less acidic alcohols, such as ethanol, is feasible in principle, but the resulting difluorobenzyl ethers are often sensitive towards hydrolysis under the work-up conditions and on contact with silica gel and can only be characterized as a transient species by GC-MS analysis of the primary reaction mixture.

The cyclohexyldithianylum triflate **11**⁺ CF_3SO_3^- can also be generated by protonation of the ketenedithio-ketal **12**^[16] with trifluoromethanesulfonic acid.^[17] The protonation is reversible at room temperature, which is indicated by the preferred formation of *trans,trans*-**2** (>98%) on applying the full fluorodesulfuration procedure, presumably via the thermodynamically more stable equatorial dithianylum cation *trans,trans*-**11**⁺. Thus, also ketenedithioketals such as **12** can be converted into the corresponding α,α -difluoroalkylethers by the one-pot reaction sequence depicted in Scheme 5. This provides an attractive synthetic alternative if the dithianylum salt is not readily available from the corresponding carboxylic acid.

The experimental findings were condensed into a tentative mechanism (Scheme 6) which was additionally investigated



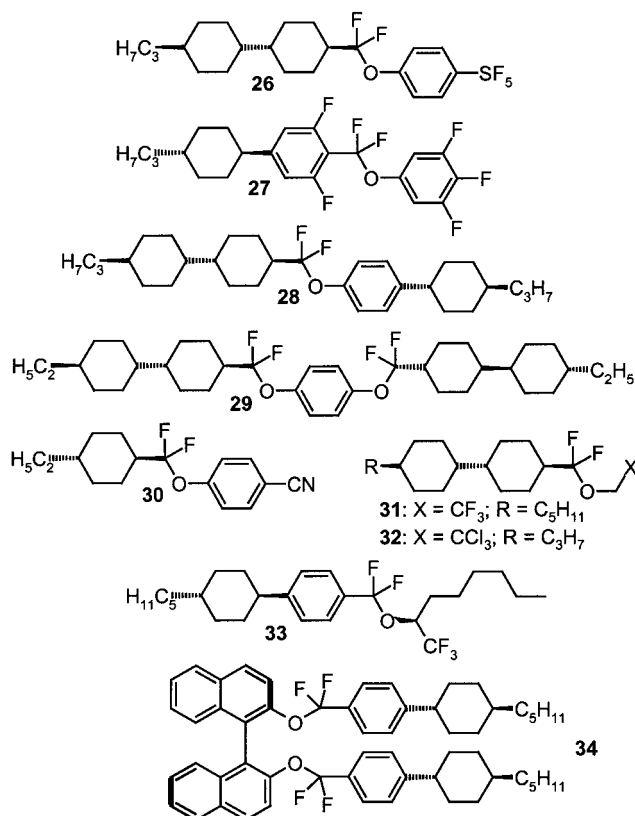
Scheme 5. Direct selective conversion of the ketenedithio-ketal **12** ($\text{R} = \text{C}_6\text{H}_{11}$) to *trans,trans*-**2**: a) 1. $\text{CF}_3\text{SO}_3\text{H}$, CH_2Cl_2 ; $0^\circ\text{C} \rightarrow 20^\circ\text{C}$ (1 h) $\rightarrow -70^\circ\text{C}$; 2. 3,4,5-trifluorophenol, NEt_3 ; -70°C ; 3. $\text{NEt}_3 \cdot 3\text{HF}$; -70°C ; $-70^\circ\text{C} \rightarrow -20^\circ\text{C}$ (*trans,trans*-**2**/*trans,cis*-**2** $\sim 98/2$; overall yield 93%).



Scheme 6. Tentative mechanistic pathway for the observed reactivity of cycloaliphatic dithianylum salts (for related proposals see also ref. [12]).

by density functional theory (DFT) calculations (B3LYP/6-31G**/B3LYP/6-31G* level of theory including unscaled zero-point vibrational energy corrections;^[18] for details see Supporting Information). Instead of the 4-alkylcyclohexylidene substructure, the 2-isopropylidene moiety was used to simplify the computational problem. The following discussion uses the numbering system of Scheme 6 but implies the isopropyl model systems. The proton affinity of **16** is $-226.5 \text{ kcal mol}^{-1}$. Surprisingly, even the addition of a bromonium ion to the dithianylum salt **17**⁺ results in the formation of the dication **20**²⁺ with an exothermicity of $-51.6 \text{ kcal mol}^{-1}$. The reaction of phenolate ($\text{R}^2 = \text{Ph}$) with **17**⁺ gives **18** ($-130.1 \text{ kcal mol}^{-1}$), and subsequent attack by Br^+ directly leads to the ring-opened product **22**⁺. The primary addition product **21**⁺ is not a stationary point at this level of theory. In the absence of a suitable nucleophilic reaction partner, **20**²⁺ can lose a proton to furnish **19**⁺. This process is endothermic by $93.6 \text{ kcal mol}^{-1}$. Alternatively, **19**⁺ might be generated directly by bromination of the ketenedithio-ketal **16** ($-184.5 \text{ kcal mol}^{-1}$). With regard to the experiments represented in Scheme 4, species **19**⁺ might be considered as a possible starting point for a series of reactions leading among others to compound **14**.

Application of the general methods described above offered an convenient access to a large variety of structurally diverse new liquid crystals and related compounds. The physical properties of a selection of the newly synthesized materials (Scheme 7) are listed in Table 1. The most striking result of the insertion of the difluoro-oxyethylene bridge into the basic phenyl-



Scheme 7. Structures of liquid crystals (26–32) and chiral dopants (33, 34) given in Table 1.

bicyclohexyl structure is the pronounced reduction of the rotational viscosity (γ_1) of **2** by 21 % compared to that of **1**. At the same time the clearing temperature is increased by 10 K and the melting point is decreased by 29 K. Similar effects are observed for most phenylcyclohexane-based materials. A detailed comparative discussion of the changes of physical properties induced by the insertion of highly fluorinated bridge elements into different locations within the mesogenic core structure will be subject of a forthcoming publication.

Starting either from inexpensive carboxylic acids or carbonyl compounds the previously elusive α,α -difluoroalkyl ethers can be conveniently prepared in high yields. The uncomplicated preparation or in situ generation of the dithianylum salts as key intermediates as well as the easy purification of the final product makes this method a highly attractive choice for industrial-scale production of liquid crystals, pharmaceuticals, and a variety of other fine chemicals.

Experimental Section

Dithianylum triflate **11**⁺CF₃SO₃[−]: 1,3-Propanedithiol (125 g, 1.16 mol) was added to a suspension of **10** (250 g, 0.89 mol) in a mixture of toluene (250 mL) and isooctane (250 mL). The milky suspension was heated to 50 °C, and trifluoromethanesulfonic acid (173 g, 1.16 mol) was added over 30 min (slightly exothermic). The resulting solution was heated to 102–104 °C, and water formed during the reaction (28 mL) was removed azeotropically over 4 h. The solution was cooled to 90 °C, and methyl *tert*-butyl ether (1 L) was added over 45 min at 90–70 °C. The suspension was cooled to 0 °C and filtered under a dry nitrogen atmosphere. The crystals were washed with methyl *tert*-butyl ether (4 × 250 mL) and dried in vacuo to yield **11**⁺CF₃SO₃[−] (402 g, 90 %) as pinkish crystals. The purity was

estimated to be about 95 % by ¹H NMR spectroscopy, and was sufficient for the further reactions. The compound slowly decomposed at about 90–100 °C; ¹H NMR (250 MHz, CDCl₃, 303 K): δ = 3.75 (t, 4H, *J* = 5 Hz), 3.15–2.95 (m, 2H), 2.60–2.45 (m, 2H), 2.17 (d, 2H, *J* = 10 Hz), 2.03–1.60 (m, 4H), 1.35–0.75 (m, 21H); ¹³C NMR (60 MHz, CDCl₃, 303 K): δ = 203.4 (s, S–C=S⁺), 121.1 (q, CF₃SO₃[−]), 57.2, 53.5, 43.2, 42.3, 38.1, 37.7, 35.5, 33.8, 32.5, 30.3, 29.5, 27.1, 23.1, 17.3, 14.5; MS (EI): *m/z* (%): 352 [*M*⁺ – CF₃SO₃H] (100).

Synthesis of **2** from the dithianylum salt **11**⁺CF₃SO₃[−]: A solution of 3,4,5-trifluorophenol (10 g, 68 mmol) in a mixture of triethylamine (7.33 g, 72 mmol) and CH₂Cl₂ (90 mL) was cooled to −70 °C. Then a solution of **11**⁺CF₃SO₃[−] (30.9 g, 62 mmol) in CH₂Cl₂ (85 mL) was added over 45 min at the same temperature. After the mixture had been stirred for 1 h, NEt₃·3HF (50 mL, 310 mmol) were added over 5 min. Then, over a period of 1 h a solution of bromine (49.5 g, 310 mmol) in CH₂Cl₂ (20 mL) was added at −70 °C. The mixture was stirred for one more hour at −70 °C and then allowed to warm up to 0 °C. The solution was poured into a mixture of 32 % aqueous NaOH (107 mL) and ice (200 g). The pH was adjusted to 5–8 by addition of 32 % aqueous NaOH (ca. 28 mL). The aqueous layer was extracted with CH₂Cl₂ (50 mL), and the combined organic extracts were filtered through 2.5 g of celite, washed with water, and evaporated to dryness. The residue was dissolved in *n*-heptane (60 mL), stirred for 30 min with 5 g of silica gel, filtered, and evaporated to dryness. The crude product was chromatographed with *n*-heptane on silica gel to yield **2** (22.8 g; 84 %) as a nematic oil which slowly crystallized (purity 99.2 %, verified by GLC and HPLC). The sample was purified further by recrystallization from *n*-heptane at −20 °C (purity > 99.9 %; GLC and HPLC). For mesophases see Table 1; ¹H NMR (250 MHz, CDCl₃, 303 K): δ = 6.82 (mc, 2H, Ar-2,6-*H*), 2.08–1.65 (m, 4H), 1.38–0.80 (m, 27H); ¹⁹F NMR (280 MHz, CDCl₃, 303 K): δ = −165.3 (mc, 1F; Ar-4-*F*), −133.8 (mc, 2F; Ar-3,5-*F*), −79.3 (d, *J* = 8.4 Hz, 2F; CF₂O); MS (EI): *m/z* (%): 432 [*M*⁺] (25), 284 [*M*⁺ – F₃PhOH] (50).

Synthesis of **2** from the ketenedithioketal **12**: Trifluoromethanesulfonic acid (0.25 mL, 2.84 mmol) was added dropwise at 0 °C to a solution of **12** (1.00 g, 2.84 mmol)^[16] in CH₂Cl₂ (15 mL). The cooling bath was removed and the mixture was stirred for 30 min at room temperature. Then it was cooled down to −70 °C and a solution of 3,4,5-trifluorophenol (0.63 g, 4.25 mmol) in toluene and triethylamine (0.71 mL, 5.10 mmol) in CH₂Cl₂ (3 mL) was added. After the mixture had been stirred for 1 h at −70 °C, NEt₃·3HF (2.29 mL, 14.2 mmol) was added. After 5 min a suspension of DBH (4.05 g, 14.2 mmol) in CH₂Cl₂ (15 mL) was added portionwise over 30 min. After stirring for additional 60 min, the mixture was allowed to warm up to −20 °C and then poured into ice-cold 1N aqueous NaOH (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were stirred for 15 min with 5 g of celite, filtered, washed with brine (2 × 30 mL), dried over Na₂SO₄, and evaporated to dryness. The residue was dissolved in *n*-hexane and filtered through a short silica gel column. Yield: 1.14 g (93 %) of **2**, containing 96.9 % *trans,trans* and 2.2 % *trans,cis* isomer (GLC). Further purification to > 99.8 % (GLC) of *trans,trans*-**2** was accomplished by crystallization from *n*-heptane at −20 °C.

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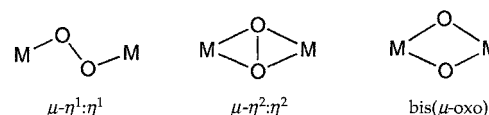
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- [21] The application-oriented evaluation of liquid crystals for use in LCDs is centered around “virtual” clearing temperatures, electrooptic parameters, and viscosities. These data are obtained by extrapolation from a standardized nematic host mixture: $T_{\text{NI,extr}}$, $\Delta\epsilon$, Δn , and γ_1 were determined by linear extrapolation from a 10% w/w solution in the commercially available Merck mixture ZLI-4792 ($T_{\text{NI}} = 92.8^\circ\text{C}$, $\Delta\epsilon = 5.27$, $\Delta n = 0.0964$). The values thus obtained are empirically corrected for changes in the order parameter. For the pure substances the mesophases were identified by optical microscopy, and the phase transition temperatures by differential scanning calorimetry (DSC).

A Short Copper–Copper Distance in a (μ -1,2-Peroxo)dicopper(II) Complex Having a 1,8-Naphthyridine Unit as an Additional Bridge**

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Proteins that utilize transition metal ions to activate molecular oxygen perform a variety of functions.^[1–4] Peroxo-bridged dimetallic species are important intermediates in these processes. The geometry of a bound peroxide group may play an important role in determining its reactivity and thus the function of the protein. Comparison of synthetic dinuclear peroxo complexes with the protein cores has helped elucidate the structures and properties of many such biological species. The μ - η^2 : η^2 side-on geometry is presently known only in dicopper-containing proteins,^[2] whereas the μ - η^1 : η^1 (μ -1,2-peroxo)-bridged structure occurs in diiron-containing proteins (Scheme 1).^[3]



Scheme 1. Selected geometric units formed upon the reaction of dioxygen with dimetallic transition metal centers.

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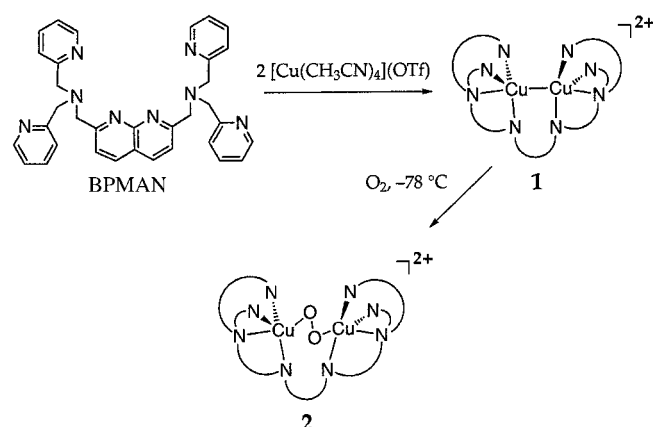
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Dicopper(II) model complexes with $\mu\text{-}\eta^2\text{:}\eta^2$ side-on-bound peroxide groups have metal–metal separations of about 3.5 Å,^[5, 6] whereas a *trans*-(μ -1,2-peroxo)dicopper(II) model complex exhibits a substantially longer copper–copper separation (4.36 Å).^[7] The structures of three (μ -1,2-peroxo)diiron(III) complexes were determined several years ago, and the metal–metal distances ranged from 3.327 to 4.000 Å.^[8–10] A recent extended X-ray absorption fine structure (EXAFS) study of a (μ -1,2-peroxo)diiron(III) intermediate in ferritin oxidation revealed a unique, μ -1,2-type peroxide bridge with a very short iron–iron separation of about 2.53 Å, a value thus far unprecedented for such species.^[11] The unusual geometry was suggested to favor release of H₂O₂ from the (peroxo)-diiron(III) intermediate, and the presence of two additional single-atom bridges was postulated to account for the short metal–metal distance.

We report here the discovery of a short (ca. 2.84 Å) copper–copper distance in a (μ -1,2-peroxo)dicopper(II) species having only 1,8-naphthyridine as an additional bridge. The rigid ligand scaffold used to assemble this unit seems well suited to afford short metal–metal distances in (μ -1,2-peroxo)dinuclear complexes. This finding is significant since it demonstrates that the presence of single-atom bridges may not be required to afford short metal–metal distances in (μ -1,2-peroxo)dimetallic centers. The short metal–metal separation observed here is very similar to those in bis(μ -oxo)dicopper(III) complexes (ca. 2.8 Å).^[12–14] Thus the present complex may model key intermediates in the formation of $\mu\text{-}\eta^2\text{:}\eta^2$ side-on peroxo structures in dicopper systems and in the conversion of (μ -1,2-peroxo) to bis(μ -oxo) species in dioxygen activation by diiron centers.

The 1,8-naphthyridine-based ligand 2,7-bis[bis(2-pyridylmethyl)aminomethyl]-1,8-naphthyridine (BPMAN) was employed as the dinucleating ligand.^[15] The dicopper(II) compound [Cu₂(bpman)](OTf)₂ (**1**; OTf = [−]OSO₂CF₃) was prepared by allowing one equivalent of BPMAN to react with two equivalents of [Cu(CH₃CN)₄](OTf) in CH₂Cl₂ and was crystallized from CH₂Cl₂/Et₂O (Scheme 2). Each copper ion is coordinated to four nitrogen atoms from BPMAN and has distorted trigonal-bipyramidal geometry if a Cu–Cu interaction is included (Figure 1).^[16] The copper–copper distance is short (2.5947(15) Å).



Scheme 2. Preparation of **1** and **2**; the OTf counterions for **1** and **2** are not shown.

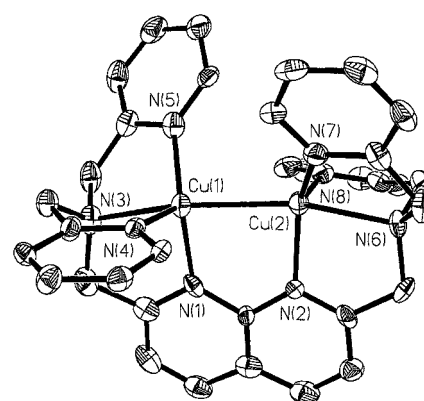


Figure 1. ORTEP diagram of [Cu₂(bpman)](OTf)₂ (**1**) showing 40% thermal ellipsoids and selected atom labels. Selected bond lengths [Å] and angles [°]: Cu(1)–N(1) 2.038(8), Cu(1)–N(3) 2.202(8), Cu(1)–N(4) 2.034(7), Cu(1)–N(5) 2.003(8), Cu(2)–N(2) 2.019(7), Cu(2)–N(6) 2.184(7), Cu(2)–N(7) 1.959(8), Cu(2)–N(8) 2.122 (8), Cu(1)–Cu(2) 2.5947(15); N(3)–Cu(1)–Cu(2) 162.5(2), N(1)–Cu(1)–N(3), 80.9(3), N(1)–Cu(1)–N(5) 126.5(3), N(1)–Cu(1)–N(4) 104.8(3), N(6)–Cu(2)–Cu(1) 167.6(2), N(2)–Cu(2)–N(6), 82.4(3), N(2)–Cu(2)–N(7) 140.5(3), N(2)–Cu(2)–N(8) 90.4(3).

Treatment of **1** with O₂ at −78 °C in CH₂Cl₂ gave a deep violet species **2** after an induction period of several minutes. The low-temperature UV/Vis spectrum revealed the exact same features as those of a well-characterized *trans*-(μ -1,2-peroxo)dicopper(II) compound prepared in the presence of two tris[(2-pyridyl)methyl]amine (TPA) ligands (λ_{max} = 415 nm (sh), ϵ = 2333 M^{−1} cm^{−1}; λ_{max} = 505 nm, ϵ = 10500 M^{−1} cm^{−1}; λ_{max} = 620 nm, ϵ = 5400 M^{−1} cm^{−1}),^[7] as depicted in Figure 2.

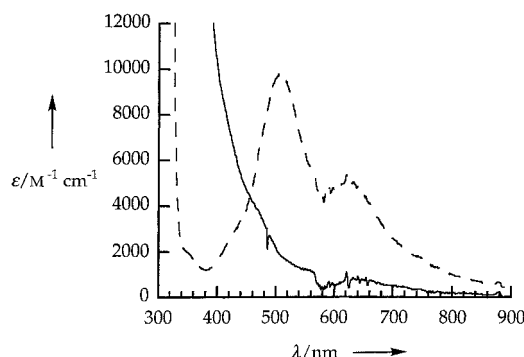


Figure 2. UV/Vis spectra for the reaction of **1** (0.06 mM) with O₂ in CH₂Cl₂. Solid line: **1** at −78 °C; dashed line: **2** generated from oxygenation of the solution of **1** at −78 °C.

A resonance Raman spectrum of **2** acquired in CH₂Cl₂ at −78 °C with excitation at 514.5 nm displayed O₂-dependent bands at 831 cm^{−1} and 561 cm^{−1}, which disappeared when the solution was allowed to warm (Figure 3). The oxygenation experiment was repeated with an isotopically labeled 1:2:1 statistical mixture of ¹⁶O₂, ¹⁶O¹⁸O, and ¹⁸O₂. The resulting purple solution exhibited three O₂-sensitive bands at 831 cm^{−1}, 813 cm^{−1} and 787 cm^{−1} having an intensity ratio of approximately 1:2:1, as shown in the inset of Figure 3. The values calculated based on a simple harmonic oscillator model for the ¹⁶O¹⁸O and ¹⁸O₂ derivatives are 808 cm^{−1} and 783 cm^{−1}, respectively. This result not only confirms the presence of a

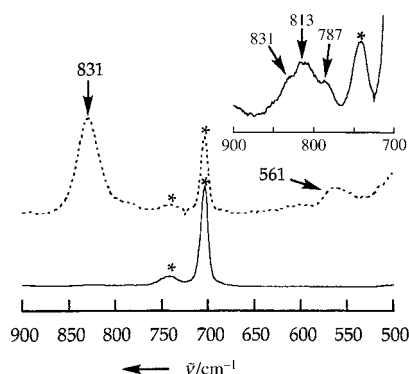


Figure 3. Resonance Raman spectra of **1** (lower curve) and **2** (upper curve) in CH_2Cl_2 at -78°C . The inset shows the spectrum of the partially generated **2** from reaction of **1** with a 1:2:1 statistical mixture of $^{16}\text{O}_2$, $^{16}\text{O}^{18}\text{O}$, and $^{18}\text{O}_2$ (* solvent bands).

peroxide bridge, but also reveals it to bind in a symmetrical bridging fashion.

Different peroxide bridging modes between two copper(II) ions display very characteristic O–O stretching bands in Raman spectra. The O–O stretch band of **2** matches very well with that of a TPA-based *trans*-(μ -1,2-peroxo)dicopper(II) complex, which occurs at 832 cm^{-1} (788 cm^{-1} with $^{18}\text{O}_2$), and where there is also an O_2 -sensitive band at 561 cm^{-1} .^[17] These results strongly imply the existence of a symmetrical μ -1,2-peroxide bridge in **2**. Other bridging modes are inconsistent with the Raman results.

To obtain further structural information about this species, X-ray absorption spectroscopy (XAS) was applied to examine frozen CH_2Cl_2 solutions of **1** and **2**. The Cu K-edge for **1** (Figure 4) features a weak $1s \rightarrow 4p$ transition at about 8982 eV ,

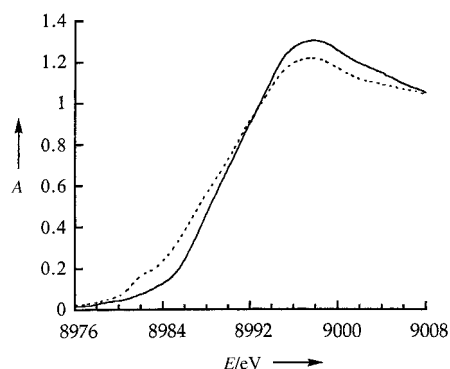


Figure 4. X-ray absorption Cu K-edges for **1** (dotted line), and **2** (solid line). A = normalized absorption.

in accord with the value expected for a dicopper(I) complex. The K-edge for **2** has a weak $1s \rightarrow 3d$ transition at about 8979 eV , characteristic of Cu^{II} . The EXAFS data of **1** are well fit by a structural model that includes 2.5 nitrogen atoms at $2.02\text{ \AA}$ and 1.5 nitrogen atoms at $2.17\text{ \AA}$. The Cu...Cu distance of $2.52\text{ \AA}$ determined from fits to the EXAFS data for the frozen solution of **1** is slightly shorter than the distance of $2.59\text{ \AA}$ found in the solid-state structure. The difference may reflect some degree of relative motion between the copper ions in solution. The Fourier transform (FT) of the EXAFS for **1** has two prominent features (Figure 5). The first

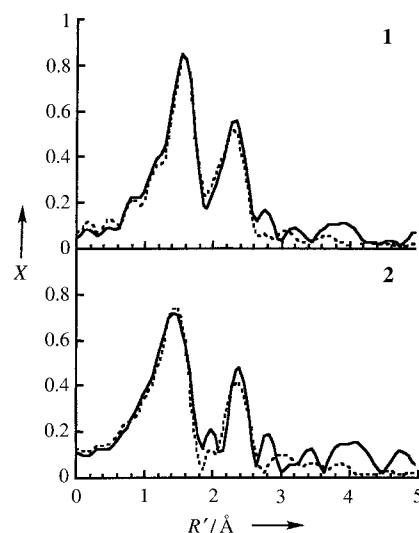


Figure 5. Fourier transforms of EXAFS data (solid lines) and representative fits to data (dotted lines) for **1** and **2**. X = Fourier transform magnitude.

peak is fit as scattering from coordinated ligands and the second peak is entirely compensated by scattering between the two copper ions. There are no additional prominent outer peaks due to longer distance Cu...C scattering.

The FT of the EXAFS data for **2** is similarly composed of two major peaks (Figure 5). The first peak is fit as scattering from three oxygen or nitrogen atoms at $1.95\text{ \AA}$ plus an additional two at $2.08\text{ \AA}$. Contraction of the average Cu–ligand distance from about $2.07\text{ \AA}$ in **1** to about $2.00\text{ \AA}$ in **2** is consistent with copper oxidation. The second FT peak at $R' \sim 2.4\text{ \AA}$ can be fit equivalently as scattering from 1 Cu or 4 C atoms (per Cu) at about $2.8\text{--}2.9\text{ \AA}$. Cu...C scattering did not contribute significantly to the fit for **1**, the Cu...Cu vector being well separated from the Cu...C contribution. Since complex **2** directly derives from **1**, the Cu...C contribution would be small owing to internal canceling, as in **1**. A fit including a Cu...Cu vector of about $2.84\text{ \AA}$ is therefore the most reasonable interpretation.

Alternative peroxide structures, as well as tetranuclear species, are highly unlikely based on Raman and UV/Vis results. A tetranuclear species would also most likely be highly charged and insoluble in CH_2Cl_2 . A tetranuclear species with a charge of $+2$ and having a related naphthyridine-based ligand does not dissolve in CH_2Cl_2 .^[18]

At -78°C , compound **2** decays to another species **3** with a half-life of about 2.5 h. An isosbestic point was observed at 382 nm during the decay. The product **3** has absorption peaks at 345 nm ($\epsilon = 4750\text{ M}^{-1}\text{ cm}^{-1}$) and 670 nm ($\epsilon \sim 100\text{ M}^{-1}\text{ cm}^{-1}$), very similar to those in a putative (μ -oxo)dicopper(II) compound reported recently.^[19] Compound **3** is unstable at higher temperatures and was not isolated.

In conclusion, by employing a 1,8-naphthyridine-based dinucleating ligand that can impose a rigid ligand scaffold, the peroxo-bridged dicopper(II) complex **2** was prepared by reacting the dicopper(I) precursor **1** with O_2 at low temperature. Spectroscopic properties and an isotope labeling experiment for **2** indicate that it contains a μ - η^1 : η^1 peroxide. The EXAFS studies reveal a short Cu...Cu distance of about $2.84\text{ \AA}$, which supports a previous conclusion that (μ -1,2-

peroxo) dinuclear species can have quite short metal–metal distances.^[11] This result suggests that a rigid ligand environment imposed at a protein active site could give rise to similar short metal–metal separations in (μ -1,2-peroxo) dinuclear species lacking single-atom bridges. The short metal-metal separation revealed in **2** is very close to those in bis(μ -oxo)dicopper(III) complexes (~ 2.8 Å)^[12–14] and shorter than those in dicopper(II) species with μ - η^2 : η^2 side-on peroxides (~ 3.5 Å).^[5, 6] Such species could be present as intermediates in conversion of μ -1,2-peroxide to μ - η^2 : η^2 side-on peroxides or bis(μ -oxo) species at biological and synthetic dinuclear centers.

Experimental Section

Preparation of compound 1: A portion of BPMA (50 mg, 0.090 mmol) in CH_2Cl_2 (0.5 mL) was added to $[\text{Cu}(\text{CH}_3\text{CN})_4](\text{OTf})$ (69 mg, 0.180 mmol) in CH_2Cl_2 (1 mL). The resulting brownish yellow solution was allowed to stir for 30 min. Vapor diffusion of Et_2O into this solution yielded yellow-brown plates suitable for X-ray crystallography (70 mg, 80%). ^1H NMR (CD_2Cl_2 , 300 MHz): δ = 4.485 (s, 8H), 4.684 (s, 4H), 7.169 (t, J = 6.5 Hz, 4H), 7.54–7.60 (m, 6H), 7.820 (t, J = 8 Hz, 4H), 8.366 (d, J = 8 Hz, 6H); FT-IR (KBr): $\tilde{\nu}$ = 3066 (m), 2938 (m), 2906 (m), 2855 (w), 1604 (s), 1506 (w), 1477 (w), 1440 (s), 1368 (w), 1277 (s), 1224 (m), 1155 (s), 1030 (s), 979 (w), 958 (m), 898 (w), 855 (w), 765 (s), 733 (w), 637 (s) cm^{-1} ; elemental analysis calcd for $\text{C}_{37}\text{H}_{34}\text{N}_8\text{O}_6\text{S}_2\text{F}_6\text{Cl}_2\text{Cu}_2$ (**1**· CH_2Cl_2): C 41.81, H 3.22, N 10.54; found: C 41.75, H 2.88, N 10.41.

XAS data collection: X-ray absorption spectra were measured on unfocused wiggler beamline 7-3 (sample **2**, 5 mm) and focused beamline 9-3 (sample **1**, 5 mm) at the Stanford Synchrotron Radiation Laboratory (SSRL), with the ring operating at 3 GeV and 50–100 mA. Samples were maintained at 10 K inside an Oxford Instruments CF1208 liquid He continuous flow cryostat. A Si(220) double-crystal monochromator was used, with harmonic rejection performed by detuning (beamline 7-3) or through a harmonic rejection mirror (beamline 9-3). Vertical 1-mm pre-monochromator slits were used to minimize beam divergence. Spectra were measured in fluorescence mode, using an ionization chamber Lytle detector for **1** with Ni filter and Soller slits and a 30-element Ge detector for **2**. Of the available 30 channels, 14 were operative. The spectrum of Cu foil was measured as an external calibrant before and after sets of four (beamline 7-3) or ten scans (beamline 9-3). External calibration was necessary as the sample matrix (CH_2Cl_2) was highly photoabsorbing such that minimal beam intensity was transmitted by the samples. The first inflection point of the Cu K-edge was set to 8980.3 eV. Multiple scans of the K-edge and EXAFS data were measured over the range 8668–9868 eV and averaged. Although EXAFS data were measured to $k = 15$ Å^{−1}, spectra were truncated at $k = 13$ Å^{−1} due to noise in the data at higher values of k .

XAS data reduction and analysis: For each spectrum, a smooth second-order polynomial was fit to the pre-edge region, then extrapolated across the entire energy range and subtracted from the data. A three-segment spline (polynomial curves of orders 2, 3, 3) was fit to and subtracted from the EXAFS region, and the data normalized at 9000 eV, using the SPLINE program (Ellis, SSRL). EXAFS data were k^3 -weighted, where the photoelectron wave vector $k = [2m_e(E - E_0)/(\hbar^2 2\pi)^2]^{1/2}$, E = energy, E_0 = energy of the onset of the EXAFS, and m_e = the mass of an electron. Phase and amplitude functions ($\phi_{\text{as}}(k)$ and $A_{\text{s}}(k)$) calculated by feff 6.0^[20] for each absorber–scatterer (a–s) pair were used in creating a simulated EXAFS spectrum, which was adjusted by a least-squares fitting process to match the data (using the EXAFSPAK programs).^[21] Absorber–scatterer distances (R_{as}) and Debye–Waller factors (σ_{as}^2) were varied for each equivalent set of backscattering atoms. Coordination numbers (N_{s}) were generally kept constant, according to the known crystal structure for **1** and/or the hypothetical structural model being tested. Other parameters included in the fits were E_0 and S_0^2 , where S_0^2 is the many-body amplitude reduction factor accounting for spectral dampening due to shake-up or shake-off processes. E_0 was allowed to vary within ranges defined by fits to similar, crystallographically characterized Cu complexes. S_0^2 was fixed at 0.9. Fits were constructed in a sequential process, where components to fits were

included on the basis of visual improvement to the EXAFS fit and reduction in a goodness-of-fit parameter R , where $R = R^2/[2\Delta k\Delta R'/\pi] - \text{no. variables in fit}$, $R = [\sum k^4(\chi_{\text{obs}} - \chi_{\text{calcd}})^2/N]^{1/2}$, N = the number of points in the EXAFS spectrum, Δk = the range over which the EXAFS was fit (3–13 Å^{−1}), and $\Delta R'$ = the range of the Fourier transform over which the fit was made ($\Delta R' = 0$ –5 Å).

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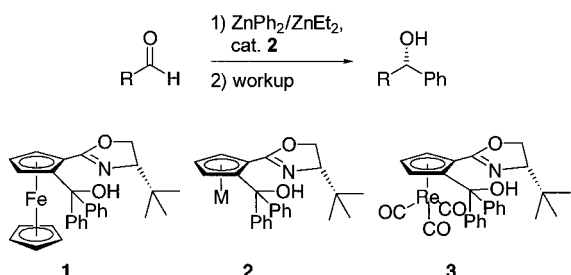
Application of a Planar Chiral η^5 -Cyclopentadienylrhenium(I)tricarbonyl Complex in Asymmetric Catalysis: Highly Enantioselective Phenyl Transfer to Aldehydes**

Carsten Bolm,* Martin Kesselgruber, Nina Hermanns, Jens P. Hildebrand, and Gerhard Raabe

Dedicated to Professor Günter Helmchen on the occasion of his 60th birthday

Asymmetric metal catalysis is one of the most active areas in modern organic chemistry, and the number of novel ligands for catalytic asymmetric transformations is growing rapidly.^[1] Among these compounds, planar chiral ferrocenes^[2] are of immense importance and some of them have already found application in industrial processes.^[3] Often, ferrocenes are superior to other metal π complexes,^[4] although for some catalyses it was found that a variation of the π -bound metal fragment can be of benefit.^[5]

Recently, we developed a system for the enantioselective, catalytic synthesis of diarylmethanol compounds from aldehydes by utilizing ferrocene **1**^[6] and a zinc species generated in situ from $\text{ZnPh}_2/\text{ZnEt}_2$ (Scheme 1).^[7] Further optimization of the process was expected to be possible by variation of the metal- π -fragment of **2**.^[8, 9] Herein, we describe the synthesis



Scheme 1. Enantioselective phenyl transfer onto aldehydes and catalytically active metal complexes.

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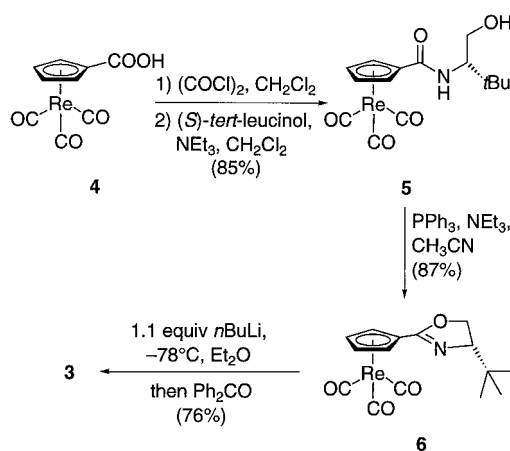
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

and application of novel cyrhetrene **3**, which was found to be superior in terms of both enantioselectivity and catalyst loading in the phenyl transfer to a wide variety of aldehydes.^[10]

Modifications of the metal- π -fragment of **2** were expected to have an impact on the steric and electronic properties of the catalyst. Assuming that decreased electron density on the ligand would result in increased Lewis acidity of the catalyst, we focussed our attention primarily on the synthesis of metal tricarbonyl complexes.^[9] There, the electron-withdrawing properties of the carbonyl groups would lower the electron density on the metal center as well as on the remaining cyclopentadienyl fragment bearing the stereogenic elements. If these electronic changes are then efficiently transferred to the catalytically active site and if the simultaneously occurring steric modifications are not counterproductive, beneficial effects in the catalysis could result. Due to its expected chemical stability rhenium(I) complex **3** appeared to be the complex of choice. To the best of our knowledge, η^5 -cyclopentadienylrhenium(I)tricarbonyl complexes have not been utilized in asymmetric catalysis, and only one nonracemic planar chiral derivative has been described.^[11, 12] Our synthesis of **3** started from cyrhetrenyl carboxylic acid **4**, which was obtained in a straightforward manner from $[\text{Re}_2(\text{CO})_{10}]$ and cyclopentadienyl carboxylic acid following an excellent, high-yielding procedure published by Jaouen et al.^[13] The cyrhetrenyl oxazoline **6**^[14] was synthesized in an analogous manner to the corresponding ferrocene derivatives via amide **5**, which was cyclized using the Appel protocol (Scheme 2).^[15] Directed



Scheme 2. Synthesis of complex **3**.

ortho-metalation^[16] of **6** using *n*BuLi in diethyl ether^[17] and subsequent quenching of the resulting lithiated species with benzophenone led to diastereomeric products in a ratio of 9:1 in favor of the product with *S,R*_p configuration.^[18] All transformations give good to excellent yields, and the compounds are crystalline and stable to air, light, and moisture.^[14]

To confirm the relative configuration of **3**, the solid-state structure of the cyrhetrenyl complex was determined by single-crystal X-ray structure analysis.^[14, 19] As depicted in Figure 1 one phenyl group of **1** is equatorial, while the other occupies an axial position with regard to the cyclopentadienyl

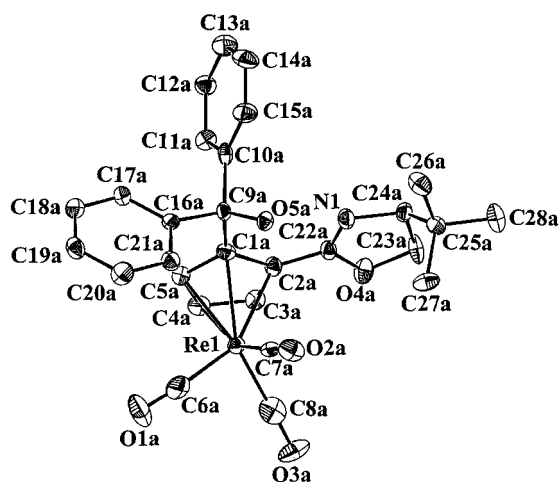


Figure 1. Structure of **3** (ORTEP plot; ellipsoids plotted with 50 % probability).

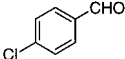
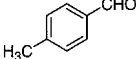
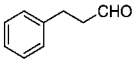
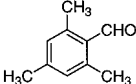
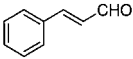
backbone. The relative location of the *tert*-butyl group at the oxazoline group is *trans* with respect to the axial phenyl group. Overall, the structural features of cyrhetrene **3** are very similar to those of ferrocene **1**, which suggested its potential use in catalysis.

The catalytic properties of **3** were explored in the asymmetric phenyl transfer from organozinc compounds to aldehydes. Initial approaches by ourselves^[7a] and others^[10] using diphenylzinc as phenyl source, encountered the difficulty that the uncatalyzed background reaction with the substrate is comparatively rapid, leading to a diminished enantioselectivity.^[20] The use of diethylzinc as an additive had been shown to be the key to significantly raise the enantiomeric excesses.^[7b, 10b] The replacement of the CpFe moiety by the Re(CO)₃ fragment now led to a further improvement of this transformation (Table 1).

For most examples, complex **3** shows higher enantioselectivity than ferrocene **1**. A significant increase was observed in reactions with *ortho*-substituted aldehydes (Table 1, entries 2 and 7) which are now among the best substrates for this transformation. Especially noteworthy is the result obtained with 2,4,6-trimethylbenzaldehyde (Table 1, entry 7; 98 % *ee*), which demonstrates that even *ortho*-disubstitution at the aromatic aldehyde is well tolerated. The reactions with other substrates follow trends that have previously been observed in catalyses with **1**: cinnamyl aldehyde displays lower levels of enantioselection (Table 1, entry 8), and aliphatic aldehydes are still somewhat problematic with respect to asymmetric induction (Table 1, entries 5 and 6). In several cases, even a catalyst loading of only 2 mol % of **3** was sufficient to achieve high *ee* values similar to the ones obtained with 10 mol % of **1** (Table 1, entries 1, 3, 5, 8).^[21]

In summary, we have described the synthesis of the η^5 -cyclopentadienylrhenium(i)tricarbonyl complex **3** and demonstrated its use in asymmetric catalysis. Compared to its analogous ferrocene derivative, cyrhetrene **3** shows significantly higher enantioselectivities in the catalyzed phenyl transfer from a phenylzinc species to aromatic and aliphatic aldehydes, leading to the currently most efficient approach for this reaction. Further studies are directed towards the use of

Table 1. Asymmetric phenyl transfer to various aldehydes.

$\text{R}-\text{CHO} \xrightarrow[\text{2) workup}]{\begin{array}{l} \text{1) ZnPh}_2 \text{ (0.65 equiv),} \\ \text{ZnEt}_2 \text{ (1.3 equiv),} \\ \text{cat. } \mathbf{3}, \text{ toluene, } 10^\circ\text{C} \end{array}} \text{R}-\text{CH(OH)-Ph}$				
Entry ^[a]	Substrate	<i>ee</i> of product [%] ^[b,c]		Absolute config. of alcohol ^[d]
		2 mol % of 3	10 mol % of 3	
1		96	98 (97)	<i>R</i>
2		83	96 (91)	<i>R</i>
3		95	95 (95)	<i>R</i>
4		85	99 (98)	<i>R</i>
5		76	83 (75)	<i>S</i>
6		74	78 (78)	<i>S</i>
7		80	98 (92)	<i>R</i>
8		88	92 (90)	<i>R</i>
9		93	98 (96)	<i>R</i>

[a] All reactions gave good to quantitative yields (>80 % on a 0.25 mmol scale). [b] Determined by HPLC using a chiral stationary phase. For exact separation conditions see Supporting Information. [c] Values in parentheses represent *ee* values obtained with 10 mol % of ferrocene ligand **1**. [d] Determined by comparison of the order of peak elution during HPLC with literature values, or tentatively assigned by assumption of an identical reaction pathway (entries 4, 6, 7, 9).

other η^5 -cyclopentadienylrhenium(i)tricarbonyl complexes in asymmetric catalysis.

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Asymmetric Catalysis, Vol. 2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 911.

- [21] In a separate study (ref. [6c]), we had shown that the use of diastereomeric mixtures of **1** can lead to high enantioselectivity. As a consequence we proposed that this phenomenon could be exploited in cases where the directed *ortho*-metalation was not completely diastereoselective. Here we have now found that using 10 mol% of a 7:1 mixture of (*S,R*_p)-**3** and diastereomeric (*S,S*_p)-**3**, the phenylation of *p*-chlorobenzaldehyde proceeded with 97% *ee*. Thus, it appears that this mixture as such can be used in catalysis. The overall process applying **3** in the aryl transfer is thereby simplified even further.

Individual Alumina Nanotubes**

Lin Pu,* Ximao Bao, Jianping Zou, and Duan Feng

Avid attention has been given to the preparation, properties, and applications of nanotubes of different materials. Nanotubes composed of carbon,^[1] tungsten disulfide (WS₂),^[2] boron nitride (BN),^[3] vanadium oxide [VO_{2.40}(C₁₆H₃₃NH₂)],^[4] titanium dioxide (TiO₂),^[5] and others, were studied during the last decade. However, the reproducible usage of nanotubes in electrical devices is complicated by the fact that the tubes exist in different chiralities and diameters.^[6] Moreover, the raw materials consist of dense networks of closely connected nanotubes, and individual tubes are often obtained by ultrasonic agitation, which may introduce defects into the tubes.^[7] Here we report on two easy and controlled electrochemical-anodizing routes for the synthesis of individual alumina nanotubes (ANTs) in a single fabricating step. The structure of ANTs provides clues to unraveling the mechanism of nanotube growth and gives valuable hints on solving the long-standing problem of the self-organization mechanism in the porous anodization of aluminum.^[8–15]

Two different preparation methods (Figure 1), designated normal stepwise anodization (NSA) and lateral stepwise anodization (LSA), were used to make ANTs. The major difference between these two arrangements is the position on the sample (Al/Si) to which the potential difference *U* is applied. For NSA, it is the bottom surface of the Si substrate, and for LSA, the top surface of the Al metal film. This results in completely different current paths for the two methods. Note, however, that the orientation of the sample is not important.

The transmission electron microscope (TEM) images in Figure 2 show a general view of the ANTs. They are attached to the anodic porous alumina (APA) mother film. In the TEM

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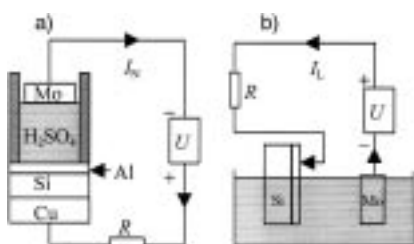


Figure 1. Sketch of preparation methods for ANTs. For details see the Experimental Section. a) NSA: After 360 s of anodization, power was turned off for 60 s, then anodizing was carried out again for 173 s. Al was almost completely oxidized after about 100 s. b) LSA: After open-circuit dissolution for 120 s, the sample was anodized for 292 s. $R = 16.9 \, \Omega$. The time depends on fabrication conditions such as the thickness of the Al film, the temperature, concentration and species of the electrolyte, and the resistance of the Al/Si interface.

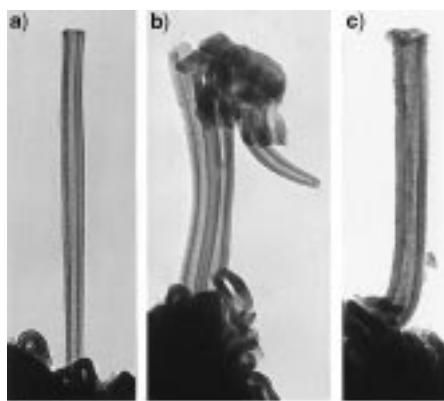


Figure 2. TEM morphologies of the ANTs. a), b) NSA tubes, c) LSA tubes. Scale bar: 100 nm.

studies, the sample holder could be tilted at angles of -30° , 0° , and $+30^\circ$ without changing the dimensions and contrast of the products; hence, they are tubelike in shape. The longest ANT observed was 650 nm in length and had outer and inner diameters of 35 and 12 nm (Figure 2a). Some bundles of ANTs (Figure 2b) were also present. The ANTs fabricated by the two methods have the same structure and differ only in size: the NSA tubes are smaller than the LSA tubes. The main factor determining the tube size is whether or not the current path of the growth method passes through the interface region.

The ANTs often appeared in the cleavage regions of the APA films. Figure 3 shows three typical cleavages of the films, with fracture morphologies that resemble a spider web, a screw thread, and concentric circles. The cleavages presumably correspond to high tensile stress in the thin APA film at zero electric field.^[16] The measured strain at failure of the film can be as high as 0.13 (13 % change in volume) for NSA samples (Figures 3a and 3b) and around 0.10 for LSA samples (Figure 3c). Although the precise mechanism of these kinds of cleavage is unclear, we assume that they are related to tube formation.

Detailed images of the cleavages are presented in Figure 4, and the cellular structure of the APA film is shown in Figure 5. In the classical model of the cellular structure of APA films^[8, 10, 11] (Figure 5b), the cells are separated by nominal

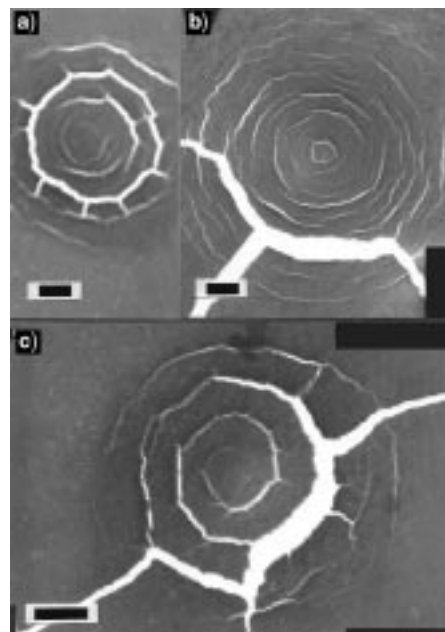


Figure 3. TEM morphologies of cleavage regions within the APA film. The fracture morphology resembles a spider web (a; NSA samples), a screw thread (b; NSA samples), or concentric circles (c; LSA samples). The ANTs often appeared in these regions. Scale bars: 2 μm .

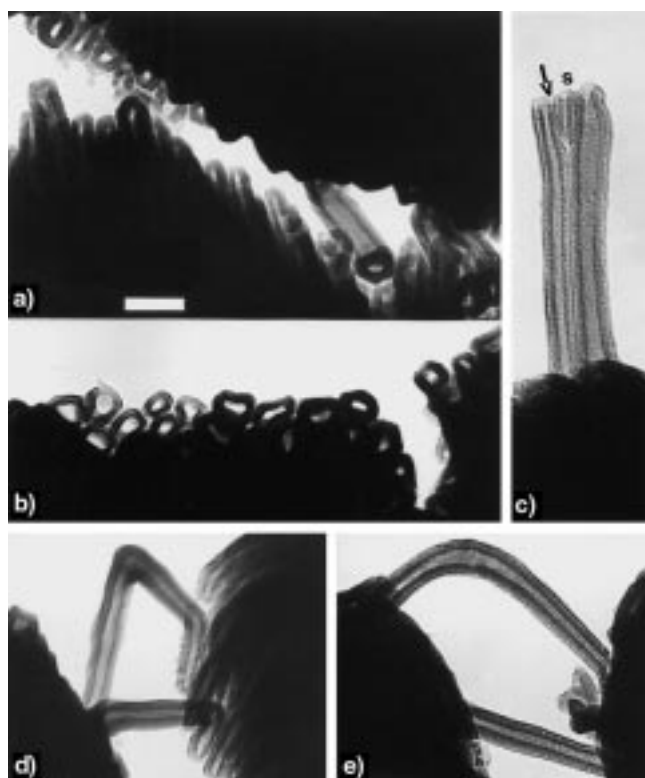


Figure 4. Detailed TEM images of the cleavage regions reveal that the ANTs are completely detached cells of the APA film (NSA samples). a) Three incompletely detached cells of the film (right-hand side of the image). b) The cleavages occurred along the cell boundary (top view). c) A short stagnant cell (marked by S) in the middle of a bundle of cells. A void underlies this cell, and cracks (indicated by an arrow) are evident along the cell boundaries. d) A bent cell. e) The image of the sample shown in Figure 4d taken after tilting the TEM sample holder at various angles reveals that the cell can be bent at an angle of nearly 90° without any observable cracking. All images have the same scale. Scale bar: 100 nm.

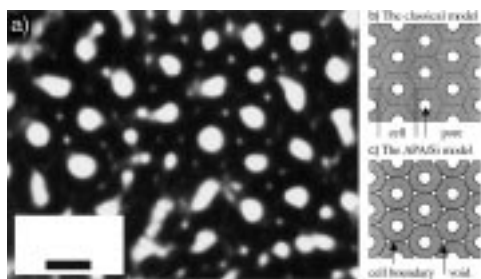


Figure 5. a) A bottom-view TEM image of the APA film reveals voids located at the junctions of three cell boundaries (LSA samples). b) Classical model of the cellular structure of an APA film. c) Refined model of the cellular structure of APA/Si, with small voids at the junctions of three cell boundaries. Scale bar: 50 nm.

boundaries (dotted lines) and arranged in a hexagonal configuration. Figures 4a and 4b reveal that the film cleavage evidently occurred along cell boundaries.^[13, 17] The right-hand side of Figure 4a shows three incompletely detached cells of the APA film. Both ends of the tubes are attached to the mother film. Figure 4d reveals clearly a tube whose closed tip is attached to the film. Figure 4e shows that an ANT can be bent at an angle of nearly 90° without any observable cracking. This good elasticity should be helpful in obtaining long, crack-free tubes.

Films anodized for a short time contain many stagnant cells which grew slowly or ceased to grow during anodization.^[8, 12] Such a cell can be seen in Figure 2b (the short tube with a closed tip on the right), and Figure 4c shows a stagnant cell S in a tube bundle. In TEM studies, we found that the region immediately underlying the cell S is completely transparent to the electron beam, that is, it is empty. We refer to it as a void and deduce that it already existed before the bundle detached from the mother film.

In addition to this void, another kind of void is often observed at the junctions of the cell boundaries (Figure 5a). Their formation mechanism might be the same as that of the defect reported by Macdonald.^[18] The refined model of an APA film based on this finding is shown in Figure 5c. It shows cell boundaries and voids located at the junctions of three neighboring cells. We may further postulate that this cellular structure is actually an incipient close-packed bundle of alumina nanotubes. Cell-boundary regions containing structural defects such as voids and cracks should provide easy paths for film cleavage, and therefore voids and the detachment of cells may be detected. Furthermore, since all observed tubes are shorter than the film thickness (around 800 nm), and incomplete detachment of cells was detected, we deduce that individual ANTs are completely detached cells of the APA film.

In contrast to conventional constant-voltage anodized films,^[10, 13] the APA/Si films fabricated by stepwise methods have a highly disordered structure. This disorder may be an important reason for the development of tubes. For NSA, when growing ends of the cells have not proceeded to the interface, the potential drop across the barrier layer should decrease slightly due to interruption of film growth by switching the power on and off and the slight temperature rise in the electrolyte (0.4–0.6 °C in our case without

agitation). These effects may cause local irregularities of the cell structure, such as stagnation, branching, merging, and inhomogeneous variation in cell diameters. Therefore, a higher local tensile stress may develop within the film. Figure 6 shows a side view of the mother film of ANTs. Evidently, the growing end of the cell is dominated by the

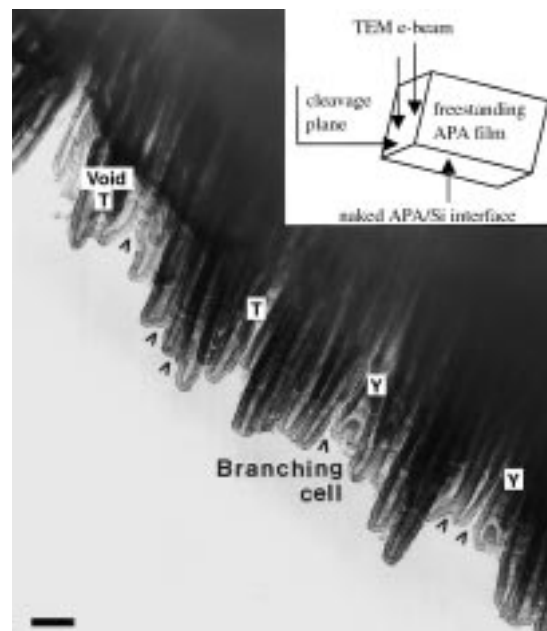


Figure 6. A side-view TEM image of the cleavage plane of the APA film (NSA samples) reveals the detailed morphology of the near-interface region. For details see text. The inset depicts the imaging arrangement. Scale bar: 100 nm.

irregularity. Except for two Y-shaped branched cells, most of the cells are truncated in a conelike or flat-headed manner. A tendency for branching is evident, as is a progressively diminishing cell diameter, which is presumably mainly due to the effect of the interface (see below). The cracks visible at the cell boundaries of these branching cells (indicated by V-shaped arrows) should provide easy paths for cell detachment. Figure 6 also shows some voids (indicated by T) within the cell-boundary region. The voids may decrease the strength of these regions, so that the thin APA film can cleave easily along the cell boundaries.

Besides the temperature, the Al/Si interface should exert a dominant effect on disordered cell growth and is thus important for the development of tubes. Because of considerable misfit within the interface region between the APA film and Si after the polycrystalline Al film is almost completely oxidized, the APA film may be easily detached from the Si substrate. Under the influence of tensile stress, thin free-standing film curls, so it cleaves easily and then develops detached cells. Furthermore, the interface can induce a nonuniform growth of the APA film in the near-interface region (Figure 6) could be attributable to the effect of the interface (Figure 7). Because the cell size is proportional to the forming voltage U_C , when the interface induces a decrease in the potential drop across the barrier layer of the cell, the

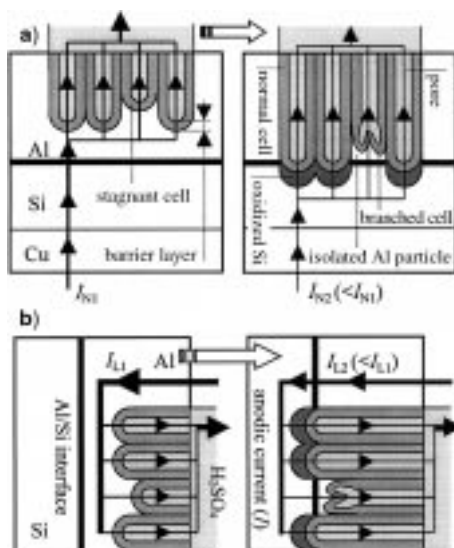


Figure 7. Schematic diagram of the effect of the substrate on the development of tubes. For details see text and the Experimental Section. a) NSA: $I_{N1} \approx U/(R_B + R_I)$, $U_{CN1} \approx I_{N1}R_B$ (left); $I_{N2} \approx U/(R_B + R_O)$, $U_{CN2} \approx I_{N2}R_B$ (right). Note that $R_I < R_O$, since the Al/Si interface consisting of native oxide is thinner than the oxidized Si layer after anodization ($I_{N1} > I_{N2}$); hence, $U_{CN1} > U_{CN2}$. b) LSA: $I_{L1} \approx U/R_B$, $U_{CL1} \approx I_{L1}R_B$ (left); $I_{L2} \approx U/(R_B + R_O)$, $U_{CL2} \approx I_{L2}R_B$ (right). From $I_{L1} > I_{L2}$ follows $U_{CL1} > U_{CL2}$.

cell will branch.^[10, 11] Nevertheless, the decrement of the forming voltage should be mainly due to the sudden increase in the electrical resistance of the anodizing circuit during this period. Additionally, slightly diminishing cell diameters near the growing ends could be due to high thermal resistance of the thin film and the interface.

The Y-shaped branched cells may be derived from stagnant cells (Figure 7). For example, in NSA samples, the thicknesses of the Al/Si interface (d_I), the oxidized Si layer (d_O), and the barrier layer (d_B) are about 4, 10, and 10 nm, respectively. In a rough estimation, it is reasonable to assume that the resistances of the Al/Si interface (R_I), the oxidized Si layer (R_O), and the barrier layer are proportional to their thicknesses. For the NSA sample (Figure 7a), the reducing ratio of the forming voltage is: $U_{CN2}/U_{CN1} \approx (R_B + R_I)/(R_B + R_O) \approx (d_B + d_I)/(d_B + d_O) \approx 1/\sqrt{2}$. Because the cell diameter is proportional to the potential drop U_C across the barrier layer of the cell, reducing the voltage by a factor of $1/\sqrt{2}$ results in the appearance of twice as many cells to maintain the original total area of the APA film, and most cells would branch into two cells of smaller diameter (Y-shaped branched cells). Under the influence of the interface, only these stagnant cells would branch dominantly until the power is turned off, because the isolated Al particles underlying the stagnant cells can sustain their continuous growth and branching. The other, normal cells, whose growing ends have already connected with or slightly penetrated into the interface region, will cease to grow at this moment. Note that the density of the stagnant cells is related to the density of the Al grain boundaries in the pre-anodized polycrystalline Al film. The branching certainly induced the highly local irregularity of the cell structure, as well as the increased stress of the APA film. It should be beneficial for the detachment of the film from the substrate

and for the separation of the cells from each other along the cell boundaries.

In conclusion, we have presented two methods for the controlled fabrication of ANTs and deduced that they are completely detached cells of the APA film. The semiconductor substrate exerts a dominant effect on the detachment of cells. This study may open fascinating possibilities for further chemical and physical explorations of nanostructures such as nanowires, cylindrical capacitors, MOSFETs, and containers.

Experimental Section

Preparation of the ANTs (see Figure 1): An electron beam evaporated 400 nm thick Al (99.99%) film on a p-type, 0.5 Ω cm, 5°-off (100) Si substrate (Al/Si) was anodized in dilute sulfuric acid (15 wt %). The potential difference U was 40 V dc. Before anodizing, the temperature of the electrolyte was $(10.0 \pm 0.2)^\circ\text{C}$. Anodization was continued until the APA film detached from the substrate. Then the free-standing film was cleaned in flowing distilled water for a prolonged period of time. After that, it was transferred to copper TEM grids and stored in a dry tube at room temperature. The specimens were directly examined with JEM-200CX and JEM-2000EX transmission electron microscopes operated at 120 kV.

Effect of the substrate on the development of tubes (see Figure 7): Since the resistances of the Al/Si interface (R_I), the barrier layer (R_B), and the oxidized Si layer (R_O) are rather large, those of the electrolyte, the series resistor ($R = 16.9 \Omega$), low-resistivity p-type Si, and Al metal can be neglected. The power voltage U is 40 V dc, and it is the forming voltage of the cell U_C , that is, the potential drop IR_B across the barrier layer, that largely determines the cell size. The difference in cell size of the two methods results from $U_{CL1} > U_{CN1}$, which is due to the interface. Formation of the Y-branched cells is also due to the interface.

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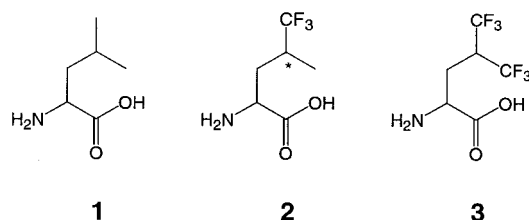
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Fluorinated Coiled-Coil Proteins Prepared In Vivo Display Enhanced Thermal and Chemical Stability**

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Incorporation of noncanonical amino acids provides a route to proteins and peptides with unique structural and chemical features.^[1] Functionality orthogonal to that of the naturally occurring amino acids, including alkenes,^[2] alkynes,^[3] aryl halides,^[4] and electroactive side chains^[5] has been incorporated efficiently into proteins prepared in bacterial cultures. We present here a general approach to the stabilization of leucine-zipper peptides and coiled-coil proteins by incorporation of the hyperhydrophobic leucine (**1**) isostere trifluoroleucine (Tfl, **2**). Trifluoroleucine was reported more than 30 years ago to support bacterial cell growth and to be incorporated into nascent proteins in the absence of leucine.^[6]



Leucine-zipper domains form coiled-coil structures comprising generic heptad repeats designated *abcdefg*, where the *d* positions are occupied predominantly by leucine residues.^[7] Our work was motivated by the conjecture that replacement of leucine with Tfl at the *d* positions of the heptad repeat should stabilize the coiled-coil dimer with respect to thermal and chemical denaturation. The choice of trifluoroleucine was based on several factors, the most important of which is the observation that many fluorocarbons behave as though they are more hydrophobic than their hydrocarbon analogues.^[8] Trifluoroleucine has been reported to be activated and charged by the *E. coli* leucyl tRNA-synthetase (LeuRS) and can be incorporated into recombinant proteins produced in

vivo.^[6] Finally, the trifluoromethyl group is chemically inert and nearly isosteric to the methyl group,^[9] suggesting that proteins and peptides outfitted with Tfl might adopt folded structures similar to those of their “wild-type” analogues.

The leucine-zipper protein A1 (Figure 1a) was used as a test protein in assays for incorporation of Tfl and hexafluoroleucine (Hfl, **3**).^[10] The design of this protein has been



Figure 1. A) Amino acid sequence of A1. The leucine positions are bold. B) Western blot analysis of A1 expression. Cultures were supplemented with leucine or with one of the analogues Tfl or Hfl. Lane 1: uninduced sample; lane 2: induced sample without supplementation; lane 3: induced sample supplemented with leucine (150 μM); lane 4: induced sample supplemented with Tfl (220 μM); lane 5: induced sample supplemented with Hfl (170 μM).

discussed previously,^[10] the primary sequence contains eight leucine residues, of which six are distributed at the *d* positions of the six heptad repeats. The capacity of each of these amino acids to support protein synthesis was determined by induction of gene expression in leucine-free culture media supplemented either with Tfl or with Hfl. Accumulation of the target protein was visualized by western blotting as shown in Figure 1b. As expected from previous results,^[6, 11] Tfl (lane 4, Figure 1b) clearly supports protein synthesis, although the yield of protein is reduced in comparison to that obtained from leucine-supplemented medium (lane 3, Figure 1b). In contrast, Hfl (lane 5, Figure 1b) does not support measurable protein synthesis under the conditions examined in this work as shown by comparison with negative controls (lanes 1 and 2, Figure 1b). The increased electrophoretic mobility of the fluorinated protein (cf. lanes 3 and 4, Figure 1b) has been observed previously for other fluorinated proteins produced by similar methods.^[11a]

To control the level of substitution of leucine by Tfl, we varied the concentration of leucine in the medium, while keeping the concentration of Tfl (as the D,L mixture) at 550 μM. The concentration of leucine ranged from 0 to 330 μM (as the L-amino acid). The extent of replacement was determined by amino acid analysis of the purified proteins. We also performed matrix-assisted laser desorption/ionization (MALDI) mass spectrometry on the protein products; in each case, the most intense signal in the mass spectrum corresponds closely to the substitution level calculated from amino acid analysis.

The results are shown in Table 1. The extent of leucine replacement decreased from 92 % in medium supplemented only with Tfl, to levels below the limit of detection in medium supplemented with 330 μM L-leucine. We were not able to reach 100% incorporation of Tfl, even in the absence of added leucine, possibly due to trace amounts of leucine liberated by cellular protein degradation. Protein yield

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Table 1. Wild-type and fluorinated proteins produced in vivo.

Protein	[Leu] in culture [μM] ^[a]	Yield [mg L^{-1}]	% Tfl by AAA ^[b]	MALDI mass ^[c] (Tfl sites)
A1-WT	330	40	0	8307.9 (0)
FA1-17	114	27	17	8361.2 (1)
FA1-29	83	25	29	n.d. ^[d]
FA1-79	23	21	79	8631.9 (6)
FA1-92	0	20	92	8739.8 (8)

[a] Concentration of L-leucine. The concentration of Tfl in culture was $550 \mu\text{M}$ (D,L mixture). [b] % Substitution determined from the diminution of the leucine mole fraction by amino acid analysis (AAA). [c] Mass of the most intense signal in the MALDI mass spectrum. Numbers in parentheses indicate corresponding numbers of sites occupied by Tfl. [d] n.d.: not determined.

decreased as the concentration of leucine in the culture medium was reduced. The yield of A1 obtained from leucine-enriched medium was 40 mg L^{-1} , twice that from medium supplemented only with $550 \mu\text{M}$ Tfl.

The secondary structures of the wild-type protein (A1-WT) and the variant containing 92% Tfl (FA1-92) were examined by circular dichroism (CD) spectroscopy (Figure 2). Both

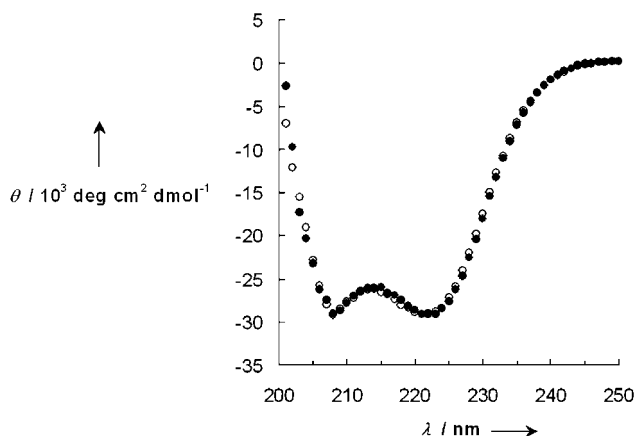


Figure 2. CD spectra of A1 (●) and FA1-92 (○) at 0 °C ($10 \mu\text{M}$ protein concentration, PBS buffer, pH 7.4). θ : molar ellipticity. PBS = phosphate-buffered saline.

proteins are more than 90% helical as determined from the molar ellipticity at 222 nm, and the extent of overlap of the spectra suggests essentially identical secondary structures. Equilibrium sedimentation indicated that both peptides formed stable dimers with dissociation constants $\leq 10 \mu\text{M}$. At high μM concentrations the peptides further associated to form higher-order species. The data were well described by a dimer-to-tetramer equilibrium, yielding dimer-to-tetramer equilibrium constants of $80.5 \mu\text{M}$ and $380.2 \mu\text{M}$ for A1-WT and FA1-92, respectively.

Previous examples of replacement of *d*-position leucine residues in leucine-zipper peptides by other natural amino acids have all resulted in reduction of coiled-coil stability.^[12] The reduction in stability observed in such experiments has been attributed to the fact that these substitutions are usually of the “large” to “small” type and cause losses in hydrophobic packing efficiency.^[13] In marked contrast, thermal and chem-

ical unfolding studies show that fluorinated variants of A1 are highly resistant to denaturation. The “melting temperature” (T_m) of FA1-92 is elevated by 13°C compared to A1-WT (Figure 3), while the midpoint concentration (C_m) for urea denaturation for FA1-92 is increased to 7 M (vs. 2.8 M for A1-WT) (Figure 4). Surprisingly, proteins with low levels of fluorination (FA1-17 and FA1-29) exhibit pronounced increases in stability. In FA1-17, for example, the single substitution of a side chain methyl group by a trifluoromethyl group results in an increase in T_m by 6°C and in C_m by about 2 M.

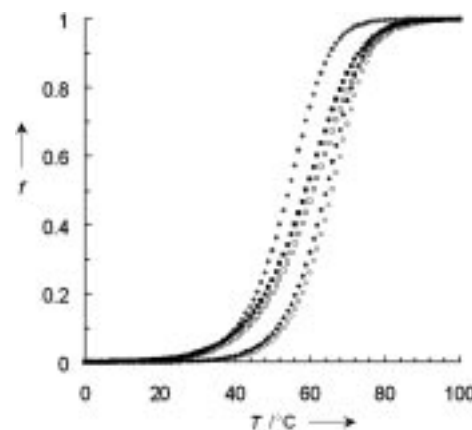


Figure 3. Thermal denaturation of partially fluorinated A1 proteins: A1-WT (●), FA1-17 (■), FA1-29 (□), FA1-79 (◆) and FA1-92 (○) ($10 \mu\text{M}$ protein concentration, PBS buffer, pH 7.4). f : fraction unfolded.

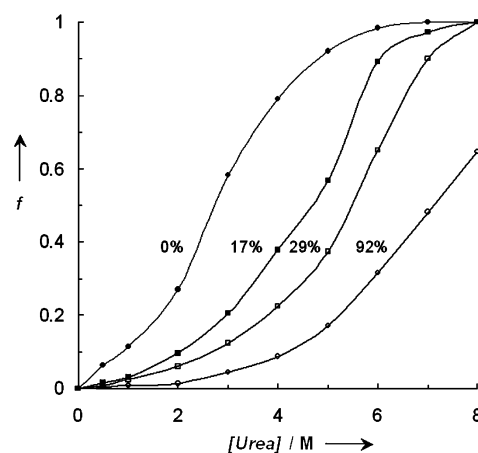


Figure 4. Urea titration of WT-A1 (●), FA1-17 (■), FA1-29 (□), and FA1-92 (○) at 0 °C. f : fraction unfolded.

Global thermodynamic fitting was used to obtain the thermodynamic quantities associated with the monomer-to-dimer transitions of A1-WT and FA1-92 (Table 2).^[14] The intermediate samples (FA1-17 and FA1-29) were not analyzed in this way because the compositional heterogeneity of these samples precludes application of a two-state transition model. It must be emphasized, however, that FA1-92 is also heterogeneous, since Tfl is incorporated into bacterial proteins as an equimolar mixture of the (2*S*,4*S*) and (2*S*,4*R*) diastereomers.^[11a] The free energy of folding for FA1-92 is $2.4 \text{ kcal mol}^{-1}$ (of monomer) more negative than for A1-WT at

Table 2. Thermodynamic data for the folding of A1-WT and FA1-92.

Protein	$T_m^{[a]}$ (10 μ M)	$T_m^{[b]}$ (1M)	ΔG° (37 °C) ^[c]	$\Delta\Delta G^\circ$	$\Delta H_m^{[d]}$ (1M)	$\Delta C_p^{[e]}$ (1M)	$C_{urea,50\%}^{[f]}$ (0 °C)
A1-WT	54	103	−10.7	−	−70.9	−252	2.8
FA1-92	67	116	−13.1	−2.4	−77.0	−272	7

[a] Midpoint of the thermal denaturation curve at 10 μ M protein concentration (PBS, pH 7.4). Units for T_m are °C. [b] Midpoint of the thermal denaturation curve extrapolated to 1M standard state using non-linear least squares fit. [c] The free energy of folding at 37 °C at 1M standard state. Units for ΔG° and $\Delta\Delta G^\circ$ are kcal mol^{−1} of monomers. [d] The enthalpy of folding at the midpoint temperature extrapolated to 1M standard state; units are in kcal mol^{−1} of monomers. [e] Heat capacity change upon folding at 1M standard state; units are in cal mol^{−1} K^{−1}. Uncertainties in T_m (1M), ΔG° , ΔH_m , and ΔC_p are $\pm 1.5^\circ$ C, 1.2, 4.8 kcal mol^{−1}, and 120 cal mol^{−1} K^{−1}, respectively. [f] Midpoint urea denaturation concentration at 0 °C in M of urea.

37 °C, which corresponds to 0.4 kcal mol^{−1} of stabilization for each Tfl site localized at the dimer interface. Consideration of the large numbers of leucine residues packed in the hydrophobic cores of many proteins leads to the conclusion that the additive stabilizing effects of Tfl might in some cases be quite substantial.

The results reported here show that one can incorporate Tfl efficiently into proteins produced in vivo, control the level of incorporation, maintain secondary and higher-order protein structure, and elevate protein stability with respect to thermal and chemical denaturation. The implications of these observations are under investigation.

Experimental Section

Materials: Tfl was prepared in an overall yield of 22 % in seven steps from β -trifluoromethylcrotonic acid, according to the procedure of Rennert and Anker with slight modifications.^[6] Hfl was prepared by modification of the procedures reported by Zhang et al.^[15] A leucine auxotrophic variant of *E. coli* strain mc1000 (F[−]lac Δ x74anaD139/(Ana Abioc-leu) Δ 7679 gal U gal K rspL), designated LAM1000, was provided by Prof. M. J. Fournier of the University of Massachusetts, Amherst. Expression vector pQEA1, which contains the A1 coding sequence, was obtained from the U.S. Army Natick RD&E Center (Natick, MA).

Analogue incorporation assay: LAM1000 strains were transformed with pQEA1 and pREP4 to yield the expression strain LAM1000/pQEA1/pREP4. Tfl and Hfl were assayed for translational efficiency using a medium shift technique.^[3] Amino acid concentrations after the medium shift were **1:** 150 μ M; **2:** 220 μ M; **3:** 170 μ M. Proteins were detected by western blotting of the whole cell lysate with an antibody specific for the N-terminal His-Tag of A1.

Protein expression and purification: M9AA medium (1 L) supplemented with 1 mM MgSO₄, 1 mM CaCl₂, 0.4 wt % glucose, 1 mg L^{−1} thiamine and the antibiotics ampicillin (200 mg L^{−1}) and kanamycin (25 mg L^{−1}) was inoculated with 10 mL of fresh overnight culture (M9) of the expression strain. After the culture had grown to OD₆₀₀ of 1.0, the medium shift procedure was applied. The cell pellet was then resuspended in 1 L M9 medium supplemented with Tfl (550 μ M) and leucine in appropriate concentrations (Table 1). IPTG (1 mM) was added after 10 min to induce protein expression. Cells were collected after 3 h by centrifugation (5000 g, 15 min, 4 °C). The pellets were resuspended in Buffer A (20 mL; 8 M urea, 0.1 M NaH₂PO₄, 0.01 M Tris, pH 8.0) and stored at −80 °C overnight. The cells were thawed rapidly at 37 °C, cell debris was sedimented (22500 g, 50 min, 4 °C), and the supernatant was applied to a Ni-NTA column (1 $\times$ 5 cm). The column was washed with 25 mL portions of Buffer A at pH 8.0, 6.5 and 5.9, sequentially. The target protein was eluted at pH 4.5.

Protein characterization: Ultracentrifugation and circular dichroism analyses were performed as described previously.^[10, 14] Analysis of CD thermal melting data was performed according to a previously described procedure

using a two-state model.^[14] For A1-WT, the concentrations used for curve fitting were 10 and 100 μ M, while concentrations of 2 and 100 μ M were used to fit data for FA1-92. The thermodynamic quantities T_m , ΔH_m , ΔC_p and K_d were parameters of the fitting procedure and are reported in the 1M standard state (Table 2).

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Unique Chemistry at Ice Surfaces: Incomplete Proton Transfer in the $\text{H}_3\text{O}^+ - \text{NH}_3$ System**

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Proton transfer is one of the central issues of chemistry and biology and is related to diverse phenomena, from acid–base neutralization to enzymatic reactions.^[1] A simple and prototypical system for studying this phenomenon is proton transfer between the hydronium ion and the ammonia molecule [Eq. (1)], which has long attracted attention.^[2–6]



The reaction proceeds instantaneously in the aqueous phase with an equilibrium constant K_{eq} of 1.7×10^9 at 298 K, and it is even more facile in the gas phase ($K_{\text{eq}} = 1 \times 10^{30}$).^[7] Molecular details of the reaction have been examined by theoretical calculations on model cluster systems.^[4–6] However, it is still not well understood how the reaction proceeds on the surface of ice, which is an important subject with relevance to the chemistry of atmospheric and interstellar ice particles, as well as proton transfer across ordered water structures in biological systems and at electrochemical interfaces. Studies of reactions on ice to date,^[8–15] focused on the ionization of HCl, indicate that chemical reactivity on ice is governed by the ability of surface water molecules to migrate and stabilize the ionized species by hydration. Recently, Pursell et al.,^[16] using transmission infrared spectroscopy, observed that the reaction of HCl and NH_3 on ice produces NH_4^+ at temperatures down to 80 K.

Here we report on proton transfer in the $\text{H}_3\text{O}^+ - \text{NH}_3$ pair prepared on ice, which we examined with the Cs^+ reactive ion scattering (RIS) method. The greatest advantage of the RIS technique is the quantitative monitoring of reactions occurring right on the monolayer surface.^[17, 18] Using this technique, we identified all the species involved in the reaction and measured their concentration variation along the reaction coordinate, which allowed us to quantify the proton transfer reaction and to understand how it is controlled by the ice surface. In this technique,^[17] a low-energy (10–100 eV) Cs^+ ion beam is scattered from a surface, and the scattered positive ions are analyzed by mass. The scattered ions are composed of reflected primaries, RIS products that are association products of Cs^+ with neutral species at the surface, and preexisting

ions ejected from the surface. It was shown^[18–20] that RIS produces ions with narrow internal energy distributions, so that even fragile molecular species can be detected.

The experiments were conducted in a reactive ion scattering chamber previously described in detail elsewhere.^[17] In the UHV chamber with a base vacuum of 3×10^{-10} Torr, Cs^+ ions produced from a surface ionization source are scattered from a sample surface at the desired collision energy. The Cs^+ current density at the sample was $2–3 \text{ nA cm}^{-2}$. The scattered ions were measured with a quadrupole mass spectrometer (QMS) with its ionizer switched off. Each spectrum consisted of at least ten scans, which took about 15 s to acquire. The beam incidence and the detector angles were both 67.5° with respect to the surface normal. The sample was a Ru(001) single crystal and was mounted on a variable-temperature (85–1500 K) stage. Ice films were grown on this surface by introducing D_2O vapor into the chamber at a pressure of 3×10^{-8} Torr and at a substrate temperature of 120 K, unless otherwise specified. At this temperature, the condensed layer is nonporous, amorphous ice.^[21] The vacuum gauge was calibrated for D_2O vapor from the absolute coverage of ice bilayer (BL) on Ru(001), checked by thermal desorption spectroscopy (TDS).^[22] To avoid substrate effects, ice films were prepared to the thickness of several bilayers. HCl and NH_3 gases were exposed through separate dosing facilities to the ice film maintained at the desired reaction temperature. Quadrupole MS was used to check the purity of the gases and to perform TDS measurements. An Auger spectrometer was used to determine the surface composition and cleanliness of the substrate.

Figure 1 compares the RIS mass spectra of D_2O -ice surfaces exposed to HCl and NH_3 . The spectrum in the presence of HCl (Figure 1a) is characterized by two kinds of peaks apart from the elastic peak of Cs^+ . 1) The peaks above m/z 133 due to reactive ion scattering, that is, pickup of surface molecules

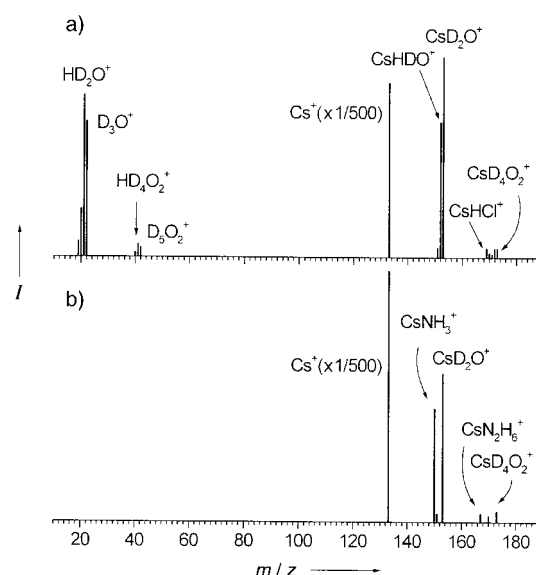


Figure 1. RIS mass spectra obtained on D_2O -ice surfaces exposed to HCl (a) and NH_3 (b) for 0.5 L ($1 \text{ L} = 1 \times 10^{-6}$ Torr s) at 100 K. The D_2O layer was 3–4 BL (BL = bilayer) thick, prepared on a Ru(001) surface. The species observed are labeled. Cs^+ peak intensity was reduced by 1/500. Cs^+ impact energy was 35 eV.

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by incoming Cs^+ . The peak at m/z 153 (CsD_2O^+) is due to pickup of a water molecule, and that at m/z 169 (CsHCl^+) is due to pickup of an HCl molecule. The peak corresponding to the water dimer is also seen at m/z 173. 2) Peaks due to low-energy sputtering, corresponding to the ejection of preexisting ions at the surface. The ions detected were HD_2O^+ and its hydration cluster (HD_4O_2^+). The presence of HD_2O^+ confirms ionic dissociation of HCl.^[8–15] The RIS products and the sputtered ions exhibit characteristic isotope exchange. For convenience, however, we will denote hereafter the chemical species only by their representative isotopes. In Figure 1 b, the RIS mass spectrum from an NH_3 -exposed ice surface is shown, in which the only signals related to ammonia are CsNH_3^+ and CsN_2H_6^+ . NH_4^+ is not ejected by low-energy sputtering, and isotope exchange between NH_3 and D_2O is insignificant. These observations indicate that NH_3 exists as a neutral molecule at the surface and not as NH_4^+ .^[11, 23]

We prepared ice surfaces containing hydronium ions by HCl exposure and then added NH_3 to examine the proton transfer between H_3O^+ and NH_3 . The ratio of the proton donor to the acceptor was changed by varying the NH_3 concentration. Separate ice surfaces were prepared for each RIS measurement to avoid contamination by Cs^+ . Figure 2 shows the result of these $\text{H}_3\text{O}^+ - \text{NH}_3$ titration measurements at 100 K. Upon addition of a small amount of NH_3 (Figure 2 a), the spectrum immediately showed a peak due to NH_3D^+ , which indicates proton transfer from D_3O^+ to NH_3 to form an ammonium ion. The absence of a CsNH_3^+ peak at this stage indicates that all of the added NH_3 molecules have reacted. Hydronium ions still are present in large excess, as can be seen from the strong D_3O^+ peak. The hydration clusters of D_3O^+ and NH_3D^+ ions are also seen, along with their isotope-exchange species. Further NH_3 exposure (Figure 2 b) resulted in an increase in the NH_3D^+ peak relative to Figure 2 a and in a concomitant decrease in intensity of the D_3O^+ peak. Importantly, a CsNH_3^+ peak appears, which indicates that a substantial portion of NH_3 remains unconsumed on ice despite the coexistence of D_3O^+ . When NH_3 was added in large excess (Figure 2 c), ammonium ions were the dominant ionic species on the surface, and the concentration of hydronium ions was very low. A certain portion of HCl remains unionized on ice at 100 K, as indicated by the CsHCl^+ peak (see Figure 2 a), and so proton transfer is also possible from molecular HCl to NH_3 to produce NH_4^+ . However, the isotopic ratio $\text{NH}_3\text{D}^+/\text{NH}_4^+$ was greater than unity, and this indicates that hydronium ions (D_3O^+ , HD_2O^+ , etc.) are the major proton donors in the present case. Moreover, key features of Figure 2 were unchanged even when we increased the ice temperature to 140 K, at which temperature HCl is almost completely ionized.^[15]

We claimed before that the ions sputtered by low-energy Cs^+ in Figures 1 and 2 are preexisting ions on ice, but it might be argued that they are generated from neutral constituents of ice by impact-induced ionization, as is often the case in secondary ion mass spectrometry with beam energies in the keV region. To clarify this issue, we measured D_3O^+ and NH_4^+ signals as a function of Cs^+ impact energy (Figure 3). NH_4^+ (■) and D_3O^+ (○) ions start to be emitted at energies of 17 and 19 eV (see also inset), respectively, when the surface was

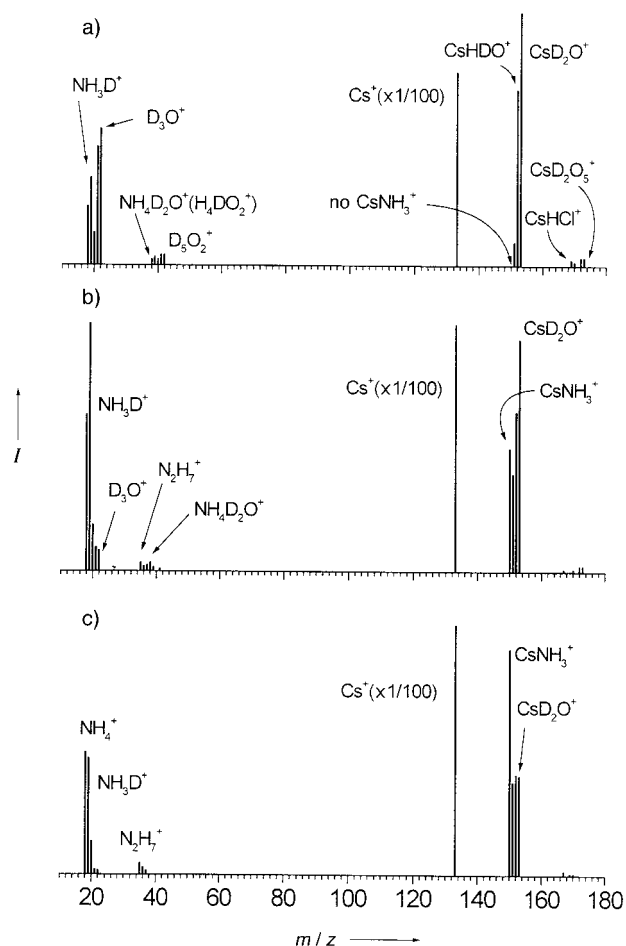


Figure 2. RIS mass spectra measured along the coordinate of the $\text{H}_3\text{O}^+ - \text{NH}_3$ reaction on ice. A D_2O (3–4 BL) surface was exposed first to 0.5 L of HCl to generate hydronium ions, and then to NH_3 at varying exposures: a) 0.02 L, b) 0.3 L, and c) 0.7 L. Sample temperature was 100 K. Cs^+ impact energy was 30 eV.

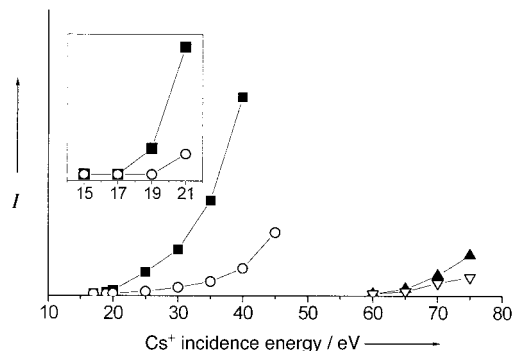


Figure 3. The intensity of hydronium and ammonium ion peaks as a function of collision energy for two types of surface. For details, see text. The beam incidence and the detector angles were both 67.5° with respect to the surface normal.

prepared by co-exposure to 0.3 L HCl and 0.15 L NH_3 on a D_2O -ice layer at 100 K. On frozen pure D_2O and NH_3 surfaces, respectively, D_3O^+ (▲) and NH_4^+ (▽) appear only above 60 eV. Evidently, a large energy gap exists for ejecting the same ion from two different surfaces, one containing preformed, chemically generated ions, and the other having only neutral species. This threshold measurement verifies that

the D_3O^+ and NH_4^+ ions in Figures 1 and 2, ejected at energies of 35 eV or less, preexist on the surfaces. Solvated cluster ions (D_3O_2^+ and N_2H_7^+) are emitted several electron volts above the thresholds of the corresponding monomers, but still well below 60 eV. Therefore, the cluster ions must also be generated from preexisting species on ice.

Figure 4a presents the intensity variations for hydronium and ammonium ion signals obtained from the titration

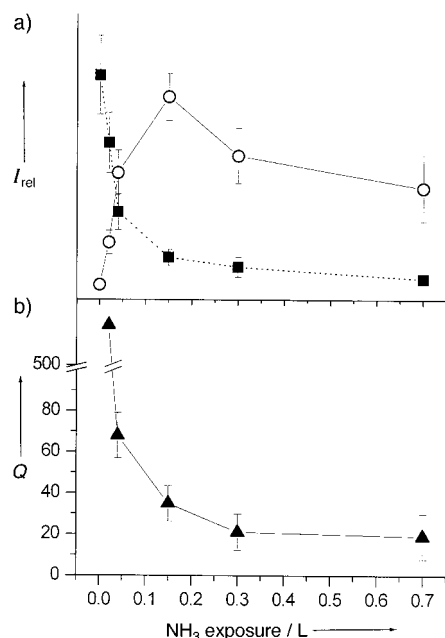


Figure 4. a) Variation of hydronium (■) and ammonium ion intensity (○) with NH_3 exposure. b) Variation of reaction quotient Q [Eq. (2)]. The experimental conditions were the same as in Figure 2.

experiment at 100 K. All isotopic intensities were added to these curves. The two curves cross at an NH_3 exposure of 0.05 L, which is considered to be the titration equivalent point. Note that the HCl and NH_3 exposures give only a relative measure for the amounts deposited on ice because the sticking probabilities of these species are uncertain. NH_4^+ peak intensity initially increases with NH_3 exposure due to proton transfer from H_3O^+ , but decreases again for NH_3 exposure greater than 0.15 L, possibly due to clustering or overlayer formation of excess NH_3 molecules around NH_4^+ , as indicated by the N_2H_7^+ peak in Figures 2b and 2c. Figure 4b presents the quotient Q of Equation (1), as defined by Equation (2). Here $I(\text{X}^+)$ represents the signal intensity of

$$Q = \frac{[\text{H}_2\text{O}][\text{NH}_4^+]/[\text{H}_3\text{O}^+][\text{NH}_3]}{I(\text{CsH}_2\text{O}^+)/I(\text{NH}_4^+)/I(\text{H}_3\text{O}^+)/I(\text{CsNH}_3^+)} \quad (2)$$

X^+ . Again, the chemical formulas do not refer to specific isotopes. Note that the relationship of Equation (2) is quantitative, although the detection sensitivities differ between protonated ions (low-energy sputtering) and unprotonated neutral species (Cs^+ RIS). This is because the various sensitivity factors appear in both the numerator and denominator of Equation (2) and hence cancel out. The Q value decreases from near infinity at an initial NH_3 exposure to

reach a limiting value of ca. 20. Clearly, except at the very beginning of NH_3 titration, reaction (1) does not go to completion on ice. All the species involved in the reaction (H_3O^+ , NH_3 , H_2O , and NH_4^+) coexist on the surface in substantial populations. We examined the Q value as a function of ice temperature and found it to increase from 15 at 85 K to 50 at 140 K for an NH_3 exposure of 0.3 L.

The Q value measured in this study is much smaller than the equilibrium constant of reaction (1) in water (1.7×10^9) or in the gas phase (1×10^{30}). Since reaction on ice is characterized by partial solvation of reactants and products by water molecules according to theory,^[13, 14] we may well expect K_{eq} of the ice reaction to lie between the gas-phase and aqueous-phase values. However, this is not the case. The result indicates that reaction (1) does not reach a thermodynamic equilibrium on ice, but is instead controlled by kinetic factors.

The variation in Q in Figure 4b can be explained by kinetic constraints of the ice surface, imposed by the restricted motions of reactant and water molecules compared to the aqueous phase. First, Q approaches K_{eq} at a very small NH_3 exposure. This implies that NH_3 molecules have high enough mobility on the surface to undergo efficient reaction with H_3O^+ . The high mobility of NH_3 molecules is reasonable, because the similar H_2O molecules are mobile under these conditions.^[24] Second, Q drops rapidly as the NH_3 concentration on ice builds up. With a substantial population of NH_4^+ at this stage, surface NH_3 molecules can encounter not only H_3O^+ but also NH_4^+ to form ammoniated cluster ions like N_2H_7^+ (Figure 2). The ammoniated cluster ions are immobile on ice and act as kinetic traps for otherwise mobile NH_3 , that is, NH_3 molecules bound to NH_4^+ can not diffuse out and react with H_3O^+ . The immobility of NH_4^+ is supported by the recent finding of Cowin et al.^[25] that H_3O^+ is immobile on crystalline ice over a substantial temperature range (30–190 K). Therefore, the kinetic barrier to proton transfer on ice must result from the extremely low mobility of solvated ions, although unbound NH_3 and H_2O molecules may diffuse well under these conditions. Since Q increases only from 15 to 50 in the temperature range of 85–140 K, the NH_4^+ mobility appears not to increase drastically over this span, and this is also consistent with the result of H_3O^+ mobility measurements.^[25] The present ice films are considered to be amorphous films, on which the mobilities may be lower than on crystalline ice due to structural inhomogeneity.^[26] The difference between amorphous and crystalline surfaces, however, is not expected to affect the major conclusions of this study that the reaction quotient is lower than the equilibrium constant and that the kinetic barrier imposed by immobile solvated ions is responsible for these phenomena. It appears that the energy released by the neutralization reaction and inelastic collisions is efficiently removed by the sublayers, so that the observed processes are largely unaffected by extraneous factors.

This quantitative study showed that the proton transfer reaction between H_3O^+ and NH_3 on ice does not reach a true equilibrium. All species of the reaction (NH_3 , NH_4^+ , H_2O , and H_3O^+) coexist even at the titration equivalent point and represent metastable states trapped between kinetic barriers. The kinetic barriers result from the immobility of solvated ions, although neutral molecules may have high mobility. In

this respect, an ice surface allows diverse chemical species to be formed and kinetically stabilized, and this may play an important role in photochemical processes on interstellar or stratospheric ice particles.

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First Example of the $\mu_3\text{-}\eta^1, \eta^2, \eta^1\text{-C}_{60}$ Bonding Mode: Ligand-Induced Conversion of π to σ C_{60} -Metal Complexes**

Hyunjoon Song, Kwangyeol Lee, Chang H. Lee, Joon T. Park,* Hong Y. Chang, and Moon-Gun Choi

A consistent theme in the chemistry of exohedral metallofullerenes has been the pursuit of new bonding modes of C_{60} with metal centers and their novel chemical reactivities. Continuous development in C_{60} -metal chemistry led to the synthesis of various π complexes with η^2 ,^[1] η^5 ,^[2] $\mu\text{-}\eta^2, \eta^2$,^[3] and $\mu_3\text{-}\eta^2, \eta^2, \eta^2\text{-C}_{60}$ ^[4] bonding modes. However, the chemistry of C_{60} σ complexes has remained relatively unexplored, although such complexes are very important in selective functionalization of C_{60} . Examples of C_{60} -metal σ complexes have scarcely been reported, and none has been structurally characterized.^[5] We are interested in the conversion of existing C_{60} bonding modes to new ones by modifying the coordination sphere of metal center(s) to which C_{60} is coordinated. Our efforts resulted in the first example of reversible interconversion between $\mu\text{-}\eta^2, \eta^2$ - and $\mu_3\text{-}\eta^2, \eta^2, \eta^2\text{-C}_{60}$ on an Os_5C cluster framework by addition of 2e-donor ligands such as carbon monoxide or benzyl isocyanide.^[3d] In contrast, a $\mu_3\text{-}\eta^2, \eta^2, \eta^2\text{-C}_{60}$ ligand on a triosmium cluster framework exhibits a drastically different behavior upon addition of benzyl isocyanide. It transforms into a new σ -type $\mu_3\text{-}\eta^1, \eta^2, \eta^1\text{-C}_{60}$ ligand with concomitant Os-Os bond cleavage, providing a new synthetic route to C_{60} -metal σ complexes. Here we report the first example of a novel ligand-induced conversion of π to σ C_{60} -metal complexes, as well as the first structural characterization of C_{60} -metal σ bonding.

A mixture of $[\text{Os}_3(\text{CO})_8(\text{CNR})(\mu_3\text{-}\eta^2, \eta^2, \eta^2\text{-C}_{60})]$ (**1**) and an excess (30 equiv) of benzyl isocyanide in $\text{C}_6\text{H}_5\text{Cl}$ was heated at 80 °C for 40 h. Removal of the volatile materials in vacuo, subsequent purification by a preparative TLC (SiO_2 , CS_2), and recrystallization ($\text{CH}_2\text{Cl}_2/n\text{-C}_6\text{H}_{14}$) afforded two brown compounds **2a** and **2b** (Scheme 1). The two compounds were formulated as $[\text{Os}_3(\text{CO})_8(\text{CNR})_2(\text{C}_{60})]$ on the basis of micro-analytical data and molecular ion isotope multiplets at m/z 1750 (highest peak) in the positive-ion FAB mass spectra.

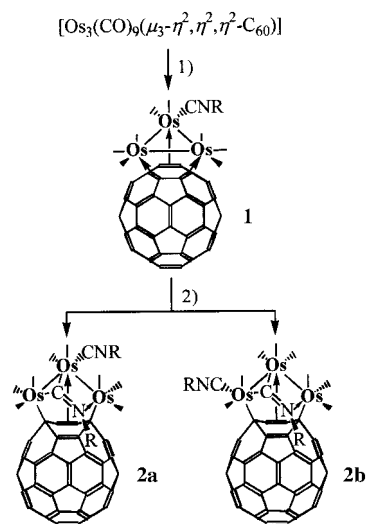
An X-ray crystallographic study revealed the structure of **2a** (Figure 1 a). The Os1-Os3 bond of the Os_3 triangle in **1** was ruptured on addition of an RNC ligand, which is coordinated

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Scheme 1. 1) 1.2 equiv of $\text{PhCH}_2\text{N}=\text{PPh}_3$, $\text{C}_6\text{H}_5\text{Cl}$, RT, 12 h, 76%; 2) 30 equiv of RNC, $\text{C}_6\text{H}_5\text{Cl}$, 80°C , 40 h, 27% (**2a**), 22% (**2b**). $\text{R} = \text{CH}_2\text{C}_6\text{H}_5$.

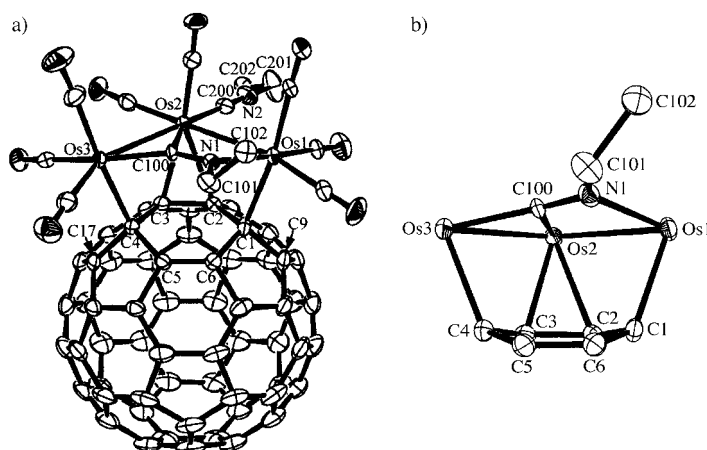


Figure 1. a) Molecular structure with atomic labeling scheme for **2a**. Only *ipso*-carbon atoms (C102 and C202) of the phenyl groups are shown for clarity. b) An expanded view of the boat-shaped $\mu_3\text{-}\eta^1, \eta^2, \eta^1\text{-C}_6$ part of the C_{60} ligand. Selected bond lengths [Å]: Os1–Os2 2.925(1), Os2–Os3 2.900(1), Os1–C1 2.25(1), Os2–C2 2.46(1), Os2–C3 2.37(1), Os3–C4 2.26(1), C1–C2 1.50(1), C2–C3 1.44(1), C3–C4 1.52(1), C4–C5 1.53(1), C5–C6 1.36(1), C6–C1 1.52(1).

to the three osmium centers in a 4e-donor $\mu_3\text{-}\eta^2(\text{C}), \eta^1(\text{N})$ bonding mode. Similar bonding of the isocyanide ligand was previously observed for an Os_6 cluster.^[6] The other isocyanide ligand (2e donor) occupies an equatorial position on the Os2 atom. The formal electron counts for Os1, Os2, and Os3 are 18, 19, and 17, respectively. The formal electron deficiency at the Os3 center appears to be compensated by a stronger Os3–C100 interaction (1.99 Å) as compared to Os2–C100 (2.18 Å). The bond lengths and angles for the terminal isocyanide and carbonyl ligands are within the expected ranges.

The two outer Os, atoms Os1 and Os3, coordinate to the C1 and C4 atoms, respectively, of the C_{60} ligand in a σ fashion, while the inner Os2 atom is π -coordinated to the C2 and C3 atoms in an η^2 mode. The two σ bonds Os1–C1 (2.25 Å) and Os3–C4 (2.26 Å), are shorter than the Os2–(C2,C3) π bond

(av 2.42 Å). The bond lengths C2–C3 (1.44 Å) and C5–C6 (1.36 Å) reveal double-bond character, and the other four C–C bonds (av 1.52 Å) exhibit single-bond character. The sums of the three angles around sp^3 -hybridized C1 ($\angle \text{C2-C1-C9} + \angle \text{C6-C1-C9} + \angle \text{C2-C1-C6} = 328^\circ$) and C4 ($\angle \text{C3-C4-C5} + \angle \text{C5-C4-C17} + \angle \text{C3-C4-C17} = 327^\circ$) are considerably smaller than those of the other four carbon atoms (av 351°) with sp^2 hybridization. Thus, the two sp^3 -hybridized carbon atoms C1 and C4 are pulled away from the smooth curvature of the C_{60} ligand, which is manifested in the boat shape of the C_6 ring, with C1 and C4 at the bow and stern positions, as shown in Figure 1b. The dihedral angles between the C2–C3–C5–C6 plane and the two adjacent planes C1–C2–C6 and C3–C4–C5 are 12.5 and 13.1° , respectively.

The cyclohexatriene-like C_6 ring of C_{60} in **1** has undergone orbital reorganization to form a 1,4-cyclohexadiene-like ring in **2a**. It can be envisaged that the 4e-donor RNC ligand formally provides two electrons to the antibonding orbital of the Os1–Os3 bond in **1** and thus results in its scission. The remaining two electrons of the RNC ligand interrupt two π interactions in **1** to give two M–C σ bonds (Os1–C1 and Os3–C4) and an uncoordinated C=C bond (C5=C6) in **2a**. The 1,4-addition isomers of σC_{60} –metal complexes have been reported previously in a few cases such as $[\text{C}_{60}\{\text{Re}(\text{CO})_5\}_2]$ ^[5a] and $[\text{C}_{60}\{\text{Mo}(\text{CO})_3(\eta^5\text{-C}_5\text{H}_4\text{CO}_2\text{Et})\}_2]$.^[5c]

The structure of **2b** is shown in Figure 2. Compound **2b** differs from **2a** only in that the terminal isocyanide ligand is coordinated to the outer Os3 atom. Other structural data of

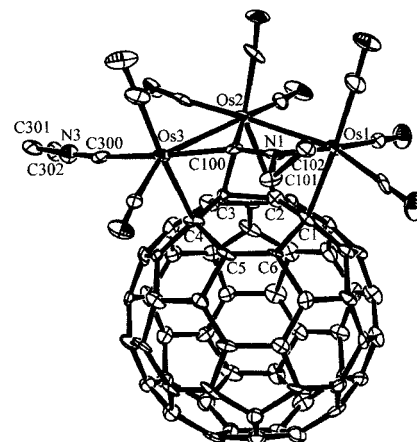


Figure 2. Molecular structure with atomic labeling scheme for **2b**. Only *ipso*-carbon atoms (C102 and C302) of the phenyl groups are shown for clarity. Selected bond lengths [Å]: Os1–Os2 2.918(1), Os2–Os3 2.913(1), Os1–C1 2.23(2), Os2–C2 2.48(2), Os2–C3 2.30(2), Os3–C4 2.25(2), C1–C2 1.43(3), C2–C3 1.47(3), C3–C4 1.53(2), C4–C5 1.50(3), C5–C6 1.33(3), C6–C1 1.53(3).

2b are essentially identical to those of **2a**. In the conversion of **1** to **2a** and **2b**, it is noteworthy that an M– C_{60} π interaction can be transformed into a σ interaction with orbital reorganization in the C_6 ring of the C_{60} ligand by electronic modification of the metal coordination sphere.

When a mixture of **1** and excess RNC in $\text{C}_6\text{H}_5\text{Cl}$ was irradiated by a medium-pressure Hg lamp for 12 h at room temperature, **2b** formed exclusively as the major product

(49%). Compound **2a** was shown to be stable towards transformation into **2b** under similar irradiation conditions, and this implies the photochemical route selectively forms **2b** from **1**. Compounds **2a** and **2b** were not interconvertible upon prolonged heating at 80 °C, that is, no intermetal movement of the isocyanide ligand occurs in these clusters.

In conclusion, we have demonstrated the first transformation of the bonding mode of C₆₀ from $\mu_3\text{-}\eta^2\text{-}\eta^2\text{-}\eta^2$ (π) to $\mu_3\text{-}\eta^1\text{-}\eta^2\text{-}\eta^1$ (σ) on an Os₃ framework induced by an external ligand (**1** → **2a** + **2b**). We have shown that the selective formation of isomer **2b** can be accomplished by UV irradiation. Efforts are currently underway to understand the thermal and photochemical conversion pathways of the π and σ C₆₀–metal interactions. Reactivity studies and selective functionalization of the C₆₀ ligand of **2a** and **2b** are also in progress.

Experimental Section

Details on the synthesis as well as full spectroscopic characterization of **1**, **2a**, and **2b** are given in the Supporting Information. For the X-ray structure analyses, data were collected on a CCD diffractometer with MoK α radiation (λ = 0.71073 Å) by using ω scans. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151706 (**1**), CCDC-151707 (**2a**), and CCDC-151708 (**2b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

2a: Analysis calcd for C₈₈H₁₄N₂O₈S₂Os₃ (**2a** · CS₂): C 55.92, H 0.77, N 1.53, S 3.51; found: C 55.50, H 0.68, N 1.29, S 3.57; IR (C₆H₁₂): $\tilde{\nu}$ = 2079 (s), 2068 (s), 2019 (s), 1986 cm⁻¹ (s) (CO); $\tilde{\nu}$ = 2189 (w), 1634 cm⁻¹ (vw) (CN); ¹H NMR (400 MHz, CS₂/CDCl₃, 298 K): δ = 7.49–6.98 (m, 10H; Ph), 5.50 (d, 1H, $J_{\text{H,H}}$ = 13 Hz; CH₂), 4.95 (brs, 2H; CH₂), 4.87 (d, 1H, $J_{\text{H,H}}$ = 13 Hz; CH₂); ¹³C NMR (carbonyl region, 100 MHz, C₆H₄Cl₂/C₆D₅CD₃, 298 K): δ = 179.96, 179.00, 178.32, 176.74, 175.74, 174.55, 173.39, 168.95; MS (FAB⁺): m/z : 1754 [M^+].

X-ray data for **2a**: Brown crystals were obtained by slow diffusion of hexane into a solution of **2a** in CS₂ at room temperature. A crystal of dimensions 0.12 × 0.14 × 0.42 mm was used for data collection: C₈₈H₁₄N₂O₈S₂Os₃ · CS₂, M_r = 1825.7; monoclinic, space group $P2_1/c$, Z = 4, ρ_{calcd} = 2.105 g cm⁻³, a = 19.4334(2), b = 10.6922(2), c = 29.0892(2) Å, β = 107.615°, V = 5760.9(1) Å³. The structure was solved by direct methods and refined by full-matrix least-squares analysis to give R = 0.0448 and R_w = 0.0695 (based on F^2) for 878 variables and 11 490 observed reflections with $I > 2\sigma(I)$ and $1.47 < \theta < 26.23$. Data collection at T = 293(2) K.

2b: Analysis calcd for C₈₄H₁₄N₂O₈Os₃: C 57.66, H 0.81, N 1.60; found: C 56.76, H 0.61, N 1.22; IR (C₆H₁₂): $\tilde{\nu}$ = 2085 (vs), 2052 (s), 2026 (vs), 2015 (w), 1992 (w), 1982 (w), 1968 cm⁻¹ (m) (CO); $\tilde{\nu}$ = 2185 (w), 1629 cm⁻¹ (vw) (CN); ¹H NMR (400 MHz, CS₂/CDCl₃, 298 K): δ = 7.49–7.19 (m, 10H; Ph), 5.66 (d, 1H, $J_{\text{H,H}}$ = 13 Hz; CH₂), 5.48 (d, 1H, $J_{\text{H,H}}$ = 16 Hz; CH₂), 5.41 (d, 1H, $J_{\text{H,H}}$ = 16 Hz; CH₂), 4.88 (d, 1H, $J_{\text{H,H}}$ = 13 Hz; CH₂); ¹³C NMR (carbonyl region, 100 MHz, C₆H₄Cl₂/C₆D₅CD₃, 223 K): δ = 181.9, 176.9, 176.1, 175.8, 175.5, 174.5, 173.2, 169.2; MS (FAB⁺): m/z : 1754 [M^+].

X-ray crystal data for **2b**: Brownish black crystals were obtained by slow diffusion of methanol into a solution of **2b** in toluene at room temperature. A crystal of dimensions 0.41 × 0.29 × 0.11 mm was used for data collection: C₈₄H₁₄N₂O₈Os₃, M_r = 1749.6; monoclinic, space group $P2_1/c$, Z = 4, ρ_{calcd} = 2.024 g cm⁻³, a = 19.9376(8), b = 23.0770(9), c = 12.8318(5) Å, β = 103.462(1)°, V = 5741.7(4) Å³. The structure was solved by direct methods and refined by full-matrix least-squares analysis to give R = 0.0779 and R_w = 0.1995 (based on F^2) for 851 variables and 8192 observed reflections with $I > 2\sigma(I)$ and $1.37 < \theta < 23.34$. Data collection at T = 193(2) K.

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Expanding the Pyrimidine Diphosphosugar Repertoire: The Chemoenzymatic Synthesis of Amino- and Acetamidoglucopyranosyl Derivatives**

Jiqing Jiang, John B. Biggins, and Jon S. Thorson*

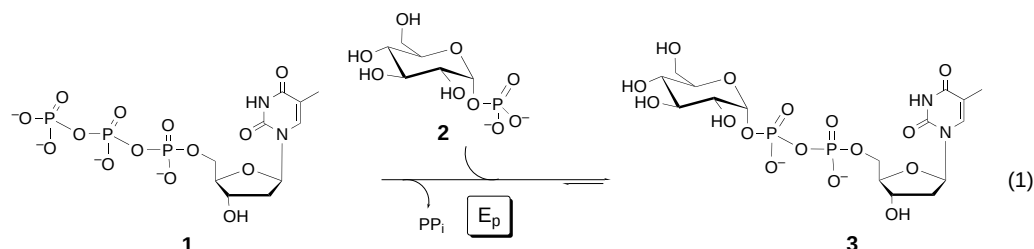
An extensive body of in vivo genetic evidence indicates that the glycosyltransferases involved in secondary metabolism are extremely promiscuous with respect to their nucleotide diphosphosugar (NDP-sugar) donor.^[1] Yet, in vitro experiments in this area are limited to only a few examples, partly because of the lack of the required NDP-sugar substrates for

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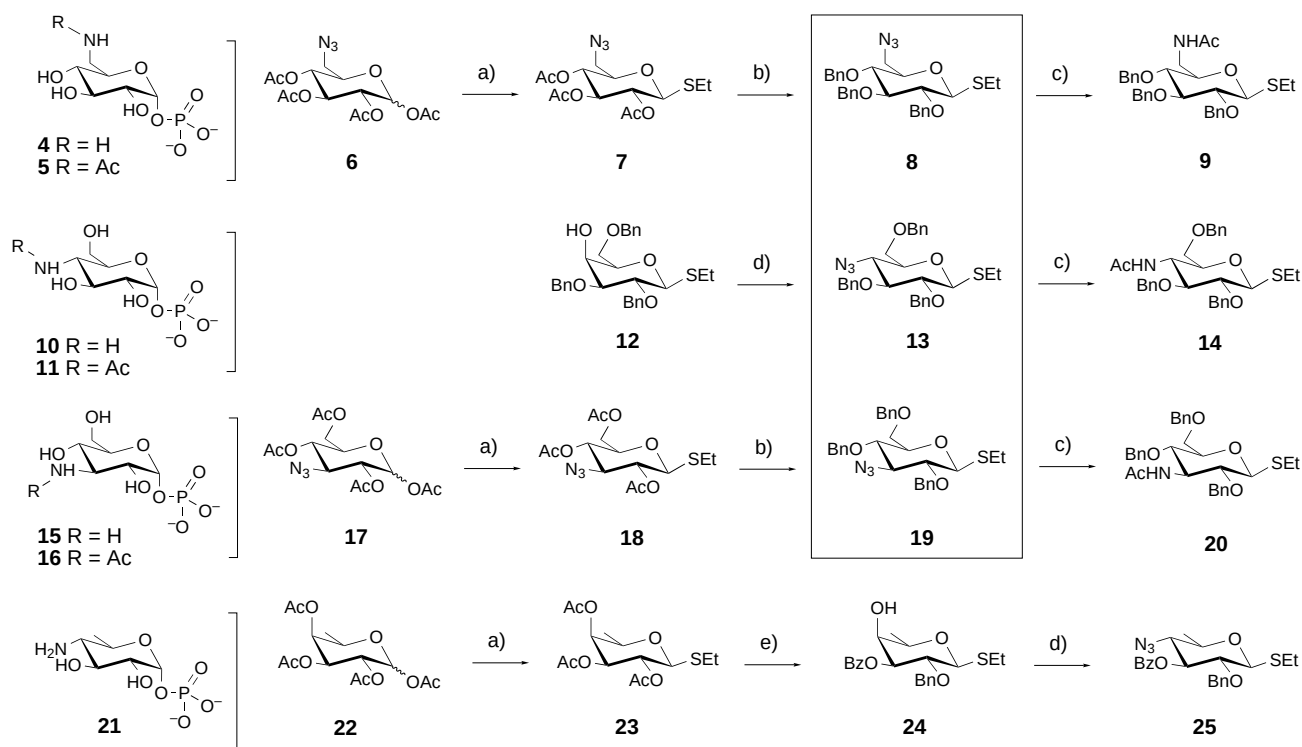
these experiments.^[2] Thus, the reliance of these unique glycosyltransferases on pyrimidine diphosphosugars (uridine (UDP)/thymidine (dTDP)) has revitalized interest in methods to expand the repertoire of UDP/dTDP-sugars.^[3] We recently reported that *Salmonella enterica* LT2 α -D-glucopyranosyl phosphate thymidyltransferase (E_p),^[4] which catalyzes the reaction shown in Equation (1), can convert a



wide array of α -D-hexopyranosyl phosphates into their corresponding dTDP- and UDP-nucleotide sugars.^[3] Herein we expand this methodology to include glycosides that are common to biological systems, namely aminodeoxy- α -D-hexopyranosyl phosphates and acetamidodeoxy- α -D-hexopyranosyl phosphates. A general chemoenzymatic method to rapidly generate these reagents is presented. This method is significant because it provides a substrate set for developing in vitro glycosylation systems. Furthermore, a direct comparison between a series of aminodeoxy- α -D-glucopyranosyl

phosphate series and their corresponding acetamidodeoxy analogues provides insight into the ability of the active site of E_p to accommodate additional steric bulk.

Only two of the aminodeoxy- α -D-glucopyranosyl phosphates examined, 2-amino-2-deoxy- α -D-glucopyranosyl phosphate (**26**; see Figure 1) and 2-acetamido-2-deoxy- α -D-glucopyranosyl phosphate (**27**; Figure 1), were commercially available. The syntheses of the remaining analogues diverged from the key intermediates **8**, **13**, and **19** (Scheme 1). 1-Ethylthio- β -D-pyranosides **8** and **19** were derived from the previously reported glycosides **6**^[5] and **17**^[6] respectively, whereas **13** was synthesized from the previously reported **12**,^[7] in a manner strategically similar to the synthesis of deoxy- α -D-glucopyranosyl phosphate.^[3] Specifically, this effective strategy invoked a protection scheme to selectively expose the position of substitution, followed by activation (with TsCl or Tf₂O; Ts = *para*-toluenesulfonyl, Tf = trifluoromethanesulfonyl) and S_N2 displacement by sodium azide. From the divergent point (**8**, **13**, and **19**), an efficient and selective reduction of the azide group with SnCl₂, followed by acetylation, gave the desired 1-ethylthio- β -D-pyranoside precursors **9**, **14**, and **20**. Finally, **9**, **14**, and **20**



Scheme 1. An overview of the key steps in the described syntheses of analogues of E_p substrates. The box highlights the point from which the aminodeoxy- α -D-glucose phosphate series and the acetamidodeoxy- α -D-glucose phosphate series diverge. Reaction conditions: a) Me₃SiSEt, ZnI₂ (84.2% overall yield); b) 1) MeONa, 2) NaH, BnBr (77.3% average overall yield, two steps); c) 1) SnCl₂, PhSH, Et₃N, 2) Ac₂O, py (84.0% average overall yield, two steps); d) 1) Tf₂O, py, 2) NaN₃ (87.7% average overall yield, two steps); e) 1) NaOMe, 2) CH₃C(OCH₃)₂CH₃, TsOH, 3) NaH, BnBr, 4) HCl/MeOH, 5) BzCl, DMAP, Et₃N (87.3% average overall yield, five steps); final steps (not shown): 1) phosphorylation, 2) reductive deprotection, 3) cation exchange to give the Na⁺ salt (44.4% average overall yield, three steps). Bn = benzyl, Bz = benzoyl, DMAP = 4-dimethylaminopyridine, py = pyridine.

were phosphorylated by the reaction with dibenzyl phosphate as previously described,^[3] and reductively deprotected to form **5**, **11**, and **16**, respectively. The same procedure also led to the conversion of azides **8**, **13**, and **19** into the desired amines **4**, **10**, and **15**, respectively. An aminodideoxy sugar, 4-amino-4,6-dideoxy- α -D-glucopyranosyl phosphate (**21**), was also synthesized from peracetylated D-fucose (**22**) by using a similar strategy (Scheme 1).

To evaluate the synthetic utility of our thymidyltransferase,^[8] E_p , α -D-glucopyranosyl phosphate, Mg^{2+} , nucleotide triphosphate (NTP), and inorganic pyrophosphatase^[9] were incubated at 37 °C for 30 min, and the extent of product formation was determined by HPLC (Figure 1).^[10] For each assay, confirmation of the product was based on high-resolution mass spectrometry (HR-MS) of the HPLC-isolated products, and in some cases also on HPLC coelution with commercially available standards.^[11] Control reactions showed that no product formation was observed in the absence of E_p , glucopyranosyl phosphate, Mg^{2+} , or NTP. The fundamental goal of this work was to assess the utility of E_p in

simplifying the synthesis of nucleotide sugar pools. Figure 1 clearly illustrates that E_p is advantageous for this task: of the nine substrate analogues tested, seven with thymidine triphosphate (dTTP) and four with uridine triphosphate (UTP) provide appreciable amounts of product (more than 50 % conversion) under the conditions described.

A comparison of the aminodeoxy- α -D-glucopyranosyl phosphate/dTTP assay results (Figure 1, **4**, **10**, **15** and **26**) with the native reaction of E_p (Figure 1, **3**/dTTP) reveals that the position of the amino substituent has absolutely no effect on product formation, and, with the exception of **4**, a similar phenomenon is observed in the presence of UTP. The divergence of **4** from this trend is consistent with our previous observations of a UTP-dependent E_p "adverse cooperation" in the presence of certain hexopyranosyl phosphates,^[3] perhaps a result of allosteric activation by dTTP.^[12] An evaluation of the acetamidodeoxy- α -D-glucopyranosyl phosphate/dTTP assays (Figure 1, **5**, **11**, **16**, and **27**), in comparison to their non-acetylated counterparts (Figure 1, **4**, **10**, **15**, and **26**, respectively), revealed that a bulky *N*-acetyl group at C2

or C3 (**16** and **27**) is tolerated, whereas the identical substituent at C4 or C6 (**5** and **11**) results in a complete loss of activity. Given that these effects most likely derive from unfavorable steric interactions, it follows that the active site of E_p is able to accommodate additional C2/C3 bulk, whereas steric interactions limit the allowed C4/C6 substitutions. To our surprise, product formation from **5**/UTP was eight times that from **5**/dTTP. This is the first example that contradicts the typical adverse UTP-dependent effect on yields, as illustrated by **4** and **16** in the present study. Finally, a comparison of aminodideoxy- α -D-glucopyranosyl phosphate (**21**)^[13] with **10** reveals that C6 deoxygenation does not affect dTTP-dependent E_p catalysis, but greatly diminishes UTP-dependent conversion (Figure 1). Given that independent deoxygenation at C6^[3] or amino substitution at C4 (**10**) have no effect on product yield (in the context of our assay conditions), data from independent substitutions may not be reliable in predicting the effects of multiple substitutions on product yield.

In conclusion, the presented work further substantiates the promiscuous nature of E_p and the advantages of exploiting this unique characteristic to synthesize an incredible array of valuable nucleotide diphosphosugar reagents. Thus, these studies will broadly impact efforts to understand and exploit the biosynthesis of glycosylated

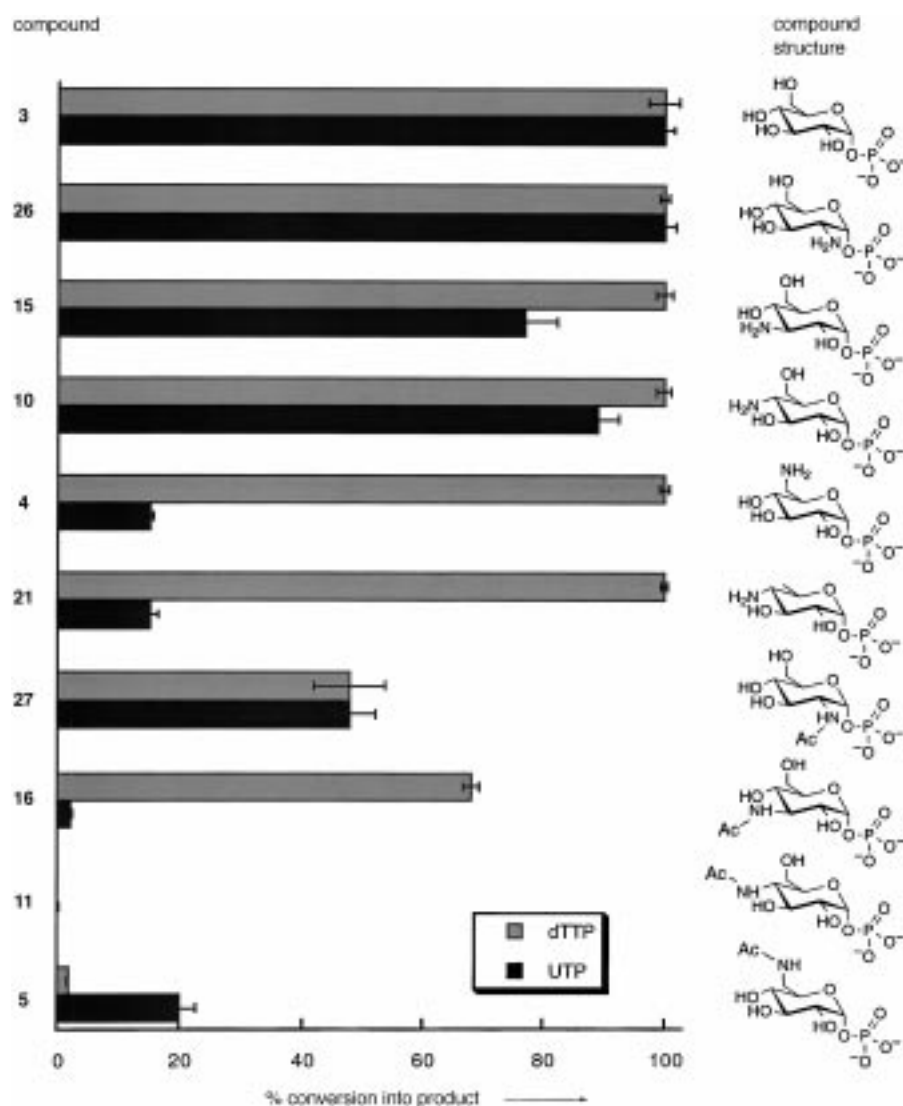


Figure 1. The E_p -catalyzed conversion of "unnatural" substrates. Percent conversion = $[A_p/(A_p + A_T)] \times 100$ (A_p = the NDP-sugar product peak integration, A_T = the NTP peak integration). The composition of all the products was confirmed by HR-MS.

bioactive natural products.^[1] Moreover, this work suggests that E_p can accept greater C2/C3 steric bulk in the substrate (relative to **3**), which opens the door to even more imaginative substitutions at these positions. Efforts are in progress to further expand the scope of this methodology.

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Note added in proof: The three-dimensional structure of E_p and the structure-based engineering of E_p to expand the methodology reported here have recently been reported (W. A. Barton, J. Lesniak, J. B. Biggins, P. D. Jeffrey, J. Jiang, K. R. Rajashankar, J. S. Thorson, D. B. Nikolov, *Nat. Struct. Biol.* **2001**, in press).

[Ru(N₂)(PiPr₃)(‘N₂Me₂S₂’)]⁺: Coordination of Molecular N₂ to Metal Thiolate Cores under Mild Conditions**

Dieter Sellmann,* Barbara Hautsch, Annette Rösler, and Frank W. Heinemann

Dedicated to Professor Ernst-Gottfried Jäger on the occasion of his 65th birthday

X-ray crystallography has revealed the structure of FeMo nitrogenase and its FeMo cofactors, however, the molecular mechanism of biological N₂ fixation has remained as unknown as low-molecular weight compounds catalyzing the reduction of N₂ under mild and biologically compatible conditions.^[1] These conditions rule out the use of alkali metals or comparably strong reductants at any stage in the design of a nonenzymatic chemical system for modeling the biological N₂ reduction. This includes the first stage, the synthesis of N₂ complexes.

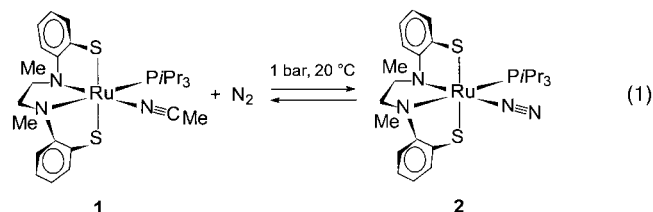
All mechanisms postulated for biological N₂ fixation consider the coordination of N₂ to the metal sulfur core of the Fe₇MoS₉ cofactors as the first key step.^[1] However, *metal sulfur complexes* that bind N₂ under mild conditions are unknown, in spite of numerous intensive efforts.^[2] There are only 12 N₂ complexes with sulfur coligands,^[3] only two of which could be prepared directly from molecular N₂.^[3a,f] Their preparation, however, required strong reductants or precursors prepared by use of strong reductants. None of these complexes meets the severe constraints with regard to mild conditions.

Our attempts to tackle this problem have focussed on sulfur ligand complexes of iron and its congener ruthenium. They

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have now led to a N_2 reaction that transforms the acetonitrile complex $[Ru(MeCN)(PiPr_3)(N_2Me_2S_2)]$ (**1**) under mild conditions into the N_2 complex $[Ru(N_2)(PiPr_3)(N_2Me_2S_2)]$ (**2**) [Eq. (1)].



The precursor MeCN complex **1** was obtained from $[Ru(Cl)_2(MeCN)_4]$ and $Li_2[N_2Me_2S_2]$ in the presence of $PiPr_3$. Complexes **1** and **2** have been completely characterized. Figure 1 shows their molecular structures.^[4]

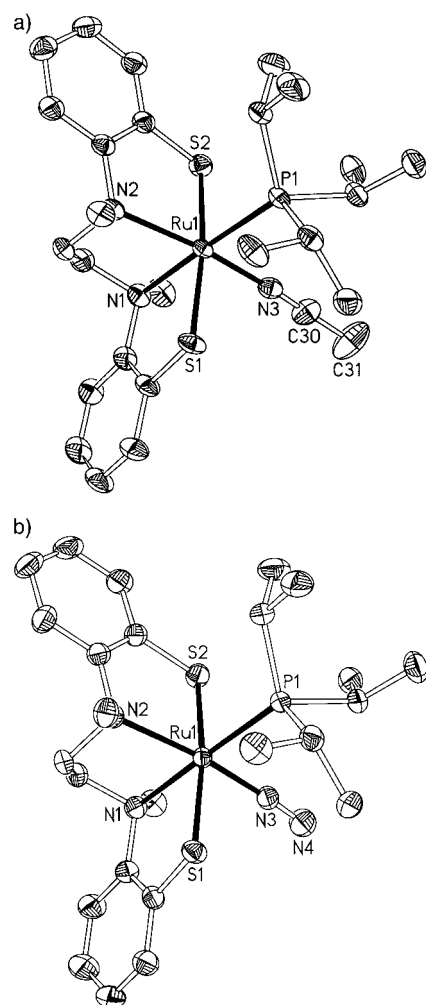


Figure 1. Molecular structures of a) **1**·MeOH and b) **2** (50% probability ellipsoids, C-bound H atoms and solvate molecules omitted). Selected distances [pm] and angles [°]: **1**·MeOH: Ru1-S1 238.52(9), Ru1-S2 237.54(9), Ru1-P1 232.84(9), Ru1-N1 225.6(3), Ru1-N2 221.9(3), Ru1-N3 199.0(3), N3-C30 114.3(5); N1-Ru1-N3 87.9(1), N2-Ru1-N3 170.0(1), Ru1-N3-C30 177.2(3); **2**: Ru1-S1 239.84(8), Ru1-S2 237.94(8), Ru1-P1 235.72(8), Ru1-N1 226.0(2), Ru1-N2 221.3(2), Ru1-N3 190.7(3), N3-N4 111.0(4); N1-Ru1-N3 89.7(1), N2-Ru1-N3 171.7(1), Ru1-N3-N4 176.9(3).

The $[Ru(PiPr_3)(N_2Me_2S_2)]$ core distances and angles of **1** and **2** are nearly identical. This holds true, in particular, for the distances Ru1-N2 *trans* to the coligands MeCN and N_2 , which are 221.9(3) pm in **1** and 221.3(2) pm in **2**. These distances are relatively short, and considerably shorter than the corresponding distance in $[Ru(CO)(PiPr_3)(N_2Me_2S_2)]$ (**3**) (229.2(4) pm).^[5] They indicate a practically identical *trans* influence of N_2 and MeCN, and explain the ready MeCN $\rightarrow N_2$ exchange of **1**. In this context, two important functions of the methyl substituents at the amine donors need to be mentioned. A comparison of $[Ru(L)(L')(N_2Me_2S_2)]$ and their analogous $[Ru(L)(L')(N_2H_2S_2)]$ parent complexes shows that the methyl substituents cause a slight elongation of the Ru-N distances and stabilize the Ru^{II} oxidation state towards oxidation.^[5] A characteristic property of $[Ru(L)(L')(N_2H_2S_2)]$ complexes is their spontaneous self-oxidation to give $[Ru^{IV}(L)(N_2S_2)]$ complexes with $N_2S_2^{4-} = 1,2$ -ethanediamido-*N,N'*-bis(2-benzenedithiolate) (**4** -).^[6]

The N_2 ligand binds end-on to the Ru center of **2**, the $\nu(N_2)$ frequency (2113 cm^{-1} , KBr) reflects a normal N_2 activation in **2** when compared with other N_2 complexes or the $\nu(CO)$ frequency of **3** (1930 cm^{-1} , KBr).^[2] In this respect, **2** looks like a regular N_2 complex. Unique for **2**, and unprecedented, however, are the mild conditions under which N_2 binds to yield metal thiolate N_2 complexes.

This raises the question why the attempts to synthesize such complexes have remained unsuccessful for such a long time. There are two major reasons. 1) It is well established that the coordination of N_2 can depend on triflingly minor looking subtleties. For example, exchange of PPh_3 for $P(p\text{-tolyl})_3$ causes instability of the Ir- N_2 bond in $[Ir(N_2)(Cl)(PPh_3)_2]$.^[7] In other words, metal and N_2 orbitals have to match precisely in order to warrant binding of N_2 . 2) Thiolate (and also sulfide) donors are principally adverse to the coordination of N_2 . Binding N_2 to a metal center requires a vacant site of coordination. Metal thiolate (or sulfide) complexes, however, are notorious for saturating vacant sites by formation of M-S-M bridges and oligo- to polynuclear complexes. In nitrogenase, such N_2 binding sites at the FeMoco may be kept vacant through steric strain and shielding provided by the enzyme protein. Low-molecular-weight thiolate complexes, however, need to achieve simultaneously the electronic “fine-tuning” of the vacant site and the delicate balance between the competing reactions of blocking this site either by N_2 or by a sulfur donor from another metal thiolate complex fragment. As yet, there is no other way than carrying out the experiments to elucidate the conditions necessary for meeting these constraints.

Preliminary experiments show that the thiolate donors of **2** are Brønsted-basic and can be protonated by HBF_4 . This constitutes an essential requirement for $2H^+/2e^-$ reductions of N_2 complexes.^[8] In addition, replacement of N_2 by H_2 yields the hydride-thiol species $[Ru(H)(PiPr_3)(N_2Me_2S_2-H)]$.

Experimental Section

All manipulations were carried out in absolute solvents under nitrogen or argon. $[RuCl_2(MeCN)_4]$ ^[9] and $N_2Me_2S_2 \cdot H_2$ ^[10] were prepared as described in the literature.

1: A solution of 'N₂Me₂S₂-H₂' (696 mg, 2.29 mmol) in MeOH (35 mL) and 1*N* LiOMe in MeOH (9.16 mL, 9.16 mmol) was added dropwise to a boiling MeOH suspension of [RuCl₂(MeCN)₄] (768 mg, 2.29 mmol) and *PiPr*₃ (0.89 mL, 4.57 mmol). The resulting yellow solution was heated for another 45 min under reflux, filtered while hot, and stored at -20 °C for 12 h. The precipitated yellow crystals were separated at -20 °C, washed with MeOH (50 mL), and dried in vacuo for 12 h (980 mg, 69%). Correct elemental analyses. IR (KBr): $\tilde{\nu}$ = 2245 (ν_{CN}) cm⁻¹; ¹H NMR (269.7 MHz, CD₂Cl₂): δ = 7.53–6.70 (m, 8H; C₆H₄), 3.33 (s, 3H; CH₃), 3.28 (s, 3H; CH₃), 3.30–2.20 (m, 4H; C₂H₄), 2.20 (s, 3H; CH₃CN), 2.19–2.09 (m, 3H; P(CH₃)), 1.36–1.24 (m, 18H; (CH₃)); ¹³C{¹H} NMR (67.7 MHz, CD₂Cl₂): δ = 157.7 (CH₃CN), 154.3, 153.9, 153.1, 151.7, 131.5, 131.2, 126.0, 125.7, 123.4, 122.0, 120.3, 119.9 (C₆H₄), 68.4, 62.0 (C₂H₄), 50.3, 47.8 (CH₃), 27.6 (d, *J*(P,C) = 18 Hz), 20.8, 19.5 (P(C₃H₇)); ³¹P{¹H} NMR (161.7 MHz, CD₂Cl₂): δ = 50 (s); FD-MS (CH₂Cl₂, ¹⁰²Ru, rel. intensity): *m/z* (%): 564 (100) [Ru(*PiPr*₃)(N₂Me₂S₂)]⁺, 605 (12) [Ru(MeCN)(*PiPr*₃)(N₂Me₂S₂)]⁺.

2: A stream of N₂ was passed through a solution of **1** (1.58 g, 2.6 mmol) in toluene (50 mL), until the ν_{N_2} IR band of **2** showed maximum intensity (ca. 30 min). At the end of the reaction, the solution was gently heated to 40–50 °C to remove liberated MeCN. After filtration, *n*-hexane (200 mL) was added precipitating unreacted **1**, which was removed after 30 min. The remaining *n*-hexane/toluene solution was reduced in volume to about 100 mL by passing a stream of N₂ through the solution. Yellow-green **2** precipitated, was separated, washed with Et₂O (3 mL), and dried in vacuo for 3 h (720 mg, 46%). Correct elemental analyses. IR (KBr): $\tilde{\nu}$ = 2113 (ν_{N_2}) cm⁻¹; ¹H NMR (269.7 MHz, THF): δ = 7.47–6.77 (m, 8H; C₆H₄), 3.42 (s, 3H; CH₃), 3.38 (s, 3H; CH₃), 3.37–2.30 (m, 4H; C₂H₄), 2.30–2.23 (m, 3H; P(CH₃)), 1.38–1.30 (m, 18H; (CH₃)); ¹³C{¹H} NMR (67.7 MHz, THF): δ = 155.8, 155.0, 153.6, 153.4, 134.0, 133.9, 128.9, 128.8, 124.4, 123.6, 123.5, 123.0 (C₆H₄), 70.7, 64.5 (C₂H₄), 54.2, 50.1 (CH₃), 30.1 (d, *J*(P,C) = 18 Hz), 23.0, 21.8 (P(C₃H₇)); ³¹P{¹H} NMR (161.7 MHz, THF): δ = 48 (s); FD-MS (THF, ¹⁰²Ru, rel. intensity): *m/z* (%): 564 (100) [Ru(*PiPr*₃)(N₂Me₂S₂)]⁺, 592 (8) [Ru(N₂)(*PiPr*₃)(N₂Me₂S₂)]⁺.

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a saturated boiling MeCN/MeOH (2:1) solution of **1** was slowly cooled to room temperature. C₂₈H₄₆N₃OPRuS₂, crystal size 0.70 × 0.60 × 0.40 mm, monoclinic, space group *P*₂₁/*n*, *a* = 1044.6(2), *b* = 1019.6(1), *c* = 2832.7(4) pm, β = 94.43(1)°, *V* = 3.0080(8) nm³, *Z* = 4, ρ_{calcd} = 1.406 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 0.74 mm⁻¹, *T* = 200 K, ω scans (10° min⁻¹); 8523 measured reflections (4.0 < 2 θ < 54.0°), 6569 unique reflections, 5350 observed reflections (*F*_o ≥ 4 σ (*F*)); 461 parameters, *wR*₂ = 0.1105, *R*₁ = 0.0446 (*F*_o ≥ 4.0 σ (*F*)). b) [Ru(N₂)(-*PiPr*₃)(N₂Me₂S₂)] (**2**). Yellow-green single crystals were grown by layering a saturated THF solution of **2** with MeOH. C₂₅H₃₉N₄PRuS₂, crystal size 0.52 × 0.46 × 0.36 mm, orthorhombic, space group *Pbca*, *a* = 1207.7(1), *b* = 1442.2(1), *c* = 3108.1(2) pm, *V* = 5.4135(7) nm³, *Z* = 8, ρ_{calcd} = 1.452 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 0.81 mm⁻¹, *T* = 220 K, ω scans (12° min⁻¹); 8713 measured reflections (4.2 < 2 θ < 58.0°), 7194 unique reflections, 5106 observed reflections (*F*_o ≥ 4 σ (*F*)); 416 parameters, *wR*₂ = 0.0886, *R*₁ = 0.0396 (*F*_o ≥ 4 σ (*F*)). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-153362 (**1**·MeOH) and CCDC-153363 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Synthesis and Characterization of RbLi₇Ge₈ with Isolated *closo*-[Li₄Ge₁₂]⁸⁻ Ions, Lithium-Capped Truncated Tetrahedra of Ge₁₂^{12-*}

Svilen Bobev and Slavi C. Sevov*

Zintl phases with isolated clusters of more than four atoms were very rare fifteen years ago, when only a few examples were known.^[1] Since then, however, this number has skyrocketed with many examples of Groups 13 (Tr = Triels) and 14 (Tt = Tetrels) as well as some heteroatomic species.^[2] Furthermore, many compounds in the A–Tt systems (A = alkali metal) were found to contain isolated deltahedral clusters, often referred to as Zintl ions, that were previously either unknown^[3] or could be crystallized from solutions only.^[4] Understanding the electronic structure and bonding in Zintl phases with deltahedral clusters combines both the assumption for complete electron transfer from the alkali metal atoms to the clusters (the Zintl–Klemm concept)^[1, 5] with the Wade's rules for electron counting in deltahedral boranes.^[6] Our interest has focused especially on clusters of

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Group 14, which initially started with the discovery of the first *nido*- Ge_9^{4-} deltahedra in the solid-state compound Cs_4Ge_9 .^[4a] This developed into systematic and thorough studies of the binary and pseudo-binary systems $\text{A}-\text{Tt}$ and $(\text{A}'/\text{A}'')-\text{Tt}$, respectively, where A' and A'' are two different alkali metals. The latter systems produced a number of interesting results, especially when A' and A'' were of very different size. Thus, the first stoichiometric silicon and germanium clathrates of type II, $\text{A}_8\text{Na}_{16}\text{Tt}_{136}$ ($\text{A}=\text{Rb}, \text{Cs}$; $\text{Tt}=\text{Si}, \text{Ge}$), were synthesized in a rational way only when the smaller sodium was combined with the much larger rubidium or cesium.^[7] Similarly, the same alkali metals combined with tin provided the novel phases $\text{A}_3\text{Na}_{10}\text{Sn}_{23}$ ($\text{A}=\text{K}, \text{Rb}, \text{Cs}$) made of clathrate layers of tin and intercalated with cations and tin tetrahedra.^[8] Lastly, an *arachno* cluster of eight atoms, a square antiprism of Sn_8^{6-} isoelectronic with Bi_8^{2+} of the same geometry,^[9] was synthesized only when lithium was combined with rubidium or potassium in the compounds $\text{A}_4\text{Li}_2\text{Sn}_8$ ($\text{A}=\text{K}, \text{Rb}$).^[10] The much smaller and more covalent lithium in the latter not only provides electrons but also stabilizes the clusters by capping the open square faces of the tin square antiprisms to form the *closo* species $[\text{Li}_2\text{Sn}_8]^{4-}$.^[10] Here we report the synthesis and structure of another lithium-based pseudo-binary compound, RbLi_7Ge_8 , which contains the largest isolated clusters of Group 14, truncated tetrahedra of Ge_{12}^{12-} stabilized similarly by lithium that caps all four hexagonal faces to form a 16-atom *closo*- $[\text{Li}_4\text{Ge}_{12}]^{8-}$ cluster.

The new compound RbLi_7Ge_8 was synthesized by direct fusion of the elements.^[11] Lithium was purposely used in a combination with a heavy alkali metal. Its substantial covalency, much smaller size, strong polarizing power, and higher electronegativity, provide for quite different interactions with the early p-block elements. These properties of lithium have been exploited quite extensively in the past and a number of novel compounds that form with lithium only have been reported.^[12–15] The heavy alkali metal, on the other hand, provides for different packing requirements and more complete electron transfer. For example, the defect diamond-type structure of Li_8Ge_8 ($=\text{LiGe}$)^[12] differs significantly from the structure of the new compound RbLi_7Ge_8 although only one of eight lithium atoms is formally “replaced” by rubidium.

The structure of RbLi_7Ge_8 was determined from single-crystal X-ray diffraction studies.^[16] It contains two different isolated germanium clusters of Ge_4^{4-} and Ge_{12}^{12-} in equimolar ratio (Figure 1). The former are the same well known tetrahedra found in the classical A_4Ge_4 ($\text{A}=\text{K}, \text{Rb}, \text{Cs}$),^[17] as well as some compounds with mixed alkali metal cations $(\text{A}'_x\text{A}''_{1-x})_4\text{Ge}_4$ for $x=0.125, 0.25$, and 0.5 .^[13] The novel clusters of Ge_{12}^{12-} are only the third type of germanium clusters in addition to the Ge_4^{4-} tetrahedra and the mono-capped square antiprisms of *nido*- Ge_9^{4-} . The geometry of Ge_{12}^{12-} is truncated tetrahedron with four triangular and four hexagonal faces (Figure 2), and all germanium atoms are three-bonded. The range of Ge–Ge distances in Ge_{12}^{12-} (2.505(2)–2.603(2) Å) is somewhat broader than that in Ge_4^{4-} (2.567(2)–2.569(2) Å), although both have exactly the same average, 2.568 Å. These distances compare also very well with distances of Ge_4^{4-} in other compounds^[13, 17] and those of Ge_9^{4-} .^[14]

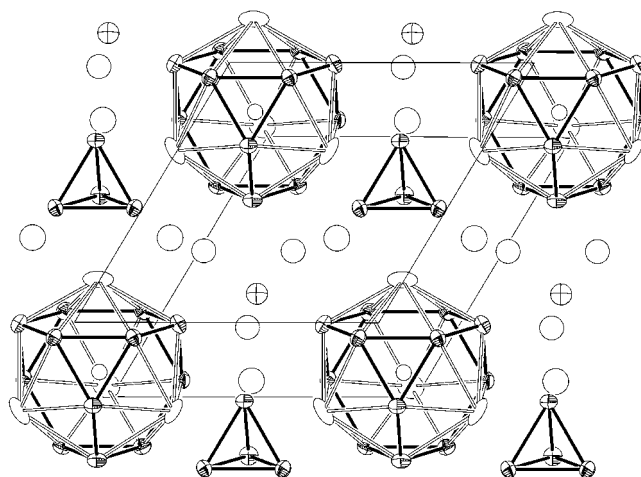


Figure 1. General view of the structure of RbLi_7Ge_8 (Ge: full ellipsoids, Li: empty ellipsoids, Rb: crossed ellipsoids, 80% probability level) with the hexagonal cell outlined. The vertices of the clusters of Ge_{12}^{12-} and Ge_4^{4-} are connected with thick full bonds, while the lithium atoms capping the faces of Ge_{12}^{12-} are connected with open lines.

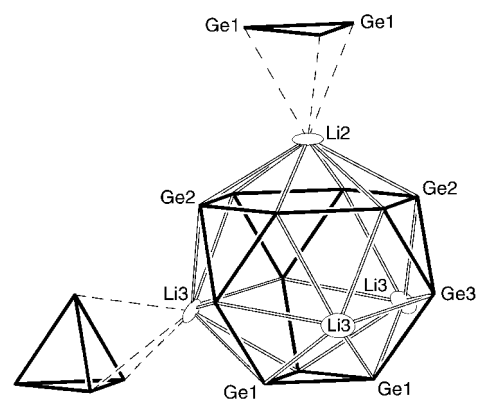


Figure 2. Structure of one *closo*- $[\text{Li}_4\text{Ge}_{12}]^{8-}$ ion, a lithium-capped truncated tetrahedron Ge_{12}^{12-} (50% thermal ellipsoids). All Ge–Ge contacts are shown with thick full bonds, while the capping Li atoms are connected with open lines. The intercluster interactions of Li2 with a triangular face of another $[\text{Li}_4\text{Ge}_{12}]$ cluster and the interactions of one of the three Li3 atoms with a neighboring Ge_4 tetrahedra are shown with broken thin lines. Intracuster distances [Å]: Ge1–Ge1 2.587(2), Ge1–Ge3 2.505(2), Ge2–Ge2 2.603(2) in Ge2–Ge2–Ge3 triangles and 2.533(2) between them, Ge2–Ge3 2.593(1), Li2–Ge2 2.95(2), Li3–Ge1 2.93(1), Li3–Ge2 2.97(2), Li3–Ge3 2.98(1).

The clusters in RbLi_7Ge_8 are well separated (the shortest intercluster distance is 4.2323(9) Å). They are arranged in nearly flat layers perpendicular to the *c* axis, and the cations are found between the layers as well as between the clusters within the layers. As expected, the cations cap faces, edges, and vertices of the clusters, and one lithium atom centers the truncated tetrahedron of Ge_{12}^{12-} . The Rb–Ge and Li–Ge distances are in the ranges 3.743(1)–4.430(2) and 2.69(5)–3.044(9) Å, respectively.

The stoichiometry and the bonding of RbLi_7Ge_8 can be readily rationalized by the Zintl–Klemm concept.^[1, 5] All germanium atoms carry a charge of 1 – each for being three-bonded. These charges are counterbalanced by exactly the same number of alkali metal cations available in the formula. In other words, RbLi_7Ge_8 is an electronically balanced

compound, a saltlike Zintl phase. Indeed, this is supported by our extended-Hückel molecular orbital calculations, the dark-to-black colored and very brittle crystals, and, most importantly, by the diamagnetism observed for the compound.^[18]

Another, perhaps more interesting way to view the bonding in this mixed-cation compound is to consider the lithium atoms capping the hexagonal faces of the truncated tetrahedra as part of the clusters. This, as already discussed, is well justified by the substantially more covalent Li–Ge interactions.^[12] Thus, Ge_{12}^{12-} is completed to a *closo*- $[\text{Li}_4\text{Ge}_{12}]^{8-}$ deltahedral cluster of 16 atoms (Figure 1 and 2). In a similar manner the square faces of the square-antiprismatic *arachno*- Sn_8^{6-} found in $\text{A}_4\text{Li}_2\text{Sn}_8$ ($\text{A} = \text{K}, \text{Rb}$) are capped by lithium to form the deltahedral *closo*- $[\text{Li}_2\text{Sn}_8]^{4-}$.^[10] $[\text{Li}_4\text{Ge}_{12}]$ is centered by another lithium atom with very similar distances to the sixteen vertices (twelve germanium and four lithium). They are in the narrow range of 2.98(4) to 3.08(3) Å, and indicate that the overall shape of the cluster is very close to spherical.

Sixteen-atom species of this geometry of tetracapped truncated tetrahedra are known but usually as interconnected in networks.^[19, 20] Despite the *closo* shape, however, it is known that such clusters “violate” Wade’s rules^[6] (intrinsically) because of their nearly ideal T_d symmetry.^[19] They require $2n+4$ cluster-bonding electrons instead of the usual $2n+2$ for *closo* clusters,^[21] which means $2 \times 16+4=36$ electrons for $[\text{Li}_4\text{Ge}_{12}]$. In addition to the bonding electrons, the vertices of such “naked” clusters should carry a lone pair of electrons each. This, however, shall not be expected for the lithium vertices since this would lead to the impossible and unrealistic charge of more than $2-$ per lithium. Instead, each capping lithium atom of $[\text{Li}_4\text{Ge}_{12}]$ is in turn “capped” by a triangle of germanium atoms from a nearby tetrahedron or another truncated tetrahedron (Figure 2) and interacts with the three lone pairs provided by these germanium atoms. The interaction can be modeled as four-center, six-electron bonding in a trigonal pyramid with an “open” base. The bases are the “capping” triangular faces of germanium which, of course, are not really open but since the lone pairs are not involved in the bonding of the triangular face they can be considered as isolated from each other. The MO diagram of such a model contains one low-lying totally bonding combination of all four orbitals, that is the Li *s* orbital and the three germanium lone pairs, and this is followed by a doubly degenerate nonbonding combination of the three lone pairs and an antibonding combination of the four orbitals. The net result for six electrons is bonding where two of the six electrons provide for the three Li–Ge bonding interactions and the remaining four electrons are the two pairs of nonbonding electrons delocalized on the three germanium atoms. The same situation is observed in $\text{A}_4\text{Li}_2\text{Sn}_8$ ($\text{A} = \text{K}, \text{Rb}$), where the lithium atoms that cap the open square faces of the square-antiprismatic Sn_8 interact also with the lone pairs of two tin atoms forming an edge of a neighboring Sn_8 cluster.^[10] The Li–Ge interactions can be viewed also as localized in resonance structures where the lithium is *exo*-bonded to one germanium atom at a time by sharing its pair of electrons, while the other two germanium atoms retain their nonbonding lone pairs of electrons. Thus, through the interactions between the capping lithium atoms and the neighboring clusters each *closo*- $[\text{Li}_4\text{Ge}_{12}]^{8-}$ cluster is

“connected” to two other such clusters along the *c* axis and to three tetrahedra in the *xy* plane.

The negated need of lone pairs on the four lithium vertices of the 16-atom clusters means that only 24 electrons are needed for lone pairs for the remaining twelve vertices, the germanium atoms. The cluster, therefore, requires total of 60 electrons which includes the 36 bonding electrons discussed above. The sixteen atoms provide total of 52 electrons, that is 4×1 from lithium and 12×4 from germanium. Thus, the $[\text{Li}_4\text{Ge}_{12}]$ cluster will have a negative charge of $8-$. The Ge_4 tetrahedra are known to carry a charge of $4-$, and therefore, the formula can be rewritten as $\text{Rb}_2\text{Li}_4\text{Ge}_{16} = \text{Rb}_2\text{Li}_{10}\{[\text{Ge}_4]^{4-}\}\{[\text{Li}_4\text{Ge}_{12}]^{8-}\}$ or as $\text{Rb}_2\text{Li}_9\{[\text{Ge}_4]^{4-}\}\{(\text{Li}[\text{Li}_4\text{Ge}_{12}])^{7-}\}$ since one lithium cation centers the big cluster.

The new compound and the other mixed-cation compounds mentioned above illustrate nicely the delicate balance between packing efficiency, electronic requirements, and covalent interactions. By using carefully selected combinations of alkali metals one can possibly change the packing modes, while the overall cation to anion ratio and, therefore, charge are kept constant. This will be, most likely, the best way towards stabilization of other yet-to-be-found compounds that are otherwise inaccessible in pure binary systems. As seen here, similarly to the *arachno*- Sn_8^{6-} that exists only in the lithium-containing $\text{A}_4\text{Li}_2\text{Sn}_8$ ($\text{A} = \text{K}, \text{Rb}$) Zintl phase as a *closo*- $[\text{Li}_2\text{Sn}_8]^{4-}$ ion,^[10] the Ge_{12}^{12-} is stabilized only in RbLi_7Ge_8 as a *closo*- $[\text{Li}_4\text{Ge}_{12}]^{8-}$ ion.

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intended to produce $\text{Rb}_3\text{Li}_{10}\text{Ge}_{23}$, the Li/Ge analogue of the known $\text{A}_3\text{Na}_{10}\text{Sn}_{23}$ ($\text{A} = \text{K}, \text{Rb}, \text{Cs}$).^[8] After the structure and the exact stoichiometry of the compound were determined from single-crystal X-ray diffraction data, RbLi_7Ge_8 was synthesized from the corresponding stoichiometric mixture of elements by heating at 1000°C for 4 h and then cooling down to room temperature at a rate of 20°C h^{-1} . All reactions were carried out in tubular niobium containers that were sealed at the two ends by arc-welding. These containers are then placed in fused-silica ampoules, and the latter are evacuated (below discharge) and sealed. Attempts to synthesize the corresponding K and Cs analogues have been unsuccessful so far. Nevertheless, these reactions yielded K_3LiGe_4 ($Pnma$, $a = 7.758(9)$, $b = 9.931(8)$, $c = 12.400(9)$ Å) and Cs_3LiGe_4 ($Cmcm$, $a = 6.944(4)$, $b = 15.510(8)$, $c = 9.88(1)$ Å) isostructural with the known K_3LiSi_4 and Cs_3LiSi_4 ,^[14] respectively. However, both reactions yielded traces of other, yet unidentified phases, and currently under way is a search for optimal compositions and reaction conditions.

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Controlled Synthesis of Cross-Linked Ultrathin Polymer Films by Using Surface-Initiated Atom Transfer Radical Polymerization**

Wenxi Huang, Gregory L. Baker,* and Merlin L. Bruening*

Covalent attachment of polymer chains to solid substrates by surface-initiated polymerization is an effective method for tailoring surface properties such as wetting, adhesion, and biocompatibility. Following R  he and Prucker’s successful work on free radical polymerization from surfaces,^[1a] several research groups recently reported the use of controlled/living polymerization techniques^[1b–h] to grow polymer chains from a surface in a well-defined manner. Several research groups also used surface-initiated polymerizations to generate patterned polymers on surfaces for lithographic applications.^[1c,e, 2, 3] The grafted polymer layers have higher resistance to wet chemical etchants than the patterned monolayers from which they are grown.

Cross-linked polymer films, compared to linear polymer brush analogues, should yield even better mechanical and chemical stability and provide new pathways to functionalized surfaces for molecular recognition. However, the preparation of cross-linked thin films is an experimental challenge. Direct polymerization of cross-linkable monomers in solution usually results in an insoluble three-dimensional polymeric gel that cannot be deposited as a uniform thin coating. Cross-linked films can be prepared by deposition of a cross-linkable polymer precursor followed by a cross-linking reaction; however, the method is not straightforward and it usually is difficult to control film thickness and the curing reaction. Herein we report direct polymerization of ethylene glycol dimethacrylate (EGDMA) from a surface to form cross-linked polymer films (Figure 1).

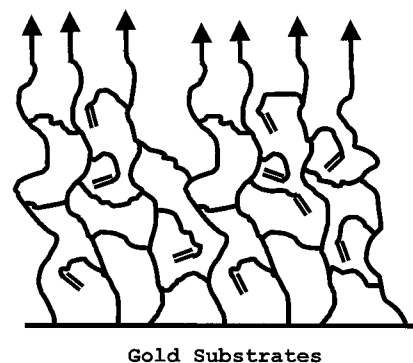


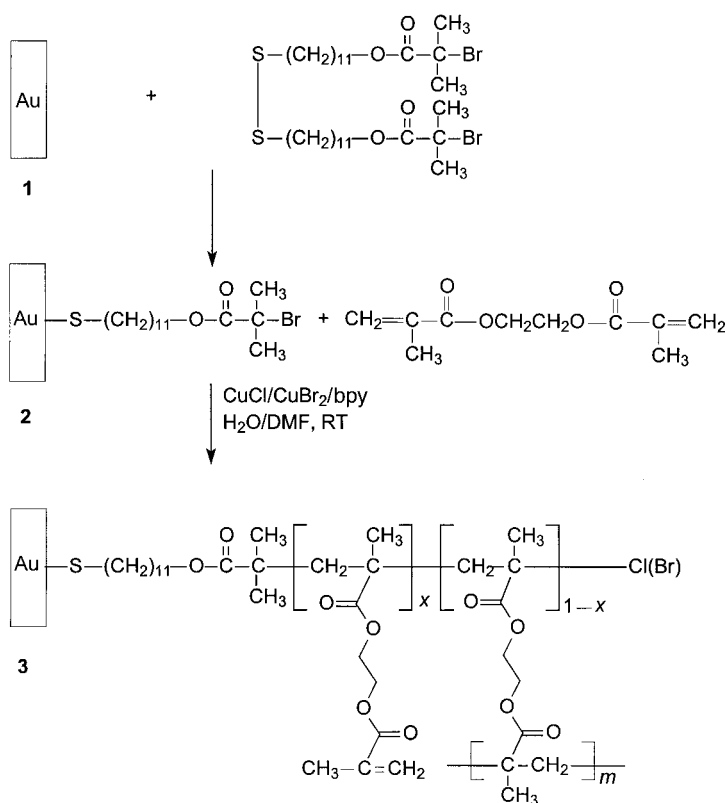
Figure 1. Schematic illustration of a cross-linked film growing from a gold substrate.

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Preparation of a well-defined cross-linked thin film by polymerization from a surface requires that there be minimal parallel formation of polymer in solution. Side reactions that cause formation of polymer in solution will result in gelation, or in the case of polymers insoluble in the polymerization medium, cross-linked polymer will precipitate onto the substrate, creating a heterogeneous film. Low-temperature polymerization is essential to insure that thermal autopolymerization will be negligible. Low-temperature processes are also compatible with substrates such as Au-thiolates that are unstable at elevated temperatures.^[4]

Scheme 1 outlines the synthetic pathway we used to prepare cross-linked, ultrathin polymer films on gold surfaces by surface-initiated atom transfer radical polymerization



Scheme 1. Synthetic outline for the preparation of cross-linked, ultrathin poly(EGDMA) (PEGDMA) films on gold surfaces.

(ATRP). Immersion of gold-coated wafers in a 1 mM ethanolic solution of the disulfide initiator for 24 h led to the formation of substrate **2**. The ellipsometric thickness of the initiator monolayer (1.8 ± 0.1 nm) and the appearance of a carbonyl peak at 1739 cm^{-1} in the reflectance FTIR spectrum of the film (Figure 2, spectrum a) confirmed monolayer formation. For surface grafting polymerization, we immersed the substrate in an EGDMA/water/dimethylformamide (DMF) mixture containing the $\text{CuCl}/2,2'$ -bipyridine (bpy) catalyst. Addition of water is necessary for rapid ATRP at room temperature. Armes et al. recently showed that water accelerates ATRP, probably because it changes the nature of the active catalyst.^[5] To extend this interesting scheme to

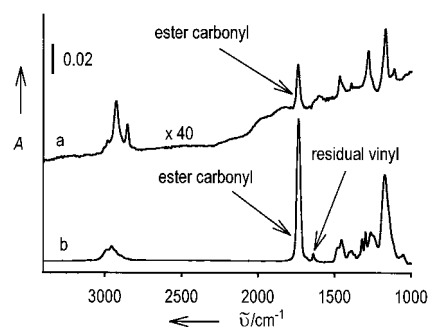


Figure 2. Reflectance FTIR spectra of a) an initiator monolayer, and b) a grafted PEGDMA layer (50 nm thick). A = absorbance.

water-immiscible, hydrophobic monomers, we added DMF to afford a homogeneous solution.

The presence of a deactivating Cu^{II} complex in solution is necessary for control of ATRP. In solution ATRP, reaction of Cu^{I} with initiator produces the Cu^{II} complex. Because of the small amount of initiator at a substrate, however, the concentration of the deactivating Cu^{II} complex is too low to control polymerization from a surface. To overcome this problem, several research groups added free initiator to the polymerization solution.^[2g,h,3] When we employed this procedure to synthesize cross-linked films by using ethyl 2-bromoisobutyrate (0.01 M) as a free initiator in solution, polymerization in solution resulted in an insoluble gel in 30 min. The gel could not be redissolved in any solvent. This experiment clearly demonstrates the need to restrict polymerization to the surface in the preparation of homogeneous, cross-linked films.

To ensure a sufficient concentration of deactivating Cu^{II} species in the solution, we added 30 mol% of CuBr_2 (with respect to CuCl) to the solution.^[6] The use of mixed-halide initiation systems also allows better control of ATRP.^[7] No gelation of the solution or precipitation of polymer was observed during film growth, indicating minimal polymerization in solution.^[8] After completion of the polymerization, the substrate was cleaned by sonication in DMF for 20 min, and dried under a flow of nitrogen. A large increase in the carbonyl peak at 1736 cm^{-1} in the reflectance FTIR spectrum (Figure 2, spectrum b) confirmed the formation of the polymer layer. In addition, a peak at 1639 cm^{-1} ($\text{C}=\text{C}$ stretching) indicates some unpolymerized EGDMA vinyl groups in the film. Residual monomer is unlikely because the film is ultrathin and was carefully cleaned with DMF. Surface Raman spectroscopy showed the presence of carbonyl and $\text{C}=\text{C}$ bond peaks at 1730 and 1640 cm^{-1} , respectively. The combination of reflectance FTIR and Raman spectroscopy demonstrated the successful growth of the poly(EGDMA)(PEGDMA) layer.

To demonstrate the “living” character of surface-initiated ATRP, we used a 60-nm PEGDMA-coated wafer as a macroinitiator in a fresh EGDMA/catalyst solution. Ellipsometry measurements showed an increase in film thickness to 300 nm after an additional reaction time of 60 h. A large increase in the carbonyl peak in the reflectance FTIR spectrum also confirmed extension of the polymer layer.

Ellipsometric measurements reveal that the cross-linked films are very uniform. The variation in thickness for a 200-nm

thick polymer film over a $1.3 \times 2.5 \text{ cm}^2$ sample was as low as 1 nm. Atomic force microscopy (AFM) images showed that this film was also microscopically homogeneous (RMS roughness of 2 nm). As the polymer chains cross-link to neighboring chains during propagation, surface reorganization after polymerization is unlikely, and the uniformity of the film suggests the polymerization is homogeneous throughout the sample.

Figure 3 shows the thickness of PEGDMA films and the absorbance ratio for the C=C (1639 cm^{-1}) and C=O (1736 cm^{-1}) stretches as a function of polymerization time. We observed a linear increase in thickness with time, consistent

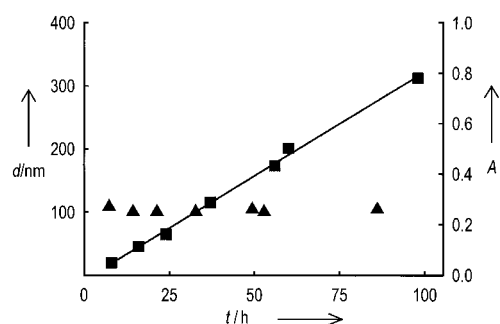


Figure 3. Time-dependence of the thicknesses (d) of grafted PEGDMA films (squares) and the integrated absorbances A (triangles) of the residual vinyl peak (1639 cm^{-1}) in reflectance FTIR spectra of grafted PEGDMA layers. The absorbance of the vinyl peaks was normalized to the carbonyl peak at 1736 cm^{-1} .

with controlled chain growth from the surface with some degree of “living” character. We can obtain predictable film thickness up to 300 nm. The constant C=C/C=O ratio during polymerization further suggests that the polymer film is homogeneous. By comparing the normalized IR absorbance of vinyl groups in PEGDMA films with that of the monomer, we estimate that 25 % of the vinyl groups remain unpolymerized in films. This suggests that coatings are about 50 % cross-linked.

The results of swelling experiments are consistent with highly cross-linked PEGDMA films. In situ ellipsometry showed that a 220-nm thick PEGDMA film increased in thickness to 280 nm when swollen in THF, while a 140-nm thick poly(methyl methacrylate) (PMMA) brush increased to 340 nm under identical conditions. The films were cycled between the swollen and dried state two times with no apparent difference in thickness values. The minimal swelling of the PEGDMA film relative to the control PMMA film is presumably due to the highly cross-linked polymer network.

In conclusion, ambient temperature ATRP in water-containing solutions enables the controlled synthesis of cross-linked PEGDMA films from gold surfaces. The product polymer films are uniform over large areas, presumably because polymerization is limited to the surface, and minimal polymer is formed in solution. This feature is crucial for avoiding physisorption of cross-linked polymers. Both swelling experiments and FTIR spectroscopy indicate that the PEGDMA films are highly cross-linked, and the “living” character of ATRP allows the growth of an additional polymer layer. The use of low polymerization temperatures and aqueous media is compatible with various substrates and should allow engineering of a variety of surfaces.

Experimental Section

EGDMA was passed through a basic alumina column, and distilled under reduced pressure before polymerizations. Gold-coated wafers (sputter coating of 200 nm of Au on 20 nm of Cr on Si(100) wafers) were cleaned in a UV/O₃ chamber for 15 min before use. Ellipsometric measurements of dried films were obtained with a rotating analyzer ellipsometer (model M-44, J. A. Woollam) at a 75° angle of incidence. Ellipsometric swelling experiments were carried out with a computer-controlled null ellipsometer (Rudolph Auto-EL II) with a He–Ne laser (632.8 nm) light source and a 70.0° angle of incidence. In situ measurements were made with a specially built trapezoidal cell containing glass windows fixed at an angle of 20.0° from the surface normal. Thickness measurements were made before and after filling the cell with purified THF. Refractive index and thickness values for all the films were calculated simultaneously from the experimental Ψ and Δ values (n values for swollen films were 1.43 (PMMA) and 1.49 (PEGDMA)). Reflectance FTIR spectroscopy was performed using a Nicolet Magna-IR 560 spectrometer containing a PIKE grazing angle (80°) attachment. AFM images were obtained in the tapping mode with a Nanoscope IIIa instrument (Digital Instruments).

The disulfide initiator ($\text{BrC}(\text{CH}_3)_2\text{COO}(\text{CH}_2)_{11}\text{S}_2$) (Scheme 1) was synthesized according to a literature procedure.^[3]

Polymerizations: To a solution of degassed monomer (42 mL; EGDMA/ $\text{H}_2\text{O}/\text{DMF}$, 3:3:8, v:v:v), CuCl (180 mg, 1.8 mmol), CuBr₂ (120 mg, 0.54 mmol), and bpy (731 mg, 2.34 mmol) were added under an argon atmosphere. The solution mixture was degassed by using three freeze–pump–thaw cycles, and warmed to room temperature with continuous stirring until a homogeneous dark brown solution formed. The monomer/catalyst solution was transferred by cannula into a degassed vial containing substrate **2**, and the reactor was kept at room temperature without stirring during polymerization.

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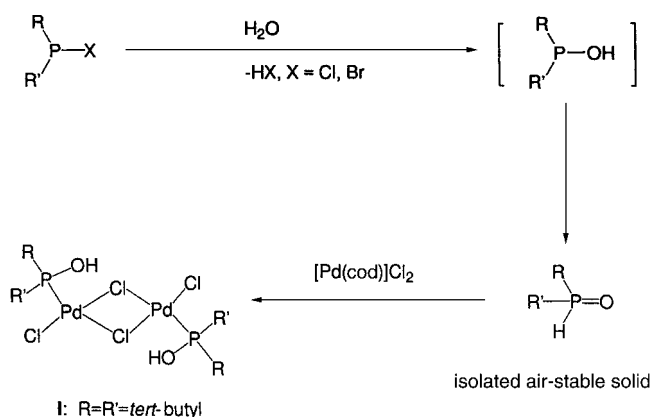
The First Phosphine Oxide Ligand Precursors for Transition Metal Catalyzed Cross-Coupling Reactions: C–C, C–N, and C–S Bond Formation on Unactivated Aryl Chlorides

George Y. Li*

Dedicated to Professor Fred Basolo
on the occasion of his 81st birthday

In recent years, transition metal catalyzed cross-coupling reactions of aryl chlorides have developed into a versatile and efficient method for a variety of synthetic transformations.^[1, 2] Furthermore, promising results in the Pd- (or Ni)-catalyzed C–C (Suzuki,^[3–6] Kumada,^[7] and Stille^[8] cross-coupling) and C–N^[9] bond-forming processes prompted us to search for new, inexpensive, and efficient air-stable ligands for potential industrial applications of these less expensive but readily available aryl chlorides. One potentially valuable and cost-saving approach is to apply combinatorial synthesis and screening methods for the discovery and development of efficient, air-stable novel catalysts.^[10, 11] Air-stable phosphine oxides (RR'P(O)H) in the presence of transition metals undergo tautomerization to the less stable phosphinous acids (RR'POH), which subsequently and expectedly coordinate to the metal centers through phosphorus atoms to form metal–phosphinous acid compounds.^[12] Deprotonolysis of the resulting phosphinous acid complex with base (e.g. NaOR, Na₂CO₃, CsF) can be anticipated to yield an electron-rich anionic compound. These results raise the interesting question of whether these phosphane-containing anionic complexes could be utilized to facilitate oxidative addition of aryl chlorides (rate-limiting step) in homogeneous catalysis^[13] to generate a variety of C–C, C–N, and C–S^[14] bonds in different environments by using cross-coupling reactions of aryl chlorides. Herein, we report the first examples of simple, readily accessible, air-stable phosphine oxides used as ligand precursors for the efficient transition metal catalyzed C–C, C–N, and C–S bond-forming reactions of aryl chlorides to access a variety of such architectures, as well as initial observations regarding the scope and mechanism. We also describe a general synthesis of binuclear chloride-bridged Pd^{II} mono-phosphinous acid complexes used as catalyst precursors for a variety of cross-coupling reactions and the X-ray crystallographic characterization of one of them.

The ligand precursors used for cross-coupling reactions were prepared either in situ or by standard sublimations (Scheme 1).^[10, 11, 15] The precatalysts were synthesized by treating transition metal precursors with monophosphine oxides in a variety of solvents at either room temperature or



Scheme 1. Synthesis of air-stable phosphine oxide ligand precursors and their corresponding phosphinous acid ligand complexes. cod = 1,5-cyclo-octadiene.

elevated temperature. The formation of these catalyst precursors was conveniently monitored by solution ³¹P NMR spectroscopy.^[16] The catalytic cross-coupling reactions were carried out in organic solvents (e.g. toluene, DMSO, dioxane) under anhydrous/anaerobic or open-to-air conditions (catalyst loading: ~1–5 mol %).^[17] The yields in Table 1 refer to products isolated by column chromatography. Known products were identified by comparison with literature data^[4–9, 14] and/or with those of authentic samples. New compounds were characterized by 1D and 2D ¹H/¹³C NMR spectroscopy, high-resolution mass spectrometry, and elemental analysis.^[17]

The [Pd₂(dba)₃]/RR'POH precatalysts are capable of catalyzing the cross-coupling reactions of aryl chlorides and arylboronic acids to yield the desired biaryls in high yields (Table 1, entries 1–6). Entries 4–6 illustrate that the electron-rich 4-chloroanisole could be coupled with arylboronic acids quantitatively. Entries 2 and 3 demonstrate that the more sterically demanding and electron-rich substrate 2-chloroanisole was coupled with 4-methylphenylboronic acid (Table 1, entry 2) and phenylboronic acid (Table 1, entry 3). The [Ni(cod)₂]/RR'POH precatalyst can be employed to mediate Kumada cross-coupling reactions of aryl chlorides and RMgX at room temperature (Table 1, entries 7 and 8). The electron-rich aryl chloride is tolerated by the present system as demonstrated by 4-chloroanisole (Table 1, entry 7). Entries 9–12 reveal that the present catalysts are also effective in the C–N bond cross-coupling reactions of aryl chlorides with a variety of amines. Entries 9, 10, and 12 illustrate aminations of aryl chlorides and alkylamines. Entry 11 shows that an aryl chloride/arylamine cross-coupling reaction produces a diarylamine. Also noteworthy are the successful catalytic activities on C–S bond-forming processes of unactivated aryl chlorides. The present air-stable phosphine oxides are capable of forming precatalysts with Pd(OAc)₂ or [Pd₂(dba)₃] to efficiently catalyze cross-coupling reactions of aryl chlorides and alkylthiols to yield novel thioethers (Table 1, entry 13). In the case of aryl bromides as substrates, the present phosphinous acids can be employed as ligands for the efficient C–S bond formations at room temperature (Table 1, entry 14).

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Table 1. Transition metal/phosphinous acid catalyzed cross-couplings of aryl chlorides with Ar-B(OH)₂, RMgX, RNH₂, and RSH compounds.^[a]

Entry	Halide	Coupling partner	Base	Temp [°C]	Time [h]	Product	Yield [%] (isolated)
1			CsCO ₃	100	12		88 ^[b]
2			CsF	100	12		83 ^[b]
3			CsF	100	12		91 ^[c]
4			CsF	100	12		97 ^[b]
5			CsF	100	12		99 ^[c]
6			CsF	100	12		99 ^[b,d]
7			none	RT	12		93 ^[e]
8			none	RT	12		96 ^[e]
9			NaOtBu	100	12		51 ^[b]
10			NaOtBu	100	12		61 ^[b]
11			NaOtBu	100	12		44 ^[b]
12			NaOtBu	100	12		67 ^[b]
13			NaOtBu	100	24		26 ^[f]
14			NaOtBu	RT	24		49 ^[f]

[a] General reaction conditions (not optimized): aryl halide (1.0 equiv), boronic acid (or RMgX, RNH₂, RSH) (1–1.5 equiv), CsF (or NaOtBu) (1.0–3.0 equiv), [Pd₂(dba)₃] (0.5–2.5 mol %; dba = *trans,trans*-dibenzylideneacetone), 1.0–5.0 mol % ligand. [b] [Pd₂(dba)₃]/(*t*Bu)₂P(O)H as precatalyst. [c] [Pd₂(dba)₃]/(*t*Bu)₂PCl/H₂O as precatalyst. [d] [Pd₂(dba)₃]/(*t*Bu)₂P(O)H or [Pd₂(dba)₃]/(2,4-(OMe)₂C₆H₃)₂P(O)H as precatalyst. [e] [Ni(cod)₂]/(*t*Bu)₂P(O)H as precatalyst. [f] [Pd₂(dba)₃]/(*t*Bu)₂PCl/H₂O as precatalyst.

Several features of these phosphinous acid ligands are noteworthy and provide both informative parallels and contrasts to the corresponding phosphane ligands^[5, 8, 9, 14] in the cross-coupling reactions of aryl chlorides. Air-stable phosphine oxides (RR'P(O)H) can be employed in the present process as ligand precursors to produce electron-rich phosphane-containing anionic complexes in the presence of

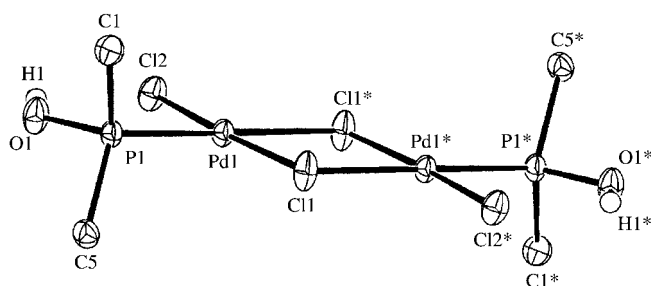
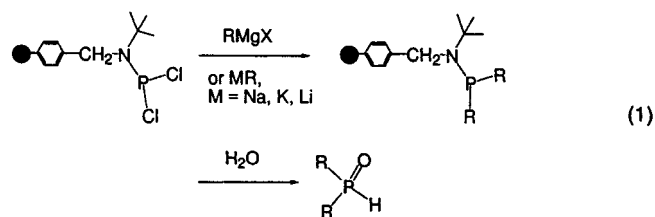
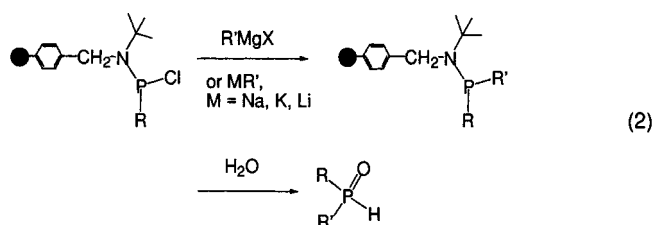


Figure 1. Structure of the dichloro(di-*tert*-butylphosphinous acid)palladium(II) dimer (ORTEP view; 50% probability). The 12 methyl groups are omitted for clarity. Selected interatomic distances [Å] and angles [°]: Pd1–P1 2.2434(6), Pd1–Cl2 2.2917(6), Pd1–Cl1 2.3188(6), Pd1–Cl1* 2.4500(6), Cl1–Pd1* 2.4500(6), P1–O1 1.5922(17); P1–Pd1–Cl2 90.36(2), P1–Pd1–Cl1 95.39(2), Cl2–Pd1–Cl1 174.23(2), P1–Pd1–Cl1* 179.109(19), Cl2–Pd1–Cl1* 88.76(2), Cl1–Pd1–Cl1* 85.48(2), Pd1–Cl1–Pd1 94.52(2), O1–P1–C5 100.47(10), O1–P1–Cl1 102.65(10), C5–P1–Cl1 116.54(10), O1–P1–Pd1 111.10(7).

bases. We found that [Pd(cod)Cl₂] reacts smoothly with phosphine oxides (RR'P(O)H), in dioxane solution, affording a new binuclear derivative shown in Scheme 1. Well-characterized examples of this type of Pd^{II} complex are extremely rare.^[12] Complex **I** was isolated and characterized by X-ray crystallography (see Supporting Information) and the structure is shown in Figure 1. As expected, the core structure of complex **I** is based on P–Pd coordination with phosphinous acid ligands (RR'POH). Important features of the structure of **I** include the O1–P1 and P1–Pd1 bond lengths of 1.5922 and 2.2434(6) Å, respectively. The O1–P1 distance is about 0.105 Å longer than the P=O double bond length in RRP(O)H and to a first approximation can be interpreted as a O–P single bond. Also noteworthy is the facile preparation of these air-stable phosphine oxide ligand precursors which can be generated as libraries by using polymer-supported synthesis [Eqs. (1) and (2)].^[10, 11]





In conclusion, these results demonstrate that air-stable phosphine oxides ($RR'P(O)H$) are ideal ligand precursors for the formation of phosphinous acid ($RR'POH$)–metal complexes for the rapid and regioselective oxidative addition of unactivated aryl chlorides in the presence of bases, and that such processes can be incorporated into efficient catalytic cycles for a variety of C–C, C–N, and C–S bond-forming processes. Noteworthy are the efficiency for unactivated aryl chlorides, as well as the simplicity, low cost, air-stability, and ready accessibility by using polymer-supported synthesis of these ligand precursors.

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434.2 Hz)) in 1,4-dioxane (6.0 mL) at room temperature for 6 h generated a brown mixture exhibiting a ^1H -coupled ^{31}P NMR resonance at $\delta = 123.4$ (singlet).

- [17] See Supporting Information for full synthetic details and characterization of new compounds. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157421. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

A Novel and Highly Stereoselective Intramolecular Formal [3+3] Cycloaddition Reaction of Vinylogous Amides Tethered with α,β -Unsaturated Aldehydes: A Formal Total Synthesis of (+)-Gephyrotoxin**

Lin-Li Wei, Richard P. Hsung,* Heather M. Sklenicka, and Aleksey I. Gerasyuto

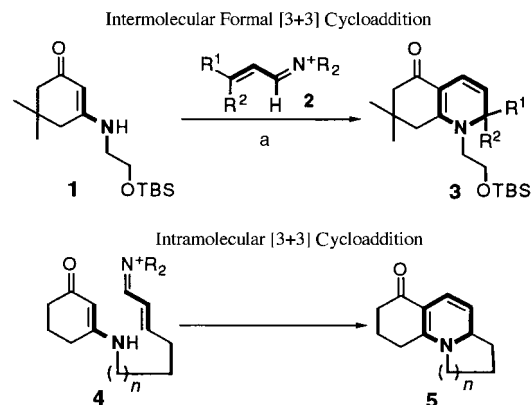
We have been exploring reactions of β -diketo equivalents **1** with α,β -unsaturated iminium salts **2** for the construction of heterocycles such as **3** (Scheme 1).^[1–3] These reactions involve a sequence consisting of a Knoevenagel condensation followed by a six π -electron electrocyclic ring-closure,^[4] thereby constituting a stepwise formal [3+3] cycloaddition^[5–7] in which two σ bonds are formed, along with a new stereocenter

adjacent to the heteroatom. This cycloaddition protocol can be classified as a sequential anionic–pericyclic strategy for which the significance in natural product synthesis has been elegantly summarized by Tietze and Beifuss.^[8] Our recent work on the use of vinylogous amides in this formal cycloaddition^[1] has allowed us to envision an intramolecular version of this reaction. Since the vinylogous amide **1**, which contains a functionalized tether, provided the formal cycloadduct **3** in good yields,^[1] it is conceivable that the vinylogous amides **4**, which are tethered with an α,β -unsaturated iminium ion, may lead to piperidinyl heterocycles **5**, attractive as intermediates in the syntheses of natural alkaloids (Scheme 1). We report herein the first stereoselective intramolecular formal [3+3] cycloaddition reaction by using vinylogous amides that are tethered with iminium ions, and its application in a formal total synthesis of (+)-gephyrotoxin.^[9–11]

Based on our previous studies, the formation of the α,β -unsaturated iminium salt prior to the addition of a β -diketo nucleophile is crucial to the regio- and chemoselectivity of the intermolecular formal cycloaddition reaction.^[1, 2a] Conditions and protocols that generate α,β -unsaturated iminium salts in the presence of the β -diketo nucleophile lead to low yields of the desired products, and/or to synthetically less useful by-products resulting from various competing reaction pathways.^[7b–e] However, the enal precursor to α,β -unsaturated iminium ions in the intramolecular variant also contains a vinylogous amide. Thus, controlling the extent of iminium ion formation before competing reactions take place is a major challenge.

To demonstrate the feasibility of an intramolecular formal [3+3] cycloaddition, the vinylogous amides **6** and **7** were prepared^[12, 13] and treated with piperidine (2.0 equiv) and Ac_2O (2.0 equiv) in EtOAc/toluene (1:2; concentration of vinylogous amides: 0.03–0.30 M) at 85 °C for 1 h (Scheme 2). These are the standard reaction conditions that have been consistently employed for the formation of iminium salts.^[1, 2] Subsequent heating at 150 °C in a sealed tube led to the isolation of the desired heterocycles **8** and **9** in yields of 80 and 68 %, respectively. Furthermore, the chiral vinylogous amide **10**^[12] led to the desired tricycle **11** in 55 % yield as a single diastereomer under the same reaction conditions. The stereochemistry of **11** was assigned by NOESY experiments.

These examples suggest that our initial concern regarding the extent of iminium salt formation was not necessary; under conditions that do not promote the formation of iminium ions, these reactions were essentially arrested. This control study suggests that even a low concentration of the iminium species is sufficient to promote this intramolecular formal [3+3] cycloaddition reaction. On the other hand, under the same standard reaction conditions, the vinylogous amide **12** did not provide the desired cycloadduct **13** in useful yields (Scheme 2). We were, however, able to observe the formation of **13** by ^1H NMR spectroscopy; thus our inability to isolate **13** from **12** may be a result of the instability of **13** under the reaction conditions and/or under the work-up conditions. This prompted us to explore other protocols suitable for generating iminium salts.



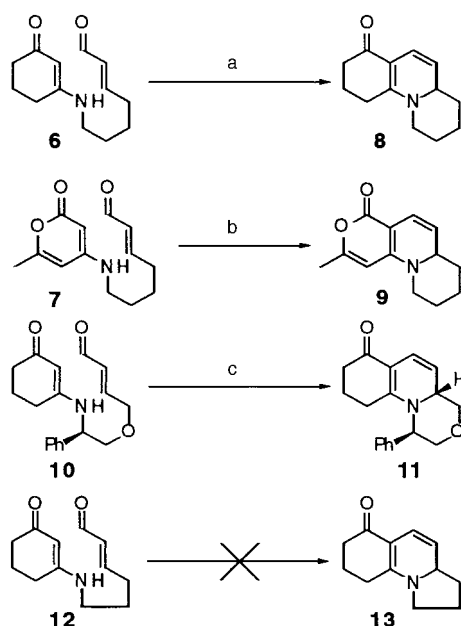
Scheme 1. [3+3] Cycloaddition reactions of vinylogous amides and α,β -unsaturated iminium salts. Reagents and conditions: a) EtOAc/toluene 1:2, 150 °C, 15–30 h, 76–80 %; TBS = *tert*-butyldimethylsilyl.

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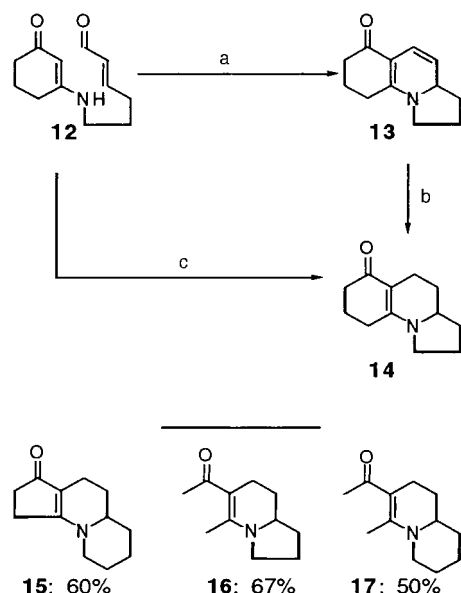
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Scheme 2. Intramolecular [3+3] cycloaddition reaction to give piperidinyll heterocycles. Reagents and conditions: a) 1) piperidine, Ac_2O , EtOAc/toluene 1:2, 85 °C, 1 h, 2) 150 °C, 3 h, 80 % over two steps; b) 1) piperidine, Ac_2O , EtOAc/toluene 1:2, 85 °C, 1 h, 2) 150 °C, 3 h, 68 % over two steps; c) 1) piperidine, Ac_2O , EtOAc/toluene 1:2, 85 °C, 1 h, 2) 150 °C, 23 h, 55 % over two steps ($\geq 95:5$).

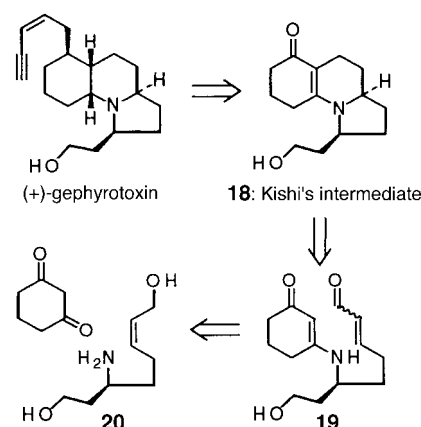
After extensive screening, the desired cycloadduct **13** was isolated in 71 % yield after **12** was heated at 90–110 °C for 1–2 h in the presence of 0.5–1.0 equivalents of piperidinium acetate salt^[14] (Scheme 3). Under these conditions, the reaction proceeded more quickly, and the product was purified by column chromatography. Compound **13** was less stable than anticipated, but to improve its stability, **13** was hydrogenated to give the tricyclic heterocycle **14** in 70 % yield.



Scheme 3. Optimized intramolecular [3+3] cycloaddition reactions. Reagents and conditions: a) EtOAc, Na_2SO_4 , piperidinium acetate (0.5–1 equiv), 90–110 °C, 1–2 h, 71 %; b) 5 % Pd/C, H_2 , EtOAc, 70 %; c) EtOAc, Na_2SO_4 , piperidinium acetate (0.1 equiv), 80 °C, 1–2 h, then 5 % Pd/C, H_2 , 65 %.

This two-step sequence was further optimized by decreasing the amount of piperidinium salt to 0.1 equivalents and decreasing the temperature to 80 °C. Most significantly, the crude reaction mixture was directly submitted to standard hydrogenation conditions, thereby avoiding the isolation of the sensitive heterocycle **13**. This one-pot protocol provided **14** in 65 % yield from **12**. This new reaction protocol was general for the successful examples described in Scheme 2 and, more significantly, worked well in the syntheses of **15–17** (Scheme 3), which were difficult to prepare under the standard conditions. Successful preparations of **16** and **17** allowed us to design syntheses of natural products from the indolizidine and quinolizidine families.^[15]

Access to the tricyclic heterocycle **14** from **12** provides an efficient entry to the tricyclic frame of gephyrotoxin.^[9] Of the three known total syntheses of (±)-gephyrotoxin,^[10] the synthesis reported by Kishi and co-workers involved the intermediate **18** (Scheme 4).^[10a] The only enantioselective

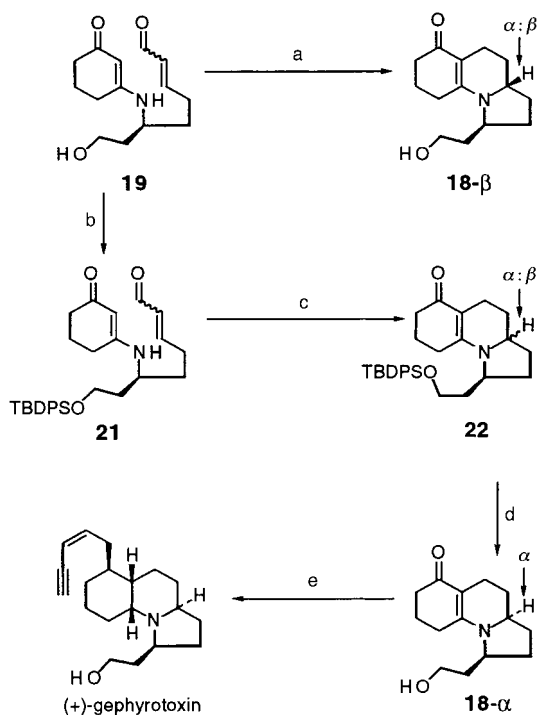


Scheme 4. Retrosynthetic analysis of gephyrotoxin.

synthesis of (+)-gephyrotoxin, which was reported by Kishi and Fujimoto, utilized the optically active **18**, which was prepared in 18 steps.^[11] We envisioned an opportunity to intercept Kishi's intermediate **18** by using our stereoselective intramolecular formal [3+3] cycloaddition reaction of the chiral vinylogous amide **19**. Compound **19** was obtained by condensation of the chiral amino diol **20**^[12] with 1,3-cyclohexanedione.

Subjecting the vinylogous amide **19** to very similar conditions to those described in Scheme 3 led to the tricyclic compound **18** in 50 % yield overall (Scheme 5). The diastereomeric ratio was very high ($\geq 93:7$) and the major isomer was assigned as **18-β** ($[\alpha]_D^{20} = -51^\circ$) by using NOESY experiments. However, **18** did not exhibit the same ^1H NMR spectroscopic or optical rotation properties as Kishi's intermediate^[11]. We speculated that the unprotected primary alcohol could play a role in controlling the conformation of **19** through hydrogen bonding with the nitrogen atom. This interaction could distort the conformation of the transition state, thus leading to the observed but undesired stereochemical outcome of the reaction.

To verify this notion, we explored a range of different silyl protecting groups and found that the reaction of *tert*-



Scheme 5. Synthesis of gephyrotoxin precursor **18**. Reagents and conditions: a) EtOAc/EtOH, Na₂SO₄, piperidinium acetate (0.5–1 equiv), 100 °C, 1–2 h, then 5% Pd/C, H₂, 50% ([α]_D²⁰ = –51°, α/β ≤ 7:93); b) TBDPSCl, imidazole; c) toluene/EtOH, Na₂SO₄, piperidinium acetate (1.0 equiv), 150 °C, 1–2 h, then 5% Pd/C, H₂, 60% from **19**, (α/β 60:40–41:59); d) 1) TBAF, CH₂Cl₂, 0 °C, 80%, 2) separation; e) Kishi's route, 11 steps.

butyldiphenylsilyl (TBDPS)-protected **21** provided the best ratio for **22-α/22-β**, which ranged from 60:40 to 41:59. The TBDPS group in **22** was removed by using tetrabutylammonium fluoride (TBAF) in CH₂Cl₂ at 0 °C, leading to a mixture of isomers **18-α** and **18-β** in 80% yield with the same ratio. Subsequent chromatographic separation of the two isomers on silica gel led to the isolation of the tricyclic compound **18-α**, which matched Kishi's intermediate. Although the stereoselectivity in the formal [3+3] cycloaddition reaction should be improved to pursue a potential total synthesis of gephyrotoxin, the overall sequence to Kishi's intermediate is short, and demonstrates the synthetic potential of this intramolecular formal [3+3] cycloaddition reaction in the synthesis of natural products.

We have described herein a unique intramolecular formal [3+3] cycloaddition reaction that uses vinylogous amides tethered with an enal functional group to give complex piperidinyl heterocycles. For example, the method has been applied to a formal total synthesis of (+)-gephyrotoxin.

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NaV₃(OH)₆(SO₄)₂: A Kagomé-Type Vanadium(III) Compound with Strong Intralayer Ferromagnetic Interactions**

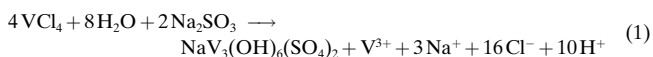
Daniel Grohol, Dimitris Papoutsakis, and Daniel G. Nocera*

Extended vanadium compounds typically exhibit an anti-ferromagnetic spin ordering among d¹ or mixed-valence d⁰/d¹ centers. In these systems, spins interact through superexchange pathways comprising neighboring vanadium subunits linked by atoms or groups. The majority of these materials are composed of layered networks of interconnected square pyramids, which result from the termination of the *z* axis of the vanadium coordination sphere by a strong axial ligand (usually oxo of vanadyl).^[1–5] The occurrence of ferromagnetic coupling in layered vanadium compounds is rare. Only vestiges of ferromagnetism have been observed in layers composed of square-pyramidal d¹ or mixed-valence d⁰/d¹ vanadium centers.^[5–8] For the d² electron count, ferromagnetic interactions have been observed, but they usually arise from the secondary effect of canted, antiferromagnetically aligned spins.^[9–11] Primary ferromagnetic interactions are implicated in short-range pairwise interactions between V^{III} centers of various binuclear compounds.^[12–15] However, we are not aware of primary ferromagnetic interactions between V^{III} centers in an extended layered material. Owing to our interest in developing the magnetism of layered vanadium compounds, we turned our attention to utilizing the lattice of the jarosite mineral (AFe₃(OH)₆(SO₄)₂, A is usually a monovalent cation)^[16] to stabilize d² vanadium centers in a layered environment. We now report a new hydrothermal synthesis that has enabled us to prepare and to structurally characterize a stoichiometrically pure jarosite-type compound of vanadium(III), NaV₃(OH)₆(SO₄)₂. Preliminary magnetic measurements reveal the unprecedented circumstance of strong ferromagnetic coupling between vanadium ions in a layered architecture.

Jarosite-type materials are notoriously difficult to prepare in pure form. Synthetic methods have relied on the precipitation of jarosite from hydrolyzed acidic solutions of sulfate anions and monovalent and trivalent cations.^[17] The monovalent cations are often replaced by hydronium ions and the coverage of the trivalent sites is incomplete (83–95% occupation).^[18, 19] Owing to these site defects, the magnetic behavior of jarosites has historically been sample dependent.^[18] With the goal of acquiring reproducible and self-consistent magnetic measurements, we sought to develop new synthetic methods that would reliably afford complete lattice coverage in jarosite-type compounds. Our approach focuses

on assembling the jarosite framework by hydrothermal oxidation–reduction methods.

The vanadium congener of jarosite, NaV₃(OH)₆(SO₄)₂, has been prepared according to Equation (1).



Reduction of V^{IV} with sulfite under acidic conditions (pH ~ 1.5) affords the title compound, which is obtained stoichiometrically pure and in single crystalline form. This redox method allows us to minimize site defects by selective reduction of the vanadium starting compound to the +3 oxidation state. Also, in contradistinction to nonredox precipitation methods, the introduction of a redox step prior to precipitation allows the crystallization of the material to be more easily controlled.

NaV₃(OH)₆(SO₄)₂ crystallizes in the rhombohedral space group *R*3̄*m*.^[20] A crystallographically unique V^{III} ion resides in a distorted octahedron, composed of four equatorial oxygen atoms (O3) from the bridging hydroxy groups and of two axial oxygen atoms (O2) from the capping sulfate groups (Figure 1, top). The vanadium pseudooctahedron is tetragonally elongated along its *z* axis. The bridging hydroxy groups connect V^{III} ions with a V–O3–V angle of 132.6(2)° to form a triangular *μ*-hydroxy trimer capped by the sulfate anion, which assumes an almost ideal tetrahedral geometry. A residual electron

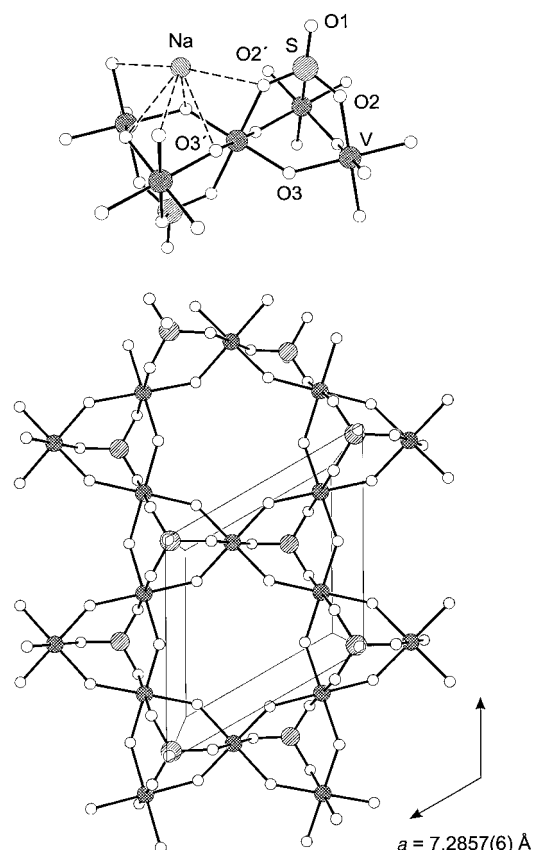


Figure 1. The X-ray crystal structure of a layer segment of NaV₃(OH)₆(SO₄)₂. The magnetic subunit of a triangular *μ*-hydroxyvanadium trimer, capped by a sulfate anion, is shown at the top of the figure. Selected bond lengths [Å] and angles [°]: V–O2 2.054(4), V–O3 1.989(2), S–O1 1.461(8), S–O2 1.476(5); O2–V–O3 92.5(1), O3–V–O3' 90.9(3).

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peak of 0.63 eÅ^{-3} at a distance of 0.89 Å from O3 indicates the presence of a hydrogen atom from the μ -hydroxy group; neutron diffraction studies confirm its location.^[21] The vanadium trimers are linked at their corners to form a Kagomé lattice^[19] in a two-dimensional hexagonal network (Figure 1, bottom). The sulfate capping groups alternately point up and down about the hexagonal network. The Kagomé layers are separated by a crystallographically unique sodium atom (d spacing $5.617(1) \text{ Å}$), which resides in the interlayer space with the same x, y coordinates as the sulfur atom. Six sulfate oxygen atoms ($d_{\text{Na-O2}} = 2.949(5) \text{ Å}$) and six hydroxy oxygen atoms ($d_{\text{Na-O3}} = 2.756(4) \text{ Å}$) surround each sodium ion.

Figure 2 shows temperature-dependent magnetic susceptibilities for $\text{NaV}_3(\text{OH})_6(\text{SO}_4)_2$ at varying applied field strengths. At 0.5 kOe , M/H increases upon cooling to a sharp

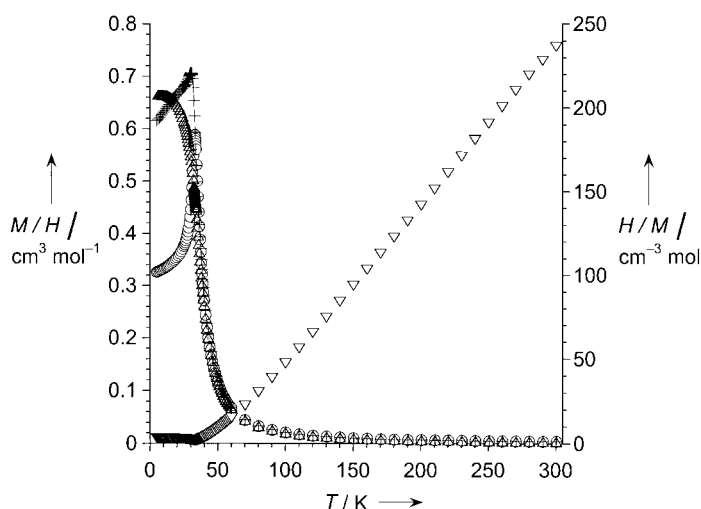


Figure 2. Temperature dependence of M/H per mole of vanadium atoms for $\text{NaV}_3(\text{OH})_6(\text{SO}_4)_2$ at applied magnetic field strengths of 0.5 ($\circ$), 5.0 ($+$), and 10.0 ($\triangle$) kOe . The H/M versus T plot (∇) was measured at an applied field of 0.5 kOe .

maximum at $T_N = 33.3 \text{ K}$, followed by a downturn. At a field strength of 10 kOe , M/H increases monotonically with decreasing temperature. The M/H curve exhibits intermediate behavior when measurements are performed in an external field of 5 kOe ; a blunt maximum is observed in the curve at 30.3 K . Plots of H/M versus T (150 – 300 K) yield a Weiss constant of $+53(2) \text{ K}$ for the three applied fields. This large and positive value indicates appreciable intralayer ferromagnetic interactions between neighboring V^{III} centers.

The field-dependence observed in Figure 2 is ascribed to strong intralayer ferromagnetic interactions and weak, field-dependent interlayer interactions. This behavior is characteristic of metamagnetism,^[22–24] which more commonly prevails for layered halides and hydroxides of divalent ions.^[25] We propose that a dominant ferromagnetic exchange interaction propagates about the magnetic sites of the triangular Kagomé lattice through the bridging hydroxy groups. In weak fields, the layers couple antiferromagnetically at $T < T_N$. As the applied field is increased, this weak antiferromagnetic coupling of spins between neighboring layers is overwhelmed, leading to the eradication of T_N .

The occurrence of ferromagnetic Kagomé layers is unusual and at variance with the antiferromagnetic exchange observed for jarosite and its derivatives.^[18, 26–29] Inasmuch as the V^{III} jarosite is isostructural with the Cr^{III} and Fe^{III} analogues, the ferromagnetism of $\text{NaV}_3(\text{OH})_6(\text{SO}_4)_2$ likely arises from the d^2 electron count of the V^{III} centers. Two electrons in an axially elongated octahedron will reside in d_{xz} and d_{yz} orbitals. Orbital symmetry models for superexchange^[30, 31] suggest the intra-layer ferromagnetism to arise from coupling along a pathway involving metal d - π and hydroxy p orbitals. Current studies are aimed at acquiring a more detailed understanding of the magnetic properties of $\text{NaV}_3(\text{OH})_6(\text{SO}_4)_2$ and its related alkali metal derivatives.

Experimental Section

A 2.0 M solution of VOCl_2 in 4.0 M HCl was prepared by the dropwise addition of VCl_4 (5.3 mL ; Aldrich) to a small amount of ice-cold water while stirring, and diluting to 25 mL . A 2.0 mL aliquot of this solution (4 mmol of VOCl_2) was transferred into the Teflon container of a 23 mL Parr pressure bomb. In a separate beaker, Na_2SO_3 (0.227 g , 1.8 mmol), NaOH (0.20 g , 5.0 mmol), and NaCl (0.117 g , 2.0 mmol) were dissolved in distilled water (8 mL). This mixture was slowly added to the Teflon container containing the VOCl_2 solution. The bomb was enclosed and placed into an oven at 202°C and the mixture was allowed to react for three days. The oven was subsequently cooled to room temperature at a $0.1^\circ\text{C min}^{-1}$ rate. Small, dark red crystals were filtered washed, and dried in air (yield 22%). Elemental analysis for $\text{NaV}_3(\text{OH})_6(\text{SO}_4)_2$: calcd: H 1.28 , Na 4.89 , V 32.51 , S 13.64 ; found: H 1.32 , Na 5.06 , V 32.85 , S 13.88 .

Magnetic susceptibility measurements were performed on powder specimens on a SQUID magnetometer (Quantum Design MPMSR2). The temperature dependence of the magnetization M was acquired in external fields of 0.5 , 5.0 , and 10.0 kOe . At low field strength, M varies linearly with the field H , and M/H represents the magnetic susceptibility of the material. As expected for materials exhibiting strong ferromagnetic interactions,^[32] M/H does not represent the actual susceptibility at high fields owing to the nonlinearity of magnetization with field strength.

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Neutral Cyclooctasulfur as a Polydentate Ligand: Supramolecular Structures of $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]_n(\text{S}_8)_m$ ($n:m = 1:1, 3:2$)*

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It is not unreasonable to suppose that the S_8 molecule, with two lone pairs of electrons on each atom, would be able to function as a Lewis base—even as a multidentate Lewis base. And yet, no structurally characterized example of coordination of the cyclooctasulfur ligand to a transition metal

complex is reported. There are several cases in which S_8 rings cocrystallize with other molecules, not covalently bound but merely packed into the crystal. These solid inclusion compounds with transition metal complexes are: $[\text{Cu}(\text{C}_{12}\text{H}_8\text{N}_2)_2]\text{I} \cdot \text{S}_8$,^[1a] $[\text{WCl}_4\text{S}] \cdot \text{S}_8$,^[1b] and $[\text{WCl}_4\text{S}(\text{thf})] \cdot \text{S}_8$,^[1c] $[\text{Co}_6(\mu\text{-S})_8(\text{CO})_6] \cdot 3\text{S}_8$,^[1d] $[\text{Cu}_4(\text{S}_5)_2(\text{C}_5\text{H}_5\text{N})_4] \cdot \text{S}_8$,^[1e] $[\text{Pt}_2\text{X}(\text{5-mpyt})_4]_2(\mu\text{-S}_4)$,^[1f] 0.5S_8 ($\text{X} = \text{Cl}, \text{Br}$; 5-mpyt = 5-methylpyridine-2-thiolate),^[1f] $[\text{M}(\text{TMTAA})_2] \cdot \text{S}_8$ ($\text{M} = \text{Cu}, \text{Ni}$; TMTAA = 5,7,12,14-tetramethyldibenzo[*b,i*]-1,4,8,11-tetraaza[14]annulenate),^[1g] $[\text{Na}[15]\text{crown-5}]_2[(\text{TaSCl}_4)_2\text{dioxane}] \cdot \text{S}_8$.^[1h]

What may well be a compound with a covalently bound S_8 molecule, $[\text{Re}_2\text{X}_2(\text{CO})_6(\text{S}_8)]$ ($\text{X} = \text{Br}, \text{I}$), was reported by W. Baratta and F. Calderazzo,^[2] but a crystal structure was not obtained. A few years later they were able to isolate the $[\text{Re}_2\text{I}_2(\text{CO})_6(\text{Se}_7)]$ complex^[3] and to show by X-ray crystallography that it contains an $\eta^2\text{-}\mu_2\text{-Se}_7$ ring. They suggested that $[\text{Re}_2\text{X}_2(\text{CO})_6(\text{S}_8)]$ may have a similar dinuclear structure with bridging halides and an η^2 -coordinated cyclooctasulfur unit. In addition, the S_8 molecule is known^[4] to coordinate to the d^{10} silver(I) ion in $[\text{Ag}(\text{S}_8)_2](\text{AsF}_6)$. As far as we know there is no other literature dealing with compounds of transition metals that contain neutral S_8 molecules as ligands. However, elemental sulfur is clearly a candidate (along with H_2 and halogens) to add coordinatively to transition metal centers, possibly as a preliminary step to the completion of an oxidative-addition process. As we have already successfully isolated and characterized a remarkable adduct of molecular diiodine with a powerful bidentate Lewis acid, dirhodium(II) tetra(trifluoroacetate), in the form of the one-dimensional (1D) chain complex $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4 \cdot \text{I}_2]_\infty$,^[5] we decided to extend that approach to elemental sulfur.

The preparation of products and growth of X-ray quality crystals have been achieved by using a solventless technique^[6] based on a sublimation–deposition procedure, in which volatile dirhodium(II) tetra(trifluoroacetate) was employed in the presence of vapors of elemental sulfur. For the latter, the thermodynamically stable form in the vapor phase at the temperatures employed is known to be S_8 molecules.^[7] Working with different ratios of Rh_2 to S_8 in the initial mixtures (from equimolar quantities to lower concentrations of S_8) we have successfully isolated two sulfur adducts of $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]$. The stoichiometries of the two products $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]_n(\text{S}_8)_m$ have been found by chemical analyses to be $n:m = 1:1$ for **1** and $n:m = 3:2$ for **2**. The new coordination compounds are relatively stable under moderate conditions, insoluble in organic solvents at room temperature, destroyed by coordinating solvents, and slowly decomposed even by noncoordinating dichloromethane to release elemental sulfur. Products **1** and **2** have been examined by X-ray crystallography.

The structure of **1** consists^[8] of dirhodium(II) tetra(trifluoroacetate) units with the eight-membered S_8 cycles 1,3-attached to their axial positions to form a zigzag 1D chain (Figure 1). Each rhodium atom of the Rh_2 unit coordinates to one sulfur atom of an S_8 molecule; the two Rh–S distances at the ends of the dimetal unit are similar, 2.516(1) and 2.578(1) Å.

The structure of **2** is particularly interesting^[9] as each S_8 molecule is 1,3,6-coordinated to three dirhodium complexes, while each Rh_2 unit binds to two different octasulfur rings.

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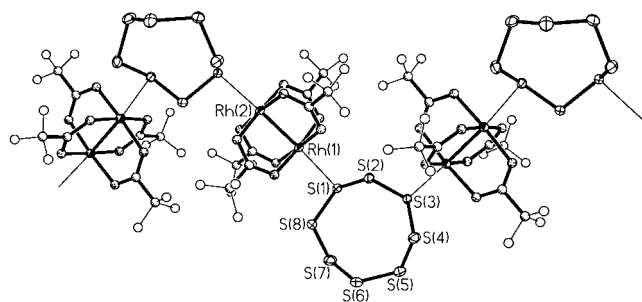


Figure 1. A fragment showing the alternating arrangement of $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]$ and coordinated cyclooctasulfur molecules in the polymeric chain of **1**. Only rhodium and sulfur atoms are labeled for clarity. Only one orientation of each disordered CF_3 groups is depicted. The S–S bond lengths (starting from S(1), clockwise): 2.046(2), 2.067(2), 2.063(2), 2.038(2), 2.041(2), 2.047(2), 2.039(2), 2.079(2) Å.

This results in a novel, pseudo-2D architecture consisting of the octagon units (4 Rh_2 and 4 S_8 blocks, Figure 2) forming a ribbon-type extended structure (Figure 3). Alternatively, the structure of **2** can be considered as built of two polymeric chains of the monoadduct **1** stapled together by an additional $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]$ molecule lying between each pair of facing S_8 rings, which brings the total composition to an $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4] : \text{S}_8$ ratio of 3:2. There is a much greater

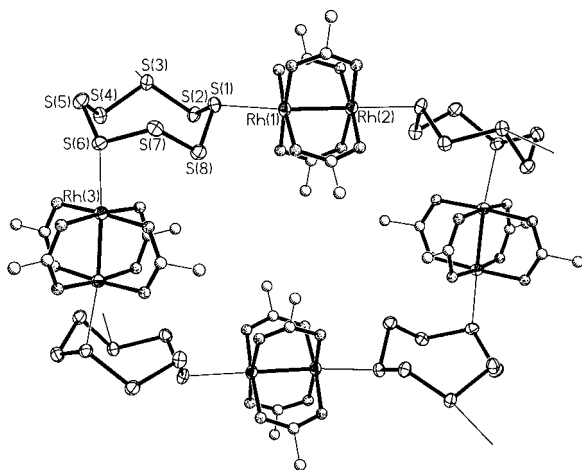


Figure 2. The elemental octagon unit built of $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]$ and S_8 rings in the crystal structure of **2**. Only crystallographically independent rhodium and sulfur atoms are labeled. Fluorine atoms of CF_3 groups are omitted for clarity. The S–S bond lengths (starting from S(1), anticlockwise): 2.054(8), 2.034(8), 2.072(8), 2.035(9), 2.058(8), 2.061(9), 2.041(9), 2.072(8) Å.

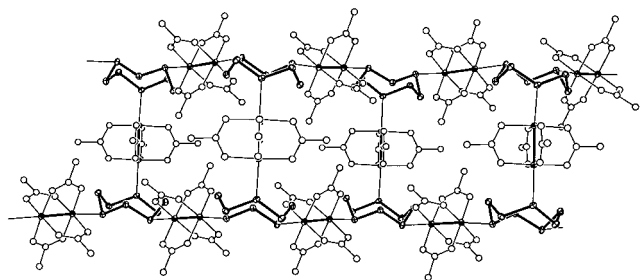


Figure 3. The pseudo-2D ribbon-type structure of **2**. Two infinite chains of $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4(\text{S}_8)]_\infty$ (**1**) are further connected by additional dirhodium tetra(trifluoroacetate) molecules. Atom labels are omitted for clarity. Fluorine atoms of CF_3 groups are also omitted.

variation in the Rh–S contacts in this structure, with one relatively short distance of 2.484(6) versus two longer ones, 2.507(6) and 2.567(6) Å. The average Rh–S distance of 2.547(1) in **1** is slightly longer than that in **2** (2.519(6) Å). The Rh–Rh–S angles are close to linear, averaging to 176.63(4)° in **1** and 174.6(2)° in **2**.

About each coordinated sulfur atom, in both **1** and **2**, there is a trigonal-pyramidal conformation with angles spanning the range 102–113°, which reflects a stereochemical activity of the lone electron pair. As far as the S_8 moiety as a whole is concerned, it retains its crown conformation in both **1** and **2**. The mean values for the S–S distances and S–S–S valence angles in the sulfur molecule are nearly identical in both adducts: 2.053(2) Å and 107.1(1)° in **1**, and 2.053(8) Å and 107.2(4)° in **2**, respectively. These data for the coordinated cyclo- S_8 ligands are in good agreement with the mean values for the S–S bond lengths (2.046(3) Å) and the S–S–S bond angles (108.2(6)°) reported for elemental orthorhombic sulfur.^[10] At the same time, the coordination of neutral sulfur atoms to rhodium centers of $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]$ is relatively strong: the $\text{Rh}^{2+} - \text{S}^0$ distances in **1** and **2** are identical to the $\text{Rh}^{2+} - \text{S}^{2-}$ bonds found^[11] for axial binding of doubly coordinated S atoms in dialkylsulfides by dirhodium(II) tetracarboxylates.

There are no significant contacts in **1** and **2** between sulfur atoms and carboxylate oxygen atoms (all longer than 3.2 Å). However, in the structure of **2** there are some long solid-state interactions between sulfur atoms of neighboring S_8 molecules; the shortest ones are 3.49 and 3.61 Å, which are comparable with the van der Waals radius sum estimate.^[12]

Reactions involving elemental sulfur typically proceed with the cleavage of one or more S–S bonds. We have succeeded in the isolation and characterization of the first transition metal complexes with coordinated neutral cyclooctasulfur moieties. The employment of a two-ended Lewis acid, $[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]$, and a potentially multidentate eight-membered sulfur Lewis base as structural units has resulted in the formation of novel extended supramolecular structures. What is more interesting is the fact that the S_8 rings function as bidentate and tridentate donor bridges thus allowing the formation of 1D and 2D architectures.

Cyclic S_8 molecules are known^[13] to be involved in thermal conversion reactions consisting of ring opening or dissociation followed by the formation of smaller intermediate species S_x ($x < 8$). It seems likely that these pathways can be dominant at temperatures much higher than those employed here for the preparation of **1** and **2**. We are interested in continuing this study, as we believe that there may exist more such adducts than have yet been detected, and that dirhodium tetra(trifluoroacetate) as a powerful acceptor and a thermally stable unit can be used to trap these reactive sulfur intermediates. Work is also in progress to extend this study to elemental selenium and phosphorus as well as to other metal trifluoroacetates.

Experimental Section

All experimental manipulations were carried out under dry, oxygen-free argon by employing Schlenk techniques. The unligated form of

[Rh₂(O₂CCF₃)₄] was obtained using a literature procedure.^[14] Sulfur powder, 99.98%, was purchased from Aldrich. The IR spectra were recorded on a Perkin-Elmer 16PC FT-IR spectrophotometer using KBr pellets. Elemental analysis was done by Canadian Microanalytical Services, Ltd.

1: [Rh₂(O₂CCF₃)₄] (0.066 g, 0.10 mmol) was mixed with sulfur powder (0.026 g, 0.10 mmol based on the S₈). The mixture was sealed in an evacuated Pyrex tube and the tube was placed in a furnace at 140 °C. The tube was kept at that temperature for about a week, and then slowly (over 24 h) cooled to room temperature. Several dozen dark violet crystals of **1** deposited in the “cold” zone of the tube, where the temperature was about 5 °C lower. Elemental analysis (%) calcd for S₈C₈F₁₂O₈Rh₂: C 10.51, S 28.00; found: C 10.35, S 28.35; IR (KBr): $\tilde{\nu}$ = 1650.0(s), 1244.6(m), 1192.5(s), 1169.5(s), 861.7(m), 804.1(w), 784.4(w) 739.8(m) cm⁻¹.

2: [Rh₂(O₂CCF₃)₄] (0.066 g, 0.10 mmol) was mixed with elemental sulfur (0.016 g, 0.063 mmol based on the S₈). The mixture was sealed in an evacuated Pyrex tube and the tube was placed in a furnace at 130 °C. The tube was kept at that temperature for about a week, and then slowly (over 24 h) cooled to room temperature. Several dark violet crystals of **2** deposited not far from the “hot” zone of the tube along with some dark brown polycrystalline solid. Red crystals of free sulfur accompanied the powdered product in the hot zone; these were mechanically separated under the microscope. Elemental analysis (%) calcd for S₁₆C₂₄F₃₆O₂₄Rh₆: C 11.59, S 20.63; found: C 11.36, S 20.80; IR (KBr): $\tilde{\nu}$ = 1653.0(s), 1258.7(m), 1234.4(m), 1190.2(s), 1142.8(w), 1130.6(w), 1094.2(w), 1075.4(w), 1050.1(m), 1018.1(w), 861.3(m), 823.8(w), 785.2(w), 737.7(m), 688.0(w) cm⁻¹.

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- [8] Crystallographic data for **1** (S₈C₈F₁₂O₈Rh₂): M_r = 914.38, dark violet block, 0.25 × 0.08 × 0.05 mm, monoclinic, space group $P2_1/c$, a = 9.1826(5), b = 16.605(1), c = 16.5885(4) Å, β = 92.267(4)°, V = 2527.4(2) Å³, Z = 4, ρ_{calcd} = 2.403 g cm⁻³, μ = 2.090 mm⁻¹, $2\theta_{\text{max}}$ = 50.18°. Nonius FAST area detector system, MoK α radiation (λ = 0.71073 Å), T = –60 °C, 14915 reflections measured, data corrected for Lorentz and polarization effects, solution by direct methods (SHELXTL V.5), full-matrix refinement of F^2 (SHELXL-93), R_1 (on F_o) = 0.0585, $wR2$ (on F_o^2) = 0.1125 for 355 parameters and 48 restraints, 4439 independent reflections, R_1 (on F_o) = 0.0496, $wR2$ (on F_o^2) = 0.1009 for 3868 reflections with $I \geq 2\sigma(I)$, highest residual peak 0.96 e Å⁻³.
- [9] Crystallographic data for **2** (S₁₆C₂₄F₃₆O₂₄Rh₆): M_r = 2486.66, dark violet plate, 0.25 × 0.08 × 0.03 mm, monoclinic, space group $C2/c$, a = 30.93(2), b = 15.911(4), c = 16.762(8) Å, β = 121.83(4)°, V = 7009(6) Å³, Z = 4, ρ_{calcd} = 2.357 g cm⁻³, μ = 2.018 mm⁻¹, $2\theta_{\text{max}}$ = 45.02°. Nonius FAST area detector system, MoK α radiation (λ = 0.71073 Å), T = –60 °C, 15755 reflections measured, data corrected

for Lorentz and polarization effects, solution by direct methods (SHELXTL V.5), full-matrix refinement of F^2 (SHELXL-93), R_1 (on F_o) = 0.1430, $wR2$ (on F_o^2) = 0.2462 for 436 parameters and 60 restraints, 4484 independent reflections, R_1 (on F_o) = 0.1047, $wR2$ (on F_o^2) = 0.2165 for 3314 reflections with $I \geq 2\sigma(I)$, highest residual peak 1.36 e Å⁻³. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-154796 (**1**) and CCDC-154797 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A Ligand-Modulated Padlock Oligonucleotide for Supercoiled Plasmids**

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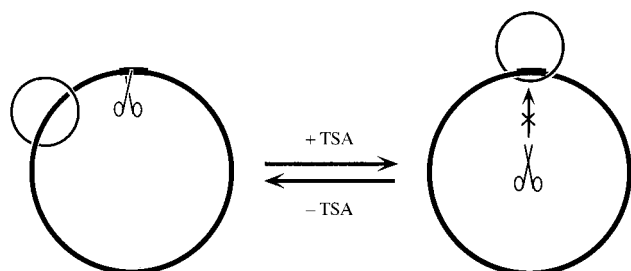
Supramolecular structures involving a circular oligonucleotide catenated to a double-stranded nucleic acid have been recently described.^[1–3] The formation of these structures involves the recognition of a specific region of the DNA by the oligonucleotide through either triple-helix formation^[1, 2] or strand displacement.^[3] The oligonucleotide can be circularized first and then loaded onto a linear DNA fragment^[1] or circularized around the DNA target after triplex formation.^[2] In the latter case, the catenated structure can be established on a circular supercoiled DNA. In both cases, the circular oligonucleotide may be able to move along the DNA, whereas in the method developed by Kuhn et al.,^[3] sliding does not occur, as the oligonucleotide is threaded between complementary strands of DNA before circularization around the displaced DNA single strand takes place. In the method that we previously described,^[2] the linear oligonucleotide is wound around the double-stranded DNA sequence through sequence-specific triple-helix formation, and then circularized by using a template oligonucleotide and T4 DNA ligase. When the target sequence was located on a plasmid, the circular oligonucleotide became catenated to the plasmid. However, it was shown to slide more than 600 bp away from

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the site of triple-helix formation when the plasmid was linearized under conditions where the triple helix is dissociated.

We have previously shown that some triple helices with a third strand that contains G and T can only be formed in the presence of triplex-stabilizing agents.^[4] Herein we investigate if this type of ligand-dependent triple helix could be used for the efficient assembly of padlock oligonucleotides around double-stranded DNA, and if the stability of the triple helix formed by the two catenated molecules could be modulated upon addition or removal of the triplex-stabilizing agent (Scheme 1). We designed a linear oligonucleotide that con-



Scheme 1. The interactions between the circular oligonucleotide and the plasmid are modulated by the triplex-stabilizing agent (TSA). When the TSA has been removed, the complex can be cleaved by a restriction enzyme (left). Addition of the TSA results in the formation of a structure that is resistant to cleavage (right).

tains a central triplex-forming sequence linked to two terminal sequences that can hybridize to a 17-mer template oligonucleotide (Figure 1a). The 5'-phosphorylated linear oligonucleotide was converted into a circular molecule by the addition of the 17-mer template and T4 DNA ligase (not shown). The number of base triplets (12) was chosen so that the oligonucleotide forms one turn around the target double-helical sequence, which is located on the pGA2 plasmid.

We previously reported the design and synthesis of a very efficient triplex-stabilizing agent, 6-[3-(dimethylamino)propyl]amino-11-methoxybenzo[*f*]quino-[3,4-*b*]quinoxaline (BQQ) (Figure 1b).^[5] Preliminary circularization experiments were carried out with a radiolabeled oligonucleotide, and the results were analyzed by using agarose gel electrophoresis (Figure 2). Under the conditions used for electrophoresis, the triple helix formed by the linear oligonucleotide and pGA2 in the presence of BQQ was dissociated (Figure 2, lane 2). In contrast, the radiolabeled oligonucleotide was shown to comigrate with the plasmid when it had been circularized in the presence of pGA2 and BQQ (Figure 2, lane 3). This comigration was not observed when the oligonucleotide was circularized before the addition of the plasmid (Figure 2, lane 5), when the triplex-stabilizing agent was omitted (Figure 2, lane 4), or in the presence of the pBl plasmid, which does not contain the target sequence (not shown). Finally, comigration was excluded upon digestion of the plasmid by *Hind*III, which linearizes the plasmid at a site located outside the oligonucleotide-binding region (Figure 2, lane 6). The circularization reaction did not alter the topology of the plasmid, which remains mostly in the supercoiled form, as observed in the case of the untreated plasmid (Figure 2,

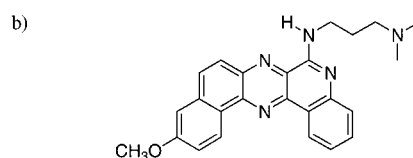
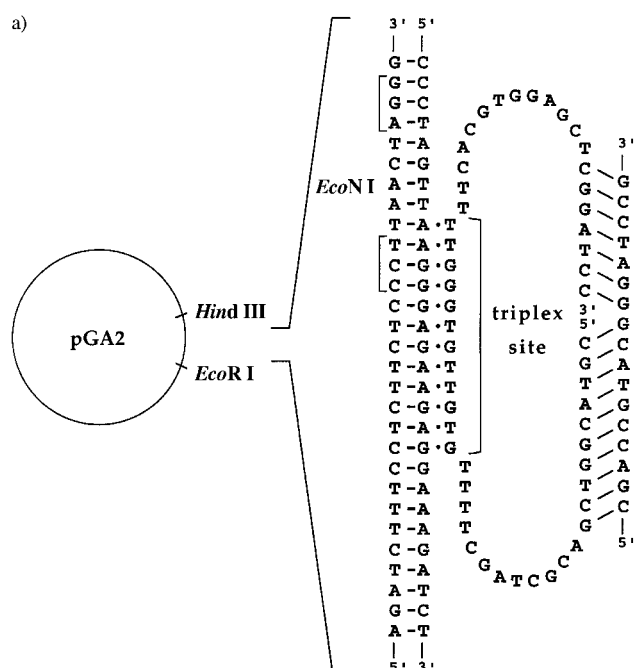


Figure 1. a) Description of the plasmid and oligonucleotides used in this study. Sequences of the 54-mer TFO and the 17-mer template are shown. The 54-mer can form a triple helix by binding to a 12 bp sequence target in the pGA2 plasmid, and its extremities can hybridize to the 17-mer template. The position of the restriction site for *Eco*NI is also indicated. b) Structure of BQQ.

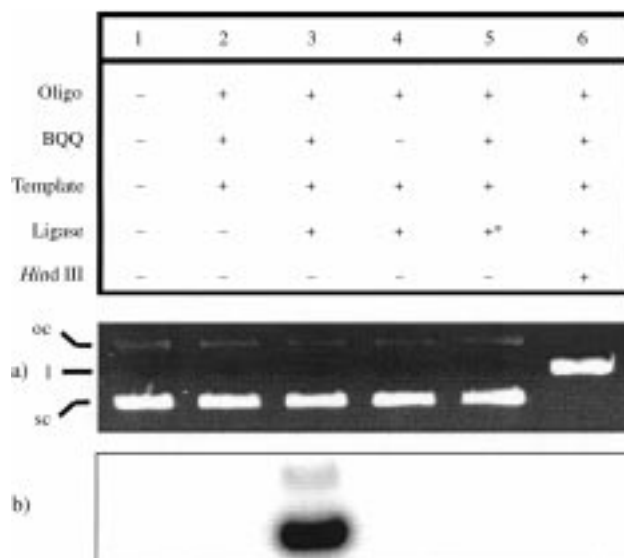


Figure 2. Ligand-induced formation of a triple-helix to give a catenated complex, as demonstrated by using agarose gel electrophoresis. The 54-mer oligonucleotide is radiolabeled and treated as indicated, before analysis on agarose gel (1%). The pGA2 plasmid was present during the ligation reaction except in lane 5 (* pGA2 was added after the circularization reaction, followed by heat denaturation of DNA ligase). In lane 6, the complex of lane 3 was digested with *Hind*III. a) Ethidium bromide staining of the gel. b) Autoradiogram of the gel. sc = supercoiled plasmid, oc = open circular form, l = linearized plasmid.

lane 1). All these data are in agreement with the proposed formation of a catenated structure that yields a sequence-specific oligonucleotide label linked to a plasmid in an irreversible (but not covalent) way owing to ligand-induced triplex formation.

We undertook further experiments to probe the efficiency of the labeling reaction and to determine whether the circular oligonucleotide could be displaced from the sequence to which it was bound during the circularization reaction. Triple-helix formation can inhibit DNA cleavage by a restriction enzyme.^[6] On the pGA2 plasmid, the *Eco*NI unique site partially overlaps the oligonucleotide-binding region (Figure 1a), and triple-helix formation inhibits the cleavage by the restriction enzyme (not shown). The circularization reaction was carried out in the presence of excess 5'-phosphorylated triplex-forming oligonucleotide (TFO). We devised a purification protocol based on the specific precipitation of plasmids in the presence of spermidine (see *Experimental Section*). This procedure allowed us to recover more than 95% of the plasmids and to get rid of all the unbound oligonucleotides. When submitted to this treatment, the pGA2 plasmid was only partially linearized by *Eco*NI, thus indicating that the triple-helical complex was not fully dissociated. Therefore, we tried to remove BQQ by heating in the presence of excess so-called "trap" oligonucleotide, which is folded into an intramolecular triple-helical structure. After this treatment, the plasmid was totally digested by *Eco*NI, as shown by agarose gel electrophoresis (Figure 3, lane 2). When BQQ (2 μ M) was

oligonucleotide is sufficient to disrupt triple-helix formation, therefore allowing digestion of the restriction enzyme.

We have shown herein that the triplex-mediated assembly of a padlock oligonucleotide around plasmid DNA can be carried out by using a triple helix that is made up of C–G·G and T–A·T base triplets (see Figure 1a), whose formation is induced in the presence of the triplex-specific ligand BQQ. The low fraction of guanines in the oligonucleotide reduces the possibility of it forming self-associated structures that may compete with triple-helix formation.^[7] The plasmid was very efficiently modified, as shown by an inhibition of more than 90% in the cleavage by the restriction enzyme. Furthermore, the structural integrity of the plasmid was not affected, as no covalent bond was formed between the oligonucleotide and the supercoiled plasmid. In addition, the noncovalent interaction that involves the formation of hydrogen bonds between the bases of the circular oligonucleotide and the plasmid can be disrupted by removing the BQQ ligand. Finally, further addition of BQQ locks the circular oligonucleotide around its target sequence on the plasmid.

Padlock oligonucleotides for single-stranded DNA have been used as tools for the specific detection of DNA sequences, using fluorescent oligonucleotides or rolling circle amplification.^[8] By combining such approaches with the method described herein, the detection of double-stranded DNA sequences should be possible without the need for a DNA denaturation step. This method also opens the route to a new type of noninvading DNA vector chemistry, as the attached circular oligonucleotide may be used as a substrate for linking any chemical moiety to a supercoiled plasmid in an irreversible, but noncovalent way. Such a strategy has potential applications in the development of nonviral vectors for gene therapy.^[9] The biological properties of the plasmid, such as its ability to be transcribed, should be intact. In its unbound state, the circular oligonucleotide may be displaced by proteins that translocate on double-stranded DNA^[10] and therefore could be used as a marker for observing their one-dimensional motion. On the other hand, locking the circular oligonucleotide around its target by the addition of a triplex-stabilizing agent may interfere with DNA–protein interactions. Furthermore, the complex described herein represents a new type of supramolecular structure in which interactions between two catenated circular molecules can be modulated by the use of a low molecular weight compound.

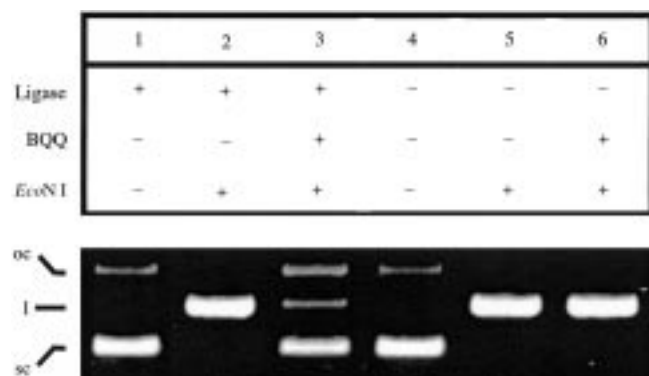


Figure 3. Restriction endonuclease probing of the padlock-modified plasmid, as revealed by agarose gel electrophoresis. Samples were prepared as described in the *Experimental Section*. The plasmid preparation contains mostly the supercoiled form (sc) of the plasmid and some open circular DNA (oc). Plasmid cleavage by *Eco*NI leads to the formation of linear plasmid (l).

again added to this plasmid, inhibition of *Eco*NI was restored (Figure 3, lane 3). When the plasmid was treated in the same way, but the ligation reaction was omitted, complete cleavage by *Eco*NI occurred (Figure 3, lane 6). Also, no inhibition could be observed when the oligonucleotide was circularized before the addition of the plasmid, or when the ligase was added, but the template was omitted (not shown). These experiments demonstrate that the oligonucleotide, which has been circularized around the target, inhibits the cleavage of the restriction enzyme in the presence of the triplex-stabilizing agent BQQ, and that removal of BQQ by the trap

Experimental Section

Plasmid pGA2 was constructed by cloning the appropriate oligonucleotide pair between the *Eco*RI and *Hind*III sites of pBluescript (Stratagene). The synthesis of the triplex-stabilizing agent BQQ has been previously described.^[5] A 5'-phosphorylated 54-mer TFO and a 17-mer template were used in the circularization experiments (see Figure 1 for sequences). A "trap" oligonucleotide that can form an intramolecular triplex (5'-CTTTCCTTCTCCTTTTGGAGAGAAGGAAAGTTTGTGGTTTGGTTGTGTGG-3') was used to remove BQQ from the samples. All these oligonucleotides, obtained from Eurogentec (Seraing, Belgium), were precipitated with ethanol, and their concentration was calculated by using a nearest neighbor model for the absorption coefficients.

For radioactive phosphorylation, TFO (10 pmol) was incubated in T4 Polynucleotide Kinase (PNK) buffer (20 μ L; New England Biolabs, NEB) with [γ -³²P]ATP (10 μ Ci, >5000 Ci mmol⁻¹, Amersham) and T4 PNK

(5 units, NEB) for 1 h at 37 °C. Unincorporated ATP was removed by using Micro Bio-Spin columns (Bio-Rad). For nonradioactive phosphorylation, TFO (300 pmol) was incubated in T4 DNA ligase buffer (50 µL—50 mM Tris–HCl, 10 mM MgCl₂, 10 mM DTT, 1 mM ATP, and 25 µg mL⁻¹ BSA, pH 7.8 at 25 °C) with T4 PNK (10 units), for 1.5 h at 37 °C. The oligonucleotide was used without any further purification.

To assemble the radiolabeled oligonucleotide and the plasmid, the 5'-labeled TFO (20 nM) was incubated with plasmid (1 µg, 50 nM final) and BQQ (20 µM) in T4 DNA ligase buffer. The sample was heated to 75 °C and slowly cooled down to 37 °C. The 17-mer oligonucleotide template (100 nM) and T4 DNA ligase (40 units) were added to achieve circularization of the oligonucleotide. The reaction products were analyzed by using a 1% agarose gel containing ethidium bromide. The gels were visualized on a UV lamp, then dried and autoradiographed by using a phosphorimager system (Molecular Dynamics).

For the unlabeled oligonucleotides, the process was the same, except that different amounts of plasmid (100 nM, 4 µg in 20 µL), TFO (1 µM), template (2 µM), and DNA ligase (400 units) were used. To remove BQQ from the triplex, the sample was diluted to 50 µL so that final buffer concentration was 50 mM Tris–HCl pH 8.0, 100 mM NaCl, 20 mM MgCl₂, and 20 µM trap oligonucleotide. The sample was heated to 80 °C and then slowly cooled to 37 °C. Spermidine (50 µL, 40 mM) was then added, and the samples were left at room temperature for 30 min with frequent vortex-mixing in order to allow plasmid compaction. After centrifugation, the pellet was washed with a solution (200 µL) containing isopropanol (50%), MgCl₂ (10 mM), NaCl (300 mM), and EDTA (25 mM), as described by Murphy et al.^[11] The plasmid was resuspended in TE buffer (40 µL, 10 mM Tris pH 8.0, 0.1 mM EDTA).

The restriction enzyme inhibition assay was carried out in the following way: the plasmid (0.2 µg) was incubated in NEB 3 buffer (40 µL—50 mM Tris–HCl, 10 mM MgCl₂, 100 mM NaCl, 1 mM DTT, pH 7.9 at 25 °C) containing BQQ (2 µM). The samples were heated to 75 °C and slowly cooled to 37 °C. The cleavage reaction was performed at 37 °C for 60 min with *Eco*NI (30 units), then stopped by the addition of SDS 2%/EDTA 0.2 M (5 µL). The samples were precipitated with ethanol (200 µL), resuspended in TE buffer (10 µL), and analyzed by agarose gel electrophoresis.

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Selective Inclusion of a Hetero-Guest Pair in a Molecular Host: Formation of Stable Charge-Transfer Complexes in Cucurbit[8]uril**

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The inclusion of two or more guest molecules in a molecular host is attractive because it provides unique opportunities to study new forms of stereoisomerism,^[1] bimolecular reactions,^[2] and molecular recognition^[3] in microenvironments. Although the inclusion of two different types of guest molecules in a host has been reported,^[4–6] the resulting complexes have been characterized only by spectroscopy. For example, the formation of pyrene-cyclodextrin-alcohol ternary complexes has been studied extensively by emission spectroscopy, but they are not stable enough to be isolated or structurally characterized.^[5] Thus, the selective inclusion of two different guests in a molecular host which leads to an isolable ternary complex is still difficult to achieve.

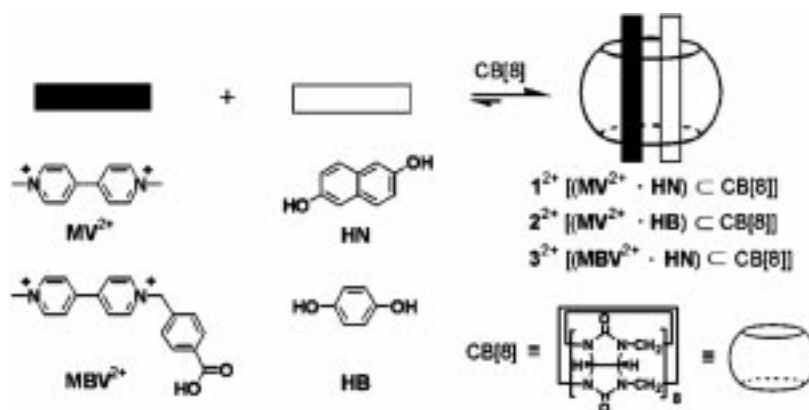
Cucurbituril (CB[6]), a macrocycle comprising six glycoluril units, has a cavity that is accessible through two identical carbonyl-fringed portals.^[7] The polar carbonyl groups at the portals and the hydrophobic cavity allow the cavitand to form stable host–guest complexes with small molecules such as protonated aliphatic and aromatic amines.^[7, 8] We recently reported new cucurbituril homologues, namely cucurbit[*n*]uril (CB[*n*]; *n* = 5, 7, and 8), that contain five, seven, and eight glycoluril units.^[9] The largest member of the cucurbituril family, CB[8], which has a cavity comparable to that of γ -cyclodextrin, can accommodate two molecules of a naphthalene derivative to form a 1:2 host–guest complex.^[9] The capability of CB[8] to form 1:2 host–guest complexes prompted us to study the inclusion of two different guests within CB[8]. Here we report the selective inclusion of a hetero-guest pair in CB[8] that is driven by a charge-transfer interaction between the guests. The resulting ternary complexes are highly stable, which enables them to be isolated and characterized by X-ray crystallography.

Host–guest interactions between redox-active viologens and cyclodextrins has been extensively studied.^[10] While methylviologen (MV²⁺) shows little interaction with β - or γ -cyclodextrin,^[10a] it readily forms a 1:1 host–guest complex with CB[8], as evidenced by ¹H NMR spectroscopy and mass

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spectrometry. The chemical shifts of the pyridinium protons of MV^{2+} are shifted to higher field upon the formation of the complex (Figure 1a, b). The major driving force for the formation of the 1:1 complex appears to be ion–dipole interactions between the positive charge of the guest and the portal oxygen atoms of CB[8]. It is interesting to note that although CB[8] has a cavity large enough to accommodate two MV^{2+} molecules, the formation of a 1:2 host–guest complex with this guest is not observed. Presumably, electrostatic repulsion between two MV^{2+} ions in the cavity disfavors the formation of the ternary complex.^[11]



Scheme 1. Inclusion of a hetero-guest pair in cucurbit[8]uril.

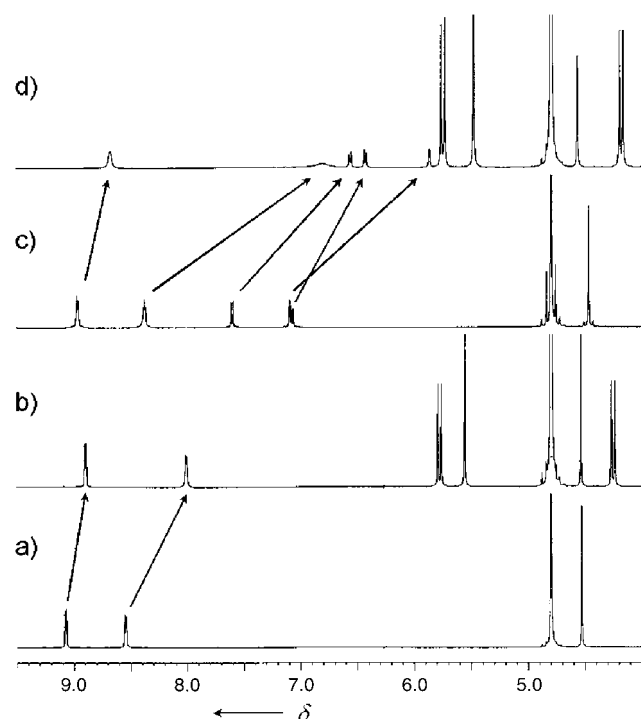


Figure 1. ^1H NMR spectra obtained in D_2O of a) MV^{2+} , b) 1:1 mixture of MV^{2+} and CB[8], c) 1:1 mixture of MV^{2+} and HN, and d) **1**.

The exclusive formation of the 1:1 complex between CB[8] and MV^{2+} prompted us to study the inclusion of a second guest into the 1:1 complex. Indeed, instantaneous and quantitative formation of the inclusion complex **1** or **2** containing a hetero-guest pair is observed upon addition of one equivalent of an electron-rich aromatic guest, such as 2,6-dihydroxynaphthalene (HN) or 1,4-dihydroxybenzene (HB), to the 1:1 complex of MV^{2+} and CB[8]. The ternary complexes **1** and **2** are also formed exclusively when their components are mixed in a 1:1:1 ratio (Scheme 1). It should be noted that the electron-rich guest molecules themselves do not bind CB[8] in the absence of MV^{2+} . Therefore, the major driving force for the inclusion of the second guest appears to be a charge-transfer interaction between the electron-rich guest and the electron-deficient MV^{2+} , as evidenced by UV/Vis spectroscopy. The 1:1:1 ternary complex **1** exhibits a charge-

transfer absorption at 580 nm which is greatly red-shifted ($\Delta\lambda = 120$ nm) and with a concomitant high increase in the intensity relative to that of a 1:1 mixture of MV^{2+} and HN in the absence of CB[8] (Figure 2). The highly enhanced charge-transfer interaction between the two guests arises from their close contact within the cavity of CB[8], which is confirmed by

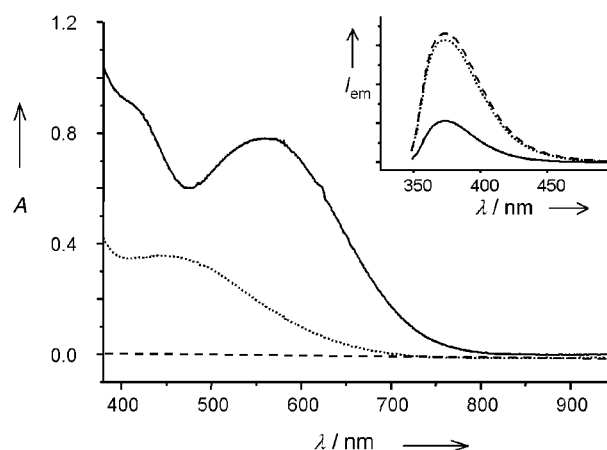


Figure 2. Absorption and emission (inset) spectra obtained in H_2O of HN (dashed line), a 1:1 mixture of HN and MV^{2+} (dotted line), and **1** (solid line). The absorption spectra of HN and **1** were taken with 5 mM solutions whereas that of the 1:1 mixture of HN and MV^{2+} was taken with a 0.5 M solution. All emission spectra were recorded with 5 μM solutions.

NMR and emission spectroscopy. All the aromatic proton signals of the guest molecules are significantly shifted to higher field in the ^1H NMR spectra upon the formation of the inclusion complexes containing a pair of hetero guests (Figure 1c, d). While little fluorescence quenching is observed when only MV^{2+} and HN are present in solution, the fluorescence intensity of HN decreases by 70% upon formation of **1**. A similar decrease in fluorescence intensity requires more than 500 equivalents of MV^{2+} in the absence of CB[8]. To the best of our knowledge, this is the first example of the selective inclusion of a hetero-guest pair in a molecular host that is driven by a charge-transfer interaction between guests.^[12, 13]

Attempts to determine the structure of **1** or **2** by X-ray crystallography were hampered by severe disorders in the guest molecules that arises from the high symmetry of their

space groups. We therefore decided to use a dissymmetric bipyridinium derivative (**MBV**²⁺) as the electron-deficient guest to lower the symmetry of the crystal system. The X-ray crystal structure of the resulting inclusion complex (**3**, Figure 3) shows the hetero-guest pair is included inside the cavity

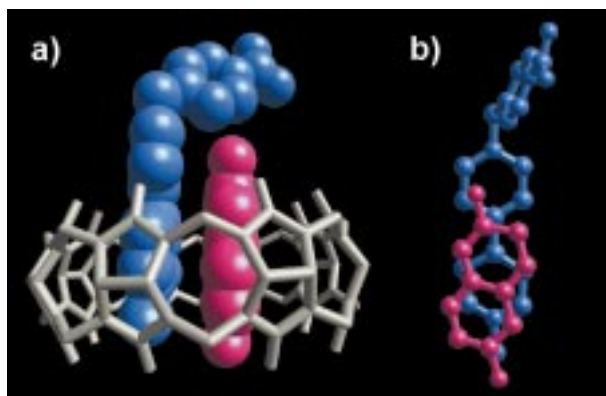


Figure 3. X-ray crystal structure of **3**²⁺: a) full view, b) alternative view without the host. CB[8] = grey, **MBV**²⁺ = blue, **HN** = magenta.

of CB[8]. While the carboxybenzylated pyridinium ring resides outside, the methylated pyridinium ring is located inside the cavity. The methylated pyridinium ring and the naphthalene ring of the donor are almost parallel, with a dihedral angle of 1.8° and a mean separation of 3.4 Å, which is consistent with the strong charge-transfer interaction observed by spectroscopy. This is probably the first example of inclusion of a hetero-guest pair in a molecular host that has been confirmed by X-ray crystallography.

In summary, we have demonstrated the selective inclusion of a hetero-guest pair in a molecular host which is driven and stabilized by a charge-transfer interaction between electron-rich and electron-deficient guests. We expect that these ternary complexes will display rich spectroscopic and electrochemical properties, which are currently being investigated. Furthermore, such selective inclusion of a hetero-guest pair provides new opportunities for studying bimolecular reactions between selected reaction partners in molecular chambers, for developing chemical sensors for biomolecules with aromatic residues,^[14, 15] and for creating elaborated supramolecular assemblies.^[16, 17]

Experimental Section

Typical procedure: 2,6-dihydroxynaphthalene (2.5 mg, 15.7 μmol) and CB[8] · (H₂SO₄) · 16H₂O (25.7 mg, 15.0 μmol) were added to methylviologen dichloride trihydrate (5.2 mg, 16.7 μmol) in water (3 mL). The violet suspension was stirred with occasional heating until all the solid materials had dissolved. The solution was then allowed to stand in a refrigerator. Dark violet crystals of **1** were obtained after 3 days (28.9 mg, 96%). **1**: ¹H NMR (500 MHz, D₂O): δ = 8.67 (s, 4H), 6.80 (brs, 4H), 6.55 (d, 2H), 6.41 (d, 2H), 5.86 (s, 2H), 5.73 (d, 16H), 5.48 (s, 16H), 4.57 (s, 6H), 4.20 (d, 16H); UV/Vis (H₂O): λ_{CT} (lg ε) = 580 nm (2.52); MS (electrospray ionization (ESI)): *m/z* (%): 837.37 (100) [*M*²⁺]; elemental analysis calcd for [(C₄₈H₄₈N₃₂O₁₆) · (C₁₂H₁₄N₂) · (C₁₀H₈O₂)] · SO₄ · 13H₂O: C 41.92, H 4.82, N 23.74, S 1.60; found: C 41.72, H 4.63, N 23.96, S 1.98.

2: ¹H NMR (500 MHz, D₂O): δ = 8.75 (d, 4H), 7.08 (d, 4H), 5.74 (d, 20H), 5.49 (s, 16H), 4.53 (s, 6H), 4.20 (d, 16H); UV/Vis (H₂O): λ_{CT} (lg ε) = 470 nm (2.41); MS (ESI): *m/z* (%): 812.10 (100) [*M*²⁺]; elemental analysis calcd for

[(C₄₈H₄₈N₃₂O₁₆) · (C₁₂H₁₄N₂) · (C₆H₆O₂)] · SO₄ · 12H₂O: C 40.91, H 4.79, N 24.58, S 1.65; found: C 40.60, H 4.43, N 24.49, S 2.05.

3: ¹H NMR (500 MHz, D₂O, 4 °C): δ = 8.48 (d, 2H), 7.96 (s, 2H), 7.73 (d, 2H), 7.43 (d, 2H), 6.48 (s, 2H), 6.21 (brs, 2H), 6.16 (d, 1H), 6.02–5.98 (dd, 2H), 5.90 (d, 1H), 5.64 (s, 2H), 5.41 (s, 1H), 5.37 (s, 1H), 5.25 (t, 16H), 4.99 (s, 16H), 4.04 (s, 3H), 3.72–3.67 (dd, 16H); UV/Vis (H₂O): λ_{CT} (lg ε) = 578 nm (2.50); MS (ESI): *m/z* (%): 850.4 (100) [*M*²⁺]; elemental analysis calcd for [(C₄₈H₄₈N₃₂O₁₆) · (C₁₉H₁₇N₂O₂) · (C₁₀H₈O₂)] · 0.5SO₄ · 10H₂O: C 45.72, H 4.63, N 23.54, S 0.79; found: C 45.93, H 4.48, N 23.36, S 0.86.

Crystal data for **3**: [(C₄₈H₄₈N₃₂O₁₆) · (C₁₉H₁₇N₂O₂) · (C₁₀H₈O₂)] · 0.5SO₄ · 25.5H₂O, *M*_r = 2302.13, monoclinic, *P*₂₁/*c*, *a* = 15.1505(5), *b* = 20.7282(6), *c* = 33.4305(1) Å, β = 100.74(1)°, *V* = 10314.8(6) Å³, *Z* = 4, ρ_{calcd} = 1.482 g cm⁻³, *T* = 223 K, Siemens SMART CCD diffractometer, MoK_α radiation (λ = 0.71073 Å), μ = 1.33 cm⁻¹. The structure was solved by the Patterson method (SHELXS-86). All non-hydrogen atoms were refined anisotropically (SHELXL-93). Final block-diagonal matrix least-squares refinement on *F*² with all 16038 reflections and 1452 variables converged to *R*₁ (*I* > 2σ(*I*)) = 0.112, *wR*₂ (all data) = 0.321, and GOF = 1.133. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-154114. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Template and Guest Effects on the Self-Assembly of a Neutral and Homochiral Helix**

Frank M. Tabellion, S. Russell Seidel, Atta M. Arif, and Peter J. Stang*

Dedicated to Professor Manfred Regitz
on the occasion of his 65th birthday

Over the past decade, the principles of recognition-driven, spontaneous self-assembly have become further elucidated. In such processes, the overall structure of the product is

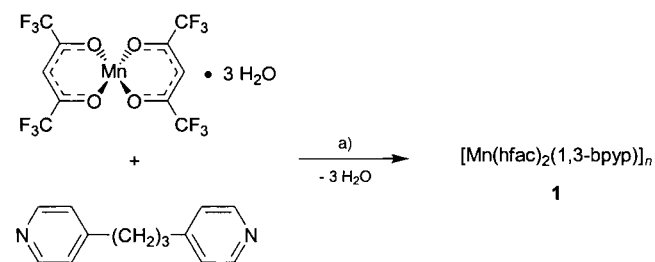
controlled by the combination of binding constraints and geometrical requirements. These intriguing discoveries have led to the development of general strategies for the design of abiotic, supramolecular entities, both discrete and infinite, that use coordination as a motif.^[1]

The coordination paradigm pioneered by Lehn and Sauvage, and as developed in the groups of Fujita, Raymond, Stang, and others for closed systems, has allowed for the synthesis of a large assortment of supramolecular polygons and polyhedra through “rational design”. This approach utilizes rigid subunits that have been pre-coded with the proper bonding and angular information, leading to highly predictable products.^[2] Concurrently, a variety of solid-state coordination polymers and infinite-network lattices have been synthesized along similar lines.^[1b, 3]

By incorporating a higher degree of flexibility into the building blocks, the amount of predefined information is reduced, and two or more different structures can arise from identical metal–ligand combinations. This strategy yields largely unpredictable products that depend mostly upon minor, experimental variations.^[4] The iron-based circular helicates made by Lehn’s group^[5] and the cadmium-based, flexible coordination networks from Fujita’s group,^[6] are dependent upon the anion or guest employed, respectively, and serve as impressive examples of this methodology.

The work presented here is concerned with tuning the assembly of a new, neutral, solid-state system and serves as a step toward bridging the gap between discrete and infinite supramolecular structures. Such work may also have implications in crystal engineering.^[7] In this study, the solid-state assembly of the highly flexible 1,3-bis(4-pyridyl)propane (1,3-bpyp) ligand and the neutral $[Mn(hfac)_2(H_2O)_3]$ ($hfac = 1,1,1,5,5,5$ -hexafluoro-2,4-pentanedionate) acceptor complex was probed under various reaction conditions.

By slow evaporation of the solvent from a previously heated 1:1 mixture of $[Mn(hfac)_2(H_2O)_3]$ and 1,3-bpyp in acetone/methanol, crystals of **1** were obtained (Scheme 1).



Scheme 1. a) MeOH / $(CH_3)_2CO$ / Δ .

As determined by single-crystal X-ray analysis,^[8] the coordination polymer **1** exhibits a helical architecture in the solid state (Figure 1). This system crystallized in the chiral space group C_2 , with two independent manganese centers per repeating asymmetric unit. Both pseudo-octahedral metal centers show *cis* coordination of the pyridine moieties and are enantiomeric. Each set of two crystallographically equivalent manganese centers constitutes a single revolution of the helix with a distance of 19.18 Å between them.

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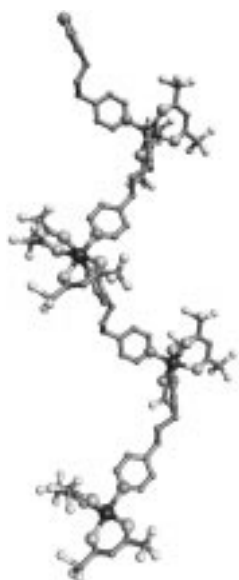


Figure 1. A segment of helical polymer **1**.

Typically, helical systems arising from achiral starting materials show an equal distribution of *P*- and *M*-helices, making them overall racemic.^[9] In this case, however, crystals that grew from a single point of nucleation exhibited spontaneous self-resolution into homochiral entities.^[10] In any given batch, multiple nucleation points led to apparently random distributions of left-handed and right-handed crystals.^[11] From careful study of the crystal packing diagram of **1**, we assume that the resulting homochirality of any particular single crystal arose from the interlocking of the hfac trifluoromethyl groups between the turns of adjacent helices as the system crystallized (Figure 2).

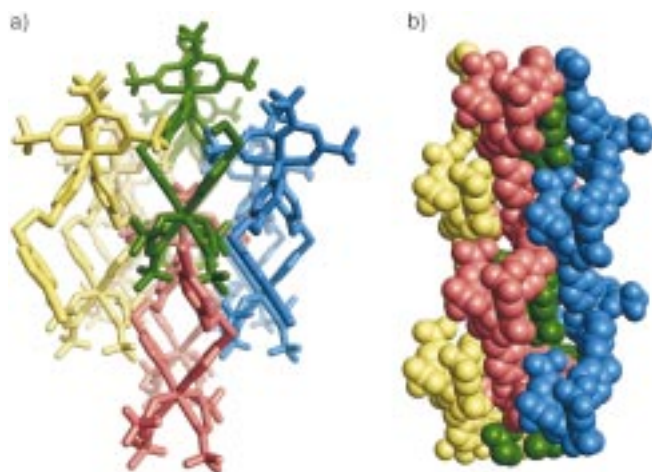
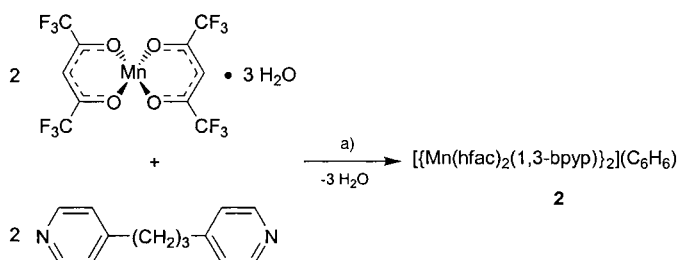


Figure 2. Representation of the crystal packing in compound **1**: a) View of **1** along the helical axis, showing the interlocking of the helices. b) Side view of **1** as a space-filling model. Protons are omitted for clarity.

A slight variation in the reaction conditions, such as crystallization in the presence of benzene, induces a dramatic effect on the solid state structure of **1**. Instead of crystallizing as an infinite helical polymer, a closed, inorganic cyclophane **2** is formed (Scheme 2). This assembly consists of two independent, enantiomeric manganese centers bridged by two 1,3-bpyr ligands, with the metals having the same coordination geometry as seen for those in **1**. As determined by single-crystal X-ray analysis,^[12] the cross-ring, manganese – manganese



Scheme 2. a) MeOH / (CH₃)₂CO / C₆H₆ / Δ; recrystallization in the presence of C₆H₆.

separation is 10.4 Å, and the shortest carbon – carbon, cross-ring separation is 6.5 Å (Figure 3).

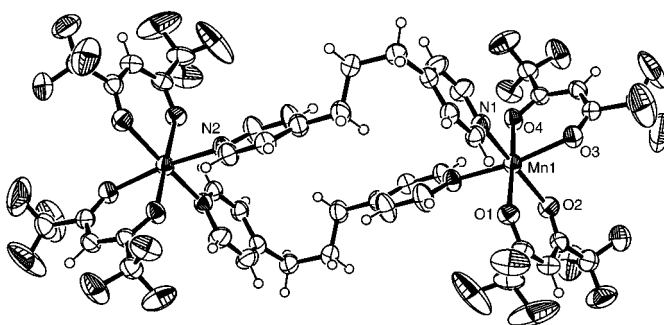


Figure 3. ORTEP drawing of the molecular structure of cyclophane **2**.

The crystal packing diagram for **2** clearly reveals that the cocrystallized benzene molecules act as templates in the formation of the ring system, suppressing any oligomerization that may occur (Figure 4). The stacking of these entities leads to the formation of intermolecular channels. The benzene molecules sit above and below the planes of **2** and do not occupy the internal cavities, which leads to the formation of alternating, sandwichlike sheets, with an inter-sheet, manganese – manganese separation of 10.3 Å.

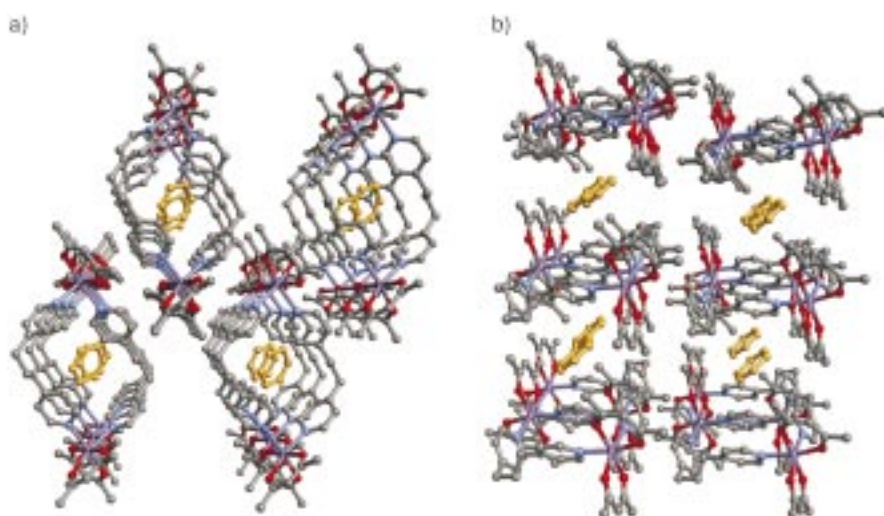


Figure 4. Crystal packing illustration of cyclophane **2**. a) Perspective view of the intermolecular channels of **2**. b) Side view showing the alternating, sandwich-like sheets of **2**. Protons and fluorine atoms omitted for clarity.

An X-ray analysis reveals that **1** acts as a host compound if the crystals are grown in the presence of 1,2-diphenylethane (1,2-dphe; Scheme 3).^[13] However, in contrast to **2**, the helical structure of **1** remains intact. Each coil of the helix includes two residues as in **1** (Figure 5). Despite these similarities, the guest molecule has a significant impact on the solid-state

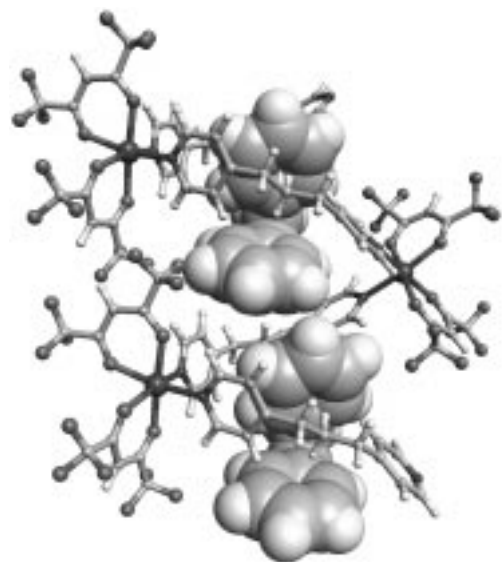
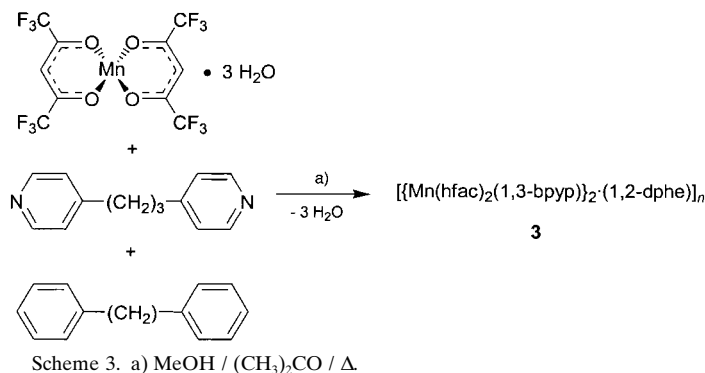


Figure 5. A section of helical polymer **3**, with the 1,2-dphe guest molecules shown as a space-filling model.

structure of **3**. For instance, the distance between the coils (10.3 Å) is considerably smaller than in **1**. Furthermore, the conformation of the coordinated 1,3-bpyp ligand changes in going from **1** to **3**, resulting in the latter having an augmented internal cavity volume per unit cell. In addition, **3** crystallizes in the achiral space group *P*2₁/*n*, and accordingly both *P*- and *M*-helices are present in equal amounts (Figure 6). We believe that this occurs as a result of the 1,2-dphe guest effectively filling the helical cavity and preventing the aforementioned interlocking of adjacent helices. Interestingly, a recognition phenomenon between the host and 1,2-dphe guest molecule occurs, with the host forcing the guest into an unfavorable, nearly eclipsed, *syn* conformation. A detailed examination of the crystal structure did not reveal an obvious interaction between the host and guest.

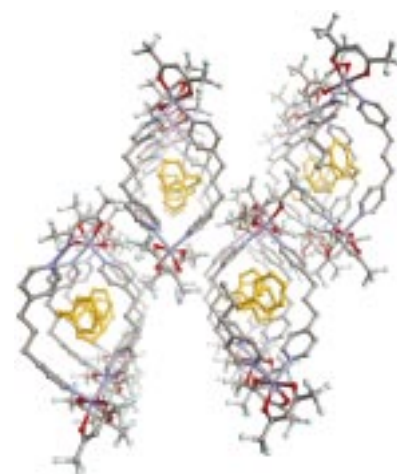


Figure 6. Crystal packing diagram of polymer **3** along the helical axis. Protons omitted for clarity.

In conclusion, the condition-dependent solid-state assembly of self-templated homochiral complex **1**, determined here by single-crystal X-ray analysis, can be tuned by varying the template or guest present. This effect results in solid-state products ranging from closed dinuclear assemblies **2** to racemic mixtures of infinite helices **3**. In addition, each of these supramolecular species are electronically neutral. To the best of our knowledge, this complex–ligand combination represents a unique case in which the supramolecular assembly can be synthesized in the presence of a template, a guest, or without either and exhibits drastic structural differences depending on the method used. This feature aids in bringing together the two fields of discrete and infinite supramolecular structures and may have implications in the area of crystal engineering.

Experimental Section

1: [Mn(hfac)₃(H₂O)₃] (1 equiv) and 1,3-bpyp (1 equiv) were placed in a mixture of methanol/acetone. The resulting solution was heated for 0.5 h during this time it became slightly darker yellow. Crystals of **1** were grown out of this solution by slow evaporation of the solvent in 87.2 % yield; elemental analysis, calcd (%) for Mn₁C₂₃H₁₆N₂O₄F₁₂: C 41.40, H 2.42, N 4.20; found: C 41.59, H 2.46, N 4.29.

2 and **3** were produced under the same reaction conditions as **1**, except the crystallization was carried out in the presence of benzene and 1,2-dphe, respectively. Product **2** was obtained in 96.9 % yield, **3** in 73.8 %; elemental analysis, calcd (%) for 2 Mn₂C₄₆H₃₂N₄O₈F₂₄ · C₆H₆: C 44.21, H 2.71, N 3.97; found: C 42.88, H 2.67, N 4.17 (note: the C value in the elemental analysis for **2** is low because of the loss of lattice benzene molecules during the drying and elemental analysis processes); elemental analysis, calcd (%) **3** Mn₂C₄₆H₃₂N₄O₈F₂₄ · C₁₄H₁₄: C 47.51, H 3.06, N 3.69; found: C 48.13, H 3.19, N 3.72.

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- [13] Crystal structure analysis of **3** at 200(1) K: $C_{60}H_{46}N_4O_8F_{24}Mn_2$, $M_r = 1516.89$, yellow prism, $0.25 \times 0.23 \times 0.20$ mm, monoclinic space group $P2_1/n$, $a = 10.2946(1)$, $b = 28.1849(5)$, $c = 22.6755(5)$ Å, $\alpha = 90^\circ$, $\beta = 98.3108(10)$, $\gamma = 90^\circ$, $V = 6510.25(19)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.548$ g cm⁻³, MoK_{α} radiation $\lambda = 0.71073$ Å, $\mu = 0.512$ mm⁻¹. Data were collected on a Nonius KappaCCD diffractometer in the range $2.20 < 2\theta < 26.05^\circ$. A total of 22624 measured reflections, 12755 unique, 7936 with $F_o^2 > 4\sigma(F_o^2)$ were used to refine 1003 parameters to $R1(wR2) = 0.0576(0.1186)$, $GOF = 1.022$, F^2 refinement in SHELXL97. A multiscan absorption correction gave min. and max. transmission factors of 0.9045 and 0.8827. The residual peaks in the final difference map ranged from -0.347 to $+0.318$ e Å⁻³. Four CF₃ groups were disordered in two different orientations with partial occupancy ranging from 0.75 to 0.92. The 1,2-dphe molecule was also disordered in two slightly different orientations with a major orientation of nearly 60%.^[14]
- [14] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge

Crystallographic Data Centre as supplementary publication no. CCDC-153290, CCDC-153291, and CCDC-153292. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Ultrafast Electron Diffraction of Transient [Fe(CO)₄]: Determination of Molecular Structure and Reaction Pathway**

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Transition metal carbonyl complexes^[1, 2] respond to ultraviolet light by the loss of one or more CO ligands and subsequent formation of coordinatively unsaturated carbonyl complexes, which are known to catalyze a variety of reactions.^[3–5] The photochemistry governing the formation of these coordinatively unsaturated species has been an active area of research both experimentally^[6–13] and theoretically,^[14–19] often focusing on the reaction pathways and molecular structures of these transient species. Among transition metal carbonyl complexes, [Fe(CO)₅] is one of the most extensively studied molecular systems. [Fe(CO)₅] absorbs strongly in the ultraviolet starting at about 350 nm (3.5 eV).^[18, 20–22] The spectrum is rather featureless, and is dominated by metal-to-ligand charge transfer transitions^[18] at high energies. Having five carbonyl ligands, an [Fe(CO)₅] molecule can dissociate into five different products ([Fe(CO)_x], $x = 4, 3, 2, 1, 0$) depending on the excitation wavelength.

In these reactions, [Fe(CO)₄] is the primary intermediate and serves as a “doorway” molecule for various subsequent reactions,^[23, 24] such as decomposition, recombination with the carbonyl ligand, and coordination with solvent molecules. Elucidating the nature of [Fe(CO)₄], including its electronic states and the corresponding molecular geometry, is important for understanding the role of intermediates in the photolysis of transition metal carbonyl complexes.

Herein we report the direct determination of the molecular structure (Figure 1) of transient [Fe(CO)₄] using diffraction with ultrashort pulses of electrons. In this way, we are able to identify the primary reaction pathway and provide details of

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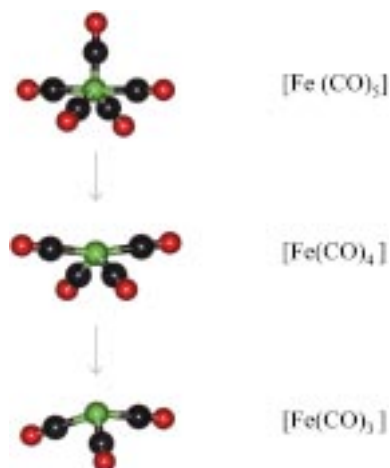


Figure 1. Structural changes accompanying the elimination of CO ligands from $[\text{Fe}(\text{CO})_5]$.

bond lengths and angles of the intermediate structure. Because of the picosecond time resolution invoked in these ultrafast electron diffraction (UED) experiments, it is possible to “freeze” the intermediate and determine its structure and pathway. For $[\text{Fe}(\text{CO})_4]$, we provide direct evidence that the molecular structure involved is that of the singlet, not triplet, pathway contrary to many suggestions in past studies.

The potential energy levels of the $[\text{Fe}(\text{CO})_x]$ species relevant to the photolysis of $[\text{Fe}(\text{CO})_5]$ are shown in Figure 2. The ground state of $[\text{Fe}(\text{CO})_5]$ is a singlet ($^1\text{A}'_1$; D_{3h}) and can be pumped into excited singlet states by absorbing ultraviolet photons. Two possible reaction pathways, the singlet and the triplet, following UV excitation have been postulated.^[8, 9, 13, 14, 16, 25] In the singlet pathway,^[8, 13, 25] the $^1\text{E}'$ state molecules of $[\text{Fe}(\text{CO})_5]$ dissociate into the singlet excited state ($^1\text{A}_1$) of $[\text{Fe}(\text{CO})_4]$, while for the triplet pathway,^[8, 9, 16] intersystem crossing to the $^3\text{E}'$ state of $[\text{Fe}(\text{CO})_5]$ is required prior to dissociation to the triplet ground state ($^3\text{B}_2$) of $[\text{Fe}(\text{CO})_4]$. For photolysis in solid matrices at low temperature, the produced $[\text{Fe}(\text{CO})_4]$ was characterized^[26] to have a structure with C_{2v} symmetry and to be in the triplet electronic ground state. This observation is consistent with other experimental results in which secondary fragments ($[\text{Fe}(\text{CO})_3]$, $[\text{Fe}(\text{CO})_2]$, and $[\text{Fe}(\text{CO})]$) in their triplet electronic ground states were observed as major products, indicating that the ground state ($^3\text{B}_2$) of $[\text{Fe}(\text{CO})_4]$ played a determining role.^[9, 10, 27]

However, it was still unclear whether $[\text{Fe}(\text{CO})_4]$ is formed directly into the triplet state or through relaxation via singlet states (Figure 2), and how the reaction proceeds to generate the subsequent secondary fragments. Early studies on the nanosecond time scale have suggested that the fragmentation follows the triplet pathway.^[9, 10] A more recent study has suggested that the $^1\text{A}_1$ state is initially formed via a very short-lived higher state of $[\text{Fe}(\text{CO})_4]$, favoring the singlet pathway.^[13] The discrepancy may originate from the difficulty associated with directly monitoring the identity of transient intermediate structure during the course of the reaction. In this respect, UED^[28–32] is a powerful method for studying the

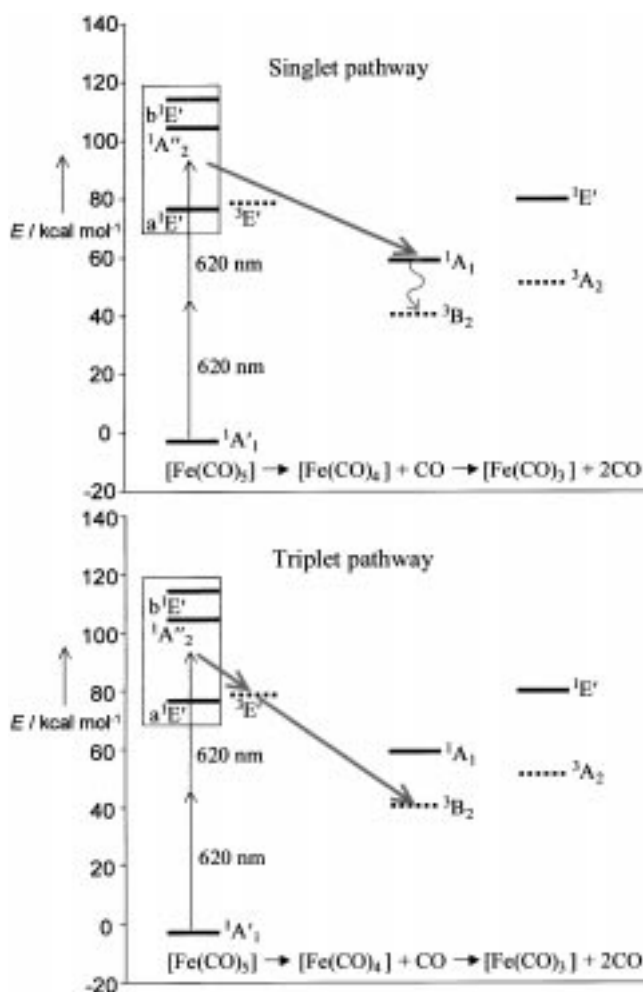


Figure 2. Scheme of the potential energy levels and pathways of the UV dissociation of $[\text{Fe}(\text{CO})_5]$. The following energies (in kcal mol^{-1}) relative to the ground state ($^1\text{A}'_1$) of $[\text{Fe}(\text{CO})_5]$ are from the literature.^[10, 14, 15, 17, 18] $[\text{Fe}(\text{CO})_5]$: $^3\text{E}'$ 78.1, $^1\text{A}'_1$ 77.2, $^1\text{A}_2$ 105.8, $^1\text{E}'$ 114.4; $[\text{Fe}(\text{CO})_4]$: $^3\text{B}_2$ 41.5, $^1\text{A}_1$ 59.0, $[\text{Fe}(\text{CO})_3]$: $^3\text{A}_2$ 53.0, $^1\text{E}'$ 80.7. The two pathways, singlet and triplet, are indicated in the two panels.

molecular structure of transient $[\text{Fe}(\text{CO})_4]$. As with conventional ultrafast spectroscopies,^[33, 34] UED utilizes a femto-second (fs) laser pulse to initiate a desired chemical reaction; however in UED, the subsequent laser pulses normally used to probe the progress of the reaction are replaced with ultrashort pulses of electrons. Diffraction patterns are then recorded to provide the internuclear distances of the molecular species involved.

The UED experiments on $[\text{Fe}(\text{CO})_5]$ were performed by using the second-generation apparatus^[28] developed in this laboratory. The time zero, when the excitation laser pulse and the probing electron pulse temporally overlap in the molecular beam, was determined by an ion-induced lensing experiment^[28] with ± 2 ps accuracy. To initiate the reaction, a fs laser pulse was focused into the gas sample beneath the needle of the free-jet expansion. The snapshots of diffraction images at a certain delay time t (-180 and $+200$ ps) were recorded and converted to the diffraction intensity data $I_{\text{tot}}(t; s)$, where $s = (4\pi/\lambda)\sin(\theta/2)$, λ is the de Broglie wavelength of the electrons, and θ is the scattering angle.

In our experiments, the time zero was determined with 2 ps accuracy and the overall temporal resolution was less than 20 ps. Thus the diffraction data obtained when probe electron pulses arrived 180 ps ahead of excitation laser pulses ($I_{\text{tot}}(-180 \text{ ps}; s)$) provided a reference signal originated only from the parent molecules $[\text{Fe}(\text{CO})_5]$, as these parent molecules were not excited by the initiating laser. In contrast, the data at +200 ps, $I_{\text{tot}}(+200 \text{ ps}; s)$, comprises the contributions from both the remaining parent molecules, $[\text{Fe}(\text{CO})_5]$, and newly formed photoproducts, $[\text{Fe}(\text{CO})_4]$. Thus, the difference between them [Eq. (1)]^[29–32] selects the reaction change induced by the fs laser pulse.

$$\Delta I_{\text{tot}}(+200 \text{ ps}; -180 \text{ ps}; s) = I_{\text{tot}}(+200 \text{ ps}; s) - I_{\text{tot}}(-180 \text{ ps}; s), \quad (1)$$

In the diffraction difference signal, ΔI_{tot} , the contributions from unreacted molecules and the background signal, which do not change in the course of the chemical reaction, are eliminated, thus highlighting the signal from the change in molecular structure under consideration.^[35] For data analysis, the difference modified molecular scattering intensity, $\Delta sM(t; t_{\text{ref}}; s)$, was obtained following the conventional definition given in Equation (2),^[36] where I_{atom} is the atomic scattering intensity ($t = +200 \text{ ps}$ and $t_{\text{ref}} = -180 \text{ ps}$ in the present case).

$$\Delta sM(t; t_{\text{ref}}; s) = s\Delta I(t; t_{\text{ref}}; s)/I_{\text{atom}}, \quad (2)$$

The corresponding difference radial distribution curves, $\Delta f(r)$, which directly give the change in internuclear distances (r) of the reaction, were then calculated from the $\Delta sM(s)$ curves according to the standard gas-phase electron diffraction equation (3),^[36] where the constant $k = 0.02 \text{ \AA}^2$, is a damping coefficient included to account for the limited s range.

$$\Delta f(r) = \int_0^{s_{\text{max}}} \Delta sM(s) \sin(sr) \exp(-ks^2) ds \quad (3)$$

With two-photon excitation at the wavelength of 620 nm, only $[\text{Fe}(\text{CO})_4]$ (both $^1\text{A}_1$ and $^3\text{B}_2$ states) and $[\text{Fe}(\text{CO})_3]$ (the $^3\text{A}_2$ state only)^[37] are energetically possible. A fit with these three possible products was performed by floating the fraction (relative to 100% parent fraction before the photolysis) of each species, and by using the structural parameters obtained from ab initio calculations.^[19] The fraction of the singlet $[\text{Fe}(\text{CO})_4]$ was $14 \pm 1\%$, while the total fraction of the triplet $[\text{Fe}(\text{CO})_4]$ and triplet $[\text{Fe}(\text{CO})_3]$ was less than 1%, indicating that the singlet $[\text{Fe}(\text{CO})_4]$ is the primary product and the formation of other species is negligible. To trace other possible secondary photofragments, a fit including triplet $[\text{Fe}(\text{CO})_2]$, triplet $[\text{Fe}(\text{CO})]$, and Fe was also performed by floating the fraction of each species, while keeping their structural parameters fixed at the values obtained from ab initio calculations.^[19] The resulting total fraction of $[\text{Fe}(\text{CO})_2]$, $[\text{Fe}(\text{CO})]$, and Fe was less than 1%, confirming that these secondary products are negligible.

Figure 3 shows the comparison between the UED data fits with $[\text{Fe}(\text{CO})_4]$ for the two different reaction pathways. The $[\text{Fe}(\text{CO})_4]$ structure in the $^1\text{A}_1$ state is very similar to that of $[\text{Fe}(\text{CO})_5]$ with one equatorial carbonyl group removed, while

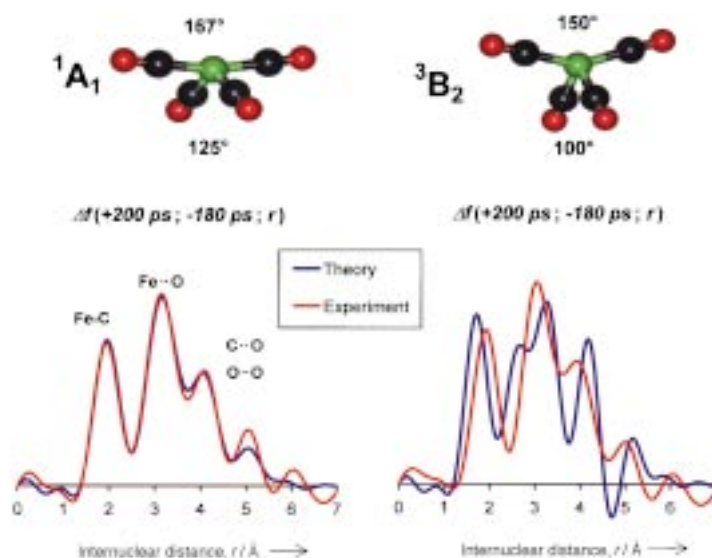


Figure 3. Ultrafast electron diffraction of the intermediate $[\text{Fe}(\text{CO})_4]$ species. Top: The structures of two possible electronic states ($^1\text{A}_1$ and $^3\text{B}_2$) for $[\text{Fe}(\text{CO})_4]$. The values for the angles are from ab initio calculations.^[19] Bottom: Comparison of experimental $-\Delta f(+200 \text{ ps}; -180 \text{ ps}; r)$ curves (red) with corresponding theoretical calculations (blue) obtained from ab initio structures of the $^1\text{A}_1$ state (left) and the $^3\text{B}_2$ state (right).

the structure of $[\text{Fe}(\text{CO})_4]$ in the $^3\text{B}_2$ state is significantly distorted.^[19] The C-Fe-C angles of the $^3\text{B}_2$ state are smaller and the Fe-C distances are longer than those of $[\text{Fe}(\text{CO})_5]$. As shown in Figure 3, the fit for the $^3\text{B}_2$ state is clearly inferior to that of the $^1\text{A}_1$ state, which gives a very good agreement between the experiment and theory. Therefore, $[\text{Fe}(\text{CO})_4]$ is formed following the singlet pathway of the reaction in its singlet excited state, $^1\text{A}_1$, rather than the ground state, $^3\text{B}_2$, at the excitation used.^[38] The $^1\text{A}_1$ state $[\text{Fe}(\text{CO})_4]$ may eventually convert into the $^3\text{B}_2$ state through intersystem crossing (thereby providing a more efficient route for the formation of the $^3\text{A}_2$ state $[\text{Fe}(\text{CO})_3]$), but intersystem crossing needs more than 200 ns,^[11, 25] which is beyond our investigated time range of up to 200 ps.

A closer examination of the $\Delta f(+200 \text{ ps}; -180 \text{ ps}; r)$ curve (Figure 3) reveals rich details of the structural changes due to the depletion of $[\text{Fe}(\text{CO})_5]$ and formation of $[\text{Fe}(\text{CO})_4]$. The two main peaks centered at about 2 Å and about 3 Å, respectively, indicate the depletion of the Fe-C and Fe...O internuclear contributions due to the liberation of CO. The shoulders beyond 3.5 Å are due to the reduction of other internuclear contributions, C...O and O...O, in the liberation process. The small peak for the C-O bond at about 1.12 Å is negative because the liberated CO ligand has a shorter bond length than that of the bound ligand (~1.15 Å), but the negative amplitude of the peak is small because the change (from 1.15 Å to 1.12 Å) is minute, causing the positive and negative contributions to nearly cancel out.

The structure of $[\text{Fe}(\text{CO})_4]$ obtained from our UED experiment was further refined by limiting the fit to a single product and floating all the independent structural parameters. The results are shown in Figure 4 and give the following structural parameters: $r(\text{Fe}-\text{C}1) = 1.81 \pm 0.03 \text{ \AA}$, $r(\text{C}1-\text{O}1) = 1.14 \pm 0.05 \text{ \AA}$, $r(\text{Fe}-\text{C}2) = 1.77 \pm 0.03 \text{ \AA}$; $r(\text{C}2-\text{O}2) = 1.15 \pm$

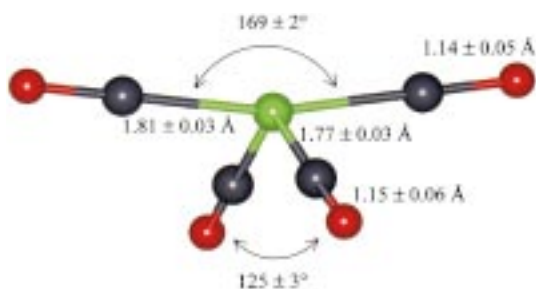


Figure 4. The refined molecular structure of $[\text{Fe}(\text{CO})_4]$ in the $^1\text{A}_1$ state, determined by ultrafast electron diffraction (see text).

0.06 Å, $\angle \text{C1-Fe-C1} = 169 \pm 2^\circ$, $\angle \text{C2-Fe-C2} = 125 \pm 3^\circ$. The error bars represent one standard deviation and do not account for systematic errors. The structure determined here is in good agreement with that determined by ab initio calculation^[19] for the $^1\text{A}_1$ state. Much earlier, Poliakoff and Turner in their studies of $[\text{Fe}(\text{CO})_4]$ found a species other than the triplet ground state and tentatively assigned the species to be in the singlet state stabilized by a CH_4 matrix at low temperatures. Their careful analysis of IR intensities led them to obtain $173.5 \pm 1^\circ$ and $125 \pm 2.5^\circ$ for C-Fe-C angles,^[26] which are remarkably close to our experimental UED values obtained for the isolated species.

In summary, the UED technique was used to study the elimination of CO ligands from $[\text{Fe}(\text{CO})_5]$. The molecular structure of the transient species was identified by using the temporal diffraction-difference approach of UED. Our results clearly showed that the major product, up to 200 ps, is the transient $[\text{Fe}(\text{CO})_4]$ formed in the $^1\text{A}_1$ state, rather than the ground $^3\text{B}_2$ state. The structure obtained from the diffraction data was further refined to give the bond lengths and angles of the transient $[\text{Fe}(\text{CO})_4]$ with a resolution of about 0.05 Å. This combined temporal and structural resolution should be of significant value in identifying transition configurations and pathways of other reactions.

Experimental Section

The second-generation UED apparatus^[28] is composed of a femtosecond laser, a picosecond electron gun, a free-jet expansion sample source, and a two-dimensional single-electron detection system. Femtosecond laser pulses from a colliding-pulse mode-locked ring dye laser were amplified in a four-stage pulsed dye amplifier pumped by a Nd:YAG laser. The amplified pulses (620 nm, 3 mJ pulse⁻¹, 30 Hz, ~ 300 fs pulse width) were then split into pump and probe laser pulses; 95% of each laser pulse (pump) was directed and focused into the gas sample beneath the needle of the free-jet expansion source in the scattering chamber. The remaining 5% (probe) was first frequency-doubled with a potassium dihydrogen phosphate crystal, and then focused onto a back-illuminated photocathode in the electron gun to generate the ps electron pulses.

The ultrashort electron pulses were accelerated to 18.8 keV (de Broglie wavelength is 0.088 Å) and focused into the scattering volume. The two-dimensional diffraction images were recorded at chosen delay times by a charge-coupled device camera at the end of a phosphor scintillator/fiber optic/image intensifier chain in the detection chamber. The electron pulse, laser pulse, and molecular beam were arranged in a cross-beam geometry, and the alignment of the three beams was controlled to within 10 μm. Time delays between the fs pump laser pulse and the ps electron pulse were controlled by a computer-driven translational stage. The diffraction images were taken with ultrashort electron pulses ($\sim 2 \times 10^4$ electrons per pulse, with temporal width of 15 ps), and the total temporal resolution is less than

20 ps. The beam waist of both the electron beam and laser beam was adjusted to be about 300 μm, and the camera length was measured to be 102.9 mm. This second-generation apparatus is now replaced with a third-generation machine which provides orders of magnitude improvement in time resolution and sensitivity.^[32]

$[\text{Fe}(\text{CO})_5]$ was purchased from Aldrich (98% purity). The sample was first purified through vacuum distillation and then transferred into a sample cell in situ. Following connection to the diffraction chamber, the sample was degassed by three cycles of freeze-pump-thaw. To provide enough molecular gas density in the scattering volume, the sample cell, gas line, and nozzle were heated to 47, 64, and 72 °C, respectively. The gas pressure in the scattering chamber during the experiment was about 4.6×10^{-4} Torr, and the pressure at the scattering volume was estimated to be about a few Torr.

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- [35] A smooth residual background with extremely small amplitude, a likely result of the interaction of probe electrons with positive ions in the gas sample generated by the intense laser pulses,^[29] was observed in our experimental ΔI_{tot} . The background was removed by fitting a smooth curve through the zero-crossing points of the theoretical ΔI_{tot} .^[29–32] The experimental ΔI_{tot} curve was smoothed by Fourier filtering^[32] (9 Å low-pass) and pixel regions showing systematic abnormalities were removed.^[32]
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- [37] The singlet $[\text{Fe}(\text{CO})_3]$ may, in principle, be generated through subsequent loss of a CO ligand from the singlet $[\text{Fe}(\text{CO})_4]$. However, consideration of the energetics eliminates this possibility. The total energy available following the dissociation of $[\text{Fe}(\text{CO})_5]$ into $[\text{Fe}(\text{CO})_4]$ and CO upon two-photon excitation at 620 nm (92 kcal mol⁻¹) is 33 kcal mol⁻¹, and at most about 65% (21 kcal mol⁻¹) of this remaining energy is retained as the internal excitation of $[\text{Fe}(\text{CO})_4]$.^[6, 9, 11] Since the energy gap between the singlet $[\text{Fe}(\text{CO})_4]$ and the singlet $[\text{Fe}(\text{CO})_3]$ is at least 22 kcal mol⁻¹, the available energy is not enough to liberate another CO ligand.
- [38] In our previous attempt^[29] to isolate the $[\text{Fe}(\text{CO})_4]$ species, 310 nm fs laser pulses were used to photolyze $[\text{Fe}(\text{CO})_5]$. Although one photon of 310 nm just falls short of the threshold for generating $[\text{Fe}(\text{CO})_2]$, $[\text{Fe}(\text{CO})]$ and Fe, it was found that in fact two-photon absorption dominated. Consequently, the major products obtained were actually $[\text{Fe}(\text{CO})_2]$, $[\text{Fe}(\text{CO})]$, and Fe rather than $[\text{Fe}(\text{CO})_4]$ or $[\text{Fe}(\text{CO})_3]$. In the present experiment, 620 nm photon excitation was used instead of 310 nm and the main absorption is two-photon. This excitation provides enough energy to break at most two Fe–C bonds, leaving $[\text{Fe}(\text{CO})_4]$ and $[\text{Fe}(\text{CO})_3]$ as major products.

Dual-Signaling Fluorescent Chemosensors Based on Conformational Restriction and Induced Charge Transfer**

Jesse V. Mello and Nathaniel S. Finney*

Fluorescent chemosensors provide a powerful optical method for spying on molecular recognition events. As a result, they have found practical application in cellular

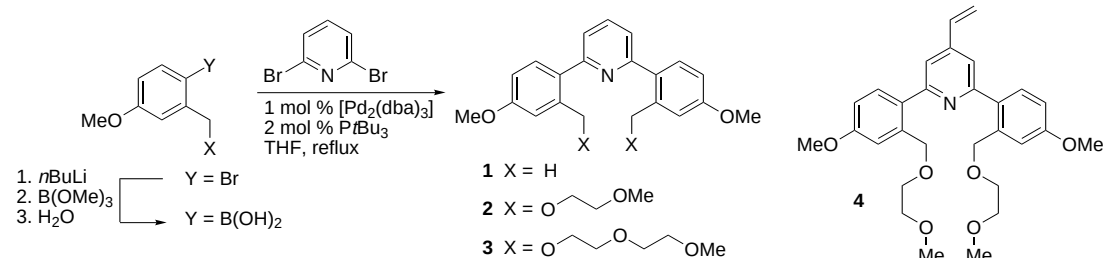
imaging, environmental monitoring, and biological assays.^[1] Chemosensors that allow the measurement of two different emissions bands have the important feature that they permit signal ratioing, which can increase the dynamic range and provide built-in correction for environmental effects.^[2] In addition, dual-channel fluorophores allow a change in perceived color as well as simple brightening, facilitating rapid visual assays.

A common feature of dual-channel fluorescent chemosensors is that substrate binding leads to enhancement of one emission channel at the expense of the other. We describe herein an exception to this generalization, in which the combination of two signaling mechanisms—conformational restriction and induction of charge transfer—allows metal binding to turn two fluorescence emission bands on independently.^[3]

Biarylpyridines **1–4** (Scheme 1) were chosen for the present study because of their synthetic accessibility and modest fluorescence emission from the locally excited (LE) state.^[4]

The unanticipated emission from an induced charge transfer (CT) state further extends the versatility of these fluorophores.^[5] The emission of **1** (1×10^{-5} M in CH₃CN) is illustrative: the neutral fluorophore exhibits strong LE emission at about 345 nm; on protonation of the pyridine nitrogen atom with trifluoroacetic acid, the LE emission is completely replaced by readily visible CT emission at about 450 nm (Figure 1).

Appending **1** with polyether metal binding domains leads to dual-channel fluorescent chemosensors that are remarkably responsive and selective given their structural simplicity. The titration of **2** (1×10^{-5} M in CH₃CN) with alkali metal and alkaline earth cations is representative (Figure 2). The addition of excess Li⁺ leads to strong (5.5-fold at λ_{max}) enhancement of the emission from the LE state, and concomitant increase in quantum yield as a result of binding-induced conformational restriction.^[6] In contrast, the addition of Mg²⁺ leads to a slight diminution of LE emission,



Scheme 1. Synthesis of biarylpyridines **1–4**. Compound **4** was synthesized analogously to **2** by using the 4-vinyl-substituted pyridine derivative. dba = *trans,trans*-dibenzylideneacetone.

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but an enhancement of CT emission. Notably, the addition of Ca²⁺ leads to simultaneous enhancement of *both* emission bands (Figure 2). The K_a values for the association of **2** with Li⁺, Mg²⁺, and Ca²⁺ are $6.7 \times 10^3 \text{ M}^{-1}$, $8.3 \times 10^2 \text{ M}^{-1}$, and $6.7 \times 10^2 \text{ M}^{-1}$ respectively.^[7, 8]

The seemingly minor structural change from **2** to **3** leads to a significantly altered metal-binding profile. While **3** still responds to Li⁺, it does so only weakly compared to **2** (I/I_0 at

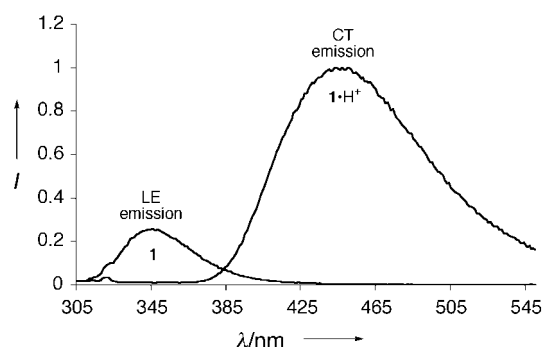


Figure 1. Emission spectra of **1**: the neutral fluorophore **1** exhibits strong LE emission at about 345 nm; the protonated form **1**·H⁺ displays a readily visible CT emission at about 450 nm.

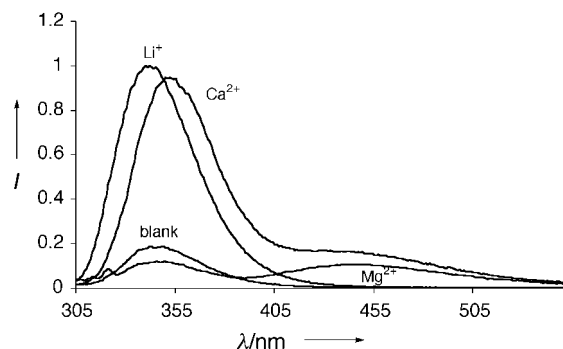


Figure 2. Curves for the titration of **2** (1×10^{-5} M in CH₃CN) with alkaline and alkaline earth cations.

$\lambda_{\text{max}} = 2.0$, $K_a = 4.0 \times 10^2 \text{ M}^{-1}$). Addition of Mg²⁺ again leads to a strong enhancement of CT emission, and the addition of Ca²⁺ leads to >10-fold enhancement of the LE without appreciable induction of CT.^[9] The K_a value ($1.7 \times 10^5 \text{ M}^{-1}$) for the combination of **3** and Ca²⁺ is very high for an acyclic polyether, and is comparable to those measured for K⁺ and [18]crown-6 in CH₃CN.^[10]

Biarylpyridine **2** is thus capable of uniquely identifying Li⁺, Mg²⁺, and Ca²⁺ ions, while **3** can readily distinguish Mg²⁺ and Ca²⁺ ions, entirely as a result of the independent signaling from two emission channels. To our knowledge, these compounds are the first chemosensors in which both fluorophore and binding mode play a role in determining the response to a given metal ion.

Judicious selection of the excitation and emission wavelengths can further enhance the sensitivity of **2** and **3**. By selectively exciting the LE or CT state, and by surveying I/I_0 ratios at all wavelengths for which emission from **2** is $\geq 50\%$ of its maximum intensity, CT fluorescence enhancements as high as 2500-fold can be observed for Mg²⁺ and as high as 605-fold for Ca²⁺ (Table 1).

Table 1. Summary of the fluorescence emission characteristics for **2** with various alkali metal and alkaline earth cations on selective excitation of the LE or CT state.

Metal ion	Excitation band	I/I_0 (LE)	I/I_0 (CT)
Li ⁺	LE	8.5	–
Mg ²⁺	CT	–	2505
Ca ²⁺	LE	6.5	134
Ca ²⁺	CT	–	605

Addition of a 4-vinyl substituent to the pyridine ring (**4**) sufficiently red shifts the LE emission that both LE and CT bands are visible. This visible emission allows **4**·Li⁺, **4**·Mg²⁺, and **4**·Ca²⁺ to be readily distinguished by eye (Figure 3), and **4** thus combines the sensitivity of fluorescence with the convenience and aesthetic appeal of a colorimetric assay.^[11]

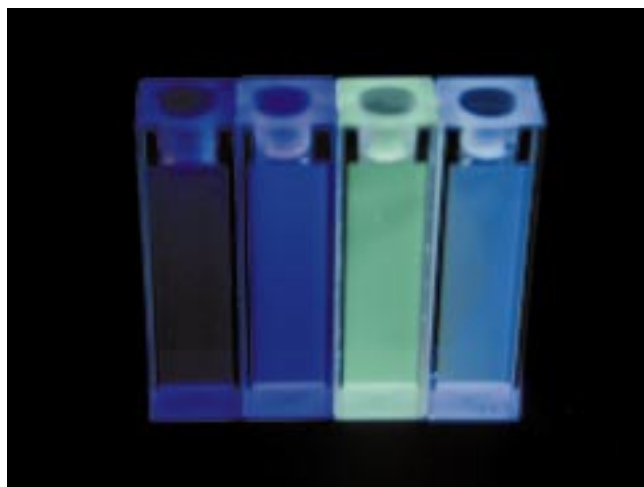


Figure 3. Visible emission observed from samples of **4** and various alkali metal and alkaline earth cations. Left to right: no metal, **4**·Li⁺, **4**·Mg²⁺, and **4**·Ca²⁺.

In a development that bodes well for the construction of combinatorial libraries of chemosensors,^[12] analogs of **4** immobilized on polystyrene resin exhibit similar emission upon UV irradiation. Elaboration of these solid-phase fluorescent chemosensors, as well as further photophysical characterization of **1**–**4**, will be reported in the near future.

Experimental Section

Fluorescence spectra were obtained on a Photon Technologies International QuantaMaster 2000 spectrophotometer, using excitation and emission slit widths of 5 nm. Fluorescence spectra were obtained using 10^{-5} M solutions of **1**–**4** in spectroscopic grade CH₃CN. No efforts were made to exclude H₂O or air. Metal solutions were prepared by dissolution of the appropriate perchlorate salt in spectroscopic grade CH₃CN. Fluorescence titrations were carried out by the addition of small volumes (5–30 μ L) of metal solution to 2.50 mL of 10^{-5} M fluorophore in a quartz cuvette; the solutions were allowed to equilibrate to full fluorescence response between aliquot additions. All liquid transfers were carried out with Eppendorf Reference pipettes.

Compounds **1**–**4** were prepared by similar methods; the preparation of **2** is representative (see Scheme 1). 2-(2-Methoxyethoxy)methyl-4-methoxyphenylboronic acid (1.52 g, 6.33 mmol, 2.20 equiv), 2,6-dibromopyridine (0.68 g, 2.88 mmol, 1 equiv), CsF (2.89 g, 19.01 mmol, 6.60 equiv), and tris(benzylideneacetone)dipalladium (0.03 g, 0.03 mmol, 0.01 equiv) were cooled to -78°C in dry THF (25 mL) under N₂. *t*-Bu₃ (1.21 mL, 0.05 M in THF, 0.06 mmol, 0.02 equiv) was added,^[13] and the solution degassed by repeated evacuation/N₂-flush cycles. The solution was warmed to room temperature, then heated to reflux for 12 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (100 mL) then washed with H₂O (2 $\times$) and saturated NaCl (1 $\times$). The organic layer was dried over MgSO₄, concentrated, and chromatographed on silica gel (30% THF–hexanes) to afford **2** (1.29 g, 2.76 mmol, 96%) as a pale yellow highly viscous oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.76 (t, 1 H, J = 7.8 Hz), 7.49 (d, 2 H, J = 8.4 Hz), 7.42 (d, 2 H, J = 7.6 Hz), 7.19 (d, 2 H, J = 3.2 Hz), 6.91 (dd, 2 H, J = 8.6, 2.6 Hz), 4.73 (s, 4 H), 3.86 (s, 6 H), 3.55 (m, 8 H), 3.36 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ = 159.6, 157.7, 137.6, 136.3, 132.5,

131.2, 121.5, 113.5, 113.2, 71.9, 71.1, 69.5, 59.1, 55.4; FTIR (neat film): $\tilde{\nu}$ = 2888 (w), 1614 (s), 1445 (s), 1241 (w), 1100 (w), 811 (s) cm^{-1} ; HRMS (MALDI): m/z : calcd for $\text{C}_{27}\text{H}_{34}\text{NO}_6$ [$M+H^+$] 468.2381; found 468.2370; TLC R_f (55% EtOAc/Hex) 0.20.

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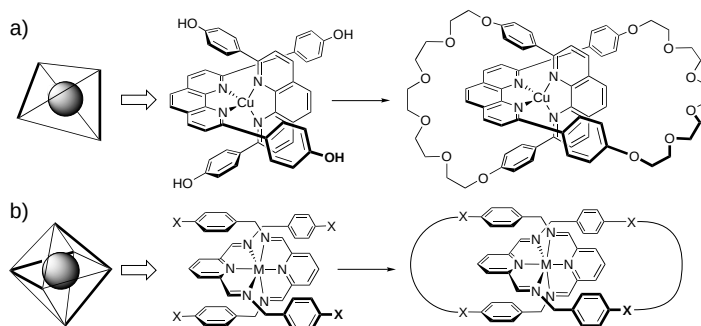
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Benzylic Imine Catenates: Readily Accessible Octahedral Analogues of the Sauvage Catenates**

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Historically, one of the triumphs of coordination chemistry has been its application to the synthesis of mechanically interlocked molecular architectures, that is catenanes, rotaxanes, and knots.^[1–10] In 1984 Sauvage et al. used the preferred tetrahedral geometry of Cu^I to organize appropriately derivatized phenanthroline ligands into a fixed mutually orthogonal orientation, whereupon a double macrocyclization reaction gave the [2]catenate in 27% yield (Scheme 1a).^[2]



Scheme 1. Synthesis of catenates by orthogonalization of coordinated ligands about metal templates with a) tetrahedral and b) octahedral coordination preference. M in (b): Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , Hg^{2+} .

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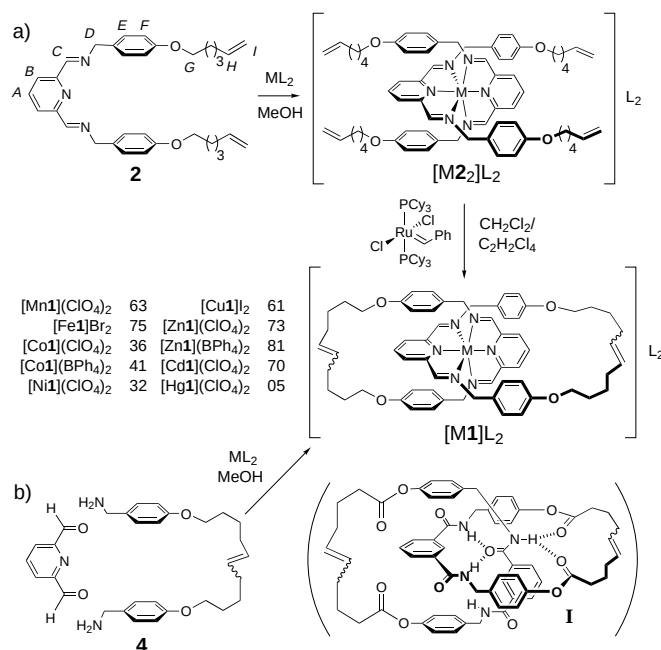
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Subsequent studies on the system boosted yields to near quantitative levels (by ring closing metathesis, RCM)^[3] and extended the interlocked architectures available to $[n]$ catenates ($n=2-8$),^[4] catenands (the demetalated, but still interlocked ligands),^[5] rotaxanes,^[6] pseudo-rotaxanes,^[7] and knots.^[8] Interlocked ligands can have remarkable properties; catenates are amongst the most stable complexes of Cu^I that exist with a neutral ligand,^[5] and catenands also stabilize^[9] the ordinarily disfavored tetrahedral geometries of Ni^I and Cu^0 . However, although other metals have been introduced^[9] and alternative trigonal-bipyrimidal “stations” employed in redox-switchable systems,^[10] the basic catenate assembly system based on a low oxidation state, tetrahedrally coordinated metal template and phenanthroline ligands has remained largely unchanged. Expanding this elegant strategy to include catenates with higher oxidation state, octahedrally coordinated metal centers is of obvious appeal (Scheme 1 b),^[11] and pioneering work in this regard has been carried out by Schröder et al.,^[12] Busch et al.,^[13] and others,^[14, 14] yet only two octahedral catenates^[14, 14] (and two knots^[15, 16]) have been described to date. Catenanes assembled by hydrogen bonds can exhibit a continuous range of (tunable) dynamic properties,^[17, 18] but the strong coordination bonds present in catenates lock the macrocyclic components in fixed positions whereas, in the absence of the metal, these rings rotate with virtually complete (but uncontrolled) freedom. The difference in the type of dynamics available to each system led us to seek a route to catenates of a size and shape that would be both compatible and interchangeable in molecular devices with benzylic amide catenanes assembled by hydrogen bonds (e.g. **I**).

The basic architecture of benzylic amide macrocycles is rather well suited to adapting to other sorts of assembly processes (Scheme 2). The rigid framework positions multiple donor groups such that they converge towards the center of the cavity, while the isophthalic spacer holds the aromatic rings in a parallel arrangement at a distance ideal for π stacking with an orthogonally bound guest. The 1,3-linked benzylic motif ensures a complete 180° turn for each fragment (in comparison to, say, the 120° turn for a diphenylphenanthroline unit) holding the endgroups in positions that promote intracomponent rather than intercomponent cyclizations.^[19] Thus, the only changes necessary to obtain a system based on metal ion chelation (i.e. arriving at complexes with the benzylic bis(2,6-diiminopyridine)catenand ligand **1**) was to replace the amide groups with imine groups and, for stability reasons, the phenolic esters with ethers (Scheme 2).

The zinc(II) perchlorate complex $[\text{Zn}_2](\text{ClO}_4)_2$ was isolated as a precipitate in 83 % yield from simple addition of a solution of the Schiff base ligand **2**^[20] in dichloromethane to a methanolic solution of $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. Imines are one of the few classes of substrates not normally compatible with olefin metathesis (indeed, the free Schiff-base ligand **2** cannot be converted into the macrocycle by RCM). However, pre-coordination ties up the imine groups and the tetraolefin complex $[\text{Zn}_2](\text{ClO}_4)_2$ smoothly underwent double macrocyclization by RCM with Grubbs' catalyst ($[\text{Ru}(\text{=CHPh})(\text{PCy}_3)_2\text{Cl}_2]$, CH_2Cl_2 , Ar, RT, 4 h) to give the zinc(II) catenate $[\text{Zn}_1](\text{ClO}_4)_2$ in 73 % yield as a mixture of *E,E*, *E,Z*, and *Z,Z* diastereomers (Scheme 2a). Exposure of the reaction mix-



Scheme 2. Synthesis of benzylic imine catenates $[\text{M}1]\text{L}_2$ by a) double macrocyclization of a preformed octahedral complex $[\text{M}_2]\text{L}_2$, b) spontaneous metal-promoted assembly of nonchelated precursors. The yields (in %) refer to route (a); the yields from route b are not yet optimized, but are uniformly higher. The ligand design is based on that of benzylic amide catenanes, e.g. **I**.^[17b]

ture to the metathesis catalyst for four days equilibrated the products to give almost exclusively the *E,E* isomer.

In contrast to the situation with the classic tetrahedral phenanthroline system, the same catenate $[\text{Zn}1](\text{ClO}_4)_2$ could also be prepared by assembling the coordinating sites in situ (Scheme 2b). Treatment of the bis-amine **4**^[21] with 2,6-pyridinedicarbaldehyde and $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in methanol resulted in the precipitation of the (*E,E*)-catenate after one hour in 53 % yield. In this case, the metal center orders the construction of the catenate about itself, through the reversible formation of four imine bonds from five components, as the lowest energy means by which it can satisfy its desired octahedral coordination geometry.

The ^1H NMR spectra of free ligand **2**, zinc(II) precursor complex $[\text{Zn}_2](\text{ClO}_4)_2$, and zinc(II) catenate $[\text{Zn}\{(E,E)\text{-}1\}](\text{ClO}_4)_2$ are shown in Figure 1 a–c. Shielding of the benzylic aromatic rings (H_E , H_F) in both the precursor complex (Figure 1 b) and the catenate (Figure 1 c) with respect to the free ligand (Figure 1 a) is indicative of the entwined (in the case of $[\text{Zn}_2]\text{L}_2$) or interlocked (in the case of $[\text{Zn}\{(E,E)\text{-}1\}]\text{L}_2$) architectures. Interestingly, subtle but significant differences take place in the shifts of all the non-alkyl chain resonances between $[\text{Zn}\{(E,E)\text{-}1\}]\text{L}_2$ and $[\text{Zn}_2]\text{L}_2$, indicating that a certain amount of reorganization of the ligands needs to occur during catenate formation.

Single crystals suitable for investigation by X-ray crystallography using a synchrotron source were obtained from slow vapor diffusion of diethyl ether into a solution of $[\text{Zn}\{(E,E)\text{-}1\}](\text{ClO}_4)_2$ in acetonitrile.^[22] The crystal structure (Figure 2) confirms the interlocked molecular architecture, the octahedral geometry around the coordinated zinc and the *E* configuration of the olefinic bonds in both rings. The benzylic

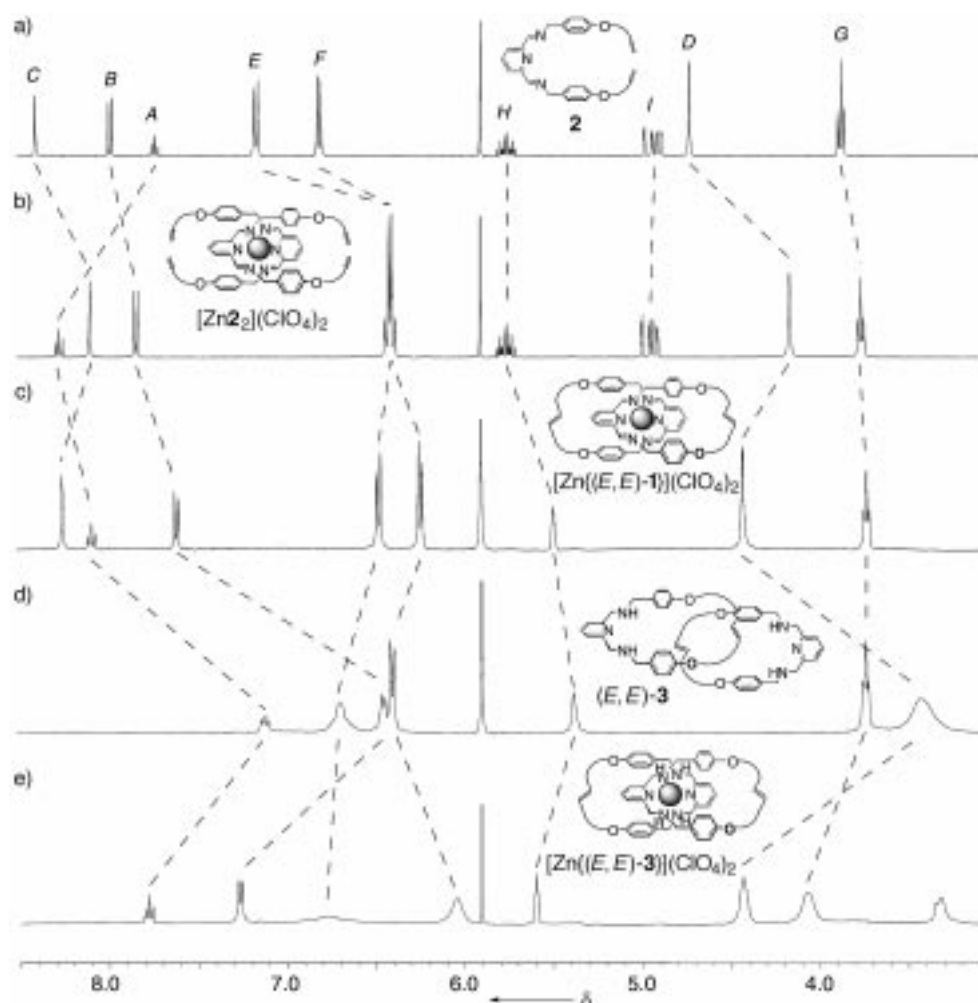


Figure 1. ^1H NMR spectra (400 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$, 298 K) of a) free Schiff-base ligand **2**, b) acyclic tetraolefin precursor complex $[\text{Zn}_2](\text{ClO}_4)_2$, c) benzylic imine catenane $[\text{Zn}\{(\text{E},\text{E})\text{-1}\}](\text{ClO}_4)_2$, d) free benzylic amine catenand $(\text{E},\text{E})\text{-3}$, and e) benzylic amine catenane $[\text{Zn}\{(\text{E},\text{E})\text{-3}\}](\text{ClO}_4)_2$. The assignments correspond to the lettering shown in Scheme 2 for compound **2**.

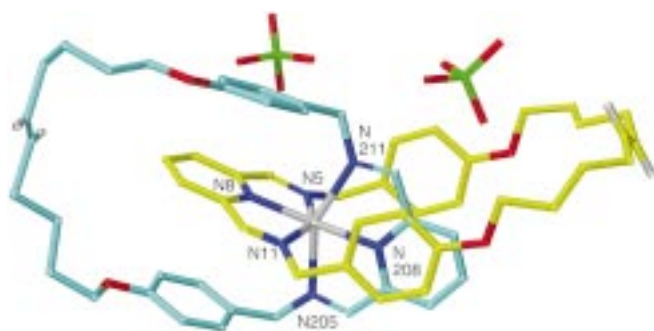


Figure 2. Structure of $[\text{Zn}\{(\text{E},\text{E})\text{-1}\}](\text{ClO}_4)_2$ as determined by X-ray crystallography.^[22] Carbon atoms of one macrocycle are shown in light blue and those of the other in yellow; oxygen atoms are red, nitrogen dark blue, chlorine green, hydrogen white, and zinc silver. Non-olefinic hydrogen atoms and a molecule of acetonitrile are omitted for clarity. Selected bond lengths [$\text{\AA}$]: Zn–N5 2.289, Zn–N8 2.048, Zn–N11 2.211, Zn–N205 2.264, Zn–N208 2.045, Zn–N211 2.276; other selected interatomic distances [$\text{\AA}$]: N5–N11 4.348, N8–N208 4.081, N205–N211 4.388; ligand bite angles [$^\circ$]: N5–Zn–N11 150.14, N205–Zn–N211 150.34.

groups of each macrocycle π -stack with the 2,6-diiminopyridine groups of the other interlocked ring, an interaction which is also clearly present in the precursor complex

$[\text{Zn}_2]\text{L}_2$ in halogenated solvents (see NMR data in Figure 1) and doubtless contributes to intracomponent rather than intercomponent cyclization occurring during RCM. Metal coordination necessarily buries the polar imine groups at the center of the molecular structure with the alkyl chains to the outside; a similar overall co-conformation to that observed in the solid state for amphiphilic benzylic amide catenanes.^[17a]

The bite angle of the ligand in $[\text{Zn}\{(\text{E},\text{E})\text{-1}\}](\text{ClO}_4)_2$ is slightly smaller (150°) than in nonmacrocyclic bis(2,6-diiminopyridine) complexes with Zn^{II} ^[13] (151°) and Ni^{II} ^[12, 13] ($151\text{--}156^\circ$), indicating that the ligand is able to adapt to the demands of its environment. Encouraged, we investigated the tolerance of the octahedral catenane assembly system by extending the RCM approach to metals both across and down the periodic table with respect to zinc (i.e. $\text{Mn} \leftarrow \text{Zn}$ and $\text{Zn} \rightarrow \text{Hg}$). The results (see Scheme 2) were uniformly satisfying with the precursor complexes and catenanes obtained in each case, often in good yields despite the

mixture of diastereomers complicating the purification process.^[23] Preliminary studies show that the same catenanes are also readily produced by the direct imine bond formation route (Scheme 2b). The crystal structures of two of these new catenanes, $[\text{Cu}\{(\text{E},\text{E})\text{-1}\}](\text{ClO}_4)_2$ and $[\text{Co}\{(\text{E},\text{E})\text{-1}\}]\text{I}_2$, were obtained by using a synchrotron radiation source (Figure 3). The bite angles in these catenanes proved larger than in the zinc system (152.1 and 152.7° (Cu), 152.9 and 154.5° (Co)) in line with observed trends with acyclic ligands, confirming the geometrical flexibility of the benzylic bis(2,6-diiminopyridine)catenand ligand system. Interestingly, all the catenanes are much more thermally stable than the corresponding precursor complexes. Whilst the acyclic coordination compounds $[\text{M}_2]\text{L}_2$ typically possess sharp melting points in the range $221\text{--}252^\circ\text{C}$, the analogous $[\text{M1}]\text{L}_2$ catenanes tend to gradually lose color and decompose at temperatures in excess of 350°C .

The properties of the zinc(II) catenane $[\text{Zn}\{(\text{E},\text{E})\text{-1}\}](\text{ClO}_4)_2$ were investigated in more detail (Scheme 3). By single-phase or biphasic extraction of $[\text{Zn}\{(\text{E},\text{E})\text{-1}\}](\text{ClO}_4)_2$ in various organic solvents (DMF, $\text{CHCl}_3/\text{H}_2\text{O}$, etc.) with up to 100 equivalents of EDTA, disodium salt, no signs of demetallating the catenane were obtained, suggesting that the

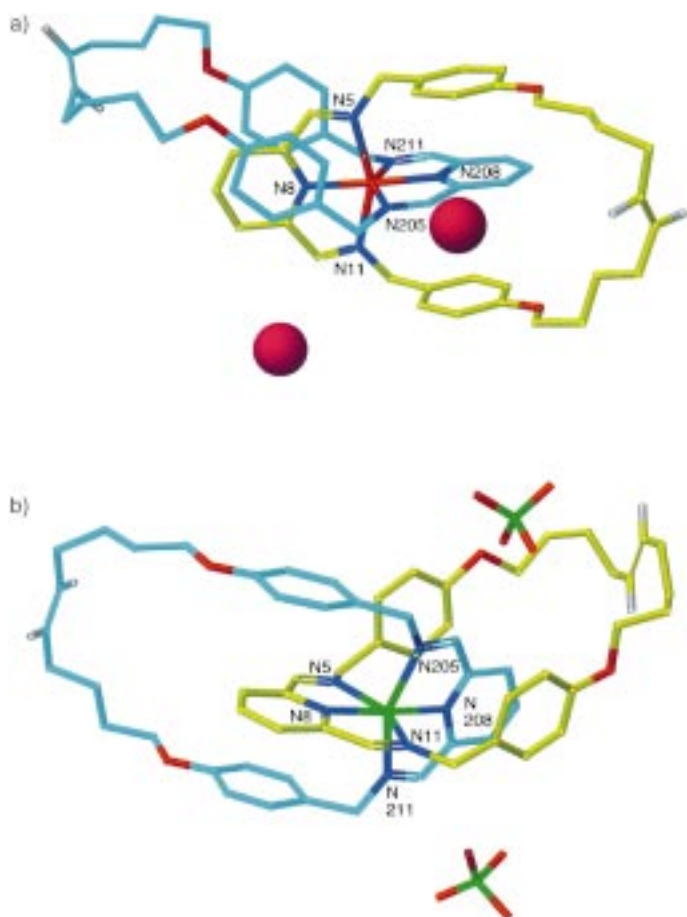
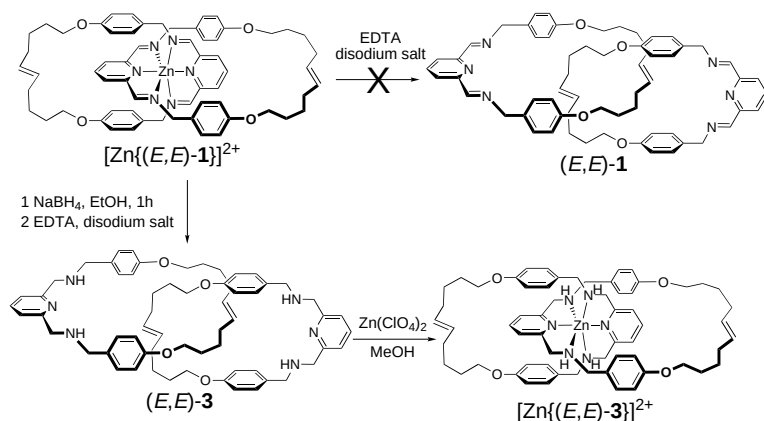


Figure 3. Structures of a) $[\text{Co}\{(E,E)\text{-1}\}]\text{I}_2$ and b) $[\text{Cu}\{(E,E)\text{-1}\}](\text{ClO}_4)_2$ as determined by X-ray crystallography.^[22] Color code as in Figure 2, cobalt red, copper green, iodide purple. Non-olefinic hydrogen atoms are omitted for clarity. Ligand bite angles [°]: N5-Co-N11 152.9, N205-Co-N211 154.5; N5-Cu-N11 152.1, N205-Cu-N211 152.7.



Scheme 3. The chemistry of the octahedral metal catenane $[\text{Zn}\{(E,E)\text{-1}\}](\text{ClO}_4)_2$. Direct demetalation is unsuccessful, but reduction of the imine groups allows extraction of the zinc to yield the free benzylic amine catenand $(E,E)\text{-3}$ (78 %). Remetalation affords the benzylic amine catenane $[\text{Zn}\{(E,E)\text{-3}\}](\text{ClO}_4)_2$ (ca. 100 %).

combination of the directional, planar diiminopyridyl coordinating motif and the tight, encapsulated architecture provides exceptional kinetic stability. However, reduction of the imine groups followed by washing with aqueous EDTA, disodium salt, resulted in the free benzylic amine catenand $(E,E)\text{-3}$. Re-

metallation proceeded smoothly to give the corresponding, clearly more labile, benzylic amine catenane $[\text{Zn}\{(E,E)\text{-3}\}](\text{ClO}_4)_2$. The ^1H NMR spectra of $(E,E)\text{-3}$ and $[\text{Zn}\{(E,E)\text{-3}\}](\text{ClO}_4)_2$ are shown in Figure 1d and e, respectively. The compact nature of the free ligand $(E,E)\text{-3}$ is convincingly demonstrated by the shielding of several resonances compared to the acyclic ligand **2**. Protons H_E and H_B for example, which intrinsically should be relatively unaffected by imine reduction, are shifted in $(E,E)\text{-3}$ by a similar magnitude to those in the $[\text{Zn}\{(E,E)\text{-1}\}](\text{ClO}_4)_2$ catenane and the $[\text{Zn}_2](\text{ClO}_4)_2$ precursor complex despite no directed inter-component interactions being present between the macrocycles in the catenand. The broad appearance of several resonances in the spectrum of the catenand is probably due to co-conformational exchange processes that are not fast on the NMR time scale at room temperature. The broadened peaks in the spectrum of the amine catenane $[\text{Zn}\{(E,E)\text{-3}\}]\text{L}_2$, however, may be a result of multiple asymmetric centers being produced by coordination of the four nitrogen atoms which are prochiral in the free ligand **3**.

In conclusion, a simple, versatile and effective route exists to octahedrally coordinated analogues of the Sauvage catenanes. This route should be extendable to the synthesis of other metal-based interlocked architectures (such as rotaxanes, shuttles, and knots), and the octahedrally coordinated catenanes should be interchangeable in possible molecular devices with catenanes assembled by hydrogen bonds. Catenanes are not only a means of stabilizing unusual oxidation states and normally disfavored geometries, but could also find uses in areas where complexes with particularly high kinetic stabilities are required, such as radiotherapy^[24] and magnetic resonance imaging,^[25] because of the wide range of metals that can adopt octahedral coordination patterns. Finally, we are well aware that metal complexes of 2,6-diiminopyridine

ligands also form an important new generation of non-metallocene olefin polymerization catalysts^[26] and that intertwined versions of such structures exhibit novel forms of columnar liquid crystalline behavior.^[27] The possible application of translationally switchable mechanically interlocked architectures (containing unsaturated metal centers in the case of potential polymerization catalysts) to these areas should be fascinating.

Experimental Section

Route (a) of Scheme 2 (RCM): Grubbs' metathesis catalyst $[\text{Ru}(\text{=CHPh})(\text{PCy}_3)_2\text{Cl}_2]$ (0.02 g, 0.0243 mmol, 20 mol %) was placed in a sealed, argon-purged, flame-dried Schlenk tube, and subjected to a constant stream of argon for ten minutes. A degassed and argon-purged solution of the $[\text{M}_2]\text{L}_2$ complex (0.122 mmol) in anhydrous dichloromethane (500 mL) was transferred to the Schlenk tube by injection over ten minutes. Reaction was allowed to continue until all the starting material was consumed as evidenced by TLC (typically 4 h), or, in order to maximize the amount of E,E diastereomer, for 4 days. The resulting solution was evaporated to dryness and purified by repeated chromatography (silica gel, 1–5 % MeOH in CH_2Cl_2 as eluent) to give the catenanes $[\text{M}_1]\text{L}_2$ as variously colored solids. Selected data for $[\text{Zn}\{(E,E)\text{-1}\}](\text{ClO}_4)_2$: yield: 112 mg, 73 %; m.p. 350 °C (decomp); ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 1.58 (m, 8H, CH_2), 1.74 (m, 8H, CH_2), 2.12 (m, 8H, $\text{CH}_2\text{CH=CH}$), 3.85 (t, 8H, $\text{J} =$

6.5 Hz, H_G), 4.49 (brs, 8H, H_D), 5.61 (t, 4H, $J = 3.0$ Hz, H_H), 6.36 (AA'BB' system, 8H, $J = 8.0$ Hz, H_E), 6.53 (AA'BB' system, 8H, $J = 8.0$ Hz, H_F), 7.70 (d, 4H, $J = 8.0$ Hz, H_B), 8.42 (t, 2H, $J = 8.0$ Hz, H_A), 8.50 (s, 4H, H_C); ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 25.89, 28.05, 31.50, 60.76, 67.17, 113.91, 127.02, 129.34, 129.97, 130.62, 144.37, 145.25, 158.24, 160.27$. FAB-MS ($m\text{BNA}$ matrix): m/z : 1126 $[\text{M} - \text{ClO}_4]^{+}$; anal. calcd for: $\text{C}_{62}\text{H}_{70}\text{O}_{12}\text{N}_6\text{Cl}_2\text{Zn}$ (1225): C 60.73, H 5.71, N 6.86%, found: C 60.46, H 5.97, N 6.67%.

Route (b) of Scheme 2: A solution of 2,6-pyridinedicarbaldehyde (0.97 g, 7.2 mmol) in methanol (10 mL) was added dropwise over 30 min to a solution of bis-amine **4** (7.2 mmol) and metal salt (ML_2 , 3.6 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 1 h after which time the $[\text{M}]\text{L}_2$ catenate could either be isolated as a precipitate by filtration, or the solvent removed under reduced pressure and the resulting solid purified as for the RCM procedure.

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- [20] Compound **2** was conveniently prepared in three steps from 4-hydroxybenzonitrile: 1) $\text{HO}(\text{CH}_2)_4\text{CH}=\text{CH}_2$, Ph_3P , DEAD, THF, 0°C , 59%; 2) LiAlH_4 , THF, $-78^\circ\text{C} \rightarrow \text{reflux}$, 94%; 3) 2,6-pyridinedicarbaldehyde, MeOH, 92%.
- [21] Compound **4** was conveniently prepared in three steps from 5-hexenyloxybenzylamine: 1) $t\text{Boc}_2\text{O}$, NEt_3 , MeOH, 87%; 2) $[\text{Ru}(\text{CHPh})(\text{PCy}_3)_2\text{Cl}_2]$, CH_2Cl_2 , Ar, RT, 24 h, 78%; 3) $\text{CF}_3\text{CO}_2\text{H}$, then NEt_3 , CH_2Cl_2 , 93%.
- [22] $[\text{Zn}\{(E,E)\text{-1}\}(\text{ClO}_4)_2 \cdot \text{C}_{62}\text{H}_{70}\text{Cl}_2\text{N}_6\text{O}_{12}\text{Zn} \cdot 0.5(\text{C}_2\text{H}_5\text{N})]$, $M_r = 1248.04$, crystal size $0.14 \times 0.08 \times 0.06$ mm, monoclinic $P2_1/c$, $a = 10.6258(5)$, $b = 17.4158(9)$, $c = 33.4757(18)$ Å, $\beta = 97.232(2)^\circ$, $V = 6145.6(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.349 \text{ Mg m}^{-3}$, synchrotron radiation (CCLRC Daresbury Laboratory Station 9.8, silicon monochromator, $\lambda = 0.69280$ Å), $\mu = 0.553 \text{ mm}^{-1}$, $T = 150(2)$ K. 22797 data (7081 unique, $R_{\text{int}} = 0.0489$, $1.65 < \theta < 21.00^\circ$) were collected on a Siemens SMART CCD diffractometer using narrow frames (0.2° in ω), and were corrected semiempirically for absorption and incident beam decay (transmission 0.83–1.00). The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 values of all data (G. M. Sheldrick, SHELXTL Manual, Version 5, Siemens Analytical X-ray Instruments, Madison, WI, **1994**) to give $wR = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2} = 0.2984$, conventional $R = 0.1087$ for F values of 7081 reflections with $F_o^2 > 2\sigma(F_o^2)$, $S = 1.066$ for 761 parameters. Residual electron density extremes were 0.974 and -0.563 e Å^{-3} . The alkyl chains were modeled by using both geometrical and displacement parameter restraints. Hydrogen atoms were added in calculated positions and constrained to a riding model. Data for the copper catenate $[\text{Cu}\{(E,E)\text{-1}\}(\text{ClO}_4)_2]$ was collected and solved as above except: $\text{C}_{62}\text{H}_{71}\text{CuN}_6\text{O}_{12}$, $M_r = 1226.69$, crystal size $0.14 \times 0.10 \times 0.01$ mm, monoclinic $P2_1/c$, $a = 10.2948(6)$, $b = 17.4273(10)$, $c = 33.1511(18)$ Å, $\beta = 96.120(2)^\circ$, $V = 5913.8(6)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.378 \text{ Mg m}^{-3}$, synchrotron radiation (CCLRC Daresbury Laboratory Station 9.8, silicon monochromator, $\lambda = 0.68950$ Å), $\mu = 0.528 \text{ mm}^{-1}$, $T = 150(2)$ K. 10342 data (3460 unique, $R_{\text{int}} = 0.0784$, $1.93 < \theta < 16.50^\circ$), correction for absorption and incident beam decay (transmission 0.9298–0.9947) $wR = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2} = 0.3840$, conventional $R = 0.1556$ for F values of 3460 reflections with $F_o^2 > 2\sigma(F_o^2)$, $S = 2.349$ for 339 parameters. Residual electron density extremes were 0.795 and -0.785 e Å^{-3} . Data for the cobalt catenate $[\text{Co}\{(E,E)\text{-1}\}_2]$ was collected and solved as the others except: $\text{C}_{63}\text{H}_{70}\text{CoI}_2\text{N}_{6.5}\text{O}_4$, $M_r = 1294.99$, crystal size $0.14 \times 0.10 \times 0.01$ mm, monoclinic $P2_1/c$, $a = 10.2948(6)$, $b = 17.4273(10)$, $c = 33.1511(18)$ Å, $\beta = 96.120(2)^\circ$, $V = 5913.8(6)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.454 \text{ Mg m}^{-3}$, synchrotron radiation (CCLRC Daresbury Laboratory Station 9.8, silicon monochromator, $\lambda = 0.68950$ Å), $\mu = 1.386 \text{ mm}^{-1}$, $T = 150(2)$ K. 28253 data (5997 unique, $R_{\text{int}} = 0.1119$, $1.93 < \theta < 20.00^\circ$), correction for absorption and incident beam decay (transmission 0.8296–0.9863), $wR = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2} = 0.2662$, conventional $R = 0.1246$

for F values of 5997 reflections with $F_o^2 > 2\sigma(F_o^2)$, $S = 1.215$ for 689 parameters. Residual electron density extremes were 0.955 and $-1.662 \text{ e } \text{\AA}^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147870 ($[\text{Zn}\{(E,E)\text{-1}\}](\text{ClO}_4)_2$), CCDC-152441 ($[\text{Cu}\{(E,E)\text{-1}\}](\text{ClO}_4)_2$), and CCDC-152442 ($[\text{Co}\{(E,E)\text{-1}\}]\text{I}_2$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [23] The yields listed in Scheme 2 are yields after chromatography or recrystallization. Sometimes the mixture of olefin diastereomers complicates purification and, in particular, is a factor in the modest yields of $[\text{Co1}]\text{L}_2$ and $[\text{Ni1}]\text{L}_2$. The very low yield of $[\text{Hg1}]\text{L}_2$ by route (a) is caused by the lability of the ligands in the precursor complex $[\text{Hg2}]\text{L}_2$, which liberates free amine or imine in the reaction and prevents RCM occurring. All compounds gave satisfactory mass spectra, elemental analysis, IR, UV/Vis, and, with the exception of the paramagnetic catenates, ^{13}C and ^1H NMR data.
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Insertion of Helium and Molecular Hydrogen Through the Orifice of an Open Fullerene**

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*Dedicated to Professor Fred Wudl
on the occasion of his 60th birthday*

One of the most exciting features of C_{60} and the higher fullerenes is that their carbon cages have inner cavities large enough to hold any atom and even small molecules.^[1, 2] The physical and chemical properties of these caged compounds (endohedral complexes) are determined by the degree of interaction established with the π -electron shell and the overall oxidation state of the complex.^[3] As such, endohedral

complexes offer a number of prospects for novel materials.^[4–6] A large effort has been invested in finding efficient methods for the preparation and purification of these compounds.^[1, 2, 7] So far, endohedral complexes have been formed with lanthanide or alkaline earth metals as charge transfer species,^[1, 2] and with the rare gases^[8, 9] or atomic nitrogen^[10] as neutral complexes. Processes using the evaporation of graphite–metal oxide composites, as well as high-pressure and high-temperature or even high-energy plasma insertions into pure fullerenes, have been reported.^[1–7] These methods constitute remarkable achievements and have already brought forth important insight into the properties of endohedral fullerene complexes. Nevertheless, they are still limited in scope and, more significantly, tend to give small amounts of material or meager incorporation fractions.

A stimulating prospect for the formation of these compounds can be described as a “molecular surgery” approach, which consists of the chemical creation of an opening within the fullerene cage (Figure 1a).^[4] The opened species would allow the introduction of an atomic or molecular species, which could be followed by the “suturing” of broken bonds back onto the original framework. Each of these steps presents unique nontrivial challenges. The development of an effective method to open up the framework of C_{60} by a one-pot reaction with bisazide **2**, to afford bislactam **1**,^[11] provides an unprecedented opportunity for the preparation of endohedral complexes. We now report the successful insertion of two small neutral gases, helium and molecular hydrogen, into the fullerene bislactam derivative **1** which results in the highest incorporation fractions for any gas to date in a direct insertion process.

Bislactam **1** has currently the largest orifice formed in the shell of a fullerene with an inviting open-mouth shape.^[4, 11] The amount of energy needed to push atoms or molecules through the orifice of **1** was first calculated using hybrid density functional theory. Activation barriers to insertion obtained as a function of guest size are listed in Table 1. The ground-state structures for empty bislactam **1**, its inclusion complexes of the inert gases He, H_2 , Ne, N_2 , and Ar, and the transition structures for their encapsulation were fully optimized at the B3LYP/3-21G level of theory, and energies were computed from these geometries using the 6-31G** basis set.^[12]

The overall insertion processes for the smallest species (He, H_2) are predicted to be slightly endothermic ($0.2\text{--}1.4 \text{ kcal mol}^{-1}$, Table 1). Patchkovskii and Thiel have investigated the encapsulation of helium by C_{60} using MP2 calculations,^[13] and found a favorable binding of $2.0 \text{ kcal mol}^{-1}$ as a result of van der Waals interactions of all sixty carbon atoms with the helium atom. These authors conclude that DFT calculations underestimate the exothermicity of He encapsulation within C_{60} by about 3 kcal mol^{-1} compared to the MP2 results, and thus the encapsulation of H_2 and He within the fullerene framework of **1** can be expected to be thermoneutral or slightly exothermic.

The predicted barrier for insertion of H_2 is nearly double that of helium, even though both species have similar van der Waals radii (1.20 and $1.22 \text{ \AA}$, respectively).^[14] The single imaginary vibrational modes at the transition states for

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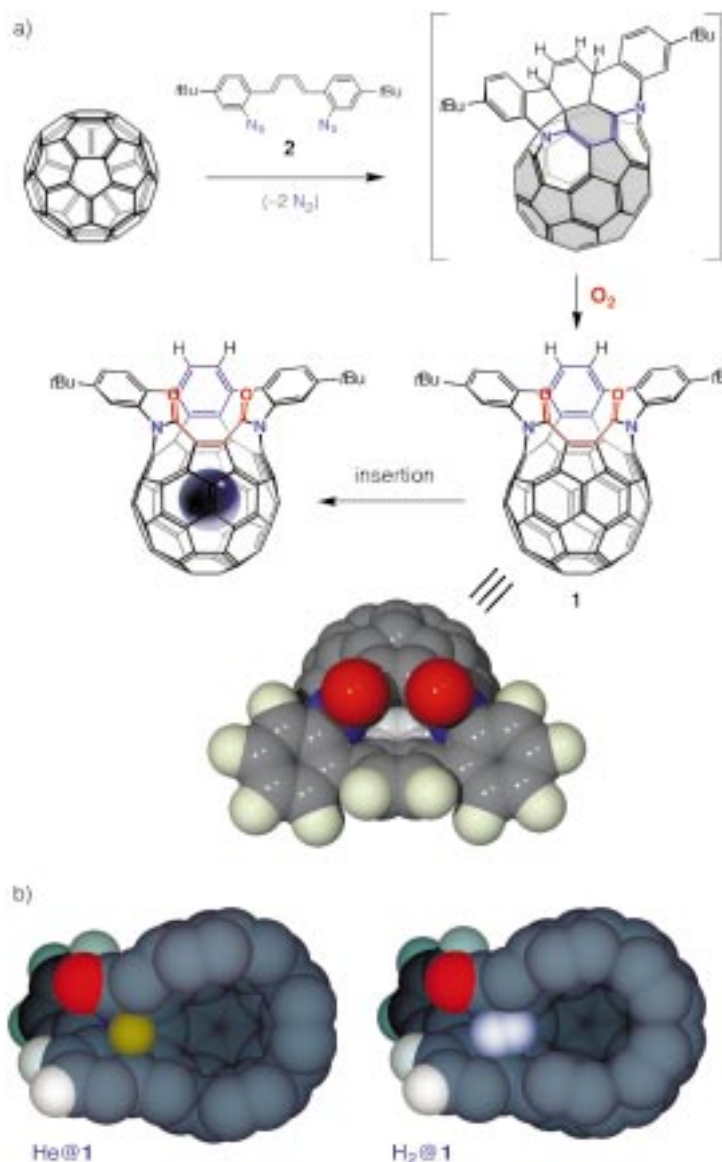


Figure 1. a) Preparation and structure of bislactam **1** and insertion of He and H₂ in this molecular container. The synthesis of the open fullerene **1** from bisazide **2** was previously reported.^[11] b) Cutout views of space-filling models for the B3LYP/3-21G transition structures of both helium and molecular hydrogen insertions.

Table 1. Predicted activation barriers for insertion and cage escape, and energies (B3LYP/6-31G**//B3LYP/3-21G, kcal mol⁻¹) of encapsulation for the neutral guests He, Ne, H₂, N₂, and Ar gases inside the open fullerene bislactam **1**. Insertion temperatures are estimated as explained in the text.

Guest	Volume ^[22] [Å ³]	Est. insertion temperature [°C]	Barrier to insertion	Energy of encapsulation	Barrier to escape
He	11.0	124	+24.5	+0.2	+24.3
H ₂	19.0	397	+41.4	+1.4	+40.0
Ne	14.6	384	+40.6	-1.1	+41.7
N ₂	35.3	1550	+112.4	+5.6	+106.8
Ar	28.9	1930	+136.3	+6.1	+130.2

He or H₂ insertions (255i and 502i cm⁻¹, respectively) clearly correspond with the exit/entrance motion of He or H₂. The fullerene cage itself undergoes practically no distortion in this

process, except for a comparatively low amplitude, strain-releasing vibration of the C=C bond between the two carbonyl groups.

The difference in barriers can be understood in terms of the varying amounts of constriction both species encounter at their respective transition states to insertion and escape (Figure 1b). With its elongated shape and larger surface area, H₂ experiences much greater steric interaction while forcing its way through the “neck” of bislactam **1**, while the spherical helium atom encounters much less surface contact. There is a roughly linear correlation between the guest volumes (He and N₂) and activation barriers for insertion (Table 1). The total surface exposed to the long narrow channel, not the shortest distance across the guest molecule, determines the barrier.

The temperatures required for guest insertion were estimated from the computed activation barriers (Table 1). These values were obtained from the Arrhenius equation using an approximated pre-exponential factor^[15] and an arbitrary 24 h reaction period. These estimates show that helium should insert relatively easily at temperatures around 100–120 °C, while H₂ would require much more drastic conditions, with temperatures of about 400 °C being necessary to effect insertion.

Besides overcoming such insertion barriers, the reaction equilibria can be assumed to lie in a thermoneutral to slightly exothermic range, as discussed earlier. However, the entropic cost for the insertion process is very high (see below). The occupied fraction of the gas at atmospheric pressure under equilibrium conditions might be expected to be small because of the small volume of the cavity. Higher pressures would therefore enhance the fraction of gas incorporated.

Incorporation experiments were initially carried out with helium. The ³He isotope constitutes a very convenient and sensitive NMR probe for environmental changes;^[9] it displays large upfield chemical shifts on insertion ($\delta = -6.3$ for ³He@C₆₀ to -28.8 for ³He@C₇₀), and does not give the same interference problems that impurities can introduce in ¹H NMR spectroscopy. Incorporation was found to occur readily, even under low helium pressure (3–4 atm, 100 °C, 8 h) using a sealed NMR tube. ³He NMR (deuterated *ortho*-dichlorobenzene ([D₄]ODCB), 31268 accumulated transients) showed a new peak at $\delta = -10.10$ relative to the reference at $\delta = 0$ for the free dissolved ³He gas. The fraction incorporated at this low pressure (0.03 %, or 0.05 % after 24 h under the same conditions) already approaches that of ³He@C₆₀ (0.1 %) prepared by the direct high pressure method.^[8, 9] The helium can be ejected by heating above 150 °C. Higher pressures were used subsequently to increase the fraction of helium inside bislactam **1**: Heating compound **1** as a crystalline powder under a helium atmosphere contained within a crimped copper tube (288–305 °C, ca. 475 atm (ca. 7000 psi) 7.5 h) in a high-pressure vessel, afforded ³He@**1** with about 1.5 % molar ratio of the gas versus a ³He@C₆₀ standard. Such high incorporation allowed for the direct experimental determination of the activation barrier for escape of ³He (Table 2, Figure 2). The change in the relative ³He signal intensities collected at four constant temperatures (80, 100, 120, and 130 °C) versus ³He@C₆₀ as the nondecomplexable standard were monitored over time

Table 2. Experimental data for the release of ^3He from bislactam **1** at four temperatures, integrated changes in ratios of $^3\text{He@1}$ to $^3\text{He@C}_{60}$, and rates of release.

T [°C]	t [h]	$^3\text{He@1}/^3\text{He@C}_{60}$	k [s ⁻¹] ($\times 10^6$)
80 $\pm$ 2	24	7.62 $\rightarrow$ 6.45	1.9
100 $\pm$ 1	12	6.45 $\rightarrow$ 3.39	14.9
120 $\pm$ 1	3	3.39 $\rightarrow$ 1.47	77.4
130 $\pm$ 0.5	1	1.47 $\rightarrow$ 0.86	148.9

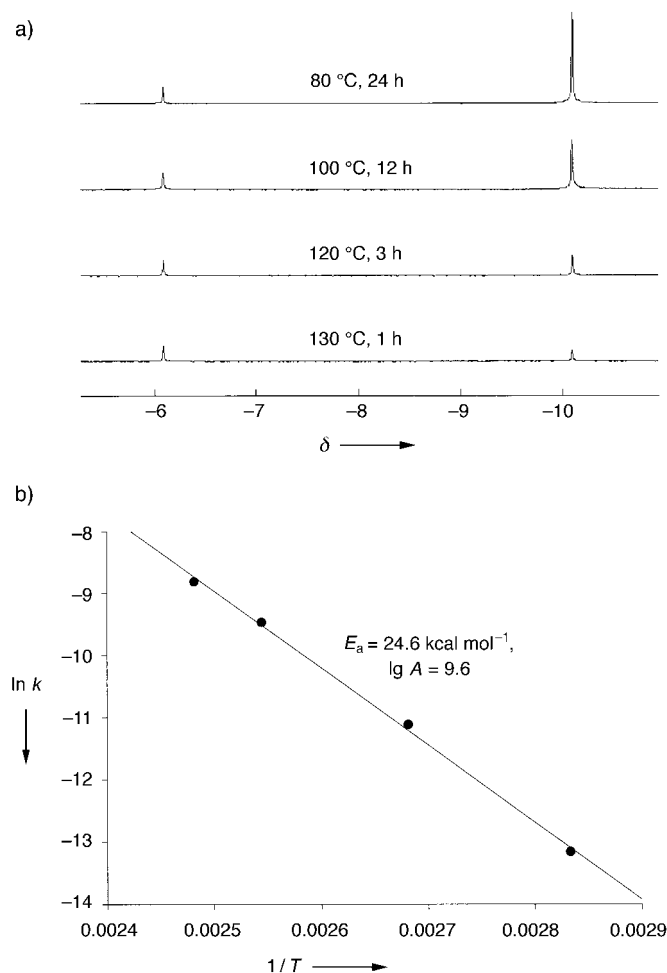


Figure 2. a) ^3He NMR spectra of $^3\text{He@C}_{60}$ ($\delta = -6.09$) and $^3\text{He@1}$ ($\delta = -10.10$) at four release temperatures. The ratios of both helium-containing compounds were compared by integration. b) Arrhenius plot for the release of helium from **1**.

(Figure 2a), with the resulting Arrhenius plot giving the excellent linear fit shown in Figure 2b. The activation barrier for escape of ^3He from the cage is $24.6 \pm 0.8 \text{ kcal mol}^{-1}$, which is in excellent agreement with the calculated value (Table 1).

The Arrhenius preexponential factor ($10^{9.6}$) corresponds to a substantially unfavorable entropy of activation ($\Delta S^\ddagger \cong -17 \text{ eu}$). Vibrational analysis of the transition structure for helium release clearly demonstrates the loss of translational degrees of freedom of the helium atom upon reaching the constrictive neck of the orifice of bislactam **1** (Figure 1b). However, when fully encapsulated within **1**, the helium atom does not significantly interact with the inner walls of the fullerene cage nor the gate orifice. The resulting practically

free motion of ^3He encapsulated in **1** is lost in the transition state for cage escape as a consequence of the constriction at the orifice. Consideration of the release of helium from the fullerene cage of **1** as a quasi-bimolecular reaction possessing a constricted transition state, rather than as a unimolecular reaction, explains the observed low pre-exponential factor and negative activation entropy. The entropy of ^3He , all translational, is 30 eu. The maximum $\Delta S^\ddagger$ value for completely restricting the translational motion of a free helium atom would thus be -30 eu , but the measured activation entropy of helium release is more than one half this value.

The incorporation of molecular hydrogen was investigated in the same manner. As expected from the calculations, the incorporation of H_2 required much more forcing conditions for insertion than helium. After several unsuccessful trials in high-boiling solvents, bislactam **1** was heated as a crystalline powder up to the limit of decomposition (400°C ,^[16] 48 h, $\leq 30\%$ of decomposed material) in a standard autoclave under 100 atm (1500 psi) of hydrogen. Purification by column chromatography (SiO_2 , toluene/EtOAc 9/1) was performed to give pure bislactam **1** together with the fraction of incorporated material $\text{H}_2\text{@1}$. The ^1H NMR spectrum showed a new peak at $\delta = -5.43$, in addition to the expected aromatic and aliphatic resonances for the bislactam moiety (Figure 3). This

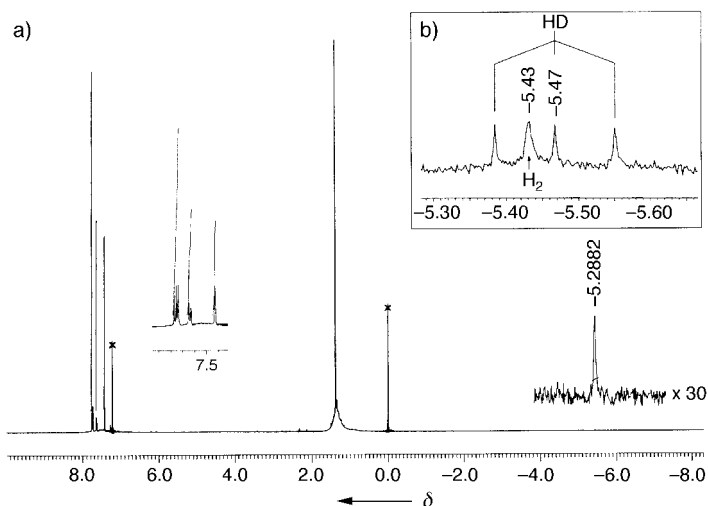


Figure 3. a) ^1H NMR spectrum of the H_2 -incorporated material. The signal corresponding to $\text{H}_2\text{@1}$ at $\delta = -5.43$ (HD@1: $\delta = -5.47$ in inset) has approximately 5% integral intensity of the aromatic signals for the empty and filled species.^[18] The reasons for the broad aromatic and *tert*-butyl peaks are not quite clear, but they also appear similarly broadened in the pristine bislactam **1** and are most likely post-purification oxidation byproducts (bislactam **1** is somewhat unstable in solution). b) ^1H NMR spectrum of the HD-incorporated material; the sample contained about 30% of H_2 as an impurity generated during the preparation of the gas from CaH_2 and D_2O .

new peak is shifted by 10 ppm upfield from dissolved H_2 ($\delta = 4.53$), measured separately, clearly lying outside the normal resonance range ($\delta = 0\text{--}10$) of most proton-containing compounds.^[17] The relative intensity for incorporated H_2 was found to be as high as 5%.^[18] This is by far the highest amount of direct incorporation in a fullerene obtained for any gas,

which bodes well for future insertions of higher fractions of these gases under extreme pressures.

A fully convincing demonstration of this incorporation was obtained by replacing H₂ with the monodeuterated species HD (309–322 °C, 15 h, 340 atm (5000 psi)).^[19] The corresponding resonance at $\delta = -5.47$ is now a triplet with a coupling constant of 41.8 Hz (Figure 3, inset), which is in accord with the literature value.^[20] Interestingly, the peak for the H₂ signal, which originated as an impurity during the synthesis of HD from CaH₂ and D₂O, appears as a much broader line than the other three HD signals. A likely explanation for this effect is that the very short bond length in the H–H molecule results in a strong dipole–dipole interaction between the two nuclei which leads to rapid relaxation and broadening since its rotation is somewhat impeded by the cage.

Comparison of the experimental chemical shifts observed for H₂ and ³He inside bislactam **1** and their calculated values gives further support to the effectiveness of these insertion experiments. ¹H and ³He NMR chemical shifts were calculated at the B3LYP/6-31G** level of theory using the Gauge Invariant Atomic Orbital (GIAO) approach.^[21] The calculated chemical shifts of He and H₂ are predicted to be strongly shielded by the fullerene π -electron shell of **1** as a result of encapsulation and shift substantially upfield (–8.6 and –8.0 ppm, respectively) versus free ³He and H₂; the experimental shielding values are $\delta = -10.10$ and -9.96 , respectively.

The successful incorporation of two gases inside bislactam **1** presages the insertion of metal ions and somewhat larger molecular species within wider openings of future fullerene derivatives.^[4] Furthermore, neon should also insert into bislactam **1** (Table 1), but this element lacks the convenience of having an NMR-active nucleus. On the other hand, the larger neutral gases N₂ and Ar cannot be incorporated within **1** under similar conditions because of the huge associated activation barriers. The important step of closing back the fullerene framework also needs to be studied. We have observed strong peak intensities from C₆₀ cations (up to 35 % (relative intensity) for the peak at $m/z = 720$ amu) being formed in the fast atom bombardment (FAB) mass spectra of bislactam **1**. This result shows that this heavily modified framework can still find its way back to the highly stable fullerene framework of C₆₀. This work shows more generally that open fullerenes afford an opportunity to study the dynamics of passage of small molecules or ions through restricted channels in chemically well-defined systems.

Received: January 8, 2001 [Z16381]

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- [18] The molar ratio was obtained from averaged integral intensities between the signal at $\delta = -5.43$ and the aromatic protons of bislactam **1**.
- [19] HD was prepared by treatment of CaH₂ with D₂O. The fraction of H₂ impurity also formed arises during this reaction from the HDO impurity present in D₂O as verified by ¹H NMR spectroscopy on the dissolved gas (C₆D₆).
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Cover Picture

Sanjoy K. Das, Jean-Maurice Mallet, Jacques Esnault, Pierre-Alexandre Driguez, Philippe Duchaussoy, Philippe Sizun, Jean-Pascal Hérault, Jean-Marc Herbert, Maurice Petitou, and Pierre Sinaÿ

The cover picture shows how thrombosis occurs in the deep veins of the lower limbs. Stasis, which results from slow and turbulent blood flow, combined with hypercoagulation, caused, for example, by a surgical procedure, may result in thrombus formation. The synthetic sulfated pentasaccharide shown in part is a potent antithrombotic compound that exerts its effect by activation of the plasma protein antithrombin III. Conformationally locked monosaccharides have now been synthesized to demonstrate that *L*-iduronic acid, one part of the pentasaccharide, must adopt an unusual distorted conformation to activate antithrombin III. Such conformational effects might be relevant in explaining the unique biological properties of glycosaminoglycans that contain *L*-iduronic acid. In the background of the picture, a flight of vampire bats is attracted by the pentasaccharide. Vampire was the name given to South American blood-sucking bats (Latin name: *desmodus rotundus*) in 1761 by the French naturalist Georges Louis Leclerc Comte de Buffon (1707–1788). These bats are known to attack cattle and, very rarely, sleeping human beings. Although their saliva has been shown to contain an anticoagulant compound, they would also be happy to benefit from the pentasaccharide mentioned above, to suck the blood out of the vein more easily. More details about this compound which would be helpful to vampire bats are reported by Petitou, Sinaÿ et al. on p. 1670 ff.



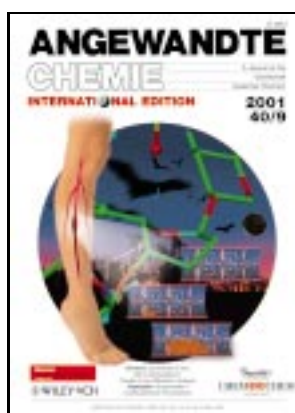
ANGEWANDTE CHEMIE

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Gesellschaft
Deutscher Chemiker

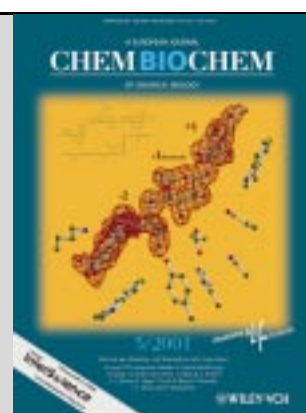
INTERNATIONAL EDITION

2001
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Pages 1557 – 1786



ChemBioChem 5/2001 is bound
in this issue of *Angewandte Chemie*.



COVER PICTURE

The cover picture shows how thrombosis occurs in the deep veins of the lower limbs. Stasis, which results from slow and turbulent blood flow, combined with hypercoagulation, caused, for example, by a surgical procedure, may result in thrombus formation. The synthetic sulfated pentasaccharide shown in part is a potent antithrombotic compound that exerts its effect by activation of the plasma protein antithrombin III. Conformationally locked monosaccharides have now been synthesized to demonstrate that L-iduronic acid, one part of the pentasaccharide, must adopt an unusual distorted conformation to activate antithrombin III. Such conformational effects might be relevant in explaining the unique biological properties of glycosaminoglycans that contain L-iduronic acid. In the background of the picture, a flight of vampire bats is attracted by the pentasaccharide. Vampire was the name given to South American blood-sucking bats (Latin name: *desmodus rotundus*) in 1761 by the French naturalist Georges Louis Leclerc Comte de Buffon (1707–1788). These bats are known to attack cattle and, very rarely, sleeping human beings. Although their saliva has been shown to contain an anticoagulant compound, they would also be happy to benefit from the pentasaccharide mentioned above, to suck the blood out of the vein more easily. More details about this compound which would be helpful to vampire bats are reported by Petitou, Sinaÿ et al. on p. 1670 ff.

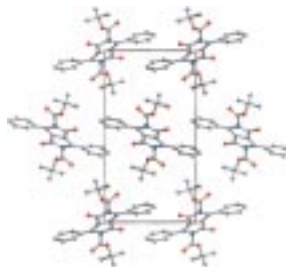


The teamwork between carbohydrate chemistry and total synthesis is surely one of the most exciting aspects of organic chemistry. In this review the contributions made by the principal author's research group in the areas of chemical synthesis and biological chemistry of carbohydrates are presented. Specifically, the use of carbohydrates as starting materials for total synthesis, the development of new technologies for carbohydrate synthesis, the construction of complex oligosaccharides in solution or on solid support, and the use of carbohydrate templates as scaffolds for peptide mimetics and other interesting compounds are discussed.

Angew. Chem. **2001**, *113*, 1624–1672

As many materials cannot be prepared in the form of single crystals appropriate for single-crystal X-ray diffraction, structure determination of such materials requires the use of powder X-ray diffraction data. However, the determination of crystal structures directly from powder X-ray diffraction data is associated with a number of intrinsic challenges. In recent years there has been substantial progress in the development of techniques to tackle these challenges. In addition to surveying these advances in methodology, the opportunities that now exist for exploiting powder diffraction in structure determination are highlighted with examples taken from diverse areas across the chemical and materials sciences. The picture shows the β phase from 1,4-diketo-2,5-di-*tert*-butoxycarbonyl-3,6-diphenylpyrrolo[3,4]pyrrole.

Angew. Chem. **2001**, *113*, 1674–1700



K. C. Nicolaou,*
H. J. Mitchell 1576–1624

Adventures in Carbohydrate Chemistry:
New Synthetic Technologies, Chemical
Synthesis, Molecular Design, and
Chemical Biology

Keywords: carbohydrates •
glycosylation • natural products •
synthetic methods • total synthesis

K. D. M. Harris,* M. Tremayne,
B. M. Kariuki 1626–1651

Contemporary Advances in the Use of
Powder X-Ray Diffraction for Structure
Determination

Keywords: powder X-ray diffraction •
structure elucidation • X-ray diffraction

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>

Cyclic Dimers of Metalloporphyrins as Tunable Hosts for Fullerenes:
A Remarkable Effect of Rhodium(III)

J.-Y. Zheng, K. Tashiro,
Y. Hirabayashi, K. Kinbara,
K. Saigo,* T. Aida,*
S. Sakamoto, K. Yamaguchi



Direct Observation of Surface-Controlled Self-Assembly of Coordination
Cages by Using Atomic Force Microscopy as a Molecular Ruler

S. A. Levi, P. Guatterri,
F. C. J. M. van Veggel,
G. J. Vancso, E. Dalcanele,*
D. N. Reinhoudt*



Probing Guest Geometry and Dynamics through Host–Guest Interactions

T. Kusukawa, M. Yoshizawa,
M. Fujita*



Fluorinated Bis(enyl) Ligands through Metal-Induced Dimerization of
Fluorinated Allenes

D. Lentz,* S. Willemsen

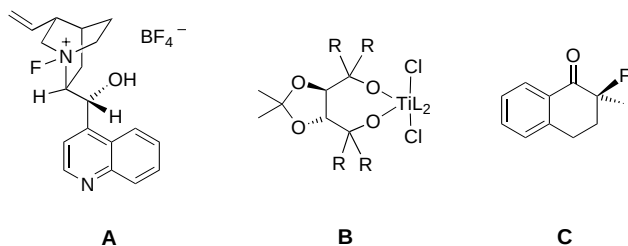
The Natural $^{12}\text{C}/^{13}\text{C}$ Ratio Allows Classification of Terpenoid Biosynthesis
According to the Methylerythritolphosphate or the Mevalonate Pathway:
Dynamic Allocation of Resources in Induced Plants

A. Jux, G. Gleixner, W. Boland*

Targeting Molecular Recognition: Exploring the Dual Role of Functional
Pseudo-Prolines in the Design of SH3 Ligands

G. Tuchscherer,* D. Grell,
Y. Tatsu, P. Durieux,
J. Fernandez-Carneado,
B. Hengst, C. Kardinal, S. Feller*

Enantioselective fluorinations made easier! Chiral *N*-fluoroammonium salts such as **A**, or chiral catalysts generated from complexes **B** (L = ligand) broaden the substrate scope for electrophilic fluorination. Starting from prochiral substrates they offer an efficient approach to chiral fluoro derivatives such as **C**. Additionally, fluorinated stereogenic centers can be generated from nucleophilic, catalytic epoxide opening.



Angew. Chem. **2001**, *113*, 1701–1704

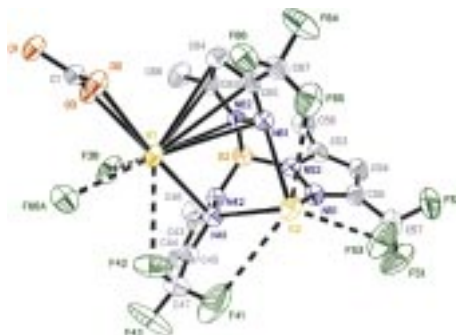
K. Muñoz* 1653–1656

Improving Enantioselective Fluorination Reactions: Chiral *N*-Fluoroammonium Salts and Transition Metal Catalysts

Keywords: asymmetric catalysis • asymmetric synthesis • fluoroorganic compounds • homogeneous catalysis • transition metals

Much more versatile than previously anticipated are the coordination modes of tris(pyrazolyl)borate ligands (scorpionates). Recent contributions in this area not only lead to a new understanding of the electronic effects, but for the first time report unusually high and low hapticities as well as novel coordination modes such as the π coordination of a pyrazolyl ring to potassium (see structure). Potentially useful new ligands have been made available through innovative synthetic routes.

Angew. Chem. **2001**, *113*, 1704–1708



F. T. Edelmann* 1656–1660

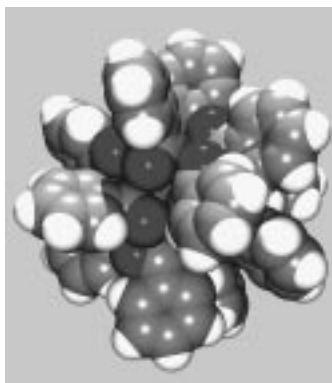
Versatile Scorpionates—New Developments in the Coordination Chemistry of Pyrazolylborate Ligands

Keywords: copper • iridium • pyrazolylborates • rhodium • samarium

COMMUNICATIONS

Esterified B₁₂ icosahedra with totally organoderivatized surfaces are obtained from the reaction of [*closo*-B₁₂(OH)₁₂]²⁻ with acetic anhydride or benzoyl chloride. The resulting “closomers”, in which each cluster vertex is substituted with an organic ester moiety, can provide camouflaged modules of variable size, shape, charge, hydrophobicity, etc. and represent the first examples of this structural motif known in chemistry. The figure displays, in a space-filling representation, the result of an X-ray analysis performed with the dodecabenzoate ester derivative.

Angew. Chem. **2001**, *113*, 1710–1712

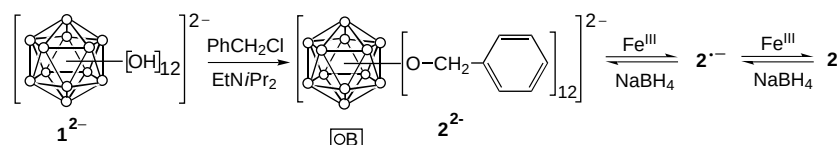


A. Maderna, C. B. Knobler, M. F. Hawthorne* 1662–1664

Twelvefold Functionalization of an Icosahedral Surface by Total Esterification of [B₁₂(OH)₁₂]²⁻: 12(12)-Closomers

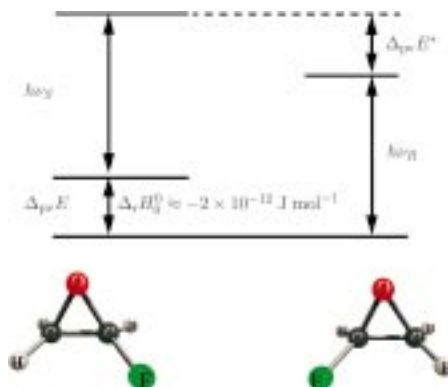
Keywords: boranes • boron • closomers • cluster compounds • esterification

Per-O-benylation of $[closo-B_{12}(OH)_{12}]^{2-}$ (**1**²⁻) using benzyl chloride followed by oxidation with two equivalents of Fe^{III} gave compound **2**, the per(benzyloxy) derivative of *hypercloso*-B₁₂H₁₂ (see scheme). Species **2** is characterized by ¹¹B NMR and electronic spectroscopy, mass spectrometry, cyclic voltammetry, and X-ray crystallography.



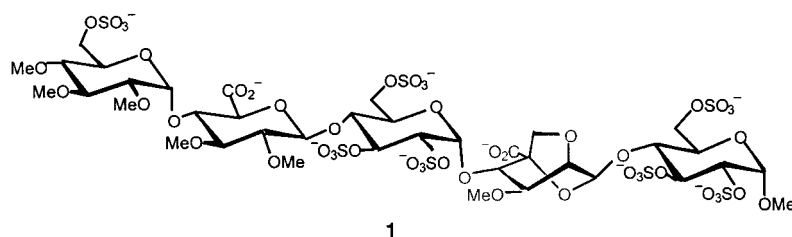
Angew. Chem. **2001**, *113*, 1713–1715

In contrast to what has been accepted, electroweak quantum chemistry predicts the heats of formation, the structures, the microwave and infrared spectra of enantiomers of chiral molecules to be different. The *R* enantiomer of fluoroxirane is calculated to be more stable than the *S* enantiomer by the minute amount of 2×10^{-12} J mol⁻¹, and the relative IR frequency shifts are $\leq 10^{-18}$ (see scheme). Nevertheless, this recently synthesized compound may prove useful for fundamental experimental tests and calculations of parity violation in chiral molecules because of its particularly simple rovibrational spectrum and its rigid cyclic structure composed of light atoms.



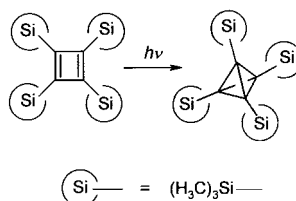
Angew. Chem. **2001**, *113*, 1716–1719

Conformational flexibility of L-iduronic acid is a key feature of this typical component of heparin. Three pentasaccharides have now been synthesized, which are analogues of the active site of heparin and in which the single L-iduronic acid is conformationally locked in either the ¹C₄, ⁴C₁, or ²S₀ form. Only the ²S₀ variant **1** was able to fully activate antithrombin inhibition of the blood coagulation factor Xa.



Angew. Chem. **2001**, *113*, 1723–1726

A route to unsubstituted tetrahedrane? One option is offered by the tetrakis(trimethylsilyl) derivative, which is generated upon irradiation of the corresponding cyclobutadiene (see scheme). Tetrahedrane itself could also possibly be accessed from the tetralithiotetrahedrane by this route.



Angew. Chem. **2001**, *113*, 1719–1720

T. Peymann, C. B. Knobler, S. I. Khan, M. F. Hawthorne* 1664–1667

Dodeca(benzyloxy)dodecaborane, B₁₂(OCH₂Ph)₁₂: A Stable Derivative of *hypercloso*-B₁₂H₁₂

Keywords: boranes • boron • closomers • cluster compounds • electron-deficient compounds

R. Berger, M. Quack,* J. Stohner 1667–1670

Parity Violation in Fluorooxirane

Keywords: ab initio calculations • chirality • electroweak quantum chemistry • oxiranes • parity violation

S. K. Das, J.-M. Mallet, J. Esnault, P.-A. Driguez, P. Duchaussoy, P. Sizun, J.-P. Héroult, J.-M. Herbert, M. Petitou,* P. Sinaÿ* 1670–1673

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

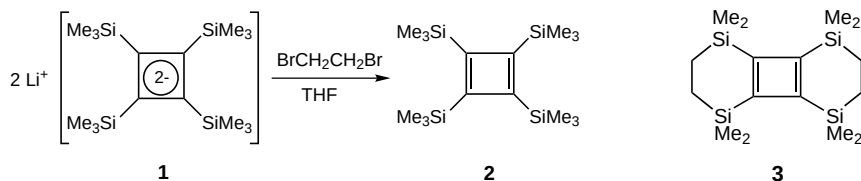
Keywords: blood coagulation • carbohydrates • glycosylation • heparin • molecular recognition

G. Maier,* J. Neudert, O. Wolf 1674–1675

Tetrakis(trimethylsilyl)cyclobutadiene and Tetrakis(trimethylsilyl)tetrahedrane

Keywords: cycloalkenes • diazo compounds • ketenimines • photochemistry • small ring systems • tetrahedranes

In less than one minute dianion **1** can be oxidized with 1,2-dibromoethane to give pure tetrakis(trimethylsilyl)cyclobutadiene (**2**, see scheme). The bridged cyclobutadiene derivative **6** was also similarly synthesized and characterized by X-ray crystallography; it exhibits a planar rectangular structure with localized C=C bonds.



Angew. Chem. **2001**, *113*, 1721–1723

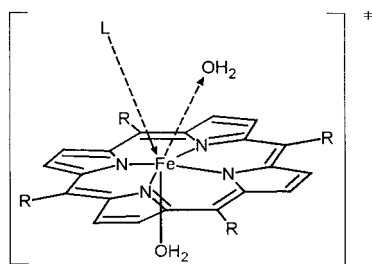
A. Sekiguchi,* M. Tanaka, T. Matsuo,
H. Watanabe 1675–1677

From a Cyclobutadiene Dianion to a
Cyclobutadiene: Synthesis and Structural
Characterization of Tetrasilyl-Substituted
Cyclobutadiene

Keywords: carbanions • cycloalkenes •
oxidation • small ring systems •
solid-state structures



The water-exchange reactions of three modified iron(III) porphyrins were studied in acidic medium as a function of temperature and pressure using ¹⁷O NMR spectroscopic techniques. The positive activation entropies and activation volumes support a dissociative mechanism (see scheme showing the transition state; L = nucleophile, H₂O, NO). A comparison with available literature data reveals that the rate and mechanism of complex-formation reactions of such metal porphyrins are controlled by the water-exchange process.

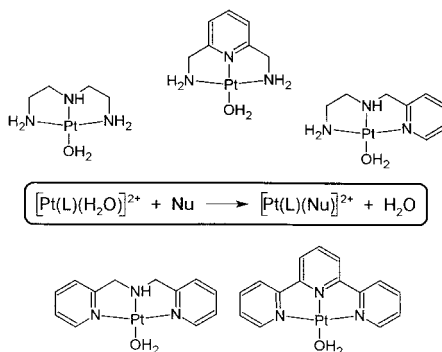


T. Schnepfensieper, A. Zahl,
R. van Eldik* 1678–1680

Water Exchange Controls the Complex-
Formation Mechanism of Water-Soluble
Iron(III) Porphyrins: Conclusive Evidence
for Dissociative Water Exchange from a
High-Pressure ¹⁷O NMR Study

Keywords: high-pressure chemistry •
iron • NMR spectroscopy •
porphyrinoids • water exchange

By a factor of 10⁴–10⁵ that is how much the reactivity of Pt^{II}(terpyridine) complexes exceeds the reactivity of the corresponding Pt^{II}-(diene) complexes in nucleophilic substitution reactions. A systematic π-acceptor study was performed on a series of aqua complexes (see scheme) to elucidate that the source of this unusual acceleration is π conjugation!



Angew. Chem. **2001**, *113*, 1730–1733

D. Jaganyi, A. Hofmann,
R. van Eldik* 1680–1683

Controlling the Lability of Square-Planar
Pt^{II} Complexes through Electronic
Communication between π-Acceptor
Ligands

Keywords: kinetics • N ligands •
platinum • thermodynamics •
tridentate ligands

Diffusion or perfusion—this is no longer the question for electroosmotic flow (EOF) through capillaries with fixed beds. The intraparticle EOF in capillary electrochromatography has been shown by using special NMR techniques and forms the basis for a further improvement in separation efficiency, mass sensitivity, and analysis speed. Electroosmotic perfusion phenomena in porous materials also play an important role in other areas, such as in the dewatering of waste sludge and the removal of contaminants from soil.

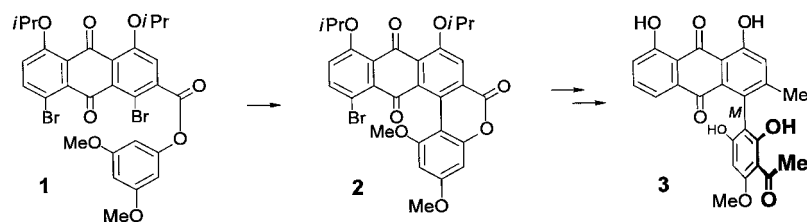
Angew. Chem. **2001**, *113*, 1741–1745

U. Tallarek,* E. Rapp, H. Van As,
E. Bayer 1684–1687

Electrokinetics in Fixed Beds:
Experimental Demonstration of
Electroosmotic Perfusion

Keywords: analytical methods •
electroosmotic flow •
liquid chromatography • mass transfer •
NMR spectroscopy

The first stereoselective access to an axially chiral arylanthraquinone, the antimalarial natural product knipholone (**3**), was achieved by application of the “lactone concept”. Key steps were the intramolecular coupling of the bromoester **1**, to give the configurationally unstable biaryl lactone **2**, and the enantioselective ring cleavage to form **3**.



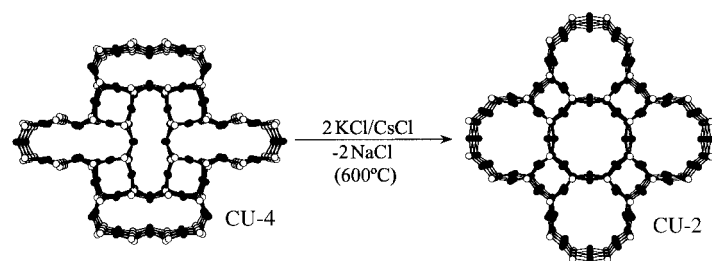
Angew. Chem. **2001**, *113*, 1733–1736

G. Bringmann,* D. Menche 1687–1690

First, Atropo-Enantioselective Total Synthesis of the Axially Chiral Phenylanthraquinone Natural Products Knipholone and 6'-O-Methylknipholone

Keywords: atropisomerism • enantiomer resolution • natural products • quinones • total synthesis

8-Ring and 16-ring channels with 5.3×5.3 Å and 4.9×17.2 Å windows, respectively, are contained in the new CU-4 phase. The larger channel exhibits an elliptical pore structure templated by an alkali metal chloride salt. CU-4 is structurally related to CU-2 (see picture), and can be chemically modified to CU-2 by an ion-exchange reaction at 600°C.



Angew. Chem. **2001**, *113*, 1754–1756

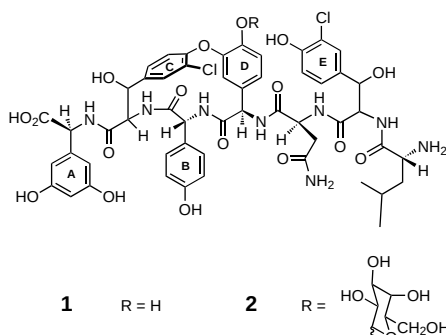
Q. Huang, S.-J. Hwu,*

X. Mo 1690–1693

High-Temperature Synthesis of an Open-Framework Compound, $\text{Na}_2\text{Cs}_2\text{Cu}_3(\text{P}_2\text{O}_7)_2\text{Cl}_2$ (CU-4), by Molten-Salt Methods

Keywords: cuprates • microporosity • solid-state structures • template synthesis • zeolite analogues

A new oxyA gene replacement mutant of *Amycolatopsis mediterranei* enabled us to isolate two peptides, SP-1132 (**1**) and SP-1294 (**2**), which only have one diaryl ether bridge. These vancomycin-type structures provide further insight into the oxidative ring-bridging steps in their biosynthesis.



Angew. Chem. **2001**, *113*, 1736–1739

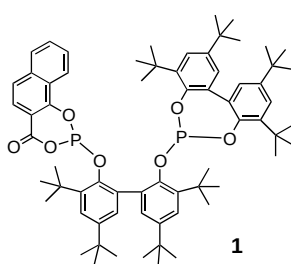
D. Bischoff, S. Pelzer, A. Hölzel, G. J. Nicholson, S. Stockert, W. Wohlleben, G. Jung, R. D. Süßmuth* 1693–1696

The Biosynthesis of Vancomycin-Type Glycopeptide Antibiotics—New Insights into the Cyclization Steps

Keywords: antibiotics • biaryls • biosynthesis • glycopeptides • structure elucidation



Going up! *n*-Selectivity and activity can be increased simultaneously in hydroformylation by the use of novel hybrid ligands such as **1** containing *O*-acylphosphite groups. For the first time these ligands deliver impressively *n*-selective rhodium-catalyzed hydroformylation of internal octenes, and this with an industrial relevant catalytic activity.



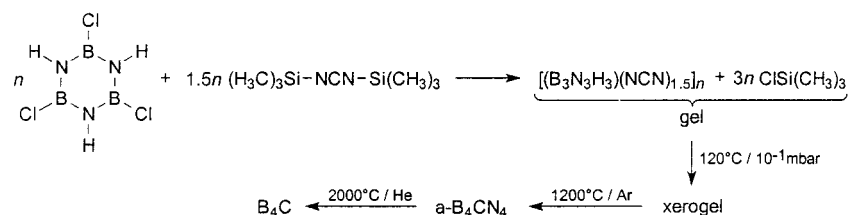
Angew. Chem. **2001**, *113*, 1739–1741

D. Selent,* D. Hess, K.-D. Wiese, D. Röttger, C. Kunze, A. Börner* 1696–1698

New Phosphorus Ligands for the Rhodium-Catalyzed Isomerization/Hydroformylation of Internal Octenes

Keywords: homogeneous catalysis • hydroformylation • isomerization • P ligands • rhodium

B-trichloroborazene reacts with bis(trimethylsilyl)carbodiimide to form non-oxide gels (see scheme). The xerogels consist of a polymeric network of borazine rings linked by carbodiimide groups. Pyrolysis at 1200°C provides amorphous ceramics with the composition $\text{BC}_{0.23}\text{N}_{1.1}\text{Si}_{0.05}\text{H}_{0.09} \approx \text{B}_4\text{CN}_4$. At 2000°C pure B_4C is formed.



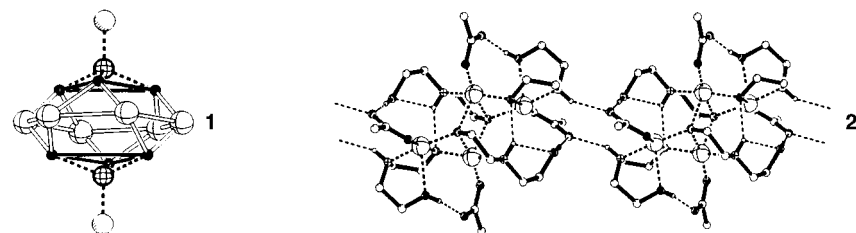
Angew. Chem. **2001**, *113*, 1751–1753

E. Kroke,* K. W. Völger, A. Klonczynski, R. Riedel 1698–1700

A Sol–Gel Route to B_4C

Keywords: boron • ceramics • gels • sol–gel process

Template effect versus hydrogen bonding in self-assembly: As predicted, the scaffold of molecular gyroscope $[(\text{NaBr})_2 \cap \text{Cu}_6\{(\text{2,5-Me}_2\text{C}_6\text{H}_3\text{CH}_2)\text{N}(\text{CH}_2\text{CH}_2\text{O})_2\}_6]$ (**1**) is generated from N-substituted diethanolamine together with a copper(II) salt and sodium bromide. However, we did not predict the one-dimensional coordination polymer $^{1}_{\infty}[\text{Cu}_4\{\text{H}[\text{HN}(\text{CH}_2\text{CH}_2\text{O})_2\}_4(\text{OAc})_4]$ (**2**) generated with an unsubstituted diethanolamine. The formation of **2** is a further impressive example of nature's virtuosity in using hydrogen bonds.



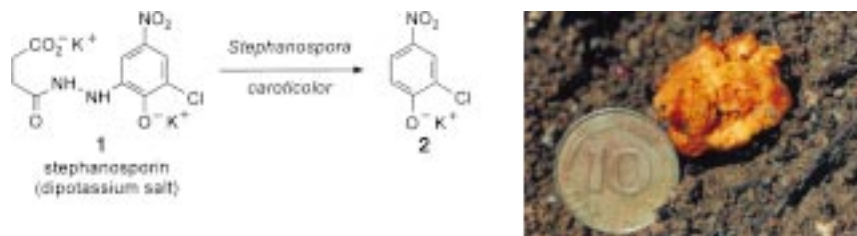
Angew. Chem. **2001**, *113*, 1745–1748

R. W. Saalfrank,* I. Bernt, F. Hampel 1700–1703

Metallacoronates or One-Dimensional Polymers through Self-Assembly—Influence of Templates and Hydrogen Bonding on Product Formation

Keywords: coordination chemistry • copper • hydrogen bonds • metallacrown ethers • supramolecular chemistry

More like an industrial fungicide than a natural product is the title compound, which occurs as the potassium salt in the carrot truffle, *Stephanospora caroticolor*, and is responsible for its orange color (see picture). On injury of the fruit body, **1** is transformed into the toxic 2-chloro-4-nitrophenol (**2**) by loss of the side chain.



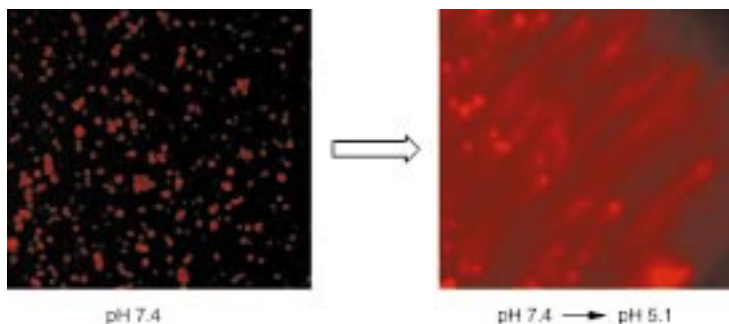
Angew. Chem. **2001**, *113*, 1749–1751

M. Lang, P. Spiteller, V. Hellwig, W. Steglich* 1704–1705

Stephanosporin, a “Traceless” Precursor of 2-Chloro-4-nitrophenol in the Gasteromycete *Stephanospora caroticolor*

Keywords: fungi • natural products • nitro compounds • organochloro compounds • phenols

Microspheres formed from a new poly(β -amino ester) degrade slowly at pH 7.4 (left fluorescence microscopy image) but dissolve quickly at pH values below 6.5 (right), to release encapsulated material rapidly and quantitatively. As the pH/solubility transition occurs within the intracellular pH range, these tiny spheres hold promise as intracellular drug delivery vehicles.



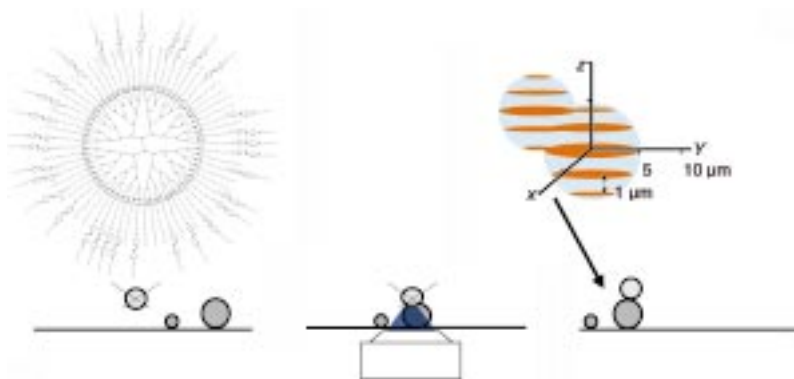
Angew. Chem. **2001**, *113*, 1757–1760

D. M. Lynn, M. M. Amiji,
R. Langer* 1707–1710

pH-Responsive Polymer Microspheres:
Rapid Release of Encapsulated Material
within the Range of Intracellular pH

Keywords: controlled release •
drug research • microspheres •
polymers • protonation

Micrometer-level billiards or rod-formation: The careful design of poly(propyleneimine) dendrimers enables the physical properties of self-assembled vesicular structures to be tuned so that they behave as hard spheres that either undergo collision in a billiardlike manner or merge (see picture).



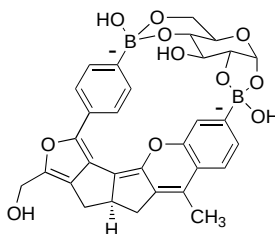
Angew. Chem. **2001**, *113*, 1760–1764

G. C. Dol, K. Tsuda, J.-W. Weener,
M. J. Bartels, T. Asavei, T. Gensch,
J. Hofkens, L. Latterini,
A. P. H. J. Schenning, B. W. Meijer,
F. C. De Schryver* 1710–1714

Merging of Hard Spheres by
Phototriggered Micromanipulation

Keywords: dendrimers •
photochemistry • self-assembly • vesicles

Greater than 400-fold selectivity for glucose over galactose, mannose, and fructose has been achieved with a receptor designed by the computer program CAVEAT. The receptor has precisely positioned boronic acid groups for cyclic boronate formation with the 1,2- and 4,6-hydroxy groups of α -D-glucopyranose (see picture) and exhibits a 50% decrease in fluorescence upon glucose binding.



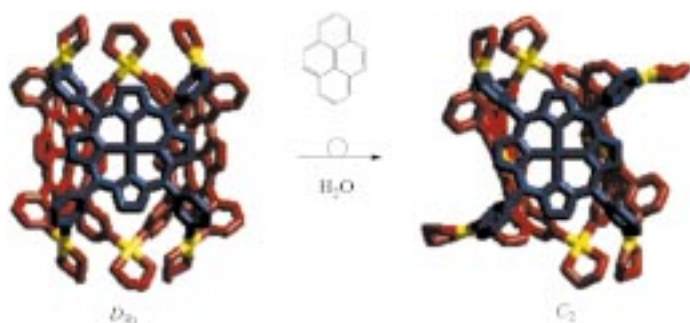
Angew. Chem. **2001**, *113*, 1764–1768

W. Yang, H. He,
D. G. Drueckhammer* 1714–1718

Computer-Guided Design in Molecular
Recognition: Design and Synthesis of a
Glucopyranose Receptor

Keywords: boron • molecular modeling •
molecular recognition • receptors •
sensors

 **A prismlike hollow structure** was assembled when three pyridyl-substituted porphyrin panels were linked by six Pd^{II} ions. A dramatic $D_{3h} \rightarrow C_2$ structural change of the prism (see scheme) was triggered by complexation of pyrene.



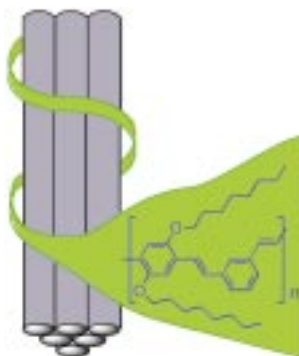
Angew. Chem. **2001**, *113*, 1768–1771

N. Fujita, K. Biradha, M. Fujita,*
S. Sakamoto, K. Yamaguchi 1718–1721

A Porphyrin Prism: Structural Switching
Triggered by Guest Inclusion

Keywords: host–guest systems •
palladium • porphyrinoids •
self-assembly • supramolecular chemistry

 **Intimate electrical contact** occurs between a substituted poly(metaphenylenevinylene) (PmPV) and bundles of single-walled nanotubes (SWNT) as evidenced by atomic force microscopy, optical, and electronic measurements carried out on single, isolated SWNT/PmPV structures (see picture). PmPV may provide a useful route toward “functionalizing” the SWNT without destroying their electrical character.



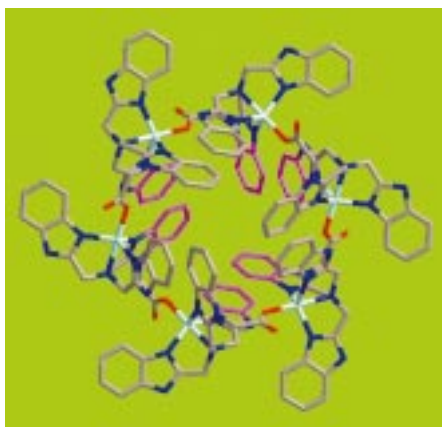
Angew. Chem. **2001**, *113*, 1771–1775

A. Star, J. F. Stoddart,* D. Steuerman,
M. Diehl, A. Boukai, E. W. Wong,
X. Yang, S.-W. Chung, H. Choi,
J. R. Heath* 1721–1725

Preparation and Properties of Polymer-
Wrapped Single-Walled Carbon
Nanotubes

Keywords: atomic force microscopy •
conducting materials •
molecular devices • nanotubes •
supramolecular chemistry

A hexanuclear flying saucer, $[\text{Cu}_6(\text{Acntb})_6]^{6+}$ (see structure), is obtained by the reaction of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ with the sodium salt of the tripodal ligand Acntb^- . Inter-molecular hydrogen bonding generates an open three-dimensional nanoporous network containing intra- and intermolecular cavities of different polarity for guest inclusion. $\text{HAcntb} = N\text{--}[N'\text{--}(\text{carboxymethyl})\text{benzimidazol-2-ylmethyl}]\text{--}N,N\text{--bis}(\text{benzimidazol-2-ylmethyl})\text{amine}$.



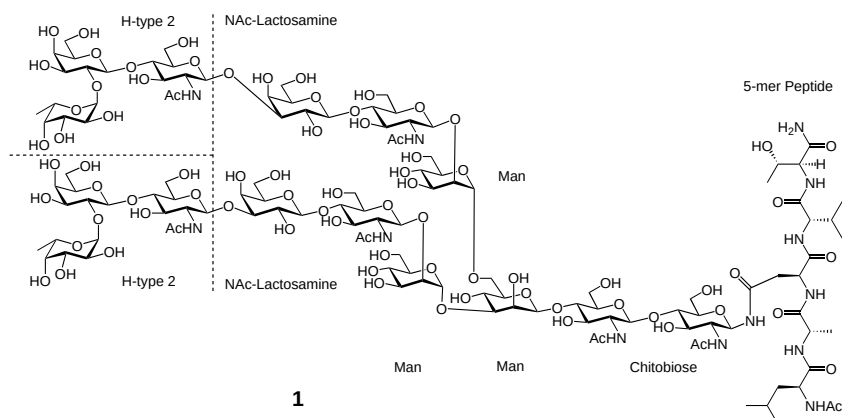
Angew. Chem. **2001**, *113*, 1775–1778

C.-Y. Su, X.-P. Yang, B.-S. Kang,*
T. C. W. Mak* 1725–1728

T_h -Symmetric Nanoporous Network Built
of Hexameric Metallamacrocycles with
Disparate Cavities for Guest Inclusion

Keywords: copper • hydrogen bonds •
macrocycles • N ligands •
supramolecular chemistry

Blood typing with the ABO classification is based on cell-surface glycoproteins. In a significant step toward the synthesis of these compounds, the laboratory synthesis of a fully functional N-linked glycopeptide featuring H-type blood group determinants **1** is described.



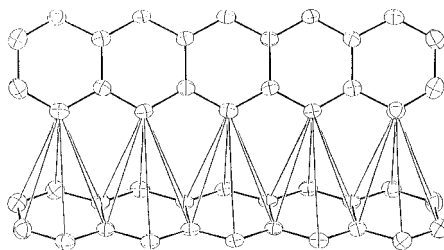
Angew. Chem. **2001**, *113*, 1778–1782

Z.-G. Wang, X. Zhang, M. Visser,
D. Live, A. Zatorski, U. Iserloh,
K. O. Lloyd,
S. J. Danishefsky* 1728–1732

Toward Fully Synthetic Homogeneous Glycoproteins: A High Mannose Core Containing Glycopeptide Carrying Full H-Type2 Human Blood Group Specificity

Keywords: antibodies • glycals • glycopeptides • glycosylamines • total synthesis

A low temperature mobility up to $10\,000\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$ at 1.7 K was observed for a new polymorphic form of pentacene ($\text{C}_{22}\text{H}_{14}$, see picture). Optical measurements show a band gap of the order of 2 eV, and transport measurements revealed a mobility above $3\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$ at room temperature.



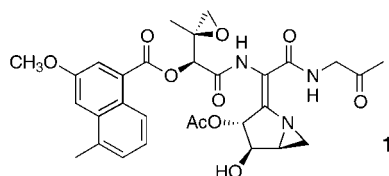
Angew. Chem. **2001**, *113*, 1782–1786

T. Siegrist,* C. Kloc, J. H. Schön,
B. Batlogg, R. C. Haddon, S. Berg,
G. A. Thomas 1732–1736

Enhanced Physical Properties in a Pentacene Polymorph

Keywords: arenes • crystal growth • polymorphism • semiconductors

A most elusive of synthetic targets, azinomycin A **1** has now been synthesized for the first time. Using a modular synthetic approach, and after considerable developmental effort, this antitumor agent has been synthesized in a stereocontrolled manner using a convergent series of fragment couplings and a final cyclization to form the structurally unique aziridino[1,2-*a*]pyrrolidine ring system.



Angew. Chem. **2001**, *113*, 1786–1789

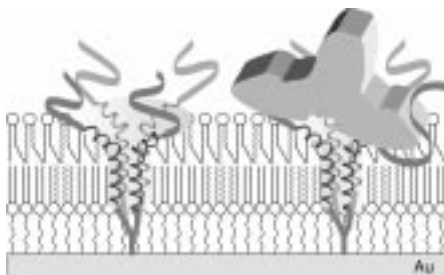
R. S. Coleman,* J. Li,
A. Navarro 1736–1739

Total Synthesis of Azinomycin A

Keywords: antitumor agents • asymmetric synthesis • natural products • peptides • total synthesis



Specific binding of an antibody to its antigen at subnanomolar concentrations has been detected electrically by impedance spectroscopy through changes in the ion-conductance of a synthetic ligand-gated ion channel (SLIC) in a supported lipid bilayer on a gold electrode (see picture).



Angew. Chem. **2001**, *113*, 1790–1793

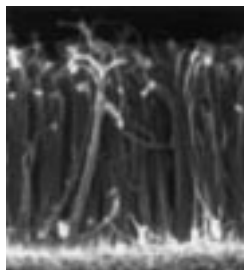
S. Terrettaz, W.-P. Ulrich, R. Guerrini,
A. Verdini, H. Vogel* 1740–1743

Immunosensing by a Synthetic Ligand-Gated Ion Channel

Keywords: antibodies • impedance spectroscopy • lipid bilayers • peptides • receptors



Fluoroalkylsilane treatment of super-hydrophobic, aligned carbon nanotube films (see electron micrograph) prepared by pyrolysis of metal phthalocyanines results in the films having both super-hydrophobic and super-lipophobic properties, namely they are super-“amphiphobic” surfaces.



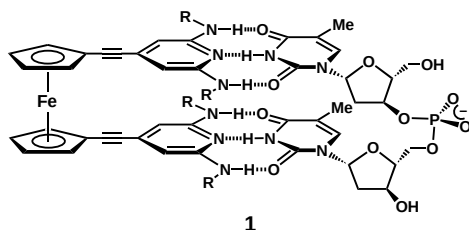
Angew. Chem. **2001**, *113*, 1793–1796

H. Li, X. Wang, Y. Song, Y. Liu, Q. Li, L. Jiang,* D. Zhu 1743–1746

Super-“Amphiphobic” Aligned Carbon Nanotube Films

Keywords: carbon • electron microscopy • nanostructures • surface chemistry • wettability

The multipoint hydrogen-bonded complex 1 (R = alkanoyl) is readily formed between a ferrocene-modified artificial receptor and a dinucleotide. This principle can be used effectively in highly selective, large-scale separations of dinucleotides from mixtures of mono- and oligonucleotides. The process is economically viable and environmentally friendly.



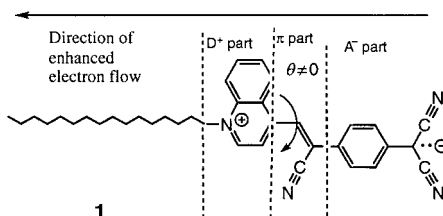
M. Inouye,* M. Takase 1746–1748

Specific Binding and Separation of Dinucleotides by Ferrocene-Modified Artificial Receptors

Keywords: hydrogen bonds • molecular recognition • nucleobases • nucleotides • receptors

Angew. Chem. **2001**, *113*, 1796–1798

45000 electrons per molecule per second: such currents and a rectification ratio of 5.38 at 2.2 V were detected between oxide-free Au electrodes for a Langmuir–Blodgett monolayer of the $D^+ - \pi - A^-$ molecule **1**.



T. Xu, I. R. Peterson, M. V. Lakshmikantham, R. M. Metzger* 1749–1752

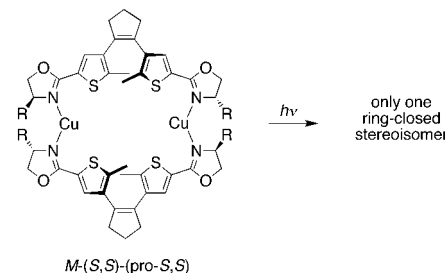
Rectification by a Monolayer of Hexadecylquinolinium Tricyanoquinodimethanide between Gold Electrodes

Keywords: conducting materials • donor–acceptor systems • gold • monolayers • rectification

Angew. Chem. **2001**, *113*, 1799–1802



Diastereoselectivities as high as 98% were the result of the photochemical ring-closure of stereochemically pure copper(I) helicates of a chiral oxazoline-substituted 1,2-dithienylethene photochrome (see scheme). The variations in optical rotation that accompany the photochromic event provide a means to read stored information in a non-destructive manner.



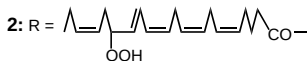
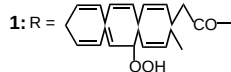
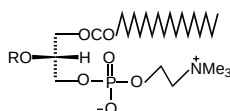
E. Murguly, T. B. Norsten, N. R. Branda* 1752–1755

Nondestructive Data Processing Based on Chiroptical 1,2-Dithienylethene Photochromes

Keywords: diastereoselectivity • helical structures • molecular devices • optical memory • photochromism

Angew. Chem. **2001**, *113*, 1802–1805

The antitumor and antimalarial activity of fish oils may involve the action of phospholipid hydroperoxides. Two such phosphatidylcholines, **1** and **2**, bearing the hydroperoxides of docosahexaenoic and eicosapentaenoic acids—the two major fatty acids in fish oils—have been synthesized. In spite of its high degree of unsaturation, **1** is sufficiently stable to permit its use in biological studies.



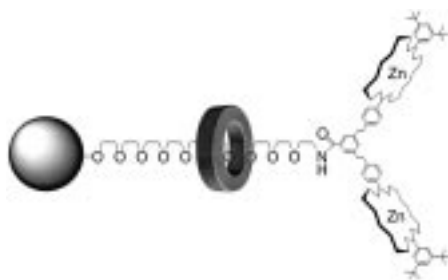
A. N. Onyango, T. Inoue, S. Nakajima, N. Baba,* T. Kaneko, M. Matsuo, S. Shimizu 1755–1757

Synthesis and Stability of Phosphatidylcholines Bearing Polyenoic Acid Hydroperoxides at the *sn*-2 Position

Keywords: fatty acids • lipids • peroxides

Angew. Chem. **2001**, *113*, 1805–1807

A tricyclic polyamide receptor threads onto the polyethylene glycol chain of a carbohydrate-attached resin, as shown by gel-phase MAS NMR spectroscopy. This observation led to syntheses of a polymer-supported pseudorotaxane and a porphyrin-stoppered rotaxane (see picture).



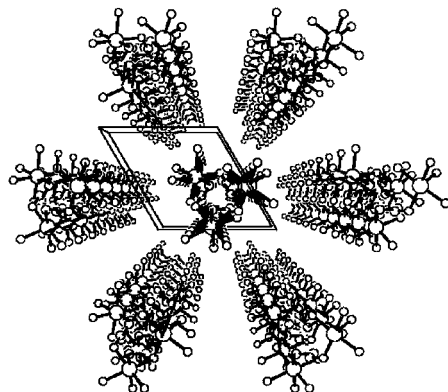
Y.-F. Ng, J.-C. Meillon, T. Ryan,
A. P. Dominey, A. P. Davis,
J. K. M. Sanders* 1757–1760

Gel-Phase MAS NMR Spectroscopy of a Polymer-Supported Pseudorotaxane and Rotaxane: Receptor Binding to an “Inert” Polyethylene Glycol Spacer

Keywords: carbohydrates •
NMR spectroscopy • rotaxanes •
supramolecular chemistry

Angew. Chem. **2001**, *113*, 1807–1810

Slow magnetic relaxation and hysteresis effects of dynamic origin have been observed above liquid helium temperature in a chain compound (see picture), comprising Co^{II} centers and organic radicals, without any evidence of phase transition to three-dimensional magnetic order. These results are the first evidence of the slow dynamics predicted for one-dimensional magnetic systems with Ising anisotropy, and they open the possibility of storing information in a single magnetic nanowire.



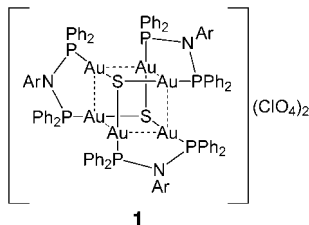
A. Caneschi, D. Gatteschi,* N. Lalioti,
C. Sangregorio, R. Sessoli, G. Venturi,
A. Vindigni, A. Rettori, M. G. Pini,
M. A. Novak 1760–1763

Cobalt(II)-Nitronyl Nitroxide Chains as Molecular Magnetic Nanowires

Keywords: bistability • chain structures •
cobalt • magnetic properties • radicals

Angew. Chem. **2001**, *113*, 1810–1813

A 1.87-eV energy gap between the lowest energy excitation maximum and the emission maximum in solution was found for the novel hexanuclear gold(I) sulfido complex **1** ($\text{Ar} = p\text{-CH}_3\text{C}_6\text{H}_4$), which has a heterocubane-type structure. Besides this abnormally large Stokes shift of around 15000 cm^{-1} , **1** exhibits intense orange luminescence in the solid state.



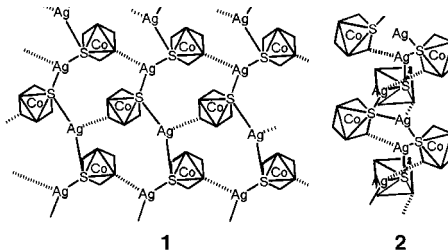
V. W.-W. Yam,* E. C.-C. Cheng,
N. Zhu 1763–1765

A Novel Polynuclear Gold–Sulfur Cube with an Unusually Large Stokes Shift

Keywords: cluster compounds • gold •
luminescence • P ligands • sulfur

Angew. Chem. **2001**, *113*, 1813–1815

Sheetlike and helical coordination polymers, $\{\Delta_L\text{-[Ag[Co(L-cys-}N,S\text{)-(en)}_2\text{] (NO}_3)_2\}_\infty$ (**1**) and $\{\Delta_L\text{-[Ag[Co(L-cys-}N,S\text{)-(en)}_2\text{] (NO}_3)_2\}_\infty$ (**2**), were obtained by treating Δ_L - and $\Delta_L\text{-[Co(L-cys-}N,S\text{)-(en)}_2\text{]}^+$ (L-cys = L-cysteinate, en = $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$) with AgNO_3 in water, respectively. Their structures are comparable to those of the β -sheet and α -helix forms of proteins. Compound **2** undergoes reversible conversion into a third compound on changing the pH of the solution.



T. Konno,* T. Yoshimura, K. Aoki,
K. Okamoto, M. Hirotsu 1765–1768

First Diastereomerically Controlled Aggregation of L-Cysteinato Cobalt(III) Octahedra, Assisted by Silver(I) Ions

Keywords: cobalt • helical structures •
S ligands • silver •
supramolecular chemistry

Angew. Chem. **2001**, *113*, 1815–1818

Most hydrogenase enzymes have organometallic active sites with CO and CN^- as ligands and metal–metal bonds. Recent evidence points to a novel 2-aza-1,3-propanedithiolate cofactor that directly participates in the heterolytic processing of dihydrogen. A close analogue of this cofactor and its organometallic subunit has been synthesized (see picture); spectroscopic, structural, and theoretical analysis of this model provides detailed insights into the properties of the proposed enzyme active site.



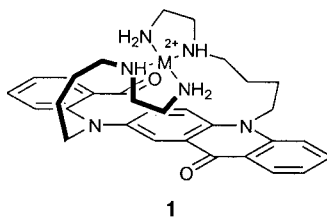
Angew. Chem. **2001**, *113*, 1818–1821

J. D. Lawrence, H. Li, T. B. Rauchfuss,*
M. Bénard,* M.-M. Rohmer 1768–1771

Diiron Azadithiolates as Models for the
Iron-Only Hydrogenase Active Site:
Synthesis, Structure, and
Stereoelectronics

Keywords: anomeric effect • cyanides •
density functional calculations •
hydrogenases • S ligands

A high-throughput fluorescence assay for amidases is demonstrated. It illustrates a new principle in enzyme assays, whereby changes in the pM value during the reaction are recorded ($\text{pM} = -\lg[\text{M}]$, M = free metal ions). An orange fluorescent quinacridone-based ligand **1** is the pM sensor (shown chelated to a reporter metal ion, $\text{M}^{2+} = \text{Cu}^{2+}$ or Ni^{2+}) that is used to monitor the release of metal-chelating amino acids by the enzymes acylase I and aminopeptidase.



Angew. Chem. **2001**, *113*, 1821–1823

G. Klein, J.-L. Reymond* ... 1771–1773

An Enzyme Assay Using pM

Keywords: enzyme catalysis •
fluorescence • hydrolysis •
metal complexes • sensors

The irreversible formation of carbonic anhydrase inhibitors from competing building block precursors is templated by the active site of the enzyme itself. The reagents are brought into close proximity of each other in a ternary complex with the enzyme (see scheme).



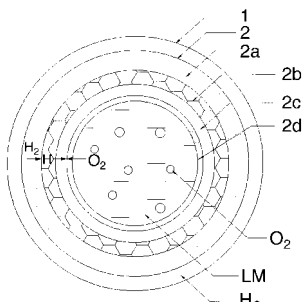
Angew. Chem. **2001**, *113*, 1824–1826

R. Nguyen, I. Huc* 1774–1776

Using an Enzyme's Active Site To
Template Inhibitors

Keywords: drug research •
enzyme inhibitors • imprinting •
molecular recognition •
template synthesis

Nonhazardous and highly selective H_2O_2 production! An H_2 -permselective membrane (2) has been developed which consists of thin films of Pd–Ag alloy (2b) and oxidized Pd (2c), and a hydrophobic polymer membrane (2d) supported on a tubular reactor wall (1). Hydrogen atoms permeate through the membrane and react with molecular O_2 in a liquid medium (LM; 2M H_2SO_4).



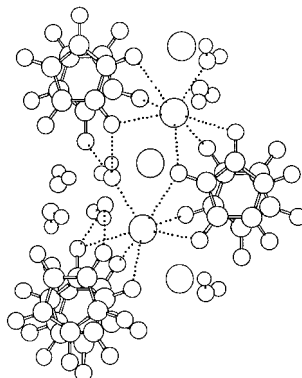
Angew. Chem. **2001**, *113*, 1826–1829

V. R. Choudhary,* A. G. Gaikwad,
S. D. Sansare 1776–1779

Nonhazardous Direct Oxidation of
Hydrogen to Hydrogen Peroxide Using a
Novel Membrane Catalyst

Keywords: heterogeneous catalysis •
membrane reactors • oxidation •
palladium • peroxides

Stacks of croconate dianions separated by K^+ ions and H_2O molecules: the crystal structure of potassium croconate dihydrate, $K_2(C_5O_5) \cdot 2H_2O$, isolated and described by Leopold Gmelin more than 170 years ago, has now been established by X-ray analysis (see picture). Since the anions have a formal charge of -2 and an interplanar separation of only $3.30 \text{ \AA}$, the structure is not easily explained in terms of a simple ionic model.



J. D. Dunitz,* P. Seiler,
W. Czechtizky 1779–1780

Crystal Structure of Potassium Croconate Dihydrate, after 175 Years

Keywords: croconates • hydrates • oxocarbons • potassium • structure elucidation

Angew. Chem. **2001**, *113*, 1829–1830



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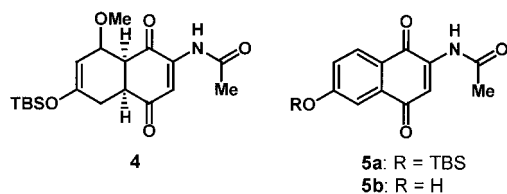
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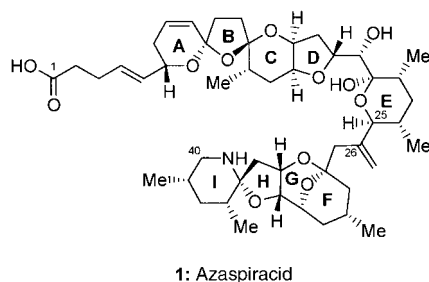
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In the communication by **S. H. Bergens** and **V. Rautenstrauch** et al. in issue 5, pp. 914–919, Equations (4) and (6) incorrectly depict (*S*)-(–)-BINAP instead of (*R*)-(+)-BINAP. (*R*)-(+)-BINAP, correctly labeled (+)-**9**, was exclusively used in this work as described in the text. The labels (+)-**9**·HBF₄, **12**, **13a**, **b**, and **17** in the text and Equation (4) and (6) also correctly refer to the (*R*)-(+)-BINAP series.

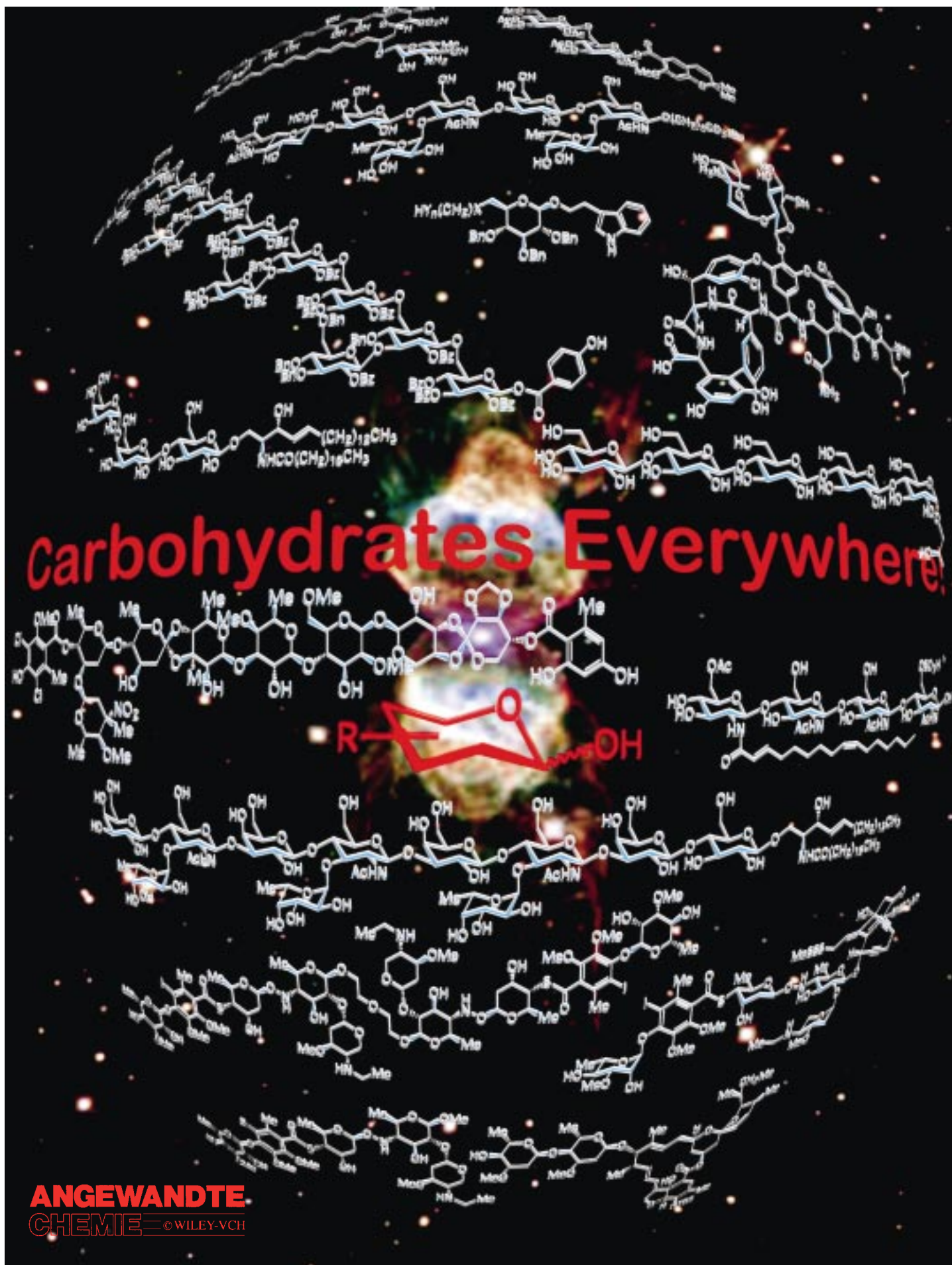
In the communication by **K. C. Nicolaou** et al. in issue 1, pp. 207–210, the structures tentatively assigned to compounds **4**, **5a** and **5b** based on NMR spectroscopy were incorrect. The correct structures have now been confirmed by X-ray crystallographic analysis (see picture). We thank Professor Ross Kelly and Professor Antonio Echavarren for inducing us to reexamine this issue (see also T. R. Kelly, M. Behforouz, A. Echavarren, J. Vaya, *Tetrahedron Lett.* **1983**, 24, 2331–2334).



In the communication by **K. C. Nicolaou** et al., in issue 7, pp. 1262–1265, the structure of the title compound azaspiracid (**1**) was inadvertently depicted incorrectly at three stereocenters. The correct structure is shown below.



The IR data for compound **3** are as follows: $\tilde{\nu}_{\text{max}} = 2925, 2861, 1697, 1460, 1373, 1255, 1149, 597 \text{ cm}^{-1}$.



The “ant nebula” (menzel 3) is shown in the background of the picture. (Reproduced with permission from NASA, ESA, and the Hubble Heritage team (STSci/AURA).) We thank R. Sahai (Jet Propulsion Lab) and B. Balick (University of Washington) for the graphical arrangement.

Adventures in Carbohydrate Chemistry: New Synthetic Technologies, Chemical Synthesis, Molecular Design, and Chemical Biology**

K. C. Nicolaou* and Helen J. Mitchell

In memory of Telemachos Charalambous

The field of carbohydrate chemistry has occupied the minds and hearts of many scientists for over a hundred years and, as we enter the twenty-first century, it continues to be both vigorous and challenging. Among the most exciting aspects of organic chemistry in the last few decades has been the interplay between the specialized sub-disciplines of carbohydrate chemistry and total synthesis, each enabling and advancing the other in new directions and towards greater heights. In this

review article we highlight our own adventures at the interface of these disciplines, which were driven for the most part by objectives in chemical synthesis and chemical biology. Specifically, we describe our interests and efforts to utilize carbohydrates as starting materials for total synthesis, to invent and develop new synthetic technologies for carbohydrate synthesis, to construct complex oligosaccharides in solution or on solid support, and to utilize carbohydrate templates

as scaffolds for peptide mimetics and for molecular diversity construction. Finally, applications of the developed synthetic strategies and enabling technologies towards the solution of biologically significant problems are discussed.

Keywords: carbohydrates • glycosidation • natural products • synthetic methods • total synthesis

1. Introduction

The abundance of carbohydrates in nature and their diverse roles in biological systems make them attractive as subjects for chemical and biological research. They are found as monomers, oligomers, or polymers, or as components of biopolymers and other naturally occurring substances. As domains of natural products, they play important roles in conferring certain physical, chemical, and biological properties to their carrier molecules. Furthermore, they have been implicated in many cellular processes, including cell–cell recognition, cellular transport, and adhesion; they appear in all cells in some form or another, for example, as peptido- and

proteoglycans, glycoproteins, nucleic acids, lipopolysaccharides, or glycolipids.^[1a] Due to their importance as building blocks, synthetic targets, and biological tools, and their potential as drug candidates, investigations into these compounds have been on the rise for some time. In this review we will recount our experiences with carbohydrates which have, for the most part, focused on new synthetic technologies, molecular design, and chemical biology studies. Our work in the carbohydrate arena has been inspired by many researchers in the field: To name but two, Stephen Hanessian^[1b] was the first to inspire this group in using carbohydrates as templates for total synthesis and Sam Danishefsky^[1c] encouraged and supported us to sustain an interest in carbohydrate chemistry.

Before we discuss our adventures in the carbohydrate area we shall briefly mention a selected number of glycosidation methods (see Scheme 1),^[2] many of which are found throughout the schemes that follow, because of their centrality within carbohydrate chemistry. The earliest known glycosidation method is that of Koenigs and Knorr^[3] (Scheme 1a), which was first reported a century ago. This reaction involves the coupling of a glycosyl bromide or chloride with a hydroxy component upon activation of the former with a heavy metal ion, typically silver or mercury.^[4]

In most glycosidation reactions, the resulting anomeric stereochemistry is controlled by the nature of the C2

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[**] A list of abbreviations can be found at the end of this article.
Telemachos Charalambous was an inspiring teacher at the Pancyprrian
Gymnasium, Nicosia, Cyprus.

substituent. Thus, when the C2 oxygen is protected with an alkyl or benzyl group the anomeric effect dominates and the α -anomer is preferentially formed (Scheme 1b). The same configuration is obtained with 2-deoxyglycosyl donors. However, when the C2 position is occupied by a participating group such as an ester (Scheme 1c), a phenylthio, or a phenylseleno group (see below), the stereochemical outcome is opposite to that of the C2 substituent (either α or β) and a 1,2-*trans* product is formed.^[5] Extensions of the Koenigs–Knorr conditions include the use of Lewis acids and phase-transfer catalysis^[6] to activate the anomeric halides.

Glycosyl fluorides, while known since 1923, were first introduced as glycosyl donors in 1981 by the Mukaiyama group (Scheme 1d).^[7] This method has found widespread applications due to a number of advantages associated with glycosyl fluorides. They are usually more stable than other halides and can often be purified by chromatography. In addition, they exhibit considerable thermal and chemical stability. Glycosyl fluorides are accessible from lactols through the action of DAST,^[8a] HF·py,^[8b] 2-fluoro-1-methylpyridinium tosylate,^[8c] hexafluoropropene,^[8d] Ph₃P/DEAD/*Et*₃OBf₄,^[8e] and Selectfluor.^[8f] Glycosyl fluorides have also been prepared from thioglycosides by treatment with NBS/DAST (Scheme 1f) and NBS/HF·py.^[9] They are activated by exposure to fluorophiles such as Lewis acids,^[10, 11] silver salts, and various metallocenes.^[12]

The trichloroacetimidate-mediated glycosidation procedure (Scheme 1g) reported by Schmidt et al.^[13] in 1980 is a very powerful method and it has been widely used in complex molecule construction. The trichloroacetimidate donors are easily prepared from lactols and trichloroacetonitrile in the presence of a base such as NaH or DBU. They are activated by acids, usually Lewis acids such as TMSOTf^[14] or BF₃·Et₂O.^[13] *O*-Acyl glycosyl donors, particularly the *O*-acetyl glycosyl

donor (Scheme 1h), are easily accessible, and they have been used extensively in glycosidation reactions upon activation with Lewis acids.^[15] Thioglycosides, particularly phenylthio- and ethylthioglycosides (Scheme 1i), have been widely applied in glycosidation and related reactions due to their ease of formation, relative stability to various reaction conditions, and convenient activation with electrophilic reagents^[16] or oxidizing agents. Glycosidations with *O*-silylated glycosyl derivatives,^[17] in the presence of TMSOTf as a catalyst, have been implemented (Scheme 1j). As first demonstrated by Kahne et al.,^[18a] glycosyl phenylsulfoxides act as mild glycosyl donors upon activation with Tf₂O (Scheme 1k). Recent advances along these lines have led to a sulfoxide-based method for forming β -mannosides.^[18b]

A related method is the direct conversion of lactols into glycosides with alcohols, Ph₂SO, and Tf₂O by Gin and co-workers (Scheme 1l).^[19] Glycals have been employed as versatile intermediates in glycosidation reactions.^[20] Thus, a number of electrophiles such as I(col)₂ClO₄,^[21] NIS,^[22] PhSeCl,^[23] PhSCl, and NBS^[24] (Scheme 1m) have been utilized to induce coupling of glycals with hydroxy components and to produce, after reductive removal of the resulting C2 substituent, 2-deoxyglycosides. Wong and co-workers^[25] have recently introduced a method for the synthesis of 2-fluorosugars by exposing glycals to Selectfluor (Scheme 1n).

Halcomb and Danishefsky used glycals extensively by opening the epoxide that is formed as an intermediate by exposure of various glycals to DMDO (Scheme 1n).^[26] The use of *n*-pentenyl glycosides as glycosyl donors, introduced by Fraser-Reid et al.,^[27] involves activation with an electrophile, followed by expulsion of the anomeric substituent and trapping of the incipient oxonium species with a hydroxy component (Scheme 1o). Glycosyl phosphates^[28a] and phos-

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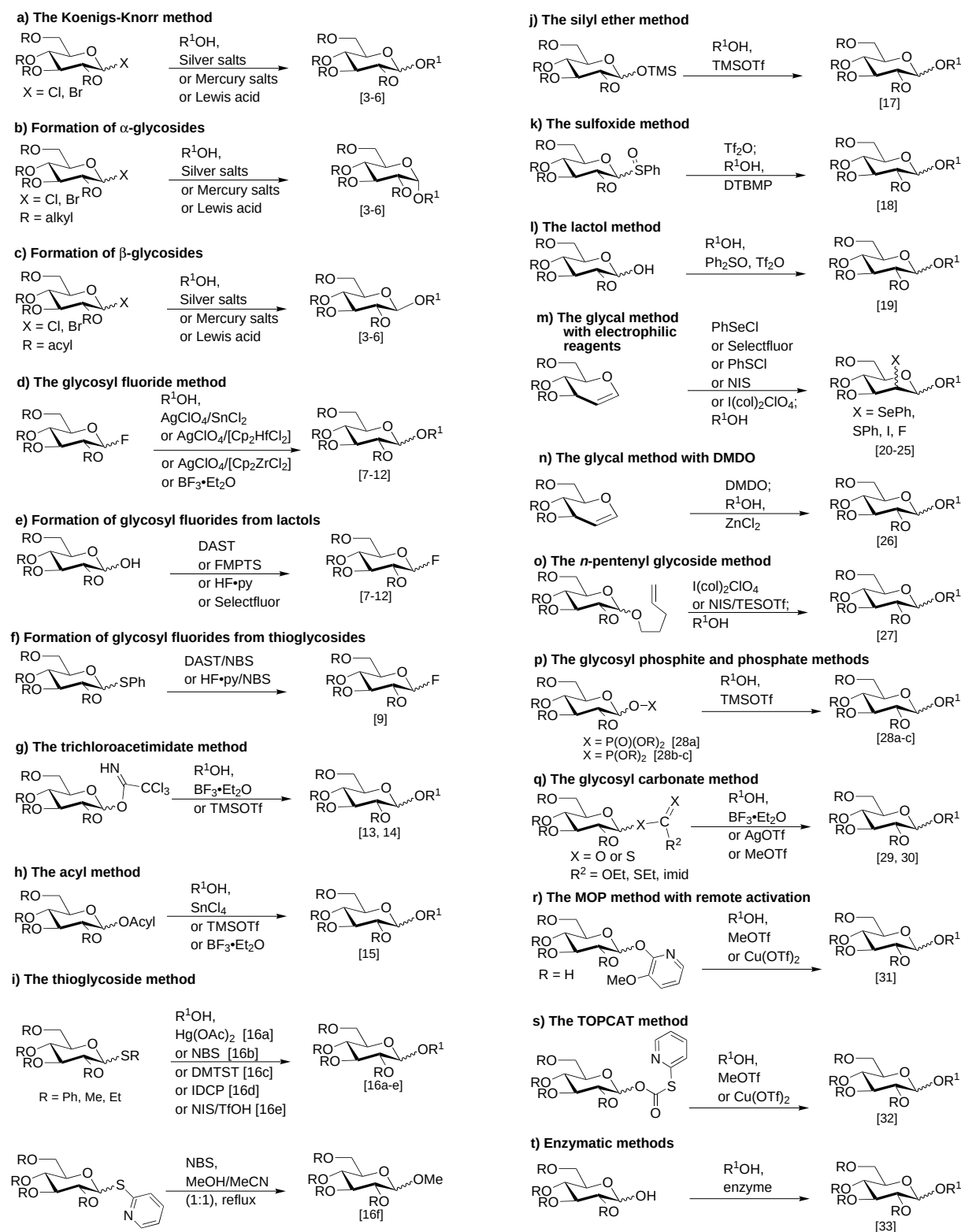


K. C. Nicolaou



H. J. Mitchell

Helen J. Mitchell was born in London in 1971. She received her BSc degree from the University of Victoria, BC, Canada, and her PhD under the guidance of Professor K. C. Nicolaou from the University of California, San Diego, where she worked on the synthesis of complex natural products including the total synthesis of the oligosaccharide antibiotic everninomicin 13,384-1 and the final stages in the total synthesis of vancomycin. She is currently continuing her studies into the synthesis of natural products with Professor K. C. Nicolaou as a postdoctoral fellow at The Scripps Research Institute. Her research interests include natural products synthesis and carbohydrate chemistry, and the application of these fields to chemical biology.



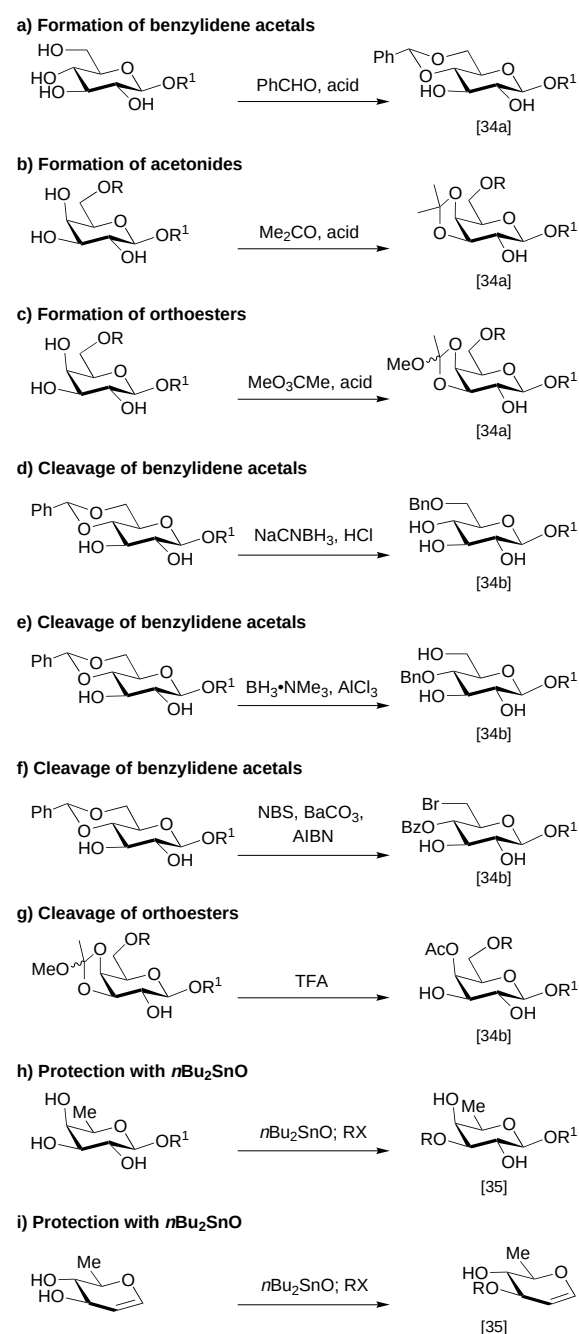
Scheme 1. General glycosidation methods. (Numbers in square brackets are literature references.)

phites^[28b, c] have been successfully employed in glycosidation reactions upon activation with TMSOTf (Scheme 1p). Various carbonate-type donors, including xanthates^[29] and imidazole thiocarbamates,^[30] have been used in glycoside-forming reactions with alcohols after activation with methylating agents (Scheme 1q). Hanessian and co-workers have devel-

oped the remote activation approach to oligosaccharides through unprotected and protected MOP glycosyl donors in the presence of catalytic amounts of methylating agents or cupric salts (Scheme 1r).^[31] Hanessian and co-workers have also employed 2-thiopyridylcarbonate sugar derivatives as donors to form glycosides upon activation with methylating

agents or $\text{Cu}(\text{OTf})_2$ (Scheme 1s).^[32] Finally, one should note the numerous successes in enzymatic glycosidations^[33] through the use of glycosidases, and glycosyl transferases and UDP-protected sugars (Scheme 1t).

At this time we also mention several very useful reactions involving the regioselective functionalization of polyol-containing mono- and oligosaccharides, as depicted in Scheme 2, which can be found throughout the syntheses to be presented. In short, these reactions involve the selective formation of acetals and orthoesters, the selective cleavage of acetals and orthoesters, and the monoprotection of polyols mediated by tin acetals. The condensation of aldehydes and ketones with carbohydrates in the presence of Lewis or protic acids to form acyclic and cyclic acetals is found in many monosaccharide



Scheme 2. Regioselective methods for protection.

syntheses,^[34a] the most common of which is the 4,6-*O*-benzylidene acetal, shown in Scheme 2a for D-glucose. The 3,4-*O*-isopropylidene (Scheme 2b) and 3,4-*O*-orthoester (Scheme 2c) are also frequently used to functionalize D-galactose (shown), as well as other derivatives.

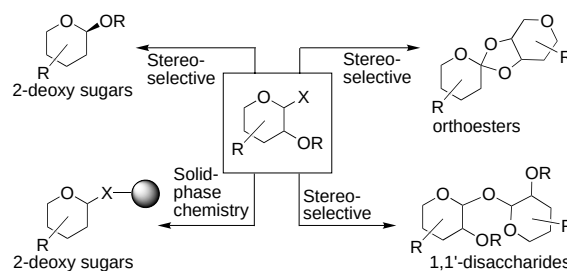
The selective cleavage of the 4,6-*O*-benzylidene group with various reagents allows entry into three types of structures.^[34b] Treatment of the 4,6-*O*-benzylidene group with NaCNBH_3 and HCl (Scheme 2d) affords the 6-*O*-benzyl derivative, while exposure to $\text{BH}_3 \cdot \text{NMe}_3$ (Scheme 2e) furnishes the 4-*O*-benzyl derivative. Finally, treatment of the 4,6-*O*-benzylidene group with NBS, BaCO_3 , and AIBN affords the 6-*O*-bromo-4-*O*-benzoyl derivative through radical cleavage (Scheme 2f), which easily leads to deoxygenation of the C6 position. The 3,4-*O*-orthoester of D-galactose can also be cleaved to afford the 4-*O*-acetate upon exposure to TFA (Scheme 2g). The regioselective acylation and alkylation of tin acetals^[35] is very useful for the selective protection of a number of polyol-containing systems, including protection of equatorial over axial hydroxyl groups (Scheme 2h) and for differentiation between two equatorial hydroxyl groups with different steric environments (Scheme 2i). While this list is by no means exhaustive, it highlights just a few of the efficient methods used in the syntheses below.

In our dealings with carbohydrates we were faced with a number of challenges and objectives. In some instances our encounters focused purely on utilizing carbohydrates as starting materials for the total synthesis of complex, non-glycosidic natural products (see Scheme 3). In these endeavors we were decisively influenced by many others, but most

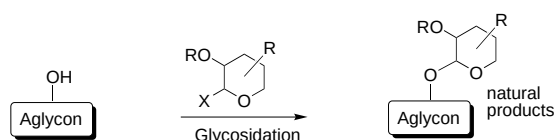


Scheme 3. Carbohydrate templates as starting materials for the construction of complex molecules.

notably by Stephen Hanessian, whose pioneering works in the field were both inspiring and exemplary. In other instances, we were challenged by difficult glycosidations for which new synthetic methods had to be developed (see Scheme 4) or new strategies had to be designed before success. Goals in these efforts varied from attaching a single carbohydrate unit onto a complex aglycon system of a natural product (see Scheme 5) to the construction of complex, naturally occurring carbohy-

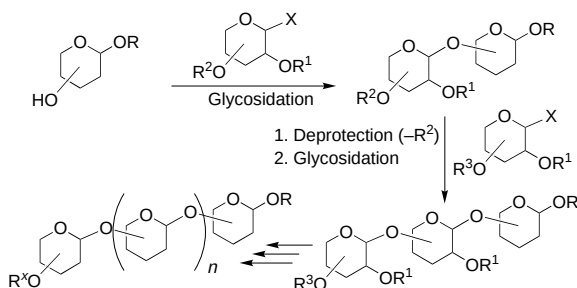


Scheme 4. New synthetic technologies in carbohydrate chemistry.



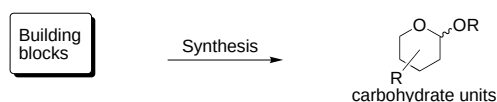
Scheme 5. Glycosidations of aglycons in the formation of natural products.

drates from simple building blocks and monosaccharides (see Scheme 6). Yet in other circumstances the need was to efficiently construct rare or difficult to access carbohydrate



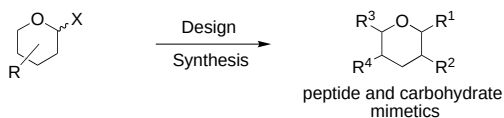
Scheme 6. Synthesis of complex oligosaccharides from simple building blocks and monosaccharides.

moieties for incorporation into larger structures as building blocks (see Scheme 7). Finally, designed carbohydrates or molecules based on carbohydrate templates were the objects



Scheme 7. New methods for the construction of carbohydrate units.

of investigation (see Scheme 8). In all of these endeavors, new chemistry or biology was the ultimate goal. In the following pages we describe these adventures, highlighting the enabling technologies that were developed along the way and the chemical biology investigations that were facilitated at the end.



Scheme 8. Design and synthesis of peptide and carbohydrate mimetics.

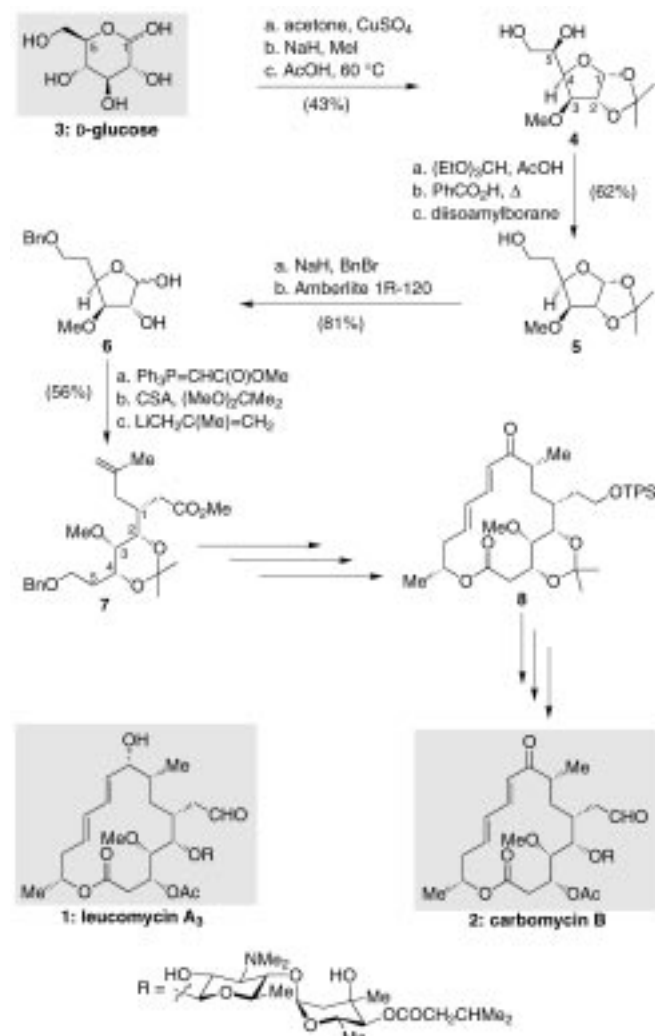
2. Carbohydrates as Starting Materials for Total Synthesis

Rich in functionality and stereochemistry, carbohydrates are excellent starting materials for total synthesis. This realization goes back decades and is, by no means, our invention. The examples from our group discussed below, however, are demonstrative of the concept and strongly support the notion of the carbohydrate “chiral pool” as a valuable source of diverse building blocks for organic synthesis. Given the renewable nature of this source, the

importance of carbohydrates in synthesis is bound to increase in the future. Advantages of using carbohydrates as starting materials include their known absolute stereochemistry, their often low cost, and their synthetic fertility. Their usefulness expands with increased ability by which synthetic chemists are able to manipulate them into new materials, which often bear little, if any, resemblance to the original structures. Imaginative ways to carry out such transformations are the trademark of elegant carbohydrate-based syntheses. The order of the following cases from these laboratories is chronological.

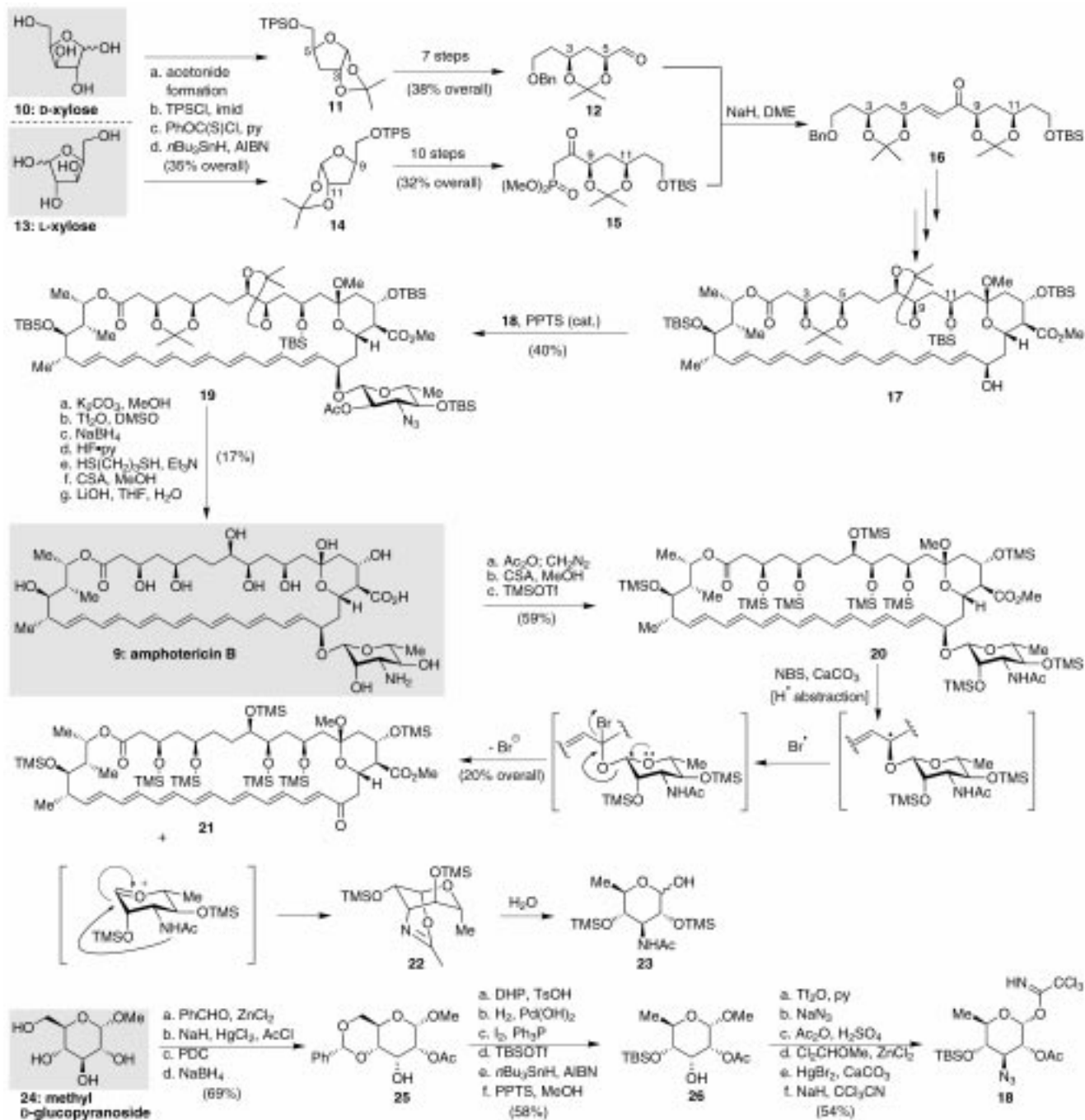
2.1. Leucomycin A₃ and Carbomycin B

Leucomycin A₃ (**1**, Scheme 9) and carbomycin B (**2**) represent two clinically important 16-membered ring macrolide antibiotics. The semisynthesis of these macrolides from D-glucose (**3**), chosen because it contained three of the required stereocenters, was reported by this group in 1981, and is shown in Scheme 9.^[36–40] Thus, D-glucose (**3**) was converted into the 1,2;5,6-bisacetonide, followed by C3 methylation and cleavage to form diol **4**. Formation of the orthoester,

Scheme 9. Semisynthesis of leucomycin A₃ (**1**) and carbomycin B (**2**) from D-glucose (**3**) (1981).^[36–40]

2.2. Amphotericin B and Amphoteronolide B

Amphotericin B (**9**, Scheme 10) is a clinically used antifungal agent, isolated from *Streptomyces nodosus* and, along with its aglycon, amphoteronolide B (shown in a protected form as **17**, Scheme 10), became the second synthetic target to be elaborated from carbohydrate building blocks by this group.^[42–51] Retrosynthetic analysis of this complex polyene macrolide suggested that certain stereochemical and symmetry elements present in amphoteronolide B could be derived from a commercially available xylose carbohydrate. In particular, it was recognized that segments C1–C6 and



Scheme 10. Synthesis of amphoteronolide B (**17**) and amphotericin B (**9**) from D- and L-xylose (**10** and **13**, respectively) and methyl D-glucopyranoside (**24**), as well as the degradation of amphotericin B (**9**) (1987).^[42–51]

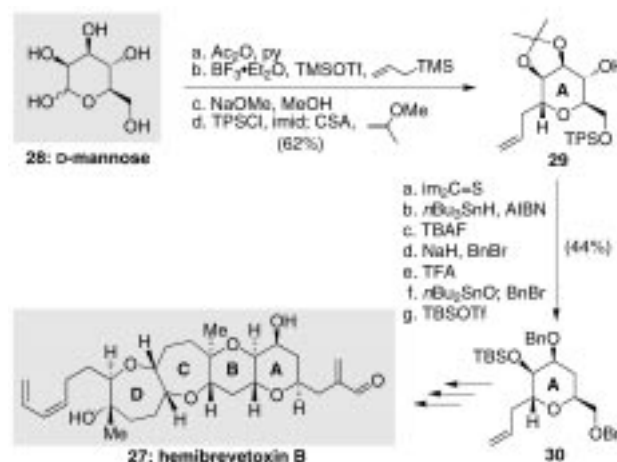
C8–C13 could be obtained from the D and L enantiomers of xylose, respectively. Thus, D-xylose (**10**) was converted into its 1,2-monoacetonide, selectively silylated at the primary position, and deoxygenated to afford intermediate **11**. Further elaboration furnished the C1–C6 fragment **12**, whose stereochemical elements could be readily transferred to the coupled product **16** and the final target **17**. The L enantiomer of xylose (**13**) was taken through a similar sequence to afford derivative **14** and, thence, through a ten-step sequence to furnish the C8–C13 keto phosphonate **15**. Coupling of these two intermediates **12** and **15** provided the larger C1–C13 fragment **16** in a highly concise and efficient manner; and the latter was further elaborated to amphoteronolide derivative **17**.

Completion of the synthesis of the requisite derivative **17** enabled attention to be focused on the final drive towards amphotericin B (**9**). The difficulty of the glycosidation step was recognized from the outset of the synthesis; this difficulty was due to the inherent instability of the aglycon unit and the target molecule, the presence of a basic nitrogen on the carbohydrate moiety, and the requirement for a β -cis-1,2-glycoside bond. Following systematic, but unsuccessful, glycosidation studies, an indirect method for forming the correct anomeric stereochemistry was ultimately developed. Thus, as shown in Scheme 10, amphoteronolide B derivative **17** was coupled with trichloroacetimidate **18** in the presence of PPTS to afford glycoside **19**. Monosaccharide **18** (derived from methyl-D-glucopyranoside **24**) incorporated an acetate group at the C2 position with the opposite configuration to that desired in order to direct the anomeric stereochemistry. This maneuver required, however, that this center be inverted after glycosidation. This goal was easily attained by Swern oxidation and subsequent reduction with NaBH₄ to afford the monosaccharide with the correct stereochemistry in 80% overall yield. Further manipulations, including reduction of the azide and removal of the protecting groups, proceeded smoothly to afford the target, amphotericin B (**9**), in high overall yield. During this total synthesis, various degradation studies were performed on amphotericin B in order to remove the carbohydrate unit for spectroscopic comparison of the resulting aglycon to synthetic material, and for supplementing the amounts of advanced intermediates that were available. As such, a novel oxidative protocol for the deglycosidation of amphotericin B using NBS and CaCO₃ was developed for the construction of enone **21** and lactol **23**.

2.3. Hemibrevetoxin B

The brevetoxins are among the most prominent toxins associated with the “red tide” phenomenon and have been implicated in massive fish kills, mollusk poisonings, and occasional human intoxications. These molecules, produced by the dinoflagellate strain *Gymnodinium breve* DAVIS, represent a class of neurotoxins which activate sodium channels and cause repetitive firing in neurons. In a program directed towards the total synthesis of the brevetoxins, new synthetic methods were developed and applied to the total synthesis of hemibrevetoxin B,^[52, 53] a molecule having a molecular size

approximately half that of the brevetoxins A and B. Retro-synthetic analysis of hemibrevetoxin B (**27**, Scheme 11) revealed that the functionality present in ring A could be traced back to commercially available D-mannose (**28**), which would



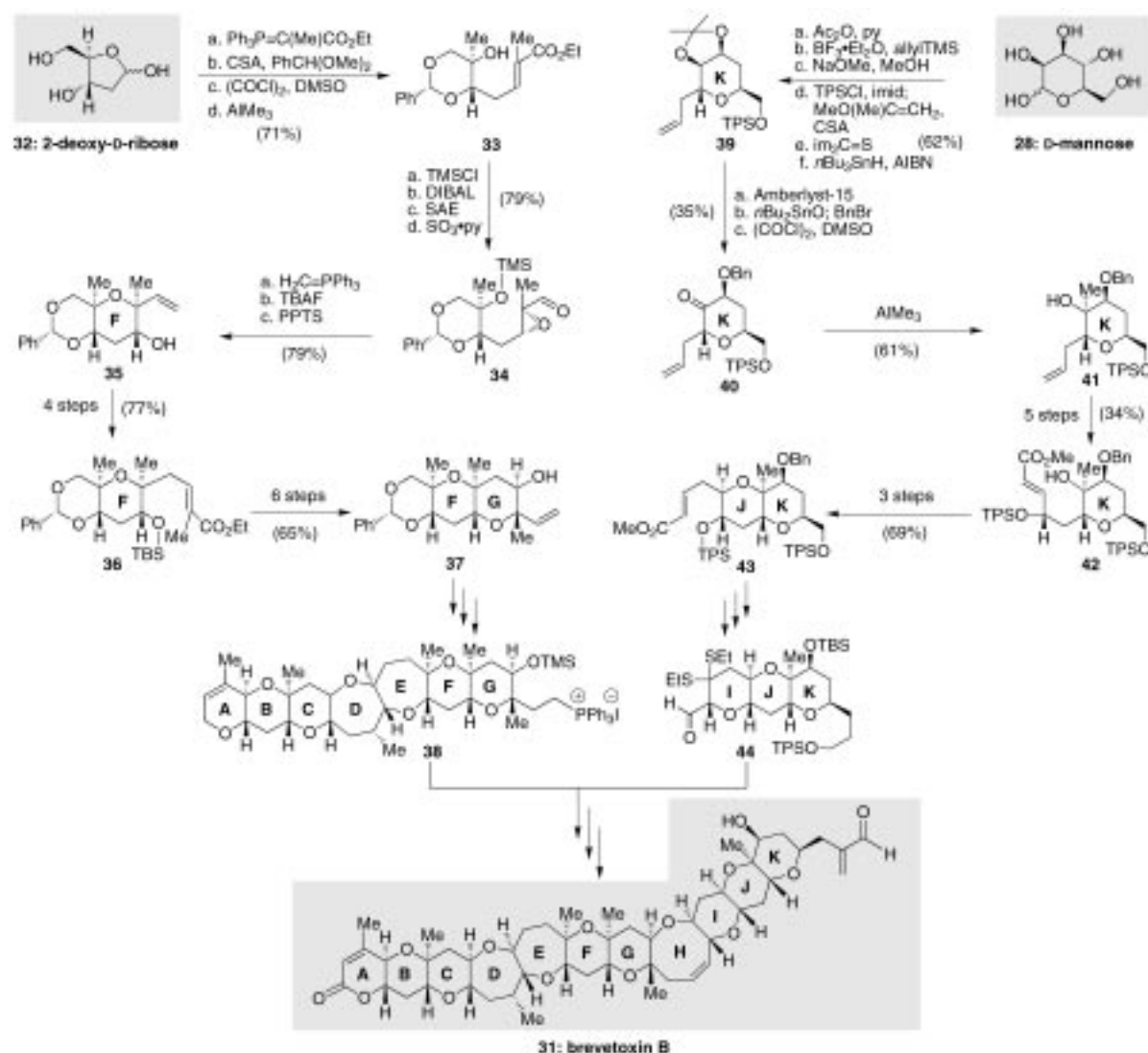
Scheme 11. Synthesis of hemibrevetoxin B (**27**) from D-mannose (**28**) (1992).^[52, 53]

provide three of the ten required stereocenters. Thus, D-mannose (**28**) was peracetylated and C-glycosidated with allyltrimethylsilane in the presence of BF₃·Et₂O and TMSOTf to afford a 7:1 ratio of α : β anomers. The resulting product was deacetylated, selectively silylated at the primary position, and converted into the 2,3-acetonide **29**. Further elaboration of **29** into the tetrahydropyran systems in a linear fashion was achieved through regio- and stereoselective epoxide-opening/ring-closing procedures, culminating in the total synthesis of hemibrevetoxin B (**27**) in 1992, the first member of the brevetoxin class to be synthesized in the laboratory.

2.4. Brevetoxin B

Brevetoxin B (**31**, Scheme 12) was the first member of this class of marine natural products to be structurally elucidated and is also one of the most potent. It has a novel polycyclic framework consisting of 11 rings (eight 6-membered, two 7-membered, and one 8-membered) fused together by *trans* junctions with 23 stereocenters. Carbohydrates seemed excellent precursors to the tetrahydropyran rings found in brevetoxins in that several of the stereocenters could be established concurrently, particularly those centers flanking the oxygens. The number of carbohydrate units to be incorporated depended upon the successful coupling of advanced intermediates in either a convergent, or sometimes, linear fashion. During the initial studies directed towards the development of novel synthetic methods and the investigation of coupling strategies, carbohydrates were used to prepare many of the model systems and several of the tetrahydropyran rings. In the final and successful linear approach to brevetoxin B,^[54–67] two of the tetrahydropyran motifs, rings F and K, were derived from carbohydrates.

As shown in Scheme 12, 2-deoxy-D-ribose (**32**) was utilized as a starting material for the F ring tetrahydropyran. Thus,

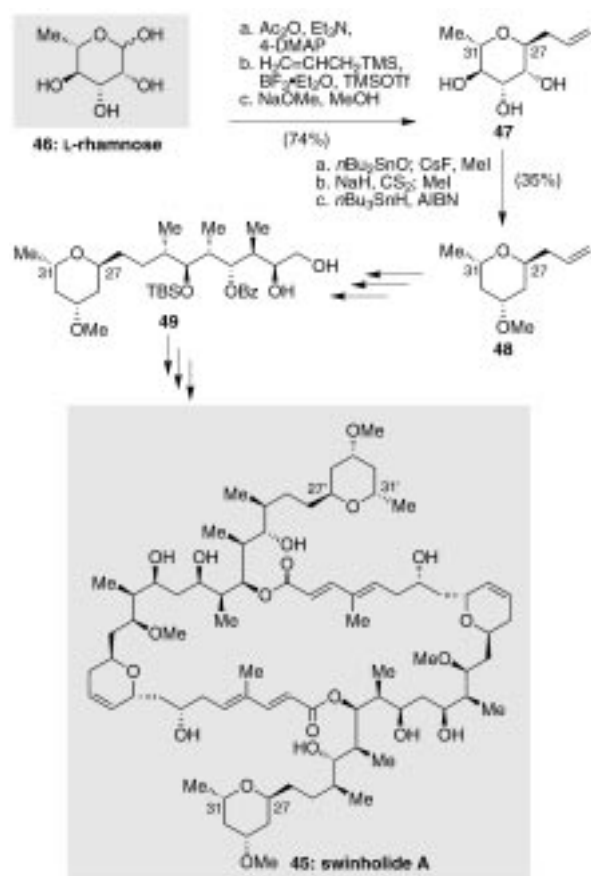


Scheme 12. Synthesis of brevetoxin B (**31**) from 2-deoxy-D-ribose (**32**) and D-mannose (**28**) (1995).^[54–67]

treatment of **32** with (carbethoxyethylidene)triphenylphosphorane was followed by formation of the thermodynamically favored benzylidene acetal, Swern oxidation of the remaining alcohol, and exposure of the resulting carbonyl compound to AlMe_3 to introduce the methyl group. Completion of ring F involved silylation of the tertiary alcohol, DIBAL reduction, Sharpless asymmetric epoxidation, $\text{SO}_3\cdot\text{py}$ oxidation, olefination, and PPTS-catalyzed epoxide-opening/cyclization to afford tetrahydropyran derivative **35** in 44% overall yield. Further elaboration of the “right-hand” side of ring F furnished FG segment **37** via **36** in 50% yield for ten steps; this segment was ultimately incorporated into the target, brevetoxin B (**31**). Scheme 12 also illustrates the conversion of D-mannose (**28**) into ring K derivative **39**, followed by completion of this ring system by removal of the acetonide with Amberlyst-15, tin acetal mediated monobenzoylation, Swern oxidation, and addition of AlMe_3 to afford tertiary alcohol **41** in 13% overall yield. Elaboration of the “left-hand” side of ring J furnished JK segment **43** in 23% yield for eight steps; this segment was again incorporated into the final target, brevetoxin B (**31**), in its total synthesis in 1995.

2.5. Swinholide A

Swinholide A (**45**, Scheme 13), a marine natural product isolated from the sponge *Theonella swinhoei*, displays impressive biological properties, including antifungal activity and potent cytotoxicity against a number of tumor cell lines. The molecular structure of swinholide A (**45**) is distinguished by a C_2 -symmetric 44-membered macrolide ring, two conjugated diene systems, two trisubstituted pyran systems, two disubstituted dihydropyran systems, and a total of 30 stereocenters. Retrosynthetic analysis of this complex macrolide revealed that the C27–C32 segment could be obtained from commercially available L-rhamnose (**46**), which would provide the correct stereochemistry for the C27, C29, and C31 centers of this pyran moiety.^[68–71] Thus, peracetylation of L-rhamnose (**46**) followed by C-glycosidation with allyl trimethylsilane in the presence of TMSOTf and $\text{BF}_3\cdot\text{Et}_2\text{O}$ and subsequent deacetylation afforded, exclusively, the desired α -glycoside **47**. Regioselective tin acetal mediated protection as a methyl ether at the C3 position was followed by Barton–McCombie deoxygenation of the remaining two alcohols to



Scheme 13. Synthesis of swinholid A (45) from L-rhamnose (46) (1995).^[68–71]

afford olefin **48**. Further elaboration of the C27–C32 segment allowed for its eventual incorporation into swinholid A (**45**).

2.6. Brevetoxin A

Brevetoxin A (**50**, Scheme 14) is the most potent neurotoxin in the brevetoxin family. Its synthetic challenge originates from the high complexity of its molecular structure consisting of 10 rings, which contain 5–9 members, inclusively, surrounded by 22 stereocenters. Retrosynthetically, D-glucose was recognized as a potential central scaffold for ring C to allow for the installation of the four stereocenters situated on this ring; the 8- and 7-membered rings (B and D) could be elaborated around this. As with the other brevetoxins, D-mannose was envisioned to provide three stereocenters present in the “right-hand” region of the molecule, encompassing the ring J tetrahydropyran moiety and allowing for facile extension of the necessary side chain. Thus, D-glucose (**3**, Scheme 14) was transformed into its 1,2;5,6-bisacetonide and deoxygenated at position C3. Selective cleavage of the 5,6-acetonide with H_5IO_6 furnished aldehyde **51**. Sequential addition of MeMgBr and Swern oxidation led to the methylketone. Reaction of the latter compound with allylmagnesium bromide in the presence of $\text{Ti}(\text{iPrO})_4$ led, stereoselectively, to the tertiary alcohol and was followed by

cleavage of the acetonide with $\text{EtSH}/\text{ZnCl}_2$, dibenzylation, I_2 -mediated hemiacetal formation, olefination, and finally, CSA-catalyzed ring closure to furnish ring C derivative **53** in 34% overall yield from **51**. Further elaboration of **53** led successively to **54** and **55**. D-Mannose (**28**) was processed in a similar fashion to that described in Schemes 11 and 12, to furnish the ring J derivative **56** in 27% yield over nine steps (Scheme 14). Further elaboration of the latter intermediate led to the IJ segment **58** and thence to **59**. The segments **55** and **59** were then coupled and elaborated to brevetoxin A (**50**) through the dithioketal cyclization strategy.^[72–79]

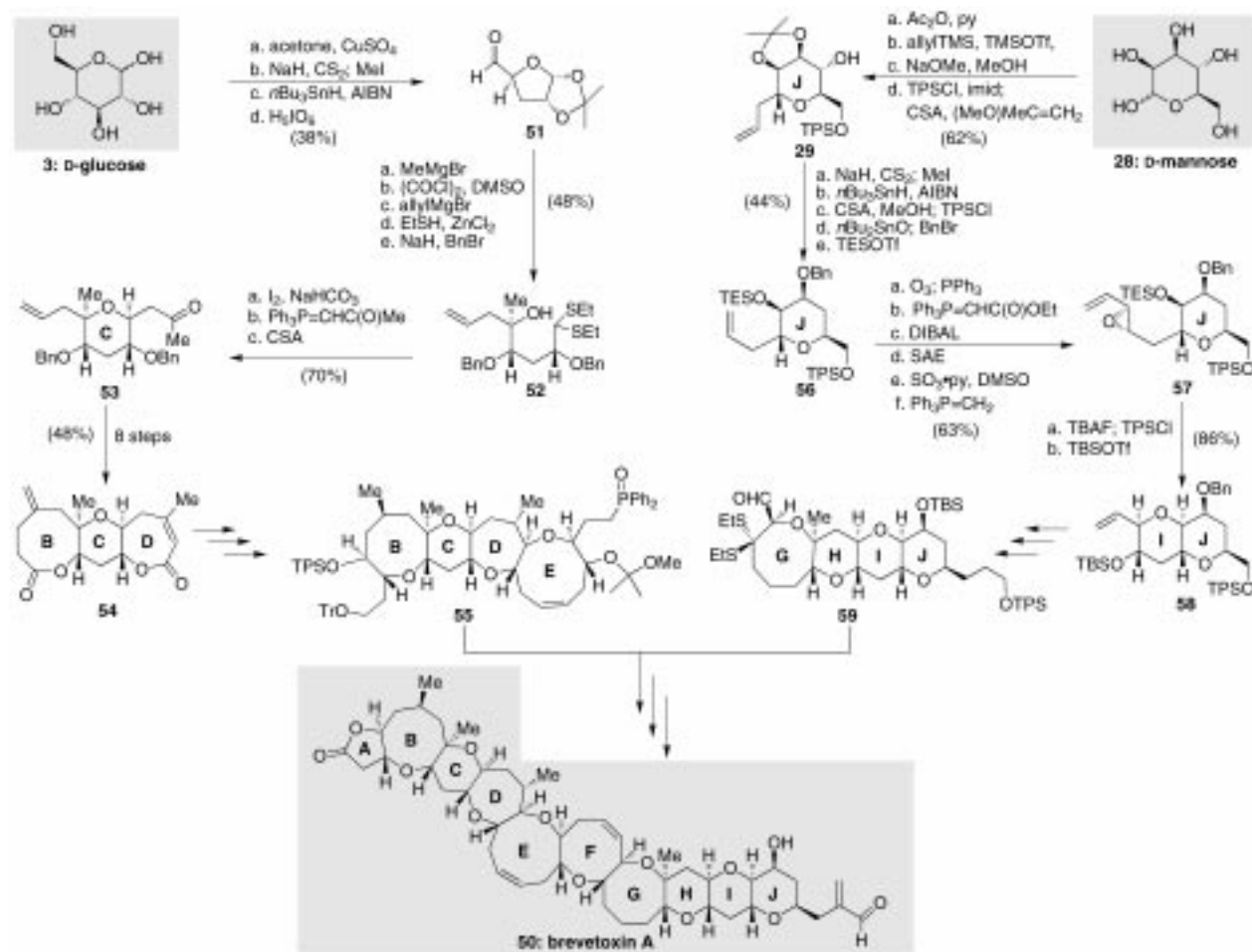
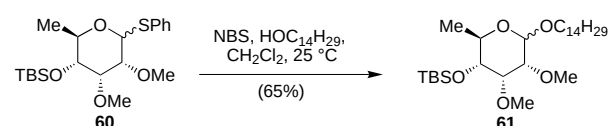
Before extending the discussion to encompass the total synthesis of complex oligosaccharide-containing natural products, it will be instructive to present a number of new methods and technologies developed en route to these natural products.

3. New Synthetic Technologies in Carbohydrate Chemistry

Over the years our excursions into the realm of carbohydrate chemistry brought us face-to-face with a myriad of challenges and provided us opportunities to discover and invent novel synthetic technologies and strategies, both for the construction of carbohydrate templates and their utilization in organic synthesis. Such methods and processes included the synthesis of activated glycosyl donors, new glycosidation procedures, new methods for C-glycosidations, new methods for the formation of 2-deoxyglycosides, 1,1'-disaccharides, and orthoesters, new strategies for solid-phase synthesis of oligosaccharides, and new processes for the construction of aminosugars and their derivatives. Below we will discuss, in chronological order, these developments and place them in perspective within the larger domain of organic synthesis.

Noting the ready availability, relative stability, and potential of thioglycosides as glycosyl donors,^[80] we searched for a non-metal based activation procedure for these intermediates (in contrast to Ferrier et al.'s original use of mercuric salts for activation^[16a]). In 1983 we reported a mild method for the synthesis of *O*-glycosides from phenylthioglycosides with NBS as an activator.^[16b] This procedure, which was preceded by a report from the Hanessian laboratories^[16f] in which NBS was utilized to activate a 2-pyridylthioglycoside to form α - and β -methyl glycosides (by solvolysis in methanol/acetonitrile (1/1) under reflux), was found to be quite general and simple to employ as demonstrated by the many substrates shown to enter the reaction. Scheme 15 shows the reaction in which phenylthioglycoside **60** was converted into *O*-glycoside **61** ($\alpha:\beta \approx 5:1$) in 65% yield upon treatment with the required straight chain alcohol in the presence of NBS in CH_2Cl_2 at 25 °C. Selected examples of this reaction are provided in Table 1.

Our 1983 publication^[16b] reporting the first practical thioglycoside-based glycosiation method with an electrophilic reagent (that is, NBS) was followed by a number of other useful modifications such as the use of DMTST (for example,


 Scheme 14. Synthesis of brevetoxin A (**50**) from D-mannose (**28**) and D-glucose (**3**) (1998).^[72–79]

 Scheme 15. NBS-promoted synthesis of O-glycosides (such as **61**) from phenylthioglycosides (like **60**) (1983).^[16b, 80]

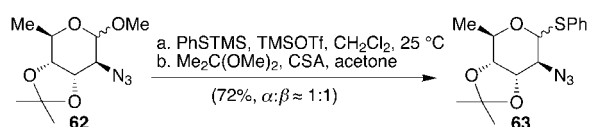
by Garegg and co-workers in 1986^[16c], IDCP (for example, by van Boom and co-workers in 1990^[16d]), and NIS/TfOH (for example, by van Boom and co-workers in 1990^[16e]). In addition, during the course of these studies a new method for the direct conversion of methyl glycosides into phenylthioglycosides was developed.^[9] As shown in Scheme 16, this procedure involves exposure of the methyl glycoside (such as **62**) to PhSTMS and TMSOTf in CH_2Cl_2 at 25 °C.

In an effort to develop a streamlined process for the synthesis of oligosaccharides, we undertook an exploration into the chemistry of glycosyl fluorides. Thus, merging the excellent glycosidation properties of glycosyl fluorides, previously reported by Mukaiyama et al.,^[7] with the newly discovered ability of phenylthioglycosides to afford glycosyl fluorides upon exposure to NBS/DAST or NBS/HF·py (**64** → **65** and **66** → **67**, Scheme 17 and Table 2), we developed the “two-stage activation” procedure for the synthesis of complex oligosaccharides.^[9] This reiterative procedure com-

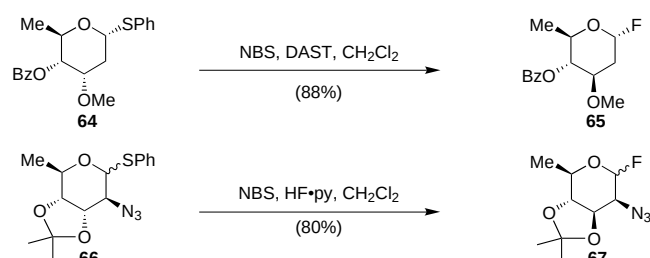
 Table 1. Selected examples of NBS-promoted synthesis of O-glycosides from phenylthioglycosides.^[16b, 80]

Phenylthioglycoside	Alcohol	O-Glycoside	Solvent	Yield [%]	$\alpha:\beta$
	HOCH_2CH_3		CH_2Cl_2	78	1:1
			MeCN	75	3:1
			MeCN	72	1:1
			CH_2Cl_2	72	9:1
			CH_2Cl_2	82	2:1

binates the differential and orthogonal reactivities of glycosyl fluorides, phenylthioglycosides, and silyl ethers to achieve a reliable sequence for oligosaccharide chain growth (Scheme 18). Thus, clean conversion of a monosaccharide



Scheme 16. Synthesis of phenylthioglycosides (such as **63**) from methyl glycosides (like **62**) (1982).^[9]

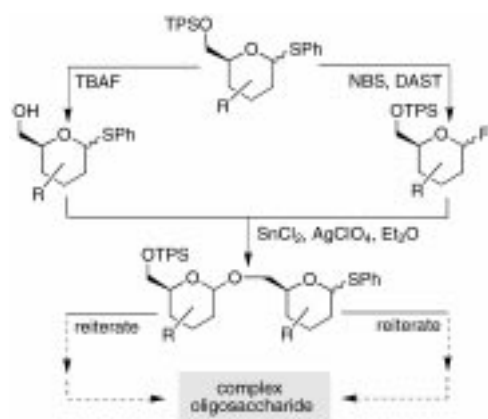


Scheme 17. Formation of glycosyl fluorides from phenylthioglycosides (1984).^[9]

Table 2. Selected examples of glycosyl fluoride formation from phenylthioglycosides.^{[a][9]}

Phenylthioglycoside	Glycosylfluoride	Method	Yield [%]	α:β
		A	82	5:1
		B	74	5:1
		A	75	1:2
		A	91	
		B	80	
		A	70	

[a] Method A: DAST/NBS; Method B: NBS/HF·py.

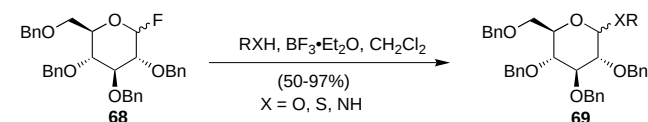


Scheme 18. Practical, reiterative synthesis of oligosaccharides by the two-stage activation procedure (1984).^[9]

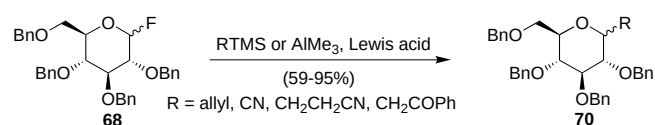
unit containing a phenylthio group at C1 and a relatively robust silyl ether group (such as TPS) at C6 to the corresponding glycosyl fluoride (NBS/DAST) and the primary alcohol (TBAF), respectively, is followed by coupling

with SnCl₄/AgClO₄ to furnish a disaccharide equipped with both a phenylthio and a silyl group. Reiteration of the process then leads to a new pair of disaccharide donor and acceptor, from which a tetrasaccharide may be formed and so on. Several applications of this technology in complex oligosaccharide synthesis have been demonstrated; some of these syntheses will be discussed below.

Further explorations of the chemistry of glycosyl fluorides led to efficient methods for the O-, N-, S-,^[11] and C-glycosidations^[81] (Schemes 19 and 20, and Tables 3 and 4). A search



Scheme 19. Synthesis of N-, O-, and S-glycosides from glycosyl fluorides (1984).^[11]



Scheme 20. Synthesis of C-glycosides from glycosyl fluorides (1984).^[81]

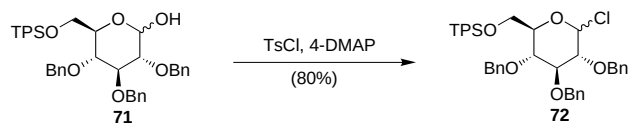
Table 3. Selected examples of the synthesis of N-, O-, and S-glycosides from glycosyl fluoride **68**.^[11]

Reagents, temperature	Products	Yield [%]	α:β
MeCO ₂ H, BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , 0 °C		97	3:2
Me ₂ CHCH ₂ CH(NBn ₂)CO ₂ H, BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , 0 °C		76	10:1
PhNH ₂ , AlMe ₃ , CH ₂ Cl ₂ , 25 °C		65	1:1
morpholine, MgBr ₂ ·Et ₂ O, CH ₂ Cl ₂ , 25 °C		90	1:10

Table 4. Selected examples of the synthesis of C-glycosides from glycosyl fluoride **68**.^[81]

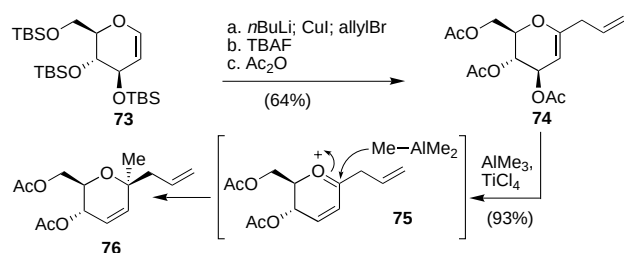
Reagents	Product	Yield [%]	α:β
allylTMS, BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , 0 °C		95	> 20:1
AlMe ₃ , toluene, 0 °C		95	> 20:1
AlMe ₂ CN, toluene, 0 °C		96	10:1
TMSCH ₂ CN, BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , 25 °C		85	3:1

for new reactions forming glycosyl halides led to a new method for forming glycosyl chlorides from lactols and tosyl chloride in the presence of 4-DMAP (Scheme 21).^[82] In



Scheme 21. Formation of glycosyl chlorides (such as **72**) from lactols (like **71**) (1984).^[82]

connection with our program directed towards the total synthesis of brevetoxin B (**31**), we developed a general and stereospecific synthesis of 1,1-dialkyl glycosides. Reported in 1986^[83] and depicted in Scheme 22, this method is exemplified



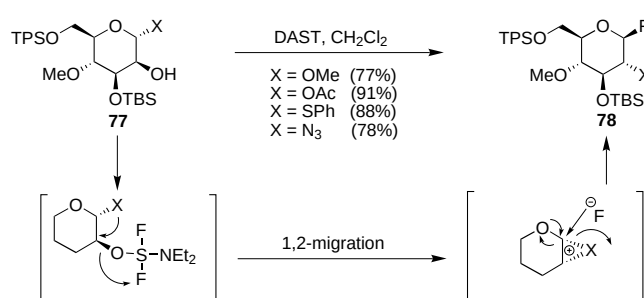
Scheme 22. Stereoselective synthesis of 1,1-dialkylglycosides (such as **76**) from glycals (like **73**) (1986).^[83]

by the synthesis of derivative **76** from glycal **73**. Thus, processing of trisilyl ether **73** through a modified Boeckman procedure followed by exchange of protecting groups furnished 1-allylated glycal **74** in 64% overall yield. Further alkylation of **74** with $\text{AlMe}_3/\text{TiCl}_4$ furnished stereospecifically, and through the indicated intermediate **75**, the 1,1-dialkylated compound **76** in high overall yield. Additional examples are illustrated in Table 5.

During our continuing explorations in the areas of functionalization of ring systems and the stereocontrolled construction of glycoside bonds, a new series of stereospecific 1,2-migrations within the pyranoside framework was discovered.^[84, 85] As illustrated in Scheme 23, treatment of 2-hydroxy carbohydrate frameworks, with various substituents at the C1 position, with excess DAST in CH_2Cl_2 at 0–45 °C led to

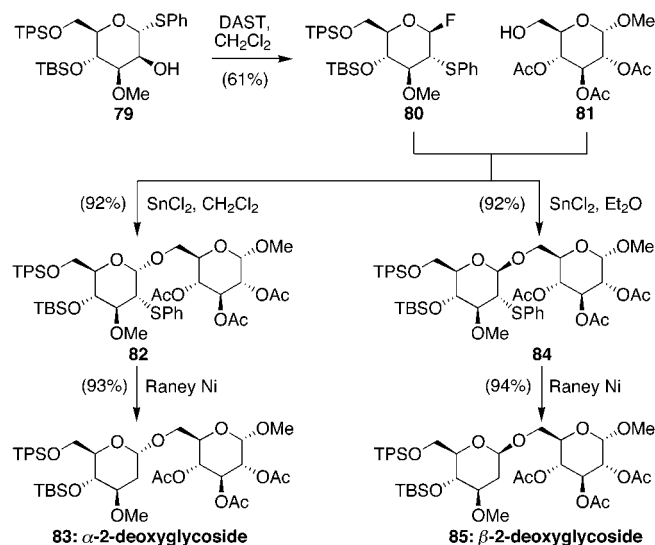
Table 5. Selected examples of 1,1-dialkylglycosides.^[83]

Reagent (R^2M)	Product		Yield [%]
	R^1	R^2	
AlMe_3	Me	Me	92
AlEt_3	Me	Et	82
TMSCN	Me	CN	82
$\text{TMSC}\equiv\text{CMe}$	Me	$\text{C}\equiv\text{CMe}$	79
allylTMS	Me	$\text{CH}_2\text{CH}=\text{CH}_2$	75
Et_3SiH	$\text{CH}_2\text{CH}=\text{CH}_2$	H	92
AlMe_3	$\text{CH}_2\text{CH}=\text{CH}_2$	Me	83



Scheme 23. DAST-promoted 1,2-migrations in carbohydrates (1986).^[84]

smooth 1,2-migration of the anomeric substituent with simultaneous installation of a fluoride at C1. Anomeric substituents capable of this migration include methoxy, acetoxy, phenylthio, azide, benzyloxy, and sugar oxy groups, and they all afford the glycosyl fluorides in high yield. Thus, in one step, this operation introduces a variety of useful functional groups at the C2 position and also a fluorine substituent at C1 with inversion of configuration at both centers. These facile migrations found a number of useful applications. To name a few, the resultant glycosyl fluorides can be employed in coupling reactions with nucleophiles to afford O-, N-, S-, and C-glycosides. Use of a group capable of rupture leads to inversion of the C2 stereochemistry, whereas reductive removal of a C2 thiophenyl group leads to 2-deoxyglycosides. The latter approach is illustrated in Scheme 24. As shown,

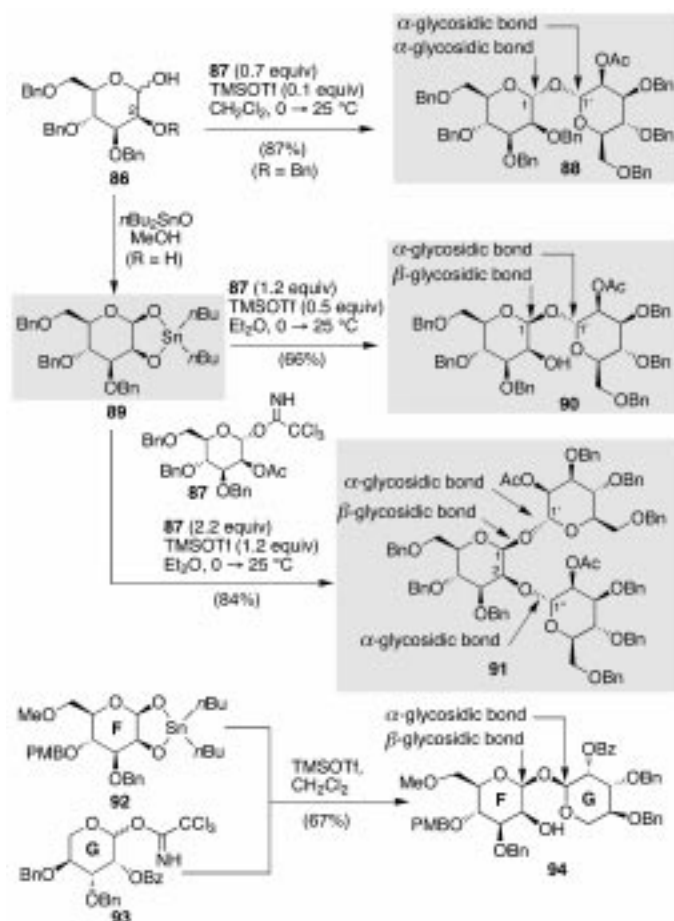


Scheme 24. Stereocontrolled synthesis of α - and β -2-deoxyglycosides from 2-hydroxy-phenylthioglycosides (1986).^[84]

DAST-promoted migration of thioglycoside **79** furnished glycosyl fluoride **80**, which underwent smooth coupling with an alcohol such as **81** in Et_2O and in the presence of $\text{SnCl}_2/\text{AgClO}_4$ to afford the disaccharide **84**. Desulfurization of **84** by Raney nickel resulted in the formation of the 2-deoxy- β -disaccharide **85**. Significantly, utilization of CH_2Cl_2 as the solvent for the coupling step, followed by desulfurization, opens entry into the 2-deoxy- α -disaccharide series of compounds such as **83**. Thus, application of this technology affords

selectively, and at will, the α - and β -glycosides with high stereocontrol.

More recently (1997), during our program directed towards the total synthesis of the everninomicin oligosaccharide antibiotics, a new technology for the construction of 1,1'-disaccharides and 1,1';1'',2-trisaccharides was developed (Scheme 25).^[86] Among the challenging features of the everninomicin antibiotics is the 1,1'-bridge linking rings F and G in



Scheme 25. Stereoselective construction of 1,1'-disaccharides and 1,1';1'',2-trisaccharides by tin acetal technology (1997).^[86]

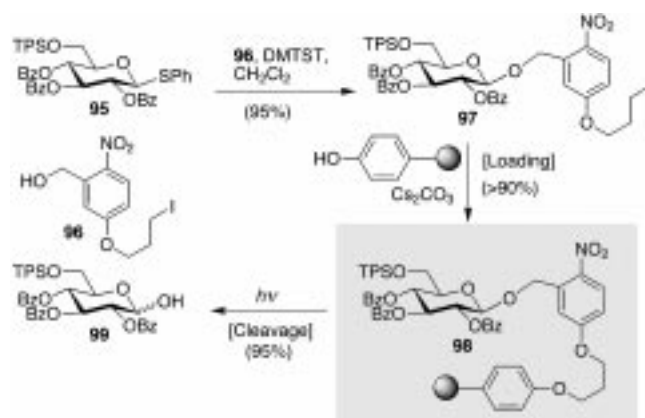
a β -mannoside fashion (see structure of everninomicin 13,384-1 (**344**), Scheme 58). Construction of a linkage of this type requires control of the stereochemistry at both anomeric centers while forming the new bond. For example, treatment of a lactol such as **86** with an activated donor **87** in the presence of TMSOTf furnished the undesired disaccharide **88** containing the 1 α ,1' α -stereochemistry. However, fixation of the anomeric configuration of **86** by conversion into the 5-membered ring stannane **89** and subsequent treatment with trichloroacetimidate **87** in the presence of TMSOTf delivered the desired 1 β ,1' α -disaccharide **90**. Other selected examples of di- and trisaccharide formation are shown in Table 6. Furthermore, exposure of stannane **89** to 2.2 equivalents of trichloroacetimidate **87** in the presence of TMSOTf furnished the 1,1':1'',2-trisaccharide **91**, in which all three glycosidic linkages were formed stereoselectively. This technology was

Table 6. Selected examples of β -linked 1,1'-disaccharides and 1,1';1'',2-trisaccharides (see Scheme 25).^[86]

Equiv 89	Donor	t [h]	Disaccharide yield [%]	Trisaccharide yield [%]
1.5		A 35	66	9
0.45		A 72	—	—
1.5		B 24	10	70
0.45		B 24	—	84
	A: X = OC(NH)CCl ₃ B: X = F			
1.5		C 48	68	—
0.45		C 96	22	47
1.5		D 48	64	—
0.45		D 72	23	32
	C: X = OC(NH)CCl ₃ D: X = F			
1.5		E 72	57	22
0.45		E 72	58	14
1.5		F 0.5	59	5
0.45		F 48	—	33
	E: X = OC(NH)CCl ₃ F: X = F			
1.5		G 0.5	72	8
1.5		G 0.5	70	12
	G: X = OC(NH)CCl ₃			

further applied to the FG model system also depicted in Scheme 25. Thus, coupling of stannane **92** and trichloroacetimidate **93** in the presence of TMSOTf furnished the desired disaccharide **94** in 67% yield. This method was eventually applied to the real system and was a necessary step in facilitating the total synthesis of everninomicin 13,384-1 (described in Section 4.18).

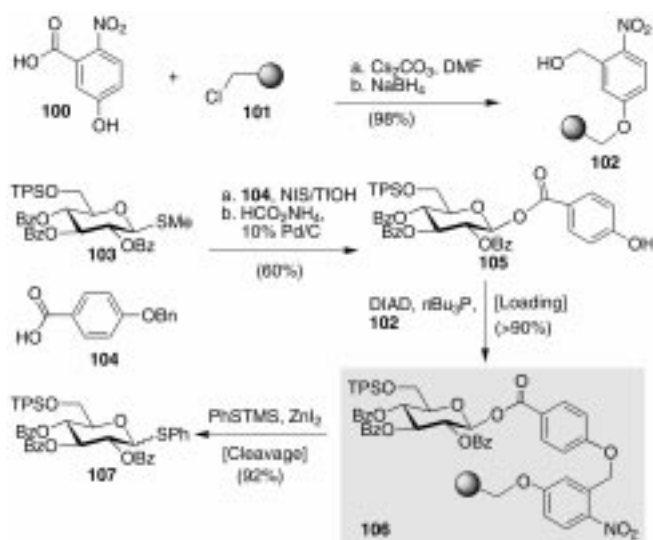
With the emergence of combinatorial chemistry as a powerful tool in the drug discovery process, solid-phase chemistry has assumed a central position in organic synthesis. In this light, the design of new linkers and strategies for the solid-phase synthesis of oligosaccharides was deemed important. Scheme 26 illustrates the synthesis and application of a first generation photolabile linker to the solid-phase synthesis of oligosaccharides, reported from these laboratories in 1997.^[87] Thus, glycosidation of 2-nitrobenzyl alcohol **96** with phenylthioglycoside **95** in the presence of DMTST afforded the β -glycoside **97**. Monosaccharide **97** was then attached to



Scheme 26. Synthesis and utilization of a photolabile linker for oligosaccharide synthesis (1997).^[87]

the phenolic polystyrene resin through its linker to afford conjugate **98**. Efficient cleavage of the carbohydrate fragment from the resin was demonstrated by irradiation in THF at 25 °C, whereby the monosaccharide **99** was afforded in 95 % yield. This linking strategy was ultimately applied to the synthesis of the complex oligosaccharide HPE, as will be described in Section 4.14.

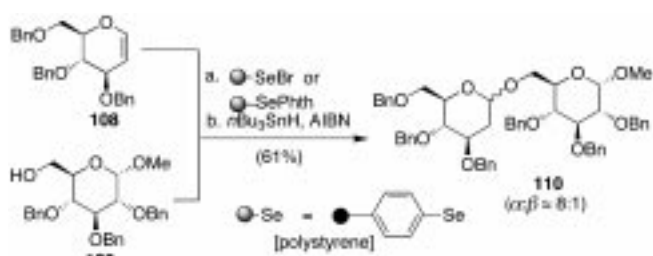
Despite its efficiency, the above method suffered from anomeric mixtures at every cleavage step and it was necessary to reactivate the cleavage product prior to possible reincorporation into the growing oligosaccharide chain. Thus, a new procedure which dealt with both of these issues by incorporating a spacer between the photolabile linker and the anomeric position of the first glycoside was developed and reported in 1998.^[88] Illustrated in Scheme 27, this new strategy



Scheme 27. Second generation strategy towards the solid-phase synthesis of oligosaccharides (1998).^[88]

appeared ideal for the block-type construction of large and diverse oligosaccharides. Thus, β -phenolic ester **105** was easily obtained from thioglycoside **103** by reaction with **104** in the presence of NIS/TfOH, followed by removal of the benzyl group to furnish **105** in 60 % overall yield. Attachment of the phenolic monosaccharide **105** to the solid support **102** was then achieved under Mitsunobu conditions to furnish conjugate **106**. Cleavage of the monosaccharide from the resin was facilitated by treatment with PhSTMS/ZnI₂ to afford thioglycoside **107**, which was directly ready for coupling as the next block. The efficiency of this procedure was demonstrated by the synthesis of a dodecasaccharide, as will be described in Section 5.3.

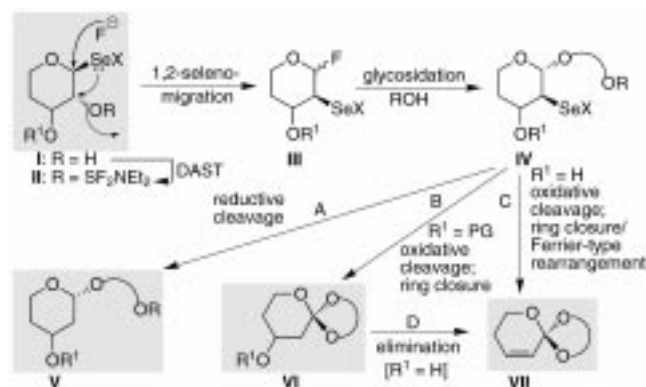
Also in 1998, the exploration of polymer-supported selenium reagents for organic synthesis led us to the synthesis of polymer-bound selenium bromide and selenium phthalimide reagents applicable to the synthesis of 2-deoxyglycosides (Scheme 28).^[89] Reaction of tribenzyl glucal **108** with the polymer-bound selenenyl bromide and alcohol **109**, followed by reductive cleavage of the newly formed selenium–carbon bond by treatment with *n*Bu₃SnH/AIBN released the 2-de-



Scheme 28. Application of organoselenium resins in the synthesis of 2-deoxyglycosides (1998).^[89]

oxyglycoside **110** with an α : β ratio of approximately 8:1. Alternatively, treatment of a mixture of the same glucal (**108**) and alcohol (**109**) with the polymer-bound selenenyl phthalimide reagent followed by radical cleavage led to disaccharide **110** as an approximately 1:1 mixture of α : β anomers.

During the total synthesis of everninomicin and recalling the 1,2-thiophenyl migrations on carbohydrate templates and the newly developed polymer-bound selenium bromide resin, a general concept for the solid- and solution-phase syntheses of 2-deoxyglycosides, orthoesters, and allylic orthoesters through 1,2-selenium migrations was proposed (Scheme 29).^[90] Thus, treatment of the readily available



Scheme 29. General concept for the stereoselective solid-phase synthesis of 2-deoxyglycosides **V**, orthoesters **VI**, and allylic orthoesters **VII** through 1,2-selenium migrations (2000). X = Ph or polystyrene.^[90]

2-hydroxy-1-selenoglycoside **I** with DAST resulted in a stereospecific 1,2-migration of the selenium moiety, with simultaneous installation of a fluoride group at C1 to furnish **III**. The desired α -glycosides **IV** resulting from participation of the seleno group, were formed upon exposure of these reactive donors **III** to various hydroxy components in the presence of Lewis acids. From **IV**, one of the following three paths could be followed:

Path A: Radical deselenation facilitated by *n*Bu₃SnH and furnishing the 2-deoxyglycosides **V**,

Path B: 2-Deoxyorthoesters **VI** could be obtained, which would require initial removal of the protecting group R and then oxidation of the selenium to the selenoxide and heating to promote the required *syn*-elimination and concomitant cyclization,

Path C: Both protecting groups (R and R¹) would be removed before subsequent oxidation and heating,

to afford the 2,3-allylic orthoesters (**VII**) through a Ferrier-type rearrangement. Furthermore, elimination of the hydroxy group of **VI** would again furnish **VII** (path D), which would allow the scope of the process to be expanded and comparisons to be made of the stereochemistries of the orthoester moieties generated from paths B and C.

Scheme 30 exemplifies the chemistry, both in solution ($R = \text{Ph}$) and on solid phase ($R = \bullet = \text{polystyrene}$) for the synthesis of 2-deoxyglycoside **117** and orthoesters **119** and **121**. Thus, treatment of **114** with DAST facilitated the 1,2-phenylseleno

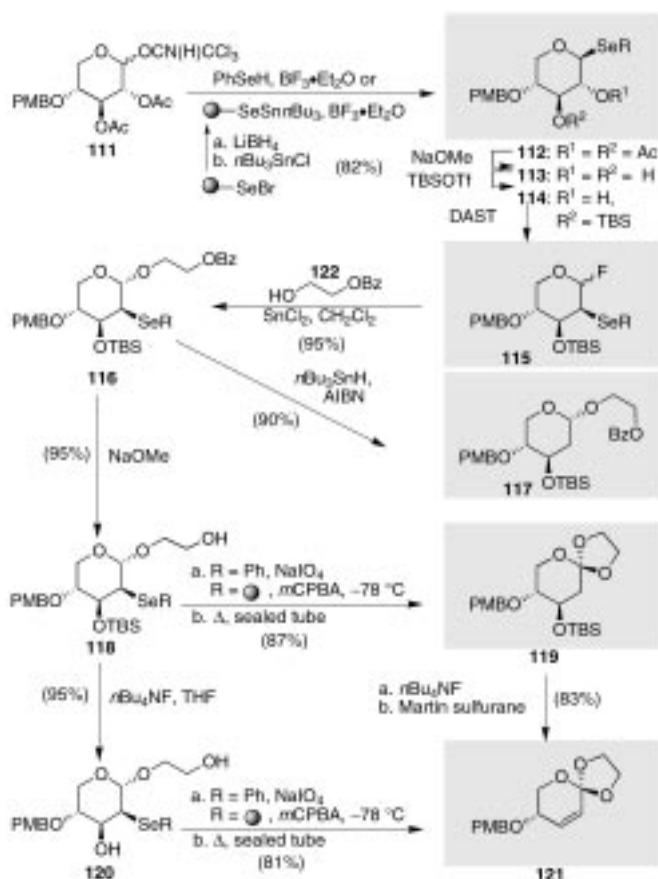
elimination, a procedure that was found useful in the stereochemical assignment of more complex orthoesters.

The solid-phase version of this chemistry required a suitable resin-bound selenol that could be manipulated in air. Towards this end, the previously reported polystyrene selenium bromide resin ($\bullet\text{-SeBr}$)^[89] was lithiated (LiBH_4 , THF) and the resulting lithioselenide resin ($\bullet\text{-SeLi}$) was quenched with excess $n\text{Bu}_3\text{SnCl}$ to furnish a colorless, odorless resin ($\bullet\text{-SeSn}n\text{Bu}_3$); this resin could be quickly filtered in air and immediately used in coupling reactions. Subsequent treatment of a coupled selenide resin (such as **118**, $R = \bullet$) with $m\text{CPBA}$ in CH_2Cl_2 at -78°C , followed by rapid filtration, transfer to a sealed tube, and heating furnished orthoester **119** in 78% yield. Diol **120** ($R = \bullet$) yielded **121** on similar treatment as expected. The generality and scope of the solid-phase synthesis of 2-deoxysugars, orthoesters, and 2,3-allylic orthoesters have been examined and have proven to be quite extensive (Tables 7 and 8).

One of the most recent developments in our laboratories involves the novel IBX-mediated introduction of an *N*-aryl amino functionality onto allylic alcohols (Scheme 31).^[91] Examples of this IBX-mediated construction of amino sugars are shown in Scheme 32. Furthermore, the method was successfully applied to the synthesis of vancosamine (**133**; Scheme 33). Thus, intermolecular Kishi–Nozaki coupling of vinyl iodide **129** with **130** led to a 1:1 mixture of alcohols which were oxidized (DMP) and reduced under Luche conditions to afford the desired isomer. Condensation of the resulting alcohol with *p*-methoxyphenyl isocyanate in the presence of DBU followed by global deprotection ($\text{HF}\cdot\text{py}$), selective primary alcohol oxidation (IBX), and protection of the anomeric hydroxy group (PMBOH , HCl(g)) furnished the cyclization precursor **132**. IBX-controlled cyclization, CAN-mediated deprotection, and basic hydrolysis completed this rapid and stereocontrolled synthesis of the targeted amino sugar, **133**.

4. Total and Partial Synthesis of Natural Products Containing Mono- and Oligosaccharides

Before embarking on ambitious schemes for the total and partial synthesis of complex oligosaccharides and carbohydrate-containing natural products, several issues require careful consideration. The first such issue to be decided is the precise moment of the carbohydrate attachment within the planned sequence so as to optimize efficiency and compatibility of functionalities in subsequent steps. The second issue pertains to the choice of glycosidation method to be employed. Compatibility is often required between large fragments, individual monosaccharides and various protecting groups. The third, and sometimes most challenging issue, has to do with the choice of protecting group ensembles, with the details ranging from the development of an overall strategy to subtle, but frequently necessary, interconversions. While such problems were discussed in detail in the full accounts of each synthesis, herein only the highlights of the overall strategies and rationales leading to these successful total and partial syntheses are presented.



Scheme 30. Synthesis of 2-deoxyglycosides and orthoesters through 1,2-phenylseleno migrations (2000).^[90]

migration affording the 2-phenylseleno-1-fluoro donor **115**. This operation was followed by coupling with alcohol **122** in the presence of SnCl_2 in CH_2Cl_2 , which lead to the selective formation of α -glycoside **116**. Exposure of **116** to $n\text{Bu}_3\text{SnH}$ /AIBN furnished 2-deoxyglycoside **117** through radical cleavage of the C–Se bond. Removal of the benzoate group from **116**, followed by oxidation of the selenium moiety to the selenoxide and subsequent heating led to the formation of 2-deoxyorthoester **119** in 87% yield. On the other hand, removal of the silyl group from **118** followed by oxidation to the corresponding selenoxide and heating in a sealed tube as described above, furnished the 2,3-allylic orthoester **121** in 81% yield, through *syn*-elimination, ring closure, and expulsion of the C3 hydroxyl group. Orthoester **119** was converted into allylic orthoester **121** by deprotection and

Table 7. Solution- and solid-phase synthesis of 2-phenylselenoglycosides and 2-deoxyglycosides (see Scheme 30).^{[a][90]}

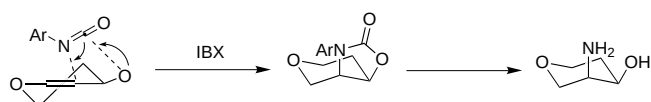
	Donor	+	Acceptor	$\xrightarrow{\text{a. SnCl}_2, \text{Et}_2\text{O or CH}_2\text{Cl}_2}$	Glycoside
Acceptors					
Donors ^[b]					
	 R = Ph (100%) R = ● (100%)		 Y = SePh (95%) Y = Se● (30% overall, >78% per step) Y = H (30% overall, >78% per step) b.		 Y = SePh (87%) Y = Se● (15% overall, >69% per step) Y = H (15% overall, >69% per step) b.
	 R = Ph (100%) R = ● (100%)		 Y = SePh (92%) Y = Se● (32% overall, >80% per step) Y = H (32% overall, >80% per step) b.		 Y = SePh (86%) Y = Se● (18% overall, >71% per step) Y = H (18% overall, >71% per step) b.
	 R = Ph (100%) R = ● (100%)		 Y = SePh (94%) Y = Se● (30% overall, >70% per step) Y = H (30% overall, >70% per step) b.		 Y = SePh (85%) Y = Se● (17% overall, >70% per step) Y = H (17% overall, >70% per step) b.
					 Y = SePh (71%) Y = Se● (11% overall, >64% per step) Y = H (11% overall, >64% per step) b.

[a] Synthesis of glycosides: a) R = Ph: acceptor (1.5 equiv), SnCl₂ (1.5 equiv), Et₂O, 0 °C, 3 h; R = polystyrene: acceptor (10.0 equiv), SnCl₂ (3.0 equiv), CH₂Cl₂, 0 °C, 3 h; b) nBu₃SnH, AIBN, benzene, 80 °C, 1 h; ● = polystyrene. [b] Donors were prepared by DAST-induced 1,2-migration from the corresponding 2-hydroxy-β-phenylselenoglycosides.

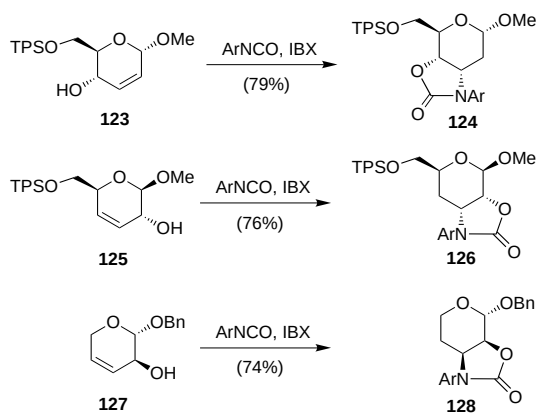
 Table 8. Solution- and solid-phase synthesis of 2-deoxyorthoesters and 2,3-allylic orthoesters (see Scheme 30).^{[a][90]}

	Glycosides	$\xrightarrow{\text{R = Ph: NaIO}_4, \text{MeOH; then heat}}$ $\xrightarrow{\text{R = ●: mCPBA, -78 °C; then heat}}$	Orthoesters
Y =			
Glycosides			
	 R = Ph or ●	 [from R = Ph] (87%) [from R = ●] (12% overall, >74% per step)	 [from R = Ph] (83%, 3.2:1) [from R = ●] (11% overall, >73% per step, 2.2:1)
	 R = Ph or ●	 [from R = Ph] (85%) [from R = ●] (20% overall, >80% per step)	 [from R = Ph] (81%, 2.7:1) [from R = ●] (5% overall, >65% per step, 1:1)
	 R = Ph or ●	 [from R = Ph] (82%) [from R = ●] (15% overall, >76% per step)	 [from R = Ph] (82%, 2:1) [from R = ●] (8% overall, >70% per step, 1:1)
	 R = Ph or ●	 [from R = Ph] (79%) [from R = ●] (19% overall, >81% per step)	 [from R = Ph] (61%, 10:1) [from R = ●] (6% overall, >70% per step, 10:1)
			 [from R = Ph] (75%, 15:1) [from R = ●] (2% overall, >57% per step, 15:1)
			 [from R = Ph] (73%, 12:1) [from R = ●] (3% overall, >61% per step, 12:1)
			 [from R = Ph] (72%, 10:1) [from R = ●] (7% overall, >68% per step, 10:1)
			 [from R = Ph] (86%, 16:1) [from R = ●] (5% overall, >69% per step, 16:1)

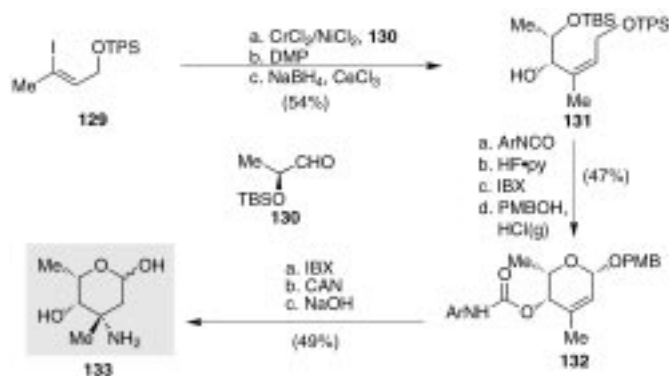
[a] Selenoxides were heated in a sealed tube at 140 °C in vinyl acetate/toluene/diisopropylamine (1/1/2) for 12 h (● = polystyrene).



Scheme 31. General concept for the IBX-mediated construction of amino sugars (2000).^[91]



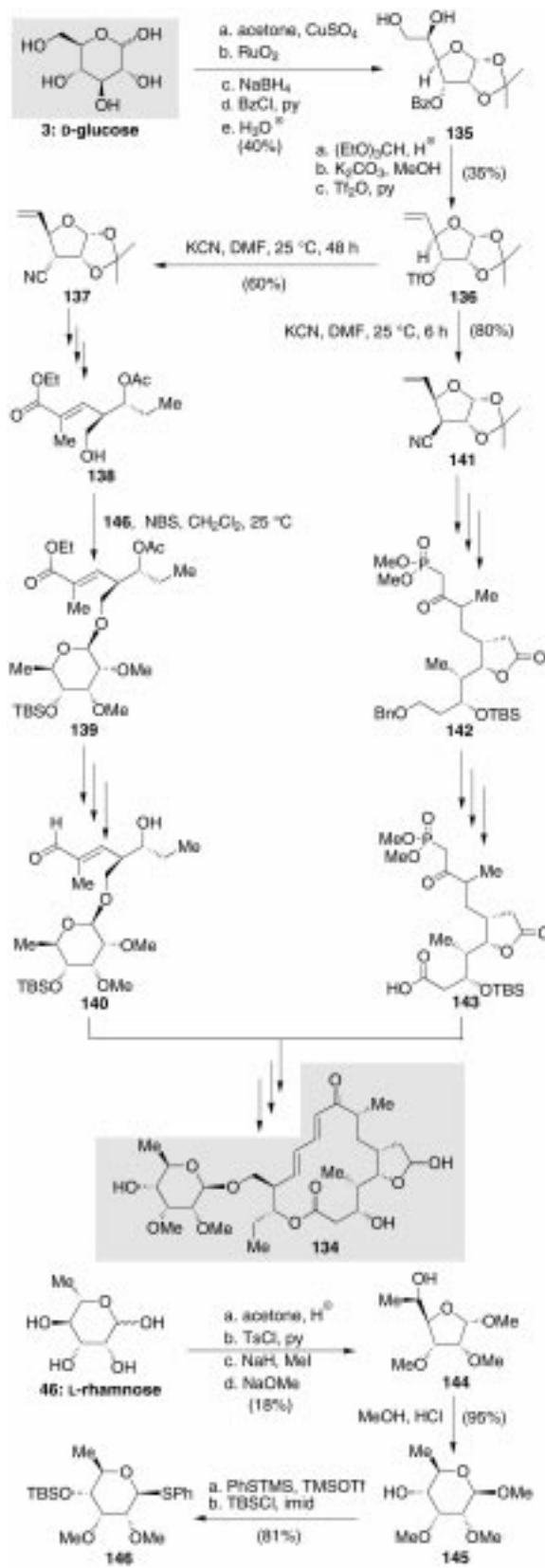
Scheme 32. Selected examples of the IBX-mediated construction of amino sugars (2000).^[91]



Scheme 33. Synthesis of vancosamine (**133**) using the IBX method (2000).^[91]

4.1. *O*-Mycinosyl Tylonolide

Within a program directed towards the synthesis of macro-lide antibiotics, in particular tylosin and amphotericin, the total synthesis of *O*-mycinosyl tylonolide (**134**, Scheme 34) was accomplished; this marked the first synthesis of a tylosin assembly containing an intact carbohydrate moiety.^[92] *O*-Mycinosyl tylonolide (**134**) is a major degradation product of tylosin and a potential biosynthetic and synthetic precursor to this antibiotic. The synthesis of this compound also falls within the scope of Section 2.1, in that the construction of the aglycon originated from carbohydrates. Thus, in a slightly modified procedure to that described for the synthesis of leucomycin A₃ and carbomycin B, D-glucose (**3**) was transformed to crystalline triflate derivative **136**, which was subsequently converted into unsaturated ester **138** and phosphonate **142** (Scheme 34). Thioglycoside **146** (derived from L-rhamnose (**46**)) was activated with NBS in CH₂Cl₂ in the presence of **138** to afford an approximately 50% yield of



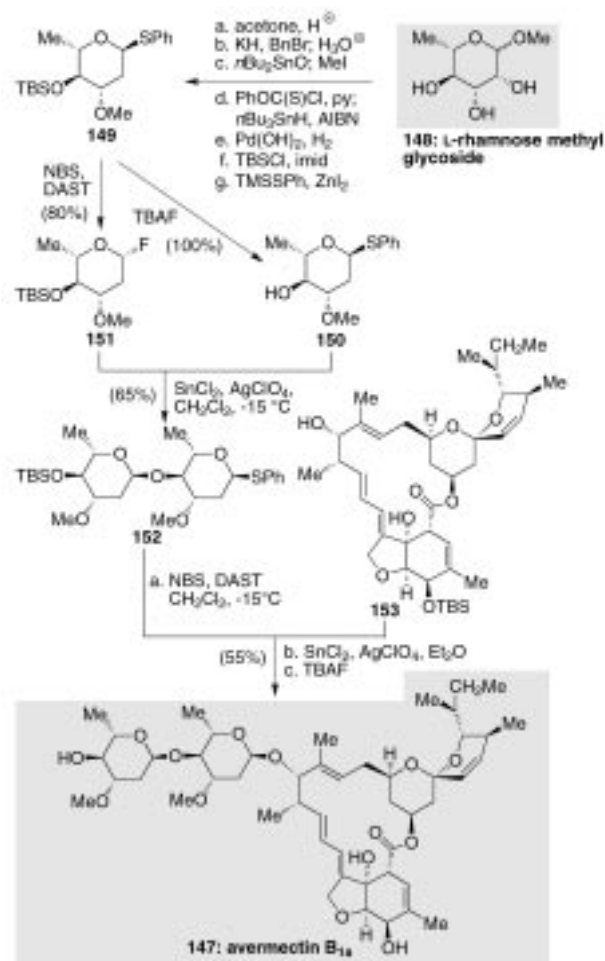
Scheme 34. Synthesis of *O*-mycinosyl tylonolide (**134**) from D-glucose (**3**) (1982).^[92]

the desired β -anomer of the expected glycoside (**139**) after separation (α : β ratio, $\approx$ 2:3). This coupling represented the first use of NBS for activation of thiophenylglycosides under

such mild conditions. Further elaborations of these intermediates led to key building blocks **140** and **143**, which were then coupled and cyclized to afford the target, *O*-mycinoyl tylonolide (**134**), in high overall yield and good selectivity.

4.2. Avermectin B_{1a}

As a demonstration of the useful nature of the two-stage activation procedure using thioglycosides and glycosyl fluorides, a semisynthesis of avermectin B_{1a} (**147**, Scheme 35) was devised and accomplished in 1984.^[9] L-rhamnose derivative

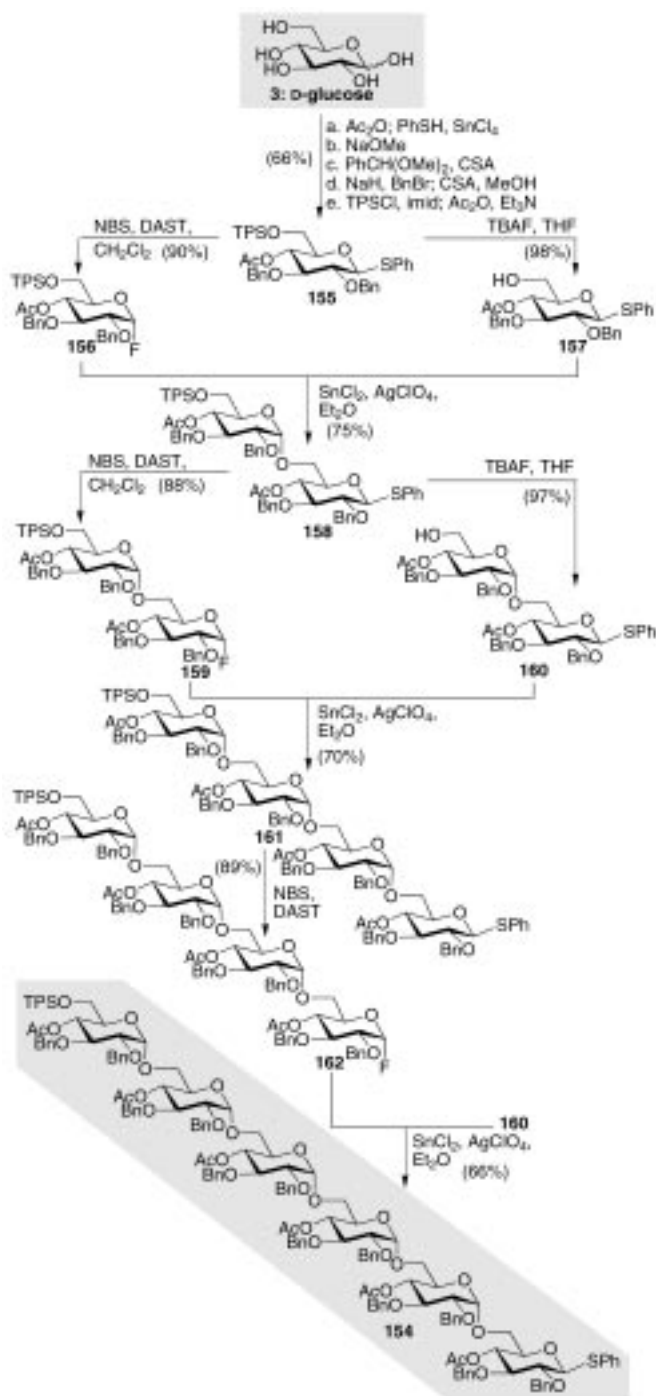


Scheme 35. Semisynthesis of avermectin B_{1a} (**147**) from L-rhamnose methyl glycoside (**148**) (1984).^[9]

148 was converted into oleandroside derivative **149**, with selective acetal formation and tin acetal mediated protection methods; this was then transformed into hydroxy component **150** and to glycosyl fluoride **151**. Smooth coupling of these two units in the presence of SnCl₂/AgClO₄ afforded exclusively the α-anomer of disaccharide **152**. Activation of the disaccharide by conversion into the corresponding glycosyl fluoride (85%) and coupling to the aglycon **153** in the presence of SnCl₂/AgClO₄ (62%) was followed by deprotection (89%), to furnish avermectin B_{1a} (**147**), and thus complete a partial synthesis of this important antiparasitic agent.

4.3. Hexasaccharide 154

The hexasaccharide **154** (Scheme 36) was targeted in an effort to further demonstrate the repetitive and block-type nature of the two-stage activation technology for the synthesis of complex oligosaccharides. This linear chain, which consists of six glucose units linked in a 1,6 fashion, was constructed in 1984.^[9] Thus, glucose derivative **155** was smoothly converted into free hydroxy derivative **157** and glycosyl fluoride **156**. Coupling of these two units in the presence of SnCl₂/AgClO₄



Scheme 36. Expedient synthesis of hexasaccharide **154** by the two-step activation procedure (1984).^[9]

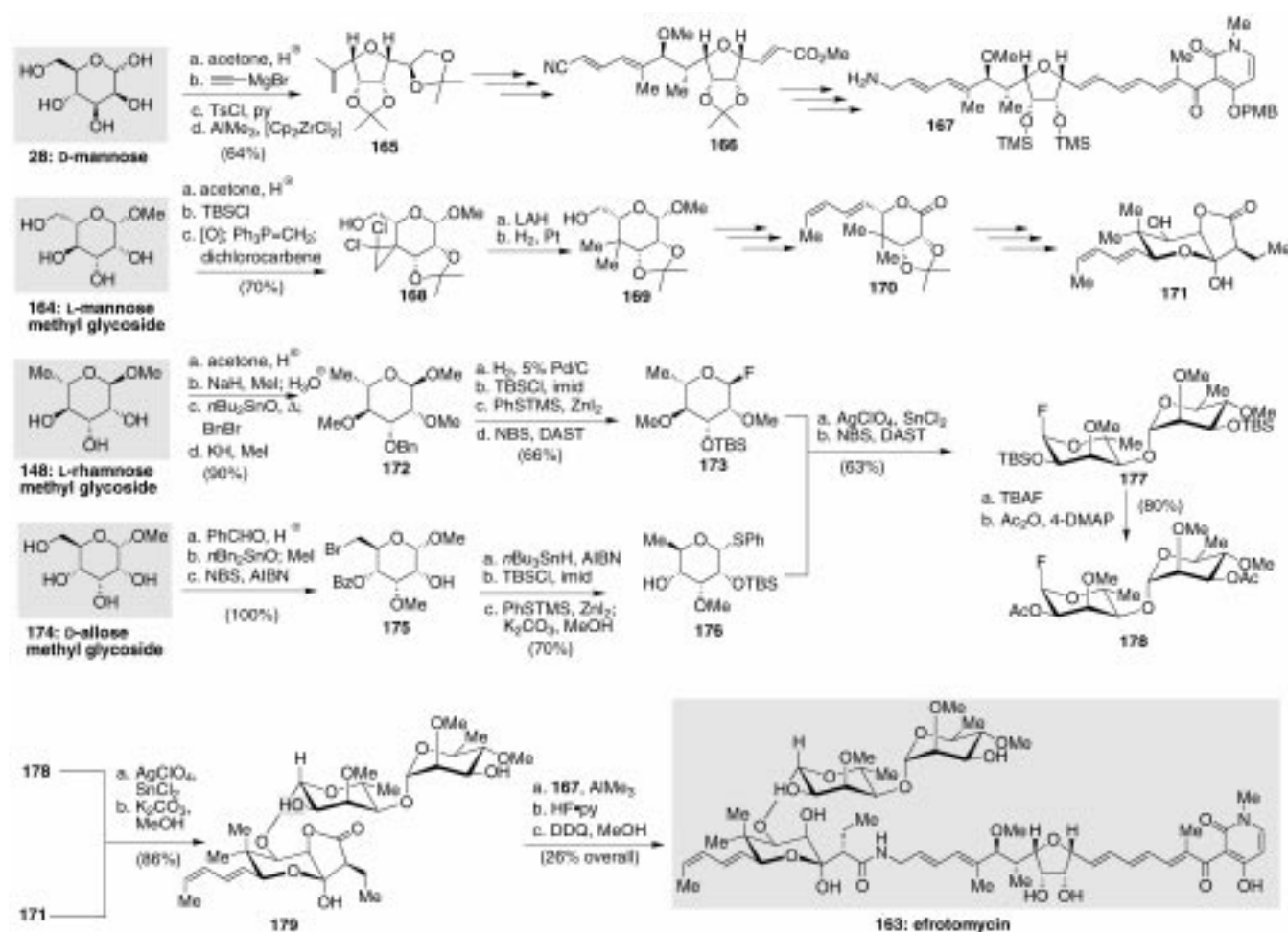
afforded the disaccharide **158** in 75 % yield. Repetition of this sequence provided tetrasaccharide **161**, which was further elongated to hexasaccharide **154** in a highly efficient manner through one more reiteration of the process.

4.4. Efrotomycin

Efrotomycin (**163**, Scheme 37), isolated from *Nocardia lactamdurans*, is a member of the elfamycin class of narrow-spectrum antibiotics. The total synthesis of efrotomycin (**163**), reported in 1985,^[93–96] included an efficient construction and attachment of the oligosaccharide domain onto the aglycon and several approaches to the goldinonolactone (**171**) and tetrahydrofuran (**167**) fragments, both from carbohydrate and noncarbohydrate starting materials.

Scheme 37 illustrates the synthesis of these key fragments using carbohydrates as chiral building blocks. D-Mannose (**28**) served as an excellent precursor to the tetrahydrofuran fragment (**167**), by providing three of the desired stereocenters and the functionality necessary for further elaboration. Thus, **28** was processed by conversion into the bisacetone, reaction with excess ethynyl magnesium bromide,

chemoselective formation of the tosylate resulting in internal displacement, and regioselective methylation with AlMe_3 in the presence of Cp_2ZrCl_2 , to provide advanced intermediate **165**. Further elaboration effected the conversion of **165** into **167** and set the stage for the final coupling. The readily available L-mannose derivative **164**, which contains three of the five stereocenters of goldinonolactone (**171**), was recognized as a potential precursor to this intermediate. Thus, conversion of **164** into the monoacetone, selective silylation, oxidation, olefination, and dichlorocarbene addition afforded adduct **168**. Sequential reduction to the geminal dimethyl compound, followed by oxidation and further homologation, afforded the complete fragment goldinonolactone (**171**). D-allose derivative **174** and L-rhamnose derivative **148** were sequentially transformed into the requisite coupling partners **176** and **173**, respectively (Scheme 37). Once again the efficiency of the two-stage activation procedure was illustrated as thioglycoside **176** and glycosyl fluoride **173** were smoothly coupled to afford the expected disaccharide. Transformation to glycosyl fluoride **177**, exchange of the C2 *O*-silyl group for a directing acetate group, and coupling with goldinonolactone fragment **171** proceeded to afford, after deacetylation, advanced intermediate **179**, as exclusively the desired β -anomer. Finally, union of the two key fragments **179**



Scheme 37. Synthesis of efrotomycin (**163**) from D-mannose (**28**), L-mannose methyl glycoside (**164**), L-rhamnose methyl glycoside (**148**), and D-allose methyl glycoside (**174**) (1985).^[93–96]

and **167** and final deprotection afforded the natural product, efrotomycin (**163**), in a highly convergent manner.

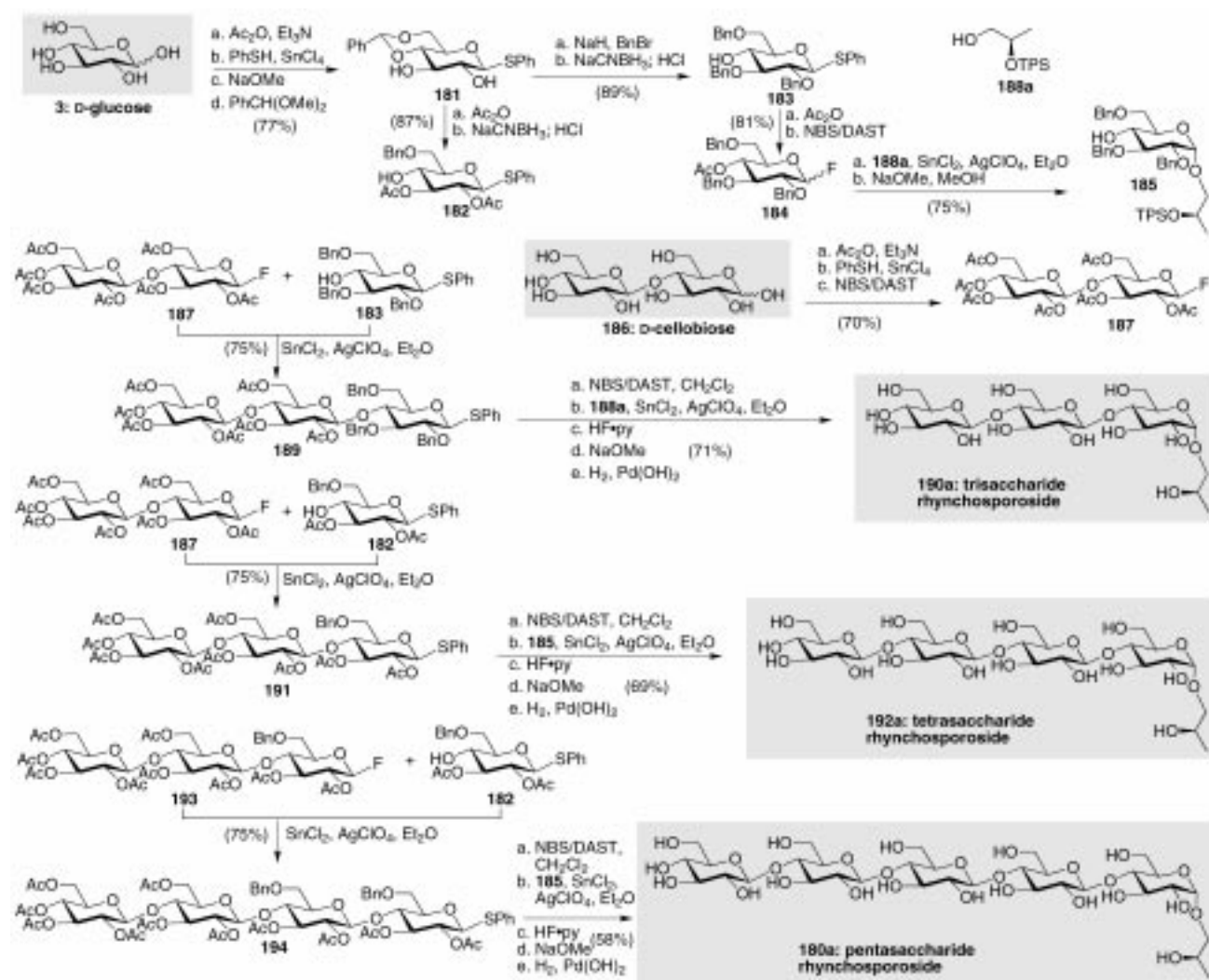
4.5. Rhynchosporosides

The rhynchosporosides (that is, **180a**, **190a**, and **192a**, Scheme 38) are a family of fungal metabolites which cause scald disease in barley and other grasses. In view of the potential economic importance of these compounds and in an effort to assist in their isolation from their natural sources, their structural elucidation, and investigations into their biological properties, a program directed towards their synthesis was undertaken. By strategically choosing the C2 substituent in each case, the mild, two-stage activation method allowed an efficient and convergent synthesis (completed in 1985,^[97]) of both the *S* and *R* series of tri-, tetra-, and pentasaccharide rhynchosporosides (*S* and *R* refer to the configuration of the side chain; *R* series shown in Scheme 38). Preliminary bioassays with the synthetic samples indicated highly destructive potency for the (*3R*)-,

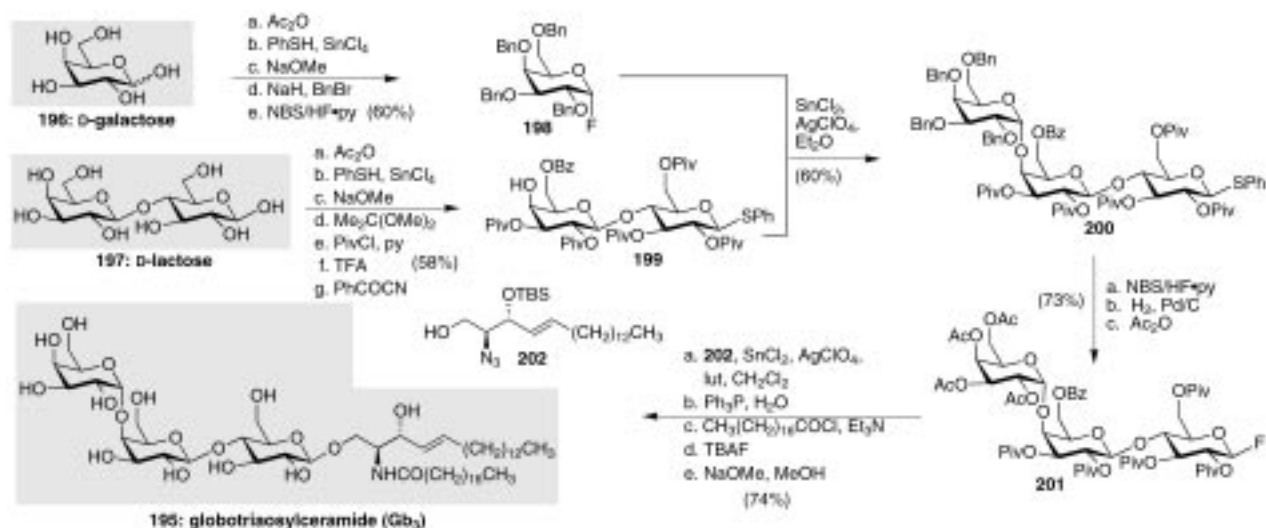
(*4R*)-, and (*5R*)-rhynchosporosides (**190a**, **192a**, and **180a**) which caused massive tip wilt and necrosis in young barley plants.

4.6. Globotriaosylceramide (Gb₃)

Glycosphingolipids are key constituents of the membranes of most cell types and are recognized as fundamental mediators of cell–cell recognition and communication, cell-growth regulation, and antibody interactions. The biological significance of these cell-markers has made them important targets for isolation, characterization, and chemical synthesis. Their difficult accessibility from natural sources made the latter objective even more urgent. A program directed towards the synthesis of various glycosphingolipids in our laboratories grew to include many members of this class of bioactive natural products. The general methodology used in these constructions is exemplified by the total synthesis of globotriaosylceramide (Gb₃) (**195**, Scheme 39), whose total synthesis was completed in 1988.^[98–100]



Scheme 38. Synthesis of rhynchosporosides **190a**, **192a** and **180a** (1985).^[97] Compounds **190b**, **192b**, and **180b** (not shown) are the corresponding *S* compounds.

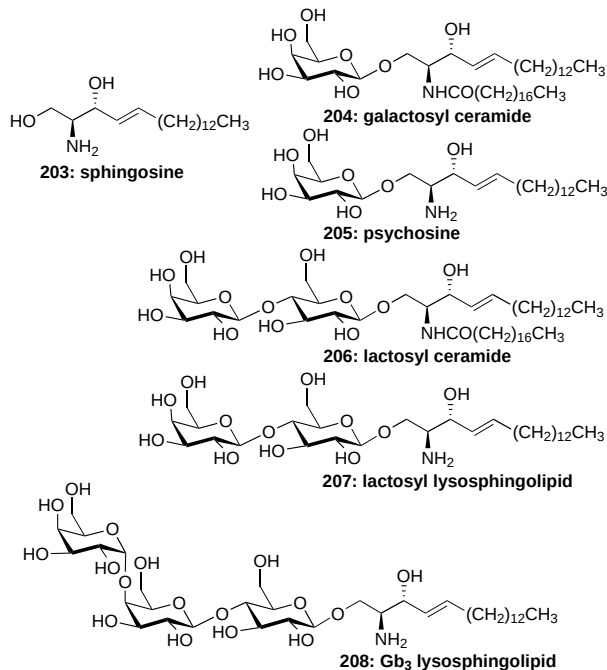


Scheme 39. Synthesis of globotriaosylceramide (Gb₃, **195**) from D-galactose (**196**) and D-lactose (**197**) (1988).^[98–100]

The required coupling partners were glycosyl fluoride **198** and phenylthio glycoside **199** according to the planned two-stage activation procedure. These were prepared from D-galactose (**196**) and D-lactose (**197**) respectively, as outlined in Scheme 39. Coupling of **198** and **199** furnished trisaccharide **200**, which was then converted into the glycosyl fluoride (NBS/HF·py, 85%). The benzyl groups were then removed (H₂, Pd/C, 90%) and the resulting product was acetylated (Ac₂O, 95%); this illustrates the chemical stability of the glycosyl fluoride moiety. The coupling of trisaccharide fluoride **201** with sphingosine equivalent **202** under the usual conditions proceeded smoothly and with complete stereo-control. Final elaboration of the sphingosine unit and global deprotections completed the synthesis of globotriaosylcer-

amide (Gb₃) (**195**), whose assigned structure could therefore be confirmed.

This synthesis demonstrated the power of the overall strategy, which was now ready for extension to more complex glycosphingolipids. In collaboration with Fiore and co-workers at the Brigham and Women's Hospital and Harvard Medical School, synthetic sphingosine, lysosphingosine, and a number of glycosphingolipids were designed, synthesized, and evaluated as inhibitors of functional responses of human neutrophils. Seven compounds were synthesized (**195** and **203–208**, Scheme 40) following the chemistry described in Scheme 39. They were then studied for neutrophil responses in aggregation, leukotriene generation, and superoxide formation.^[101] The results of these aggregation studies are illustrated graphically in Figure 1. Overall, the studies provided evidence that sphingolipids do not exhibit selective



Scheme 40. Synthetic sphingolipids **203–208** that were tested, along with **195**, for their ability to either inhibit or stimulate the aggregation of human neutrophils (1990). (See Figure 1.)

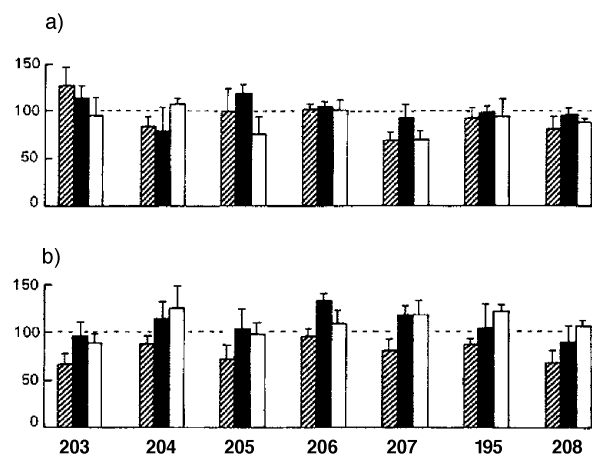


Figure 1. Aggregation response of human neutrophils: actions of synthetic sphingolipids (see Scheme 40) at noncytotoxic levels. Concentrations of the sphingolipids: ▨ = 1, ■ = 0.1, and □ = 0.01 μM. Conditions: 15 min, 37 °C in PBS (pH 7.45), then addition of either a) fMetLeuPhen (0.5 μM) or b) PMA (0.1 μM). Changes in light transmittance were monitored for 15 min. The results are expressed as percentage change in agonist-induced neutrophil aggregation (maximal 100%) after exposure to synthetic sphingolipids. Reproduced with permission from ref. [101].

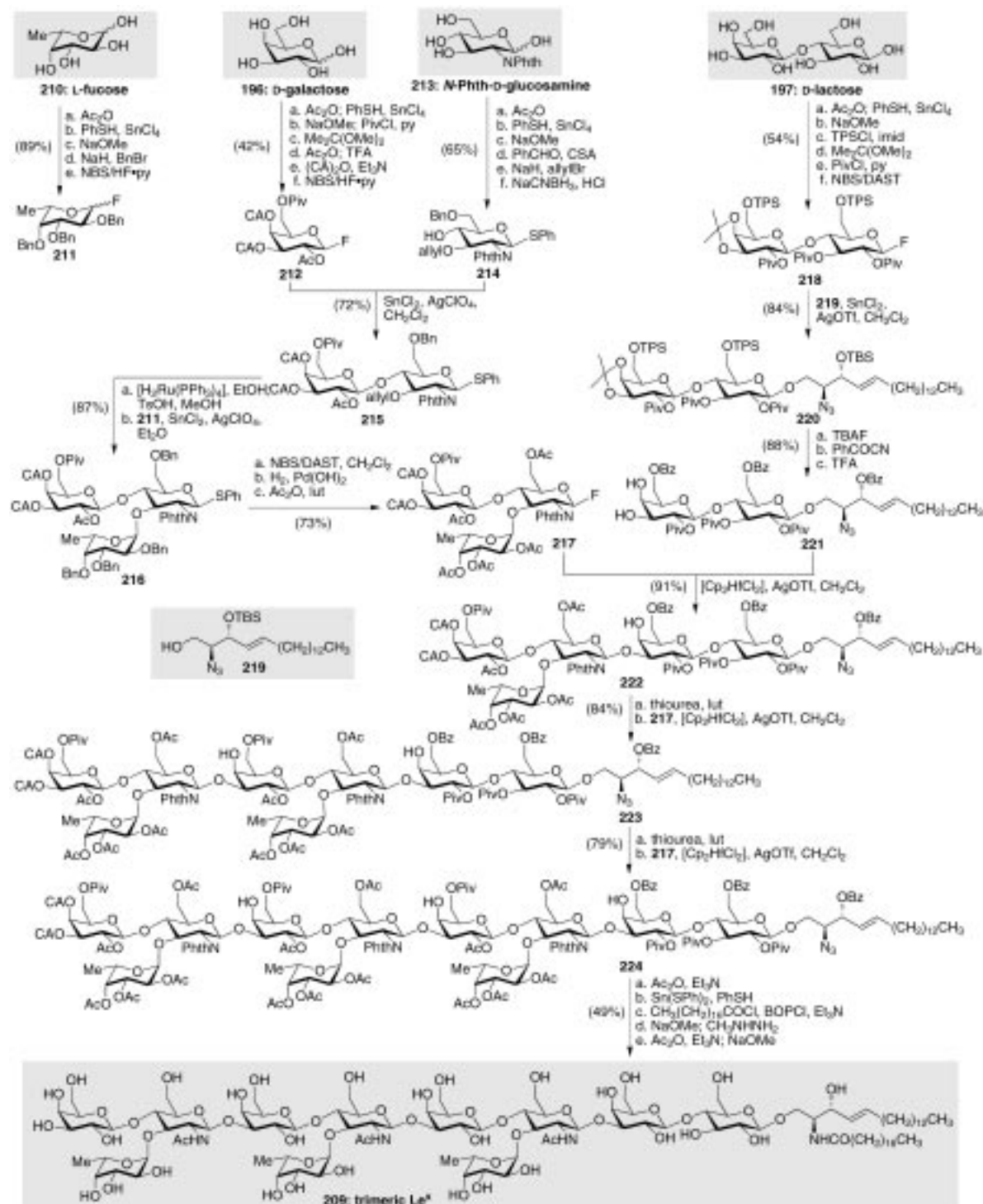
inhibition of functional responses of human neutrophils, when added to intact cells

4.7. Trimeric Le^x

Glycosphingolipids carrying the Lewis antigen X (Le^x) determinant [gal-β-14-(fuc-α-13)-glcNAc] are known to accumulate in a wide variety of human cancers. Their extreme

scarcity coupled with their potential applications in diagnostics and immunotherapy made them prime targets for chemical synthesis. In 1990, the total synthesis^[102] of three members of this class of compounds (monomeric, dimeric, and trimeric Le^x) based on the two-stage activation procedure were reported from these laboratories.

Scheme 41 summarizes the synthesis of the most complex of the three, trimeric Le^x (**209**), in which careful selection of protecting groups allowed, not only for high selectivity in the



Scheme 41. Synthesis of trimeric Le^x (**209**) from D-galactose (**196**), L-fucose (**210**), D-lactose (**197**), and N-phthaloyl-D-glucosamine (**213**) (1990).^[102]

sequence, but also for exclusive formation of the desired stereochemistry of all glycoside bonds. The coupling of lactosyl fluoride **218** (obtained from D-lactose as shown in Scheme 41) and sphingosine equivalent **219** afforded glycoside **220**, and was followed by further functionalization, to furnish lactosyl ceramide segment **221**. The construction of the Le^x trisaccharide intermediate **217** proceeded from the readily available glucosamine derivative **214** and galactosyl fluoride intermediate **212**, whose origins were traced back to *N*-phthaloyl-D-glucosamine (**213**) and D-galactose (**196**), respectively. Coupling of **212** and **214** furnished disaccharide **215**, and was followed by selective removal of the allyl group and subsequent coupling with fucosyl fluoride **211** (obtained from L-fucose (**210**) as indicated) to afford trisaccharide **216**. Conversion of thioglycoside **216** into the glycosyl fluoride with NBS/DAST, followed by protecting group exchange, furnished the requisite trisaccharide fragment **217**. The coupling of **217** and **221** under the influence of AgOTf/[Cp₂HfCl₂]^[12b] proceeded regioselectively at the more reactive C3 position to afford β-pentasaccharide **222**. Selective removal of the monochloroacetate groups from **222** was accomplished with thiourea in 93% yield. Reiteration of the deprotection and coupling procedure with another molecule of glycosyl fluoride **217** led sequentially to octasaccharide **223** and finally undecasaccharide **224**. Generation of trimeric Le^x (**209**) from **224** proceeded smoothly as indicated. The completion of this synthesis demonstrated the practicality of the two-stage activation procedure in highly complex situations and provided significant quantities of this important glycosphingolipid for potential diagnostic and therapeutic applications.

4.8. Sialyl Le^x

Identification of sialyl Le^x type molecules as binding ligands of ELAM-1 (endothelial leukocyte adhesion molecule 1) generated considerable excitement given the connection of ELAM-1 to inflammation and related disorders. Sialyl Le^x (**225**, Scheme 42) and sialyl dimeric Le^x (derivative **232** shown in Scheme 43) are ELAM-1 binding ligands, which have also

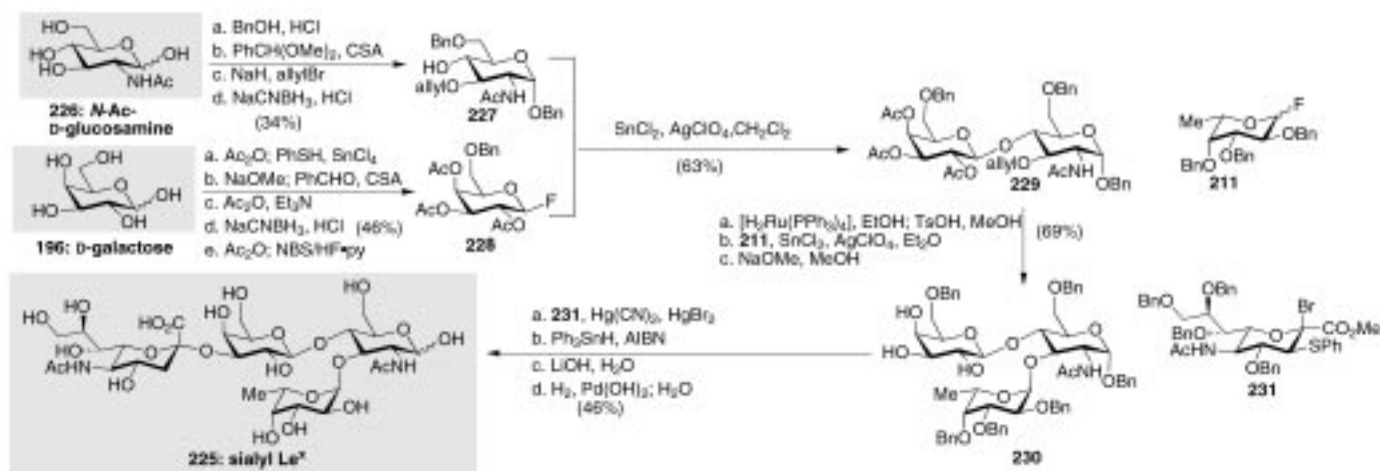
been identified as tumor-associated oligosaccharides. As such, and in view of potential therapeutic and tumor-cell marking applications, these molecules became high-priority targets for chemical synthesis immediately following their identification. The total synthesis of sialyl Le^x (**225**), reported from these laboratories in 1991, relied on the thiophenyl group to facilitate and control β-2-deoxyglycoside formation.^[103]

Monomeric Le^x component **230** was synthesized (Scheme 42) by modification of the chemistry developed in the synthesis of trimeric Le^x (**209**) (described above, Scheme 41). Thus, key building blocks **227** and **228** (derived from *N*-acetyl-D-glucosamine (**226**) and D-galactose (**196**), respectively, by regioselective benzylidene acetal cleavage reactions) were coupled to provide disaccharide **229** in 63% yield. Removal of the allyl group from **229**, followed by coupling with L-fucose derivative **211** and deacetylation, afforded triol **230**. Selective coupling with sialic derivative **231** in the presence of Hg(CN)₂/HgBr₂, followed by reductive removal of the thiophenyl group and global deprotection, afforded sialyl Le^x (**225**).

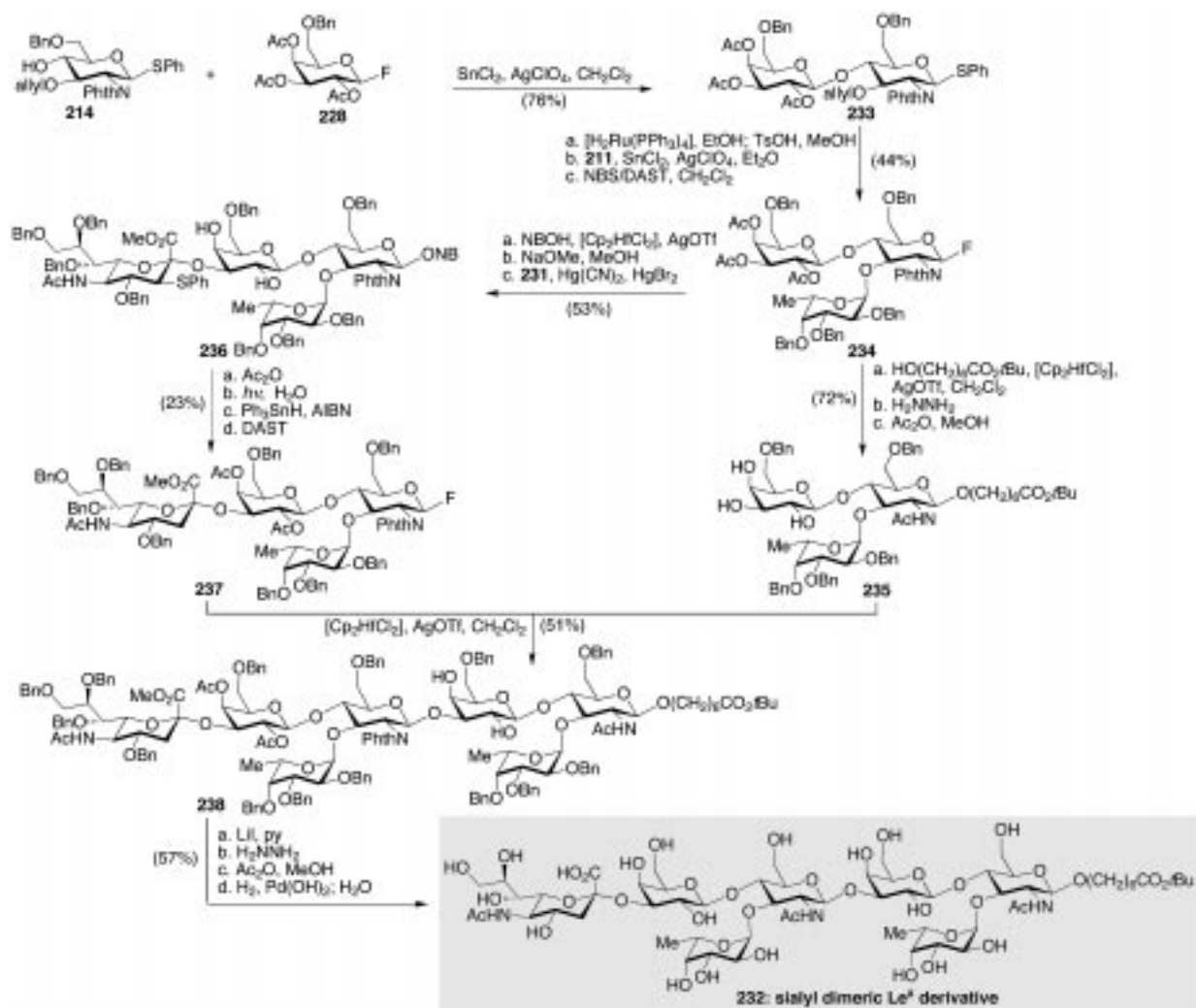
In order to further understand the structure–function relationship of sialyl Le^x and to develop sialyl Le^x mimetics, conformational studies based on two-dimensional NMR techniques were performed, in combination with MM2 molecular mechanics, in collaboration with the Wong group at Scripps.^[104] In addition, and in collaboration with the same group, the Ca²⁺ binding properties of the sialyl Le^x and deoxygenated fucose analogues were examined by pneumatically assisted electrospray mass spectrometry, and provided evidence that Ca²⁺ is coordinated primarily to the GalGlcNAc moiety of sialyl Le^x.^[105, 106]

4.9. Sialyl Dimeric Le^x

Among the naturally occurring ELAM-1 binding oligosaccharides, sialyl dimeric Le^x occupies a prominent position due to its molecular complexity and potential as a highly potent substrate. The total synthesis of sialyl dimeric Le^x derivative **232** (Scheme 43), equipped with an anchoring device for



Scheme 42. Synthesis of sialyl Le^x (**225**) from *N*-acetyl-D-glucosamine (**226**), D-galactose (**196**), L-fucose (**210**), and sialic acid derivative **231** (1991).^[103]



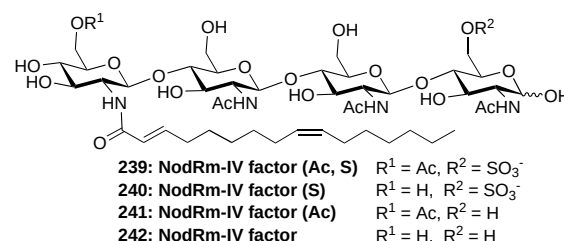
Scheme 43. Synthesis of sialyl dimeric Le^x derivative **232** from *N*-phthaloyl-D-glucosamine (**213**), D-galactose (**196**), L-fucose (**210**), and sialic acid derivative **231** (1992).^[107]

further chemical and biological studies, was reported from these laboratories in 1992.^[107] Trisaccharide fluoride **234** was synthesized by modification of the chemistry developed in the synthesis of sialyl Le^x described above and was a key building block for the rapid and convergent assembly of the sialyl dimeric Le^x skeleton.

Thus, as shown in Scheme 43, trisaccharide fluoride **234** was converted into trihydroxy compound **235** by glycosidation, deacetylation, and *N*-acetylation. Compound **234** was also converted into sialyl derivative **236** by glycosidation with nitrobenzyl alcohol (94%), deacetylation (98%), and coupling with sialic acid derivative **231** (56%) to afford, regio- and stereoselectively, tetrasaccharide **236**. Acetylation of the remaining hydroxyl groups, photolytic cleavage of the *O*-nitrobenzyl glycoside system, radical cleavage of the thiophenyl group, and finally treatment with DAST resulted in the formation of tetrasaccharide fluoride **237**. Glycosylation of triol **235** with tetrasaccharide fluoride **237** again proceeded regioselectively to afford the heptasaccharide **238**. Global deprotection furnished the targeted sialyl dimeric Le^x derivative **232** in pure form for biological investigations.

4.10. NodRm-IV Factors

Nodulation factors (Scheme 44) are important signaling molecules involved in the symbiosis between bacteria of the family *Rhizobium* and legumes. They are typically sulfated



Scheme 44. Structures of selected NodRm-IV factors.

lipooligosaccharides of *N*-acetyl-D-glucosamine (**226**). Secreted by the microorganism *Rhizobium meliloti*, these molecules elicit the formation of nitrogen-fixing root nodules. They display high specificity in that sulfated NodRm-IV factors **239** and **240** are active only on alfalfa, whereas nonsulfated

NodRm-IV factors **241** and **242** are active only on pea and vetch. The synthesis of the most challenging member of this group of naturally occurring substances, NodRm-IV (Ac, S; **239**), is presented in Scheme 45.^[108]

The strategy required careful design of protecting group tactics in order to incorporate the required functionality into the repeated units. Thus, coupling of glucosamine derivative **243** (obtained from *N*-phthaloyl-D-glucosamine **213** as shown) and glycosyl fluoride **244** (also obtained from **213**) furnished disaccharide **246**. The acetyl group was then removed and the coupling procedure was repeated to afford trisaccharide **247**. The directing phthalimide moieties were then replaced with acetyl groups and the resulting hydroxy trisaccharide was coupled with an additional unit of glycosyl fluoride **245**, to furnish tetrasaccharide **248** stereoselectively. Generation of the free amine, followed by incorporation of the fatty acid chain **249**, generated the fully protected derivative **250**. Selective deprotections and installation of the acetyl and sulfate groups completed the synthesis of this biologically interesting molecule, rendering it available for biological studies.

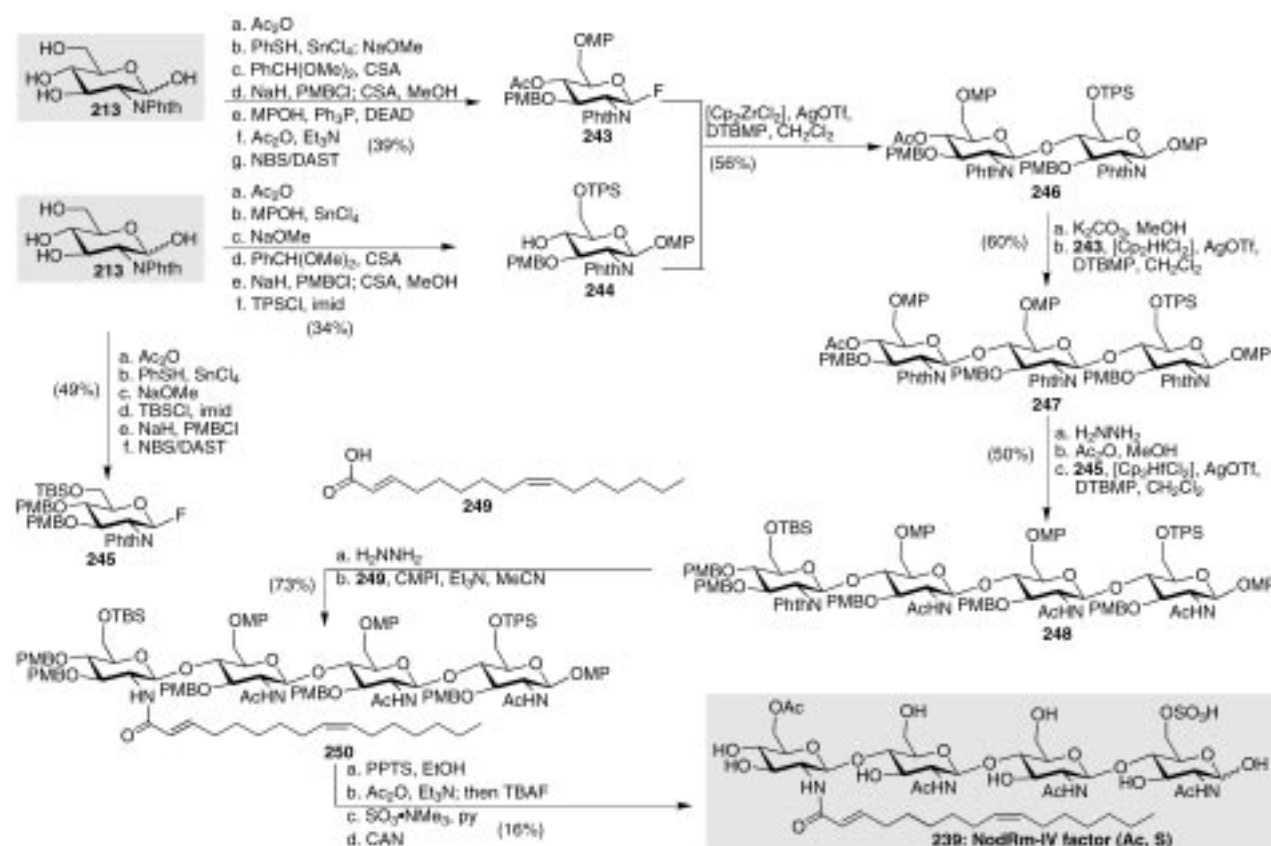
A version of NodRm-IV (Ac, S; **239**) that was tritiated across the C9–C10 olefin of the acyl side chain was chemically synthesized.^[109] Its binding characteristics were studied in collaboration with Cullimore's group at Toulouse and were found to be consistent with a single class of binding sites.^[109] Competition with modified Nod factors indicated that the binding was independent of the *O*-acetyl, the sulphate group, or the degree of unsaturation on the fatty acid. However, both

the side-chain and the oligosaccharide moieties were required for high affinity binding. More recently, Demont-Caulet et al. have synthesized NodRm-IV factors with acyl side chains of different length and unsaturations and studied their effects on nodule formation.^[110]

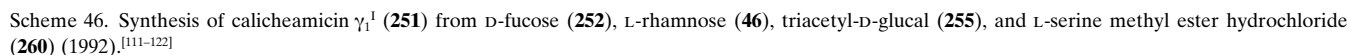
4.11. Calicheamicin γ_1^I

In 1987, a new class of antitumor antibiotics, the enediyne, was reported and led to considerable excitement in the chemical and biological communities. The molecular structure of calicheamicin γ_1^I (**251**, Scheme 46), one of the first to be disclosed and amongst the most prominent members of the class, embodies a rigid dioxygenated bicyclic core containing a 1,5-diyne-3-ene (enediyne) system and a single, but highly unusual, oligosaccharide appended at C8 which includes an oxyimino glycosidic linkage and an iodinated, hexasubstituted thiobenzoate unit. While the key elements to the biological activity of calicheamicin γ_1^I (**251**) lie within its enediyne core and the series of events emanating from it, which lead to DNA destruction in tumor cells by Bergman cyclization, the oligosaccharide domain serves important roles in delivery and recognition, in that it binds to duplex DNA with remarkable selectivity, particularly to TCCT, TCTC, and TTTT sequences.

Our total synthesis of calicheamicin γ_1^I (**251**) reported in 1992 includes a considerable body of carbohydrate chemistry as highlighted in Scheme 46.^[111–122] Retrosynthetic analysis of



Scheme 45. Synthesis of NodRm-IV factor **239** from *N*-phthaloyl-D-glucosamine (**213**) (1992).^[108]



involving a [3,3]-sigmatropic rearrangement of a thionoimidazolidine carrying an enol ether was developed to install both the sulfur atom and to deoxygenate the C2 center. The required building blocks **254**, **259**, **263**, **265**, and **269** were constructed as shown in Scheme 46 from D-fucose (**252**),

triacetyl-D-glucal (**255**), L-serine methyl ester hydrochloride (**260**), L-rhamnose (**46**), and 3,4,5-trimethoxytoluene, respectively. Of particular note during these syntheses was the epoxidation and opening of intermediate **256** with *m*CPBA, followed by the radical cleavage of the benzylidene acetal with NBS, migration of the aryl ester, and glycosidation under Mitsunobu conditions, finally affording enol ether **259**. In addition, the use of *n*Bu₂SnO to selectively protect the C3 position of the D ring in the synthesis of intermediate **265** is noteworthy.

The assembly of the desired oligosaccharide began with the coupling of ring A, compound **254**, with glycosyl fluoride **263** (corresponds to ring E) to afford the targeted AE disaccharide; this was deprotected (NaH, ethylene glycol) and selectively oxidized to hydroxyketone **266** with the highly useful tin acetal technology in 59% overall yield. The latter compound (**266**) was then condensed with aminooxyglycoside **259** in the presence of PPTS to afford the corresponding oxime (single isomer, configuration not assigned), which was further subjected to silylation, DIBAL reduction, and thionimidazole formation to afford substrate **267**. Thermal treatment of **267** in toluene at 110 °C induced the expected [3,3]-sigmatropic rearrangement, which led to thiocarbamate **268** in high overall yield. Alternatively, coupling of phenol **269** with trichloroacetimidate **265** was smoothly promoted with BF₃·Et₂O, to furnish glycoside **270** stereoselectively. Further elaboration of **270** led to acid chloride **271**, whose coupling with the thiol derived from **268** (NaSMe, EtSH) proceeded under the influence of 4-DMAP and Et₃N to afford pentacyclic system **272**. The silyl enol ether of the latter compound was selectively cleaved (TBAF, AcOH) and the resulting ketone was reduced stereoselectively (K-Selectride) to the α -hydroxy compound; this was then silylated, photolytically deprotected at the reducing end, and activated as a trichloroacetimidate in high overall yield, ready for attachment to the aglycon portion of the molecule. The latter goal was accomplished when the trichloroacetimidate **273** was coupled to aglycon **274** to furnish, after DIBAL reduction and Mitsunobu reaction (AcSH, Ph₃P, DEAD), compound **275**. Final elaboration of **275** in six steps led to calicheamicin γ_1^I (**251**).

In collaboration with Paloma and Chazin at the Scripps Research Institute, extensive 1D and 2D ¹H NMR studies were undertaken to establish the molecular basis for the mode of DNA binding of **251** and to probe the origins of the sequence selectivity of the interaction between this potent antitumor antibiotic and DNA.^[123, 124] Comparative analysis of the DNA complex formed with and without the aglycon demonstrated the critical role of the oligosaccharide domain in the molecular interactions leading to binding and sequence-specific recognition in the minor groove of the DNA duplex. In addition, in collaboration with Joyce from the same institute, the sequence-specific DNA cleavage activity of **251** was studied using a synthetic 20-mer DNA substrate that contained a single TCCT–AGGA target site (Figure 2). As expected, cleavage of the target DNA occurred at a single, preferred site within the radiolabeled strand, corresponding to the 5'-C residue within the TCCT sequence (Figure 3).^[125, 126]



Figure 2. Synthetic 20-mer duplex DNA containing a single TCCT–AGGA target site (boxed region) for recognition by calicheamicin. Arrows denote sites of calicheamicin-induced DNA cleavage.^[125]

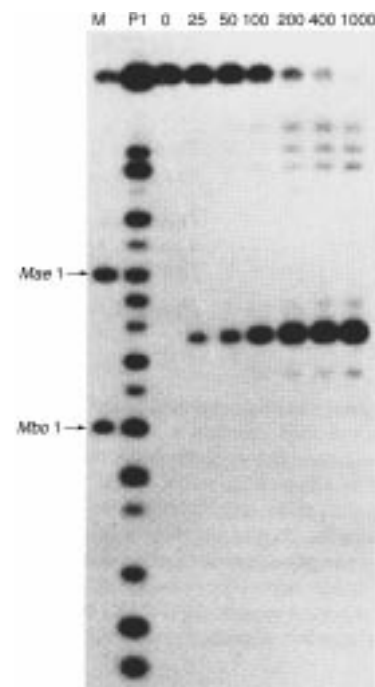


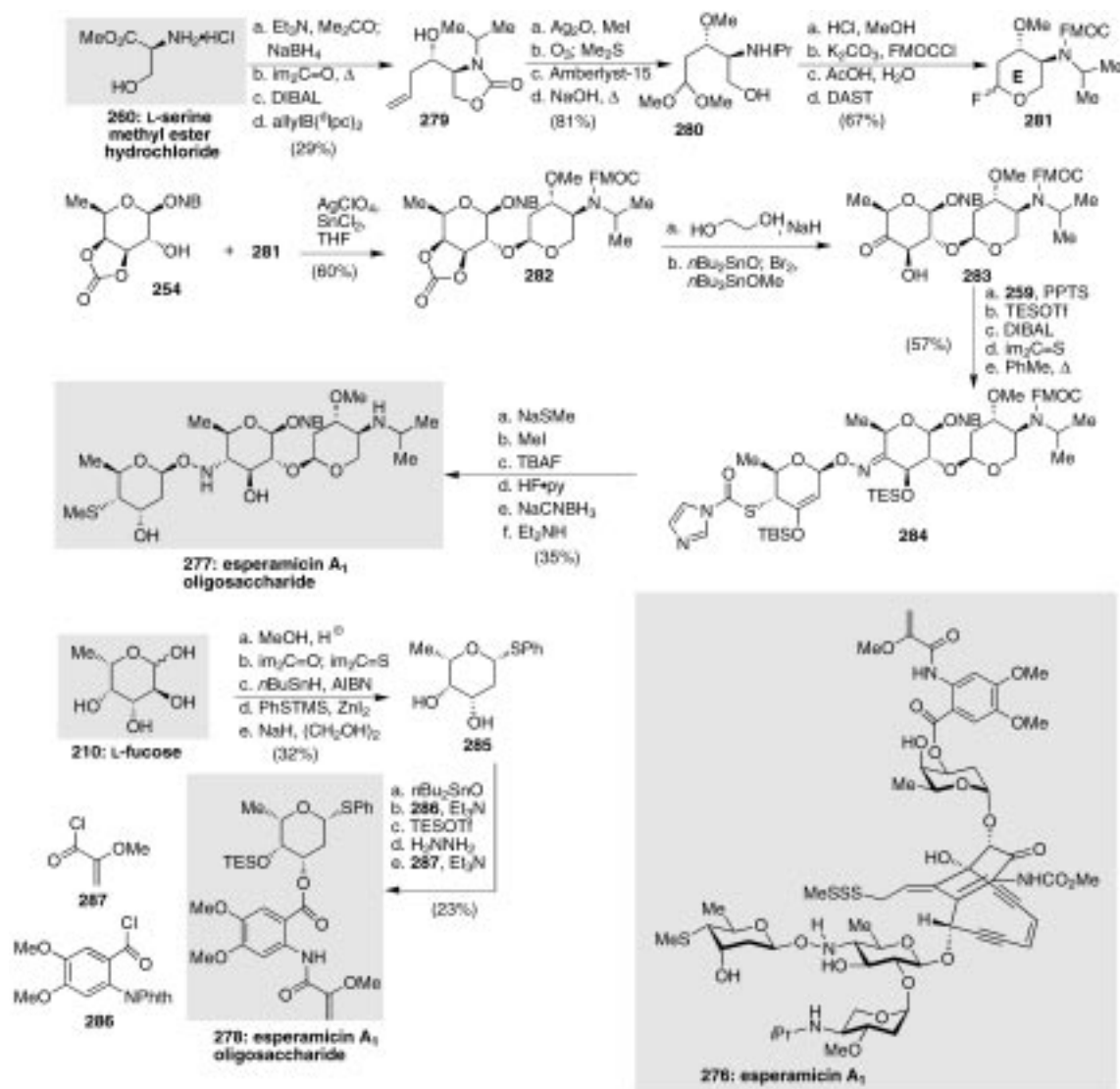
Figure 3. Autoradiogram of a denaturing polyacrylamide gel showing products of calicheamicin-induced DNA cleavage with the [5'-³²P]-labeled, TCCT-containing strand. M: marker lane containing an equimolar mixture of the products of DNA digestion with either *Mae*I (cleaves 5'-CTAG) or *Mbo*I (cleaves 5'-GATC) restriction enzymes. P1: oligonucleotide ladder resulting from partial DNA digestion with P1 nuclease (generates 3'-OH termini). Lanes 0–1000: products of DNA digestion in the presence of calicheamicin γ_1^I (concentrations: 0–1000 nM; incubation at 37 °C for 6 min). Reproduced with permission from ref. [125].

4.12. Esperamicin A₁ Carbohydrate Domains

The carbohydrate units of esperamicin A₁ (**276**) have also been synthesized (Scheme 47), with similar strategies to those for calicheamicin γ_1^I (**251**, Scheme 46).^[127, 128] Thus, ring A alcohol **254** was coupled with the modified ring E fluoride **281** to afford disaccharide **282**. Processing of **282** proceeded in a similar manner as before to afford thioester **284** in high overall yield. Thioester cleavage, methylation, deprotection, and finally, oxime reduction afforded the fully deprotected esperamicin A₁ trisaccharide **277**. The second oligosaccharide, **278**, was derived from L-fucose (**210**) and acyl chlorides **286** and **287**, as depicted in Scheme 47.

4.13. Sulfated Le^x and Le^a

The recognition of the important roles of selectins in the recruitment of leukocytes to inflammation sites through



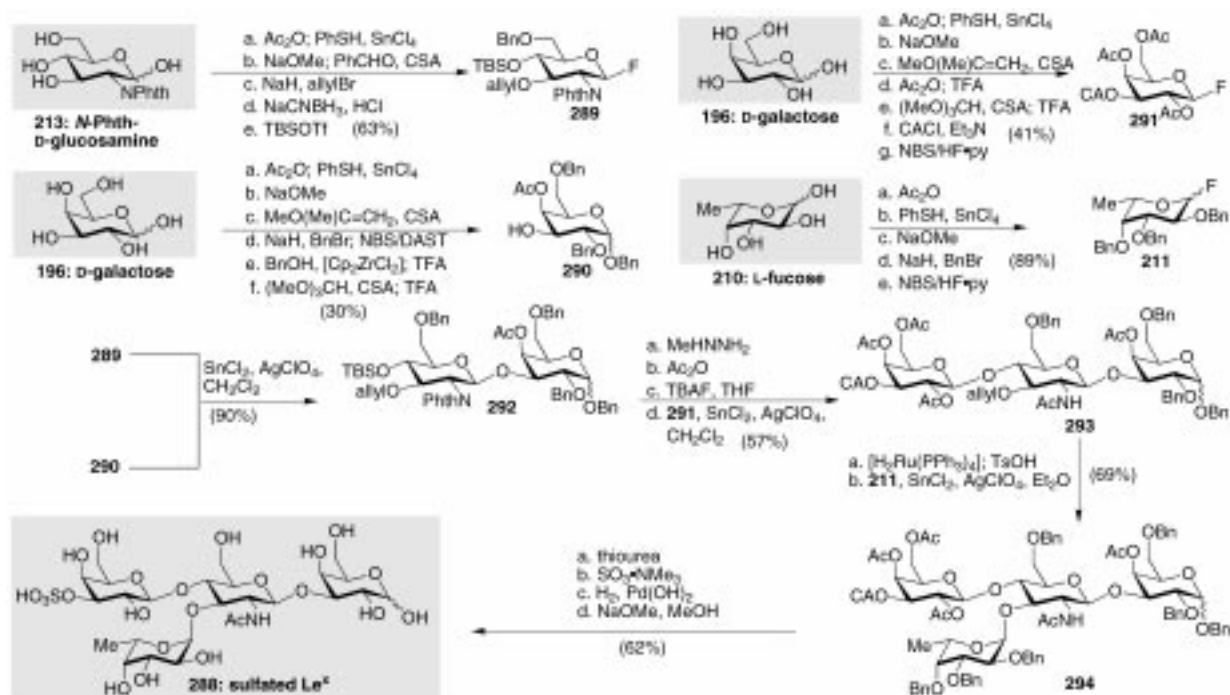
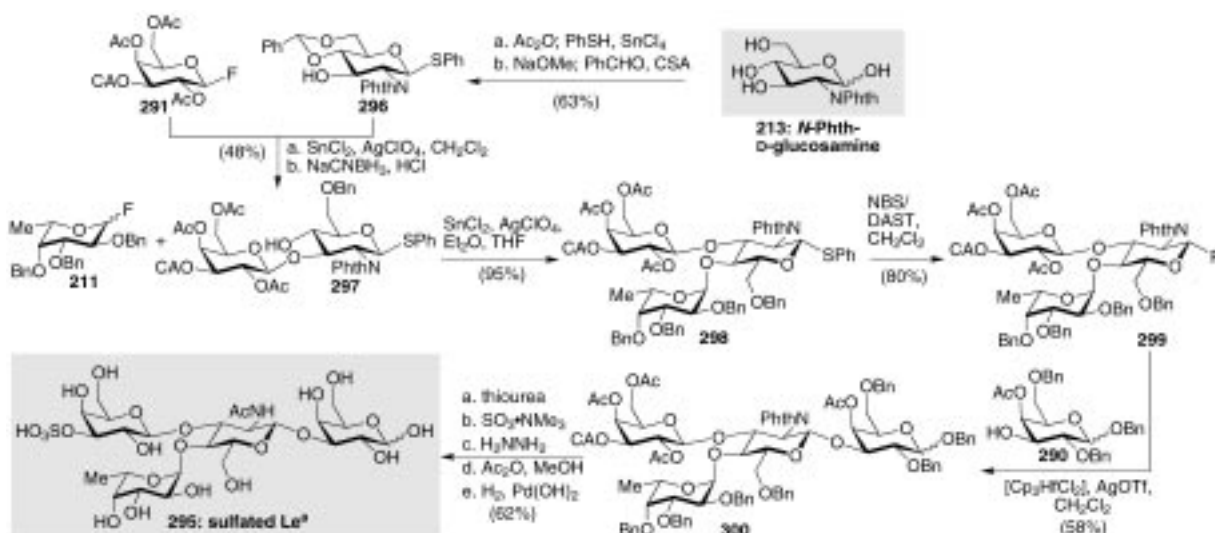
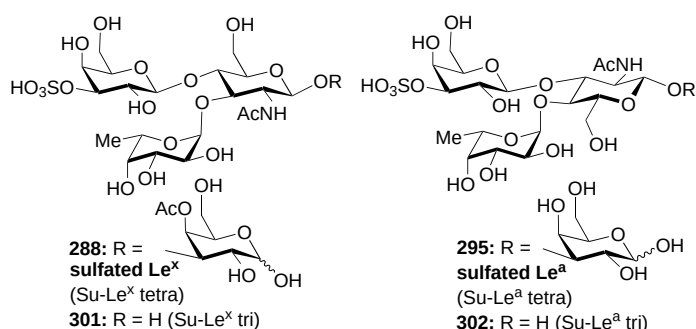
Scheme 47. Synthesis of esperamicin A₁ oligosaccharides **277** and **278** from D-fucose (**252**), triacetyl-D-glucal (**255**), L-fucose (**210**), and L-serine methyl ester hydrochloride (**260**) (1992).^[127, 128]

vascular adhesion has evoked extensive studies in this field over the last few years. Such studies led to the isolation and identification of the two sulfated tetrasaccharides, **288** (sulfated Le^x) and **295** (sulfated Le^a), as naturally occurring ligands for E-selectin with binding affinities similar to that of the sialylated compound (sialyl Le^x). The potential of these compounds in biology and medicine made them prime targets for chemical synthesis. In 1993 we reported the first total synthesis of **288** and **295** as well as their trisaccharide analogues **301** and **302** (see Scheme 50). Scheme 48 summarizes the synthesis of sulfated Le^x (**288**) that utilizes glycosyl fluoride chemistry in the key coupling processes.^[129] Thus, the four required building blocks (**289–291** and **211**) were synthesized from *N*-phthaloyl-D-glucosamine (**213**), D-galactose (**196**), and L-fucose (**210**). Glycosyl fluoride **289** and alcohol **290** were coupled to afford, stereoselectively, disaccharide **292**, in which the phthalimide was subsequently exchanged for an acetate, and then the TBS was cleaved to enable coupling with glycosyl fluoride **291** to afford trisaccharide **293**. The allyl group was removed from **293** and the

fourth carbohydrate moiety (**211**) was introduced stereoselectively to form **294**. Finally, selective removal of the trichloroacetate was followed by sulfation and deprotection to furnish sulfated Le^x (**288**) in high overall yield.

The sulfated Le^a compound **295** was constructed as shown in Scheme 49. The starting carbohydrates were the same as for **288** but the sequence was modified by judicious choice of protecting groups, reagents, and conditions to provide the final target in good overall yield. In this case, the selective opening of a benzylidene acetal was performed on a disaccharide, leading directly to the coupling with the next monosaccharide unit. Notable, once again, is the admirable performance of the two-stage activation procedure in this synthesis.

The chemically synthesized sulfated Le^x (**288** and **301**) and Le^a (**295** and **302**; Scheme 50) oligosaccharides were investigated in collaboration with Feizi's group,^[130] in addition to other Le oligomers. Their ability to support E-selectin binding when converted into neoglycosphingolipids, as well as their ability to inhibit E-selectin binding to immobilized lipid-

Scheme 48. Synthesis of sulfated Le^x (288) from D-galactose (196), L-fucose (210), and N-phthaloyl-D-glucosamine (213) (1993).^[129]Scheme 49. Synthesis of sulfated Le^a (295) from D-galactose (196), L-fucose (211), and N-phthaloyl-D-glucosamine (213) (1993).^[129]Scheme 50. Synthesized and biologically evaluated (see Figure 4) sulfated Le^x (288, 301) and Le^a (295, 302) molecules (1993).

linked sialyl Le^a, Le^x, and sulfated Le^a pentasaccharides was studied. Initial results established that sulfated Le^a tetra- and pentasaccharides were the most potent oligosaccharide ligands for human E-selectin. Later studies^[131] targeted the binding specificity of the leukocyte-adhesion molecule L-selectin (leukocyte homing receptor) towards the structurally defined sulphated oligosaccharides. The results are shown in Figure 4.

4.14. Heptasaccharide Phytoalexin Elicitor (HPE)

Heptasaccharide phytoalexin elicitor (HPE, **303**, Scheme 51) is a naturally occurring substance isolated from

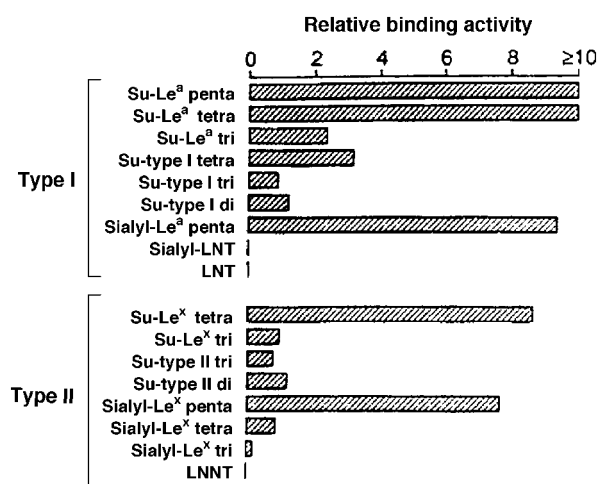
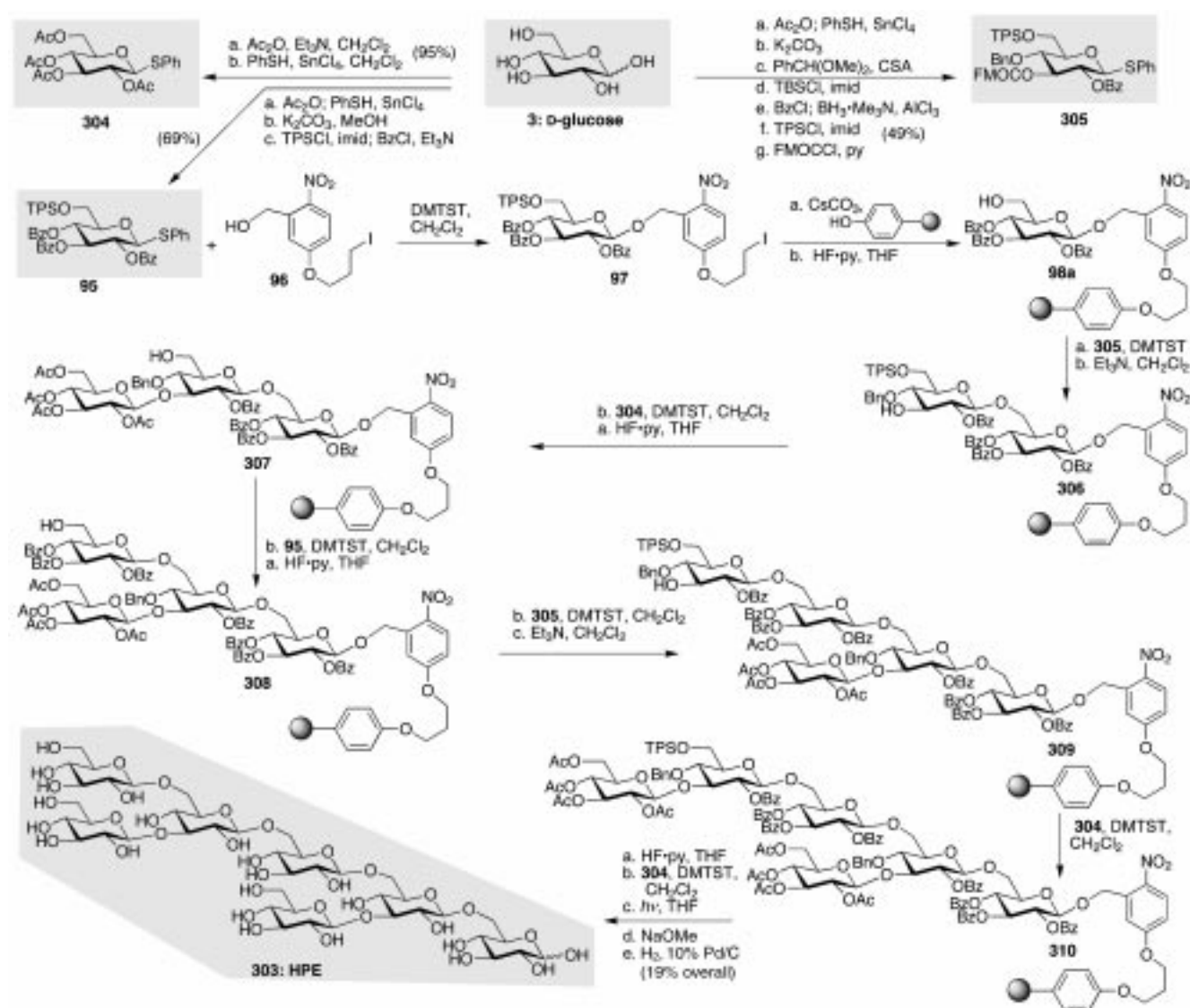


Figure 4. Relative L-selectin binding affinities of lipid-linked oligosaccharides (see Scheme 50), investigated with the quantitative microwell binding assay. Binding affinities relative to the binding affinity of sulphated Le^x trisaccharide (Su-Le^x tri) were calculated from binding curves. Reproduced with permission from ref. [131].

the mycelial walls of the fungus *Phytophthora megasperma*. Exhibiting potent phytoalexin elicitor activity with nanomolar binding properties toward its receptor, HPE (**303**) was the first natural product to be synthesized on solid phase by this group and, at that time (1997), represented the largest branched oligosaccharide ever constructed on solid support from monosaccharide units in a reiterative manner.^[87] This target molecule presented an ideal opportunity to test the applicability of the novel phenolic polystyrene-based photolabile linker strategy described in Section 3 (Scheme 26).

Thus, D-glucose (**3**) was converted into the three required building blocks **95**, **304**, and **305** by standard chemistry, and compound **95** was coupled with **96** and linked onto the resin ($\rightarrow$ 98, see Scheme 26) to afford conjugate **98a** upon desilylation. Carbohydrate unit **305** was then coupled onto the growing oligosaccharide chain to furnish, after removal of the Fmoc group, monohydroxy compound **306**, whose reiterative elaboration to resin conjugate **310** proceeded through intermediates **307**–**309**. From **310** the targeted HPE deriva-

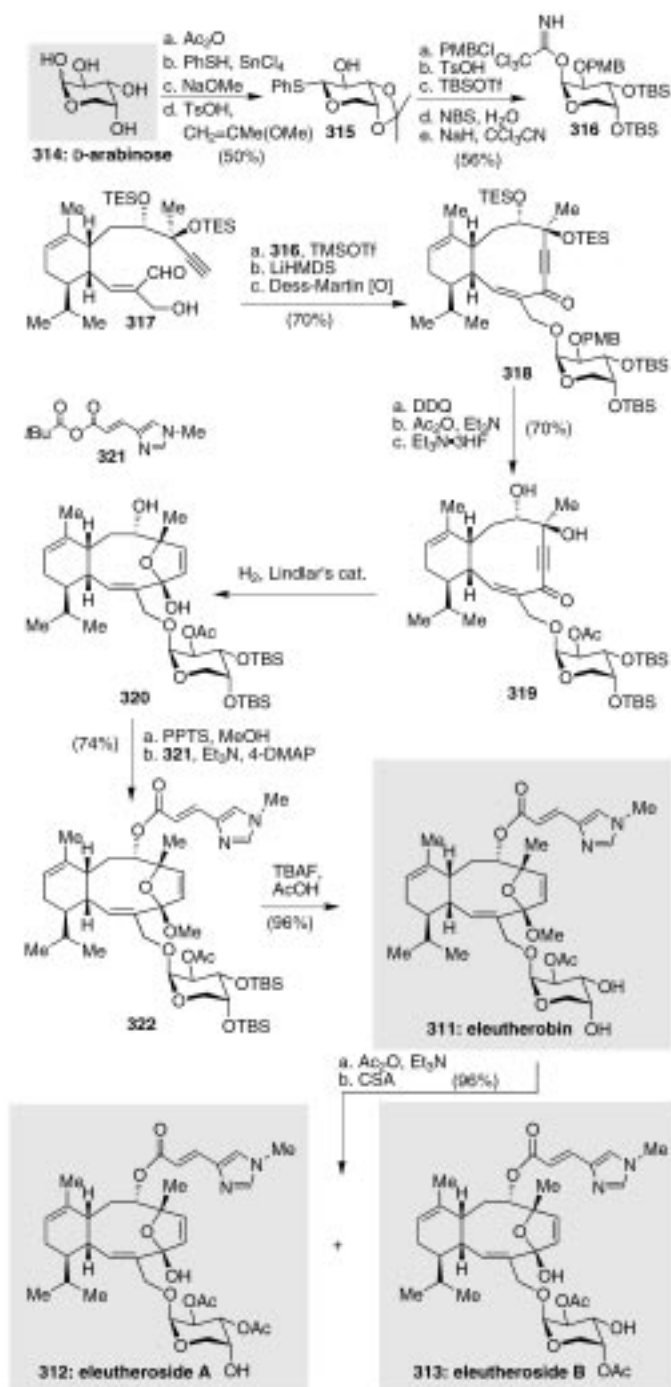


Scheme 51. Solid-phase synthesis of heptasaccharide phytoalexin elicitor (HPE, **303**) from D-glucose (**3**) (1997).^[87]

tive (**303**) was generated by desilylation, attachment of the final carbohydrate unit (**304**), photolytic cleavage, and removal of the protecting groups (19% overall yield).

4.15. Eleutherobin

Eleutherobin (**311**, Scheme 52) is a recently discovered antitumor agent isolated from an *Eleutherobia* species of soft corals and exhibiting a taxol-like mechanism of action in polymerizing and stabilizing microtubules. The total syntheses

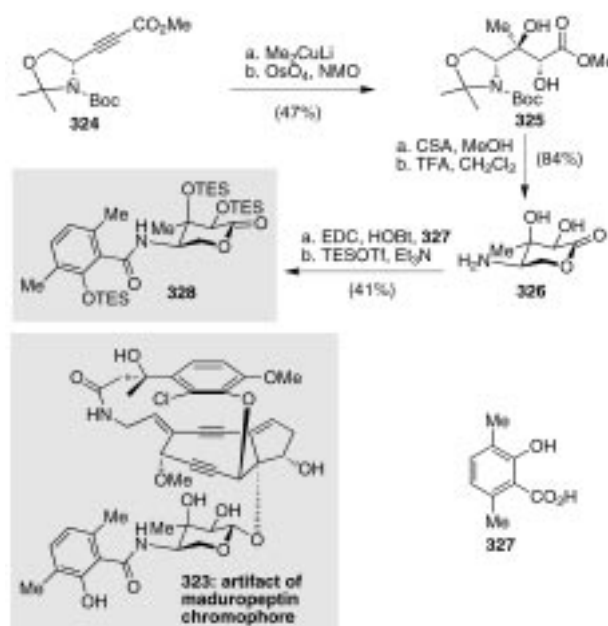


Scheme 52. Synthesis of eleutherobin (**311**) and eleutherosides A (**312**) and B (**313**) from D-arabinose (**314**) (1997).^[132–135]

of eleutherobin (**311**) and its relatives, eleutherosides A (**312**) and B (**313**), were completed in these laboratories in 1997; this allowed confirmation of the absolute stereochemistry and paved the way for library construction and chemical biology studies.^[132–135] All three natural products contain acetylated arabinose moieties. Thus, D-arabinose (**314**) was converted into trichloroacetimidate derivative **316** via thioglycoside **315**, by employment of selective acetonide formation and a nonparticipating PMB group at the C2 position. Compound **316** was then coupled to primary alcohol **317** through the catalytic action of TMSOTf to afford, predominantly, the desired β -glycoside (54% yield). Upon ring closure by the corresponding acetylide and oxidation, the 10-membered ring ketone **319** was obtained and was further elaborated to eleutherobin (**311**), eleutheroside A (**312**), and eleutheroside B (**313**).

4.16. Maduropeptin Chromophore Carbohydrate Domain

Maduropeptin, a complex of macromolecular antibiotics, was isolated from the broth filtrate of *Actinomadura madurae* in 1991. It was reported that maduropeptin consists of a 1:1 complex of an acidic, water soluble 32 kDa carrier protein and a nine-membered ring enediyne chromophore that possesses impressive antibacterial and antitumor properties. The naked chromophore proved to be too labile for isolation; but in the presence of methanol, an artifact of maduropeptin, compound **323** (Scheme 53), was isolated and characterized. As a prelude to a total synthesis of maduropeptin, madurosamine derivative **328** representing the carbohydrate domain of this architecturally unusual natural product, was constructed from the D-serine derived intermediate **324**, as summarized in Scheme 53.^[136, 137]



Scheme 53. Synthesis of madurosamine derivative **328** of the artifact of maduropeptin chromophore (**323**) from D-serine derivative **324** (1997).^[136, 137]

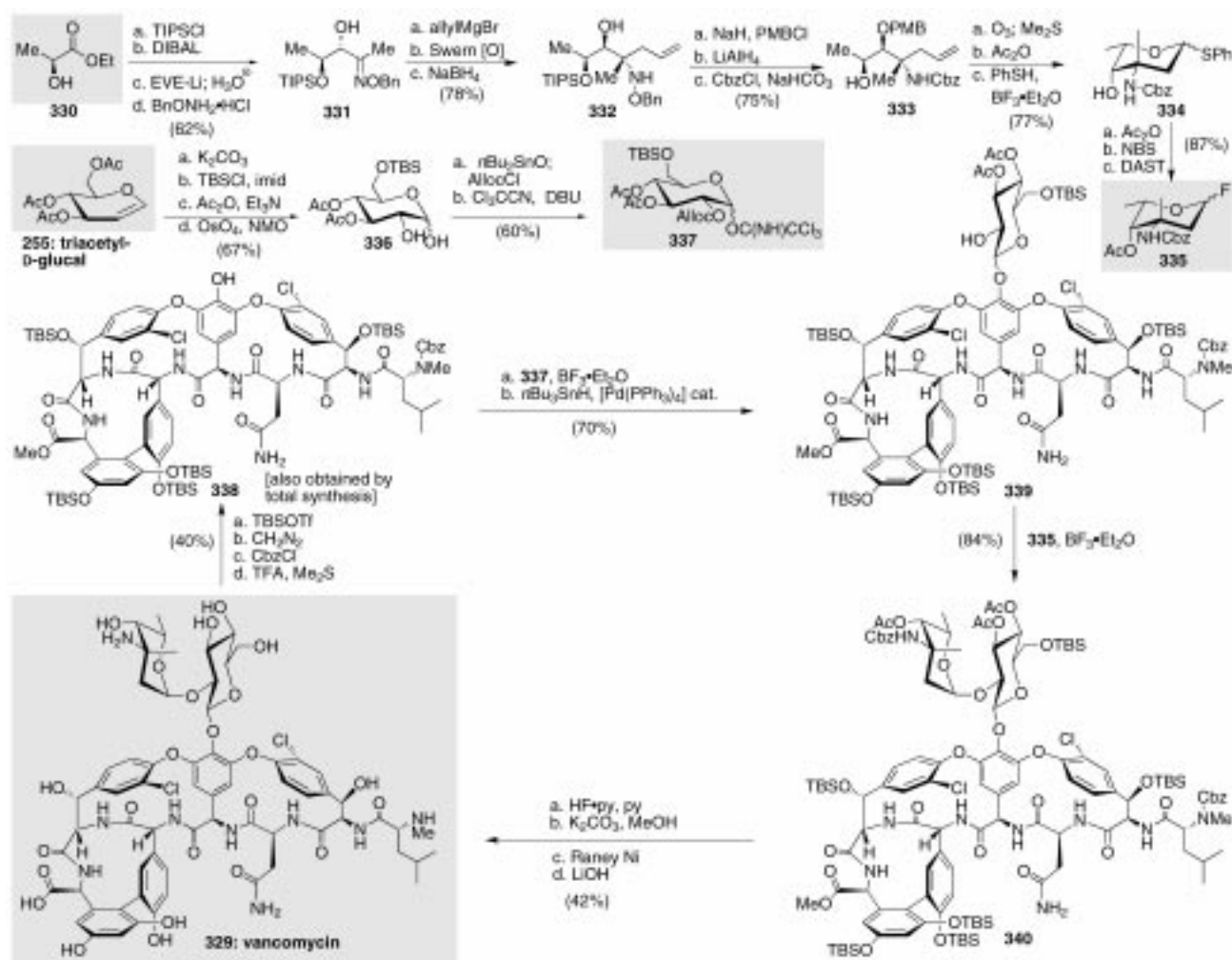
4.17. Vancomycin

Vancomycin (**329**, Scheme 54), isolated from the fermentation broths of *Streptomyces orientalis*, belongs to a rather large class of antibiotics collectively known as glycopeptide antibiotics. It is used clinically as a last line of defense against resistant strains of Gram positive bacteria, particularly methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus* species. Vancomycin's mode of action includes binding to the D-Ala-D-Ala terminus of the growing peptidoglycan framework of the cell wall, and subsequent inhibition of transglycosidation (polymerization) and transpeptidation (cross-linking) so causing cell lysis.^[138]

Vancomycin (**329**) possesses a unique molecular architecture, consisting of a disaccharide moiety (a glucose and a vancosamine) attached onto a rigid cyclic heptapeptide framework, aglycon (**338**). The sugar moieties play important roles in delivering these antibiotics to their targets by enhancing their solubility. The strategy for the final stages of the total synthesis of vancomycin (**329**) included reaction of a suitably protected vancomycin aglycon acceptor with appropriately functionalized glucose and vancosamine donors. It was proposed that a participating group at C2 of the glucose moiety could facilitate β -glycosidation, and that the

anomeric effect could influence the glycosidation to deliver the required α -glycoside bond linking the two sugar units.

Model studies proved instrumental in developing the final plan for the total synthesis of vancomycin (**329**), which involved a stepwise glycosidation approach utilizing acceptor **338** and donors **337** and **335** (Scheme 54). The required building blocks **337** and **335** were synthesized from triacetoxyl-D-glucal (**255**) and ethyl L-lactate (**330**), respectively, and then attached onto the aglycon sequentially. Thus, glycosidation of phenol **338** with excess trichloroacetimidate **337** in CH_2Cl_2 and in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78°C proceeded smoothly to afford the monosaccharide in 82% yield. The C2 hydroxyl group of the glucose moiety was liberated by reaction with $n\text{Bu}_3\text{SnH}/[\text{Pd}(\text{Ph}_3\text{P})_4]$ in wet CH_2Cl_2 , leading to the new glycoside acceptor **339** (85% yield). The second glycosidation was achieved by treatment of alcohol **339** with glycosyl fluoride **335** in CH_2Cl_2 and in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -35°C to afford the fully protected vancomycin derivative **340** in 84% yield and with an approximately 8:1 ratio of $\alpha:\beta$ stereoselectivity. Chromatographically separated **340** was then subjected to desilylation (excess $\text{HF} \cdot \text{py/py}$) and deacetylation (K_2CO_3 in MeOH), to form the Cbz-protected vancomycin methyl ester (95% yield). Finally, treatment with Raney Ni in $n\text{PrOH}:\text{H}_2\text{O}$ (2:1) caused removal of the Cbz



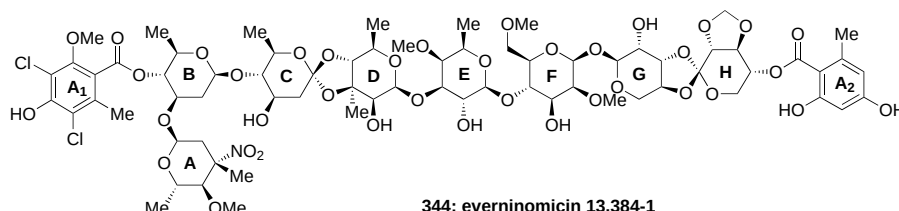
Scheme 54. Synthesis of vancomycin (**329**) from triacetoxyl-D-glucal (**255**) and L-ethyl lactate (**330**) (1999).^[139–141]

groups (without dechlorination), and subsequent saponification of the resulting vancomycin methyl ester with LiOH in THF:H₂O (1:1) at 0 °C furnished vancomycin (**329**) in 85 % yield. Further studies with vancomycin led to a novel degradation strategy to transform vancomycin (**329**) into protected aglycon derivative **338**, by silylation, methyl ester formation, Cbz protection, and hydrolysis of the sugars in good overall yield.^[139–141]

Upon completion of this total synthesis, a solid-phase version was developed and a number of interesting analogues have since been designed, semisynthesized, and tested for biological activity. The solid-phase synthesis of vancomycin (**329**) followed similar lines to the strategy described above and is summarized in Scheme 55.^[142a] A key factor in the success of this strategy was the use of a selenium-based safety-catch linker in which resin-bound selenoether **342** was cleaved with H₂O₂ to furnish allylester **343**, which was subsequently removed with *n*Bu₃SnH and [Pd(PPh₃)₄]. Facilitated by these synthetic technologies, target-accelerated combinatorial synthesis of vancomycin back-to-back dimers led to the discovery of a number of highly potent antibiotics active against vancomycin-resistant enterococci. In this study, D-Ala-D-Ala-containing targets were utilized to induce rate accelerations in the olefin metathesis or disulfide bond formation to cause dimerization of monomeric vancomycin analogues.^[142b]

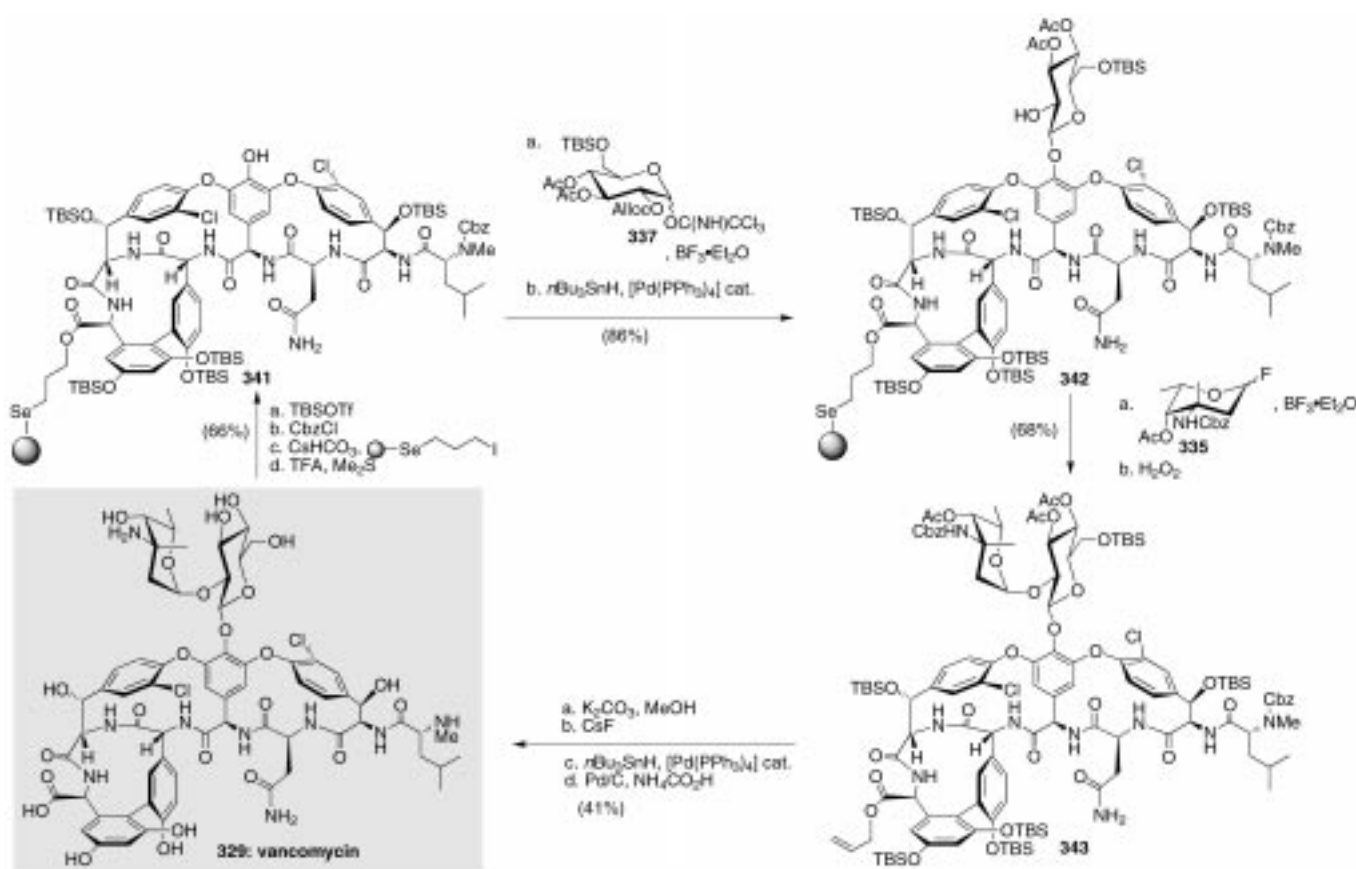
4.18. Everninomicin 13,384-1

Everninomicin 13,384-1 (Ziracin, **344**), a member of the orthosomicin class of antibiotics, represents a promising new weapon against drug-resistant bacteria including methicillin-resistant Staphylococci and vancomycin-resistant Streptococci and Enterococci. Isolated from *Micromonospora*



carbonacea var. africana (found in a soil sample collected from the banks of the Nyiro River in Kenya), **344** possesses a complex oligosaccharide structure containing two sensitive orthoester moieties and terminating with two highly substituted aromatic esters. In addition, it hosts within its structure a 1,1'-disaccharide bridge, a nitrosugar (evernitrore), 13 rings, and 35 stereogenic centers.

Retrosynthetic analysis of **344** indicated that fluoride **375** (A₁B(A)C fragment, Scheme 57) and diol **394** (DEFGHA₂ fragment, Scheme 58) could be the penultimate building blocks for the intended construction. The larger fragment **394** was further disconnected at the EF glycosidic bond to unravel fragments **387** (DE, Scheme 58) and **383** (FGHA₂,



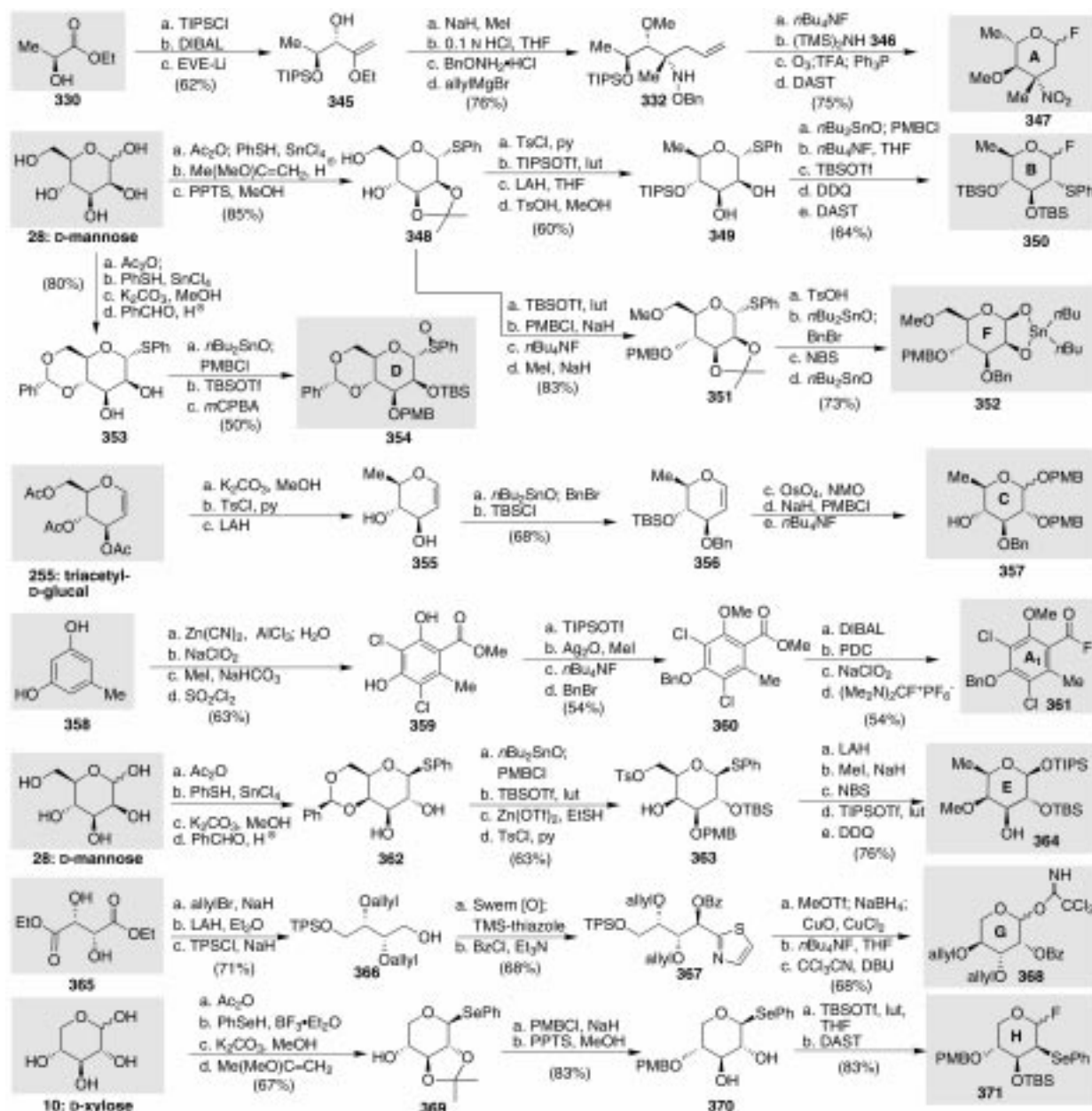
Scheme 55. Solid-phase semisynthesis of vancomycin (**329**) (2000).^[142a]

Scheme 58) as potential key intermediates for its construction. Crucial to this total synthesis were 1,2-phenylseleno- and 1,2-phenylthio migrations, as described above in the methodologies section, that set the stage for the stereocontrolled syntheses of the CD and GH orthoesters and β -2-deoxyglycoside bond between rings B and C.

Scheme 56 summarizes the construction of the requisite building blocks **347**, **350**, **352**, **354**, **357**, **361**, **364**, **368**, and **371**. The construction of the evernitrore donor **347** involved an improved sequence along the lines of our original syntheses of both evernitrore and vancosamine.^[139] Thus, methylation of alcohol **345** (derived from ethyl lactate (**330**)) with NaH/MeI, hydrolysis to the corresponding ketone with aqueous HCl, conversion into the oxime, and addition of allylmagnesium bromide furnished **332** (see Scheme 54). Silyl group exchange ($n\text{Bu}_4\text{NF}$; $(\text{TMS})_2\text{NH}$ (**346**), TMSCl) and ozonolysis, followed

by sequential exposure to TFA and Ph_3P resulted in generation of the lactol, which was subsequently converted into glycosyl fluoride **347** upon treatment with DAST (75% overall yield). Building block B **350** was prepared by tosylation of the primary hydroxyl group of intermediate **348** (derived from D-mannose (**28**)), silylation, reduction with LAH, and acidic methanolysis of the acetonide group to afford diol **349**. Selective protections ($n\text{Bu}_2\text{SnO}/\text{PMBCl}$, desilylation, resilylation, DDQ deprotection) and exposure to DAST caused the desired 1,2-migration of the thiophenyl group leading to the targeted glycosyl fluoride **350**.

Building block F **352** was synthesized from the readily available thioglycoside **348** as follows (Scheme 56). Selective silylation (TBSOTf/2,6-lutidine, 97%), PMB protection ($\text{NaH}/\text{PMBCl}/n\text{Bu}_4\text{NI}$), desilylation, and methylation (NaH/MeI) furnished acetonide **351** in 83% overall yield. Acidic



Scheme 56. Synthesis of building blocks **347**, **350**, **352**, **354**, **364**, **352**, **368**, **371**, and **361** required for the total synthesis of everninomicin 13,384-1 (**344**) (1999).^[143–146]

methanolysis (TsOH/MeOH), selective benzylation, and rupture of the phenylthio group with NBS/H₂O furnished the corresponding lactol, which was converted to the desired tin acetal **352** by exposure to *n*Bu₄SnO in refluxing MeOH. Building block D was constructed from benzylidene **353** (derived from D-mannose (**28**)) by regioselective tin acetal mediated protection (*n*Bu₂SnO/PMBCl/*n*Bu₄NI), silylation (TBSOTf/2,6-lutidine), and oxidation of the sulfur group with *m*CPBA to afford the desired sulfoxide **354**. Building block C (**357**) was constructed in five steps from the readily available glucal **355**. Thus, tin acetal mediated benzylation of **355** (*n*Bu₂SnO/*BnBr*/*n*Bu₄NI) and silylation (TBSOTf/imidazole) led to compound **356**. Hydroxylation (OsO₄/NMO), PMB protection (NaH/PMBCl/*n*Bu₄NI), and exposure to *n*Bu₄NF generated the desired building block **357** in 68 % overall yield.

The acyl fluoride **361** was formed from 5-methylresorcinol (**358**); a Gattermann reaction and core chlorination produced the fully substituted benzene ring. The synthesis of ring E **364** also began from D-mannose (**28**). PMB monoprotection of compound **362** (*n*Bu₂SnO/PMBCl/*n*Bu₄NI) and silylation (TBSOTf/2,6-lutidine), followed by cleavage of the benzylidene group (Zn(OTf)₂/EtSH) and selective tosylation of the primary hydroxyl group (TsCl/py), furnished **363**. LAH reduction, methylation (NaH/MeI), and cleavage of the phenylthio group (NBS/H₂O), followed by silylation (TIPSOTf/2,6-lutidine) and removal of the PMB group (DDQ), furnished the desired building block **364**.

Ring G trichloroacetimidate **368** was derived from diethyl-L-tartrate (**365**) by double allylation and reduction of both ester groups, followed by monosilylation to furnish hydroxy silyl ether **366**. Swern oxidation and exposure to TMS/thiazole afforded, after acidic workup (PPTS/MeOH) and benzylation, the homologated chain **367**. Thiazole cleavage (MeOTf; NaBH₄; CuO; one-pot reaction) and desilylation (*n*Bu₄NF) led to the lactol which was converted into the trichloroacetimidate **368**.

Building block H **371** was derived from D-xylose (**10**) as follows. Peracetylation of **10** (Ac₂O/Et₃N/4-DMAP), treatment with PhSeH/BF₃·Et₂O, basic methanolysis (K₂CO₃/MeOH), and exposure to CH₃(CH₃O)C=CH₂/TFA furnished the 2,3-acetonide **369**. Protection (NaH/PMBCl/*n*Bu₄NI, 95 % yield) and acetonide cleavage (PPTS/MeOH) then afforded diol **370**. The hydroxy group at the C3 position of the latter compound was selectively silylated, and then treatment with DAST furnished the targeted 2-phenylselenoglycosyl fluoride **371**.

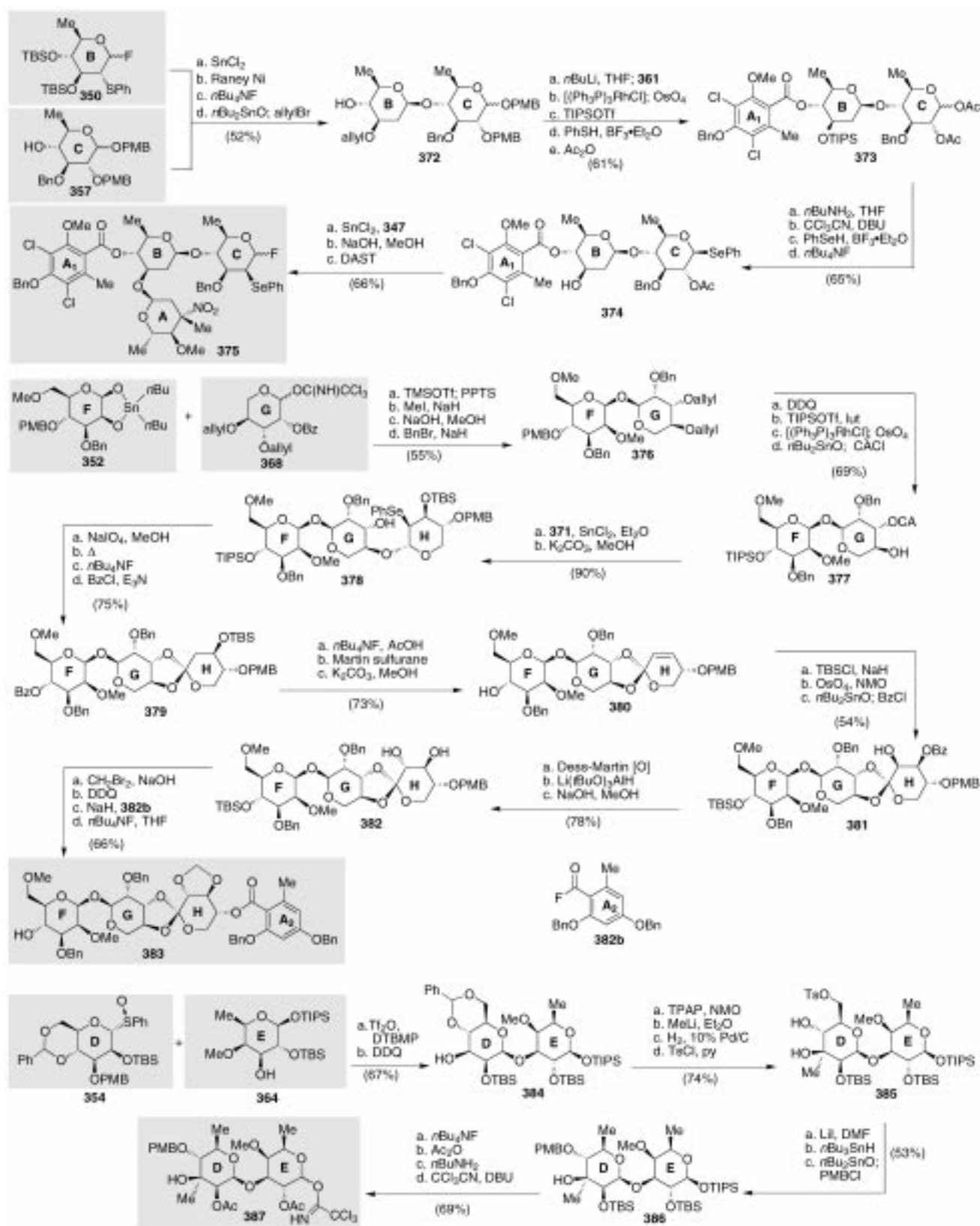
Scheme 57 shows the stereoselective coupling of building blocks **347**, **350**, **357**, and **361** to form the A₁B(A)C fragment **375**. Thus, SnCl₂-mediated coupling of glycosyl fluoride **350** with alcohol **357**, followed by reductive cleavage of the 2-thiophenyl group (Raney Ni), desilylation (*n*Bu₄NF), and selective monoallylation (*n*Bu₂SnO-allylbromide), furnished alcohol **372** in 52 % overall yield. Formation of the aromatic ester linking **372** and **361** mediated by *n*BuLi, followed by removal of the allyl group, silylation, PMB removal, and acetylation afforded diacetate **373**. Exposure of diacetate **373** to *n*BuNH₂ led to selective cleavage of the C1 acetate, and the liberated lactol was then converted into the β-phenylselenoglycoside via the trichloroacetimidate. Finally, removal of the

TIPS group furnished A₁BC fragment **374**. Attachment of the evernitro fragment **347** onto the A₁BC chain proceeded smoothly under the influence of SnCl₂, and basic hydrolysis of the acetate group led to the 2-hydroxy compound, whose treatment with DAST produced the targeted 2-phenylselenoglycosyl fluoride **375** in excellent yield and with inversion of stereochemistry at C2 of ring C.

The assembly of building blocks **352**, **368**, and **371** to form the targeted FGHA₂ intermediate **383** required the use of the new technology for the construction of 1,1'-disaccharides (Scheme 25). The coupling of tin acetal **352** with trichloroacetimidate **368** proceeded smoothly under the catalytic influence of TMSOTf in CH₂Cl₂ and led, after PPTS-induced cleavage of the intermediate TMS ether, to the desired 1,1'-disaccharide linkage. Methylation, debenzoylation, and benzylation afforded disaccharide **376**. The PMB group of ring F was replaced with a TIPS group (DDQ, 91 % yield; TIPSOTf/2,6-lutidine, 97 % yield) and removal of the allyl protecting groups was followed by tin acetal mediated chloroacetylation to furnish **377**. Coupling of **377** with glycosyl fluoride **371** (SnCl₂, Et₂O) proceeded smoothly to give stereoselectively, and following deacetylation, trisaccharide **378**.

Trisaccharide **378** was now poised for a Sinaï orthoester formation. Thus, oxidation of the phenylseleno group with NaIO₄, followed by heating of the crude selenoxide in a mixture of vinyl acetate, toluene, and diisopropylamine (2:2:1) in a sealed tube at 140 °C, effected sequential *syn* elimination (*syn* towards the anomeric position) and ring closure, furnishing the orthoester in 81 % yield and with approximately 8:1 diastereoselectivity. Exchange of protecting groups and subsequent dehydration with Martin sulfurane eventually led to olefin **380**, which was set for a dihydroxylation reaction. Treatment of the highly sensitive olefinic orthoester with NMO/OsO₄ in the presence of quinuclidine led to a *cis*-1,2-diol, which was then regioselectively converted into the monobenzoate **381** by treatment with *n*Bu₂SnO/BzCl. Oxidation (Dess–Martin periodinane) and reduction with Li(*t*BuO)₃AlH inverted the configuration at the C2 position of the H ring and, following debenzoylation, afforded *trans* diol **382**. Transformation of the resulting *trans*-1,2 diol system into the desired methylene acetal functionality was achieved by slowly adding it to a mixture of aqueous NaOH, CH₂Br₂, and *n*Bu₄NBr at 65 °C. The remaining steps for the completion of the synthesis of **383** involved DDQ-induced removal of the PMB group, esterification of the resulting compound with the acyl fluoride **382b**, and removal of the TBS group from ring F.

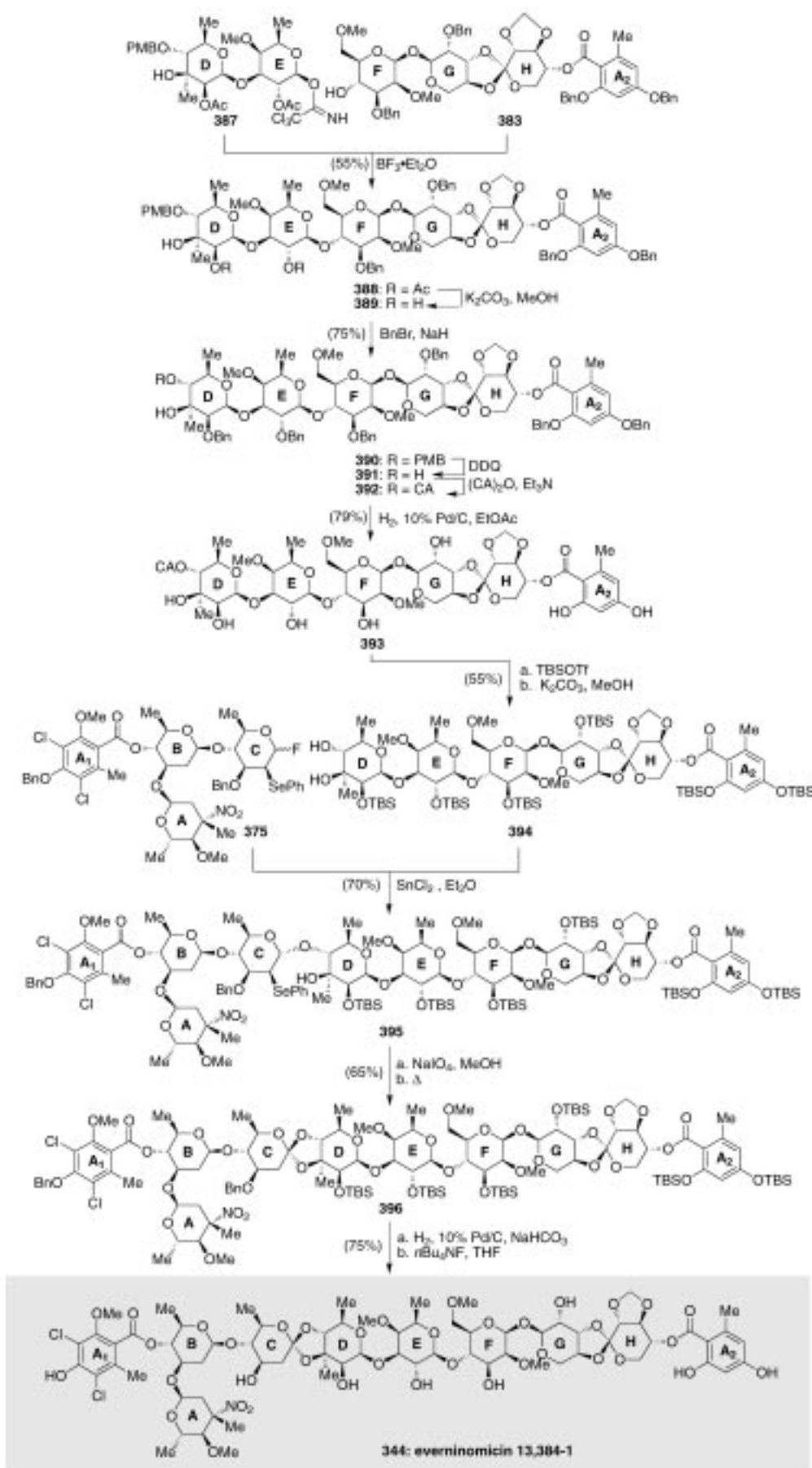
The construction of key intermediate **387** from fragments **354** and **364** was achieved by the Kahne sulfoxide glycosidation technology (Scheme 57). Thus, stereoselective coupling of sulfoxide **354** with acceptor **364** proceeded in the presence of Tf₂O and DTBMP, to afford the β-mannoside in 71 % yield. Removal of the PMB group (DDQ, 95 %), oxidation to the corresponding ketone (TPAP/NMO), and exposure of the latter compound to MeLi in Et₂O produced the desired tertiary alcohol in high overall yield. The benzylidene group was removed by hydrogenolysis (97 % yield) and the primary hydroxyl group was selectively tosylated to afford **385**. Replacement of the tosylate with an iodide, reduction with



Scheme 57. Synthesis of the A₁B(A)C, DE, and FGHA₂ fragments (**375**, **387**, and **383**, respectively) of everninomicin 13,384-1 (**344**) (1999).^[143–146]

*n*BuSnH/AIBN, and PMB protection led to **386**. Desilylation and peracetylation was followed by removal of the anomeric acetate and conversion into the trichloroacetimidate to afford **387**.

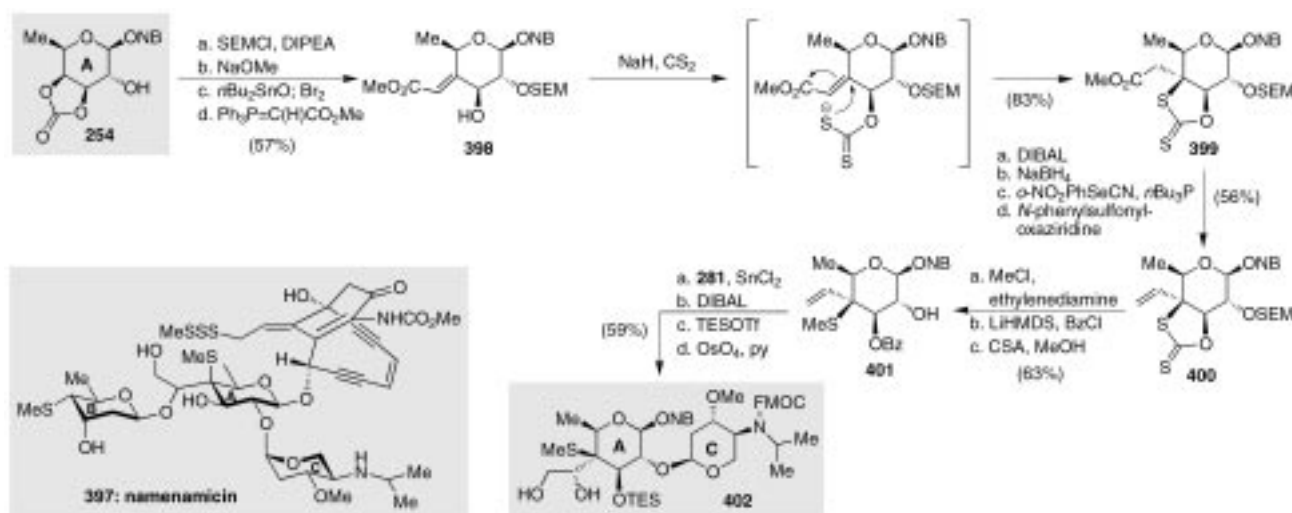
The coupling of the key intermediates **387** and **383** and the elaboration of the resulting fragment to the next advanced key intermediate, **394**, is shown in Scheme 58. Thus, reaction of the trichloroacetimidate **387** with fragment **383** furnished

Scheme 58. Completion of the total synthesis of everninomicin 13,384-1 (**344**) (1999).^[143–146]

oligosaccharide **388** with the desired β -glycoside configuration (between rings E and F). Several subsequent protecting group exchanges afforded DEFGHA₂ fragment **394**, ready for the next coupling. Coupling of the A₁B(A)C glycosyl fluoride donor **375** with **394** proceeded smoothly and with complete stereocontrol to afford the 2-phenylselenoglycoside **395**. Formation of the remaining orthoester site was then accomplished with equal facility under the Sinay conditions to afford the fully protected everninomicin 13,384-1 derivative **396** as a single isomer. Generation of everninomicin 13,384-1 (**344**) from **396** entailed hydrogenolysis (H_2 , Pd/C, NaHCO_3 , $t\text{BuOMe}$) and desilylation ($n\text{Bu}_4\text{NF}$, THF) leading to **344**. As a result of this synthesis,^[143–146] the stage is now set for further advances in the antibiotics field, including semi-synthesis of designed analogues, solid-phase synthesis, and chemical biology studies.

4.19. Namenamicin Carbohydrate Domain

Namenamicin (**397**, Scheme 59), recently isolated from an ascidian (*Polysyncrator lithostrontum*), is notably the only enediyne natural product of marine origin. Although its trisaccharide domain is reminiscent of esperamicin A₁, it contains an unprecedented and unusual linkage between rings A and B. Beginning with the same ring A intermediate (**254**) used in the calicheamicin synthesis (see Scheme 46), a cyclic xanthate based approach to the ring A thioether was initiated. Thus, **254** was trans-



Scheme 59. Synthesis of namenamicin A–C disaccharide **402** (1999).^[147]

formed into olefin **398** in four steps. Treatment of **398** with NaH and CS₂ afforded cyclic xanthate **399**. Subsequent exchange of protecting groups and elimination, followed by coupling with fluoride **281** (see Scheme 47) and dihydroxylation, furnished diol **402**.^[147]

4.20. Macrophyllside D Heptaacetate

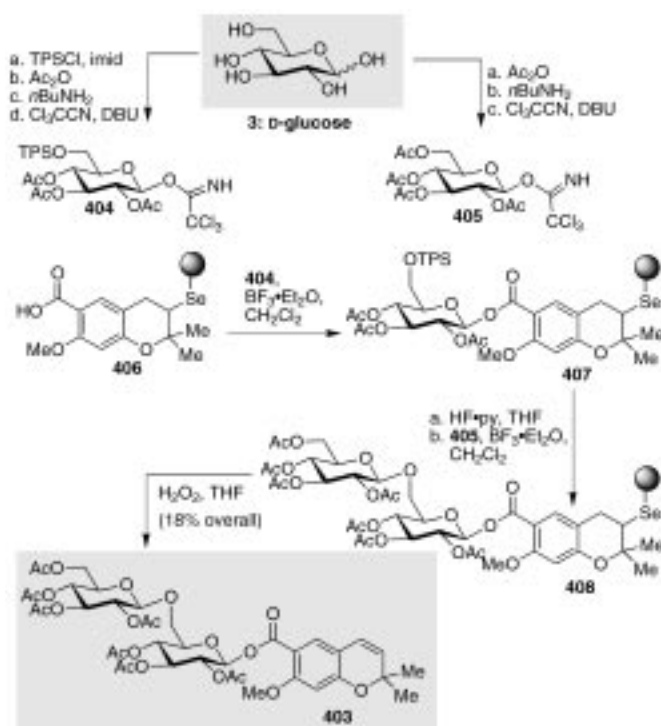
In defining the versatility of a selenium-linking strategy for the solid-phase synthesis of benzopyran-containing natural products and related compounds, the synthesis of macrophyllside D heptaacetate (**403**, Scheme 60),^[148, 149] a deriva-

tive of a chromene glycoside isolated from *Gentiana macrophylla*, was developed from resin-bound selenoether **406**. The requisite trichloroacetimidate donors **404** and **405** were obtained by standard chemistry from D-glucose (**3**). Carboxylic acid resin **406** was treated with trichloroacetimidate **404** in the presence of BF₃·Et₂O to smoothly furnish ester **407** in 91% yield. Selective deprotection with HF·py (89%) followed by a second coupling between the resin-bound monosaccharide and trichloroacetimidate **405** under similar conditions afforded **408** as a single anomer and in 57% yield. Finally, the disaccharide was cleaved from the resin (H₂O₂, THF) to afford heptaacetylated macrophyllside **403** in 18% overall yield based on **406**.

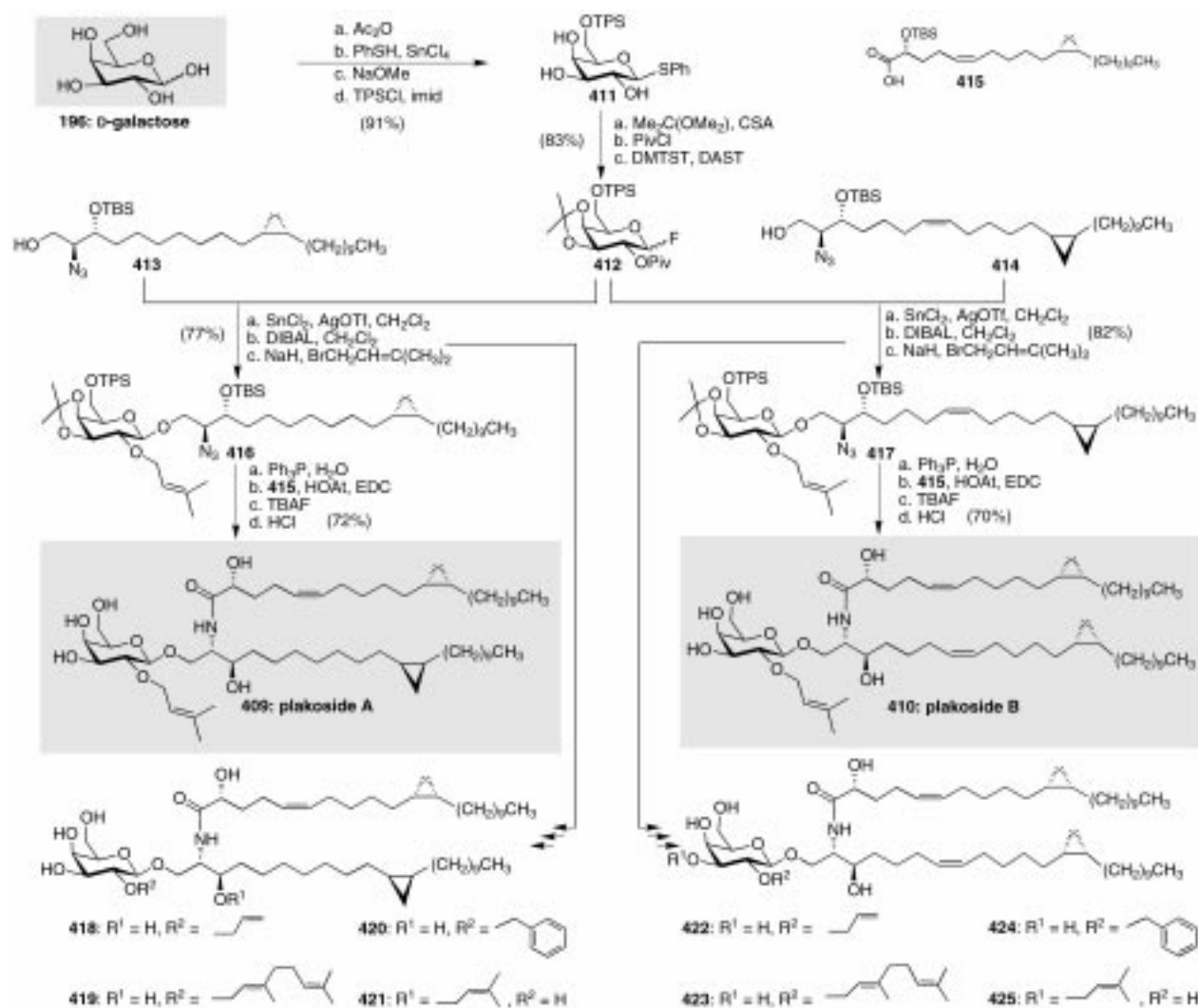
4.21. Plakosides A and B

Plakosides A (**409**) and B (**410**) (Scheme 61), recently isolated from the marine sponges *Plakortis simplex*, are potent immunosuppressive agents and contain interesting functionalities not common to other glycosphingolipids. Among these features are a cyclopropane ring on their sphingosine chain and a prenyloxy group on the C2 position of the carbohydrate moiety, which makes them interesting candidates for total synthesis, library construction, and chemical biology studies. The total synthesis of these target molecules, recently developed in our laboratories, is summarized in Scheme 61.^[150] Thus, galactosyl fluoride **412**, obtained from D-galactose (**196**) in seven steps, was coupled with azidosphingosine **413** to afford the expected β-glycoside in 93% yield. DIBAL cleavage of the pivalate ester was followed by installation of the prenyloxy group at the C2 position to afford **416**. Completion of the synthesis required reduction of the azide group, coupling with carboxylic acid **415**, and removal of the protecting groups to afford plakoside A (**409**) in high overall yield.

Plakoside B (**410**) and several designed analogues (such as **418–425**) were constructed by similar methods (Scheme 61). The biological activities of plakosides A and B and their analogues were evaluated in collaboration with a research



Scheme 60. Solid-phase synthesis of peracetyl macrophyllside D (**403**) from D-glucose (**3**) (2000).^[148, 149]

Scheme 61. Total synthesis of plakosides A (**409**) and B (**410**), and analogues thereof (2000).^[150]

group at Novartis^[150] to provide information about immuno-suppressive activity (MLR and Con A response) and potential cytotoxic and cytostatic effects (bone marrow cell proliferation). The IC_{50} values of the plakosides and several analogues synthesized in this program in comparison to reference compounds are provided in Table 9.

5. Design and Synthesis of Novel Carbohydrates for Chemical Biology Studies

One of our strongest motivations for developing carbohydrate-based enabling technologies was to facilitate studies in biology and medicine. Thus, we have utilized the developed chemistry in the construction of combinatorial libraries for chemical biology investigations and structure-activity relationship studies in several instances, including with vancomycin, the plakosides, and the benzopyran-type structures discussed above. Another field of investigation, that of DNA-binding molecules, was inspired by the mode of action of calicheamicin γ_1^1 . Yet another endeavor was initiated to capitalize on the structure and functionality of the carbohydrate ring framework as a scaffold upon which to design and

Table 9. Inhibitory effects of plakosides A (**409**) and B (**410**), their analogues **418–425**, and two reference compounds (Tests: MLR, the Con A response, and the bone marrow cell proliferation assays).^[150]

Compound	MLR	IC_{50} [μM]		Bone marrow cell proliferation
		Con A response		
cyclosporin A	0.014	0.14		> 1
azathioprine	0.028	0.15		0.050
409	> 50	> 50		50
410	> 50	> 50		> 50
418	7.1	30		3.3
419	28	> 50		18
420	> 50	> 50		> 50
421	28	30		24
422	> 50	> 50		40
423	> 50	> 50		> 50
424	> 50	> 50		50
425	> 50	> 50		29

build peptide and carbohydrate mimetics. Finally, a series of designed oligosaccharides with potential in biology were synthesized that exploited both solution- and solid-phase synthetic technologies. In the following section we will highlight a number of such investigations.

5.1. DNA-Binding Oligosaccharides

The observation that the calicheamicin γ_1^I oligosaccharide binds to certain DNA sequences (in particular TCCT, TCTC, and TTTT) with considerable selectivity, and knowledge of the importance in biology and medicine of sequence-specific small molecules that bind to DNA, prompted us to initiate a program aimed at the design, chemical synthesis, and study of a number of calicheamicin γ_1^I oligosaccharide analogues. In order to study the effect of the iodine atom on the binding properties of calicheamicin's oligosaccharide to DNA, a series of ring C analogues ($R = \text{Me, H, F, Cl, or Br}$, see structure **426**) were synthesized by applying the chemistry developed during the total synthesis of the natural product (see Scheme 46). The results of the binding studies with these synthetic molecules revealed the importance of the iodide residue in conferring high affinity ($I \approx \text{Br} > \text{Cl} > \text{Me} > \text{F} > \text{H}$) to the molecule (Table 10).^[126] These molecules were also used in NMR studies to define the precise mode of binding of the oligosaccharide to DNA's minor groove.^[123, 124]

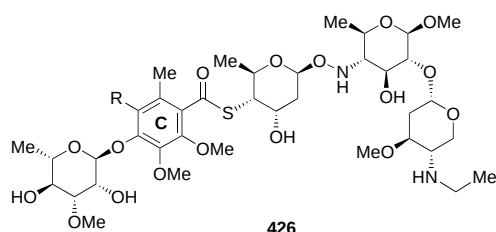
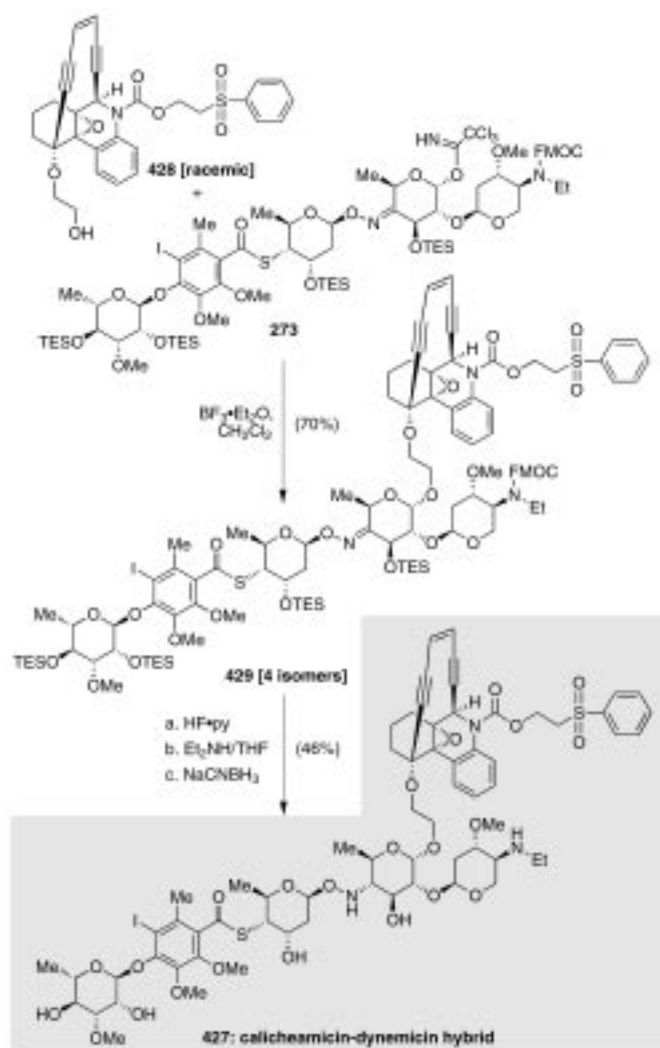


Table 10. Binding affinity of calicheamicin γ_1^I and various analogues of the calicheamicin oligosaccharide at a single TCCT–AGGA site within duplex DNA.

Ligand	$K_{\text{obs}}^{\text{[a]}}$ [μM]	$\Delta G^{\text{[b]}}$ [kcal mol ^{−1}]	$\Delta\Delta G^{\text{[c]}}$ [kcal mol ^{−1}]
calicheamicin γ_1^I (251)	0.135 ± 0.006	−9.7	–
I sugar 426a	4.1 ± 0.4	−7.6	2.1
Br sugar 426b	10.0 ± 1.7	−7.1	2.6
Cl sugar 426c	32.0 ± 3.3	−6.4	3.3
F sugar 426d	44.0 ± 3.1	−6.2	3.5
Me sugar 426e	38.0 ± 5.0	−6.3	3.4
H sugar 426f	180.0 ± 19.0	−5.3	4.4

[a] K_{obs} is the apparent dissociation constant of either calicheamicin (K_{D}) or the calicheamicin oligosaccharide (K_{I}). [b] $\Delta G = RT \ln K_{\text{obs}}$; $T = 310.15 \text{ K}$. [c] $\Delta\Delta G$ is ΔG for the oligosaccharide relative to ΔG for intact calicheamicin γ_1^I .^[126]

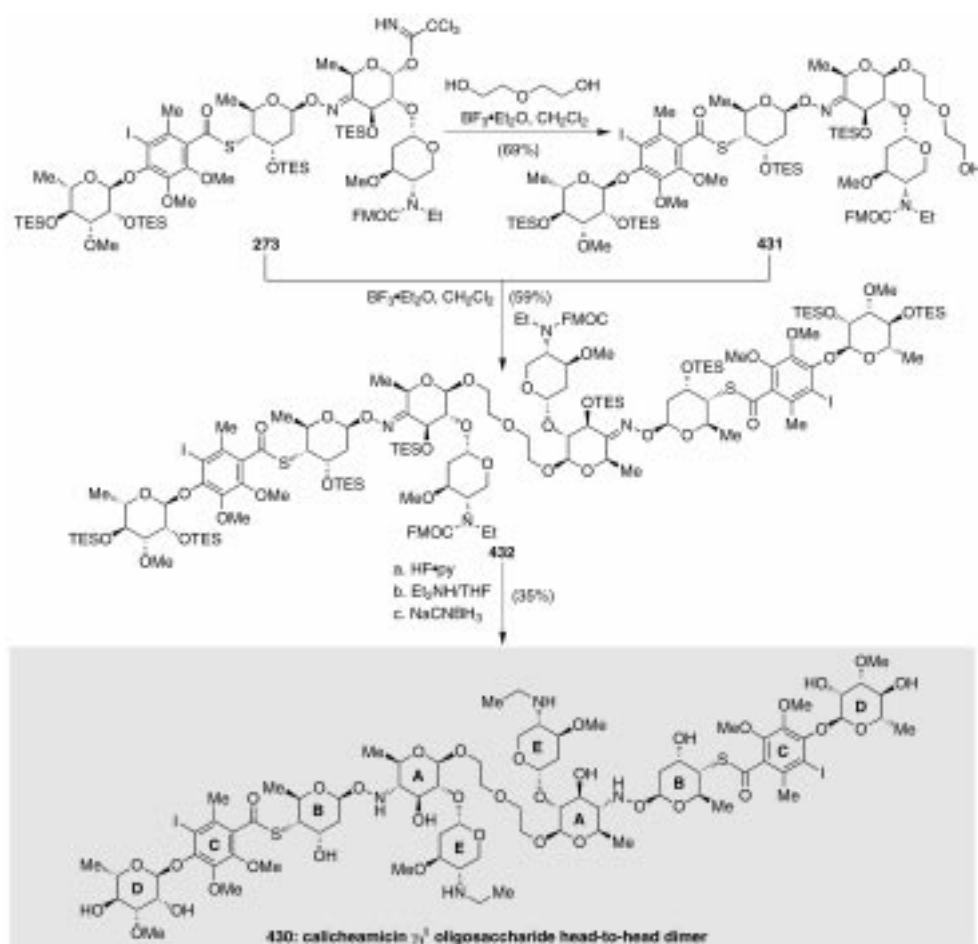
In an effort to prepare totally designed DNA-cleaving molecules with sequence selectivity, we attempted to merge the chemistry of calicheamicin γ_1^I with that of dynemicin, another novel enediyne antibiotic.^[151, 152] Thus, synthetic DNA-cleaving molecule **428** (Scheme 62), which was designed based on the structure and mechanism of action of dynemicin, was coupled with the calicheamicin oligosaccharide trichloroacetimidate **273** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to produce conjugate **429** as an anomeric mixture. The α -anomer **429** (shown) was then converted into the targeted calicheamicin–dynemicin hybrid **427** whose DNA-cleaving properties were studied. Interestingly, neither the potency nor its



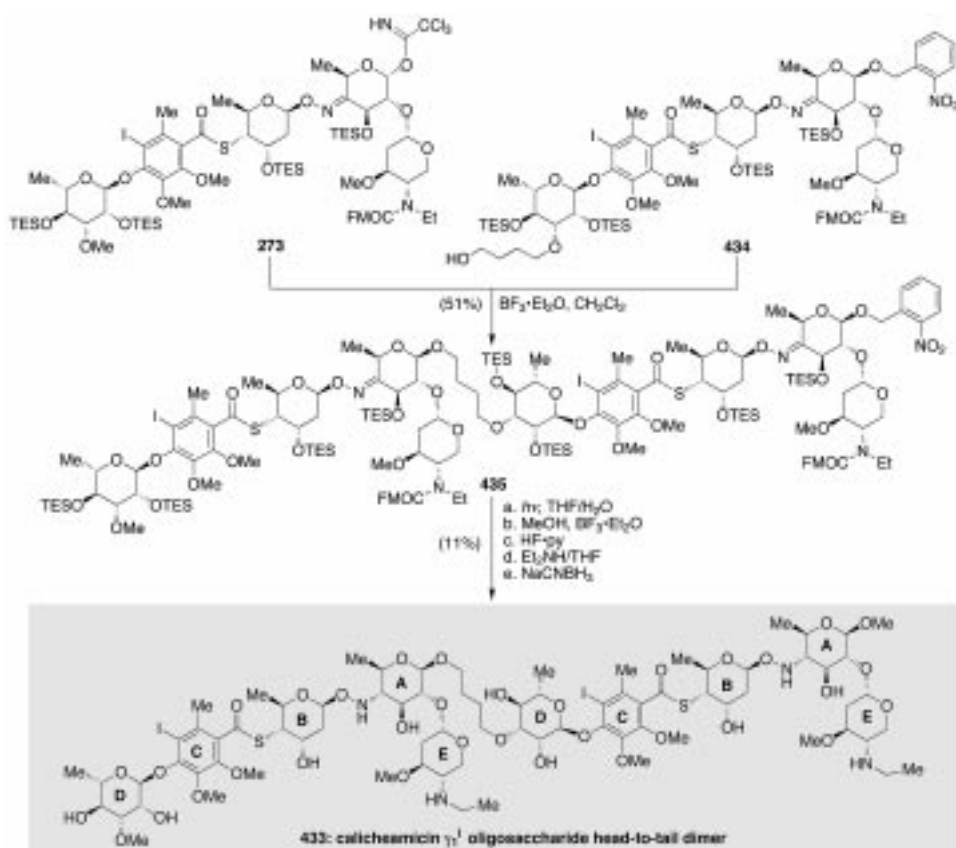
Scheme 62. Synthesis of calicheamicin–dynemicin hybrid **427** (1992).^[151, 152] (Only one diastereoisomer, of the four prepared, is shown.)

selectivity matched those of calicheamicin γ_1^I . This underscores the importance of precisely fitting the “molecular warhead” domain of the molecule within its receptor for optimal activity.

In another study within this area, and following NMR and computer modeling studies, both the head-to-head (Scheme 63) and the head-to-tail (Scheme 64) dimers (**430** and **433**, respectively) were designed and synthesized with the appropriate length tethers. For the synthesis of the head-to-head dimer **430** (Scheme 63), one equivalent of the oligosaccharide trichloroacetimidate **273** was reacted with diethylene glycol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to furnish the desired β -anomer, which was subsequently reacted with a second equivalent of the oligosaccharide trichloroacetimidate **273** under the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ conditions to afford the desired dimer **432**. Global deprotections, followed by reduction of the oxime with sodium cyanoborohydride in the presence of Lewis acid, led to the targeted, head-to-head dimer **430**. The head-to-tail dimer **433**, which has the potential of growth to higher homologues, was synthesized as shown in Scheme 64. Thus, compound **434** with the optimum size and point of attachment



Scheme 63. Synthesis of the calicheamicin γ_1^I oligosaccharide head-to-head dimer **430** (1995).^[153–158]



Scheme 64. Synthesis of calicheamicin γ_1^I oligosaccharide head-to-tail dimer **433** (1996).^[153–158]

of the tether, was constructed using standard chemistry and then glycosidated with trichloroacetimidate **273** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, to furnish dimer **435**. Further manipulations including photolytic cleavage of the anomeric nitrobenzyl ether, methyl glycoside formation, deprotection, and reduction of the oxime provided the targeted, head-to-tail dimer **433**.^[153, 154]

Both dimers **430** and **433** exhibited interesting DNA-interacting properties, by binding selectively to TCCT-rich sites with an affinity approximately 1000 times higher than the monomeric oligosaccharide. Figures 5 and 6 depict auto-

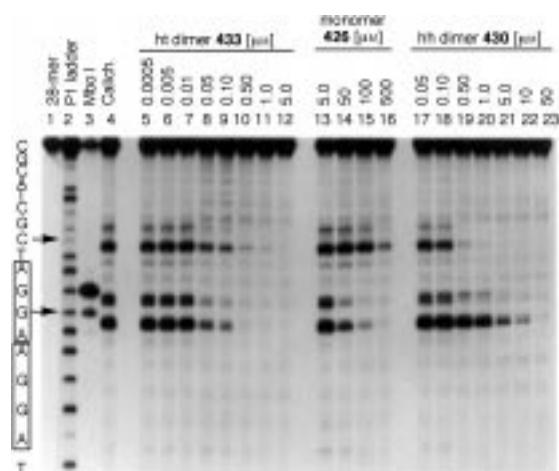


Figure 5. Autoradiogram of denaturing polyacrylamide gel showing products of calicheamicin-induced DNA cleavage of a $[5'\text{-}^{32}\text{P}]$ -labeled AGGAAGGA-containing DNA duplex in the presence of oligosaccharides **426a** (monomer), **430** (head-to-head dimer, hh dimer), or **433** (head-to-tail dimer, ht dimer). Lane 1: 28-mer. Lane 2: 28-mer ladder resulting from partial digestion with nuclease P1. Lane 3: marker lane containing the products of DNA digestion with *Mbo*I restriction enzyme. Lane 4: products of DNA cleavage with calicheamicin ($2.5 \mu\text{M}$). Lanes 5–23: products of DNA cleavage with calicheamicin ($2.5 \mu\text{M}$) in the presence of head-to-tail dimer **433** (lanes 5–12), monomer **426a** (lanes 13–16), and head-to-head dimer **430** (lanes 17–23). Reproduced with permission from ref. [154].

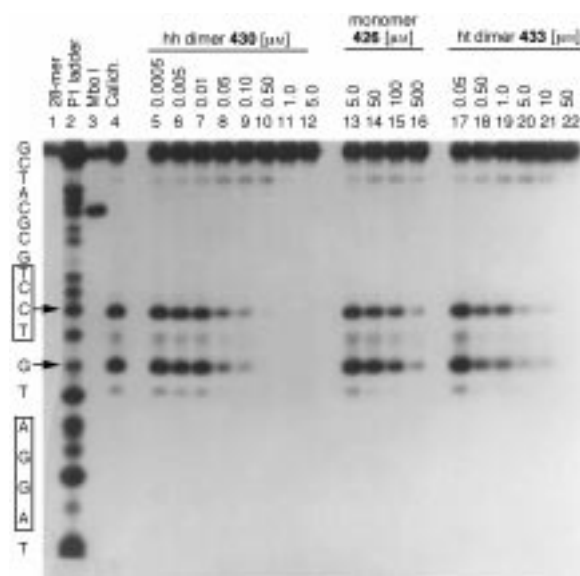


Figure 6. Autoradiogram of denaturing polyacrylamide gel showing products of calicheamicin-induced DNA cleavage of $[5'\text{-}^{32}\text{P}]$ -labeled CGTAGCCGTAGGATG–TCCTGCGCATGCG DNA duplex in the presence of oligosaccharides **426a** (monomer), **430** (head-to-head dimer, hh dimer), and **433** (head-to-tail dimer, ht dimer). Lane 1: 28-mer. Lane 2: 28-mer ladder resulting from partial digestion with nuclease P1. Lane 3: marker lane containing the products of DNA digestion with *Hha*I restriction enzyme. Lane 4: products of DNA cleavage with calicheamicin ($2.5 \mu\text{M}$). Lanes 5–22: products of DNA cleavage with calicheamicin ($2.5 \mu\text{M}$) in the presence of dimer **430** (lanes 5–12), monomer **426a** (lanes 13–16), and dimer **433** (lanes 17–22). Reproduced with permission from ref. [154].

radiodiagrams of the gels showing products of calicheamicin-induced DNA cleavage in the presence of the monomeric and dimeric synthetic calicheamicin oligosaccharides. Figure 7 illustrates the proposed mode of binding of monomeric and dimeric oligosaccharides to the minor groove of duplex DNA based on molecular modeling.^[153–158]

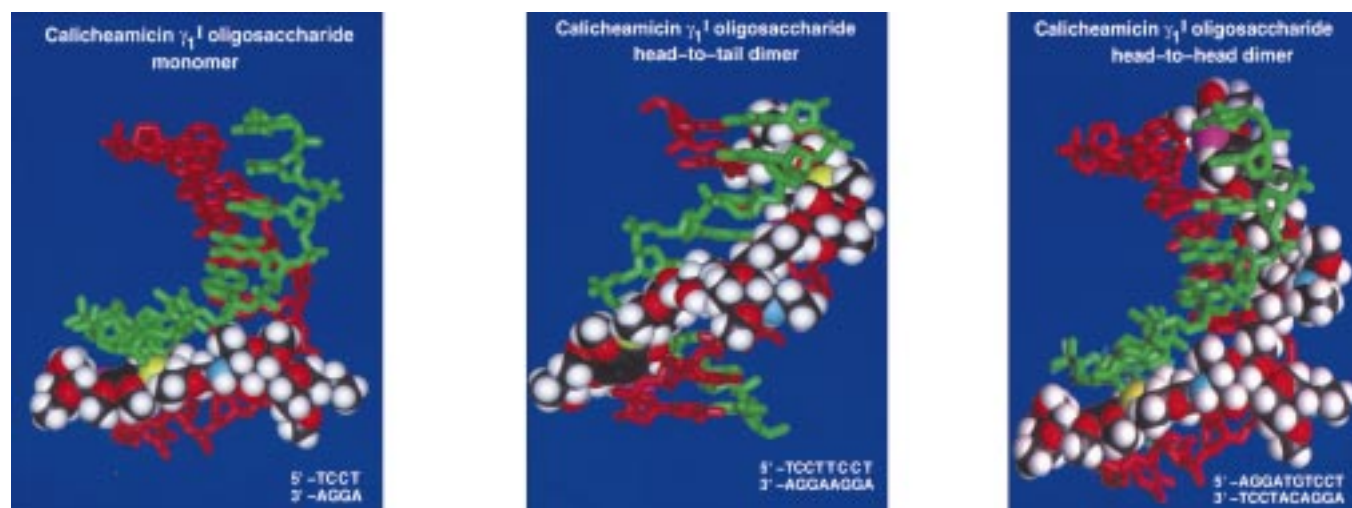
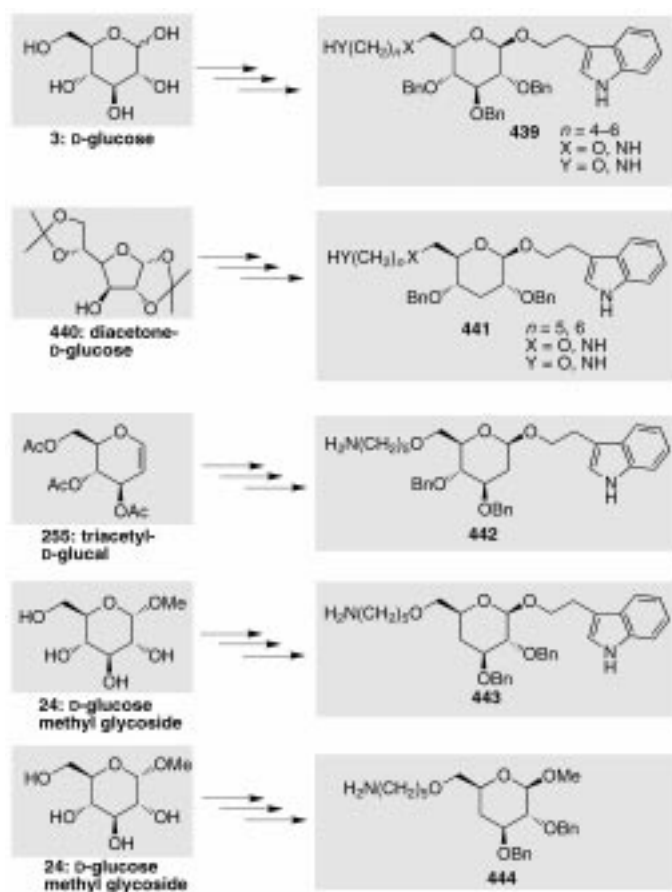


Figure 7. Computer-generated molecular models of oligosaccharide–DNA complexes. Left: monomer **426a** bound to 5'-TCCT–AGGA-3'. Center: head-to-tail dimer **433** bound to 5'-TCCTTCCT–AGGAAGGA-3'. Right: head-to-head dimer **430** bound to 5'-AGGATGTCCT–AGGACATCCT-3'. The DNA strands are displayed in green and red. Color code for the oligosaccharide atoms: C black, H white, O red, N blue, S yellow, I purple. Modeling studies and interactive docking were done on a SGI Indigo-2 workstation with Insight II (Biosym Technologies, Inc., San Diego, CA). Pictures were created using AVS (AVS Inc., Waltham, MA) and locally developed modules on a DEC Alpha 3000/500 computer with a Kubota Pacific Denali graphics card. Reproduced with permission from ref. [154].

5.2. Carbohydrate-Based Peptidomimetics

In 1988, and in collaboration with Hirschman and Smith at the University of Pennsylvania, we initiated a research program based on the concept of utilizing carbohydrate frameworks as templates for the design and synthesis of peptide mimetics.^[159, 160] This principle was originally demonstrated with the design, synthesis, and biological investigation of glucose-based somatostatin analogues (**439** and **441–444**, Scheme 65). Inspection of these structures and comparison



Scheme 65. Synthesis of carbohydrate-based peptidomimetics (1992, with Hirschmann and Smith).^[159, 160]

with those of somatostatin (**436**) and the previously synthesized cyclic hexapeptides **437** and MK-678 (**438**) reveal their resemblance to the parent compounds in that they retain critical amino acid side chains in the proper spatial orientation; yet they differ from them in that they are devoid of both the peptide backbone and the metabolically fragile amide bonds. Based on molecular modeling and NMR studies, the analogues shown in Scheme 65 and others like them were designed. Their chemical syntheses proceeded smoothly from the indicated starting materials by standard chemistry. Biological evaluation of the synthetic materials revealed μM binding affinities to the peptide hormone somatostatin receptor (SRIF) in a dose-dependent manner (see Table 11). This first report sparked several other related studies in which

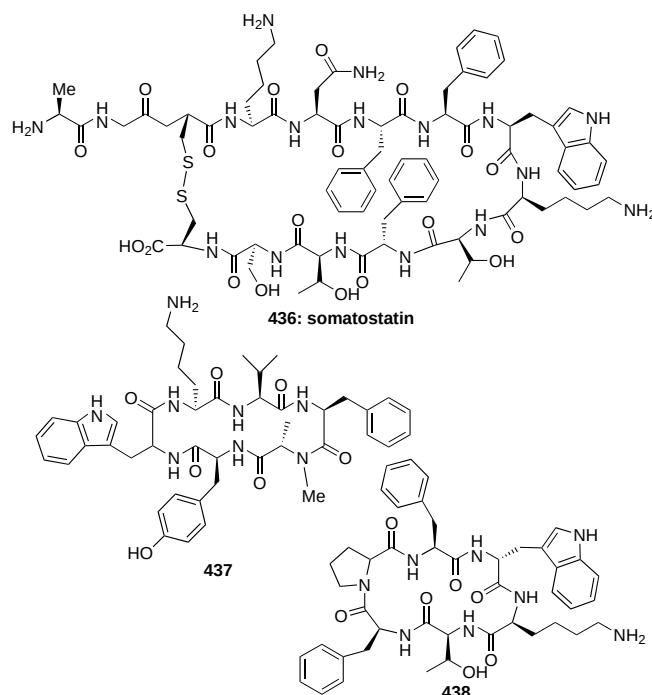


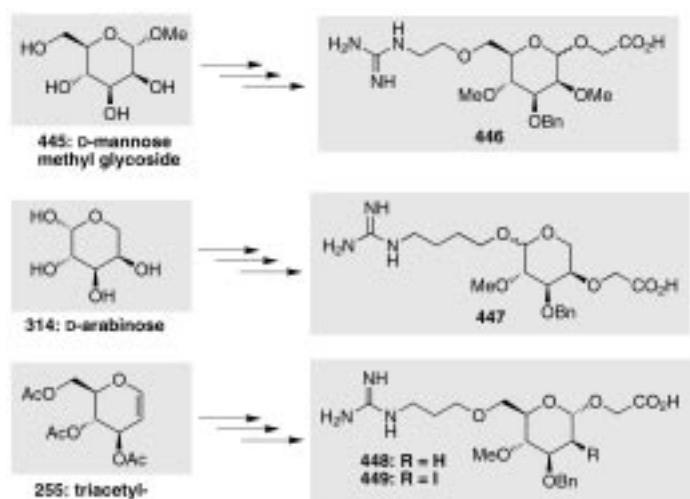
Table 11. In vitro SRIF binding affinities of selected peptides and peptidomimetics.^[159, 160]

Compound			IC ₅₀ ^[a] [μM]	
Peptide				
somatostatin (436)			0.00083	
437			NT	
MK-678 (438)			0.0023	
Sugar peptidomimetics			IC ₅₀ [μM]	
O-linked	N-linked	<i>n</i>	O-linked	N-linked
439 a	439 e	5	15.0	14.0
439 b	439 f	4	NT	NT
439 c	439 g	6	11.0	5.1
441 a	441 c	5	8.4	10.0
441 b	441 d	6	6.6	34.0
442		5	35.0	
443		5	47.0	

[a] ^{125}I -Tyr¹¹-SRIF; NT: Lower affinity than that of **439e** at a concentration of 2×10^{-5} M; dose response curve not obtained.

carbohydrate templates were utilized to construct peptide mimetics and other related molecules.^[161]

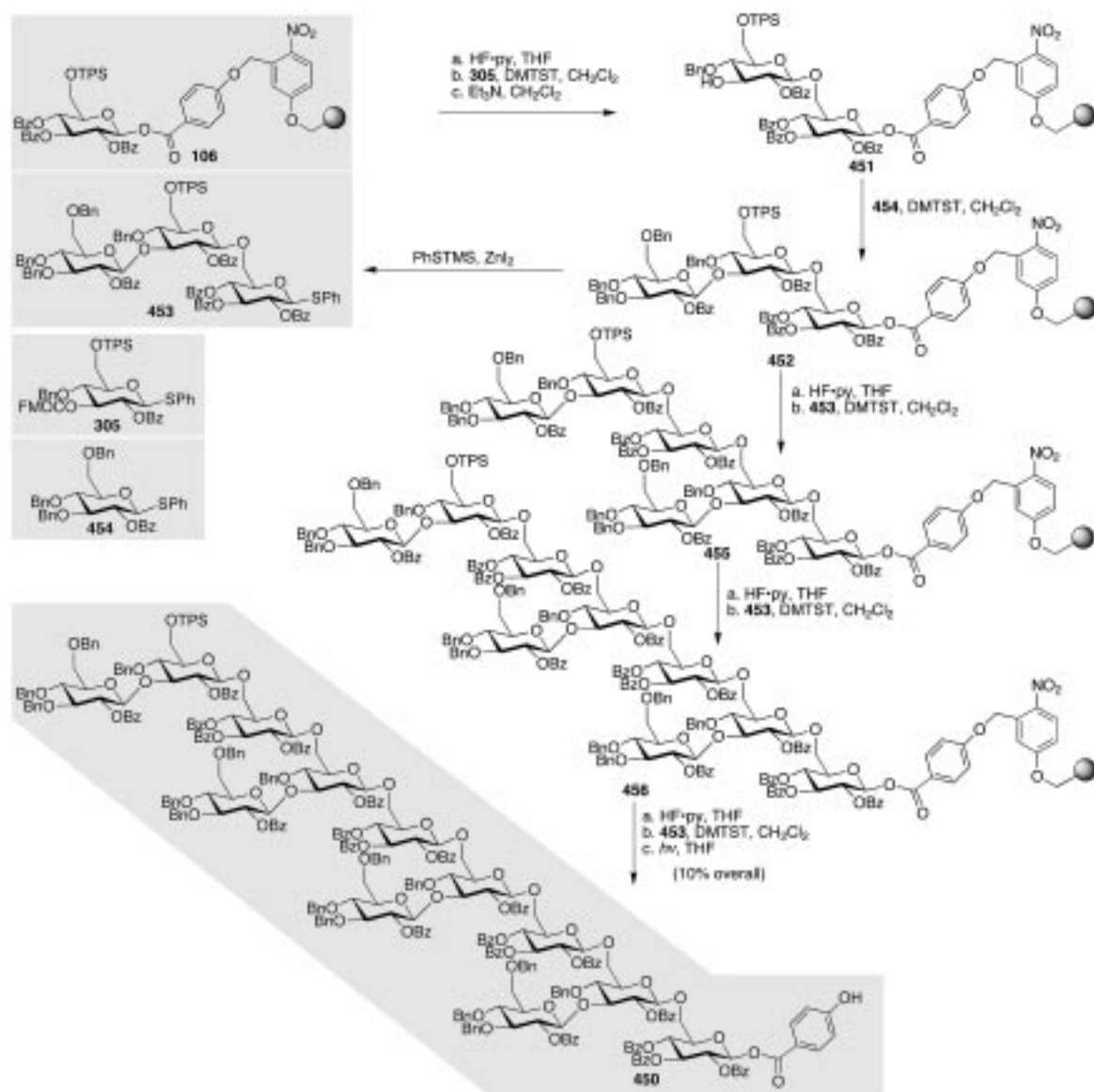
In a recent example from our laboratories at the Scripps Research Institute, a library of carbohydrate-based peptide mimetics of cRGDFV (a cyclic peptide which is a known antagonist of integrin $\alpha_v\beta_3$) was designed, synthesized, and screened in search of angiogenesis inhibitors.^[162] A number of these compounds **446–449**, together with summaries of their syntheses, are shown in Scheme 66. The compounds were prepared from D-mannose methylglycoside (**445**), D-arabinose (**314**), and triacetoxy-D-glucal (**255**). Preliminary biological data indicated that, unlike **439a** (Scheme 65 and Table 11), these compounds do not bind to integrin $\alpha_v\beta_3$. Compounds **446–449** were also tested in other cell adhesion assays against the integrin $\alpha_{IIb}\beta_3$, and compound **449** showed a weak inhibition of cell adhesion mediated by $\alpha_{IIb}\beta_3$ (IC_{50} value: $85 \mu\text{M}$).



Scheme 66. Synthesis of carbohydrate-based mimetics of cRGDTV (1997).^[162]

5.3. Large Oligosaccharides

In a rather daring venture, the modified photolabile linking strategy described above (Scheme 27) was applied to the synthesis of the branched dodecasaccharide **450** (Scheme 67), which represents one of the largest oligosaccharides to be synthesized on solid phase.^[88] Thus, resin-bound trisaccharide **452** was constructed from resin-bound monosaccharide **106** (Scheme 27) and monosaccharides **305** and **454**. This trisaccharide resin **452** was then cleaved releasing the subsequently used building block trisaccharide **453**. Following removal of the silyl group from resin **452**, treatment with **453** in the presence of DMTST furnished hexasaccharide-conjugate **455**. Reiteration of the process (desilylation and coupling with trisaccharide **453**) led to nonasaccharide **456** and the corresponding dodecasaccharide conjugates. Photolytic cleavage from the resin furnished the targeted dodecasaccharide **450**. The advantages of this method include high convergence, high yielding glycosidation steps, and maintenance of anomeric



Scheme 67. Solid-phase synthesis of model dodecasaccharide **450** (1998).^[88]

integrity during the loading and unloading steps, which make the method applicable to larger and more diverse carbohydrate systems as well as amenable to automation.

6. Summary and Outlook

The blend of carbohydrate chemistry described within this article has been a source of enormous satisfaction and reward for all of us involved in it. It would not have been possible without the pioneering works of those who dedicated their careers to this important field of chemistry and who gave us the framework and the tools to shape our own research, which was primarily directed at the chemical synthesis and chemical biology of natural and designed molecules. If in the process of borrowing chemistry from the carbohydrate chemists, we have contributed some novelty back to the field, we feel fortunate and blessed. It is our hope that, through this review, the reader will benefit by realizing the awesome power of carbohydrate chemistry in providing enabling technologies for delivering highly complex molecules and facilitating chemical biology and drug discovery endeavors.

Despite the great strides, however, there still remain gaps in our ability to fully control the stereochemistry of the glycosidation process, as well as to make it, in general, as efficient as its peptide and phosphate bond forming counterparts. Solutions for such gaps are needed before we can truly enjoy the widespread and rapid construction of any given oligosaccharide at will, either by solution- or solid-phase methods. Automation will then become routine and will further facilitate both chemical and biological investigations. Indeed, as the human genome is fully deciphered, it will be up to such major breakthroughs in chemistry, with combinatorial synthesis of small organic molecule libraries, to confront the drug discovery process through identification, validation, and modulation of disease relevant targets.

Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azobisisobutyronitrile
alloc	allyloxycarbonyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluoride
Bz	benzoyl
CA	chloroacetyl
CAN	cerium ammonium nitrate
Cbz	benzyloxycarbonyl
CMPI	<i>N</i> -methyl-2-chloropyridinium iodide
col	2,4,6-trimethylpyridine (collidine)
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DHP	3,4-dihydro-2 <i>H</i> -pyran
DIAD	diisopropylazodicarboxylate
DIBAL	diisobutylaluminumhydride
DIPT	diisopropyl tartrate
4-DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DMTST	(dimethylthio)methylsulfonium trifluoromethanesulfonate
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
DTBMS	di- <i>tert</i> -butylmethylsilyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EVE-Li	2-lithio-ethylvinylether
Fmoc	9-fluorenylmethoxycarbonyl
FMPTS	2-fluoro-1-methyl pyridinium tosylate
HMDS	bis(trimethylsilyl)amide
HOAt	7-aza-1-hydroxy-1 <i>H</i> -benzotriazole
HOBt	1-hydroxybenzotriazole
IBX	<i>o</i> -iodoxybenzoic acid
IDCP	iodobis(collidine) perchlorate
im	imidazolyl
imid	imidazole
KSAE	Katsuki–Sharpless asymmetric epoxidation
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lut	2,6-dimethylpyridine (lutidine)
<i>m</i> CPBA	3-chloroperoxybenzoic acid
MOM	methoxymethyl
MOP	3-methoxypyridyloxy
MP	4-methoxyphenyl
Ms	methanesulfonyl
NB	nitrobenzyl
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMO	4-methylmorpholine- <i>N</i> -oxide
PBS	phosphate-buffered saline
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
Phth	phthaloyl
Piv	pivaloyl
PMA	phorbol 12-myristate 13-acetate
PMB	<i>p</i> -methoxybenzyl
PPTS	pyridinium 4-toluenesulfonate
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
SAE	Sharpless asymmetric epoxidation
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammoniumperruthenate
TPS	triphenylsilyl
Tr	triphenylmethyl (trityl)
Ts	4-toluenesulfonyl (tosyl)
UDP	uridine-5'-diphosphate

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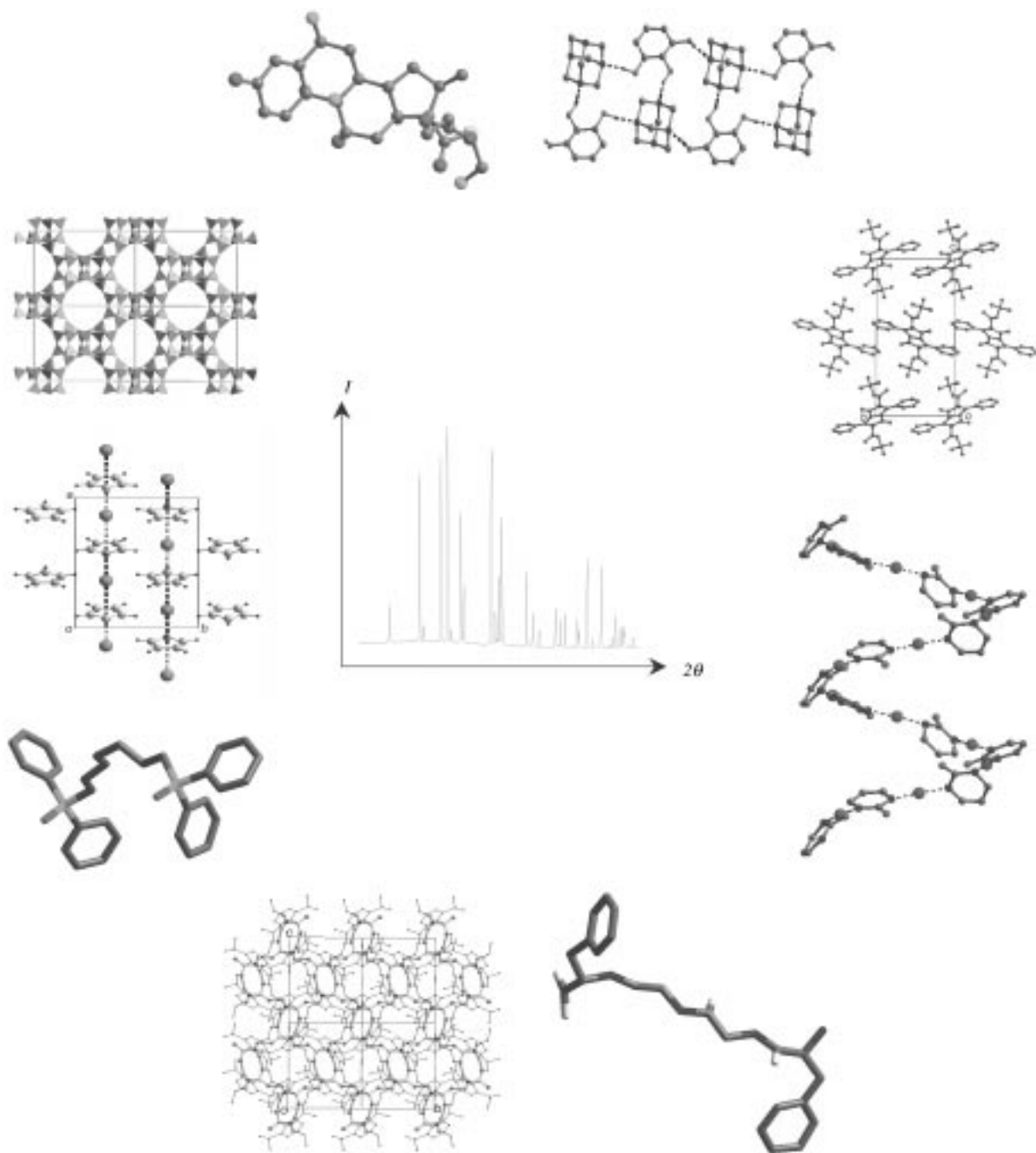
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X-Ray Powder Diffraction



Contemporary Advances in the Use of Powder X-Ray Diffraction for Structure Determination

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Many crystalline solids cannot be prepared in the form of single crystals of sufficient size and/or quality for investigation using single-crystal X-ray diffraction techniques, and the opportunity to carry out structure determination using powder diffraction data is therefore essential to understand the structural properties of such materials. Although the refinement stage of the structure determination process can be carried out fairly routinely from pow-

der diffraction data using the Rietveld profile refinement technique, solving crystal structures directly from powder data is associated with several intrinsic difficulties. Nevertheless, substantial progress has been made in recent years in the scope and potential of techniques in this field. This article aims to highlight the types of structural problems for which structure determination may now be tackled directly from powder diffraction data, and contem-

porary applications across several chemical disciplines are presented. A brief survey of the underlying methodologies is given, with some emphasis on recently developed techniques for carrying out the structure-solution stage of the structure-determination process.

Keywords: powder X-ray diffraction • X-ray diffraction • structure elucidation

1. Introduction

Single-crystal X-ray diffraction is undoubtedly the most important and powerful technique for elucidation of crystal and molecular structures, and many of the most important scientific advances in the 20th Century emanated from the use of this technique. There is every reason to forecast that the central importance of this technique, both in the physical and biological sciences, will be sustained throughout the 21st Century, particularly by exploiting new opportunities created by advanced synchrotron radiation sources. In emphasizing the power of single-crystal diffraction methods, however, it is important not to overlook the intrinsic requirement that a single crystal of appropriate size and quality must be available for the compound of interest. Clearly this requirement imposes a natural limitation on the types of materials and systems that may be studied. How then do we proceed towards the structural characterization of crystalline solids that do not give single crystals of appropriate size and quality? In this case, powder X-ray diffraction can provide the way forward. Although the lower limits in terms of the size and quality of crystals for which study by single-crystal X-ray

diffraction is feasible are continually being extended by developments in instrumentation (e.g. so-called “microcrystal” diffraction facilities) and software for data analysis (e.g. for twinned crystals), there remains a substantial subset of crystalline materials which give rise to good quality powder diffraction data but are not amenable to investigation by single-crystal diffraction techniques. The opportunity to establish a detailed structural understanding of such materials clearly relies on the availability of methods for structure determination from powder diffraction data. Fortunately, the last decades of the 20th Century have seen considerable progress in the scope and potential of techniques in this field, and there is every reason to be confident that this progress will continue in the foreseeable future.

The aim of this article is to highlight, for a general chemical audience, some of the areas in which progress has been made in recent years in the development and application of procedures for structure determination by using powder X-ray diffraction data. The main emphasis is on highlighting, through examples (see Section 3), the types of problems that have been tackled successfully to date, with particular emphasis on those problems that have been made tractable by advances in methodology in the last three or four years. As the literature up to about 1996 has been reviewed in detail elsewhere,^[1] this article does not aim to provide a comprehensive coverage of all research in the field up to the present time. Instead, we aim to give a contemporary snapshot of the types of structural problems that are within the scope of

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present methodologies for structure determination from powder diffraction data, placing emphasis on applications involving complete structure determination from powder diffraction data (i.e. examples in which indexing, structure solution, and structure refinement have been carried out directly using the powder diffraction data). We focus in particular on the (generally) more challenging structure-solution stage of the structure-determination process, rather than on structure refinement, although clearly both structure solution and refinement are important components of the complete structure-determination process. However, we note that many important applications of Rietveld refinement from powder diffraction data have made use of known structures (related to the structure of interest), or information from other experimental or computational techniques, to derive an initial structural model for refinement. Such examples do not involve structure solution directly from the powder diffraction data, and are considered to lie outside the province of this article. Section 2 provides a brief overview of techniques used in different stages in the structure-determination process, again with emphasis on contemporary advances in techniques for structure solution, and Section 5 gives a more detailed

discussion of these techniques and the procedures for their application. Section 4 discusses some comparisons and contrasts between the use of single-crystal diffraction data and powder diffraction data in structure determination.

The examples highlighted in this article are confined entirely to the use of powder X-ray diffraction data, although we note that, in general, many of the principles and techniques covered here are equally applicable to the case of neutron powder diffraction data. The intrinsic complementarity of X-ray diffraction and neutron diffraction is discussed elsewhere.^[1, 2]

2. Overview of Methods and Strategy

2.1. General Aspects

In the diffraction pattern from a crystalline solid (either for single crystal or powder samples), the positions of the diffraction maxima depend on the periodicity of the structure (i.e. the dimensions of the unit cell), whereas the relative intensities of the diffraction maxima depend on the distribu-

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tion of scattering matter (i.e. the atoms, ions, or molecules) within the repeating unit. Crystal structure determination from diffraction data can be divided into three stages: 1) unit-cell determination (“indexing”) and symmetry determination (space-group assignment), 2) structure solution, and 3) structure refinement. Determination of the unit cell requires consideration of the peak positions, whereas space-group assignment, structure solution, and structure refinement also require consideration of the relative intensities of diffraction maxima.

In *structure solution*, the aim is to derive an approximate description of the crystal structure, starting from no knowledge of the actual arrangement of atoms, ions, or molecules in the unit cell. If the approximate structure solution is a sufficiently good representation of the true structure, a good quality structure may then be obtained by refinement of this structural model against the experimental diffraction data in the *structure refinement* stage. For powder diffraction data, refinement of crystal structures can be carried out fairly routinely using the Rietveld profile refinement technique.^[3, 4] In general, however, structure solution from powder diffraction data is a significantly greater challenge than structure refinement. A schematic overview of the different stages of structure determination from powder diffraction data is shown in Figure 1.

Although single-crystal and powder diffraction patterns contain the same intrinsic information, in the former this information is distributed in three-dimensional space whereas in the latter the three-dimensional diffraction data are “compressed” into one dimension, which generally leads to considerable overlap of peaks in the powder diffraction pattern.^[5] Such peak overlap obscures information on the intensities of individual diffraction maxima, and constitutes the main reason for difficulties in solving crystal structures directly from powder diffraction data. In this Section, we provide an overview of the techniques that are currently available for structure solution from powder diffraction data. These techniques can be subdivided into two categories: “traditional” and “direct-space” approaches.

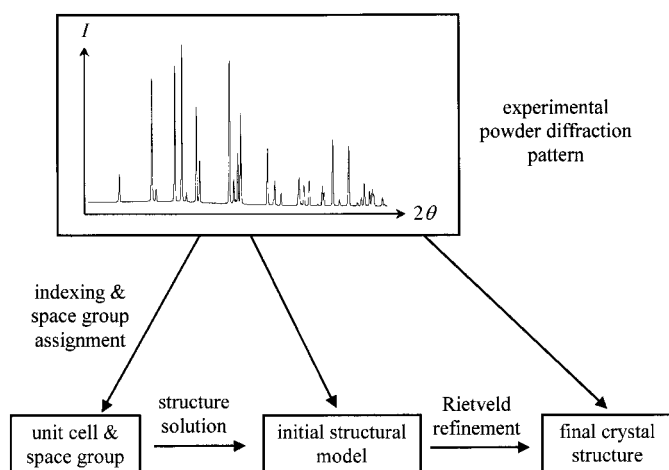


Figure 1. Schematic diagram to illustrate the different stages involved in complete structure determination from powder diffraction data (note that in some cases the situation may be more complex than implied by this diagram).

2.2. Traditional Approaches for Structure Solution

In the *traditional approach* for solving crystal structures from powder diffraction data,^[1, 6–13] the aim is to extract the intensities $I(hkl)$ of individual reflections directly from the powder diffraction pattern, and then to use these $I(hkl)$ data in the types of structure solution calculation that have been developed for single-crystal diffraction data. These techniques include direct methods and Patterson methods.^[14, 15] However, as a consequence of the peak-overlap problem discussed above,^[5] it is often difficult to extract unambiguous values of the intensities $I(hkl)$ of the individual diffraction maxima. Unreliable values of the extracted intensities $I(hkl)$ can lead to severe difficulties in subsequent attempts to solve the structure using such “single-crystal-like” techniques. To overcome this problem requires either improved techniques for extracting and utilizing peak intensities or alternative structure-solution strategies that allow the experimental powder diffraction profile to be used directly “as measured” without requiring individual intensities $I(hkl)$ to be extracted. Several important developments in the techniques for extracting and utilizing peak intensities have been reported.^[16–25] With regard to details of the traditional techniques for structure solution and their implementation, ref. [1] gives a comprehensive survey of the literature in this field up to 1996, with refs. [12, 13] extending this discussion into subsequent years. Nevertheless, we highlight the following papers which provide details of some of the main programs used in this field: SIRPOW (together with EXTRA in the package EXPO),^[26] SIMPEL,^[27] XLENS,^[28] and ROTSEARCH.^[29, 30]

Herein, we focus our discussions of methodology on alternative structure-solution strategies developed in recent years.

2.3. Direct-Space Approaches for Structure Solution

In the *direct-space approach*^[1, 31, 32] for solving crystal structures from powder diffraction data, trial crystal structures are generated in direct space (independently of the experimental powder diffraction data). The suitability of each trial structure is assessed by direct comparison between the powder diffraction pattern calculated for the trial structure and the experimental powder diffraction pattern. The comparison between the experimental and calculated powder diffraction patterns is quantified using an appropriate figure-of-merit. To date, the majority of direct-space approaches have used the weighted profile R factor R_{wp} (for example, see refs. [33–36]) which is the R factor normally used in Rietveld refinement.^[3, 4] As R_{wp} considers the entire digitized powder diffraction profile, rather than the integrated intensities of individual diffraction maxima, peak overlap is implicitly taken into account—the digitized powder diffraction data are used directly “as measured”, without further manipulation. The use of R_{wp} to assess the correctness of a structural model clearly requires that the peak-shape and peak-width parameters used to construct the calculated powder diffraction pattern are consistent with those that define the experimental powder diffraction pattern. In practice, this can be readily established

by prior analysis of the peak shapes and peak widths in the experimental powder diffraction pattern (see Section 5.2.2). Other definitions of figure-of-merit such as full profile χ^2 ^[37] or those based on extracted peak intensities^[38] have also been used to assess the agreement between calculated and experimental powder diffraction data within the context of direct-space solution strategies.

The direct-space strategy for structure solution aims to find the trial crystal structure that has the lowest possible R factor, and the approach is equivalent to exploring a hypersurface $R(\Gamma)$ (Figure 2) to find the global minimum on the hypersurface. Here Γ represents the set of variables that defines the

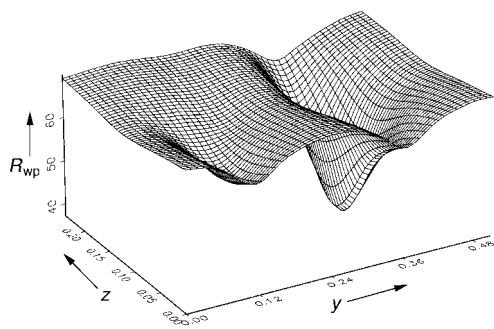


Figure 2. A two-dimensional section through the R_{wp} hypersurface for lithium zirconate ($\text{Li}_6\text{Zr}_2\text{O}_7$). The structural model used to calculate R_{wp} comprised only the zirconium atom (the dominant X-ray scatterer), and thus the structure is specified by three variables—the position (x, y, z) of the zirconium atom. The two-dimensional section $R_{wp}(y, z)$ shown was obtained by fixing the x -coordinate of the zirconium atom at the value in the known structure of lithium zirconate. The deep minimum in R_{wp} corresponds to the correct structure solution, but the plot clearly shows the existence of other significant local minima.

structure, as described in more detail below. In principle, any technique for global optimization may be used to locate the lowest point on the $R(\Gamma)$ hypersurface, and success has been achieved using Monte Carlo,^[33, 39, 40] simulated annealing,^[34–38, 41] grid search,^[42–45] and genetic algorithm^[46–49] search methods as the basis of direct-space techniques for powder structure solution. Note that the references cited for each technique are intended to be illustrative rather than exhaustive—more citations for each technique are given in Sections 3 and 5.

As we focus here on structure solution, we assume that the unit cell dimensions ($a, b, c, \alpha, \beta, \gamma$) and space group are already known from prior analysis of the experimental powder diffraction pattern (see also Section 5.1). We also assume that the contents of the unit cell (for example, the types and number of atoms, ions, or molecules) are known, at least to a sufficiently good approximation, but that the positions and structural arrangement of these constituents within the unit cell are not known. In direct-space techniques, the structure is defined in terms of a “structural fragment” comprising an appropriate collection of atoms within the asymmetric unit, and is defined by a set (denoted Γ) of variables representing the location of the structural fragment within the unit cell. For a collection of independent atoms, the set Γ would comprise the fractional coordinates (x, y, z) for each of these atoms. However, when the structural fragment

comprises a molecule of known constitution, it is greatly advantageous to specify the structural fragment in terms of the position and orientation of the molecule as a whole, together with any variables describing unknown aspects of the intramolecular geometry (such as torsion angles), rather than in terms of the fractional coordinates (x, y, z) of each individual atom. Thus, for a molecular fragment, the position may be defined by the fractional coordinates (x, y, z) of the center-of-mass or a predefined pivot atom, the orientation may be defined by rotation angles (θ, ϕ, ψ) around a set of orthogonal axes, and the intramolecular geometry may be specified by a set of n variable torsion angles $\{\tau_1, \tau_2, \dots, \tau_n\}$. These concepts may be extended to the case of two or more (identical or nonidentical) molecular fragments within the asymmetric unit.

In general, the bond lengths, bond angles, and any known torsion angles (i.e. if the molecular conformation, or aspects of it, are known already) are fixed, and may be taken either from standard values for the type of molecule under study or from the known geometry of a similar molecule (in almost all cases, it is unnecessary to consider bond lengths and bond angles as variables at the structure solution stage). Ideally, the structural fragment should include all atoms with significant scattering power (i.e. all non-hydrogen atoms in the case of powder X-ray diffraction) within the asymmetric unit, but it may sometimes be advantageous to omit certain atoms to restrict the number of variables to be optimized (the omitted atoms may be found later by difference Fourier techniques^[1]). Clearly the choice of structural fragment in any given structure solution problem is not unique, although certain choices of structural fragment may have significant advantages over others.

2.4. Comparison of Traditional and Direct-Space Approaches

While any comparison of contrasting methodologies must be carried out only with extreme caution, it is nevertheless relevant to make some remarks on the differences between the traditional and direct-space approaches for structure solution from powder diffraction data. The fundamental differences between traditional and direct-space approaches have been outlined above, and here we discuss some practical implications of these differences.

First, we consider aspects of the experimental powder diffraction data itself. As traditional techniques require the intensities of individual reflections extracted directly from the experimental powder diffraction pattern, the reliability of these techniques should be enhanced considerably by using data of higher resolution, as the extent of peak overlap is reduced accordingly. Thus, powder X-ray diffraction data recorded using a synchrotron radiation source^[50, 51] should generally be advantageous over data recorded on a conventional laboratory diffractometer (provided there is no severe sample-limited broadening associated with the material under investigation). On the other hand, for direct-space techniques which use a figure-of-merit based on a profile R factor, the important requirement is not high resolution per se, but rather

that the peak profiles are well-defined and accurately described by the peak-shape and peak-width functions used in the structure-solution calculation (as discussed in more detail in Section 5.2). Thus, for direct-space techniques, synchrotron data do not necessarily have intrinsic advantages over laboratory data, particularly if the peak broadening in the synchrotron data is sample-limited rather than instrument-limited.

Second, for structure solution by traditional techniques (as for single-crystal diffraction data), the complexity of the problem generally depends on the number of atoms to be located in the asymmetric unit, whereas for structure solution by direct-space techniques, the main limiting factor is the dimensionality of the hypersurface to be explored (i.e. the number of variables in the set Γ). Thus, the complexity of a direct-space search procedure (and in general the computational time required to achieve successful structure solution) depends more directly on the number of degrees of freedom in the optimization rather than the number of atoms in the asymmetric unit. As an illustration, direct-space structure solution for a molecule that is large but essentially rigid would generally be more straightforward than structure solution for a molecule that is small but completely flexible (with several torsional degrees of freedom). The greatest challenge in the application of direct-space techniques arises when the number of degrees of freedom required to define the structural fragment is large, and arises either when there is considerable molecular flexibility (i.e. the structural fragment is defined by a significant number of variable torsion angles) and/or when there is more than one independent molecule in the asymmetric unit. Nevertheless, as discussed in Section 3, advances have been made in solving crystal structures that present challenges in each of these categories.

Third, direct-space techniques may be particularly advantageous when the structure contains structural units of well-defined (known) geometry, and for this reason direct-space techniques have found particularly wide application in the case of molecular solids. Similarly, extended framework structures constructed from well-defined building units are also directly amenable to the advantages of direct-space strategies. Traditional techniques, on the other hand, generally do not involve *input* of prior structural knowledge (with some important exceptions, such as fragment based Patterson search techniques^[29, 52]), although such knowledge is clearly crucial for the subsequent interpretation of electron-density and Patterson maps. Thus, for problems in which sufficient structural information is already available, there may be certain intrinsic advantages in the use of direct-space techniques, in the sense that prior structural knowledge is used actively *during* the structure solution calculations. Self-evidently, the use of prior structural knowledge in this way is advantageous only if it is confidently known to provide a reliable description of the particular system under investigation.

Fourth, the global-optimization search algorithms embodied within the direct-space techniques for structure solution require, in general, more time to run than typical calculations employing traditional methods for structure solution. However, traditional methods are often less “robust” in the sense

that they may often not lead to a satisfactory result, and further computational effort will not, in general, enhance the prospects of successful structure solution further. Furthermore, structure solutions obtained from traditional methods are often incomplete, and may require substantial time to complete the structure (for example using difference Fourier techniques) before final structure refinement can be carried out. As most direct-space approaches (Monte Carlo, simulated annealing, and genetic algorithm methods) are stochastic in nature, it is strongly recommended to run the structure solution calculation several times from different random starting structures—clearly, obtaining the same structure solution from these independent calculations provides strong support that the true global optimum (i.e. the correct structure solution) has been found.

Another important feature of direct-space approaches is that they are based on similar principles to the applications of global-optimization techniques in energy simulations. Thus, as the energy hypersurfaces $E(\Gamma)$ used in energy-based structure prediction calculations and R factor hypersurfaces $R(\Gamma)$ used in direct-space techniques for structure solution are based on the same parameter space Γ , there are direct opportunities to define hybrid hypersurfaces $G(\Gamma)$ which blend $E(\Gamma)$ and $R(\Gamma)$ together in an appropriate functional form. If the hybrid function $G(\Gamma)$ is defined appropriately, the use of the $G(\Gamma)$ hypersurface in structure solution may have significant advantages over the $R(\Gamma)$ hypersurface. Recently, a strategy has been proposed^[53] for combining R factor and energy within the context of a direct-space strategy for structure solution from powder diffraction data, in which the hybrid figure-of-merit uses energy information to guide the calculation towards regions of parameter space corresponding to plausible structures, and the R factor is then used (under the control of a sliding weighting function) as the main criterion for comparing different energetically plausible structures.

3. Examples of Structure Determination from Powder Diffraction Data

As discussed in Section 1, many crystalline materials cannot be prepared as crystals of sufficient size and/or quality for single-crystal diffraction studies. Indeed, for many materials of industrial importance, it is actually advantageous to prepare and apply the material in microcrystalline form, for example to increase surface area (e.g. catalysts), to increase dispersibility (e.g. pigments) or to give optimal solubility properties (e.g. pharmaceuticals). Furthermore, most synthetic chemists will be familiar with situations in which, after submitting crystals to the departmental crystallographer, they are told that the crystals are too small, twinned, or simply not good enough to proceed with structure determination. In all these cases, progress towards understanding the structural properties of the materials of interest can be made by exploiting powder diffraction.

Although the majority of the crystal structures that have been determined to date from powder diffraction data are inorganic or framework materials, considerable advances in instrumentation and software for data analysis in recent years

have brought about a rapid evolution in the scope and potential of carrying out structure determination from powder diffraction data for all types of crystalline materials, including molecular solids. As a consequence, the structural properties of materials from many more areas of chemical and materials sciences have now been determined successfully from powder diffraction data.

There are no specific types of materials that can or cannot be studied by powder diffraction, although the optimal technique to be used for structure solution may vary from one class of material to another. The suitability of a material for structure determination depends more on the quality of the powder diffraction data that can be obtained and to some extent the nature of the asymmetric unit (e.g. the number and type of atoms, and how much information is already known about the atomic arrangement (e.g. molecular geometry)). However, for successful structure determination, it is highly desirable (although not essential in certain cases, as shown in Section 3.4) that a monophasic powder sample of good crystallinity should be available for the material of interest.

This section highlights some of the structures that have been determined and structural problems that have been tackled from powder diffraction data in recent years, with examples taken from a range of fields and chosen to illustrate the current scope and expanding potential of powder diffraction in structure determination. New techniques devel-

oped for powder structure solution in recent years (particularly direct-space techniques) have made greatest impact in the area of molecular crystallography, and we focus on examples from this field. The increasing number and complexity of organic materials for which complete structure determination has been carried out from powder X-ray diffraction data is illustrated in Figure 3.

3.1. Studies of Intermolecular Interactions and Crystal Engineering

In crystal engineering, the primary interest centers on understanding the intermolecular aggregation (e.g. hydrogen bonding schemes) in crystals, and subsequently exploiting this understanding in the design of materials with specific desired structures. Although methods are available for the prediction of hydrogen-bonding patterns in specific systems, a detailed description of the hydrogen-bonding pattern in a given system must, in general, be derived from analysis of experimental data. Materials of interest in this field are ideal for direct-space structure solution techniques, particularly when the structures consist of molecular building blocks of well-defined geometry and the main objective is to determine the relative organization of these building blocks within the crystal structure.

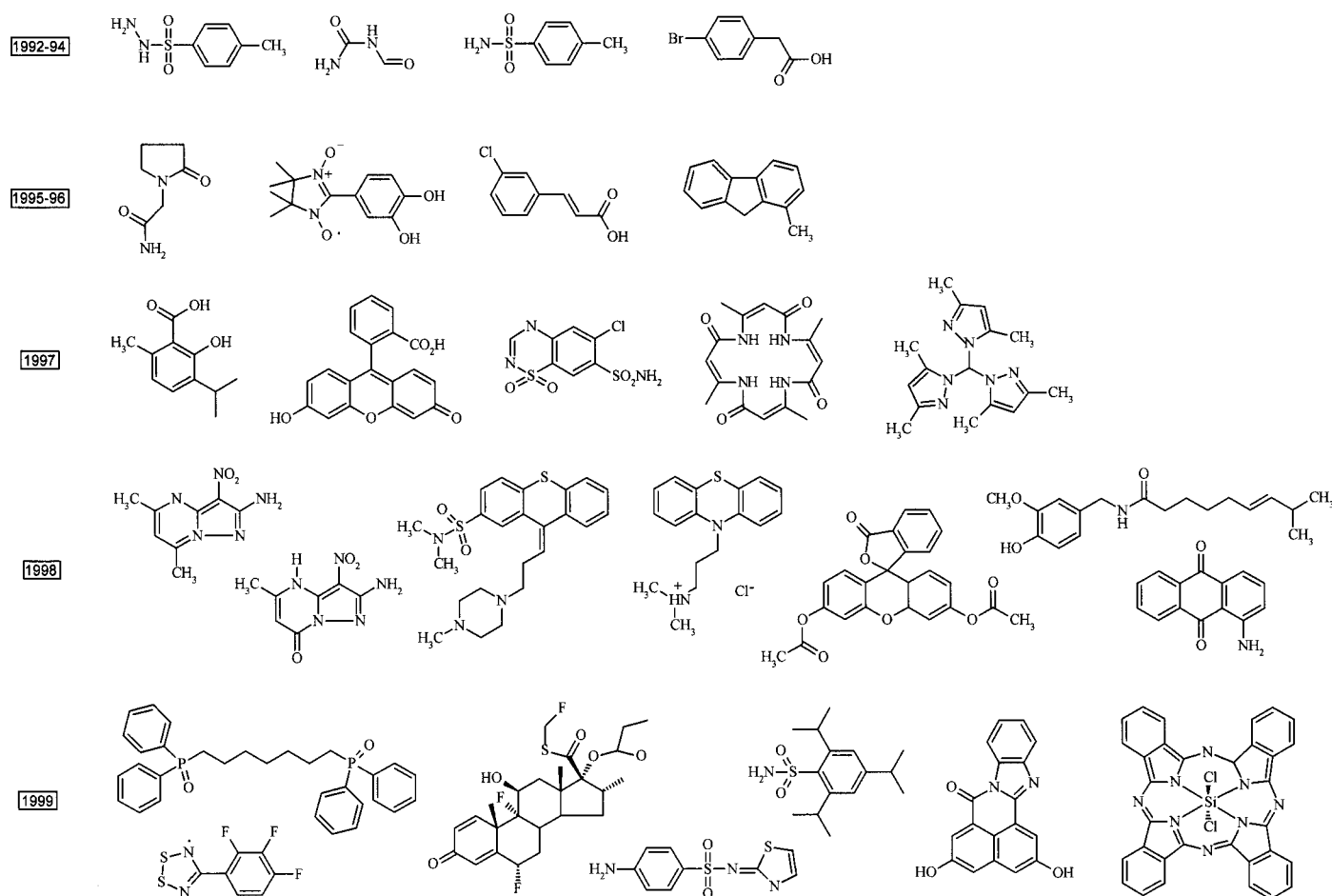


Figure 3. Examples of some of the previously unknown molecular crystal structures for which complete structure determination from powder diffraction data has been carried out in recent years (note that the set of structures shown is representative rather than exhaustive).

Here we highlight the recent structure determination of 2,4,6-triisopropylbenzene sulfonamide ($((\text{CH}_3)_2\text{CH})_3\text{-C}_6\text{H}_2\text{SO}_2\text{NH}_2$)^[54] from powder diffraction data. Crystal-structure solution of this material was initially attempted during a study in which the structures of three related sulfonylamino compounds (4-toluenesulfonamide, benzenesulfonylhydrazide, and 4-toluenesulfonylhydrazide) were solved from powder diffraction data by traditional techniques, and their hydrogen-bonding patterns rationalized.^[55] Although the original powder X-ray diffraction data recorded for 2,4,6-triisopropylbenzene sulfonamide at ambient temperature on a laboratory powder X-ray diffractometer were successfully indexed, attempts to solve the structure by traditional techniques were unsuccessful. In the recent study, synchrotron X-ray powder diffraction data were recorded at low temperature, and a relatively straightforward direct-space (Monte Carlo) structure solution calculation was carried out. The structural fragment used in the Monte Carlo calculation comprised the complete molecule (excluding the hydrogen atoms of the methyl groups), with the nitrogen atom entered as an oxygen atom and considered equivalent to the other oxygen atoms in the sulfonylamino group (as no significant discrimination between these atoms would be expected at the structure solution stage). Intramolecular flexibility was introduced in the form of rotation of the isopropyl and sulfonylamino groups relative to the aryl ring (see Figure 4a). Thus, with the molecule also subjected to translation and rotation within the unit cell, each structure considered in the structure solution calculation was defined by ten variables $\{x, y, z, \theta, \phi, \psi, \tau_1, \tau_2, \tau_3, \tau_4\}$. At the structure refinement stage, the nitrogen and oxygen atoms in the sulfonylamino group were readily identified. In the crystal structure, the molecular conformation is found to have the C–H bond of each isopropyl group lying approximately parallel to the plane of the aryl ring, as commonly found in other structures of this type. Elucidation of the crystal structure of this material enables rationalization of the hydrogen-bonding pattern (Figure 4b), which comprises two motifs commonly observed in sulfonamides but not normally occurring together in a given structure. The propagation of these two hydrogen-bonding motifs generates a continuous two-dimensional sheet in which 8-membered and 20-membered rings alternate in a checker-board pattern.

X-ray powder diffraction has also been used in the structure determination and structural investigation of a hydrogen-bonded molecular solid formed by the 2-(3,4-dihydroxyphenyl)-nitronyl nitroxide radical (see Figure 3—second molecule listed under 1995–96), which is of interest with regard to its magnetic properties.^[56] This structure was also solved by an approach that utilizes knowledge of molecular geometry, but based on a full-symmetry Patterson fragment search^[29] rather than operating in direct space. The structure was completed using a rigid-body Rietveld refinement and subsequent rationalization confirmed that the molecular aggregation in this material is directed by hydrogen bonding.

The structure determination of $\text{Ph}_2\text{P}(\text{O})(\text{CH}_2)_7\text{P}(\text{O})\text{Ph}_2$,^[57] which is described in detail in Section 3.3, was also part of a wider crystal-engineering study^[58] of materials in the family $\text{Ph}_2\text{P}(\text{O})(\text{CH}_2)_n\text{P}(\text{O})\text{Ph}_2$. The structure solution of the unsol-

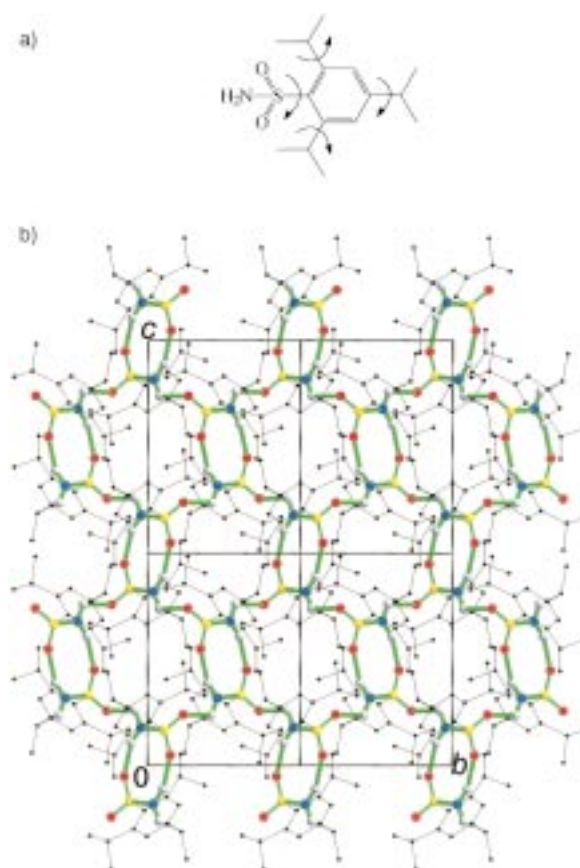


Figure 4. a) Molecular structure of 2,4,6-triisopropylbenzene sulfonamide, with arrows showing the variable torsion angles in the structure-solution calculation. b) View of part of the crystal structure of 2,4,6-triisopropylbenzene sulfonamide showing the 8-membered and 20-membered hydrogen-bonded rings in the (100) plane. Thin black lines represent bonds to carbon, whereas S–N and S=O bonds and N–H $\cdots$ O=S hydrogen bonds are shown by thick green lines.

vated crystal form of $\text{Ph}_2\text{P}(\text{O})(\text{CH}_2)_5\text{P}(\text{O})\text{Ph}_2$ has also been tackled recently from powder diffraction data.^[59]

In the application of direct-space structure solution methods, the presence of more than one type of molecule in the asymmetric unit increases the complexity of the problem, both in terms of the number of degrees of freedom (for two rigid molecules, there are 12 variables in the set $\Gamma = \{x_1, y_1, z_1, \theta_1, \phi_1, \psi_1\}$ and $\{x_2, y_2, z_2, \theta_2, \phi_2, \psi_2\}$) and to some extent in terms of *R* factor discrimination. An example^[60] concerns structure determination of the 1:1 cocrystal formed between 1,2,3-trihydroxybenzene and hexamethylenetetramine, using data measured on a conventional laboratory powder X-ray diffractometer. The structure (Figure 5) can be rationalized in terms of puckered hydrogen-bonded molecular ribbons that are linked into a continuous three-dimensional framework by C–H $\cdots$ π (arene) interactions.

Another example concerns the crystal structure of 4-(2,3,4-trifluorophenyl)-1,2,3,5-dithiadiazolyl, which is of interest in the field of molecular magnetic materials. The structure has been determined^[61] from powder diffraction data using a direct-space approach based on simulated annealing. In this case, the structural fragment used in the structure-solution calculation comprised two chemically identical, but crystallographically independent, molecules.

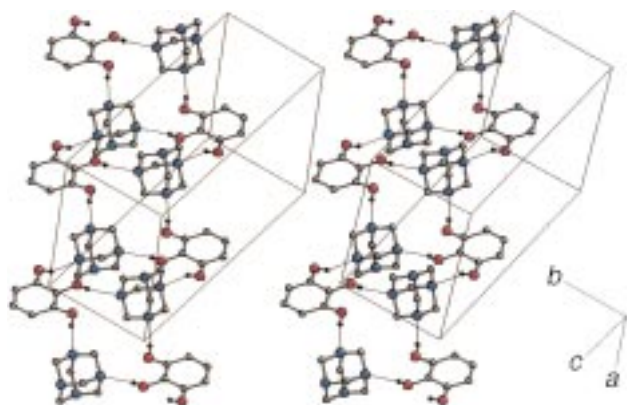


Figure 5. Stereoview of the structure of the cocrystal formed between 1,2,3-trihydroxybenzene and hexamethylenetetramine showing the hydrogen-bonded molecular ribbons running parallel to the *a* axis.

3.2. Pharmaceutical Materials

Many drug substances are administered in the form of polycrystalline powders. In such cases, in addition to the intrinsic pharmacological activity of the drug molecule itself, knowledge of the crystal structure is crucial for fully understanding and optimizing the pharmaceutical properties. Relevant aspects in this regard include understanding and controlling solubility, bioavailability, and the conditions for handling and administration. Importantly, a given drug substance administered in different polymorphic forms may lead to very different results. For all these reasons, knowledge of the crystal structures of pharmaceutical materials is of considerable importance, and in many cases powder diffraction provides the only possible route to this information. In addition, the quest to produce and fully characterize all accessible polymorphs^[62–64] of a given drug substance has become an area of intense activity within the pharmaceuticals industry in recent years (motivated in part by patenting, registration, and litigation issues), and powder diffraction again has a direct role to play in this regard.

The crystal structures of a number of substances of pharmaceutical interest have been determined from powder diffraction data. Although the first demonstration^[65] of *ab initio* structure solution of a molecular crystal from powder diffraction data by traditional techniques was for the previously known structure of cimetidine (Figure 6) using direct methods, there are only a few other pharmaceutical substances, such as chlorothiazide^[66] (a clinically used diuretic compound) and the polymorphic form V of sulfathiazole^[67] (an antibacterial drug), for which structure solution using traditional techniques has been reported. The majority of reported structure determinations in this field have employed

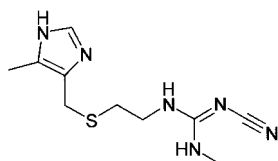


Figure 6. Molecular structure of cimetidine.

direct-space techniques for structure solution. Examples include a metastable polymorph of piracetam^[68] (a drug used in human therapeutics) studied using the atom–atom potential method and chloroxylenol^[69] (an antiseptic) solved using a

combination of maximum-entropy and Monte Carlo approaches (see Section 5.3.5). Direct-space approaches have been used to solve the structures of a number of pharmaceutical materials containing conformationally flexible molecules, including ibuprofen^[70, 71] (using a genetic algorithm technique) and the tranquilizers promazine hydrochloride and thiothixene^[38] (using a simulated annealing technique). The internal degrees of freedom in the structure-solution calculation for thiothixene and the molecular conformation found in the final refined crystal structure are shown in Figure 7. This example illustrates the use of structural knowledge and conformational flexibility in constructing a molecular model for direct-space techniques. While allowing five internal degrees of freedom, the piperazine ring was fixed in a chair conformation and the stereochemistry (*E* versus *Z*) around the C=C bond was fixed in accordance with prior chemical knowledge, thus giving an adequate description of the molecule while keeping the amount of flexibility to the minimum required.

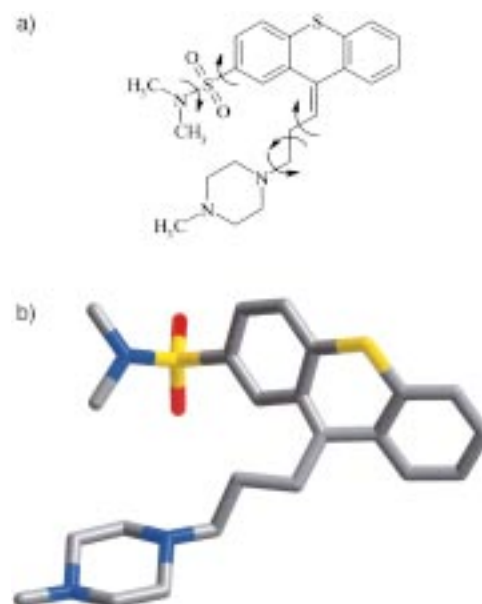


Figure 7. a) Molecular structure of thiothixene, with arrows showing the variable torsion angles in the structure-solution calculation. b) The molecular conformation of thiothixene found in the crystal structure determined from powder diffraction data.

Another example from the pharmaceutical field concerns structure determination of a new polymorph (form 2) of fluticasone propionate,^[72] a synthetic anti-inflammatory steroid (Figure 8a). In attempts to produce crystals of fluticasone propionate of controlled size and morphology for pharmaceutical applications, crystallization in a supercritical-fluid medium was carried out, and was found to yield a new polymorph (form 2). As form 2 was obtained only by the supercritical crystallization method, yielding polycrystalline powder samples, structural characterization of form 2 was not possible by single-crystal diffraction. Structure solution from powder diffraction data was carried out using the genetic-algorithm technique, leading (following Rietveld refinement) to the crystal structure shown in Figure 8b.

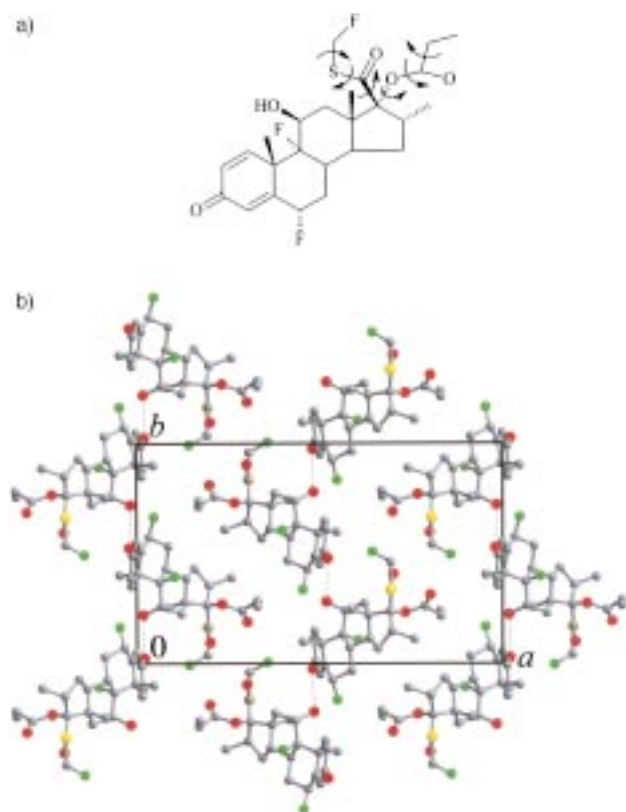


Figure 8. a) Molecular structure of fluticasone propionate, with arrows showing the variable torsion angles in the structure-solution calculation. b) The crystal structure of form 2 of fluticasone propionate (hydrogen atoms not shown) viewed along the *c*-axis. Dashed lines indicate hydrogen-bonding interactions.

3.3. Other Organic Materials

X-ray powder diffraction data has been used for crystal structure determination of an increasing number of organic compounds in other fields, and these examples reflect the trends in the structure-solution methods used for molecular materials and the recent growth in the complexity of the problems tackled. As discussed in Section 2.4, the traditional approach for structure solution does not rely on prior knowledge of the geometry of a well-defined structural fragment. However, for “equal-atom” structures (e.g. organic compounds containing no atom heavier than oxygen), the absence of dominant scatterers can make the problems encountered in traditional structure-solution methods particularly severe.^[1] To our knowledge, the first previously unknown “equal-atom” organic structure to be solved using direct methods was formylurea.^[73] Subsequently, only a few other structures of organic materials have been solved in this way, although the use of high-quality synchrotron X-ray powder diffraction data has been shown to enhance the capabilities of the traditional approach, as illustrated in the structure determination of fluorescein diacetate.^[74]

The first material of unknown crystal structure to be solved by a direct-space approach was *p*-BrC₆H₄CH₂CO₂H^[33] using the Monte Carlo method, followed by other examples using the same method, including 1-methylfluorene^[75] and 3-chloro-*trans*-cinnamic acid.^[76] The first previously unknown crystal

structure to be solved by the genetic-algorithm approach was *ortho*-thymotic acid.^[46] Other reported structure determinations from powder diffraction data have included 2,6-naphthalene-dicarboxylic acid and dimethyl 2,6-naphthalenedicarboxylate,^[77] as well as materials of potential biological interest including stereoisomeric cyclotetrapeptides derived from 3-aminobutanoic acid,^[78] two nitric oxide donors based on pyrazolo[1,5-*a*]pyrimidine derivatives^[79] and an enzyme inhibitor 4-amidinoindanone guanyldrazone.^[80] In other examples, powder X-ray diffraction data have been used in conjunction with computer modeling techniques for structure determination of globular molecules such as norbornane,^[81] norbornene,^[82] and (*R,S*)-camphor.^[83]

In all the materials discussed above, the structural fragment is essentially a rigid molecule with at most a few variable torsion angles. However, more complex systems defined by a significant number of torsional degrees of freedom are within the current scope of direct-space structure solution techniques. Thus, direct-space approaches have been used in the complete structure determination of materials such as capsaicin^[38] (Figure 9, the “hot” component of chilli peppers), for which ten variable torsion angles were used to define the structural fragment, and heptamethylene-1,7-bis(diphenylphosphane oxide) (Ph₂P(O)(CH₂)₇P(O)Ph₂),^[57] the structure solution of which is now described in detail.

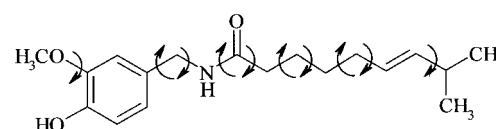


Figure 9. Molecular structure of capsaicin, with arrows showing the variable torsion angles in the structure-solution calculation.

The X-ray powder diffraction pattern of Ph₂P(O)(CH₂)₇P(O)Ph₂ was recorded using a conventional laboratory powder X-ray diffractometer, and structure solution was carried out using our genetic-algorithm technique.^[49] The structural fragment used in this calculation comprised all non-hydrogen atoms in the molecule, with all bond lengths and bond angles fixed at standard values. A considerable amount of flexibility was required to define the molecular conformation—thus, four torsion angles define the orientations of the phenyl rings (which were themselves constrained to be planar) relative to the remainder of the molecule, and eight torsion angles describe the conformation of the alkyl chain. With the whole molecule also subjected to translation and reorientation within the unit cell, each structure considered in the structure-solution calculation was defined by 18 variables ($\{x, y, z, \theta, \phi, \psi, \tau_1, \tau_2, \dots, \tau_{12}\}$; Figure 10a). In the genetic algorithm structure-solution calculation, the population of crystal structures was allowed to evolve subject to well-defined mating and mutation procedures, leading to the improvement in the quality of the population shown in Figure 11. The best structure in the final generation was used as the starting structural model for Rietveld refinement. In the crystal structure, the molecule adopts a conformation with a *gauche* bond at one position in the alkyl chain (Figure 10b).

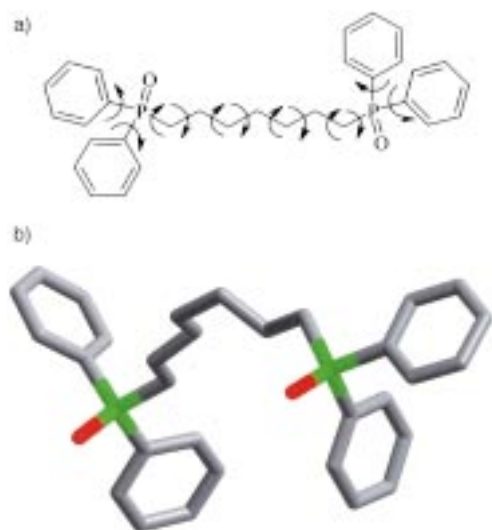


Figure 10. a) Molecular structure of $\text{Ph}_2\text{P}(\text{O})(\text{CH}_2)_7\text{P}(\text{O})\text{Ph}_2$, with arrows showing the variable torsion angles in the structure solution calculation. b) The molecular conformation of $\text{Ph}_2\text{P}(\text{O})(\text{CH}_2)_7\text{P}(\text{O})\text{Ph}_2$ found in the crystal structure determined from powder diffraction data.

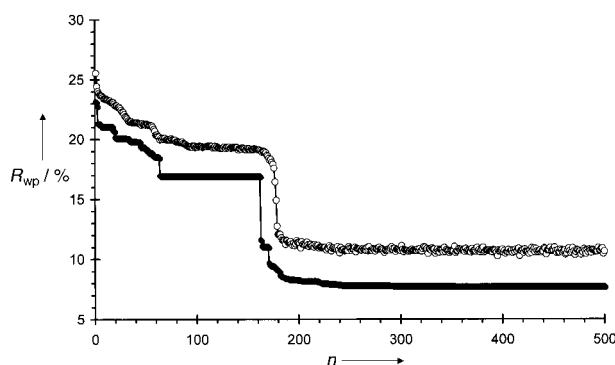


Figure 11. Evolutionary Progress Plot showing the evolution of R_{wp} for the best structure in the population (filled circles) and the average value of R_{wp} for the structures in the population (open circles) as a function of generation number in the genetic algorithm structure solution calculation for $\text{Ph}_2\text{P}(\text{O})(\text{CH}_2)_7\text{P}(\text{O})\text{Ph}_2$.

It could not have been predicted that this specific molecular conformation would be adopted in the crystal structure, highlighting the importance of allowing conformational flexibility in the structure-solution calculation. The fact that the structure of this material was determined successfully using experimental data collected on a conventional laboratory powder X-ray diffractometer emphasizes that the use of synchrotron data is not essential for powder structure solution, even in the case of complex systems.

Recently, the structure determination of the oligopeptide Phe-Gly-Gly-Phe from powder diffraction data has been reported.^[84] The structure was solved using a modified version^[85] of the genetic-algorithm technique, based on Lamarckian evolution (discussed in Section 5.3.4). The structure-solution calculation involved 17 structural variables, including 11 variable torsion angles to define the conformation of the Phe-Gly-Gly-Phe molecule (with all peptide groups $\text{R}^1\text{-CO-NH-R}^2$ maintained as planar units with the O-C-N-H dihedral angle fixed at 180°).^[86] The crystal structure exhibits a number of interesting features, including

hydrogen-bonded ribbons of Phe-Gly-Gly-Phe molecules analogous to an antiparallel β -sheet, and a double-helix arrangement of hydrogen-bonded chains involving the end groups of the molecules.

In addition to the use of the direct-space techniques highlighted above, variants of the traditional approach in which some knowledge of molecular geometry is incorporated within the structure-solution calculation have also been used. Thus, Patterson-fragment search methods have been used to solve a number of organic crystal structures, including the sublimated form of tris(3,5-dimethylpyrazol-1-yl)methane,^[87] L-carvone, and DL-carvone.^[30]

3.4. Organometallic Complexes

For coordination and organometallic compounds, the presence of a few metal atoms (dominant X-ray scatterers) often simplifies the process of structure solution.^[88] Conversely, however, in some cases the presence of a highly dominant scatterer can mask information in the diffraction data concerning the organic component of the material, such that structure solution and structure completion may be more difficult for that part of the structure.

In view of the presence of heavy atoms, it is not surprising that most reported cases of the structure solution of organometallic materials from powder X-ray diffraction data have employed traditional techniques. An example is cyclopentadienyl rubidium,^[89] for which the direct methods program SIRPOW^[90] was used to locate the rubidium and carbon atoms. In Rietveld refinement, the cyclopentadienyl rings were set up as rigid bodies to stabilize the refinement. An interesting aspect of this study is that the powder sample actually contained two polymorphs of cyclopentadienyl rubidium. Initial attempts to index the powder diffraction pattern failed because of the presence of the two phases, but closer inspection revealed that the peaks could be subdivided into two sets: narrow peaks (with instrument-limited peak widths) and substantially broader peaks. By subdividing the experimental data in this way, both phases were indexed and the structures solved using the approach described above. The structures of the two polymorphs of cyclopentadienyl rubidium determined in this study are shown in Figure 12. The use of synchrotron X-ray powder diffraction data was important in this case, as different types of sample broadening could not be distinguished with the lower instrumental resolution of a conventional laboratory powder X-ray diffractometer.

The crystal structure of silicon phthalocyanine dichloride (SiPcCl_2) has been determined recently^[91] from powder diffraction data, with structure solution carried out using a direct-space approach based on the Monte Carlo method. Knowledge of this crystal structure has been used, in conjunction with scanning tunneling microscopy data, to understand the structural properties of both low-coverage and high-coverage films of SiPcCl_2 deposited on silicon surfaces. In another direct-space application, the structure of the malaria pigment β -haematin has been determined^[92] from powder diffraction data, in this case employing a simulated annealing method for structure solution.

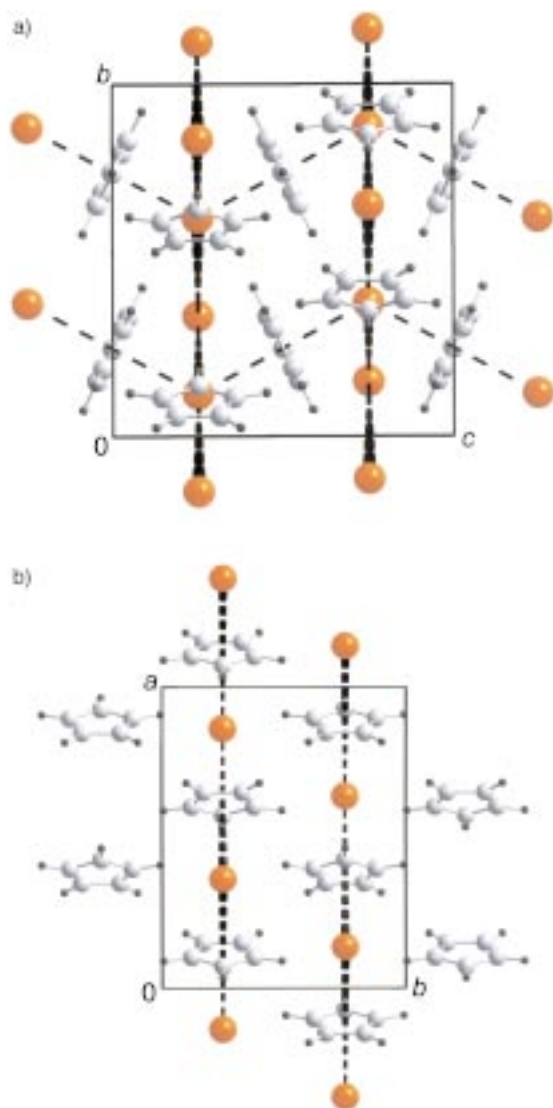


Figure 12. Crystal structures of the two polymorphs of cyclopentadienyl rubidium: a) form I, and b) form II. Dashed lines show distances between near-neighbor rubidium atoms.

3.5. Zeolites and Related Materials

Zeolites are microporous solids with a wide-range of commercial applications in catalytic, adsorption, and separation processes.^[93–95] As these technologically important properties of zeolites are closely related to their crystal structures, knowledge of the structural properties is central to the design and development of applications of these materials. Unfortunately, however, many synthetic zeolites are available only as powders and cannot be studied using conventional single-crystal diffraction techniques. In such cases, a combination of techniques, such as powder X-ray diffraction, electron microscopy, high-resolution solid state NMR, computer simulation, and model building is commonly used to obtain structural information.^[8, 96–98] The crystal structures of a number of zeolitic materials have been solved and refined directly from powder diffraction data, leading to structural knowledge of several new materials and new zeolite structure types.^[99] Early examples involving structure solution using traditional ap-

proaches included $\text{AlPO}_4\text{-12-TAMU}$,^[100] sigma-2 clathrasil,^[101] and anhydrous VPI-5.^[102]

A more recent example concerns the large pore, pure silica polymorph ITQ-4.^[103] Laboratory X-ray powder diffraction data were used initially to determine the unit cell parameters and high-resolution solid-state ^{29}Si NMR showed that there are four different silicon environments in the asymmetric unit. High-resolution synchrotron X-ray powder diffraction data were then used to solve the structure by using the direct-methods program SIRPOW,^[90] giving the positions of all the framework atoms. These positions were used as the starting structural model for Rietveld refinement. This structure represents a new zeolite with an exceptionally large pore volume (Figure 13). However, structure solution of zeolitic materials is not often carried out so straightforwardly, and the problems encountered with structure determination in other fields are often exacerbated by the occurrence of disorder, faulting, and other structural defects.

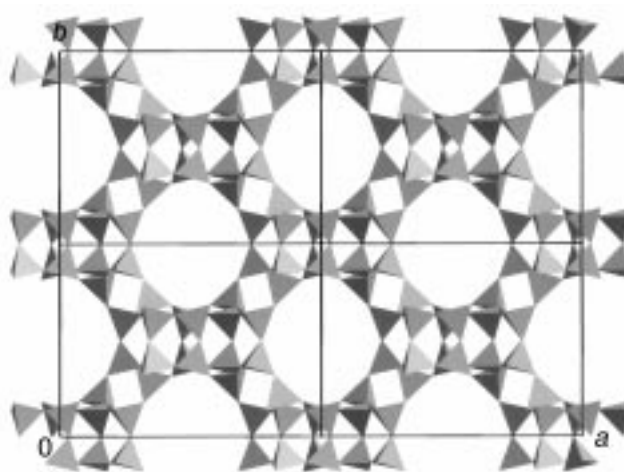


Figure 13. Structure of the large-pore material ITQ-4 (unit cell dimensions are $a = 18.65$, $b = 13.50$, $c = 7.63$ Å, $\beta = 102.0^\circ$).

To overcome difficulties encountered in this field, traditional structure-solution methods are often combined with model building, as used in the structure solution of RUB-10^[104] and $\text{AlPO}_4\text{-18}$.^[105] New structure-solution techniques have also been developed by researchers with particular interest in this area. One of the first methods^[19] focused on the redistribution of the intensities of overlapping reflections based on the enhancement of a Patterson map. The resulting data were used to solve the structure of SAPO-40, for which previous attempts using equipartitioned data failed. Other methods for structure determination include the use of structure envelopes^[106] (see Section 5.3.5), and the FOCUS method,^[107–109] which uses powder diffraction data in combination with chemical information in the form of a specialized topology search specific to zeolites.^[110] An example of a zeolitic structure (VPI-10) solved using the FOCUS method is shown in Figure 14. Simulated annealing has also been adapted for application to zeolite framework structures,^[111, 112] with reliable information on the geometric characteristics of tetrahedral species (Si, Al, etc.) in zeolite frameworks

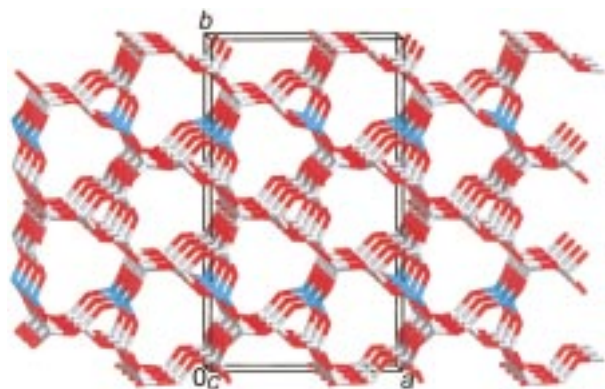


Figure 14. The framework structure of the zincosilicate material VPI-10 solved from powder diffraction data using the FOCUS method. Si: gray; O: red; Zn: blue.

incorporated into the calculation of the figure-of-merit (cost function) used to rank possible framework topologies. This technique has been used to solve the structures of UiO-7^[113] and ERS-7.^[114] It is clear that the active use of such structural knowledge in the structure determination process enhances the ability to solve more complex zeolitic structures from powder diffraction data.

The structure of the relatively complex material UTD-1^[115] has recently been solved using an experimental approach in which several different (but related) powder diffraction patterns are recorded for a textured sample (i.e. a sample exhibiting preferred orientation of the crystallites—see Section 5.5). In this way, data that are more “single-crystal-like” in character can be obtained, and in the case of UTD-1 a standard direct methods program was sufficient to solve the structure from such data.

3.6. Polymers

Polymers are of well-proven, wide-ranging technological importance, and it is clearly important to be able to develop a structural understanding of these materials, to rationalize their solid-state properties, and further exploit their applications. Despite the huge molecular size, crystalline polymeric materials are well suited for structure determination as the asymmetric unit often comprises a simple monomer unit. However, good quality polymer crystals are often difficult to obtain, and practitioners in this field often turn to fiber diffraction. When fibers are not available, structural information may be obtained from powder diffraction data.

In the case of organic polymers, poor crystallinity often manifests itself in the broadening of diffraction peaks, which renders traditional techniques for structure solution unsuitable. As a result, examples of successful structure determination (such as poly(*p*-phenylene terephthalate),^[116] poly(hydroxybutyrate),^[117] and azomethine block-copolymers^[118]) have invoked molecular modeling to generate energetically and sterically favorable models, which are then compared and refined against the experimental powder diffraction data.

More traditional methods can be used to study metal-organic polymers which are normally more crystalline than

organic polymers.^[88] In addition, the presence of a metal atom (i.e. a dominant X-ray scatterer) in the structure can simplify the structure solution process. One research group working in the field of metal diazoles has solved the structures of a number of polymeric complexes directly from powder diffraction data, including those of $[\{\text{Cu}(\text{pz})\}_n]$ and $[\{\text{Ag}(\text{pz})\}_n]$ (Hpz = pyrazole),^[119] $[\{\text{Ag}(\text{imz})\}_n]$ (Himz = imidazole),^[120] $[\{\text{NiX}_2(\text{pydz})\}_n]$ (X = Cl or Br; pydz = pyridazine),^[121] and $[\{\text{MX}_2(\text{bipy})\}_n]$ (M = Ni or Cu; X = Cl or Br; bipy = 4,4'-bipyridyl).^[122] In these cases, structure solution was carried out using the direct-methods program SIRPOW^[90] or a grid search technique^[123] to locate the dominant X-ray scatterer, and the positions of the remaining ligand atoms were established from simple packing and symmetry considerations. These materials exhibit many interesting structural features. An example concerns $[\text{Cu}(\text{pymo})_n]$ (Hpymo = 2-hydroxypyrimidine)^[124] was found to be unsuitable for study by single-crystal powder diffraction techniques. Crystal-structure determination from powder data using traditional structure-solution methods revealed that helical polymers and separate hexamers coexist in an ordered fashion in the same crystal phase (Figure 15)—a structural feature that has not previously been reported in any field.

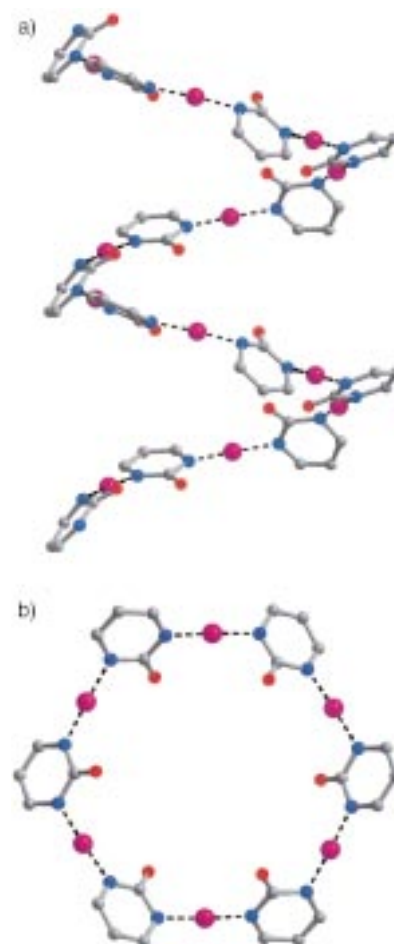


Figure 15. The structural components a) linear polymers and b) cyclic hexamers found in the crystal structure of $[\text{Cu}(\text{pymo})_n]$. In the crystal structure, the polymer chains are threaded through the cyclic hexamers, which are stacked on top of each other to generate a channel-like arrangement (not shown).

A family of polymer electrolyte complexes, comprising salts dissolved in poly(ethylene oxide) (PEO), has also been studied by powder diffraction. PEO is a high molecular weight polymer with repeat unit $\text{CH}_2\text{CH}_2\text{O}$. Although the crystal structures of the $(\text{PEO})_3 \cdot \text{NaClO}_4$ ^[125] and $(\text{PEO})_3 \cdot \text{LiCF}_3\text{SO}_3$ ^[126] complexes were determined by Rietveld refinement of a model based on a known structure, no such structural models were available for other complexes, for which structure solution has been carried out directly from powder diffraction data. Thus, the structure of the complex formed between NH_4SCN and PEO (stoichiometry $(\text{PEO})_4 \cdot \text{NH}_4\text{SCN}$) was solved using traditional direct methods, subsequently enabling the structure refinement of the isostructural systems $(\text{PEO})_4 \cdot \text{KSCN}$ ^[127] and $(\text{PEO})_4 \cdot \text{RbSCN}$.^[128] However, in the case of $(\text{PEO})_3 \cdot \text{LiN}(\text{SO}_2\text{CF}_3)_2$ ^[37] and $(\text{PEO}) \cdot \text{NaCF}_3\text{SO}_3$ ^[129] attempts to refine the structures using a known structure as the starting point were unsuccessful, as was structure solution by traditional approaches. Instead, progress was made using a flexible direct-space approach for structure solution based on a simulated-annealing protocol. Recently,^[130] the structure of the $(\text{PEO})_6 \cdot \text{LiAsF}_6$ complex has also been determined from powder diffraction data, with structure solution again carried out using a simulated-annealing approach.

3.7. Pigments and Dyes

By definition, pigments are colored solid particles that are insoluble in the medium in which the pigment is applied (for example, in paints, plastics, and printing inks), whereas dyes are soluble materials which are used in dissolved or dispersed states in their applications.^[131] Clearly the physical properties of pigment materials depend on both molecular and crystal structure. Most pigments can be prepared only as fine powders (poor solubility often prevents growth of good quality single crystals from solution), and for this reason many pigments have eluded crystal-structure determination by single-crystal diffraction techniques. Furthermore, it is important to recognize that for good dispersion and the optimization of other pigment properties, it is generally necessary to prepare and apply real pigment materials as microcrystalline particles. For these reasons, structural characterization of pigment materials falls directly within the scope of powder structure-determination techniques.

Apart from those based on azo chromophores, the majority of organic materials of interest in this field involve heterocyclic chromophores such as phthalocyanines, quinacridones, and anthraquinones, and in general these molecules can be described as rigid structural units of well-defined geometry. Not surprisingly, for most structures in these classes, structure determination from powder diffraction data has focused on direct-space techniques for structure solution, or approaches that combine crystal modeling together with analysis of powder diffraction data. Examples include 6,13-dichlorotriphenyldioxazine,^[132] 1-aminoanthraquinone^[133] and the X form of metal-free phthalocyanine.^[134]

A crystal-modeling approach has also been used to solve the structure of a perinone pigment—2,5-dihydroxybenzo-

$[d,e]\text{benzo}[4,5]\text{imidazo}[2,1-a]\text{isoquinolin-7-one}$ ^[135] (see Figure 3—sixth molecule listed under 1999)—representing the only crystal structure published so far for this class of pigments. Firstly, the powder diffraction pattern was indexed and although a number of possible space groups were consistent with the data, space groups that are rare for organic systems were rejected. The geometry of the molecule used in the structure-solution calculation was constructed from the crystal structures of materials containing similar fragments, and the molecule was assumed to be planar. However, the positions (*exo* or *endo*) of the hydrogen atoms of the hydroxyl groups could not be assigned a priori, and calculations were therefore carried out separately for each of the four conformers (and for each space group). In this regard, it is important to note that energy calculations require the inclusion of hydrogen atoms (whereas structure-solution calculations from powder X-ray diffraction data would not). The crystal structure was “solved” by minimization of intermolecular energy by a steepest-descent algorithm, starting from random crystal-packing arrangements, and the structures obtained were then “screened” by comparison with the experimental X-ray powder diffraction data. A structure giving good agreement between the calculated and experimental powder diffraction patterns was found (although it was not actually the lowest-energy structure found). Refinement of this structure was then carried out by using rigid-body Rietveld analysis.

Other examples from this field have required the introduction of conformational flexibility in the structure-solution calculation, and have been tackled by using direct-space techniques (particularly the Monte Carlo method). Thus, structure determination of the red phase of fluorescein (which finds applications as a yellow dye with intense green fluorescence) from powder diffraction data^[39] represented the resolution of a long-standing structural problem.

Another example concerns the structure determination of 1,4-diketo-2,5-di-*tert*-butoxycarbonyl-3,6-diphenyl-pyrrolo[3,4]-pyrrole (DPP-Boc), an important derivative of the commercial red pigment 1,4-diketo-3,6-diphenyl-pyrrolo[3,4-*c*]pyrrole (DPP). An approach developed recently to ensure good dispersion of pigments (such as DPP) in the application medium of interest involves the introduction of the pigment chromophore as a molecule (called a “latent” pigment) which is readily soluble in the application medium. Subsequently, the insoluble pigment particles are generated *in situ* through an appropriate chemical reaction of the latent pigment. The importance of DPP-Boc lies in its use as a latent pigment,^[136] it undergoes a thermal reaction (involving removal of the *tert*-butoxycarbonyl groups) to produce DPP (Figure 16). Recently, routine powder X-ray diffraction studies of this system revealed the existence of a new polymorph (β phase) of DPP-Boc^[137, 138] in addition to a previously known polymorph (α phase). Here we describe the structure determination of the β phase from powder X-ray diffraction data. After determination of the unit cell, density considerations in conjunction with solid-state ^{13}C NMR spectroscopic data suggested that the asymmetric unit comprises half the DPP-Boc molecule. The structural fragment used for structure solution comprised all the non-hydrogen atoms in the

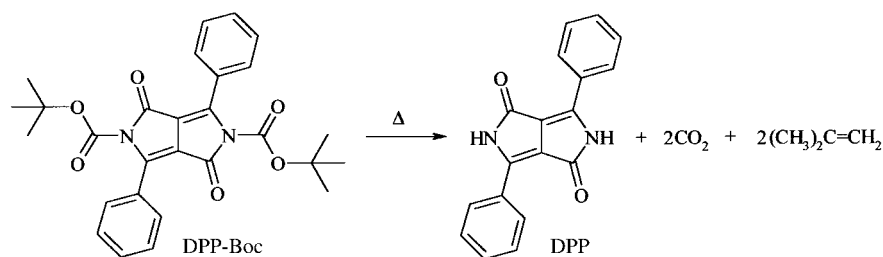


Figure 16. Thermal decomposition of the “latent” pigment DPP-Boc (left) to produce the pigment material DPP (right).

asymmetric unit, and the molecular inversion center was constrained to reside on a crystallographic inversion center (space group $P\bar{1}$). A Monte Carlo calculation was then carried out involving free reorientation of the whole molecule around this pivot point and variation of four torsion angles within the *tert*-butoxycarbonyl group (Figure 17a). The structure with lowest R_{wp} found in the structure solution calculation was then used as the starting model for Rietveld refinement. As for the known α phase of DPP-Boc, the molecules in the β phase (Figure 17b) are stacked in columns, although details of the stacking arrangement and the structural relationships between columns differ significantly between the two polymorphs. Clearly powder diffraction played a pivotal role in the study of this material, both in the initial identification of a new polymorph and in the subsequent structure determination.

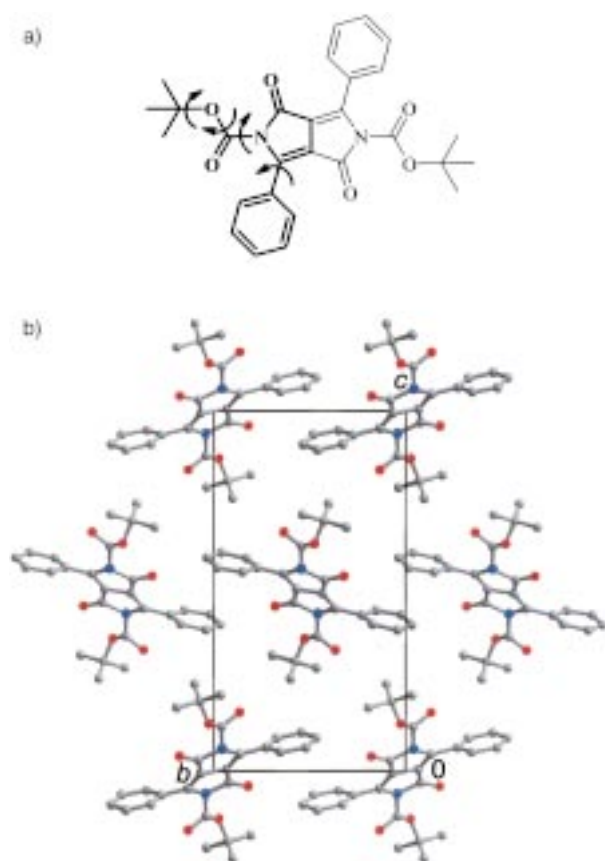


Figure 17. a) Molecular structure of DPP-Boc. The structural fragment used in the structure-solution calculation represents half the molecule (shown as bold), and the arrows indicate the variable torsion angles. b) The crystal structure of the β phase of DPP-Boc, determined directly from powder diffraction data.

3.8. Solid-State Reactions

It is well known^[139–141] that to develop an understanding of the chemical reactivity of solids relies, in the first instance, on knowing the structural properties of the solid and hence establishing the geometric relationships between the molecules, atoms, or ions that are involved in the reaction. Thus, the ability to determine the crystal structures of

reactive materials is a crucial prerequisite for understanding the chemical transformations that occur within them, as illustrated by the following examples.

It has been known since the 1850s^[142, 143] that solid sodium chloroacetate undergoes a polymerization reaction at sufficiently high temperature to produce polyglycolide and sodium chloride [Eq. (1)]. However, an understanding of this reaction



and its mechanism was not previously possible, as sodium chloroacetate is microcrystalline and structural information could not be determined using single-crystal X-ray diffraction methods. Recently,^[144] the structure of sodium chloroacetate (Figure 18) was determined directly from powder X-ray

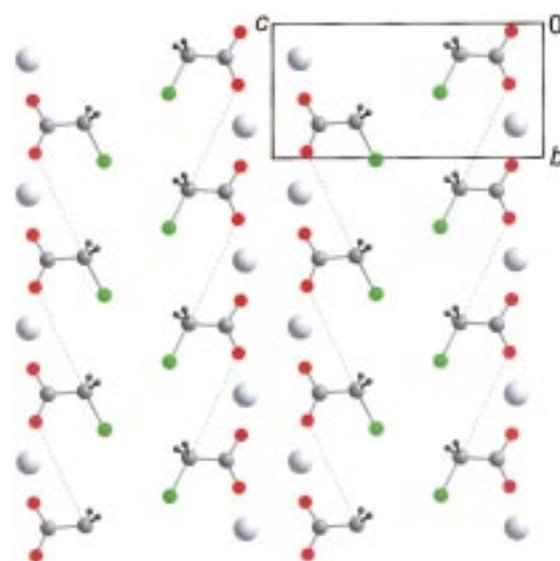


Figure 18. A section of the crystal structure of sodium chloroacetate, with dotted lines indicating the propagation of the polymerization reaction within rows of chloroacetate anions along the b -axis.

diffraction data, with the structure solution carried out using the Monte Carlo method. From knowledge of the crystal structure, the polymerization reaction to produce polyglycolide may be rationalized directly on the basis of a topochemical reaction pathway. The crystal structures of various lithium halogenoacetates have also been determined recently from powder diffraction data,^[145] and provide a basis for understanding the chemical reactivity of these systems.

4. Powder Diffraction Versus Single-Crystal Diffraction

As highlighted throughout this article, one of the main areas of application of powder diffraction is the structural characterization of microcrystalline materials that are unsuitable for investigation by single-crystal diffraction techniques, and as such powder diffraction has considerable importance in several disciplines of solid-state and materials sciences. In addition to this intrinsic difference between powder diffraction and single-crystal diffraction, we now consider some other comparisons and contrasts between these techniques and their applications.

An important application of powder X-ray diffraction across several fields concerns studies of structural changes associated with phase transitions and chemical reactions in solids. From the practical point of view, powder diffraction experiments may be carried out fairly straightforwardly to monitor structural changes in a solid as a function of the variation of external conditions (such as temperature, pressure, or exposure to gaseous atmospheres of varying composition), and in general such *in situ* studies are more readily carried out by powder diffraction techniques than single-crystal diffraction techniques. Furthermore, it is well known that phase transitions and chemical reactions in single-crystals are often associated with a reduction in crystal quality, for example through twinning, fracturing, or indeed the production of a polycrystalline “daughter” phase from a single-crystal “parent”. Clearly there are intrinsic limitations concerning the prospects of monitoring such transformations using single-crystal diffraction, whereas powder diffraction data recorded for the same systems may show little or no deterioration in quality throughout the transformation. In addition, some solid materials of interest (for example, certain clathrate hydrates) may not exist under conditions of ambient temperature and pressure, and for such materials that require synthesis, handling, and characterization under nonambient conditions, powder diffraction generally provides a more straightforward approach for structural characterization than single-crystal diffraction techniques.

In more general terms, crystal twinning and certain other types of defects are a major source of problems in single-crystal diffraction studies (many crystals grow intrinsically in a twinned manner), but may have little or no bearing on the quality of powder diffraction data for the same sample. Thus, the ability to carry out structure determination from powder diffraction data should be unaffected by the occurrence of twinning in the individual crystallites within the powder, provided each individual twin is still sufficiently large that particle-size effects do not give rise to serious line broadening.

In the industrial context, it is important to emphasize that powder diffraction allows materials to be investigated directly under the conditions in which they are used in specific applications, whereas single-crystal diffraction (by virtue of the requirement to prepare and study a single crystal) might not. For example (see also Section 3.2), solid pharmaceutical substances are often administered into the body as compacted powders in the form of tablets. For such materials, it may be important to understand directly (for example, from powder

diffraction studies of the tablets) whether they undergo any structural transformation as a consequence of the compaction process. If such transformations do occur, the crystal structure of the actual material administered into the body may be very different from the structure, determined by single-crystal diffraction, of a crystal of the same material grown from solution.

It is relevant to compare the quality of structural information that can be obtained by structure determination using powder versus single-crystal diffraction data. In general, the final structural parameters obtained from powder diffraction data are not as accurate or precise as those that could be determined for the same material from single-crystal diffraction data (assuming that single crystals were available). Thus, although significant differences in bond lengths characteristic of different bond types (for example C=O versus C–OH) may be readily distinguished from powder data, slight deviations from standard bond lengths and bond angles can not, in general, be reliably assessed. For good quality powder diffraction data, the positions of hydrogen atoms can also be determined (for example, see refs [65, 146]), although such atoms are normally placed in calculated positions during structure refinement calculations (rather than explicitly refined). If crystals suitable for single-crystal X-ray diffraction experiments are available, it is clear that this approach remains the technique of choice for accurate and/or routine structure determination. Indeed, it is relevant to note the importance of optimizing crystal-growth strategies to enhance the opportunities of obtaining single crystals of sufficient size and quality for any particular material of interest.^[147]

In addition to the use of powder diffraction in allowing structure determination of microcrystalline materials that are unsuitable for investigation by single-crystal diffraction techniques, it has many other important roles in the structural investigation of crystalline materials. Structure determination from powder diffraction data ensures that the bulk solid sample is investigated, in contrast to the potentially unrepresentative procedure of selecting an individual crystal from the sample, as done in single-crystal diffraction. Clearly any individual crystal within a bulk solid sample might not be representative of the bulk material, and could be a different polymorph or an impurity. Thus, when a structure is solved from single-crystal diffraction data, it is good practice to check that this structure is actually representative of the bulk material from which the single crystal was selected, and powder diffraction provides a direct means of checking this fact. Regrettably, this simple step is often ignored. To illustrate the necessity of using powder diffraction in this regard, we consider the case of *p*-formyl-*trans*-cinnamic acid (*p*-FCA),^[148] which exists in two polymorphic forms—one polymorph (β phase) is photoreactive under UV irradiation, whereas the other polymorph (γ phase) is photostable. There are well-established correlations^[139–141] between the structural properties and photoreactivities of a wide range of derivatives of *trans*-cinnamic acid in the solid state. It was therefore of much interest when the structure (from single-crystal X-ray diffraction) of the photoreactive β phase of *p*-FCA was reported^[149] to represent an exception to these well-established correlations. However, it was shown subsequently^[148]

(Figure 19) that the powder X-ray diffraction pattern calculated using this reported structure is actually in agreement with the experimental powder X-ray diffraction pattern of the photostable γ phase of *p*-FCA. Therefore, the crystal structure reported from single-crystal X-ray diffraction to be the

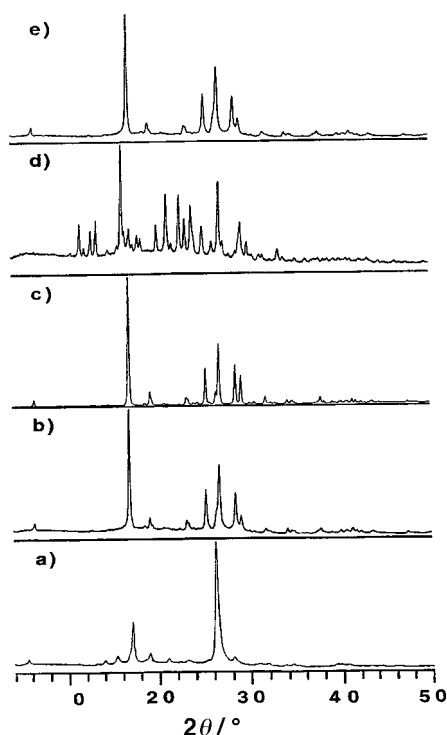


Figure 19. Powder X-ray diffraction patterns:^[148] a) recorded for a sample of *p*-FCA crystallized from ethanol (β phase); b) recorded for a sample of *p*-FCA crystallized from acetone (γ phase); c) simulated on the basis of the crystal structure reported in ref [149]; d) recorded for the sample of *p*-FCA crystallized from ethanol (β phase) following UV irradiation; e) recorded for the sample of *p*-FCA crystallized from acetone (γ phase) following UV irradiation.

β phase of *p*-FCA was actually the structure of the γ phase (and therefore did not represent a structurally anomalous photoreactive *trans*-cinnamic acid derivative). Thus, the actual single crystal (γ phase) selected for the single-crystal diffraction study in the original work^[149] was not representative of the bulk material (β phase). This example demonstrates clearly the importance of using powder diffraction data to confirm that a structure determined from single-crystal data is actually representative of the bulk polycrystalline sample. Other examples of the importance of adopting this strategy have been noted.^[150–152]

In summary, while new and improved radiation sources (both laboratory-based X-ray sources and new generations of synchrotron sources) may be expected to continue to allow single crystals of smaller and smaller size to be investigated by single-crystal diffraction methods in the future, there are clear areas of application in which powder diffraction techniques are essential. Furthermore, in spite of the advances that have allowed single-crystal diffraction experiments to be carried out on micro-crystals, there remains a significant range of materials for which the crystallite sizes are too small to be

physically handled as single crystals (e.g. in single-crystal diffraction experiments), but sufficiently large to give powder diffraction patterns of good quality.

5. Overview of Techniques Used in Structure Determination from Powder Diffraction Data

5.1. Indexing

As discussed in Section 2.1, the first stage of crystal-structure determination from powder diffraction data involves determination of the unit cell dimensions (a , b , c , α , β , γ) by “indexing” the powder diffraction pattern (although the unit-cell dimensions may sometimes be known independently—for example, from electron diffraction data). Clearly it is possible to proceed with structure solution and refinement only if the correct unit cell is found at this stage. Unfortunately, difficulties encountered in the reliable indexing of powder diffraction patterns using existing techniques is often found to be the limiting step in the structure determination process.

The most widely used programs for indexing powder diffraction data (ITO,^[153] TREOR,^[154] DICVOL,^[155] and CRYSFIRE^[156]) all consider the measured positions of peak maxima for a number (usually about 20) of selected peaks. General reviews are given in refs. [157–159]. In contrast to recent advances in techniques for structure solution, there has been relatively little fundamental development of indexing methods since the pioneering work several years ago.

As already mentioned, experimental powder diffraction patterns typically have considerable peak overlap and sometimes peak displacements, which can lead to problems in indexing using the methods described above. For example, certain peaks which may be crucial for correct indexing may be obscured or completely unresolved because of peak overlap. Another problem arises when an impurity phase (or a second polymorph of the material of interest) is present within the powder sample, and often constitutes an intractable problem for indexing by existing methods (unless the presence of the impurity phase(s) is known in advance). Indexing can also fail if there is significant zero-point error in the detector or poor definition of peak positions because of poor sample crystallinity or poor instrumental resolution.

Given the clear requirement for new indexing strategies, methods that use all regions of the powder diffraction pattern (including the overlapped peaks) are particularly appealing. On this basis, a new indexing strategy based on whole-profile fitting and global optimization using a genetic algorithm has been developed recently.^[160] In this method, trial unit cells (a , b , c , α , β , γ) are generated using a genetic-algorithm strategy, and the quality of each trial unit cell is assessed using a whole-profile fitting procedure. A method for indexing powder diffraction data using a genetic algorithm within the conventional indexing strategy (i.e. requiring a set of extracted peak positions) has also been proposed.^[161]

After the powder diffraction pattern has been indexed successfully, the space group may be assigned by identifying the conditions for systematic absences. If the space group

cannot be assigned uniquely, structure-solution calculations should be carried out separately for each of the plausible space groups. Knowledge of the unit-cell volume and space group, together with density considerations, should allow the contents of the asymmetric unit to be established. Information obtained from other experimental techniques (for example, high-resolution solid-state NMR spectroscopy) may be particularly helpful in confirming the number of molecules and/or structural units in the asymmetric unit.

5.2. Powder Diffraction Profiles

5.2.1. Definition of a Powder Diffraction Profile

The complete powder diffraction profile (either for an experimental or calculated powder diffraction pattern) may be described in terms of the following components: 1) the peak positions (which depend on the unit-cell dimensions), 2) the peak intensities (which depend on the positions of atoms in the unit cell, and atomic-displacement parameters), 3) the peak shapes and peak widths (which may be described using 2θ -dependent analytical functions), and 4) the background intensity distribution. The peak shape depends on characteristic properties of both the instrument and the sample, and different peak-shape functions are appropriate under different circumstances. The most common peak shape for powder X-ray diffraction is the pseudo-Voigt function,^[162] which represents a hybrid of Gaussian and Lorentzian character, although several other types of peak-shape function may be applicable under different circumstances. These peak shapes and the types of analytical functions that are commonly used to describe the 2θ dependence of the peak width are described in detail elsewhere.^[4]

5.2.2. Analysis of Powder Diffraction Profiles Prior to Structure Solution

As discussed in Section 2.2, traditional techniques (as well as some implementations of direct-space techniques, as discussed in Section 2.3) for structure solution from powder diffraction data require a set of accurate intensities of individual reflections extracted directly from the experimental powder diffraction pattern (through so-called “pattern decomposition” methods, such as the techniques of Pawley and Le Bail (reviewed in ref. [1]), which involve fitting the complete powder diffraction profile to establish the intensities of each of the underlying diffraction maxima). Advances in the techniques for peak extraction in this regard have been referenced in Section 2.2.

As discussed in Section 2.3, most implementations of direct-space structure-solution methods have used a profile-based figure-of-merit (such as R_{wp}), and therefore do not use the intensities of individual reflections extracted from the powder diffraction pattern. However, for such direct-space techniques, analysis of the powder diffraction pattern prior to structure solution is also very important. With such figures-of-merit, a reliable comparison between calculated and experimental powder diffraction patterns requires that the parameters defining the peak positions (unit-cell parameters and

zero-point offset), the peak shape (peak width, peak-shape function and peak-mixing parameters) and the background intensity distribution used in calculating the powder diffraction pattern for each trial structure accurately reflect those in the experimental powder diffraction pattern. It is clearly of paramount importance that reliable values of these parameters are established *prior to* the structure-solution calculation, requiring detailed analysis of the powder diffraction profiles in the experimental powder diffraction pattern. In general, this step is carried out either by peak-shape fitting of a few selected peaks, or by procedures for fitting the whole powder diffraction pattern by refinement of the parameters (see Section 5.2.1) that define the profile. Such fitting of the complete experimental powder diffraction profile should involve refinement of the unit-cell parameters, the background intensity distribution, zero-point shift parameters, peak-width parameters, and peak-shape parameters, *with the use of arbitrary peak intensities* (i.e. without using any structural model to determine the peak intensities). Careful prior analysis of the experimental data in this way ensures that the profile parameters used subsequently in structure-solution calculations provide a reliable description of the experimental powder diffraction pattern.

5.3. New Strategies for Structure Solution

Over recent years, there has been substantially increasing interest in the opportunities to determine crystal structures directly from powder diffraction data, and an ever increasing number of different types of materials have been studied (as discussed in Section 3). In terms of structure determination of molecular solids from powder diffraction data, for example, the recent advances have resulted largely from the development of direct-space techniques for structure solution. Although the application of these methods is not confined to molecular solids, these techniques have already made great impact in the study of organic molecular materials for which traditional approaches for powder structure solution have generally had limited success. Here we provide more details of the methodology underlying direct-space techniques for structure solution, recognizing that the methodology underlying traditional techniques has been reviewed extensively elsewhere.^[1, 6–13]

5.3.1. The Structural Fragment

In the direct-space approach, each trial crystal structure is defined by a set of variables Γ , representing the position, orientation, and intramolecular geometry of the structural fragment. The choice of structural fragment for any particular problem is not necessarily unique. For the general case of a rigid molecule, six variables are required: $\Gamma = \{x, y, z, \theta, \phi, \psi\}$. For the general case of a molecule with a number (n) of unknown torsion angles τ_i , the structural fragment is defined by $(6+n)$ variables: $\Gamma = \{x, y, z, \theta, \phi, \psi, \tau_1, \tau_2, \dots, \tau_n\}$. When the molecules occupy special positions in the crystal structure, the number of variable degrees of freedom is reduced. For example, when a molecular inversion center resides on a crystallographic inversion center, the molecule has no trans-

lational degrees of freedom, and there are $(3+m)$ variables: $\Gamma = \{\theta, \phi, \psi, \tau_1, \tau_2, \dots, \tau_m\}$ (where m is the number of variable torsion angles in half the molecule)—see the example discussed in Section 3.7. For the case of two or more molecules in the asymmetric unit (for example, cocrystals), the structural fragment comprises a separate set of variables Γ for each molecule—see the example discussed in Section 3.1.

As discussed in Sections 2.4 and 3, other structural information or knowledge can be used in conjunction with direct-space approaches to reduce the extent of parameter space that needs to be searched in the structure-solution calculation. For example, regions of parameter space that correspond to unreasonably short contacts between nonbonded atoms or between independent molecules in the unit cell may be excluded from the direct-space search procedure (although, in the case of Monte Carlo and simulated annealing methods, care must be taken to ensure that the excluded regions of parameter space do not restrict plausible pathways leading towards the correct structure).

In general, the complexity of direct-space structure-solution calculations increases as the number of variables required to define the structural fragment increases (i.e. as the number of degrees of freedom in the global-optimization calculation increases). While the majority of applications of direct-space structure solution have included the complete asymmetric unit (with hydrogen atoms usually omitted) in the structural fragment, some applications have sought rational approaches for reducing the number of degrees of freedom. For example, in the structure solution of *p*-BrC₆H₄CH₂CO₂H using the Monte Carlo method,^[33] two separate calculations were carried out: in the first calculation, translation of the dominant scatterer (Br atom) within the unit cell was determined, and then after establishing the correct position of the Br atom, reorientation of the -C₆H₄CH₂ part of the molecule around the fixed position of the Br atom found in the first calculation.

Another approach that has been used to simplify the structural fragment within the context of direct-space structure solution is the so-called “pseudo-atom” method. This strategy has been applied in a number of cases for structure solution of coordination compounds.^[163, 164] In the first stages of structure solution, cyclic fragments in these structures were each represented by a single pseudo-atom (with similar total scattering power), allowing the center-of-gravity of each of the cyclic fragments to be approximately located. Subsequently, the complete cyclic fragments were introduced in the calculation at the positions located by the pseudo-atoms, to determine their orientations, with only limited translation of the fragments allowed.

5.3.2. Grid Search Methods

The most straightforward (but least efficient) direct-space approach for structure solution is based on a grid search procedure, in which the molecule is moved systematically throughout the unit cell. Thus, by changing the values of the variables in the set Γ using predefined grid increments in each variable, all possible packing arrangements for the system of interest are assessed systematically. This exhaustive search procedure can be very demanding computationally, even

when the number of variables is relatively modest, and consequently the study of conformationally flexible molecules may be prohibitively time consuming by this approach. For this reason, most structure-solution problems tackled using grid search procedures have been cases in which the structural fragment has comprised a dominant scatterer or a rigid molecule^[42, 44, 45, 123, 134] although the study of a system with some conformational flexibility has been reported.^[43]

5.3.3. Monte Carlo and Simulated Annealing Techniques

The foundations of the Monte Carlo and simulated-annealing techniques^[165–167] are very closely related, and both involve the generation of a sequence of structures (each denoted Γ_i for $i = 1, 2, \dots, j, j+1, \dots, N$) for consideration as potential structure solutions. We begin by focusing on the Monte Carlo method, as implemented first in ref. [33] and applied subsequently to a wide variety of problems^[39, 54, 60, 75, 76, 91, 138, 144]. Each structure generated during the Monte Carlo calculation is derived from the previous structure by a random displacement of the structural fragment within the unit cell. The procedure for each Monte Carlo move (described here for the general case in which structure Γ_{j+1} is generated from structure Γ_j) comprises the following steps (see Figure 20).

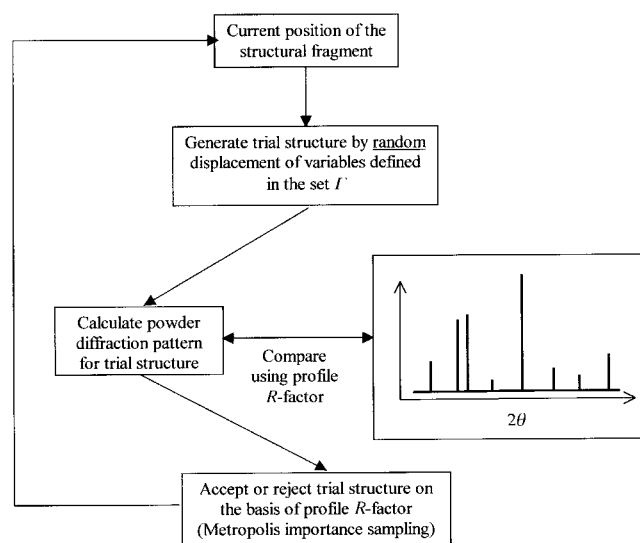


Figure 20. Summary of the steps involved in carrying out an individual Monte Carlo “move”.

1) Starting from structure Γ_j , a trial structure $\Gamma_{j,T}$ is generated by making small random displacements to each of the variables in the set $\{x, y, z, \theta, \phi, \psi, \tau_1, \tau_2, \dots, \tau_n\}$ (or in some cases a subset of these variables). The agreement between the powder diffraction pattern calculated for the trial structure and the experimental powder diffraction pattern is then assessed, for example using R_{wp} .

2) The trial structure is then accepted or rejected by considering the difference $Z = R_{wp}(\Gamma_{j,T}) - R_{wp}(\Gamma_j)$ between the values of R_{wp} for structures $\Gamma_{j,T}$ and Γ_j and invoking the importance sampling algorithm developed by Metropolis et al.^[165] If $Z \leq 0$, the trial structure is automatically accepted,

whereas if $Z > 0$, the trial structure is accepted with probability $\exp(-Z/S)$ and rejected with probability, $[1 - \exp(-Z/S)]$, where S is an appropriate scaling factor. If the trial structure is accepted, structure Γ_{j+1} is taken to be the same as $\Gamma_{j,T}$. If the trial structure is rejected, structure Γ_{j+1} is taken to be the same as Γ_j . The parameter S may be fixed or may be varied in a controlled manner during the calculation. Clearly the higher the value of S , the greater the probability that trial structures with $Z > 0$ will be accepted (note that S operates in a manner analogous to temperature in applications of Monte Carlo techniques in energy simulations).

The above procedure is repeated to generate a large number of structures, with each structure derived from the previous one through small random displacements in the values of the structural variables in the set Γ . Figure 21 shows

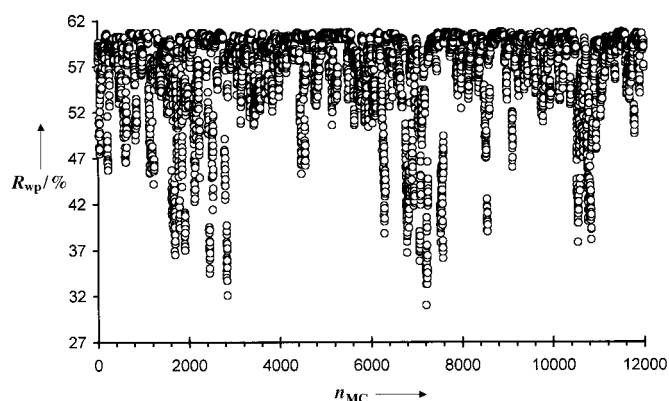


Figure 21. A typical plot of R_{wp} for trial structures generated in a Monte Carlo structure solution calculation versus the corresponding Monte Carlo move number n_{MC} .

a typical plot of R_{wp} for trial structures generated in a Monte Carlo structure-solution calculation as a function of Monte Carlo move number. After a sufficiently wide-range of parameter space has been explored, the best structure solution (corresponding to lowest R_{wp}) is used as the starting model for structure refinement. It is important to emphasize that the Monte Carlo method does not represent minimization of R_{wp} (except if $S=0$), but explores parameter space in a manner that gives emphasis to regions with low R_{wp} , but with the ability to escape from local minima in R_{wp} .

The fundamental difference between Monte Carlo and simulated-annealing techniques concerns the way in which the parameter S is used to control the sampling algorithm. In the Monte Carlo method, S may be fixed or varied manually, whereas in simulated annealing, S is decreased systematically according to an annealing schedule or temperature-reduction procedure.^[167] A detailed description of the methodology underlying some simulated-annealing methods is given in refs. [32, 36]. The simulated-annealing method was first used in structure determination from powder diffraction data to solve the previously known crystal structure of benzene from simulated powder diffraction data.^[34] Although this example concerned a rigid molecule of high symmetry, the problem

was complicated by the assumption of space group $P1$, which requires the positions and orientations of all four molecules in the unit cell to be found independently. The simulated-annealing technique has since been applied to real experimental powder diffraction data in cases of rigid^[35] and flexible^[36–38, 41, 91] molecules. Details of the simulated-annealing methods adopted differ in several respects, including details of the temperature-reduction procedure and definition of the figure-of-merit.

5.3.4. Genetic-Algorithm Technique

Genetic Algorithms^[168–170] are optimization techniques based on the principles of natural evolution, and involve the familiar evolutionary operations of mating, mutation, and natural selection. By natural selection, the fittest members of a population survive and procreate, leading to improved individuals in subsequent generations, and leading ultimately to the optimal individual.

The possibility of using genetic-algorithm techniques in structure solution from powder diffraction data was realized independently by two research groups. Our approach^[46, 48, 49, 53, 57, 72, 84, 85, 171, 172] and the approach of Shankland, David and coworkers^[47, 71, 173] differ in the definition and handling of the fitness function, as well as other aspects of the way in which the genetic algorithm is implemented. Details can be found in the papers cited. A schematic flow-chart of our implementation of the genetic algorithm^[49] is shown in Figure 22.

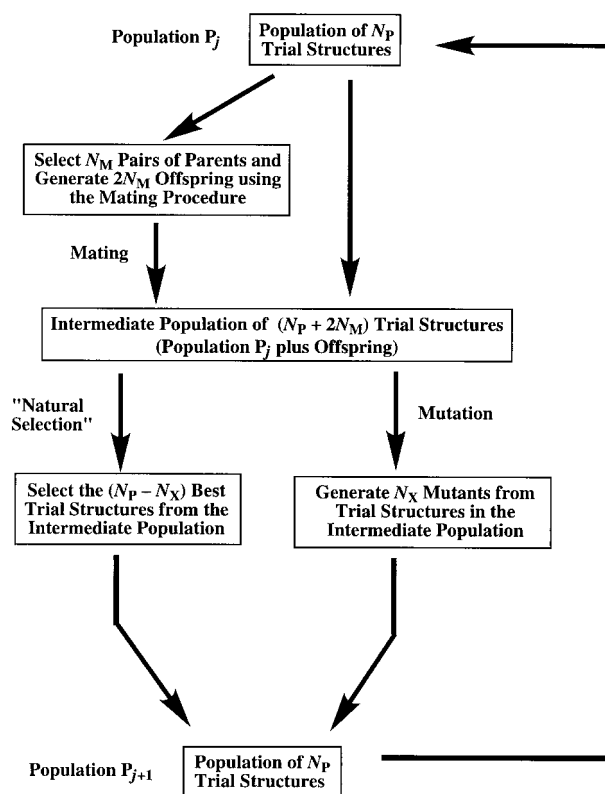


Figure 22. Flow chart representing the evolution of the population from one generation (population P_j) to the next generation (population P_{j+1}) in the genetic algorithm for powder structure solution.^[49]

In the genetic-algorithm approach for structure solution, the evolution of a population of trial crystal structures is investigated. Each member of the population is uniquely characterized by the set of variables Γ (see Section 5.3.1), and the set Γ can be regarded to define its “genetic code”. The initial population P_0 contains N_p randomly generated structures, and the population then evolves through subsequent generations by applying the evolutionary operations of mating, mutation, and natural selection. The number N_p of structures in the population is constant for all generations, and N_M mating operations and N_X mutation operations are performed in the evolution of the population from one generation to the next.

The probability that a given structure survives into subsequent generations, and the probability that it takes part in mating, depend on its fitness. In our implementation of the genetic algorithm,^[49] the fitness of a structure is defined as a function of its weighted profile R factor R_{wp} , and fitness therefore measures how well the structure agrees with the experimental powder diffraction data. A number of fitness functions $F(\rho)$ have been used, where it is convenient to use the scaled R factor $\rho = [R_{wp} - R_{min}] / [R_{max} - R_{min}]$, with R_{min} and R_{max} representing the lowest and highest values of R_{wp} in the current population, respectively. The values of R_{min} and R_{max} are continually updated as the population evolves during the genetic-algorithm calculation, representing “dynamic scaling” of the fitness function.

Before each mating operation, a structure (with fitness F) is chosen from the population at random and is allowed to participate in mating if $F > \mathfrak{R}$, where $\mathfrak{R}$ is a random number generated between 0 and 1. A second structure is then found using the same selection procedure, and the two structures are allowed to mate with each other. This procedure is repeated until N_M pairs of parents have been selected. Mating (cross-over) between two selected parents is carried out by combining the genetic codes of the two parents, although the actual strategy used depends on the complexity of the structural fragment. As an example, for a structural fragment with two torsional degrees of freedom, one method for mating involves partitioning the eight variables that define each structure into four groups $\{x, y, z | \theta, \phi, \psi | \tau_1 | \tau_2\}$. Two offspring are then generated, with each offspring taking two complementary groups from each parent. This operation may be carried out in three different (but equiprobable) ways from a given pair of parents, and thus mating the parents $\{x_a, y_a, z_a | \theta_a, \phi_a, \psi_a | \tau_{1a} | \tau_{2a}\}$ and $\{x_b, y_b, z_b | \theta_b, \phi_b, \psi_b | \tau_{1b} | \tau_{2b}\}$ leads with equal probability to one of the following pairs of offspring:

- $\{x_a, y_a, z_a | \theta_a, \phi_a, \psi_a | \tau_{1b} | \tau_{2b}\}$ and $\{x_b, y_b, z_b | \theta_b, \phi_b, \psi_b | \tau_{1a} | \tau_{2a}\}$
- $\{x_a, y_a, z_a | \theta_b, \phi_b, \psi_b | \tau_{1a} | \tau_{2b}\}$ and $\{x_b, y_b, z_b | \theta_a, \phi_a, \psi_a | \tau_{1b} | \tau_{2a}\}$
- $\{x_a, y_a, z_a | \theta_b, \phi_b, \psi_b | \tau_{1b} | \tau_{2a}\}$ and $\{x_b, y_b, z_b | \theta_a, \phi_a, \psi_a | \tau_{1a} | \tau_{2b}\}$

Many other methods for mating the two parents may be implemented, each with specific advantages under particular circumstances.

Each mating operation leads to two offspring, giving a total of $2N_M$ offspring in each generation. These offspring together with all N_p structures from the previous generation give rise to an intermediate population of $(N_p + 2N_M)$ structures. These structures are then ranked according to fitness in preparation for the natural-selection process (see below). If two or more

structures are identical within predefined tolerance limits, all but one of these structures is eliminated from the intermediate population.

In each generation, some mutant structures are also generated to maintain diversity within the population (note that mutations create new genetic material within the population, whereas mating redistributes the existing genetic material). For mutation, N_X structures are selected at random from the intermediate population, and mutants are generated from these structures by making random changes to one or more variables in the set Γ . These changes may be new random values (static mutation) or small random displacements from the existing value (dynamic mutation). It is important to note that the “parent” structures used to create the mutants are not replaced by the mutants, but remain within the intermediate population.

As shown in Figure 22, the next generation is constructed by taking the $(N_p - N_X)$ members of highest fitness from the intermediate population (analogous to “natural selection” in biological evolution) together with the N_X mutant structures generated from the intermediate population. On passing from one generation to the next, the best structure in the population (corresponding to R_{min}) must either improve or remain the same, and the overall quality of the population (assessed from the average value of R_{wp}) usually improves. Figure 11 shows a typical plot of the evolution of R_{wp} for the best structure in the population and the average value of R_{wp} for the structures in the population as a function of generation number in a genetic-algorithm structure-solution calculation.

The evolutionary cycle shown in Figure 22 is repeated for a specified number of generations or until convergence is reached. Typically, our genetic-algorithm structure-solution calculations have involved a population size (N_p) of a hundred (or fewer) structures, and typically 50 to 100 mating operations (N_M) and 10 to 20 mutation operations (N_X) are carried out in each generation. In general, a few hundred generations are usually sufficient to obtain the correct structure solution.

In our most recent implementation of the genetic-algorithm method,^[85] each new structure generated during the calculation is subjected to local minimization of R_{wp} with respect to the structural variables in the set Γ , and only these minimized structures are used subsequently in the evolution of the population. Introduction of local minimization in this way improves the efficiency of the calculation in terms of a significant reduction in the number of generations required to find the correct structure solution. Furthermore, the reliability and reproducibility in terms of finding the correct structure solution (for example, in repeated runs from different random initial populations) are also substantially improved. These advantages of introducing local minimization of R_{wp} may be attributed to a favorable combination of stochastic (i.e. the genetic algorithm) and deterministic (i.e. the minimization) components within the global-optimization strategy. As the genetic characteristics of each structure sampled on the R_{wp} hypersurface become modified in the minimization step depending on the nature of its local environment, the genetic algorithm incorporating local minimization represents Lamarckian (rather than Darwinian) evolution.

In comparison with other approaches for global optimization, we note that genetic-algorithm methods simultaneously investigate different regions of parameter space. Furthermore, information from different regions of parameter space is passed actively between different members of the population by the mating operation. In implementing genetic-algorithm techniques, there is considerable scope for diversity in the methods and rules for carrying out the different evolutionary operations and in the definition of the fitness function. Furthermore, details of the flow-chart shown in Figure 22 may differ from one implementation to another. To fully understand how to optimize the genetic-algorithm approach for particular types of structural problem or particular sets of diffraction data, it is necessary to consider and assess a wide-range of strategies for carrying out the different evolutionary operations.^[49, 174]

5.3.5. Combinations of Techniques

Direct-space approaches have also been used in combination with other techniques to facilitate structure solution. An example concerns the use of structure envelopes to reduce considerably the region to be explored by direct-space techniques and hence the computer time required to solve the structure. One such approach is based on a combination of the maximum entropy and likelihood method^[175] and the Monte Carlo method, and has been used to study organic materials.^[69] The maximum entropy and likelihood method is used to generate an electron-density map which establishes the regions of the asymmetric unit in which the molecule is most likely to be located. At lower than atomic resolution, this map is then investigated visually and a molecular model is fitted to the electron-density map. The structural model generated in this way is then modified within the structure envelope by means of a Monte Carlo calculation.

In a related approach, the structure envelope is defined by a periodic nodal surface generated from a few strong low-index reflections extracted from the powder diffraction pattern followed by exploration of this region of parameter space by using a grid search procedure.^[106] The success of this procedure has been demonstrated for organic and ionic materials as well as zeolite structures. In some cases, the initial fit of the model to the structure envelope is sufficiently good to allow Rietveld refinement to proceed directly, without the need for subsequent improvement using a direct-space structure solution calculation.

5.4. Rietveld Refinement

In Rietveld refinement of a crystal structure from powder diffraction data,^[3, 4] every point in the digitized powder diffraction profile is considered as an individual intensity measurement. In Rietveld refinement, the calculated powder diffraction pattern is compared, point by point, with the experimental powder diffraction pattern, and selected parameters defining the structural model and/or the profile are adjusted by least-squares methods to obtain an optimal fit between the experimental and calculated powder diffrac-

tion patterns. Several criteria can be used^[4, 162] to assess the agreement between the experimental and calculated powder diffraction patterns, and the most common figure-of-merit is the weighted profile *R* factor R_{wp} . Some commonly used programs for Rietveld refinement are GSAS,^[176] FULLPROF,^[177] PROFIL,^[178] DBW,^[179] and RIETAN.^[180]

For successful Rietveld refinement, the initial structural model (from the structure solution) must be a sufficiently good representation of the correct structure. As Rietveld refinement can often suffer from problems of instability, it is generally necessary to use geometric restraints (soft constraints) based on standard molecular geometries to bias the refinement towards structurally reasonable results and to prevent excessive shifts in the atomic positions. In general, the introduction of restraints allows more parameters to be refined than would be possible in unrestrained refinement from the same experimental data, and indeed refinement is often successful only if appropriate restraints are imposed.

5.5. Other Considerations

General experimental factors relating to the measurement of powder diffraction data have been reviewed elsewhere,^[11] and here we highlight only certain selected aspects.

First, we consider the relative merits of using synchrotron X-ray powder diffraction data versus conventional laboratory powder X-ray diffraction data (see also Section 2.4), recognizing that the good vertical collimation and high brightness of synchrotron radiation lead to powder diffraction data of higher resolution and often of improved signal/noise ratio. With high resolution, problems arising from peak overlap can be alleviated to some extent, allowing less ambiguity in the intensities of individual reflections extracted from the powder diffraction pattern. In this regard, synchrotron radiation is generally advantageous when traditional techniques (or a direct-space technique using a figure-of-merit based on extracted intensities) are to be used for structure solution. The higher resolution of synchrotron data may also be particularly advantageous at the stage of indexing the powder diffraction pattern. As discussed in Section 3, however, much successful structure determination has been achieved using conventional laboratory powder X-ray diffraction data, and in general, the use of synchrotron data is essential only in certain specific cases.

Second, structure solution from powder diffraction data has a good chance of success only if the experimental powder diffraction pattern contains reliable information on the intrinsic relative intensities of the diffraction maxima, which requires that there is no substantial "preferred orientation" in the powder sample. Preferred orientation arises when the crystallites in the powder are oriented preferentially in certain directions, and can be particularly severe when the crystal morphology is strongly anisotropic (e.g. long needles or flat plates). When there is a nonrandom distribution of crystallite orientations in the sample, the measured relative peak intensities differ from the intrinsic relative diffraction intensities, limiting the prospects for determining reliable structural information from the powder diffraction pattern. The existence of preferred orientation can be detected by meas-

uring powder diffraction data for the same sample in different sample holders (e.g. capillary versus flat sample) or for different measurement geometries (e.g. reflection versus transmission). Experimental approaches for reducing the extent of preferred orientation include the use of a capillary or end-loading sample holder, mixing the sample with an amorphous material, spray-drying, or appropriate grinding to induce a crystal morphology that is as isotropic as possible. For experimental data affected by preferred orientation, corrections can be made during structure refinement^[181] once a sufficiently good structural model is known. Methods have also been reported^[182, 183] for the early detection of preferred orientation (by mathematical means) and the application of corrections based on statistical analysis of extracted intensities.

In general, direct-space structure solution techniques are probably more robust than traditional techniques when the experimental data are affected by preferred orientation, presumably because a substantial amount of structural knowledge is already input into the calculation through the use of a structural fragment. Thus, the Monte Carlo method has led to the successful structure determination of benzoic acid,^[184] 5-bromonicotinic acid,^[185] and the 1:1 cocrystal formed between 1,2,3-trihydroxybenzene and hexamethylenetetramine^[60] from experimental powder diffraction data known to be significantly affected by preferred orientation. In these cases the structure solution process was carried out in the normal manner and corrections for preferred orientation were only introduced at the refinement stage.

6. Concluding Remarks

The techniques and methods presented here for structure determination from powder diffraction data represent powerful additions to the range of experimental techniques that may be used for structure determination of solids. In recent years, significant advances in the opportunities for structure determination from powder diffraction have arisen mainly from advances in techniques for overcoming the intrinsic problems encountered in the structure-solution stage of the structure-determination process. The examples highlighted in this article represent a contemporary snapshot of the current status of this field, and there is every reason to be confident that the progress made in recent years (illustrated in Figure 3) will continue long into the future. Thus, the future application of the techniques that are now available promises to reveal new and important insights in several areas for which structural characterization by single-crystal diffraction techniques has hitherto proven intractable.

Looking towards the future, continued advances in the capabilities and efficiencies of the techniques used at each stage of the structure-determination process, coupled with continual improvements in the instrumentation for data collection and in the speed of computers for data analysis, will allow existing problems to be tackled more routinely and will extend the boundaries of the methodology towards larger and more challenging problems. Undoubtedly the ultimate aim is to extend the application of powder diffraction

techniques into the biological arena, and the recent demonstration^[186] of the successful refinement of a *known* protein structure (the 1261-atom protein metmyoglobin) from synchrotron X-ray powder diffraction data provides a glimpse of future possibilities for the complete structure determination of new protein structures from powder diffraction data. While substantial further development and optimization of techniques for structure solution are required before this dream may become a reality, it is nevertheless relevant to note that, in the field of molecular crystallography, the current scope of powder diffraction techniques for complete structure determination is somewhat comparable to the state-of-the-art in single-crystal diffraction around the 1950s.^[187] We may forecast with optimism that the future evolution in the capabilities of powder diffraction techniques for structure determination will mirror the developments that have taken place in the capabilities of single-crystal diffraction techniques in the last 50 years.

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Improving Enantioselective Fluorination Reactions: Chiral *N*-Fluoroammonium Salts and Transition Metal Catalysts**

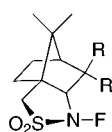
Kilian Muñiz*

Within the still-growing field of enantiomerically pure compounds, research into chiral fluorinated molecules is gathering momentum due to the unique properties of the carbon–fluorine bond, and the importance of the fluorine moiety in molecules of pharmaceutical and biological interest is undisputed.^[1] Among all the asymmetric processes towards organofluoro compounds, the direct synthesis of fluorinated stereogenic centers remains especially challenging. Basically, two different routes are conceivable for their asymmetric construction: 1) nucleophilic substitution reactions with a fluoride anion and 2) electrophilic addition of fluoronium cations to activated or masked carbanions. First attempts on enantioselective nucleophilic fluorination date back to the pioneering work of Hann and Sampson.^[2] In an ambitious dehydroxylation/fluorination sequence the authors treated a racemic α -trimethylsiloxy ester with half an equivalent of an enantiomerically pure proline-derived aminotrifluorosulfurane in hope of achieving a kinetic resolution. Unfortunately, the fluorinated product was obtained without significant enantiomeric excess.

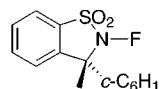
Ever since then, routes towards fluorinated stereogenic centers have relied on electrophilic fluorine sources for substitution reactions.^[3] This caused the development of a variety of suitable achiral N-F-fluorinating reagents^[4] and their exploitation in diastereoselective fluorinations that are characterized by efficient substrate control and reasonably high diastereoselectivities.^[5a] Important contributions were made by Davies and co-workers,^[5b–d] Enders et al.,^[5e] Taylor et al.,^[3] and Liotta and co-workers.^[5f] At about the same time, chiral nonracemic N-fluoro compounds were developed for direct enantioselective fluorination of C–H acidic substrates.

Initial work on reagent control by Diferding and Lang, who introduced chiral *N*-fluorosultam **1a**,^[6] was followed by the

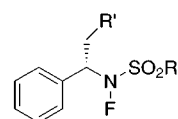
introduction of modified structures **1b,c**^[7] and the development of related compounds such as **2**^[8] and **3**.^[9] All these



1 a: R = H
b: R = Cl
c: R = OCH₃



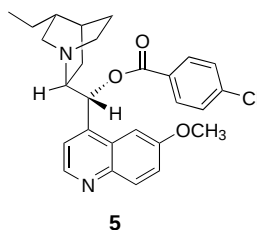
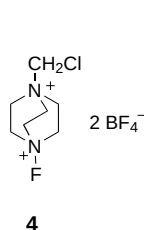
2



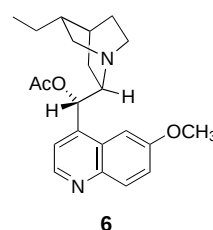
3 (R' = H, OAc;
R'' = CH₃, *p*-Tol)

chiral reagents require a sulfonamido group for activation of the N–F bond. Metalated enolates generated in situ serve as substrates and the enantiomeric excesses generally reach satisfying values of up to 80 %. However, the disadvantage of these reagents is their tiresome multistep synthesis with use of hazardous fluorine sources, such as FClO₃ or F₂ itself.

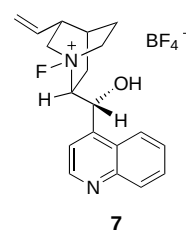
Recently, two reports have described the preparation and application of enantiopure *N*-fluoroammonium salts from cinchona alkaloids. In an elegant contribution, Takeuchi and co-workers used an in situ protocol to generate the active fluorinating species from each of the neutral compounds **5** and **6**, with Selectfluor **4**.^[10] (Selectfluor is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).^[11] It is also known as F-TEDA.) Independently, Cahard et al.



5



6



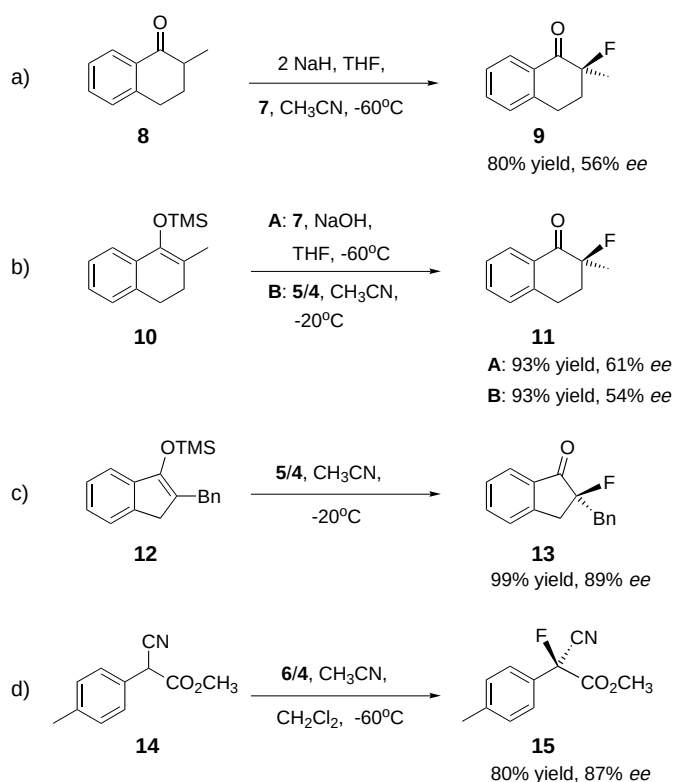
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described the synthesis of preformed cinchona alkaloid ammonium salts such as **7**.^[12, 13]

With the conventional in situ generation of metallated enolates, **7** could be employed for enantioselective fluorination of α -methyl tetralone (**8**, Scheme 1a). Two equivalents of base were necessary to deprotonate the acidic hydroxyl functionality of **7** in order to prevent competitive enolate



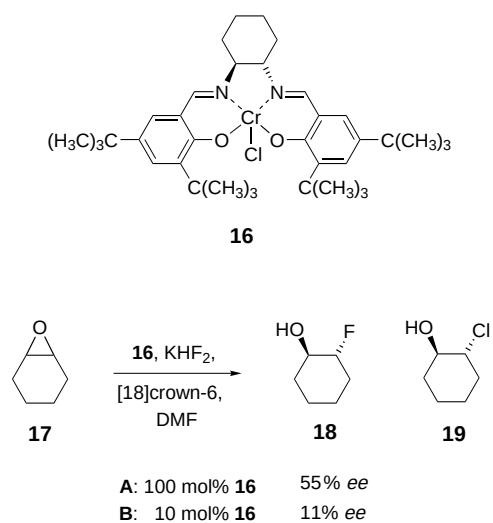
Scheme 1. Representative examples of enantioselective fluorinations with chiral quaternary *N*-fluoroammonium salts. TMS = trimethylsilyl, Bn = benzyl.

protonation. Unlike the cases for the unreactive neutral compounds **1–3**, preformed silyl enol ether **10** was now cleanly fluorinated by both the synthesized reagent **7** and the combination of **4** and **5** (Scheme 1b). This shows that the cationic nature of the new reagents results in higher fluorination power. However, since in the present systems both rate and enantioselectivity appear to be highly dependent on the reaction temperature, a precise comparison of the results is difficult. Under otherwise unchanged conditions, Takeuchi and co-workers observed an increase in *ee* value for five-membered substrates such as **12** relative to the *ee* value observed for **11** (Scheme 1c). Further successful examples include β -keto esters (up to 80% *ee*) and acyclic β -cyano esters such as **14** (Scheme 1d). For the latter case, preformation of the ammonium reagent from **6** and **4** was required to achieve high enantioselectivity.

Obviously, the switch from neutral N–F compounds to N–F ammonium salts did not only have a strong beneficial effect on reactivity; the commercial availability of both Selectfluor and cinchona alkaloids also ensures easy accessibility of the chiral reagents. Still, from an economical point of view a catalytic version of the process would certainly be desirable. Preliminary ^{19}F NMR studies reveal that the F^+ transfer from Selectfluor onto the cinchona alkaloid is seemingly fast and irreversible,^[10, 13] which brings a catalytic version within reach.^[14]

Within the context of asymmetric synthesis, it is intriguing that no use of chiral nonracemic metal complexes for fluorination reactions was reported for a long time. Given the extreme success of asymmetric metal-mediated and

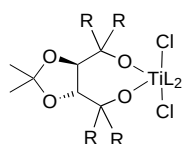
-catalyzed processes,^[15] such an approach must appear highly attractive. Bruns and Haufe have now described the first examples of a transition metal complex mediated asymmetric ring-opening (ARO) of both *meso*- and racemic epoxides by formal hydrofluorination.^[16] Initial attempts with chiral Eu^{III} complexes led to very low asymmetric induction. Opening of cyclohexene oxide **17** with potassium hydrogen difluoride in the presence of [18]crown-6 and a stoichiometric amount of Jacobsen's chiral chromium salen complex **16**^[17a] finally yielded two products **18** and **19** in an 89:11 ratio and 92% combined yield, with the desired product **18** being formed with 55% *ee*. Limiting **16** to a catalytic amount of 10 mol% led to an increase in the ratio of **18**; however, the enantiomeric excess dropped to 11% (Scheme 2).



Scheme 2. First nucleophilic enantioselective epoxide opening with enantiopure transition metal Lewis acid **16**.

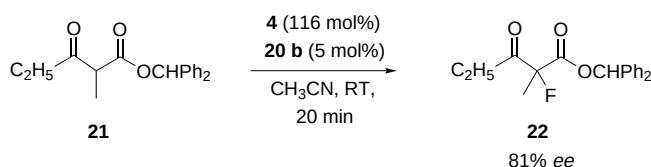
In the stoichiometric reaction the low extent in which chloride-promoted ring opening occurs is noteworthy. In a stoichiometric ARO of **17** with **16** and TMSN_3 , Jacobsen reported complete incorporation of the chloride atoms,^[17a] which indicates that under the reaction conditions no anion exchange takes place at the metal complex prior to ring opening. Since in the present case Cl^- displays a much higher nucleophilicity than F^- , an identical product distribution should have been expected. The fact, however, that this is not the case, leads to the conclusion that the chromium complex acts as a conventional Lewis acid that activates the epoxide for ARO by F^- . The amount of chloride incorporation is likely to be the consequence of competing ring opening by free chloride ions generated under the reaction conditions. One can almost assume that the present catalytic system cannot be operating by the cooperative mechanism^[17a,b] that has been so successful in the related AROs described by Jacobsen.^[17c] Furthermore, the dramatic drop in enantioselectivity in the catalytic reaction suggests that the fluoride source does not allow for rapid release of the catalyst after the ARO has occurred, which thus results in uncatalyzed, unselective ring opening. Final conclusions will have to await further detailed mechanistic investigation.^[18]

A first real breakthrough in transition metal catalyzed fluorination has recently been achieved by Hintermann and Togni.^[19] In their work, monosubstituted β -keto esters such as **21** were chosen as starting materials and focus was placed on Lewis acid activation. It was anticipated that the necessary enolization of the β -keto esters would be accelerated by catalytic amounts of metal complexes. From kinetic screening, complexes based on titanium emerged as the most suitable catalysts, and TADDOL-modified^[20] titanium complexes **20a** and **20b** were the most successful ones in terms of asymmetric induction. Isolation of these complexes, which during the course of this work^[19] was achieved for the first time, was necessary to guarantee reproducibility and enantioselectivity. In the presence of 5 mol % of catalyst and a slight excess of the fluorinating agent **4**, conversion into fluorinated products such as **22** occurred smoothly in acetonitrile at room temperature (Scheme 3). Not surprisingly, the sterically more elaborated complex **20b** gave rise to higher enantioselectivities than **20a** (62–90% *ee* versus 28–59% *ee* for the given examples) but it is interesting to see that it also represents the more reactive catalyst: for example, in the presence of **20b** the reaction time for conversion of **21** is 20 minutes, while with **20a** it is 2 hours!



20 a: R = Ph, L₂ = (CH₂OCH₃)₂

b: R = 1-Nph, L₂ = 2 NCCH₃



Scheme 3. First enantioselective electrophilic fluorination reaction catalyzed by enantiopure Ti-TADDOLates **20a,b**. The absolute configuration of the product is unknown.

Current understanding of the reaction suggests that an unprecedented mechanism is operating. Unlike classical Lewis acid catalyzed reactions,^[21] the metal complex does not activate the carbonyl moiety but is thought to enhance the degree of enolization and thus create the necessary nucleophilic enol structure for reaction with the fluorinating agent.^[22]

Regarding enantioselectivities this new catalytic fluorination can readily compete with the results from stoichiometric reactions with chiral N–F compounds, and the fact that both the TADDOL ligands and the fluorine source *Selectfluor* are commercially available makes it the most convenient method presently at hand. Since the reaction is so far limited to β -keto esters, it will be interesting to see whether this catalyst system can be transferred successfully to other substrate classes. Clearly the enantioselective synthesis of fluorinated stereo-

genic centers other than quaternary ones remains a huge challenge. Future work could also aim to combine the two novel fluorination procedures. Especially where reaction rate is concerned, combined use of (achiral) transition metal catalyst and substoichiometric amounts of cinchona alkaloids might give rise to successful complementary catalytic systems.

To summarize, the development of novel enantioselective fluorination methods with the aid of either chiral N-fluoroammonium salts or transition metal catalysts has established truly practical routes towards chiral fluorinated compounds. Despite the current mechanistic uncertainties it appears that a door has been opened for exciting and promising further development of asymmetric (catalytic) fluorination reactions in the near future.^[23]

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Versatile Scorpionates—New Developments in the Coordination Chemistry of Pyrazolylborate Ligands

Frank T. Edelmann*

More than 30 years after their discovery poly(pyrazolyl)-borate ligands (scorpionates) still belong to the work horses in coordination chemistry.^[1] These anions, normally associated with the name Trofimenko, are among the most often used complex ligands.^[2,3] This is true for various main group elements as well as numerous transition metals, lanthanoids, and actinoids. These ligands are so popular due to their reliability and accountability as spectator ligands, which normally do not interfere with the reaction scenarios occurring at the metal centers. Tris(pyrazolyl)borates ($\text{Tp} \equiv \text{HB}(\text{pz})_3$) generally coordinate as tridentate ligands through three nitrogen atoms of the pyrazole rings ($\kappa^3\text{N},\text{N}',\text{N}''$), thereby providing effective steric shielding of the metal center.^[3,4] By introducing suitable substituents (e.g. Me, CF_3 , *t*Bu, Ph) particularly in the 3-position of the pyrazolyl rings this effect can be tuned to a large extent. Cone angles much larger than 180° can be achieved with the use of such sterically demanding scorpionate ligands, which, for example, have been utilized to realize unusual bonding (e.g. monomeric zinc hydroxides).^[3] Besides the very common $\kappa^3\text{N},\text{N}',\text{N}''$ coordination mode the tridentate $\kappa^3\text{N},\text{N},\text{B}-\text{H}$ type^[5] and the bidentate $\kappa^2\text{N},\text{N}'$ coordination^[6] are also known. Higher hapticities could thus far only be achieved in cases where the substituents in 3-position of the pyrazole rings contained additional donor atoms. For example, the three pyridyl substituents of the ligand Tp^{py} make it potentially hexadentate.^[7] Due to their identical charge, facial coordination, and the fact that both may formally act as six-electron donors, the Tp^- ions have often been compared to the cyclopentadienyl ligands.^[3]

Several recent contributions have demonstrated that the coordination modes of tris(pyrazolyl)borate ligands can be far more versatile than hitherto anticipated. In addition to new findings concerning the electronic properties of the scorpion-

ates, unknown coordination modes as well as novel reaction patterns have been discovered.

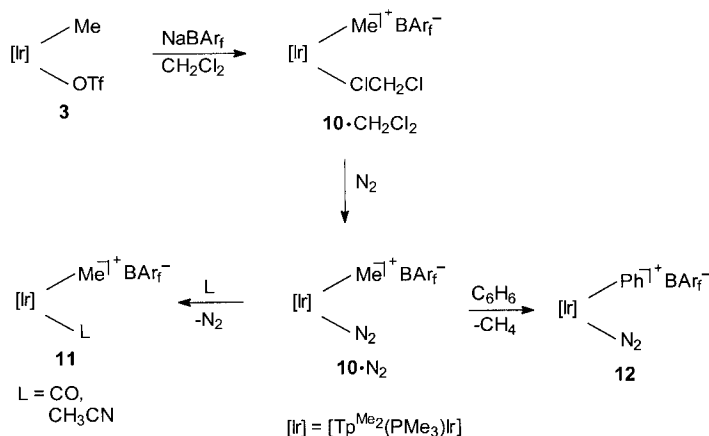
1. Electronic Effects

With respect to its steric bulk the hydrotris(3,5-dimethylpyrazolyl)borate anion (Tp^{Me_2})⁻ is regarded as a steric equivalent of the pentamethylcyclopentadienyl (Cp^*) ligand.^[3d] However, conflicting reports can be found in the literature on the electron-donating properties of hydrotris-(pyrazolyl)borate (Tp) and Tp^{Me_2} in comparison to C_5H_5 (Cp) and C_5Me_5 (Cp^*).^[8] Most researchers claim that the ligands Tp and Tp^{Me_2} are stronger electron donors than Cp and Cp^* . In a recent study on C–H activation reactions by $[(\text{Tp}^{\text{Me}_2})\text{Ir}]$ complexes Bergman et al. were able to show the opposite effect, that is that the Tp^{Me_2} derivatives are *less electron rich* than the corresponding $[\text{Cp}^*\text{Ir}]$ complexes.^[9] The starting point for this investigation was the known fact that the iridium(III) complexes $[\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{Me})][\text{OTf}]$ (**1**, $\text{OTf} = \text{OSO}_2\text{CF}_3$) and $[\text{Cp}^*(\text{PMe}_3)\text{IrMe}(\text{ClCH}_2\text{Cl})][\text{BAR}_f]$ (**2**, $\text{BAR}_f = \text{B}[3,5-(\text{CF}_3)_2\text{C}_6\text{H}_3]_4$) are capable of cleaving C–H bonds in a wide variety of hydrocarbons under extremely mild conditions.^[10] As part of the search for robust ligands for the stabilization of the reactive cationic Ir^{III} species the triflate **3** was synthesized as the first target molecule (Scheme 1).

The first evidence for a reverse electronic effect of the Tp^{Me_2} ligand came from the finding that the Ir–O bond (212.8(5) pm) in **3** is shorter than that in the Cp^* derivative **1** (221.6(10) pm).^[10] In good agreement it was found that the reaction of $[\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{H})_2]$ (**4**) with $[(\text{Tp}^{\text{Me}_2})(\text{PMe}_3)\text{Ir}(\text{H})_2\text{H}][\text{OTf}]$ (**5**) results in quantitative formation of $[\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{H})_3][\text{OTf}]$ (**6**) and $[(\text{Tp}^{\text{Me}_2})(\text{PMe}_3)\text{Ir}(\text{H})_2]$ (**7**). Thus the equilibrium lies heavily in favor of the protonated (i.e. more strongly basic) Cp^* complex. This result was further confirmed by a comparison of the IR stretching absorbances of $[(\text{Tp}^{\text{Me}_2})\text{Ir}(\text{CO})_2]$ (**8**, 2039, 1960 cm^{-1})^[6a] and $[\text{Cp}^*\text{Ir}(\text{CO})_2]$ (**9**, 2020, 1953 cm^{-1}) which were reported by Graham et al.^[11] Here too it becomes clear that the metal center in the Tp^{Me_2} compound is *less electron rich*.

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In the case of C–H activation by $[\text{Cp}^*\text{Ir}]$ complexes it was possible to substantially increase the reactivity of $[\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{Me})][\text{OTf}]$ (**1**) through formation of the cationic complex $[\text{Cp}^*(\text{PMe}_3)\text{IrMe}(\text{ClCH}_2\text{Cl})][\text{BARf}]$ (**2**).^[10b] Analogous treatment of **3** with NaBARf in CH_2Cl_2 surprisingly afforded the cationic dinitrogen complex **10**· N_2 (Scheme 1),

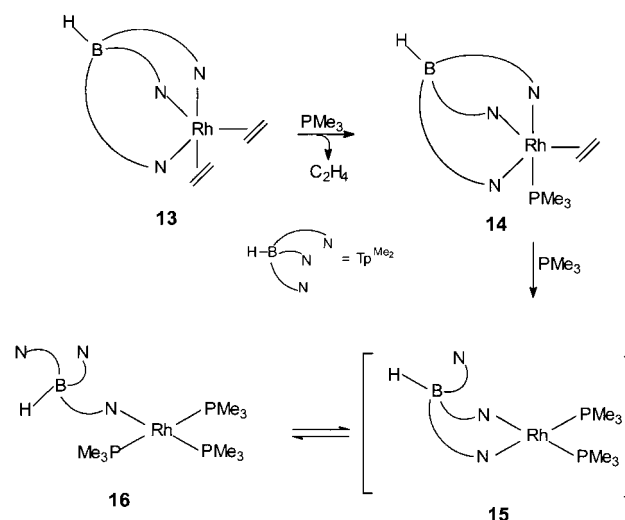


Scheme 1. Preparation and reactivity of the cationic $[(\text{Tp}^{\text{Me}_2})\text{Ir}^{\text{III}}]$ complexes **10**· CH_2Cl_2 and **10**· N_2 .^[9]

which is the first reported structurally characterized complex of this type. The thermally very labile CH_2Cl_2 complex **10**· CH_2Cl_2 can be isolated in the absence of N_2 , while under nitrogen atmosphere **10**· N_2 is instantaneously generated again. Both N_2 and CH_2Cl_2 are rapidly displaced by donor ligands such as CO or MeCN under quantitative formation of the cationic complexes **11**. Benzene reacts with **10**· N_2 at room temperature to yield the phenyliridium complex **12** and methane.^[9]

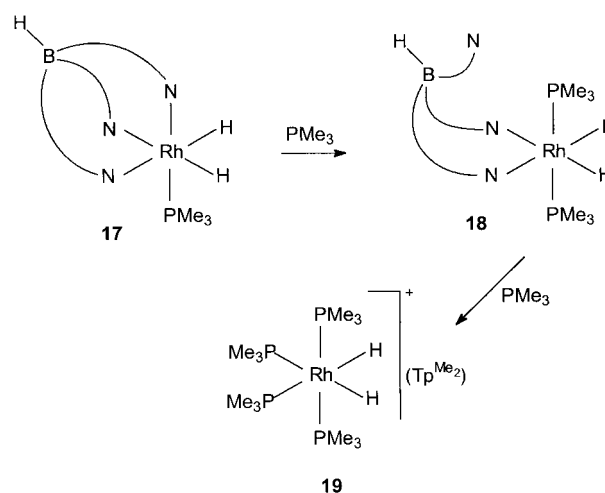
2. Novel Coordination Modes

Recently several authors have reported on new coordination modes of tris(pyrazolyl)borate anions. Both unusually low (κ^1 , “ κ^0 ”) and high (κ^5) hapticities have been realized or unambiguously proven for the first time. Here too a comparison with the corresponding cyclopentadienyl complexes is of interest. Variable coordination modes are well documented for cyclopentadienyl complexes.^[12] An instructive example is the reaction of $[\text{CpRe}(\text{NO})(\text{Me})(\text{PMe}_3)]$ with PMe_3 in which products with $\eta^5\text{-C}_5\text{H}_5$, $\eta^3\text{-C}_5\text{H}_5$, and $\eta^1\text{-C}_5\text{H}_5$ coordination and even ionic “ η^0 ”- C_5H_5^- derivatives have been detected.^[13] Recently, Paneque, Monge, and Carmona et al. were able to realize similar denticity changes in a rhodium pyrazolylborate system and thereby isolate for the first time an ionic complex containing a “naked” κ^0 - Tp^{Me_2} ligand.^[14] In the course of this investigation it was possible to interconvert $\text{Tp}^{\text{Me}_2}\text{-}\kappa^3\text{N}$, $\kappa^2\text{N}$, $\kappa^1\text{N}$, and “ κ^0 ” complexes. Treatment of either $[(\text{Tp}^{\text{Me}_2})\text{Rh}(\text{C}_2\text{H}_4)]$ (**13**) or $[(\text{Tp}^{\text{Me}_2})\text{Rh}(\text{C}_2\text{H}_4)(\text{PMe}_3)]$ (**14**) with an excess of PMe_3 (ca. 5–6 equivalents, 20 °C) according to Scheme 2 afforded the stable tris(phosphane) complex **16** as the final product. Under modified reaction conditions it was possible to isolate the bis(phosphane) intermediate **15**, albeit not in an analytically pure form.



Scheme 2. Formation of the tris(phosphane)rhodium(I) complex **16** involving $\text{Tp}^{\text{Me}_2}\text{-}\kappa^1\text{N}$ coordination.^[14]

The long $\text{Rh}\cdots\text{H}(\text{B})$ separation of 259(4) pm in **16** is in agreement with the presence of a $\text{Tp}^{\text{Me}_2}\text{-}\kappa^1\text{N}$ coordination.^[14] The reaction sequence shown in Scheme 3 produced the most

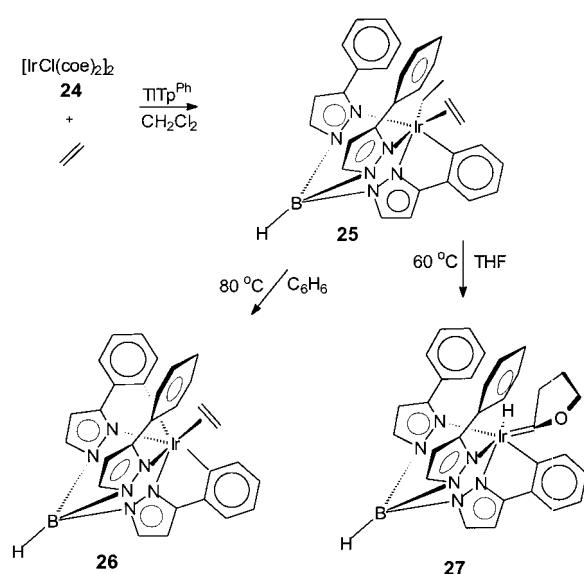


Scheme 3. Preparation of the saltlike compound **19** containing a “naked” tris(pyrazolyl)borate ion ($\text{Tp}^{\text{Me}_2}\text{-}\kappa^0\text{N}$).^[14]

interesting result. Heating of the dihydrido complex $[(\text{Tp}^{\text{Me}_2}\text{-}\kappa^3\text{N})\text{Rh}(\text{H})_2(\text{PMe}_3)]$ (**17**) in the presence of PMe_3 initially yielded the isolable bis(phosphane) $\text{Tp}^{\text{Me}_2}\text{-}\kappa^2\text{N}$ complex **18** and subsequently the unusual ionic compound $[(\text{Tp}^{\text{Me}_2}\text{-}\kappa^0\text{N})\text{Rh}(\text{H})_2(\text{PMe}_3)_3][\text{Tp}^{\text{Me}_2}]$ (**19**), which could also be generated by treatment of $[(\text{Tp}^{\text{Me}_2})\text{Rh}(\text{H})_2(\text{PMe}_3)_4]\text{Cl}$ (**20**) with KTp^{Me_2} . A crystal structure determination of the analogous complex $[(\text{Tp}^{\text{Me}_2})\text{Rh}(\text{H})_2(\text{PMe}_3)_4][\text{Tp}]$ (**21**) confirmed the presence of the first saltlike complex containing “naked” tris(pyrazolyl)borate anions ($\text{Tp}^{\text{Me}_2}\text{-}\kappa^0\text{N}$). There is no bonding interaction between the Rh^{III} center and the Tp^- ion. The stepwise change in the denticity of pyrazolylborate ligands from κ^3 to “ κ^0 ” as reported here for the first time may have important implications in catalytic uses of Tp metal complexes. As another novelty among the low-denticity coordination modes of

scorpionate ligands the $\kappa^2N, B-H$ coordination involving an agostic B-(μ -H) metal interaction should be mentioned here. Two examples have been reported recently, that is the compounds $[(Tp^{Me_2,4-Cl-\kappa^2N,B-H}Rh(CO)(PMePh_2)_2)]$ (**22**)^[15] and $[Tp^{Me_2-\kappa^2N,B-H}Rh\{P(C_7H_7)_3\}]$ (**23**).^[16] According to studies by Herberhold et al. **23** is a rhodium(i) complex of the sterically demanding tris(1-cyclohepta-2,4,6-trienyl)phosphane ligand, for which the $Tp^{Me_2-\kappa^2N,B-H}$ coordination involving a nonlinear B-(μ -H)-Rh bridge could be unambiguously proven by X-ray diffraction.^[16]

Denticities beyond κ^4 were unknown for Tp^R ligands where R contained no heteroatom. Recently, Slugovc and Carmona et al. reported for the first time on the unusual κ^5 coordination of hydrotris(3-phenylpyrazolyl)borate ligands (Tp^{Ph}).^[17] The reaction of $[[IrCl(coe)_2]_2]$ (**24**, coe = cyclooctene) with ethylene and $TiTp^{Ph}$ in CH_2Cl_2 initially produced the cyclometalated complex $[(Tp^{Ph-\kappa^4N,N,N,C^{Ph}}Ir(Et)(\eta^2-C_2H_4)]$ (**25**) (Scheme 4). Prolonged heating (17 h) in refluxing benzene



Scheme 4. Preparation of the cyclometalated complexes $[(Tp^{Ph-\kappa^4N,N,N,C^{Ph}}Ir(Et)(\eta^2-C_2H_4)]$ (**25**) and $[(Tp^{Ph-\kappa^5N,N,N,C^{Ph}}Ir(\eta^2-C_2H_4)]$ (**26**).^[17]

converted **25** into the novel bis-cyclometalated species $[(Tp^{Ph-\kappa^5N,N,N,C^{Ph},C^{Ph}}Ir(\eta^2-C_2H_4)]$ (**26**) which was formed as the only product. This compound is the first instance of κ^5 coordination of a scorpionate ligand in which the substituents at the pyrazolyl rings contain no donor atoms. If the same thermolysis reaction is carried out in refluxing THF the Fischer-carbene complex **27** is formed as the sole product.

Yet another entirely new aspect of scorpionate coordination chemistry is the η^5 coordination of a pyrazole ring. Despite the formal similarities with the cyclopentadienyl ligands (vide supra),^[3] a π interaction between a pyrazolylborate ligand and a metal center has never been encountered. A first successful approach was recently reported by Gorun et al.^[18] The reaction of CuCl with $KTp^{CF_3,Me}$ ($Tp^{CF_3,Me}$ = hydrotris(3-trifluoromethyl-5-methylpyrazolyl)borate) unexpectedly afforded a blue complex of the composition $[(KTp^{CF_3,Me})_2(CuCO_3)]_2$ (**28**) in 11% yield. Atmospheric

CO_2 must be responsible for the formation of the carbonate ligand, since the preparation of **28** was carried out in air. A $[(\mu^4-CO_3)_2Cu_2K_4]$ unit forms the central part of the complex molecule. Of special interest is the coordination environment around the potassium center (Figure 1). One of the coordination hemispheres of K1 is occupied by two carbonate

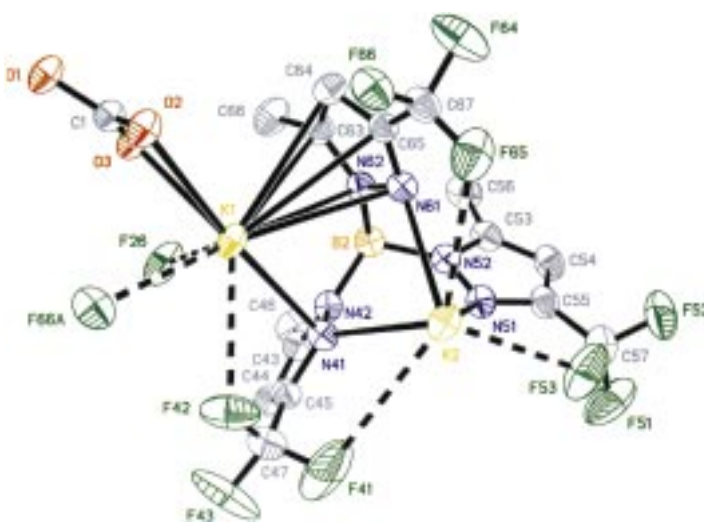


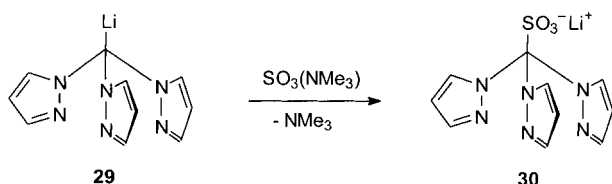
Figure 1. Section of the molecular structure of $[(KTp^{CF_3,Me})_2(CuCO_3)]_2$ (**28**) clearly showing the π coordination of a pyrazolyl ring.^[18]

oxygen atoms, one N atom of the $Tp^{CF_3,Me}$ ligand, and three fluorine atoms. On the opposite side the potassium ion is located directly above the center of a pyrazole ring, thus allowing a comparison with the η^5 -cyclopentadienyl coordination in polymeric KCp .^[19] With an average value of 337 pm the corresponding K-C (pyrazolyl) distances are somewhat longer than those in KCp (av 305.6 pm). Nevertheless these values clearly indicate for the first time the presence of η^5 coordination involving a scorpionate pyrazole ring, which results in a formal coordination number of 9 around the K1 center.

3. New Ligands

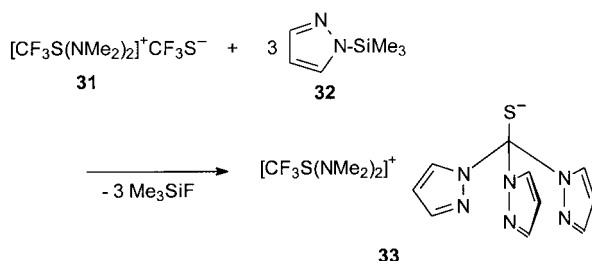
Very recent work on scorpionate coordination chemistry has also made important contributions to increase the number of potentially useful ligands, either through deliberate syntheses or by unexpected transformations of coordinated ligands. The most interesting achievements in this area will be discussed here. A hitherto unsolved problem in the chemistry of hydrotris(pyrazolyl)borates and related anions was the preparation of water-soluble ligands by introduction of suitable substituents. Such derivatives are expected to be highly useful in the synthesis of enzyme model complexes, which are soluble and stable under physiological conditions. Two recent papers by Kläui et al.^[19] as well as Mews et al.^[20] provide decisive new impulses. Both synthetic routes are remarkably simple.

Kläui's approach involves treatment of lithiated tris(pyrazolyl)methane (**29**) with sulfur trioxide-triethylamine complex to afford the lithium salt of tris(pyrazolyl)methane sulfonic acid (**30**) in one step (Scheme 5, 48% yield).^[19]

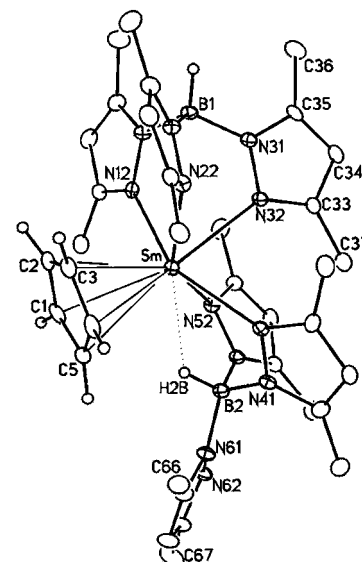
Scheme 5. Preparation of tris(pyrazolyl)methanesulfonate (**30**).^[19]

Compound **30** is highly water-soluble and the solutions are stable over a wide pH range. At pH 0 traces of free pyrazole can be detected only after several weeks, while at pH 13 no decomposition is observed at all. The analogous potassium salt can be prepared from **30** through a metathetical reaction with K_2CO_3 . With respect to potentially useful ligands for enzyme models^[3c, 21] the lithium salt of the sterically demanding tris(3-*tert*-butylpyrazolyl)methane sulfonate anion ($\text{Tpms}^{\text{tBu-}}$) was also prepared according to Scheme 5. Treatment of this compound with TINO_3 in methanol/water afforded the thallium salt $\text{TlTpms}^{\text{tBu-}}$, which was shown to adopt a dimeric structure in the solid state. Initial experiments already revealed that the new anions may act as tripodal nitrogen donor ligands in transition metal complexes.

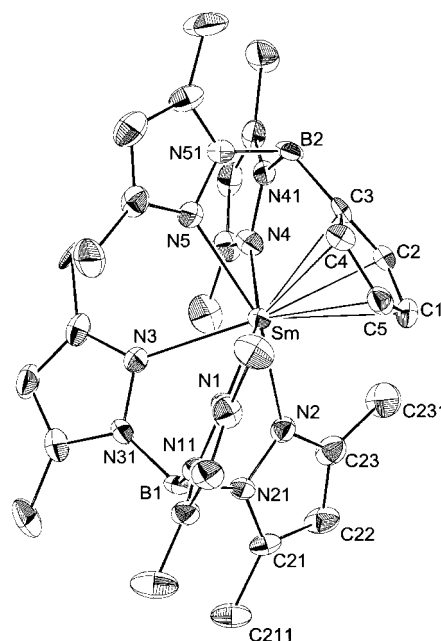
A completely different, though no less straightforward synthetic route was reported by Mews et al.^[20] The basic idea of this work is the nucleophilic substitution of the fluorine atoms in the CF_3S^- ion (present as the $[\text{CF}_3\text{S}(\text{NMe}_2)_2]^+$ salt **31**) by five-membered nitrogen heterocycles, which are employed as their *N*-silylated derivatives (**32**). For example, treatment with three equivalents of *N*-trimethylsilylpyrazole yields the hitherto unknown tris(pyrazolyl)methane thiolate (pz_3CS) ion (present as the $[\text{CF}_3\text{S}(\text{NMe}_2)_2]^+$ salt **33**; Scheme 6). This synthesis is highly variable since different cations as well as other *N*-trimethylsilyl azoles can be successfully employed. These new anions too can be expected to exhibit a rich coordination chemistry with main group and transition metals.

Scheme 6. Synthesis of $[\text{CF}_3\text{S}(\text{NMe}_2)_2][\text{pz}_3\text{CS}]$ (**33**).^[20]

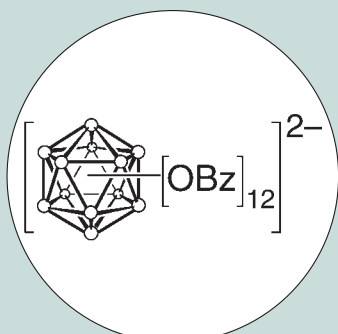
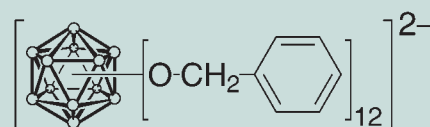
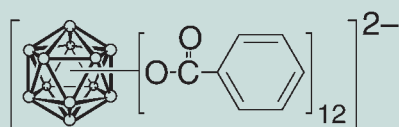
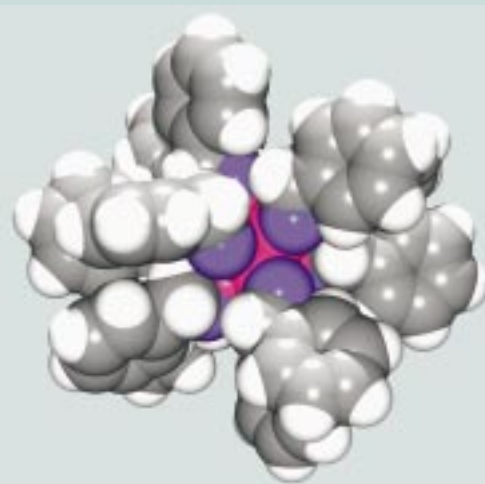
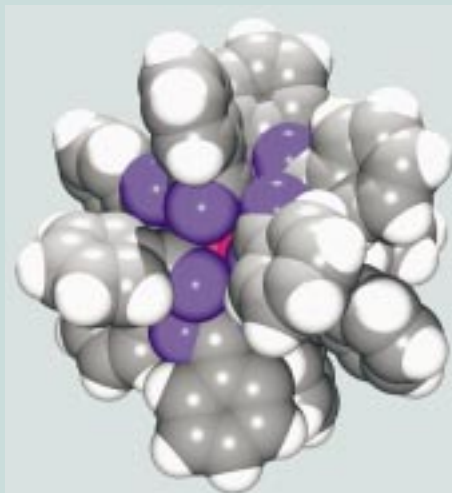
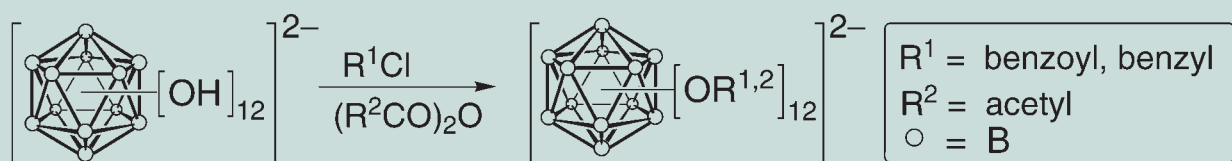
The synthesis of the unprecedented cyclopentadienylbis-(pyrazolyl)borate ligand in the coordination sphere of samarium, which was reported by Marques and Takats et al.,^[22] was certainly not anticipated. Despite its insolubility in the usual organic solvents the samarium(II) complex $[\text{Sm}(\text{Tp}^{\text{Me}_2})_2]$ (**34**) is highly reactive.^[23] Treatment with $[\text{TiCp}]$ in THF solution leads to precipitation of metallic thallium and formation of the first mixed Tp/Cp lanthanoid complex, $[(\text{Tp}^{\text{Me}_2})_2\text{Sm}(\text{Cp})]$ (**35**), which could be structurally characterized by X-ray diffraction (Figure 2). The cyclopentadienyl ligand in **35** is η^5 -

Figure 2. Molecular structure of $[(\text{Tp}^{\text{Me}_2})_2\text{Sm}(\text{Cp})]$ (**35**).^[22]

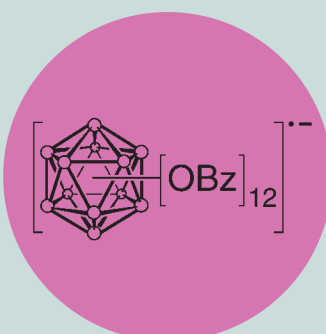
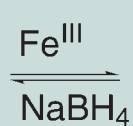
coordinated to samarium. As a response one of the Tp^{Me_2} ligands partially peels off by adopting a $\kappa^3\text{N},\text{N},\text{B}-\text{H}$ coordination mode. Prolonged heating of **35** under vacuum at 165°C transformed it into an intensely yellow colored solid, from which the novel complex $[(\text{Tp}^{\text{Me}_2})\text{Sm}\{\text{HB}(3,5\text{-Me}_2\text{pz})_2(\text{C}_5\text{H}_4)\}]$ (**36**; $3,5\text{-Me}_2\text{pz} = 3,5\text{-dimethylpyrazolyl}$) could be isolated by fractional crystallization from a toluene/hexane mixture. A single-crystal X-ray structure analysis (Figure 3) revealed the presence of one intact Tp^{Me_2} unit and one uniquely modified ligand in which a pyrazolyl moiety has been replaced by a C_5H_4 ring. The synthesis of the new dianionic $[\text{HB}(3,5\text{-Me}_2\text{pz})_2(\text{C}_5\text{H}_4)]^{2-}$ ligand by thermally induced intramolecular C–H activation in **35** opens the way to a new class of “heteroscorpionates” which can be expected to offer versatile applications in coordination chemistry.

Figure 3. Molecular structure of $[(\text{Tp}^{\text{Me}_2})\text{Sm}\{\text{HB}(3,5\text{-Me}_2\text{pz})_2(\text{C}_5\text{H}_4)\}]$ (**36**).^[22]

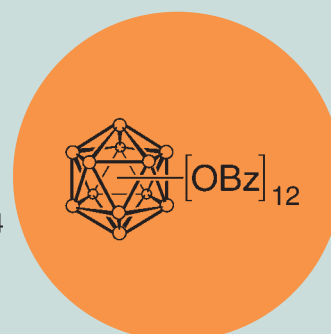
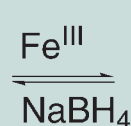
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closo



hypercloso



hypercloso

Globular molecules with an icosahedral core—12(12)-closomers—are obtained by total esterification of $[\text{B}_{12}(\text{OH})_{12}]^{2-}$.

For details as well as for the transformation of an anionic ester into the neutral *hypercloso* analogue see the following two communications.

Twelffold Functionalization of an Icosahedral Surface by Total Esterification of $[\text{B}_{12}(\text{OH})_{12}]^{2-}$: 12(12)-Closomers**

Andreas Maderna, Carolyn B. Knobler, and M. Frederick Hawthorne*

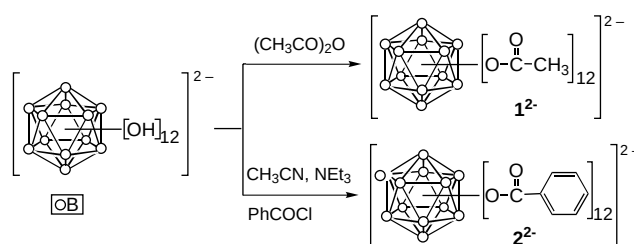
The synthesis of globular molecules in which precisely constructed organic chains are grown from the vertices of closed polyhedra (defined here as closomers^[1]) has remained a challenge to chemists interested in new applications ranging from materials science to medicine. Intense interest in the related chemistry of dendrimers, macromolecules having regular and highly branched architectures,^[2] suggested the challenge of closomer synthesis. Closomers may retain the globular nature of dendrimers while introducing as variables the discrete properties of the polyhedral core (e.g. geometry, number of reactive vertices, electronic structure, ionic charge, redox capabilities, paramagnetism, chromophoric properties, and hydrophobicity).

Only a few polyhedral clusters have been evaluated for this purpose, the most prominent being C_{60} . Hirsch et al. synthesized C_{60} derivatives containing up to six amphiphilic dendritic substituents and used these compounds to form artificial membranes and vesicles.^[3, 4] Other cluster species bearing multiple organic substituents include silsesquioxanes, siloxane clusters in which each silicon atom is bridged by three oxygen atoms and attached to an organic moiety.^[5]

Of special interest for use as closomer cores are the polyhedral boranes and carboranes. The parent aromatic polyhedral borane $[\text{closo-B}_{12}\text{H}_{12}]^{2-}$ is a robust icosahedral cluster stabilized by three-dimensional delocalization of thirteen bonding electron pairs.^[6, 7] We recently reported the efficient perhydroxylation of $[\text{closo-B}_{12}\text{H}_{12}]^{2-}$ by treatment with 30 % hydrogen peroxide leading to $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$.^[8]

Here we report the synthesis of closomers derived from $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ in which each hydroxy function is converted into a carboxylate ester. The syntheses of closomers containing benzyl ether substituents and having the B_{12} core charges -2 , -1 , and 0 are reported in the subsequent communication.^[9]

The dodecaacetate $\mathbf{1}^{2-}$ (Scheme 1) was formed in 43 % yield by reaction of $\text{Cs}_2[\text{closo-B}_{12}(\text{OH})_{12}]$ with acetic anhydride at the reflux temperature for three days. $\text{Cs}_2\mathbf{1}$ is soluble in water and methanol and moderately soluble in acetonitrile and acetone. The ^{11}B NMR spectrum of $\text{Cs}_2\mathbf{1}$ shows a symmetrical singlet at $\delta = -16$ which is not significantly different from that of the starting material, $\text{Cs}_2[\text{closo-B}_{12}(\text{OH})_{12}]$. However, if the esterification reaction does not proceed to completion the



Scheme 1. Esterification of $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ with acetic anhydride or benzoyl chloride leads to a total organoderivatization of its icosahedral surface: syntheses of the 12(12)-closomers^[1] $\mathbf{1}^{2-}$ and $\mathbf{2}^{2-}$.

^{11}B NMR spectrum of the partly esterified $[\text{closo-B}_{12}(\text{OH})_{12-n}(\text{OAc})_n]^{2-}$ ($n = 1-11$) appears as an asymmetric signal resulting from the reduced symmetry of the B_{12} icosahedron. In this case, the reaction with acetic anhydride can be repeated to complete the esterification of all twelve hydroxy functions. The ^1H NMR spectrum of $\text{Cs}_2\mathbf{1}$ exhibits a singlet at $\delta = 1.9$ for the methyl protons; the ^{13}C NMR spectrum displays a signal at $\delta = 174$ for the carbonyl functions and a signal at $\delta = 22$ for the methyl groups. The electrospray mass spectrum (negative mode) reveals the molecular ion peak of $\mathbf{1}^{2-}$ at m/z 839.2, $[\mathbf{1}^{2-} + \text{H}]^-$, and a peak for the dinegatively charged cluster at m/z 419.1, $\mathbf{1}^{2-}$. Figure 1 presents the result of the single-crystal X-ray structure analysis of $\text{Cs}_2\mathbf{1}$.^[10] Dianion $\mathbf{1}^{2-}$ is centrosymmetric and the B_{12} cage has approximate icosahedral symmetry with B–B bond lengths ranging from 1.776(3) to 1.843(3) Å and B–O bond lengths of 1.440(2) to 1.449(2) Å.

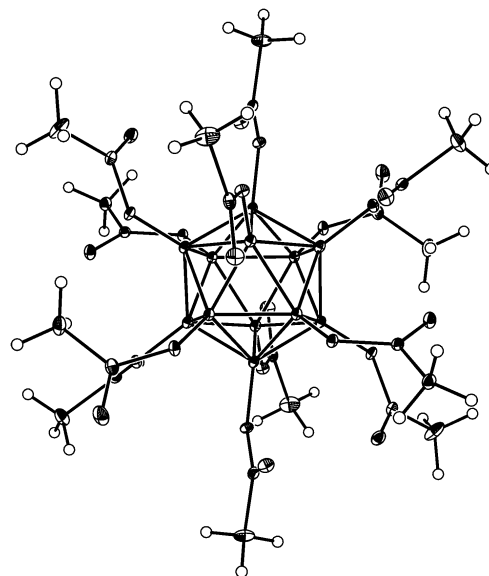


Figure 1. Structure of the dodecaacetate ester $\mathbf{1}^{2-}$ (ORTEP diagram). The ellipsoids represent a 30 % probability level.

An important requirement for the success of the closomer esterification reaction is the dissolution of the $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ ion reactant, whose solubility is dependent upon the identity of the cations employed. The dicesium salt, $\text{Cs}_2[\text{closo-B}_{12}(\text{OH})_{12}]$, is only soluble in warm water and is partially soluble in carboxylic acid anhydrides containing short carbon chains, such as acetic or propionic anhydrides, and at elevated temperatures. Conversion of the Cs_2 salt into

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the $[\text{Bu}_4\text{N}]_2$ salt increases the solubility of $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ in organic solvents and enables the synthesis of carboxylate esters from acid chlorides in 1,2-dichloroethane or acetonitrile at their reflux temperatures. Reaction of $[\text{NBu}_4]_2[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ with an excess of benzoyl chloride in the presence of triethylamine in acetonitrile gave the dodecabenzoate ester $\mathbf{2}^{2-}$ in 52% yield following a reaction time of 10 days (Scheme 1). The electrospray mass spectrum of $\mathbf{2}^{2-}$ in the negative mode reveals a peak at m/z 1584.0 for $[\mathbf{2}^{2-} + \text{H}]^-$ and a peak at m/z 791.5 for $\mathbf{2}^{2-}$. Surprisingly, the electrospray mass spectrum in the positive mode does not indicate the presence of equivalent amounts of the cations expected for $\mathbf{2}^{2-}$. The data reveal a significant disparity in the signal strengths of the observed negative ions and the observed positive ions of the same sample.^[11] The ^1H and ^{13}C NMR data display the signals expected for $\mathbf{2}^{2-}$ alone, while the ^{11}B NMR spectrum shows a symmetrical singlet at $\delta = -16$. Based on the mass spectrometry and NMR data, which both lack the presence of a detectable cation in amounts equivalent to $\mathbf{2}^{2-}$, we surmise that the dodecabenzoate $\mathbf{2}^{2-}$ was isolated in its diprotonated form $[\text{H}]_2\mathbf{2}$ or as a dihydronium salt $[\text{H}_3\text{O}]_2\mathbf{2}$. This assumption is supported by the existence of a weak signal in the electrospray mass spectrum in the positive mode at m/z 1586 for $[\mathbf{2}^{2-} + 3\text{H}]^+$. The existence of this positive closomer ion indicates that the multiple protonation of $\mathbf{2}^{2-}$ is indeed possible. At present we cannot determine whether $\mathbf{2}$ was isolated as $[\text{H}]_2\mathbf{2}$ or $[\text{H}_3\text{O}]_2\mathbf{2}$, but to simplify the further discussion we will assume it to be the dihydronium salt $[\text{H}_3\text{O}]_2\mathbf{2}$. This species was presumably formed during the chromatographic purification of $\mathbf{2}^{2-}$ on silica gel by interaction of $\mathbf{2}^{2-}$ with proton sources associated with the silica. The species assumed to be $[\text{H}_3\text{O}]_2\mathbf{2}$ is soluble in dimethyl sulfoxide and dimethylformamide and poorly soluble in acetonitrile and methanol.

Addition of tetraphenylarsonium chloride to a solution of $[\text{H}_3\text{O}]_2\mathbf{2}$ in dimethylformamide gave $[\text{Ph}_4\text{As}]_2\mathbf{2}$ as a white solid which is quite soluble in methanol and acetonitrile. Figure 2 displays the result of an X-ray structure analysis of

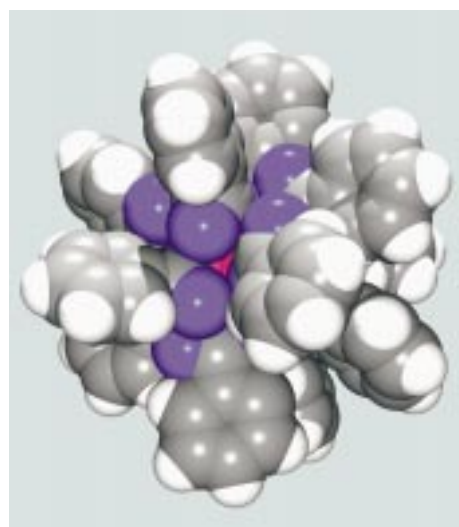
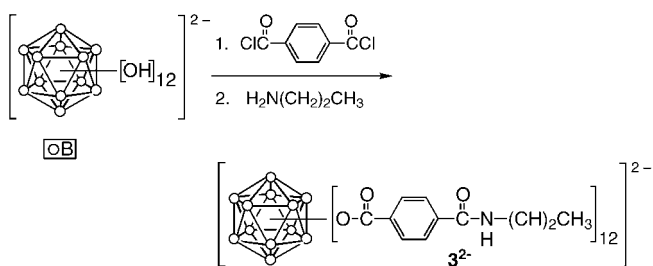


Figure 2. Space-filling representation of the structure of the dodecabenzoate ester $\mathbf{2}^{2-}$. White H; gray C; purple O; magenta B. The B_{12} cluster is almost completely camouflaged by the twelve benzyloxy groups.

$[\text{Ph}_4\text{As}]_2\mathbf{2}$ as a space-filling representation.^[10b, 12] The ion $\mathbf{2}^{2-}$ is centrosymmetric with approximate icosahedral symmetry in the B_{12} cage; the B–B distances range from 1.768(4) to 1.828(4) Å, and the B–O distances from 1.416(3) to 1.429(3) Å. The space-filling representation of $\mathbf{2}^{2-}$ displays the impressive camouflage of the dinegatively charged B_{12} cluster by the twelve benzyloxy groups which almost completely cover its icosahedral surface.

Of particular interest for the use of closomers as cores for the further synthesis of macromolecules and dendritic structures is the development of a synthetic strategy which provides additional connecting sites for chain functionalization and extension. One way of approaching this goal is the utilization of bifunctional carboxylic acid chlorides which link each hydroxy group in $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ with a primary or secondary amine. This strategy was successfully demonstrated by the reaction of $[\text{NBu}_4]_2[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ with excess terephthaloyl chloride followed by addition of *n*-propylamine (Scheme 2). The formation of the *n*-propylamine-linked



Scheme 2. Functionalization of 12(12)-closomers^[1] with twelve amide groups by employing terephthaloyl chloride for the esterification of $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ followed by reaction with *n*-propylamine.

closomer $\mathbf{3}^{2-}$ was proved by fast atom bombardment (FAB) mass spectrometry which revealed its molecular ion peak at m/z 2604 for $[\mathbf{3}^{2-} + \text{H}]^-$. An optimized procedure for $\mathbf{3}^{2-}$ and conceptually related species is currently being developed in our laboratories and will be reported elsewhere.

The synthesis of esters employing acid anhydrides or acid chlorides is one of the oldest known organic reactions. The simplicity of this chemistry contrasts with the novelty of the 12(12)-closomer^[1] esters described here in that *all* hydroxy groups in $[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ can be converted into ester functions leading to total organoderivatization of its icosahedral surface. The resulting 12(12)-closomers represent the first examples of this structural motif known in chemistry. These new closomeric structures can provide camouflaged mono-dispersed molecules and nanoparticles of variable size, shape, charge, hydrophobicity, etc., designed to accomplish a huge variety of specific functions important to a broad spectrum of technology ranging from materials science to biomedicine.

Experimental Section

Solvents and liquid reagents were dried and distilled according to standard procedures.

All reactions were carried out under moisture-free conditions using argon as the inert gas. $[\text{NBu}_4]_2[\text{closo-B}_{12}(\text{OH})_{12}]^{2-}$ was obtained from $\text{Cs}_2[\text{closo-}$

$B_{12}(OH)_{12}$]^[8] by cation exchange using cation exchange resin and was dried at 60 °C in vacuo for 24 h before use. NMR spectra were obtained on a Bruker ARX 500 spectrometer, electrospray mass spectra on a Perkin-Elmer Sciex API III triple quadrupole mass spectrometer, and FAB mass spectra were obtained on a VG ZAB-SE mass spectrometer.

Cs₂-1: A suspension of Cs₂[*closo*-B₁₂(OH)₁₂] (48 mg, 0.080 mmol) in acetic acid anhydride (6 mL) was heated with stirring at reflux for three days under argon. The brown reaction mixture was cooled to room temperature and the volatiles were removed in vacuo. The residue was dried in vacuo at 50 °C for 10 h. The solid was dissolved in water (6 mL) at room temperature, the suspension filtered, and the filtrate cooled at 3 °C for 60 min. The resulting suspension was again filtered using a 0.2 µm filter and the water removed in vacuo to give Cs₂-1 as a light brown solid in sufficient purity for further use (38 mg, 0.034 mmol, 43 %). Further purification can be achieved by recrystallization from acetic anhydride. Single crystals suitable for X-ray structure analysis were obtained from a solution in acetonitrile/water with the addition of a small amount of thiourea. ¹H NMR (500 MHz, D₂O): δ = 1.9 (s); ¹³C NMR (126 MHz, D₂O): δ = 22.0 (Me), 174.0 (CO); ¹¹B NMR (160 MHz, D₂O): δ = -16; ESI-MS (negative mode, water): *m/z*: 839.2 [¹²⁻+H]⁻, 419.1 ¹²⁻.

[H₃O]₂-2: To a suspension of [NBu₄]₂[*closo*-B₁₂(OH)₁₂] (47 mg, 0.058 mmol) in dry acetonitrile (30 mL) were added benzoyl chloride (0.40 mL, 480 mg, 3.5 mmol) and dry triethylamine (2 mL, 1.452 g, 14.3 mmol). The reaction mixture was heated with stirring at reflux for 10 days under argon. The brown suspension was cooled to room temperature, filtered, and the volatiles were removed in vacuo. The resulting dark brown solid was purified by filtration over silica gel by employing CH₂Cl₂, followed by THF, and finally acetonitrile as the mobile phases. The first two mobile phases eluted colored impurities and elution was continued until the eluate was colorless. The mobile phase was then changed to acetonitrile. The acetonitrile fractions were collected, the solvent was removed in vacuo, and the solid was washed with THF and warm water to give pure [H₃O]₂-2 as a white solid (49 mg, 0.030 mmol, 52 %). ¹H NMR (500 MHz, [D₆]DMSO): δ = 8.0 (m, 24H), 7.4 (m, 12H), 7.1 (m, 24H); ¹³C NMR (126 MHz, [D₆]DMSO): δ = 163.6 (CO), 134.7, 130.7, 130.1, 127.2; ¹¹B NMR (160 MHz, [D₆]DMSO): δ = -16; ESI-MS (negative mode, acetonitrile): *m/z*: 1584.0 [²²⁻+H]⁻, 791.5 ²²⁻.

[Ph₄As]₂-2: To a solution of [H₃O]₂-2 (40 mg, 0.025 mmol) in DMF (2 mL) was added a solution of [Ph₄As]Cl (31 mg, 0.074 mmol) in DMF (2 mL). Subsequent addition of water (4 mL) gave [Ph₄As]₂-2 as a white precipitate which was washed twice with warm water and dried in vacuo (59 mg, 0.025 mmol, 100 %). Single crystals suitable for X-ray structure analysis were obtained from a solution in methanol.

¹H NMR (500 MHz, CD₃CN): δ = 8.0 (m, 24H), 7.8 (m, 8H), 7.7 (m, 16H), 7.6 (m, 16H), 7.4 (m, 12H), 7.1 (m, 24H); ¹³C NMR (126 MHz, CD₃CN): δ = 165.1 (CO), 135.7, 135.4, 134.1, 131.8, 131.7, 131.0, 128.3; ¹¹B NMR (160 MHz, CD₃CN): δ = -15.

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- [1] Closomers are defined as polyhedra whose surfaces support polyatomic substituents. In the formulation below, the first number indicates the total number of cluster vertices potentially available for substitution, while the second number refers to the number of attached substituents. The designation 12(12)-closomer indicates a polyhedron containing 12 vertices and 12 substituents.
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- [10] a) Cs₂-1·2SC(NH₂)₂, triclinic, space group *P* $\bar{1}$ with *a* = 10.953(6), *b* = 11.334(7), *c* = 11.532(7) Å, α = 91.918(11)°, β = 113.221(9)°, γ = 112.575(9)°, *V* = 1185.6(12) Å³, *Z* = 1. Data were collected on a Bruker SMART 1000 using MoK α radiation, $2\theta_{\max}$ = 56°, giving 5436 unique reflections and the structure was solved by direct methods. The final discrepancy index was *R* = 0.020, *R_w* = 0.048 for 4914 independent reflections with *I* > 2σ(*I*). b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151203 (Cs₂-1·2SC(NH₂)₂) and CCDC-151204 ([Ph₄As]₂-2). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [11] The signal strengths in the negative ion mode for ²²⁻ and [²²⁻+H]⁻ relative to the cations observed in the positive ion mode was estimated from the ratio of signal intensities obtained in the two modes under identical scanning and detector settings with the same solution and in the absence of reagents that might enhance ion intensities in either mode and assuming similar ionization efficacy for positive and negative ions. For a salt with the composition AB₂ (A: anion, B: cation) the signal intensities for the negative and the positive ions are expected to be equivalent to the ratio of 1:2. The measured signal intensities of anions and cations in the same sample reveal only a ratio of about 1:0.18.
- [12] [Ph₄As]₂-2, triclinic space group *P* $\bar{1}$ with *a* = 13.873(2), *b* = 15.680(2), *c* = 16.280(2) Å, α = 65.368(2)°, β = 66.727(2)°, γ = 80.638(2)°, *V* = 2957.2(7) Å³, *Z* = 1. Data were collected on a Bruker SMART ccd diffractometer using MoK α radiation, $2\theta_{\max}$ = 56.6°, giving 13554 unique reflections and the structure was solved by Patterson and heavy atom methods. The final discrepancy index was *R* = 0.054, *R_w* = 0.159 for 7763 independent reflections with *I* > 2σ(*I*).^[10b]

Dodeca(benzyloxy)dodecaborane, B₁₂(OCH₂Ph)₁₂: A Stable Derivative of hypercloso-B₁₂H₁₂**

Toralf Peymann, Carolyn B. Knobler, Saeed I. Khan, and M. Frederick Hawthorne*

In agreement with Wade's rules, the framework of a polyhedral borane requires 2*n*+2 (*n* = number of vertices) skeletal electrons to form a *closo* cage.^[1] These rules have been employed to successfully classify and rationalize the structures of the polyhedral boranes.^[2] Exceptions to Wade's rules have been reported for species having an apparent *closo* structure in which the number of framework electrons is less than the required 2*n*+2. These electron-deficient cages are

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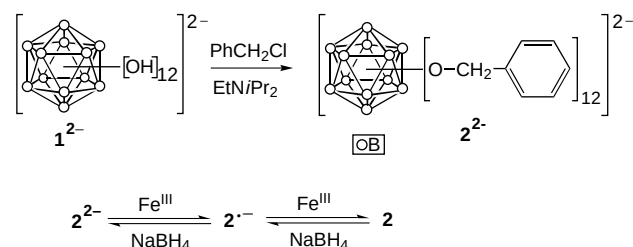
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designated as *hypercloso* clusters.^[3] For cages with a framework composed solely of boron vertices such *hypercloso* species include paramagnetic anions with $2n+1$ electrons, such as $[B_nH_n]^{+}$, $[B_nX_n]^{+}$ ($X = \text{halogen}$),^[4] $[B_{12}Me_{12}]^{+}$,^[5] and the neutral boron halides B_nX_n with $2n$ electrons.^[6] The stability of the persubstituted *hypercloso* polyhedral boranes has been attributed to a combination of both steric protection and electron donation provided by the substituents.^[3]

Here we report the per-O-benylation of $[closo-B_{12}(OH)_{12}]^{2-}$ (1^{2-})^[7] to produce $[closo-B_{12}(OCH_2Ph)_{12}]^{2-}$ (2^{2-}); the reversible one-electron oxidation of 2^{2-} to paramagnetic $[hypercloso-B_{12}(OCH_2Ph)_{12}]^{\cdot -}$ ($2^{\cdot -}$); and the synthesis and structure of a novel electron-deficient *hypercloso* species: the neutral *hypercloso*- $B_{12}(OCH_2Ph)_{12}$ (**2**), the first characterized derivative of *hypercloso*- $B_{12}H_{12}$.^[8] Although the latter borane has not been synthesized, it has been the subject of numerous computational studies.^[3, 9]

The precursor for the synthesis of *hypercloso*-**2**, $[closo-B_{12}(OH)_{12}]^{2-}$ (1^{2-})^[7] is especially attractive due to its sheath of twelve identical hydroxy functions.^[7, 10] The preceding communication^[11] reports the synthesis of species in which the twelve hydroxy functions of 1^{2-} have been converted to carboxylic acid esters. These dodecafunctionalized structures in which twelve organic substituents emanate from the vertices of the icosahedral surface have been designated as closomers and differentiated from dendritic structures.^[11]

The anion 1^{2-} (PPN salt, PPN: bis(triphenylphosphoranyl)idene)ammonium) was per-O-benzylated in acetonitrile at the reflux temperature employing benzyl chloride in the presence of ethyldiisopropylamine (Scheme 1). After a reaction time of



Scheme 1. Synthesis of *hypercloso*- $B_{12}(OCH_2Ph)_{12}$ (**2**) by per-O-benylation of $[closo-B_{12}(OH)_{12}]^{2-}$ (1^{2-}) followed by oxidation with two equivalents of Fe^{III} .

six days the salt $Na[PPN][closo-B_{12}(OCH_2Ph)_{12}]$ ($Na[PPN]-2$) was obtained in 48% yield. During the product isolation procedure sodium borohydride was added to reduce spurious amounts of the radical species $2^{\cdot -}$ formed during the reaction. Prolonged reaction times led to lower yields of 2^{2-} , presumably due to the decomposition of paramagnetic *hypercloso*- $2^{\cdot -}$ produced by the oxidation of 2^{2-} with excess benzyl chloride. Shorter reaction times, on the other hand, led to decreased yields because of the incomplete conversion of 1^{2-} to 2^{2-} .

An ion with m/z 708.2 (100%) is observed by electrospray mass spectrometry for 2^{2-} ; in the positive-ion mode signals ascribed to the two cations, Na^+ and PPN^+ , are observed. The ^{11}B , ^1H , and ^{13}C NMR data confirm the icosahedral symmetry of species 2^{2-} . The UV/Vis spectrum of K_2-2 , obtained from $Na[PPN]-2$ through metathesis, has absorption bands at 210,

233, and 260 nm. Figure 1 depicts the solid-state structure of 2^{2-} determined by an X-ray diffraction study of $Cs[PPN]-2$.^[12] The cage of dianion 2^{2-} has icosahedral symmetry with the B–B bond lengths covering the narrow range of 1.781(4) to 1.824(4) Å and B–O bond lengths of 1.434(3) to 1.451(3) Å. Salts of anion 2^{2-} slowly air-oxidize and develop a purple tint upon exposure to air due to the formation of $2^{\cdot -}$.

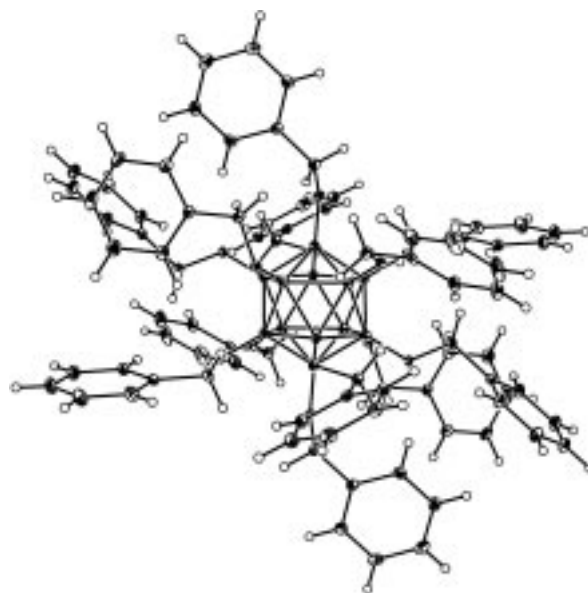


Figure 1. Structure of $[closo-B_{12}(OCH_2Ph)_{12}]^{2-}$ (2^{2-}) (ORTEP diagram). The ellipsoids represent a 30% probability level.

Chemical one-electron oxidation of 2^{2-} employing Fe^{III} afforded the purple, paramagnetic monoanion $2^{\cdot -}$ as its PPN^+ salt in 90% yield (Scheme 1). A broad (200 G) EPR signal with $g = 2.1997$ was observed with $[PPN]-2$. Negative-ion electrospray mass spectrometry of $[PPN]-2$ gave a peak at m/z 1416.0 (100%) corresponding to the formulation $[hypercloso-B_{12}(OCH_2Ph)_{12}]^{\cdot -}$. The UV/Vis spectrum of $[PPN]-2$ in acetonitrile exhibits an intense band in the visible region at 537 nm accompanied by strong absorption in the UV due to the presence of benzyl groups. The crystal structure of $[PPN]-2 \cdot C_6H_6$ confirms the monoanionic nature of $2^{\cdot -}$.^[12b, 13] In contrast to 2^{2-} the boron cage of species $2^{\cdot -}$ is more distorted from icosahedral symmetry (B–B 1.768(4)–1.840(4) Å) and the B–O distances (1.398(3)–1.419(3) Å) are shortened by about 0.03 Å.

The sequential two-electron oxidation of 2^{2-} with Fe^{III} in ethanol affords **2** as a dark-orange solid (Scheme 1). The purple anion-radical $2^{\cdot -}$ is observed as an intermediate in this overall reaction. An ion at m/z 1415.8 (100%) assigned to the formula $[B_{12}(OCH_2C_6H_5)_{12}]^{\cdot -}$ is recorded for **2** by fast atom bombardment mass spectrometry. The ^{11}B NMR spectrum of **2** exhibits a singlet at $\delta = 43.3$, a downfield shift of 58 ppm relative to the singlet observed at $\delta = -14.8$ for 2^{2-} . The ^1H and ^{13}C NMR spectra exhibit broad signals, probably due to paramagnetic impurities or spurious reduction of **2** to $2^{\cdot -}$ in solution. A detailed study concerning the redox stability of **2** is currently under way and will be reported elsewhere. The

visible spectrum of orange **2** in acetonitrile solution exhibits a strong absorption at 467 nm.

A crystal of **2** suitable for X-ray diffraction studies was obtained from acetonitrile.^[12b, 14] Most importantly, the solid-state structure of **2** reveals a *hypercloso* borane cage with only approximate icosahedral geometry (D_{3d}). A detailed analysis of the bonding parameters demonstrates this departure from icosahedral symmetry. Notably, the B–B distances observed in **2** are in the broad range of 1.755(2) to 1.918(2) Å and should be compared with the corresponding distances of 1.781(4)–1.824(4) Å in **2**^{2−} and 1.768(4)–1.840(4) Å in the paramagnetic anion **2**^{2−}. Conspicuously, the B–O distances observed in **2** are shortened by about 0.06 Å with respect to those in **2**^{2−} and by about 0.02 Å relative to those in **2**^{2−} (**2**: 1.369(2)–1.404(2) Å; **2**^{2−}: 1.434(3)–1.451(3) Å; **2**^{2−}: 1.398(3)–1.419(3) Å).

A more detailed examination of the distorted icosahedral geometry of **2** reveals that the six longest B–B bonds (B–B 1.910(2)–1.918(2) Å) are located in two opposing symmetry-related boron triangles (B4, B5, B2', see Figure 2) and (B4', B5', B2). The remaining shorter B–B bond lengths (1.755(2)–1.864(2) Å) are similar to those observed in **2**^{2−} and **2**^{2−}. The B–O bond lengths of **2** may be divided into two groups, as well. The six shorter B–O bond lengths (1.369(2)–1.378(2) Å) are associated with the oxygen atoms attached to the boron vertices of the elongated triangles. The six longer B–O bonds (1.398(2)–1.404(2) Å) are associated with the remaining boron vertices. All B–O–C bond angles deviate from the ideal sp³ bond angle by more than 10°. The bond angles associated with the shorter B–O bonds (123.2(1)–123.4(1)°) are about 2° larger than the corresponding angles about the oxygen atoms of the longer B–O bonds (121.5(1)–121.7(1)°).

The distorted icosahedron of **2** (Figure 2) has approximate D_{3d} symmetry with the C_3 axis penetrating the centers of the elongated triangles (B4, B5, B2') and (B4', B5', B2). Previously, neutral B₁₂ clusters structurally similar to the distorted icosahedron of **2** have been observed in elemental boron. In β -rhombohedral boron, three structural types of B₁₂ clusters are present.^[15] One of these icosahedra displays D_{3d}

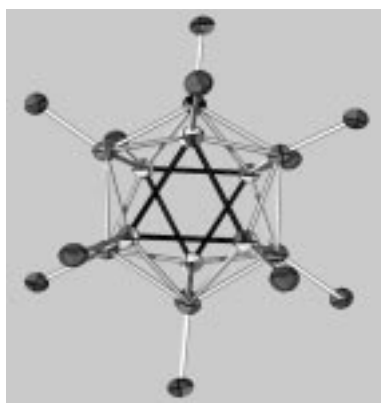


Figure 2. The distorted icosahedron (point group D_{3d}) of *hypercloso*-B₁₂(OCH₂Ph)₁₂ (**2**) without the benzyl groups and viewed along the C_3 axis. The boron atoms (B4, B5, B2', front, and B4', B5', B2, rear) form two triangles (dark gray) with elongated B–B distances (see text). The B–O bonds originating at these six B atoms are shortened relative to the other B–O bonds present in **2** due to back-bonding from oxygen.

symmetry with two triangular faces having elongated edges (long B–B bonds 1.801 Å, short B–B bonds 1.751–1.767 Å). Furthermore, a distorted icosahedron with D_{3d} symmetry has been identified as an energy minimum in computations carried out on an HF/6-31G(d) level for [*hypercloso*-B₁₂H₁₂]^[9]. An undistorted icosahedral [*hypercloso*-B₁₂H₁₂] structure would have partially occupied fourfold degenerate HOMOs. A Jahn–Teller distortion to the observed D_{3d} structure removes this degeneracy.^[9]

In a comparison of the structures of the per(benzyloxy) icosahedral boranes [B₁₂(OCH₂Ph)₁₂]^{n−} ($n = 0–2$), it becomes apparent that the range of B–B bond lengths widens with a decrease in the number of skeletal electrons. On the other hand, the B–O bond lengths shorten concomitantly with the loss of cluster electron density suggesting the presence of considerable double-bond character in **2** attributed to enhanced π -backbonding of the exo-oxygen atoms to the electron-deficient *hypercloso*-icosahedron. Indeed, the shortest B–O bonds of **2** are associated with those oxygen atoms attached to the more electron-poor boron triangles (B4, B5, B2') and (B4', B5', B2) having the longest B–B bonds.

The redox chemistry of **2** was studied by cyclic voltammetry. The cyclic voltammogram of **2** (100 mM (*n*Bu)₄NPF₆, Ag/AgCl, acetonitrile) shows reversible one-electron transfer processes with $E_{1/2} = 0.46$ and 0.0 V which are attributed to the two couples **2**/**2**^{2−} and **2**^{2−}/**2**^{2−}, respectively.

In summary, we have presented the per-O-benylation of **1**^{2−} affording **2**^{2−}, the one-electron oxidation of **2**^{2−} to paramagnetic **2**^{2−} and the subsequent one-electron oxidation of **2**^{2−} to **2**. The stability of the neutral *hypercloso*-species **2** is ascribed to both oxygen π -backbonding and steric encumbrance resulting from its twelve benzyloxy substituents. The crystal structure of **2** revealed a Jahn–Teller distortion from icosahedral geometry (point group D_{3d}), similar to one B₁₂ cluster observed in β -rhombohedral boron, and shortened B–O bonds characteristic of B–O π -backbonding.

Experimental Section

Na[PPN]-2: A solution of [PPN]₂-**1**^[7] (0.60 g, 0.43 mmol), ethyldiisopropylamine (0.89 mL, 5.1 mmol), and benzyl chloride (2.9 mL, 26 mmol) in acetonitrile (15 mL) was heated at reflux for six days under nitrogen. All volatile materials present in the purple reaction mixture containing **2**^{2−} were removed in vacuo and ethanol (20 mL) was added. The resulting suspension was kept at −18 °C overnight and a grayish purple solid was removed by filtration. This solid was dissolved in warm ethanol, and sodium borohydride (0.04 g, 1 mmol) was added to decolorize the suspension by reducing **2**^{2−} to **2**^{2−}. The solvent was removed in vacuo and the residue extracted with acetonitrile. The extracts were combined and evaporated to produce a residue which was recrystallized from ethanol. After seven days at −18 °C, crystals of Na[PPN]-**2** were collected by filtration (m.p. > 250 °C; 0.40 g, 0.20 mmol, 48 % yield). Electrospray MS (MeCN): negative-ion mode: m/z (%): 708.2 (100) [**2**]^{2−}; positive-ion mode: m/z (%): 22.7 (50) [Na]⁺, 63.8 (95) [Na+MeCN]⁺, 104.9 (70) [Na+2MeCN]⁺, 539.0 (100) [PPN]⁺; ¹¹B NMR (160 MHz, acetone): $\delta = -14.8$ (s); ¹H NMR (400 MHz, [D₆]acetone): $\delta = 7.60–7.52$ (m, 30H, Ph of PPN⁺), 7.38–7.02 (m, 60H, CH₂Ph), 5.57 (s, 24H, CH₂Ph); ¹³C NMR (126 MHz, [D₆]acetone): $\delta = 145.8$ (C1, CH₂Ph); 127.2, 126.7 (2C2, 2C3, CH₂Ph), 125.0 (C4, CH₂Ph), 68.3 (CH₂Ph).

K₂-2: To a warm solution of Na[PPN]-**2** (350 mg, 0.18 mmol) in ethanol (10 mL) was added a solution of CH₃COOK (350 mg, 3.57 mmol) in ethanol (5 mL). The mixture was kept at −18 °C for one week. The formed crystals were separated by filtration and dried to yield K₂-**2** (260 mg,

0.17 mmol, 94%). No PPN⁺ resonances were observed by ¹H NMR spectroscopy. UV/VIS (MeCN): λ (ϵ) = 210 (6.8×10^4), 233 (2.1×10^4), 260 nm (6×10^3).

[PPN]-2: To a solution of Na[PPN]-2 (100 mg, 0.050 mmol) in warm ethanol (10 mL) was added a solution of FeCl₃·6H₂O (14 mg, 0.050 mmol) in ethanol (5 mL). The purple reaction solution was stirred for 30 min at 25 °C and then kept at –18 °C for 3 h. Dark purple crystals precipitated which were separated by filtration, recrystallized from ethanol, and dried (m.p. 197 °C) to yield [PPN]-2 (90 mg, 0.046 mmol, 90 %). Electrospray MS (MeCN), negative-ion mode: m/z (%): 1416.0 (100) [2][–]; VIS (MeCN): λ (ϵ) = 537 nm (1.4×10^4); EPR (solid, 273 K): $g = 2.1997$.

2: A sample of K₂-2 (100 mg, 0.067 mmol) was dissolved in ethanol (10 mL) and a solution of FeCl₃·6H₂O (45 mg, 0.166 mmol) in ethanol (5 mL) was added. The reaction mixture turned purple and then dark red. The suspension was stirred for 1 h at room temperature and the precipitate was removed by filtration. The orange-brown solid was recrystallized from ethanol (m.p. 155 °C) to give 2 (80 mg, 0.057 mmol) in 84 % yield. FAB-MS (acetone), negative-ion mode: m/z (%): 1324.7 (25) [2 – CH₂Ph][–], 1415.8 (100) [2][–], 1506.7 (70) [2 + CH₂Ph][–]; ¹B NMR (160 MHz, acetone): $\delta = 43.3$ (s); VIS (MeCN): λ (ϵ) = 467 nm (1.7×10^4).

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- [12] a) Cs[PPN]-2, triclinic, space group $P\bar{1}$, $a = 9.986(2)$, $b = 14.039(3)$, $c = 18.441(4)$ Å, $\alpha = 90.062(4)$, $\beta = 93.348(3)$, $\gamma = 90.238(4)$ °, $V = 2580.6(8)$ Å³, $Z = 1$, $2\theta_{\max} = 56.6$ °, $\rho = 1.343$ Mg m^{–3}, $\lambda(\text{MoK}\alpha) = 0.71069$ Å, 100 K. Of the 11868 unique reflections measured, 7291 were considered observed ($I > 2\sigma(I)$). Data were corrected for Lorentz and polarization effects but not for absorption, $\mu = 0.455$ mm^{–1}. The structure was solved by statistical methods. $R = 0.042$, $wR = 0.065$; b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-148658 (2), CCDC-148659 (Cs[PPN]-2) and CCDC-148660 ([PPN]-2·C₆H₆). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [13] [PPN]-2·C₆H₆, triclinic, space group $P\bar{1}$, $a = 17.761(8)$, $b = 18.786(8)$, $c = 20.588(9)$ Å, $\alpha = 65.156(7)$, $\beta = 65.725(8)$, $\gamma = 63.417(8)$ °, $V = 5360(4)$ Å³, $Z = 2$, $2\theta_{\max} = 56.66$ °, $\rho = 1.259$ Mg m^{–3}, $\lambda(\text{MoK}\alpha) = 0.71069$ Å, 100 K. Of the 24400 unique reflections measured, 14575 were considered observed ($I > 2\sigma(I)$). Data were corrected for Lorentz and polarization effects but not for absorption, $\mu = 0.106$ mm^{–1}. The structure was solved by statistical methods. $R = 0.073$, $wR = 0.186$.

[14] 2, triclinic, space group $P\bar{1}$, $a = 10.107(3)$, $b = 15.014(4)$, $c = 15.033(4)$ Å, $\alpha = 114.893(4)$, $\beta = 103.118(5)$, $\gamma = 102.823(5)$ °, $V = 1880.8(9)$ Å³, $Z = 1$, $\rho = 1.25$ Mg m^{–3}, $\lambda(\text{MoK}\alpha) = 0.71069$ Å, 100 K. Of the 11869 unique reflections measured, 8403 were considered observed ($I > 2\sigma(I)$). Data were corrected for Lorentz and polarization effects, and for absorption, $\mu = 0.079$ mm^{–1}. The structure was solved by statistical methods. $R = 0.048$, $wR = 0.118$.

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Parity Violation in Fluorooxirane**

Robert Berger, Martin Quack,* and Jürgen Stohner

Dedicated to Professor Paul von Ragué Schleyer on the occasion of his 70th birthday

Van't Hoff pointed out more than a century ago^[1] that the heat of formation and the entropy of enantiomers of chiral molecules must be exactly equal for symmetry reasons. Traditional quantum chemistry which only includes the electromagnetic interaction finds just this symmetry.^[2] However, electroweak quantum chemistry which includes parity violation predicts an energy and entropy difference. One of the greatest challenges in the current understanding of fundamental aspects of the structure and dynamics of chiral molecules concerns the experimental proof of the role of parity violation because of the weak nuclear interaction.^[3] Experimental spectroscopic approaches have been proposed for some time. One of these approaches is to measure directly the heat of reaction $\Delta_r H_0^0$ for the transformation of *S* into *R* enantiomers which is related to the parity violating energy difference $\Delta_{\text{pv}} E$ ^[3, 4] as shown in Equation (1).

$$\Delta_r H_0^0 (S \rightleftharpoons R) \approx N_A \Delta_{\text{pv}} E \quad (1)$$

Another approach is measuring certain frequency shifts of the enantiomers, for instance in NMR,^[5] microwave,^[6] IR,^[6–10] or Mößbauer^[11] spectra of *R* and *S* enantiomers (see the diagram in Figure 1).

The recent theoretical discovery^[12, 13] that parity-violating effects in chiral molecules are typically one to two orders of magnitude larger than previously anticipated^[14, 15] has stimulated intensified theoretical^[16–22] and experimental interest^[6, 10, 11] in this field. Of particular importance are experi-

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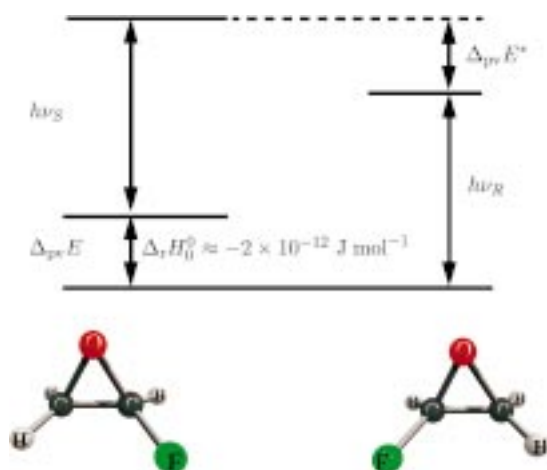


Figure 1. Scheme of energy levels and structures of fluorooxirane enantiomers. The structure of (*R*)-fluorooxirane (right) as used in the calculations was obtained by a full structure optimization using MP2 with a TZ2P basis set and is consistent with experimental data from high-resolution spectra.^[24] The dashed line indicates that the direct optical transition to this *S* state from the *R* ground state is forbidden.

ments on chiral molecules in the low frequency “optical” (infrared^[10]) domain, where the currently best relative frequency uncertainty of about 10^{-13} has been obtained in the CO₂-laser emission range around 1000 cm⁻¹. This uncertainty is still three to four orders of magnitude greater than the effects calculated for one useful test molecule CHBrClF.^[20–22] A prerequisite for any such experiment, as well as for the proposed direct measurement of $\Delta_{\text{pv}}E$ ^[4] is a rovibrationally line resolved and analyzed optical spectrum of the chiral molecule under consideration. While until 1994 there was to our knowledge not a single example where such an analysis had been achieved for a chiral molecule, since that time three cases in parallel have been successfully studied in our laboratory: CHBrClF,^[6, 23] 2-fluorooxirane,^[24] and (2,2-²H₂)thiirane-1-oxide.^[25, 26]

Fluorooxirane (Figure 1) is a particularly interesting molecule because it contains only atoms of the first row of the periodic table, rendering fundamental and accurate calculations possible. Because of its rather rigid, cyclic structure it has a particularly simple infrared spectrum in the CO₂-laser range. Fluorooxirane as well as related compounds might prove to be crucial for future experimental and theoretical efforts. We present here the first calculations on the parity-violating energy difference $\Delta_{\text{pv}}E$ as well as vibrational and rotational frequency shifts for this compound.

Our general theoretical approaches to parity violation have been described elsewhere.^[13, 19–21] Herein we follow closely our approach used for CHBrClF.^[20, 21] Briefly, we have used the multiconfiguration linear response (MC-LR) approach^[19] in the random phase approximation (RPA), and complete active space self consistent field (CASSCF) limit.

An estimate of rotational and vibrational frequency shifts between *R* and *S* enantiomers is obtained by using a coordinate dependent parity-violating potential, $V_{\text{pv}}(\vec{q})$ ^[20, 21] which has been calculated using RPA (if not specified otherwise). $\vec{q}$ describes a suitable set of molecular coordinates (here, reduced vibrational normal coordinates). Figure 2

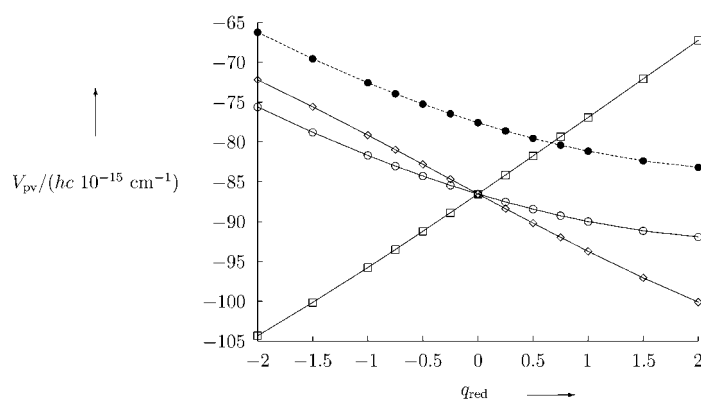


Figure 2. Parity violating potential V_{pv} [10⁻¹⁵ cm⁻¹] as obtained for (*R*)-fluorooxirane from RPA (○, full lines) and CASSCF calculations (●, dashed line) with a triple zeta basis set augmented by two sets of polarization functions (TZ2P). The dimensionless reduced normal coordinate (q_{red}) dependence of V_{pv} is shown for the present choice of vibrational phases of the three modes displayed here (v_7 (□), v_8 (◇), v_9 (○ and ●) correspond to δ -C-F-H bending, δ -CH₂ bending, and the C-F stretching mode).^[24]

shows as an example V_{pv} for three different modes including the C-F stretching vibration v_9 .

By analyzing the coordinate dependence of V_{pv} we are able to calculate estimates for the vibrational wavenumber shifts between (*R*)- and (*S*)-fluorooxirane from the polynomial coefficients used to fit the coordinate-dependent parity-violating potential for each mode j of the $3N - 6$ vibrational modes, where N is the number of atoms ($N = 7$).

Table 1 summarizes the most relevant coefficients $p_0(j)$ to $p_2(j)$ from a third-order polynomial fit $V(q_j) \approx \sum_{i=0}^3 p_i(j) q_j^i$, where $p_0(j)$ is related to $\Delta_{\text{pv}}E$ by Equation (2).

$$E^{(R)} - E^{(S)} = \Delta_{\text{pv}}E = 2 \times V_{\text{pv}}(\vec{q} = \vec{0}) \approx 2 \times p_0(j) = 2 \times \tilde{p}_0(j) \times hc \approx -155 \times 10^{-15} \text{ cm}^{-1} \times hc \quad (2)$$

This corresponds to a value for $\Delta_{\text{r}}H_0^0$ of about -2×10^{-12} J mol⁻¹ (obtained with CASSCF). Thus, (*R*)-fluorooxirane is more stable than (*S*)-fluorooxirane. The vibrational wavenumber shift for mode j in the separable harmonic adiabatic approximation (SHAA) is given by Equation (3).^[21]

$$\Delta_{\text{pv}}\tilde{\omega}(j) = \tilde{\omega}^{(R)}(j) - \tilde{\omega}^{(S)}(j) \approx 2 \times \tilde{p}_2(j) \quad (3)$$

As shown in Table 1 the value of $\Delta_{\text{pv}}\tilde{\omega}/\tilde{\omega}$ is very dependent on the absolute magnitude as well as on the sign of the relative shift. For the C-F stretching mode v_9 we find Equation (4).

$$\Delta_{\text{pv}}\tilde{\omega}_9/\tilde{\omega}_9 \approx 1.2 \times 10^{-18}. \quad (4)$$

The last column of Table 1 shows anharmonic vibrational wavenumber shifts obtained within the separable anharmonic adiabatic approximation (SAAA)^[21] for some selected modes as expectation values of the parity-violating potential V_{pv} with one-dimensional vibrational wavefunctions ($|0\rangle$ for the ground state and $|1\rangle$ for the first vibrationally excited state) according to Equation (5).

$$\Delta_{\text{pv}}\tilde{\nu}/\tilde{\nu} = 2 \times (\langle 1' | V_{\text{pv}} | 1' \rangle - \langle 0' | V_{\text{pv}} | 0' \rangle) / (hc\tilde{\nu}). \quad (5)$$

Table 1. The most relevant parameters $\tilde{p}_0, \tilde{p}_1, \tilde{p}_2$ [10^{-15} cm^{-1}] obtained by fitting the energy points $V_{\text{pv}}(q_j)$ calculated ab initio for (*R*)-fluorooxirane with RPA for each vibrational reduced normal coordinate q_j ($j = 1-15$) to a third-order polynomial. The root-mean-square deviation of the fit to the analytic polynomial is between 10^{-4} and 3×10^{-3} ; standard deviation from the fitting procedure are given in parenthesis in units of the last significant digits. The last columns give $\Delta_{\text{pv}}\tilde{\omega}/\tilde{\omega}$ and $\Delta_{\text{pv}}\tilde{\nu}/\tilde{\nu}$ [10^{-19}] obtained from $\tilde{p}_2$ in the SHAA and for some selected modes in the SAAA.^[21] See text for details.

Mode <i>j</i>	$\nu_{\text{exp}}^{[\text{a}]}$ [cm^{-1}]	$\tilde{p}_0$ [10^{-15} cm^{-1}]	$\tilde{p}_1$ [10^{-15} cm^{-1}]	$\tilde{p}_2$ [10^{-15} cm^{-1}]	$\Delta_{\text{pv}}\tilde{\omega}/\tilde{\omega}$ [10^{-19}]	$\Delta_{\text{pv}}\tilde{\nu}/\tilde{\nu}$ [10^{-19}]
1	3078	− 86.5287(4)	2.7877(6)	− 0.089(2)	− 0.54	
2	3050	− 86.5253(11)	1.8263(16)	0.2223(6)	1.37	
3	3011	− 86.5280(1)	− 1.4644(2)	− 0.1129(1)	− 0.71	
4	1479	− 86.5308(13)	− 2.2998(20)	0.2136(7)	2.77	
5	1383	− 86.5309(14)	1.2452(21)	− 0.3045(7)	− 4.26	
6	1284	− 86.5278(1)	5.1859(1)	0.1871(1)	2.83	
7	1156	− 86.5278(3)	9.4739(4)	0.1848(1)	3.11	5.91
8	1135	− 86.5272(8)	− 7.3957(12)	0.0927(4)	1.59	3.92
9	1126	− 86.5289(5)	− 4.1706(8)	0.6904(3)	12.02	15.15
9	1126	− 77.5797(7) ^[b]	− 4.3123(10) ^[b]	0.7149(4) ^[b]	12.45 ^[b]	15.70 ^[b]
10	1085	− 86.5309(14)	2.0286(22)	0.1605(8)	2.92	3.33
11	968.21267(5)	− 86.5311(15)	10.1087(22)	0.3232(8)	6.56	2.35
12	866.637(3)	− 86.5281(3)	2.2411(4)	1.1911(2)	27.37	26.59
13	755	− 86.5254(10)	− 6.3877(16)	− 0.7525(6)	− 20.05	− 4.26
14	510	− 86.5240(17)	2.5165(25)	− 0.1326(9)	− 5.18	
15	432	− 86.5269(4)	9.9593(6)	0.2311(2)	10.60	

[a] Ref. [24]. [b] CASSCF using an active space of six electrons in six orbitals.

Table 2 displays the vibrational wavenumber shifts for selected modes of the dideuterated species 2-fluoro-(3,3-²H₂)-oxirane as obtained within the SHAA and SAAA. With $\Delta_{\text{pv}}E$, $\Delta_{\text{pv}}E^*$ (Figure 1) can be estimated from Equation (5).

Table 2. Vibrational wavenumber shifts calculated for selected modes of (*R*)-2-fluoro-(3,3-²H₂)-oxirane. Parity-violating potentials for the polynomial fit have been calculated using the RPA and CASSCF with an active space of six electrons in six orbitals. For the C–F stretch CASSCF (mode 7) gives, $\Delta_{\text{pv}}E/hc = 2\tilde{p}_0 \approx -155.155 \times 10^{-15} \text{ cm}^{-1}$, as expected, very similar to the value of $-155.159 \times 10^{-15} \text{ cm}^{-1}$ for the ¹H isotopomer.

Mode <i>j</i>	$\nu_{\text{exp}} [\text{cm}^{-1}]^{[\text{a}]}$	Method	$\Delta_{\text{pv}}\tilde{\omega}/\tilde{\omega}$ [10^{-19}]	$\Delta_{\text{pv}}\tilde{\nu}/\tilde{\nu}$ [10^{-19}]
7	1101.32909(3)	RPA	4.6	11.4
		CAS	4.9	12.3
9	982.0232(3)	RPA	15.3	14.2
		CAS	12.9	11.8

[a] From ref. [24].

The parity-violating potential also gives rise to a change in equilibrium geometry which can be used to estimate the relative shift of the rotational constants caused by V_{pv} .^[21] The minimum position $\tilde{q}_{\text{min}}$ in dimensionless reduced normal coordinates is given by Equation (6). The corresponding relative shift^[21] $\Delta_{\text{pv}}X_e/X_e$ in rotational constants X with $X = A, B, C$ is summarized in Table 3 for (*R*)-fluorooxirane.

$$q_{\text{min}}(j) \approx -\frac{\tilde{p}_1(j)}{\tilde{\omega}_j^2} \quad (6)$$

Table 3. Rotational constants X ($X = A, B, C$) [cm^{-1}] determined by experiment and ab initio calculations for (*R*)-¹H₃C₂OF and dimensionless relative shifts $\Delta_{\text{pv}}X_e/X_e$ [10^{-18}] caused by V_{pv} .

<i>X</i>	Exp. ^[a]	Ab initio (this work)	$\Delta_{\text{pv}}X_e/X_e$
<i>A</i>	0.6703127(6)	0.67039	0.105
<i>B</i>	0.2449829(6)	0.24497	− 0.369
<i>C</i>	0.2139151(5)	0.21345	− 0.019

[a] Ref. [24].

We can compare these observable rotational and vibrational wavenumber shifts to those obtained for (*R*)- and (*S*)-CHBrClF.^[20–22] For the C–F stretching mode of CHBrClF (in the spectral region of the CO₂ laser), Equation (7) applies.

$$|\Delta_{\text{pv}}\tilde{\omega}_4/\tilde{\omega}_4| \approx |\Delta_{\text{pv}}\tilde{\nu}_4/\tilde{\nu}_4| \approx 8 \times 10^{-17} \quad (7)$$

As is expected from the presence of two relatively heavy nuclei (Cl, Br), this shift is larger than for fluorooxirane. While the frequency shifts of fluorooxirane are too small to be detected by present day techniques, the energy difference between *R* and *S* enantiomers indicated by Equation (8) corresponds to a period of motion for parity change $\tau_{\pm}$ of about 200 s with an initial time evolution in the μs to ms range that should be measurable by the technique proposed in reference [4].

$$\tau_{\pm} = h/\Delta_{\text{pv}}E \quad (8)$$

According to the estimates presented in reference [4] a value of $\Delta_{\text{pv}}E$ would be sufficient to generate a detectable signal for parity change, if the parity-violating energy difference were on the order of the early theoretical estimate for light molecules,^[14, 15] $N_A \Delta_{\text{pv}}E = 2 \times 10^{-14} \text{ J mol}^{-1}$. As the signal at early times increases quadratically with $\Delta_{\text{pv}}E$ the value for fluorooxirane calculated here would thus improve the experimental situation by a factor of 10^4 . It should be noted that the “motion” of parity change is no simple motion in space (or in normal coordinate space). It rather corresponds to an “isomerization” between delocalized “strange parity isomers” of chiral molecules (see refs. [3, 4, 27] for details). This type of experiment (while difficult to carry out) together with our new theoretical result for $\Delta_{\text{pv}}E$, brings measurements of a parity violating energy difference into the realm of the doable. One may compare the present case with the early pioneering experiment on IR frequency shifts also in a “light-atom

molecule", camphor, where $\Delta\nu/\nu \approx 10^{-8}$ was achieved.^[9] Even if more recent techniques could provide higher resolving power,^[10] a full rotational analysis for the IR spectrum of camphor would be more difficult than for fluorooxirane, and the experiment itself does not provide a value for $\Delta_{\text{pv}}E$. The data calculated here are also sufficient for an estimate of the equilibrium constant for racemization^[28] from Equations (9) and (10) where x and y explicitly show the deviation from unity of the prefactor and the exponential factor.

$$K_{\text{eq}}^{R,S} = \frac{q_R}{q_S} \exp(-\Delta_r H_0^0/RT) = \frac{q_{\text{vib},R} q_{\text{rot},R}}{q_{\text{vib},S} q_{\text{rot},S}} \exp(-\Delta_r H_0^0/RT) \quad (9)$$

$$\approx (1+x)(1+y) \quad (10)$$

Within the SHAA,^[20,21] the equilibrium constant for racemization at 300 K is $K_{\text{eq}}^{R,S} \approx 1 + 8.20 \times 10^{-16}$ with $x \approx -1.01 \times 10^{-17}$ and $y \approx 8.30 \times 10^{-16}$. These values have been obtained with perturbation theory and high precision arithmetic (MAPLE V).^[29] To our knowledge, this is the first time that these contributions have been explicitly estimated, although it should be understood that the harmonic approximation is not quite adequate.^[28]

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

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The conformational flexibility^[1] of L-iduronic acid, a typical monosaccharide component of heparin, most probably explains its remarkable protein adaptability and resulting diverse biological activities.^[2,3] The analysis of this feature has been the matter of a long controversy,^[4] which not surprisingly originates from the complexity of the heparin primary structure. A major breakthrough in heparinology has been the identification,^[5,6] followed by the total synthesis,^[7,8] of a well-defined pentasaccharide sequence inserted into the heparin chain, which specifically binds to antithrombin (AT)—a physiological inhibitor of activated blood coagulation factors—and amplifies its action. This is the molecular origin of the anticoagulant and antithrombotic activities of heparin.

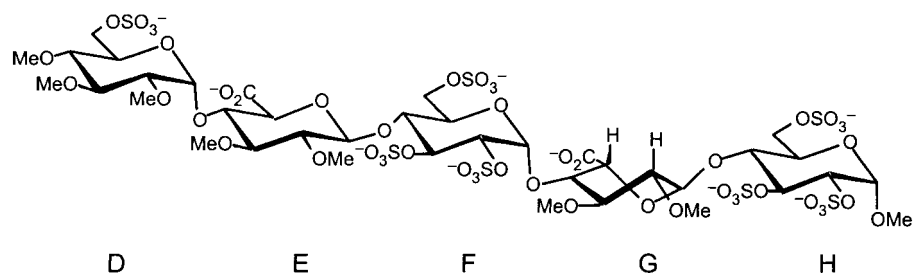
The ¹H NMR spectroscopic data of this original synthetic pentasaccharide in aqueous solution were easily extracted and

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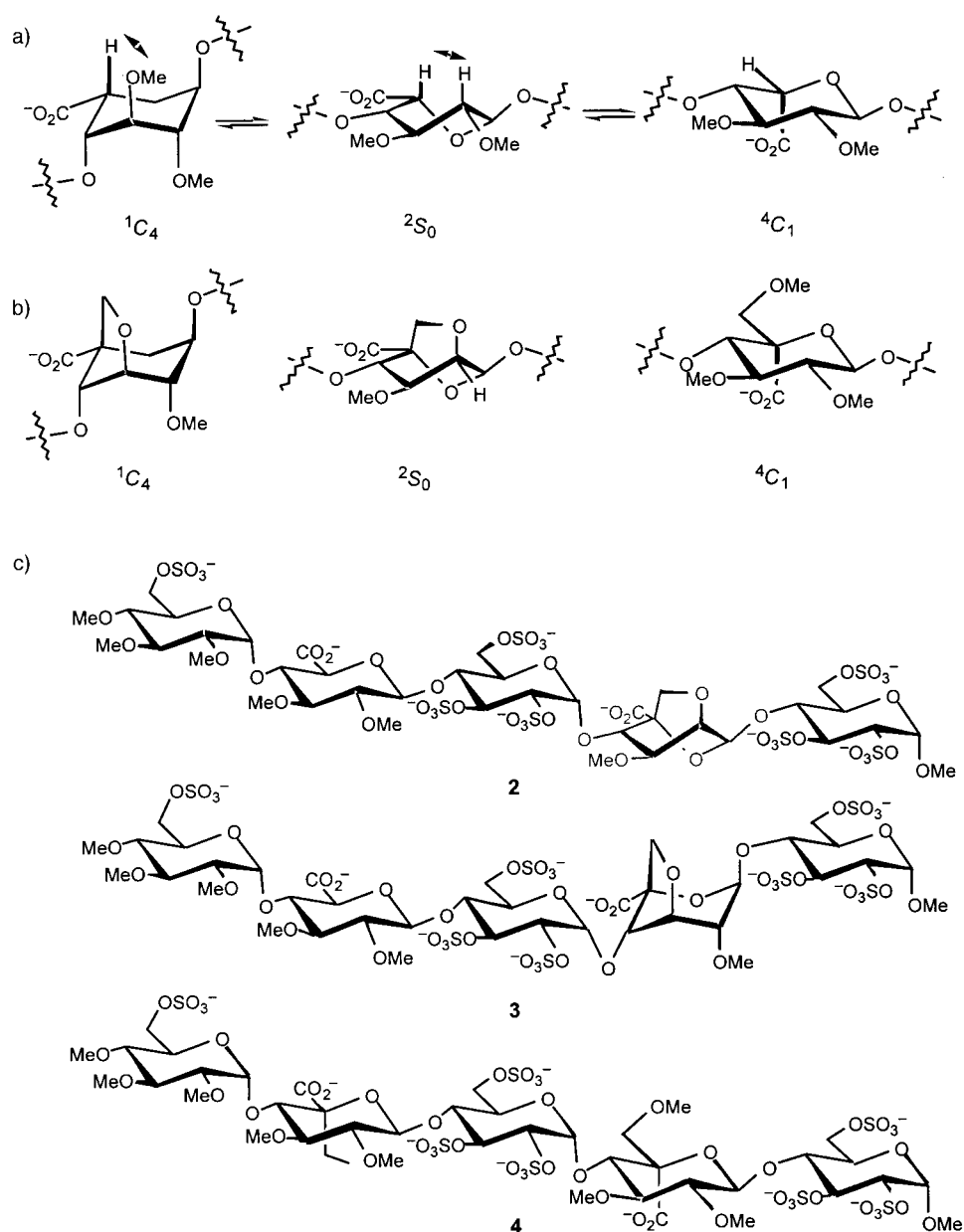
were best explained by taking into account the participation of the unusual ${}^2S_0$ skew-boat conformer in addition to the classical ${}^4C_1$ and ${}^1C_4$ chair forms of the single L-iduronic acid component.^[9] This was confirmed by force field studies and energy computations.^[10] The ${}^2S_0$ conformer was shown to be the major contributor to the conformational equilibrium of L-iduronic acid in this pentasaccharide.^[11]

In order to establish the relationship between conformation and AT activity, we performed total syntheses of three pentasaccharides in which the single L-iduronic residue is conformationally locked, either in the ${}^1C_4$, ${}^4C_1$, or ${}^2S_0$ form. The known^[12] synthetic methylated pentasaccharide **1** (Scheme 1) was chosen as the reference compound for several reasons. Firstly, it binds strongly to AT and selectively inhibits the blood coagulation factor -Xa; secondly, the presence both of methoxy groups in place of free hydroxyl functions and of O- in place of N-sulfonates largely simplifies the corresponding synthetic approach. Lastly, the hydroxyl group at the C-2 position of L-iduronic acid unit G in **1** is methylated and not sulfated. Among the various sulfate groups present in the original pentasaccharide, the one on the C-2 atom of L-iduronic acid was found not to be essential for activity. This auspicious feature is critical, inasmuch as it is a prerequisite for the synthesis of a locked ${}^2S_0$ skew-boat conformer.

In the conformational formula of **1** shown in Scheme 1 the L-iduronate unit G is represented exclusively for the sake of simplicity in its ${}^2S_0$ form. There is actually an equilibrium in aqueous solution between the three conformers: ${}^1C_4 \rightleftharpoons {}^2S_0 \rightleftharpoons {}^4C_1$ (Scheme 2a). As indicated in



Scheme 1. The synthetic pentasaccharide **1** selected as the reference compound in this work.



Scheme 2. a) The three most energetically stable conformers of the methylated iduronic acid unit G of the biologically active pentasaccharide **1**. b) The three conformationally locked L-iduronic acid mimics, which have been synthesized and inserted in **1** in place of the unit G. c) The three resulting synthetic analogues of the biologically active pentasaccharide **1** in which the L-iduronic acid G unit is unambiguously locked in either the ${}^1C_4$, ${}^2S_0$, or ${}^4C_1$ form, as shown in (b).

Scheme 2b, we have locked the L-iduronate ring G in one of these conformations, and the three corresponding pentasaccharides **2–4** (Scheme 2c) have been synthesized.

The ${}^1C_4$ and ${}^4C_1$ chair forms are well-defined conformers which are rather easy to lock. The challenging chemical question is how to isolate the ${}^2S_0$ form from the pseudorotational itinerary of the pyranoid ring.^[13] We reasoned that a covalent connection between carbon atoms C-2 and C-5 would necessarily confine this itinerary to the section ${}^2S_0 \rightleftharpoons {}^{2,5}B \rightleftharpoons {}^5S_1$. More precisely, a one-atom bridge

would freeze the unwanted ${}^{2,5}B$ conformation, whereas a more flexible two-atom bridge would probably allow the equilibrium between the three forms, and a shift toward the more stable skew-boat form. In the case of L-iduronic acid, this equilibrium would be shifted to the wanted and favorable ${}^2S_0$, wherein the substituents are equatorially and isoclinally oriented (see Scheme 2b).

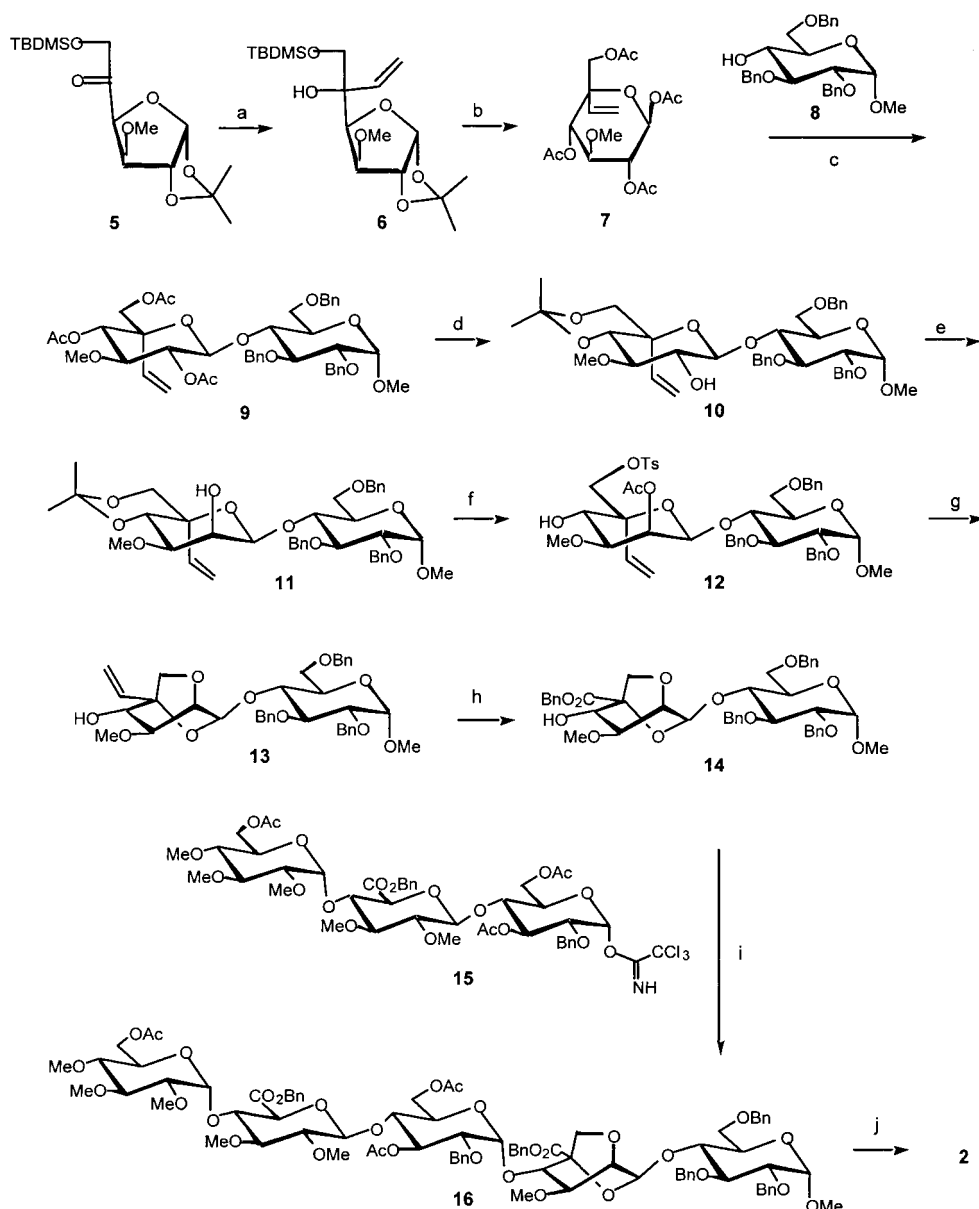
In order to bridge the C-2 and C-5 positions, we first synthesized a protected disaccharide **9** (Scheme 3). The easily available^[14] ketone **5** was transformed in three steps into the

tetraacetate **7**. The first step, the face-selective addition of vinyl magnesium bromide, is explained by a chelation of the magnesium to the ring oxygen atom of **5**. The β -acetate **7**, whose structure has been confirmed by NMR spectroscopy, is well suited^[15] for selective 1,2-transglycosylation of the known^[16] alcohol **8**. The derivative **9** was then easily transformed (see Scheme 3) into the key alcohol **14**, which is a locked protected equivalent of the G-H section of the pentasaccharide **1**. The known^[17] trisaccharidic imidate **15**, which has successfully been used for the synthesis of the

parent active pentasaccharide **1**, was then condensed with the alcohol **14** to afford the protected pentasaccharide **16**. A sequence of well-established reactions^[18] then gave the pentasaccharide **2**. Comparison of the ${}^1H$ NMR coupling constants of the locked L-iduronic acid residue in **2** ($J_{1,2} = 1.3$, $J_{2,3} = 1.4$, $J_{3,4} = 2.7$, $J_{2,4} = 0.5$ Hz) with those reported by Köll et al.^[19] for methyl-2,6-anhydro- β -D-mannopyranoside derivatives that exist in the ${}^2S_0$ conformation ($J_{1,2} = 1.2$ – 1.4 , $J_{2,3} = 1.2$ – 2.4 , $J_{3,4} = 3.0$ – 3.4 , $J_{2,4} = 0.7$ Hz) confirms that our derivative adopts a similar conformation. Much to our delight, the ${}^2S_0$ -locked pentasaccharide **2** was able to strongly activate AT with respect to factor Xa (Table 1).

As shown schematically in Scheme 4, a pivotal compound of type **9** has also been used to construct ${}^1C_4$ - and ${}^4C_1$ -locked blocks, which were then transformed into the two pentasaccharides **3** and **4**.^[20, 21] A pentasaccharide similar to **3** has already been synthesized,^[22] but it bears a sulfate group at the C-2 position of L-iduronic acid so its properties cannot be directly compared with those of our locked compounds to assess the influence of the conformation of L-iduronic acid on the biological properties. It should be noted that the ${}^4C_1$ chair conformation of the G unit of **4** is ensured by the methoxymethyl group attached to the C-5 atom, which replaces the hydrogen atom of L-iduronic acid (Scheme 2b).

As shown in Table 1, the two pentasaccharides **3** and **4**, which contain the G unit locked in the ${}^4C_1$ and ${}^1C_4$ conformations, respectively, only very slightly potentiate

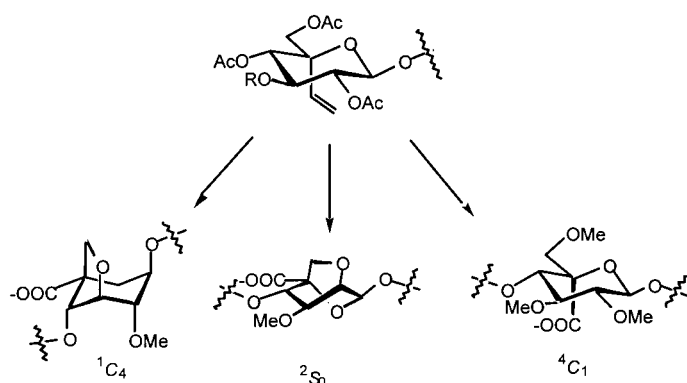


Scheme 3. General strategy used to synthesize the pentasaccharide **2**. a) $CH_2=CHMgBr$, THF, $0^\circ C$, 1 h, 70%; b) 1. IR-120 H^+ ion-exchange resin, H_2O , $80^\circ C$, 6 h; 2. Ac_2O , pyridine, RT, 16 h, 75% (two steps); c) **8**, TMSOTf, CH_2Cl_2 , $-78^\circ C$, 2 h, 85%; d) 1. MeONa, MeOH, $0^\circ C$ then RT, 3 h; 2. $(CH_3O)_2C(CH_3)_2$, *p*-TsOH, acetone, RT, 16 h, 70% (two steps); e) 1. $(COCl)_2$, DMSO, CH_2Cl_2 , $-78^\circ C$, 45 min; 2. $LiEt_3BH$, THF, $-78^\circ C$ then RT, 1 h, 70% (two steps); f) 1. Ac_2O , pyridine, RT, 3 h; 2. $AcOH$, $60^\circ C$, 2 h, 70% (two steps); 3. TsCl, pyridine, RT, 3 h, 80%; g) NaOH, EtOH, $70^\circ C$, 3 h, 70%; h) 1. O_3 , CH_2Cl_2 , $-78^\circ C$, Me_2S , then 2-methyl-2-butene, *t*BuOH, H_2O , NaH_2PO_4 , $NaClO_2$, RT, 16 h; 2. BnBr, Bu_4NI , $KHCO_3$, DMF, RT, 5 h, 80% (three steps); i) TBDMSOTf, CH_2Cl_2 , Et_3O , $-20^\circ C$, 30 min, 67%; j) 1. H_2 , Pd/C, AcOH, $40^\circ C$, 12 h; 2. NaOH, H_2O , $55^\circ C$, 3 h, 86% (two steps); 3. $Et_3N \cdot SO_3$, DMF, $55^\circ C$, 18.5 h, 85%. Bn = benzyl, DMF = dimethylformamide, DMSO = dimethyl sulfoxide, TBDMS = *tert*-butyldimethylsilyl, Tf = triflate = trifluoromethanesulfonyl, TMS = trimethylsilyl, Ts = tosyl = toluene-4-sulfonyl.

Table 1. Activity *a* against factor Xa by the pentasaccharides **1**–**4** and the reference compound **17**.

Compound	<i>a</i> [u mg ^{−1}] ^[c]
1 ^[a]	1208 ± 63
2	1073 ± 61
3	115 ± 3
4	43 ± 3
17 ^[b]	1345 ± 65

[a] The activity against factor Xa of the genuine nonmethylated synthetic pentasaccharide is 1013 ± 52 u mg^{−1}. [b] Compound **17** is a synthetic nonlocked reference analogue of **1** in which the H-5 atom of the D-glucuronic acid unit E has been replaced by an ethyl group. [c] The values are the mean activities against factor Xa (*n* = 3). Human factor Xa (71 nkat per vial), antithrombin, and S-2222 substrate (Bz-Ile-Glu-Gly-Arg-pNA) were from Chromogenix (Mölndal, Sweden). The activity was determined in buffer by an amidolytic method adapted from Teien and Lie.^[29] For an accurate comparison, compound concentrations were determined by ¹H NMR spectroscopy with reference to an internal standard. u = the inhibitory effect, in the same assay, of one unit of the IVth International heparin standard, Bz = benzoyl.



Scheme 4. Our synthetic strategy is based on the construction of a key structural element in which the C-5 atom is harnessed with two appendages, an equatorially oriented protected hydroxymethyl group and an axially oriented vinyl group. Through classical manipulations, this architecture can be selectively converted into one of the three conformers.

the inhibition of the blood coagulation protease factor Xa. This work unambiguously demonstrates for the first time that the AT-bound L-iduronic acid unit G adopts the unusual ²S₀ conformation and clearly explains how the unique conformational behavior of L-iduronic acid translates in terms of biological activity.

It is likely that the accessibility of the three conformers is the basis for the high versatility of glycosaminoglycans (GAGs) that contain L-iduronic acid for binding to basic sites of interacting proteins. Although the ²S₀ skew-boat conformer nicely governs the antithrombotic activity of heparin, it could very well be that the chair forms are critical in other situations, such as high affinity for fibroblast growth factors.^[23] The availability of the three synthetic locked conformers offers a unique opportunity to replace any flexible L-iduronic acid residue in a GAG chain by a conformationally defined counterpart, thus providing a direct tool for general exploration of the relationship between conformational flexibility and biological properties of GAGs.

As laid out by Barton,^[24] a conformational analysis of cyclic molecules is critical for the understanding of their biological action. We have demonstrated here that the conformational

changes of the pyranose ring have important significance in the biology of heparin. Other recent studies have also emphasized the importance of boat or skew-boat conformers in biology.^[25–28] We believe that the importance of the conformational flexibility of carbohydrates is now very clear and is going to emerge as a key feature in this field of science.

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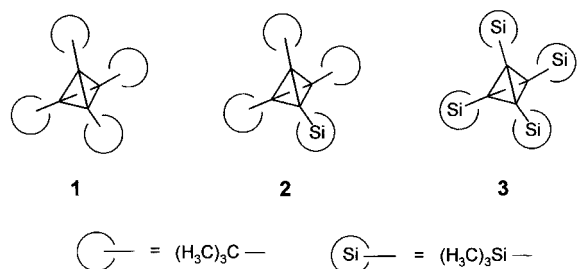
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Tetrakis(trimethylsilyl)cyclobutadiene and Tetrakis(trimethylsilyl)tetrahedrane**

Günther Maier,* Jörg Neudert, and Oliver Wolf

Dedicated to Professor Hansgeorg Schnöckel on the occasion of his 60th birthday

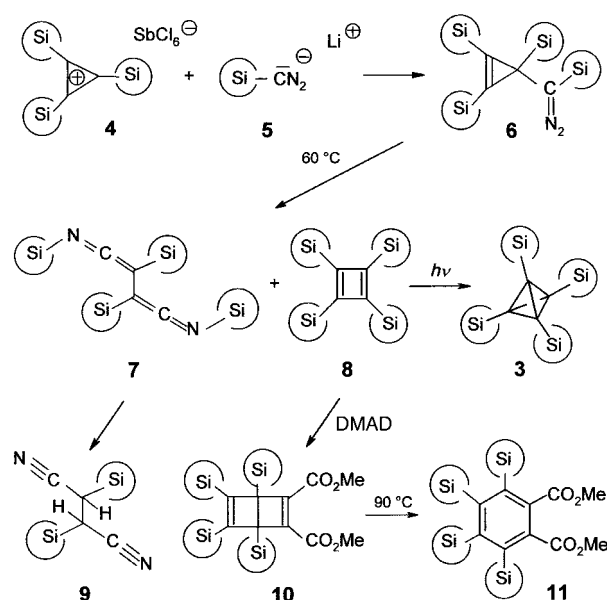
Tetrakis(trimethylsilyl)tetrahedrane (**3**) is of interest in several respects. The “corset effect”, that is, the stabilization by the accumulation of four voluminous substituents,^[1] should be smaller in **3** than in the tetra-*tert*-butyl derivative **1**, the first



stable tetrahedrane,^[1] because of the longer C–Si bonds.^[2] On the other hand the four σ -donor substituents in **3** should particularly favor the tetrahedrane ring skeleton, an observation we made previously in the case of tri-*tert*-butyl(trimethylsilyl)tetrahedrane (**2**).^[3] These influences will add up to a high barrier for the thermal isomerization of tetrahedrane **3** into cyclobutadiene **8**. Another aspect is even more enticing: The high s-character of the bonds pointing from the ring skeleton to the substituents^[1c, 4] should enable the trimethylsilyl groups of **3** to be easily replaced. On this basis a route to tetralithiotetrahedrane^[5]—and perhaps even to the unsubstituted tetrahedrane—can be envisaged.

One apparent procedure for the synthesis of tetrahedrane **3** is the photoisomerization of tetrakis(trimethylsilyl)cyclobutadiene (**8**). In analogy to tetra-*tert*-butyl^[6] and tri-*tert*-butyl(trimethylsilyl)cyclobutadiene,^[3] the starting materials for tetrahedranes **1** and **2**, it is also possible to prepare **8** by using the “cyclopropenyldiazomethane route”. The report of Sekiguchi et al.^[7] on an alternative way to **8**, namely by the mild oxidation of the corresponding cyclobutadiene dianion, is the motive for us (in agreement with the Japanese group) to describe our own efforts directed to the generation of cyclobutadiene **8** and tetrahedrane **3** (Scheme 1).

Trimethylsilyl[1,2,3-tris(trimethylsilyl)-2-cyclopropen-1-yl]-diazomethane (**6**) can be isolated as a yellow oil in 11 % yield through the coupling of tris(trimethylsilyl)cyclopropenylium hexachloroantimonate^[8] (**4**) with lithiated (trimethylsilyl)di-



Scheme 1. Syntheses of **7**, **3**, and **8** as well as the confirmation reactions.

azomethane (**5**). Six further products are also formed, whose structures were elucidated.

Many attempts were needed to find the appropriate conditions for the transformation of **6** into cyclobutadiene **8**. Neither the photochemical^[6] nor the CuCl-catalyzed thermal^[3] elimination of nitrogen succeeded. However, cyclobutadiene **8** is formed (according to NMR-spectroscopic analysis in 45 % yield) upon warming **6** in an inert medium (benzene, cyclohexane, methylcyclohexane) to 60 °C. Surprisingly bis(ketenimine) **7** is observed as a second product, which means that on thermal excitation, diazo compound **6** partly splits off nitrogen and the thus-generated carbene undergoes a ring expansion to cyclobutadiene **8**. Parallel to this reaction an isomerization of cyclopropenyl diazomethane **6** into tetrakis(trimethylsilyl)pyridazine occurs, which immediately undergoes a ring opening accompanied by migration of two trimethylsilyl groups under the reaction conditions to give the 2,3-bis(trimethylsilyl)-1,3-butadiene-1,4-dione-bis(trimethylsilyl)imine (**7**). This reaction is reminiscent of the isomerization of hexakis(trimethylsilyl)benzene to the thermodynamically more stable 1,1,3,4,6,6-hexakis(trimethylsilyl)-1,2,4,5-hexatetraene, reported by Sakurai and Sekiguchi et al.^[9]

Both thermolysis products **7** and **8** are sensitive to air and moisture. This fact complicates their separation into pure components. The presence of cyclobutadiene **8** can be proved not only by NMR spectroscopy (see Table 1) but also by the following experiment: The addition of dimethyl acetylenedicarboxylate (DMAD) to the reaction mixture after thermolysis of diazo compound **6** enables adduct **10** to be isolated, which at 90 °C gives quantitatively the dimethyl ester of tetrakis(trimethylsilyl)phthalic acid (**11**). After evaporation of the solvent from the solution of **7** and **8** in vacuo, it is possible to capture preferentially the more volatile bis(ketenimine) **7** under high vacuum conditions. The IR spectrum of **7**, obtained from this procedure and measured in an argon matrix at 10 K, showed a band at 2112 cm^{−1}, which is typical for a ketenimine.

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Table 1. NMR spectroscopic data of compounds **6**–**11**.^[a]

6 : yellow oil; ¹ H NMR (CDCl ₃): δ = 0.26 (18H), 0.15 (9H), –0.03 (9H); ¹³ C NMR ([D ₈]toluene): δ = 141.1 (C=C), 38.6 (C=N ₂), 16.4 (ring-C), –0.1 (2 SiMe ₃), –0.35 (SiMe ₃), –0.4 (SiMe ₃)
7 : colorless oil; ¹ H NMR (C ₆ D ₆): δ = 0.35 (18H), 0.20 (18H); ¹³ C NMR (C ₆ D ₁₂): δ = 177.1 (C=C=N), 26.3 (C=C=N), 0.5 (SiMe ₃), 0.4 (SiMe ₃)
8 : red-brown crystals; ¹ H NMR (C ₇ D ₁₄): δ = 0.09 (36H); ¹³ C NMR (C ₇ D ₁₄): δ = 171.59 (ring-C), 0.08 (SiMe ₃)
9 : colorless solid (m.p. 139 °C); ¹ H NMR (C ₆ D ₆): δ = 1.46 (2H), 0.06 (18H); ¹³ C NMR (C ₆ D ₁₂): δ = 119.3 (C=N), 16.4 (C-H), –3.2 (SiMe ₃)
10 : colorless solid (m.p. 95 °C); ¹ H NMR (CDCl ₃): δ = 3.56 (6H), 0.21 (18H), 0.20 (18H); ¹³ C NMR (CDCl ₃): δ = 171.9 (C=O), 163.0 (C=C), 148.0 (C=C), 65.3 (ring-C), 51.3 (OMe), 1.5 (SiMe ₃), 1.3 (SiMe ₃)
11 : colorless solid (m.p. 165 °C); ¹ H NMR (CDCl ₃): δ = 3.79 (6H), 0.32 (18H), 0.28 (18H); ¹³ C NMR (CDCl ₃): δ = 171.3 (C=O), 166.9 (C=C), 144.9 (C=C), 135.7 (C=C), 52.2 (OMe), 4.6 (SiMe ₃), 3.4 (SiMe ₃)

[a] ¹H NMR: 400.1 MHz, ¹³C NMR: 100.6 MHz, chemical shifts are relative to TMS. All compounds gave correct elemental analyses or high resolution mass spectra.

Together with the NMR data and the fact that hydrolysis yields the dinitrile **9** of 2,3-bis(trimethylsilyl)succinic acid, the structure of **7** can be assumed with confidence.

The many attempts to photoisomerize **8** into tetrahedrane **3** by variation of the wavelength, temperature, and solvent demanded high persistence. Practically all variants led to a fragmentation into two molecules of bis(trimethylsilyl)acetylene. However, there was one exception: Irradiation of the mixture of **7** and **8** in deuterated methylcyclohexane at –130 °C in a photoreactor (254 nm) for a long time resulted in the appearance of signals in the NMR spectra, which, by comparison with those measured for **2**,^[3] could arise from tetrakis(trimethylsilyl)tetrahedrane (**3**). The final proof of the successful photochemically induced transformation of **8** into **3** was achieved with a pure sample of cyclobutadiene **8** which was given to us by Sekiguchi.^[7, 10] The NMR signals of **8** had nearly disappeared after irradiation of the sample for 70 hours under the above-mentioned conditions. The newly formed NMR signals of practically equal intensities can be attributed to bis(trimethylsilyl)acetylene [¹H: δ = 0.12; ¹³C: δ = 0.01 (SiMe₃), 113.48 (acetylenic-C)] and tetrakis(trimethylsilyl)-tetrahedrane (**3**) [¹H: δ = 0.10; ¹³C: δ = –0.03 (SiMe₃), –20.46 (ring-C)]. The strong upfield shift of the ring-C atoms is typical for tetrahedranes.^[1, 3]

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From a Cyclobutadiene Dianion to a Cyclobutadiene: Synthesis and Structural Characterization of Tetrasilyl-Substituted Cyclobutadiene**

Akira Sekiguchi,* Masanobu Tanaka, Tsukasa Matsuo, and Hidetoshi Watanabe

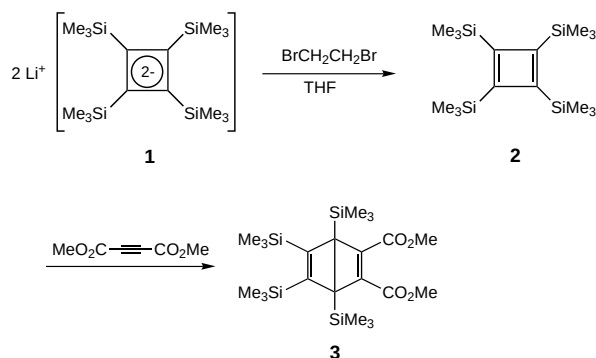
The fascinating chemistry of cyclobutadiene (CBD) and its derivatives has been studied from the point of view of their structures, properties, and reactivities.^[1, 2] The parent molecule, CBD, was initially generated by the oxidative treatment of [(η⁴-C₄H₄)Fe(CO)₃] with Ce^{IV} ions.^[3] After that, it was observed—through the use of photochemical reactions—at low temperature in inert matrices,^[4] and at room temperature in a hemiacarcerand.^[5] In contrast, some CBD derivatives, stabilized by steric effects, have been isolated, and parts of their molecular structures determined by X-ray crystallography.^[6] For the most part, these compounds were prepared by the photolysis of cyclopentadienone derivatives or diazo compounds. However, the methods used to prepare CBD are sometimes very tedious and have undesirable side photo-reactions.^[7]

Recently, we succeeded in synthesizing the dilithium salt of the tetrakis(trimethylsilyl)cyclobutadiene dianion, the first aromatic CBD²⁻ ion with a six π-electron system, by the reaction of the cobalt complex of CBD derivative **2** with lithium metal in THF.^[8] An interesting aspect is that CBD²⁻ is one of the best candidate precursors for CBD. Herein we report on a new and easy synthetic route from a CBD dianion to a CBD derivative that proceeds by a two-electron oxidation reaction.

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We chose 1,2-dibromoethane ($\text{BrCH}_2\text{CH}_2\text{Br}$) for the oxidation of the anion of **1**. The reaction of **1** with excess $\text{BrCH}_2\text{CH}_2\text{Br}$ in THF at room temperature produced tetrakis(trimethylsilyl)cyclobutadiene (**2**) in 64% yield (Scheme 1).^[15] The reaction time (ca. 1 min) for this transformation was quite important to obtain pure CBD **2**. The Diels–Alder cycloaddition product with ethylene generated from $\text{BrCH}_2\text{CH}_2\text{Br}$ was also produced at longer reaction times. CBD **2** readily reacted with dimethyl acetylenedicarboxylate to yield quantitatively a 1:1 adduct, the Dewar benzene derivative **3**.^[9]

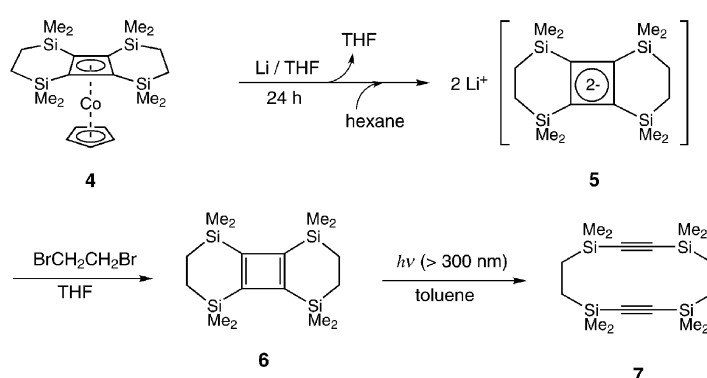


Scheme 1. Synthesis and reaction of tetrakis(trimethylsilyl)cyclobutadiene (**2**).

Pure compound **2** was isolated as air-sensitive pale red crystals by vacuum sublimation (ca. $100^\circ\text{C}/0.01$ Torr). Compound **2**, the first CBD derivative with four heteroatomic substituents, was characterized by NMR spectroscopy. Only one signal at $\delta = 0.15$ was observed for the methyl groups in the ^1H NMR spectrum of **2** in $[\text{D}_6]$ benzene. The ^{29}Si NMR spectrum showed a signal at $\delta = -16.7$, which was shifted downfield relative to that of compound **1** ($\delta = -23.7$, $\Delta\delta = 7.0$). Two signals appeared at $\delta = 0.0$ (methyl carbon atoms) and $\delta = 172.1$ (quaternary carbon atoms) in the ^{13}C NMR spectrum of compound **2**. The signal at $\delta = 172.1$ was also significantly shifted downfield relative to that of compound **1** ($\delta = 104.1$, $\Delta\delta = 68.0$) by the two-electron oxidation. Single crystals of a size suitable for characterization by X-ray diffraction have not yet been obtained.^[10]

Next, we designed the bridged CBD derivative 3,3,6,6,9,9,12,12-octamethyl-3,6,9,12-tetrasilatricyclo[6.4.0.0^{2,7}]-dodeca-1(8),2(7)-diene (**6**) to investigate any structural information that may be obtained when the cyclobutadiene ring is fixed with two six-membered rings. A new precursor **5** was prepared by the reaction of the cobalt complex **4** with lithium metal in THF.^[11, 12] The reaction of **5** with $\text{BrCH}_2\text{CH}_2\text{Br}$ in THF occurred readily to give the cyclobutadiene derivative **6** (Scheme 2). CBD **6** was fully characterized by NMR spectroscopic and X-ray crystallographic analysis.

The X-ray diffraction data were collected at 105 K. An ORTEP drawing of compound **6** is shown in Figure 1.^[13] The central four-membered ring of **6** shows a planar rectangular structure with localized C–C double bonds. The internal bond angles of the four-membered ring range from



Scheme 2. Synthesis and photochemical reaction of octamethyl-3,6,9,12-tetrasilatricyclo[6.4.0.0^{2,7}]-dodeca-1(8),2(7)-diene (**6**).

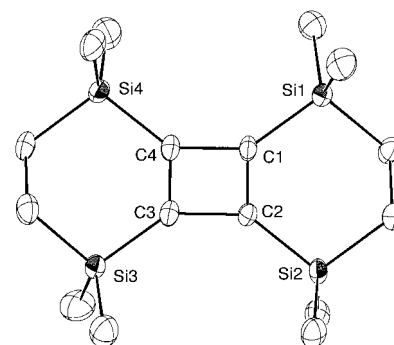


Figure 1. ORTEP drawing of the structure of **6** with thermal ellipsoids shown at the 50% probability level (hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: C1–C2 1.364(7), C1–C4 1.578(6), C2–C3 1.583(6), C3–C4 1.353(7), C1–Si1 1.863(5), C2–Si2 1.854(5), C3–Si3 1.861(5), C4–Si4 1.859(5); C2–C1–C4 90.1(4), C2–C1–Si1 126.5(4), C4–C1–Si1 143.4(4), C1–C2–C3 89.5(4), C1–C2–Si2 128.4(4), C3–C2–Si2 142.0(4), C4–C3–C2 90.3(4), C4–C3–Si3 126.7(4), C2–C3–Si3 142.9(4), C3–C4–C1 90.1(4), C3–C4–Si4 128.0(4), C1–C4–Si4 141.9(4).

89.5(4) to 90.3(4) $^\circ$ (av 90.0°) and the sum of the bond angles is 360.0° . The central four-membered ring is essentially planar, as determined by the dihedral angles of $1.1(4)^\circ$ for C1–C2–C3/C1–C3–C4 and $1.0(4)^\circ$ for C1–C2–C4/C2–C3–C4. The C–C double bond lengths (C1=C2 1.364(7), C3=C4 1.353(7) Å) are comparable to the typical value for a C–C double bond (1.34 Å). In contrast, the C–C single bond lengths (C1–C4 1.578(6), C2–C3 1.583(6) Å) are longer than the typical value for a C–C single bond (1.54 Å).

The main cause of the elongation of the single bonds may be the steric repulsion between the methyl groups on the Si atoms. Similar structural features were observed in the cyclobutadiene fused to two seven-membered rings in 3,3,7,7,10,10,14,14-octamethyl-5,12-dithiatricyclo[7.5.0.0^{2,8}]-tetradeca-1(9),2(8)-diene (1.344 and 1.600 Å),^[6b] and in 3,3,7,7,10,10,14,14-octamethyltricyclo[7.5.0.0^{2,8}]-tetradeca-1(9),2(8)-diene (1.339 and 1.597 Å).^[6j] The Si–C (quaternary carbon atoms) bond lengths of compound **6** (1.854(5)–1.863(5) Å; av 1.859 Å) are quite normal. The positions of the four Si atoms slightly deviate from the plane of the four-membered ring (C1–C2–C3–C4), as determined by the vector plane angles between the C1–C2–C3–C4 plane and the Si–C bond ($0.97(2)$ – $3.70(2)^\circ$).

Since the present cyclobutadiene derivatives are highly perturbed by the four silyl groups, we have also examined

their reactivities. The two-electron reduction of **2** and **6** with lithium metal in THF afforded the quantitative formation of the corresponding dianions **1** and **5** within a few hours. Thus, we can now easily perform the interconversion between the CBD and the CBD²⁻ ion. Irradiation of CBD **2** in [D₈]toluene with a 500-W high-pressure mercury lamp with a filter ($\lambda > 300$ nm) at room temperature yielded bis(trimethylsilyl)-acetylene through cleavage of the C–C bond. No tetrahydra-derivative was observed under these conditions. Interestingly, in the case of **6**, the cyclic diyne compound 2,2,5,5,8,8,11,11-octamethyl-2,5,8,11-tetrasilacyclododeca-1,6-diyne (**7**)^[14] was produced after irradiation (Scheme 2). Thus, the cyclobutadiene ring system of **6** undergoes an interconversion of the two rectangular forms in solution at room temperature. It is likely that this bond-switching process is completely blocked in the crystalline lattice at 105 K.

Experimental Section

2: Crystals of **1** (160 mg, 0.32 mmol) were placed in a reaction tube with a magnetic stirrer and then evacuated. Degassed THF (3 mL) and 1,2-dibromoethane (1.88 g, 10 mmol) were introduced by vacuum transfer, and the solution was stirred for a short time (1 min). The solvent was removed in vacuo, and then degassed hexane (3 mL) was introduced by vacuum transfer. The lithium bromide was removed by filtration and the filtrate was concentrated. The residue was then sublimed (ca. 100 °C/0.01 Torr) to afford pale red crystals of **2** (70 mg, 64 %). M.p. 122–123 °C; ¹H NMR ([D₆]benzene, TMS): δ = 0.15 (s, 36H; CH₃); ¹³C{¹H} NMR ([D₆]benzene, TMS): δ = 0.0 (CH₃), 172.1 (C); ²⁹Si{¹H} NMR ([D₆]benzene, TMS): δ = –16.7; HR-MS calcd for C₁₆H₃₆Si₄: 340.1894; found: 340.1891.

Compound **6** was prepared by an analogous procedure as compound **2**, but starting from compound **4**, and in 81 % yield. ¹H NMR ([D₈]toluene, TMS): δ = 0.07 (s, 24H; CH₃), 0.77 (s, 8H; CH₂); ¹³C{¹H} NMR ([D₈]toluene, TMS): δ = –3.1 (CH₃), 8.2 (CH₂), 173.4 (C); ²⁹Si{¹H} NMR ([D₆]benzene, TMS): δ = –18.8; HR-MS calcd for C₁₆H₃₂Si₄: 336.1581; found: 336.1581.

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- [9] Spectroscopic data for **3**: colorless crystals; m.p. 92–93 °C; ¹H NMR ([D₆]benzene, TMS): δ = 0.31 (s, 18H; CH₃), 0.32 (s, 18H; CH₃), 3.37 (s, 6H; CH₃); ¹³C{¹H} NMR ([D₆]benzene, TMS): δ = 1.6 (CH₃), 1.7 (CH₃), 51.0 (CH₃), 65.7 (C), 148.1 (C=C), 163.3 (C=C), 172.7 (C=O); ²⁹Si{¹H} NMR ([D₆]benzene, TMS): δ = –11.0, –3.2.
- [10] Preliminary X-ray diffraction analysis of **2** at 120 K showed a rectangular structure for the cyclobutadiene ring. However, the refinement was unsatisfactory as a result of the poor quality of the crystals.
- [11] Spectroscopic data for **4**: yellow crystals; m.p. 252–254 °C; ¹H NMR ([D₁]chloroform, TMS): δ = 0.02 (s, 12H; CH₃), 0.13 (s, 12H; CH₃), 0.59–0.69 (m, 4H; CH₂), 0.73–0.83 (m, 4H; CH₂), 4.92 (s, 5H; CH); ¹³C{¹H} NMR ([D₁]chloroform, TMS): δ = –1.0 (CH₃), –0.3 (CH₃), 8.6 (CH₂), 79.1 (CH), 80.6 (C); ²⁹Si{¹H} NMR ([D₁]chloroform, TMS): δ = –9.0.
- [12] Spectroscopic data for **5**: pale yellow crystals; ¹H NMR ([D₈]toluene, TMS): δ = 0.35 (s, 24H; CH₃), 1.19 (s, 8H; CH₂), 1.34 (brs, 8H; THF), 3.49 (brs, 8H; THF); ¹³C{¹H} NMR ([D₈]toluene, TMS): δ = 2.5 (CH₃), 12.4 (CH₂), 25.5 (THF), 68.7 (THF), 102.1 (C, quint, $J(^{13}\text{C}, ^6\text{Li}) = 1.2$ Hz); ²⁹Si{¹H} NMR ([D₈]toluene, TMS): δ = –24.2; ⁶Li{¹H} NMR ([D₈]toluene, TMS): δ = –5.1.
- [13] Crystal structure analysis of **6**: A single crystal (0.40 × 0.30 × 0.20 mm) was sealed in a capillary glass tube for the data collection. Diffraction data were collected at 105 K on a MacScience DIP2030K Image Plate Diffractometer employing graphite-monochromated MoK α radiation ($\lambda = 0.71070$ Å). Crystal data: C₁₆H₃₂Si₄, $M_r = 336.78$, monoclinic, space group $P2_1/c$, $a = 9.5770(6)$, $b = 19.631(2)$, $c = 12.184(1)$ Å, $\beta = 113.116(4)^\circ$, $V = 2106.8(3)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.062$ g cm^{–3}, $\text{GOF} = 1.129$. The final R factor was 0.0980 ($R_w = 0.2550$) for 4736 reflections with $I_o > 2\sigma(I_o)$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152460. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Water Exchange Controls the Complex-Formation Mechanism of Water-Soluble Iron(III) Porphyrins: Conclusive Evidence for Dissociative Water Exchange from a High-Pressure ^{17}O NMR Study**

Thorsten Schnepfensieper, Achim Zahl, and Rudi van Eldik*

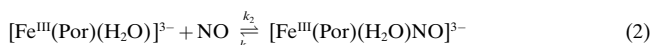
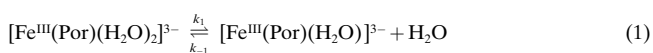
Transition metal porphyrins have received considerable attention from many groups, especially as a result of their catalytic activity in various oxidation processes.^[1–3] Of fundamental interest is their high reactivity coupled to the ability to undergo fast ligand-substitution reactions and the redox cycling that forms an essential aspect of their solution-phase chemistry.^[4–6] The investigated iron porphyrins are known to be model complexes for a number of enzymes and proteins. These heme proteins serve a wide-range of functions, and the nature of the axial ligand on the iron is thought to play a key role in controlling the properties of the heme proteins. Of particular interest are the oxidizing enzymes peroxidases, cytochrome P-450's, and catalases.^[7,8] In addition, various reports point to the important role of the metalloporphyrins such as cytochrome oxidase,^[9] nitrile hydratase,^[10] and catalase^[11] as target molecules in mammalian biology. Mechanistic studies on and the substitution behavior of various metalloporphyrins have been reviewed.^[12,13]

In 1980 Hunt and co-workers^[14] studied the water-exchange reactions of two water-soluble Fe^{III} porphyrins using ^{17}O NMR spectroscopic techniques. Both complexes, *meso*-tetrakis(*N*-methyl-4-pyridyl)porphine (H_2TMPyP) and *meso*-tetrakis(*p*-sulfonatophenyl)porphine (H_2TPPS), exhibited water-exchange reactions that are several orders of magnitude faster than aquated Fe^{III} ions in acidic medium.^[15] These complexes were considered to be model compounds for aqueous porphyrin chemistry, since in aqueous solution the axial interaction of water with the metal is of fundamental importance in both ligand-substitution and redox processes. The fast water-exchange reactions were characterized by significantly positive activation entropies, but no mechanistic conclusions were drawn from this data.^[14]

In the meantime, the application of high-pressure kinetic techniques has contributed significantly towards the elucidation of inorganic reaction mechanisms in general,^[16] and that of solvent-exchange processes on transition metal centers in particular.^[17] As far as we know, no studies have been

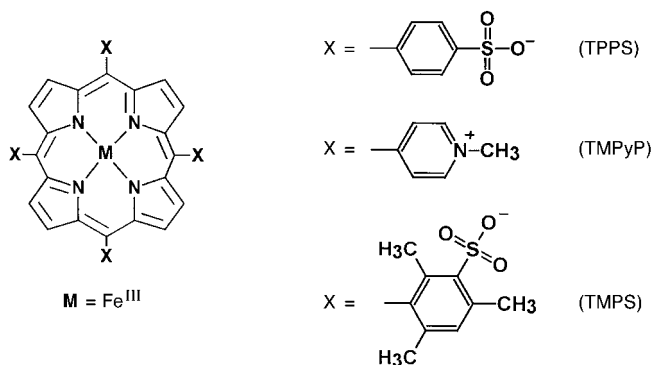
performed on water-exchange reactions of water-soluble porphyrin complexes using high-pressure NMR spectroscopic techniques. Some mechanistic information on such reactions was obtained indirectly from the effect of pressure on ligand-substitution reactions of complexes of the type $[\text{M}(\text{TPPS})(\text{H}_2\text{O})_2]^{3-}$ and $[\text{M}(\text{TMPyP})(\text{H}_2\text{O})_2]^{5+}$, where $\text{M} = \text{Co}^{\text{III}}$, Rh^{III} , and Cr^{III} .^[18–20] In these reactions the rapid substitution of water by thiourea and thiocyanate was characterized by significantly positive volumes of activation, from which a dissociative ligand-substitution mechanism was concluded. However, a clear distinction between a dissociative interchange (I_d) or a limiting dissociative (D) mechanism was not possible.

Quite recently, with the aid of laser flash-photolysis techniques, Ford and co-workers^[21] studied the reversible binding of NO to $[\text{Fe}^{\text{III}}(\text{TPPS})(\text{H}_2\text{O})_2]^{3-}$ and $[\text{Fe}^{\text{III}}(\text{TMPS})(\text{H}_2\text{O})_2]^{3-}$, ($\text{H}_2\text{TMPS} = \text{meso}$ -tetrakis(sulfonato-mesityl)porphine). They suggested a dissociative mechanism on the basis of significantly positive volumes of activation found for both the “on” and “off” reactions. Their mechanistic interpretation of the data followed the concept of a dissociative (D) mechanism and consisted of reaction steps (1) and (2), Por = porphyrin.



Under the selected experimental conditions, $k_{\text{on}} = k_1 k_2 [\text{NO}] / k_{-1}$ and $k_{\text{off}} = k_{-2}$. The effect of pressure on k_{on} resulted in positive activation volumes, $+13 \pm 1$ and $+8.3 \pm 1.5 \text{ cm}^3 \text{ mol}^{-1}$, for por = TMPS and TPPS, respectively, underlining the overall dissociative nature of the binding reaction. The complexity of the rate expression for k_{on} , however, did not allow a more detailed interpretation since $\Delta V^\ddagger(k_{\text{on}}) = \Delta V^\ddagger(k_1) + \Delta V^\ddagger(k_2) - \Delta V^\ddagger(k_{-1})$. The authors argued, as in the cases mentioned above,^[18–20] that $\Delta V^\ddagger(k_2) - \Delta V^\ddagger(k_{-1})$ is expected to be small as a result of the rapid binding of NO and H_2O , respectively, such that $\Delta V^\ddagger(k_{\text{on}})$ mainly presents $\Delta V^\ddagger(k_1)$.

We have now studied the water-exchange reactions of $[\text{Fe}^{\text{III}}(\text{TPPS})(\text{H}_2\text{O})_2]^{3-}$ (1), $[\text{Fe}^{\text{III}}(\text{TMPyP})(\text{H}_2\text{O})_2]^{5+}$ (2), and $[\text{Fe}^{\text{III}}(\text{TMPS})(\text{H}_2\text{O})_2]^{3-}$ (3), that is, reaction (1), in more detail using high-pressure ^{17}O NMR spectroscopic techniques.



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

The selected porphines TPPS, TMPyP, and TMPS vary in steric hindrance and charge, and thus allow the influence of these factors on the water-exchange process to be studied. The results clearly support the operation of a dissociative mechanism in all cases and enable a more detailed interpretation of the activation volumes reported for the complex-formation reactions mentioned above.

Temperature dependence: An analysis of the data for the three investigated porphyrins (see Figures 2–4 in the Supporting Information) gave the activation parameters summarized in Table 1. The fastest exchange rates are observed for the negatively charged $[\text{Fe}^{\text{III}}(\text{TMPS})(\text{H}_2\text{O})_2]^{3-}$ and $[\text{Fe}^{\text{III}}(\text{TPPS})(\text{H}_2\text{O})_2]^{3-}$ complexes, with $k_{\text{ex}} = (2.1 \pm 0.1) \times 10^7 \text{ s}^{-1}$ and $k_{\text{ex}} = (2.0 \pm 0.1) \times 10^6 \text{ s}^{-1}$ at 298 K, respectively. The decrease in rate constant for the TPPS complex is associated with an increase in $\Delta H^\ddagger$ from $61 \pm 1 \text{ kJ mol}^{-1}$ to $67 \pm 2 \text{ kJ mol}^{-1}$. The positive charged porphyrin $[\text{Fe}^{\text{III}}(\text{TMPyP})(\text{H}_2\text{O})_2]^{5+}$ is less labile with $k_{\text{ex}} = (4.5 \pm 0.1) \times 10^5 \text{ s}^{-1}$ at 298 K, for which $\Delta H^\ddagger$ increases further to $71 \pm 2 \text{ kJ mol}^{-1}$. For all the investigated porphyrins almost an identical entropy of activation, $100 \pm 10 \text{ J K}^{-1} \text{ mol}^{-1}$, was found. This large positive value suggests that a dissociative water-exchange mechanism is operative in all cases.

By way of comparison, Hunt and co-workers^[14] found significantly lower, but almost equal values for the activation enthalpy for the oppositely charged complexes of TPPS and TMPyP. In addition, they found k_{ex} to be 20 times larger for the TPPS than for the TMPyP complex. These differences were ascribed to an entropic effect since their values for the activation entropy differed significantly. The data of Hunt and co-workers^[14] were calculated under the assumption that only one water molecule is coordinated to the metal center in both systems. However, according to data published later, two water molecules are bound to the TMPS^[22] and TPPS, as well as to the TMPyP^[23] complexes in an octahedral coordination geometry. This assumption could have led to deviations in the reported rate and activation parameters, since the number of coordinated water molecules affects the data calculation. In addition, as a 400 MHz NMR spectrometer was employed in our study more accurate data can be expected.

On the basis of our data, steric hindrance on the porphyrin increases k_{ex} by a factor of 10, as expected for the effect of steric decompression on a dissociative activation process, whereas the positively charged TMPyP complex has an exchange rate that is approximately 50 times lower than that of the TMPS complex. That k_{ex} for the negatively charged complexes is significantly higher than for the TMPyP system,

suggests that the crucial factor for the exchange rate, besides the steric decompression, is the negatively charged peripheral substituents that increase the electron density on the metal center and labilize the axial metal–ligand (water) bonds.

Pressure dependence: From the temperature-dependence data, appropriate temperatures were selected for the pressure-dependence measurements. Plots of $\ln(1/T_{\text{ex}})$ versus pressure for all three $[\text{Fe}^{\text{III}}(\text{Por})(\text{H}_2\text{O})_2]$ complexes are shown in Figure 1. In all cases, the plots are linear within the experimental error limits and the volume of activation could be calculated directly from the slope ($= -\Delta V^\ddagger/RT$). Very similar values are obtained for complexes **1** and **2**, $\Delta V^\ddagger = +7.9 \pm 0.2$ and $+7.4 \pm 0.4 \text{ cm}^3 \text{ mol}^{-1}$, respectively, compared to the significantly higher value of $+11.9 \pm 0.3 \text{ cm}^3 \text{ mol}^{-1}$ for the sterically demanding complex **3** (see Table 1).

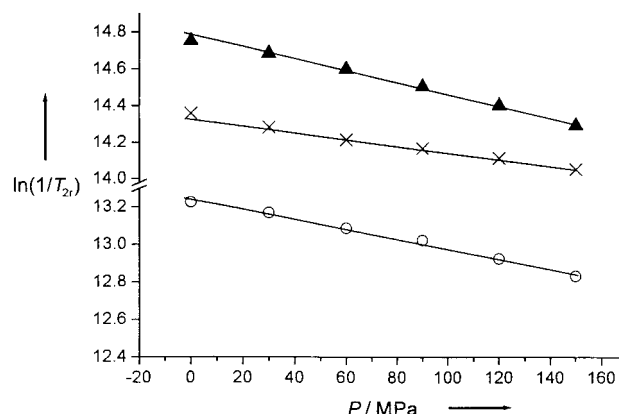


Figure 1. Pressure dependence of T_{ex} for water exchange on $[\text{Fe}^{\text{III}}(\text{TPPS})(\text{H}_2\text{O})_2]^{3-}$ ($\circ$, 288 K), $[\text{Fe}^{\text{III}}(\text{TMPyP})(\text{H}_2\text{O})_2]^{5+}$ ($\times$, 318 K), and $[\text{Fe}^{\text{III}}(\text{TMPS})(\text{H}_2\text{O})_2]^{3-}$ ($\blacktriangle$, 279 K). For experimental conditions see Figures 2–4 in the Supporting Information.

It follows that the opposite charges on complexes **1** and **2** do not affect the substitution mechanism of coordinated water, and the reported $\Delta V^\ddagger$ data support the operation of a dissociative interchange (I_d) mechanism.^[16, 17] The introduction of steric hindrance through the bulky mesityl groups on complex **3** enhances the water-exchange rate, and the more positive $\Delta V^\ddagger$ value suggests that substitution of coordinated water follows a limiting dissociative (D) mechanism. In fact, the reported value of $+11.9 \pm 0.3 \text{ cm}^3 \text{ mol}^{-1}$ in the latter case is very close to the limiting value of $+13 \text{ cm}^3 \text{ mol}^{-1}$ predicted for water exchange on an octahedral metal complex following a limiting dissociative mechanism.^[17, 24, 25] This means that the

Table 1. Rate and activation parameters for water-exchange reactions of iron(III) porphyrin complexes. The errors shown are standard deviations given by the computer program.

	k_{ex}^{298} [s^{-1}]	$\Delta H^\ddagger$ [kJ mol^{-1}]	$\Delta S^\ddagger$ [$\text{J K}^{-1} \text{ mol}^{-1}$]	$\Delta V^\ddagger$ [$\text{cm}^3 \text{ mol}^{-1}$]	$k_{\text{ex}}^{\text{[a]}}$ [s^{-1}]	Ref.
$[\text{Fe}(\text{TPPS})(\text{H}_2\text{O})_2]^{3-}$ 1	$(2.0 \pm 0.1) \times 10^6$ $(1.4 \pm 0.01) \times 10^7$	67 ± 2 57.3 ± 0.4	99 ± 10 84.5 ± 1.3	$+7.9 \pm 0.2^{\text{[b]}}$ —	$7.5 \times 10^5/8.5 \times 10^5$ —	this work [14]
$[\text{Fe}(\text{TMPyP})(\text{H}_2\text{O})_2]^{5+}$ 2	$(4.5 \pm 0.1) \times 10^5$ $(7.8 \pm 0.1) \times 10^5$	71 ± 2 57.7 ± 0.4	100 ± 6 61.5 ± 1.3	$+7.4 \pm 0.4^{\text{[c]}}$ —	$2.1 \times 10^6/2.7 \times 10^6$ —	this work [14]
$[\text{Fe}(\text{TMPS})(\text{H}_2\text{O})_2]^{3-}$ 3	$(2.1 \pm 0.1) \times 10^7$	61 ± 1	100 ± 5	$+11.9 \pm 0.3^{\text{[d]}}$	$3.8 \times 10^6/3.9 \times 10^6$	this work

[a] For comparison with the value of k_{ex} from the temperature-dependence data at normal pressure, the value of k_{ex} from the pressure-dependence data was extrapolated to normal pressure at the temperature at which $\Delta V^\ddagger$ was determined. [b] Measured at 288 K. [c] Measured at 318 K. [d] Measured at 279 K.

degree of bond cleavage in the transition state is significantly higher for complex **3** than in **1** and **2**.

Returning to the motivation for this work, our results on the water-exchange mechanism of the porphyrins studied are in excellent agreement with the mechanistic interpretation offered by Ford and co-workers^[21] for the complex-formation reactions of **1** and **3** with NO. Their reported activation volumes of $+8.3 \pm 1.5$ and $+13 \pm 1 \text{ cm}^3 \text{ mol}^{-1}$ for these reactions, respectively, are almost identical to those reported for the water-exchange reactions in the present study. Their conclusion that the observed $\Delta V^\ddagger$ for the "on" reaction with NO mainly represents $\Delta V^\ddagger(k_1)$ for reaction (1), is perfectly correct as shown by the data reported here. Thus the formation of **1** and **3** is not only controlled by the rate but also by the mechanism of the water-exchange process. Depending on the structural and electronic situation this process tends to occur according to an I_a or D mechanism, the complex-formation reactions with nucleophiles such as NO follow the same mechanism.

The water-exchange rate and associated activation enthalpy of iron(III) porphyrins are significantly affected by the charge on the porphine and to a lesser degree by steric compression. The mechanism of the process, however, is controlled by steric factors and varies between a dissociative interchange and a limiting dissociative mechanism. Thus the lability of the axial-bound solvent molecules in these systems plays a key role in the mechanism and substitution behavior of porphyrin- and heme-based systems. High-pressure NMR spectroscopic techniques present a powerful tool to add to the mechanistic understanding of such processes, which could lead to a more profound understanding of the reactions and processes in biologically relevant macrocyclic systems such as metmyoglobin and cytochrome P-450.

Experimental Section

$\text{Na}_3[\text{Fe}^{\text{III}}(\text{TPPS})(\text{H}_2\text{O})_2]$ ($\text{Na}_3\text{-1}$) was synthesized as described elsewhere.^[26] $[\text{Fe}^{\text{III}}(\text{TMPyP})(\text{H}_2\text{O})(\text{OH})](\text{pts})_4$ (**2-pts**), where pts = *p*-toluenesulfonate, and $\text{Na}_3[\text{Fe}^{\text{III}}(\text{TMPS})(\text{H}_2\text{O})_2]$ ($\text{Na}_3\text{-3}$) were purchased from Frontier Scientific Ltd. Fine Chemicals Utah, USA, and used without further purification. Ca. 20% enriched ^{17}O -labeled water (D-Chem Ltd. Tel Aviv, Israel) was used for the ^{17}O NMR water-exchange measurements. NaClO_4 (Aldrich) was used to adjust the ionic strength to 0.5 M, and HClO_4 (**1** and **3**) and tosyllic acid (**2**) were used to adjust the pH of the solution. No salt was added in the case of **2** to avoid precipitation. The porphyrin samples were prepared by combining weighted amounts of salt, perchloric or tosyllic acid, and water. The resulting solution was transferred to the NMR tube. The pH was determined on identical samples prepared in ordinary water. The water exchange measurements were performed at pH 3 (for **1** and **3**) and pH 1.1 (for **2**), where only the monomeric aqua forms of the porphyrins are present in solution. The complex concentrations were $3.4 \times 10^{-2} \text{ M}$ (**1**), $2.0 \times 10^{-2} \text{ M}$ (**2**), and $3.0 \times 10^{-2} \text{ M}$ (**3**).

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Controlling the Lability of Square-Planar Pt^{II} Complexes through Electronic Communication between π -Acceptor Ligands**

Deograti Jaganyi, Andreas Hofmann, and Rudi van Eldik*

Dedicated to Professor Ernst-G. Jäger on the occasion of his 65th birthday

Studies on the substitution mechanism of low-spin d^8 square-planar complexes for many years centered around the σ *trans* influence or *trans* effect.^[1] For Pt^{II} complexes this has involved detailed systematic studies of different *trans* groups^[2] using a range of different nucleophiles.^[3] Mechanistic studies established that ligand-substitution reactions of Pt^{II} complexes mainly occur by an associative process involving a trigonal-bipyramidal intermediate. In recent years, volumes of activation ($\Delta V^\ddagger$) obtained from high-pressure kinetic measurements, have been used in distinguishing mechanistic pathways of substitution reactions; negative values indicating

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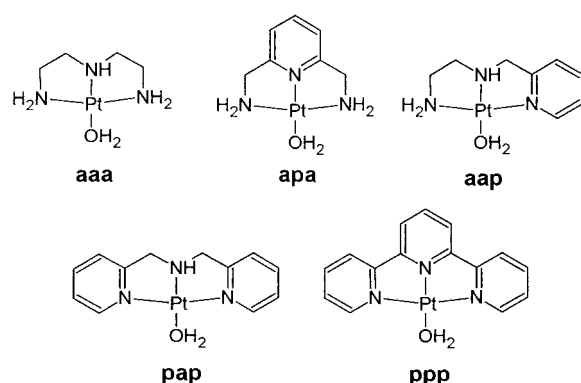
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an associative-reaction route.^[4] New experimental evidence has been published showing that the exchange of some sulfides or sulfoxides at Pt^{II} complexes, such as *cis*-[PtPh₂(Et₂S)₂], *cis*-[PtPh₂(Me₂S)₂], and [Pt(bph)(SR₂)₂] (R = Me and Et, bph = biphenyl), proceed under the influence of a σ *trans* influence and/or *trans* effect according to a dissociative mechanism in which a three-coordinate intermediate is formed.^[5]

It has also been known for a long time that the rate of substitution of Pt^{II} complexes is enhanced when groups having strong π -acceptor properties are attached to the metal center.^[5, 6] The acceleration has been ascribed to the reduction of charge on the metal center by the employed ligand and results from back-donation of electrons from the filled d-orbitals of the Pt^{II} center into the empty antibonding or nonbonding orbitals of the ligand.^[7] Application of extended Hückel theory, molecular electrostatic potential, and ab initio calculations have been used to demonstrate the π -acceptor properties of specific ligands.^[5] In addition, the π effect has been noted to be an important factor in the search for a possible mechanistic changeover in the substitution behavior of square-planar complexes. The displacement of thioethers by CO, which has π -acceptor capabilities, in systems such as *cis*-[PtR₂S₂] (R = Me or Ph; S = R₂S or Me₂SO),^[5] prevents the substitution process from following a dissociative mechanism. Thus the presence or absence of π back-bonding is responsible for the mechanistic changeover in the case of thioether complexes of Pt^{II}.

Despite its importance and influence in substitution reactions of Pt^{II} complexes, there has been no systematic study carried out to investigate the π -acceptor (*cis* and *trans*) effect in more detail. In an effort to gain more insight into this property, a detailed study of its influence both in the *cis* and *trans* position has been undertaken using monoaqua Pt^{II} complexes with tridentate N-donor ligands. The results clearly show that it is not so much the π -acceptor effect that controls the rate of the substitution process, but more importantly the communication between different π -acceptor ligands, an effect not recognized before.

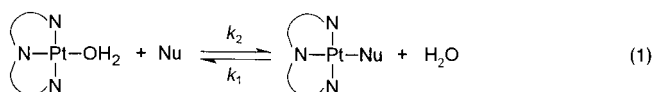
Five complexes, [Pt(diethylenetriamine)H₂O](CF₃SO₃)₂ (**aaa**), [Pt{2,6-bis(aminomethyl)pyridine}H₂O](CF₃SO₃)₂ (**apa**), [Pt{N-(pyridyl-2-methyl)-1,2-diaminoethane}H₂O](ClO₄)₂ (**aap**), [Pt{bis(2-pyridylmethyl)amine}OH]ClO₄ (**pap**), and [Pt(terpyridine)H₂O](BF₄)₂ (**ppp**) (Scheme 1) were synthesized. The



Scheme 1. Structures of the investigated Pt^{II} complexes; the CF₃SO₃ and ClO₄ counterions are not shown.

aqua complexes were prepared by hydrolysis of the corresponding chloro complexes (see Experimental Section). These complexes allow a systematic study of the π -acceptor effect of the ligands in the *cis* and *trans* position on the ligand-substitution behavior of the complexes.

The substitution of coordinated water [Eq. (1)] by three different nucleophiles (Nu), thiourea (TU), 1,3-dimethyl-2-thiourea (DMTU), and 1,1,3,3-tetramethyl-2-thiourea



(TMTU), was investigated under pseudo first-order conditions using stopped-flow techniques. The reactions were carried out at a pH between 2 and 3 where the complexes exist in the aqua form, and the temperature was maintained at 25 °C.

The pseudo first-order rate constants, k_{obs} , calculated from the kinetic traces were plotted versus the concentrations of the entering nucleophiles. Straight lines were obtained with y-axis intercepts near to zero, indicating that Equation (2) can be used to represent k_{obs} since k_1 , which is from the reverse aquation reaction, is practically zero.

$$k_{\text{obs}} = k_1 + k_2[\text{Nu}] \approx k_2[\text{Nu}] \quad (2)$$

Concentration dependencies of k_{obs} for DMTU as the entering ligand are shown in Figure 1 (note that this is a double y-axis plot in which the data for **ppp** are presented by

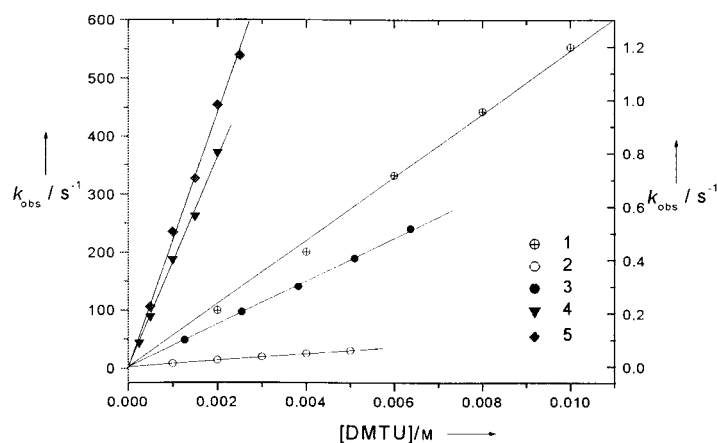


Figure 1. Dependence of observed rate constant k_{obs} [s⁻¹] on the concentration of DMTU as the entering nucleophile at 25 °C in aqueous medium; [NaClO₄] = 0.1M, pH 2–3. 1 = **aaa** (⊕), 2 = **apa** (○), 3 = **aap** (●), 4 = **pap** (▼), and 5 = **ppp** (◆). The concentration of DMTU used for **aaa** (⊕) has been divided by 10.

the y-axis on the left). To accommodate the **aaa** data on the same scale, its true DMTU concentration had to be divided by ten. The second-order rate constants k_2 are in Table 1, along with the pK_a values of the complexes. These values were determined spectrophotometrically and kinetically by recording the UV/Vis spectra and rate constants, respectively, over a wide pH range.

Table 1. Second-order rate constants and pK_a values determined kinetically and from UV/Vis measurements, respectively; ionic strength 0.1 mol dm^{-3} (NaClO_4), $T = 25^\circ\text{C}$.

Nucleophile	$k_2 [\text{M}^{-1} \text{s}^{-1}]$				
	aaa	apa	aap	pap	ppp
TU	$29.1 \pm 0.4^{[a]}$	101.1 ± 0.7	110 ± 1	393 ± 2	$163\,400 \pm 2230$
DMTU	11.9 ± 0.2	41.2 ± 0.3	80.4 ± 0.5	393 ± 5	$216\,970 \pm 2980$
TMTU	3.2 ± 0.02	12.3 ± 0.1	29.3 ± 0.2	182 ± 2	$152\,900 \pm 2700$
	pK_a				
kinetic	6.35 ± 0.03	5.96 ± 0.05	5.60 ± 0.06	5.30 ± 0.03	4.42 ± 0.05
thermodynamic	$6.26 \pm 0.10^{[a]}$	6.04 ± 0.08	5.71 ± 0.03	5.53 ± 0.07	4.62 ± 0.04

[a] Data are in good agreement with the data in ref. [12].

It is reasonable to assume that the σ *trans* effect is the same for pyridine and amine ligands.^[8] It is also known that the electronic influence of the *cis* ligands is usually small.^[1, 7] Thus, it can be concluded that the observed kinetic effects are mainly because of π -acceptor effects. The data clearly demonstrate that by introducing the pyridine unit with π -acceptor properties to the **aaa** complex, the rate of substitution of coordinated water increases significantly by at least a factor of four in going from **aaa** to **apa**, the effect for the other ligands being much larger.

The *cis* effect is more dominant than the *trans* effect. The values of k_2 for the reactions with TU are only 10% larger, but in the case of DMTU and TMTU, k_2 doubles from **apa** (the *trans* complex) to **aap** (the *cis* complex). These observations on the π *cis* effect are contrary to what is generally known. The σ *cis* effect has generally been accepted to be always smaller than its *trans* counterpart.^[1, 7]

The structures of the selected complexes are such that the π effect of the different pyridine ligands should be additive or at least increase with the number of pyridine ligands. In going from **aap** to **pap**, it is reasonable to expect an increase in k_2 similar to that observed in going from **aaa** to **aap**, that is, a doubling of the π *cis* effect. This is indeed approximately the case. Furthermore, in going from **aaa** to **ppp**, k_2 is expected to increase in a similar way as the combined effect of **apa** and **pap** compared to **aaa**. However, the observed increase in k_2 , a factor of between 5.6×10^3 and 4.8×10^4 in going from **aaa** to **ppp** is much larger than predicted on the basis of the combined effects observed for **apa** and **pap**, (between 47 and 219) for the different entering nucleophiles. This means that the very large labilization effect observed for the **ppp** complex cannot simply arise from the combination of the π -acceptor effects of the three pyridine groups. In fact, the conjugated nature of the chelate must be responsible for this significant increase in lability, that is, electronic communication within the chelate controls the overall observed π -acceptor effect.

The nucleophiles selected have different degrees of steric hindrance and nucleophilicity. The results in Table 1 show that substitution of coordinated water depends on the steric nature of the nucleophiles. The most sterically hindered nucleophile TMTU reacts significantly slower than the less hindered TU in going from **aaa** to **apa**. The trend in the results as one moves from **aaa** to **ppp** is that the effect of steric hindrance on the rate of the substitution process diminishes, and disappears totally in the case of the **ppp** complex. This can be accounted for by the increase in electrophilicity of the Pt^{II} center in the

series of complexes reaching a maximum for **ppp**. In the latter case, the metal center seems to be so electrophilic that the steric bulk of the entering nucleophile plays no significant role. In fact, the higher nucleophilicity of DMTU and TMTU, as a result of the inductive effects of the methyl substituents, seem to overcompensate for the decrease in k_2 expected as a result of increased steric hindrance.

The dependence of k_2 upon the basicity of the complexes is shown in Figure 2, where $\log k_2$ is plotted against the pK_a values of the aqua complexes. The least-squares fit for four of

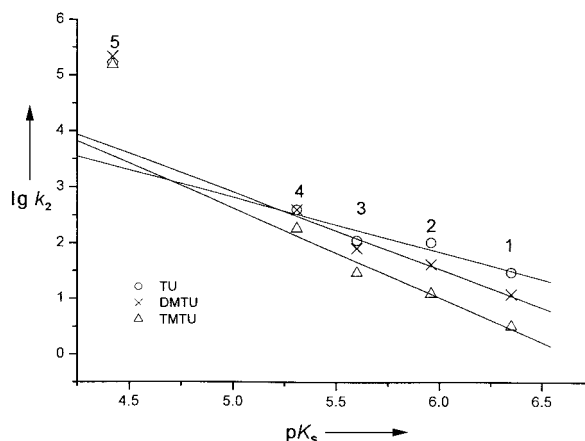


Figure 2. Plot of $\log k_2$ versus the pK_a of the aqua complexes at 25°C for different entering nucleophiles TU $\circ$, DMTU $\times$, and TMTU $\triangle$. 1 = **aaa**, 2 = **apa**, 3 = **aap**, 4 = **pap**, and 5 = **ppp**.

the complexes (excluding **ppp**) resulted in reasonable straight lines with slopes of -1.0 ± 0.2 , -1.4 ± 0.2 , and -1.6 ± 0.2 for the entering ligands TU, DMTU, and TMTU, respectively. The pK_a values serve as a measure of the electron density around the Pt^{II} center, which will control the electrophilicity of the metal center, the strength of the $\text{Pt}-\text{OH}_2$ bond, and therefore the acidity of the coordinated water molecule. The values of k_2 clearly depend on the basicity of the complexes; the rate of displacement of coordinated water increases with decreasing pK_a value, that is, with the increasing electrophilicity of the metal center which controls the rate of the associative substitution process. The increase in reactivity from **aaa** to **pap** results from the increase in π -acceptor properties of the chelate, which decreases the electron density on the metal center and decreases the pK_a value. The presence of the π -acceptor ligand(s) promotes the electrophilicity of the metal center and accounts for the observed correlation

between $\lg k_2$ and pK_a . The more negative slopes observed in Figure 2 for the more sterically hindered nucleophiles DMTU and TMTU, results, as discussed above, from the smaller effect of steric hindrance on the reaction rate of the more electrophilic complexes.

The **ppp** complex is therefore unusually reactive in comparison to the other complexes and also does not fit into the $\lg k_2$ versus pK_a relationship. The explanation offered for a similar system, where chloride was the leaving group, is that the strain on the ring system was the cause of the acceleration.^[9] This is only one of the possible factors that can influence the process. From this study, we can conclude that the π -effect in this system is not just because of the addition or combination of the individual *cis* and *trans* effects. The formation of the two five-membered aromatic rings involving the Pt^{II} center in the **ppp** complex is an important property that has a large influence on the observed reactivity; the presence of aromaticity allows for a much more extensive π -conjugated system. The consequence of this is a more electronically drained Pt^{II} center, as also indicated by the trend in the pK_a values, and a system capable of effectively stabilizing the five-coordinate transition state and/or intermediate through π back-bonding. A detailed study of the temperature and pressure dependencies of the investigated reactions has also been undertaken and the results will be reported in a forthcoming full report on this topic.

In summary, we have shown that it is possible to investigate the π -acceptor effect without the interference from the σ -donor effect that is much stronger and usually camouflages the π -effect. The π *cis* effect is certainly greater than the π *trans* effect. The investigation has revealed for the first time that the rate of substitution is inversely proportional to the basicity of the complex as a whole and not just that of the leaving or entering group. It has also shown that it is possible through π -acceptor effects to tune the pK_a of the complex, which in turn controls the lability of the complex. Most important, however, is our finding that the electronic communication between the π -acceptor ligands as in the case of the **ppp** complex, is responsible for the drastic increase in lability observed in this particular case. It has recently been shown^[10] that when this electronic communication between two aromatic rings is destroyed, the substitution rate is decreased by a factor of 60. The π -acceptor effects on their own (in the *cis* and/or *trans* position) are in the absence of such a direct communication of minor significance in affecting the lability of d^8 square-planar complexes.

Experimental Section

The ligands diethylenetriamine, bis(2-pyridylmethyl)amine, and terpyridine were obtained from Aldrich and used without further purification. *N*-(pyridyl-2-methyl)-1,2-diaminoethane was synthesized according to the literature method,^[11a] whereas 2,6-bis(aminomethyl)pyridine was prepared following a method used to synthesize 6-(aminomethyl)-2,2'-bipyridine by using 2,6-bis(bromomethyl)pyridine as starting material.^[11b,c] Synthesis of **aaa** and **ppp** was performed according to literature methods.^[11d,e] The preparation of the chloroplatinum precursor for **pap**, **aap**, and **apa** was performed according to a procedure similar to that used for the preparation of the chloro complex of **ppp**.^[11f] The latter two were treated with silver triflate to produce the required aqua complexes. For **pap**, the chloro complex was hydrolyzed using sodium hydroxide to give the hydroxy

complex which was precipitated from solution with the help of excess sodium perchlorate. Microanalysis and ^1H NMR spectra were used to check the purity of all the complexes. An Applied Photophysics SX 18MV stopped-flow instrument coupled to an online data acquisition system was used in all kinetic measurements.

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Electrokinetics in Fixed Beds: Experimental Demonstration of Electroosmotic Perfusion**

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The concept of an intraparticle forced convection to reduce the resistance to mass transfer of a stagnant mobile phase in liquid chromatography has received considerable attention over the last decade, both from a theoretical and a particle engineering point of view.^[1–9] By tuning the permeability of the porous particles to typical drops in column pressure, the actual pressure gradient in a fixed bed may act as a driving force for an intraparticle flow^[10] so that an already small, but non-zero flow component assists or even dominates the slow diffusion of large molecules and reduces the hold-up dispersion that arises from stagnant zones. An important aspect in the design of particles has been the hierarchical architecture of the pore network to which several sets of pores may contribute.^[1, 7, 9] The term perfusion chromatography differs from diffusion-limited operations in that it specifically refers to any separation process in which the intraparticle velocity is not zero.^[2] However, a mobile-phase perfusion with pressure-driven flows may be operative only when relatively high drops in column pressure and particles with large pores (that have a low adsorptive capacity) are used. In any case, the intraparticle fluid velocity remains very small compared to the velocity in the interparticle pore space.

It has also been clearly demonstrated over the last decade that an electroosmotic flow field in packed capillaries can offer significantly superior dispersion characteristics relative to pressure-driven flow.^[11–13] The ultimate gain in the performance of an electrokinetically driven mobile phase for capillary electrochromatography (CEC) thus currently attracts tremendous attention, because it is still unclear which factors determine the limits of such an improvement and when the limits actually appear in practice. A study of the transport phenomena must include a careful consideration of the effects of the column walls, the column-to-particle diameter ratio, flow heterogeneity on a macroscopic (column) and a microscopic (pore) level, intraparticle transport characteristics, as well as film mass transfer resistance.

Electroosmotic perfusion phenomena in combination with capillary transport models play an important role in many areas of the physical and life sciences, such as in the

dewatering of waste sludge or the removal of contaminants from soil.^[14] In CEC, which uses the electrokinetics to drive both the liquid and the (usually charged) solute through fixed particulate beds, an intraparticle convection mechanism for improving mass transfer is largely unexplored. Only a few studies indicate the existence of an intraparticle electroosmotic flow (EOF) and the potential that this effect, together with electrophoretic selectivity, may offer in separation science.^[15–21] In simple electrokinetic terms the Helmholtz–Smoluchowski equation implies that the average EOF velocity in a pore segment of the particles is relatively independent of the pore geometry if the characteristic dimension, like the pore radius (r_{pore}), is much larger than the thickness of the electrical double layer (κ^{-1}), namely, $\kappa r_{\text{pore}} \gg 1$.^[22–25] We then expect a rather flat flow profile over the cross-section of any pore and it also suggests that film mass transfer resistance is negligible in CEC over a wide range of conditions.^[26] A particular feature is that average pore velocities can still be significant compared to the typical purely diffusive timescales even when $\kappa r_{\text{pore}} \rightarrow 1$ and r_{pore} is only a few nanometers.^[22, 23] For thin electrical double layers, these considerations leave the intraparticle tortuosity factor (τ_{intra}) as one of the most critical parameters that determine the extent of electroosmotic perfusive solute transport. τ_{intra} also reflects the pore connectivity and consequently that fraction of the pore space which transects the particles without dead-end branching and should allow a net EOF to develop.^[21]

Herein we provide clear evidence for the existence and enormous impact of an electroosmotic perfusion mechanism in porous media. We studied the performance of pressure-driven flows and EOF through a fixed bed consisting of charged porous particles packed into a capillary by using a pulsed field gradient NMR method as a noninvasive motion-encoding technique that operates (on the millisecond time-scale) directly on the nuclear spin of the fluid molecules (for example, $^1\text{H}_2\text{O}$).^[27] Detailed descriptions of this approach concerning its implementation on the capillary dimension and the application to dispersion, flow, and mass-transfer studies in chromatographic media have recently been published.^[28, 29] We start with an analysis of the axial dispersion as a function of the particle Péclet number (Pe) for both modes of fluid flow, then complement these data by the selectively measured dynamics of the intraparticle mass transfer, and also address the influence of thermal effects. Our results are finally discussed in regard to the hierarchical design of these particles and thereby achieved correlation of pore interconnectivity in a bidisperse pore network.

The effective axial dispersion coefficient (D_{ax}) is obtained from the complex NMR signal $E_{\Delta}(\mathbf{q})$ at an observation time (Δ) that is sufficient to allow the complete exchange of fluid molecules between intraparticle and interparticle pore spaces (steady-state) and the development of a Gaussian displacement distribution [Eq. (1)].^[27]

$$E_{\Delta}(\mathbf{q}) = \exp(i2\pi\mathbf{q} \cdot \mathbf{u}_{\text{av}}\Delta - 4\pi^2\mathbf{q}^2 D_{\text{ax}}\Delta) \quad (1)$$

$\mathbf{u}_{\text{av}}$ is the column cross-sectional averaged velocity and $\mathbf{q}$ is a wave vector that encodes fluid motion ($i^2 = -1$). Based on these dispersion coefficients, which include the intraparticle

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mass transfer kinetics, Figure 1 shows a comparison of the electroosmotic and pressure-driven flows at increasing Pe (this is better known in chromatography as the reduced velocity). The EOF shows an overwhelming enhanced performance over pressure-driven flow, and the regime in which

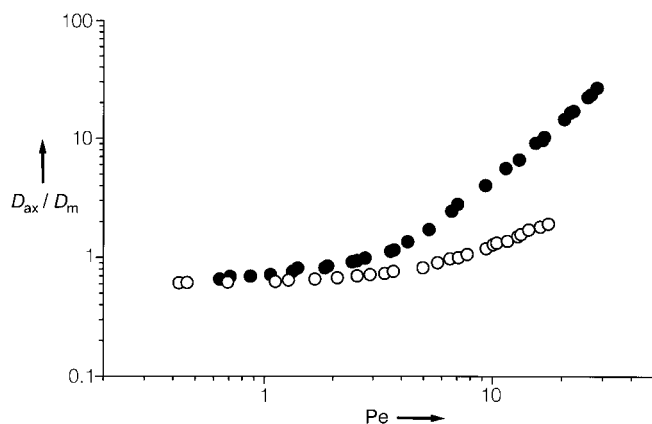


Figure 1. Axial dispersion (D_{ax}/D_m) versus the particle Péclet number ($Pe = u_{av}d_p/D_m$) for a 1 mM sodium tetraborate buffer solution at pH 9.13 in a pressure-driven flow (●) and EOF (○). The ^1H NMR measurements were performed with a special capillary-NMR set up on a 0.5 T electromagnet with open access,^[28, 29] and the charged porous particles were packed in a 250 μm i.d. fused-silica capillary. The diffusion coefficient of water is $D_m(25^\circ C) = 2.25 \times 10^{-5} cm^2 s^{-1}$.

molecular diffusion still controls the dispersion ($D_{ax}/D_m < 1$) extends to much higher Pe . This has already been shown by other research groups.^[16, 17, 19] However, it is difficult to relate this improvement quantitatively to any physical mechanism because these data (as in conventional chromatography) are acquired over only a limited range of Pe . This range is hardly sufficient to separate (for example, by a power-law analysis $D_{ax} \propto Pe^\alpha$) adequately between dispersion processes originating in the flowing and in the stagnant zones of the packed bed.^[30, 31] In pressure-driven flows stochastic velocity fluctuations in the interparticle pore space cause mechanical dispersion which grows linearly with Pe , while regions of zero velocity inside the bed particles and close to their external surface give rise to nonmechanical contributions that grow as Pe^2 and $Pe \ln(Pe)$, respectively.^[32] In all cases (flow heterogeneity, film mass transfer, and intraparticle diffusion), an electrokinetically driven mobile phase may show a superior performance and D_{ax} only reflects the combined kinetics.

To obtain more direct evidence of the operation of an intraparticle EOF we made a series of NMR measurements within a temporal domain where the exchange of fluid molecules between intraparticle and interparticle pore space environments is not complete over time Δ (unsteady-state). Then, $E_\Delta(q)$ contains discrete contributions from both fluid fractions (stagnant and flowing). By extracting the average number of molecules $A_{intra}(\Delta)$ that are still remaining in the spherical particles at times Δ , this procedure allows a selective study of the intraparticle mass transfer kinetics [Eq. (2)].^[28, 33]

$$\frac{A_{intra}(\Delta)}{A_{intra}(0)} = A_{norm}(\Delta) = \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-4n^2 B_{intra} \Delta) \quad (2)$$

In the case of purely diffusive mass-transfer kinetics the rate constant B_{intra} can be further analyzed to calculate the intraparticle diffusion coefficient ($B_{intra} = \pi^2 D_{intra}/d_p^2$) by using the independently measured average particle diameter (d_p). Figure 2 compares the exchange kinetics for a constant

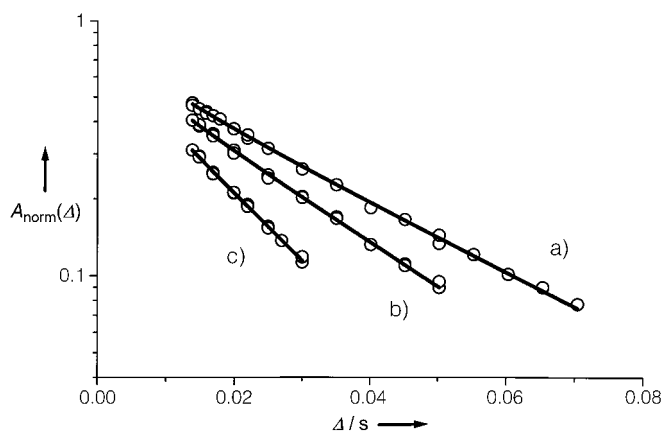


Figure 2. Influence of pressure and potential gradients on stagnant mobile phase mass transfer. The solid lines are best fits of the data to Equation (2) using the pure (a) and effective (b, c) diffusion model. a) Pressure gradient only ($D_{intra} = 1.42 \times 10^{-5} cm^2 s^{-1}$). b, c) Effect of a superimposed potential gradient ($E = 47.4 kV m^{-1}$): b) $D_{ap} = 1.84 \times 10^{-5} cm^2 s^{-1}$ (1 mM sodium tetraborate), and c) $D_{ap} = 2.72 \times 10^{-5} cm^2 s^{-1}$ (3 mM sodium tetraborate) at pH 9.13.

pressure gradient along the column with those acquired with an additional potential gradient. While the pressure field around the porous particles alone has hardly any measurable influence on diffusion-limited transport ($D_{intra} = 1.42 \times 10^{-5} cm^2 s^{-1}$), the electric field enhances significantly the exchange of fluid molecules, and hence increases the intraparticle mass transfer coefficient B_{intra} .

This behavior is most probably caused by an electroosmotic perfusion mechanism (and by the existence of an intraparticle electroosmotic flow velocity), but can also be influenced by thermal effects (through the molecular diffusion coefficient D_m at the actual buffer temperature). In the case of perfusion, the apparent diffusivity D_{ap} , which is calculated with the simple diffusion model of Equation (2), in fact resembles a combination of an intraparticle EOF and molecular diffusion ($D_{ap} > D_{intra}$). This convection-augmented diffusivity^[3-5] is a key parameter in characterizing the improved performance arising from mobile-phase perfusion and is based on the linear driving force approximation.^[34-36] Figure 2 shows that D_{ap} even exceeds the molecular diffusivity (D_m) of the fluid at higher buffer concentration, and thus leaves the tortuosity-limited regime.

To account for the influence of thermal effects on intraparticle mass transfer we conducted a series of measurements at constant temperature within the capillary while increasing the applied potential gradient (still being the ultimate driving force for any intraparticle EOF). This effect is achieved by a variation of the buffer concentration and adjusting the potential gradient so that the product of electric field strength (E) and electric current (I) remains constant. The variation of

the buffer concentration at unchanging EI (and consequently at the same thermal level) results in an automatic modification of E . The results shown in Figure 3 demonstrate

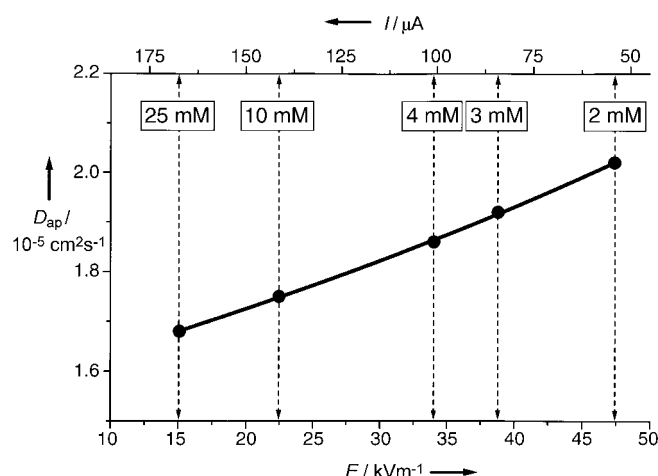


Figure 3. Dependence of the stagnant mobile phase mass transfer kinetics on the electric field strength at a constant level of heat dissipation in the capillary ($EI = 2.54 \text{ W m}^{-1}$). While E increases, the buffer concentration (and the electrical current I) decreases from 25 to 2 mM sodium tetraborate (and I from 169 to 54 μA).

a clear dependence of the apparent diffusivity on the electric field strength. This systematic, almost linear, increase in D_{ap} from 1.67 to $2.02 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ can only be explained on the basis of a convective transport mechanism. By contrast, a constant diffusivity (independent of E) is expected when the intraparticle mass transfer is purely diffusive, that is, only achieved by molecular diffusion at the actual (but constant) buffer temperature. The electroosmotic perfusion will be of considerable importance in the separation of slowly diffusing solutes ($D_{\text{m}} \ll 10^{-5} \text{ cm}^2 \text{ s}^{-1}$) and promises intraparticle Péclet numbers well above unity.^[21]

To correlate our results with concrete particle characteristics, we now focus on the topology of the intraparticle pore network. These hierarchically structured particles are engineered by clustering inter-adhering microspheres in several steps. The resulting particles consist of two relatively discrete sets of pores, namely, large gigapores^[5] (400–600 nm, with $d_{\text{pore}}/d_{\text{p}} > 10^{-2}$) and macropores (50–100 nm).^[37] More importantly, this hierarchical design produces an excellent correlation of the interconnectivity between these two sets of pores and minimizes dead-end branching. The gigapores transect the particle as a whole and form the primary basis for intraparticle EOF (Figure 4). The macropores are also large enough to allow an EOF by adjustment of the buffer concentration—within a convenient range—to the actual pore dimensions so that $\kappa r_{\text{p}} \gg 1$. Perfusive solute transport, which in addition utilizes the set of smaller pores, is impossible with pressure-driven flows! As the liquid phase is continuous and incompressible, the volume flow and the radial distribution of velocities in an interconnected pore depend on fluid body forces which originate in all neighboring pores, actually in the medium as a whole. Thus, although the microscopic

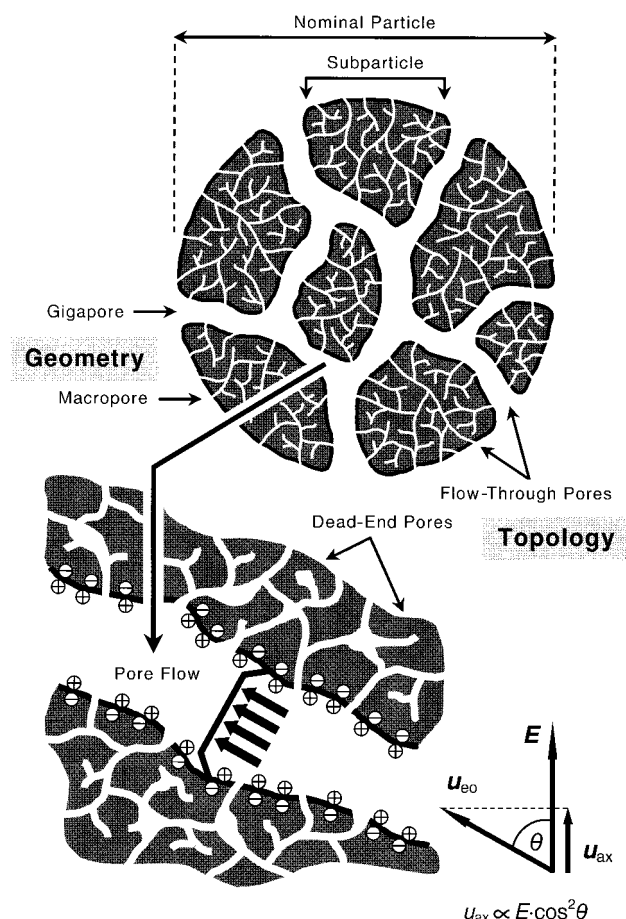


Figure 4. Pore network of a hierarchically structured particle with a bidisperse distribution of pore sizes. In general, the axis of a virtually isolated pore is at an angle θ to the electric field vector E . When $\kappa r_{\text{p}} \gg 1$, the presence of a pluglike EOF with a linear pore velocity (u_{eo}) proportional to $E \cos \theta$ is suggested. An unfavorable orientation of pores ($0 < \theta < 90^\circ$) reduces or even prevents ($\theta = 90^\circ$) pore-level EOF in this decoupled single-channel view. In an unconsolidated porous medium, in contrast, all these pores are usually interconnected.

flow profiles then become convex or concave and deviate from a perfect plug-flow behavior, it also means that (viscous) flow through perpendicular pores ($\theta = 90^\circ$) can be achieved. By contrast, no net flow exists in a dead-end pore.

Thus, a more important aspect concerning the intraparticle pore network appears to be the pore interconnectivity rather than the average diameter of the pores. Even for small pores, the buffer concentration—at least within the practical range that can be obtained, but which is still a wide range—can be matched with the pore dimensions, so that $\kappa r_{\text{p}} \gg 1$ (and at least $\kappa r_{\text{p}} > 1$) is guaranteed.

In this context, the tortuosity factor τ_{intra} relates the steady-state intraparticle diffusion coefficient to the bulk molecular diffusivity ($\tau_{\text{intra}} = D_{\text{m}}/D_{\text{intra}}$). By using the value for D_{intra} obtained from the diffusion-limited mass-transfer kinetics (Figure 2) we calculate a $\tau_{\text{intra}} = 1.58$, which is close to values previously measured for very similar supports.^[28] This value suggests a high correlation of pore interconnectivity and the small amount of dead-end pores (see Figure 4) in hierarchically structured media, which is in good agreement with results of numerical studies (although there is no unique

relation between interconnectivity in a network model and the experimental tortuosity factor).^[9, 21, 38, 39]

Our data demonstrate that a significant enhancement in the performance of CEC over capillary HPLC lies in the different dimension of the perfusion mechanism. The intraparticle tortuosity factor τ_{intra} plays a key role in achieving that goal in both cases, and may also have a sensitive influence on pore migration for charged solutes. Further development in CEC particle technology should focus on the minimum pore size of the through-pore network which still allows a significant intraparticle EOF at decent buffer concentrations, while keeping the surface-to-volume ratio of the pore space attractive for the separation (gigapores, which are used in pressure-driven flows, are not required for electroosmotic perfusion). CEC is easily realized with nanoparticles using hierarchically structured media of micrometer dimension, which leaves molecular diffusion as the ultimate limitation to performance.^[40, 41] Thus, the perfusive EOF field translates to an even higher separation efficiency than can currently be achieved in CEC, increased mass sensitivity in on-line coupling schemes (such as nano-ESI-MS), and the possibility of using pressurized CEC for higher analysis speed and flow stability, without significant increase in dispersion.

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First, Atropo-Enantioselective Total Synthesis of the Axially Chiral Phenylanthraquinone Natural Products Knipholone and 6'-O-Methylknipholone**

Gerhard Bringmann* and Dirk Menche

Dedicated to Professor Wolfgang Kiefer on the occasion of his 60th birthday

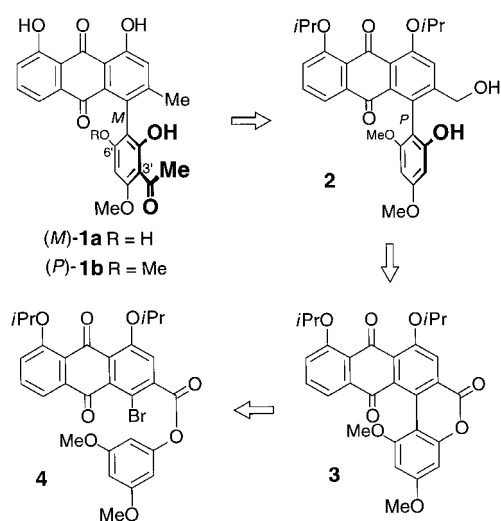
Among the more than one hundred anthraquinone natural products with biaryl axes,^[1] phenylanthraquinones,^[2–4] like knipholone (**1a**)^[2] and 6'-O-methylknipholone (**1b**),^[3] occupy a special position: Since they are constitutionally unsymmetric, they are most likely formed biosynthetically by a directed, enzymatic biaryl coupling and not merely by a “chemical” dimerization of the corresponding monoanthraquinones. A further hint at such an enzymatic origin of **1a** and **1b** is the fact that they are optically active and are thus axially chiral. First isolated by Dagne and Steglich in 1984,^[2] knipholone (**1a**) and related phenylanthrachinones have been found in numerous African plant species of the genera *Bulbine*, *Bulbinella*, and *Kniphofia* (all Asphodelaceae),^[4] which are widely used in folk medicine.^[2, 5]

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Only recently the axial configuration of knipholone (**1a**) has been determined to be *M*, by quantum chemical CD calculations.^[6] Due to its interesting structure (including the rotationally hindered biaryl axis) and its good antimalarial activity with only little cytotoxicity,^[7] knipholone (**1a**) constitutes an attractive synthetic target, as do related phenyl-anthraquinone natural products. In this paper, we report on the atroposelective total synthesis of knipholone (**1a**) and the likewise naturally occurring 6'-*O*-methyl ether **1b** and, thus, on the first stereoselective approach to axially chiral anthraquinone natural products.^[8]

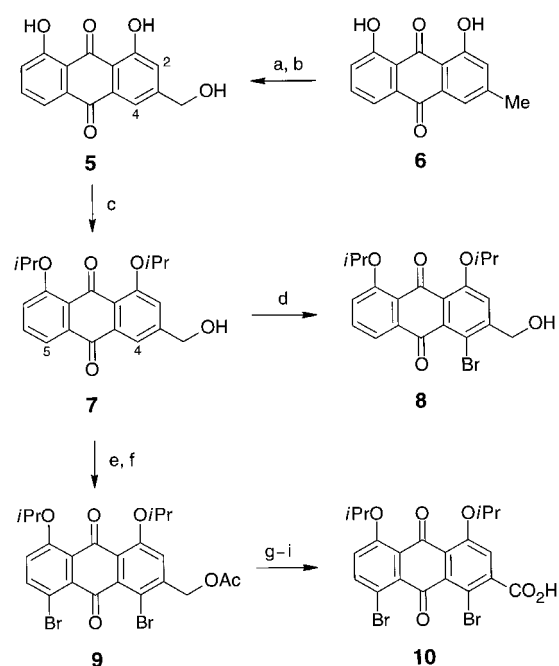
For the directed construction of the biaryl axis we chose the "lactone method" as developed in our group.^[9] Envisaged key steps of the resulting synthetic strategy (Scheme 1) were the intramolecular biaryl coupling of the bromoester **4** to give the biaryl lactone **3**, the atropo-enantioselective cleavage of **3** to provide the "open" biaryl **2**, and the regioselective introduction of an acetyl group on C-3'.



Scheme 1. Retrosynthetic analysis of knipholone (**1a**) and its 6'-*O*-methyl ether **1b**.

The "upper" molecular halves of the target molecules **1a** and **1b** correspond to the natural product chrysophanol (**6**). For the synthesis of a suitably functionalized anthraquinone building block (Scheme 2), one can start directly from the likewise natural^[10] aloë-emodin (**5**), whose side chain is already oxygenated. This can be conveniently obtained in large quantities from purchasable aloin^[11] or, as we describe here, from chrysophanol (**6**), which is commercially available or can easily be prepared by total synthesis.^[12]

Radical side-chain bromination of **6** with subsequent bromine/hydroxy group exchange gave aloë-emodin (**5**) in a smooth reaction; compound **5** can be now conveniently prepared on a multi-gram scale. A selective bromination of the diacetate of **5** in the 4-position, as required, has already been described in the literature.^[13] However, this actually takes place exclusively at C-2 under the given conditions, so that a different synthetic strategy had to be pursued here. The desired activation of the 4-position was finally successful, as could be unambiguously shown by NMR spectroscopy (HMBC, NOE), after steric blocking of the "northern part"



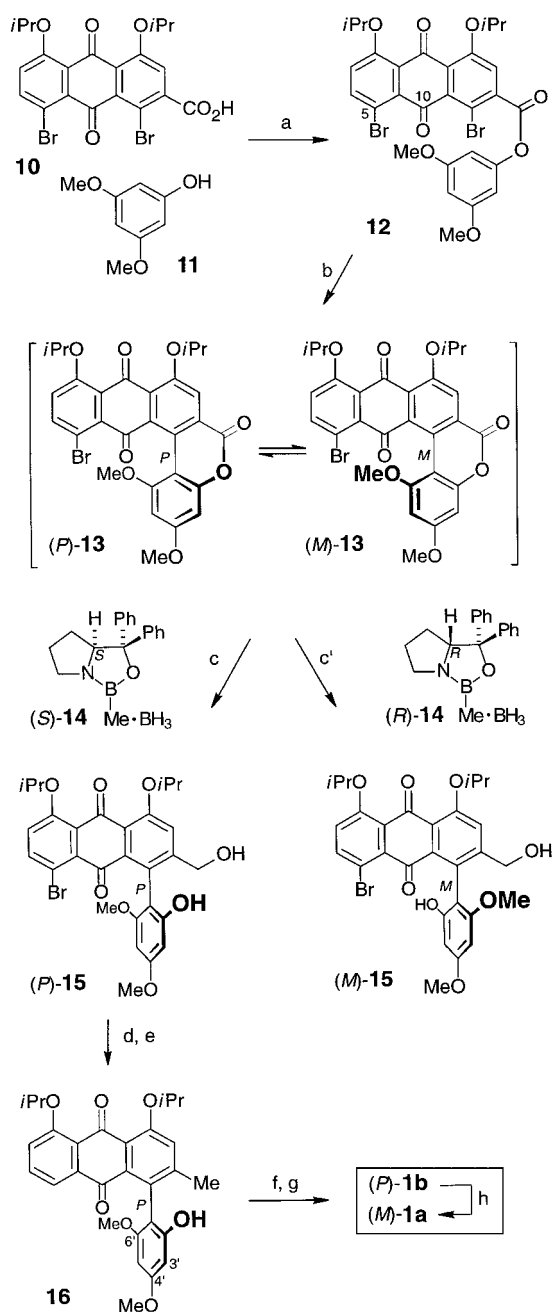
Scheme 2. Synthesis of the anthraquinone building block **10**. a) NBS, (PhCO₂)₂, CCl₄, reflux, 6 h; b) CaCO₃, dioxane/H₂O, 120 °C, 7 h, 71 % (over two steps); c) *i*PrI, Cs₂CO₃, acetone, reflux, 4 d, 72 %; d) Br₂, NaOAc, CHCl₃/CCl₄, reflux, 2 h, 32 %; e) Ac₂O, pyridine, 50 °C, 3 h, 94 %; f) Br₂ (4 equiv), NaOAc, CHCl₃/CCl₄, 70 °C, 3 h, 89 %; g) KOH, MeOH, 70 °C, 2 h, 91 %; h) MnO₂, CH₂Cl₂, RT, 6 h, 93 %; i) NaClO₂, amidosulfuric acid, NaOAc, dioxane/H₂O/HOAc, RT, 97 %. NBS = *N*-bromosuccinimide.

of **5** by *O*-isopropylation and subsequent bromination of **7** to give **8** (Scheme 2).

Due to the necessary resolution of regioisomeric bromination products, the sensitivity of the side chain to oxidation under the bromination conditions, and the low yields that were obtained, it seemed, however, far more convenient to introduce *two* bromo-substituents, that is, at C-4 and C-5, straightaway after protection of the free hydroxy group of **7** by *O*-acetylation. The bromination then proceeded smoothly to give **9** in 89 % yield. The second bromine at C-5, which was functionally not required, did not interfere with any of the following reaction steps (see below). From **9**, the anthraquinone carboxylic acid **10** could easily be prepared by hydrolysis of the ester and stepwise oxidation (Scheme 2).

Thus, the building block **10** was available in a suitably activated and protected form and in sufficient quantities. For the "lower" half of the molecule, which in its free form is also a natural product (xanthoxylin),^[14] the precursor was, however, not a trioxacetophenone, but the acetyl-free phenolic compound **11** (Scheme 3). According to preliminary investigations it seemed more favorable not to have the acetyl group (as present in **1a** and **1b**) in the molecule from the beginning, but to introduce it only after the scheduled subsequent reduction steps.

The ester **12**, synthesized from **10** and **11**, was submitted to the conditions of a Pd-catalyzed intramolecular biaryl coupling.^[9] The concern that the "lower" carbonyl group of the quinoid system (C-10) might prevent or, at least, hamper the ring closure to form the lactone **13** proved to be unfounded: In



Scheme 3. Atropo-enantioselective coupling of the molecular halves of knipholone (**1a**). a) DCC, DMAP, $\text{CH}_2\text{Cl}_2/\text{DMF}$, $0^\circ\text{C} \rightarrow \text{RT}$, 1 h, 90%; b) $\text{Pd}(\text{OAc})_2$ (60 mol %), PPh_3 (1.2 equiv), NaOPiv (2 equiv), DMA, 130°C , 4.5 h, 68%; c) (*S*)-**14** (3 equiv), BH_3 (4 equiv), THF, 0°C , 1 h, 81%, 96% *ee* (after crystallization from dichloromethane/diethyl ether/*n*-hexane >99% *ee*); c') analogous procedure with (*R*)-**14**; d) $(\text{CBrCl}_2)_2$ (1.5 equiv), polymer-bound PPh_3 (3 equiv), CH_2Cl_2 , RT, 10 min; e) Pd/C (10 mol %), H_2 , MeOH, 48% (over 2 steps); f) TiCl_4 (6 equiv), CH_2Cl_2 , $-20^\circ\text{C} \rightarrow \text{RT}$, 2 h, 89%; g) Ac_2O , TiCl_4 , $-20^\circ\text{C} \rightarrow \text{RT}$, 1 h, 82%; h) AlBr_3 (5 equiv), chlorobenzene, 80°C , 2 h, 41%. DCC = *N,N'*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformamide, DMA = *N,N*-dimethylacetamide, NaOPiv = sodium pivalate.

the presence of $\text{Pd}(\text{OAc})_2$, **12** was smoothly coupled intramolecularly to give **13**. The bromine atom at C-5, which was not required for the cyclization, remained unaffected.

Through the following conversions (see below) it became obvious that—despite the oxygen functionality at C-10—the

bridged biaryl **13** was configurationally unstable; this fortunate circumstance permitted the subsequent ring-cleavage reactions to be performed highly efficiently, according to the principle of a dynamic kinetic resolution. The oxazaborolidine-assisted borane reduction, which has also been successfully used on previous occasions, proved to be the most effective method for this purpose.^[9, 15] By means of this so-called CBS reaction,^[16] the lactone in the rapidly interconverting mixture of the atropo-enantiomers (*P*)-**13** $\rightleftharpoons$ (*M*)-**13** could be cleaved selectively; such that depending on the oxazaborolidine enantiomer used, (*S*)-**14** or (*R*)-**14**, either the desired atropisomer (*P*)-**15** or, optionally, the undesired “wrong” enantiomer (*M*)-**15** could be obtained in high atropisomeric excesses (up to 96% *ee*) through an atropo-enantiodivergent reaction.^[17] The optical purity of the product (for example, of the required *P* isomer) could be further enhanced (to >99% *ee*) by a simple crystallization step. The small quantities of the (almost) racemic mother liquor thus obtained (14% *ee*) can—if desired—be recycled into the process, by oxidation (MnO_2 , NaClO_2) and cyclization (DCC, DMAP) back to the configurationally unstable lactone (71% chemical yield).

With the phenylanthraquinone framework now constructed enantioselectively, including the correct configuration at the biaryl axis, the benzylic oxygen function of **15** was reductively eliminated by hydroxy/bromine group exchange and hydrogenolytic removal of the bromine substituent. For this, the reaction conditions could be controlled in such a way that, within a one-pot reaction, the additional, no longer required bromine functionality at C-5 was simultaneously removed. After cleavage of the *O*-isopropyl protective groups with titanium tetrachloride, the likewise TiCl_4 -mediated, strictly regioselective introduction of the acetyl group at C-3' was achieved by the use of acetic anhydride. The 6-*O*-methylknipholone (**1b**) thus obtained proved to be chromatographically and spectroscopically identical with authentic **1b** from *Bulbine capitata*.^[3] This first synthesis of a phenylanthraquinone natural product confirms, in all details, the structure as established by Abegaz and co-workers.^[3]

For the synthesis of knipholone (**1a**) itself, it was still necessary to cleave the methoxy group at C-6'. While nucleophilic reagents (such as LiPH_2)^[18] almost exclusively attacked the “wrong” ether functionality at C-4', a selective *O*-demethylation of the 6'-oxygen functionality was achieved with AlBr_3 . The (+)-knipholone (**1a**) thus obtained was identical in all respects to an authentic sample from *Bulbine frutescens*^[6] and to the data^[2] published for **1a** by Dagne and Steglich.

As demonstrated for the atropo-enantiodivergent cleavage of **13** to form (*P*)- or (*M*)-**15**, the strategy for the first synthesis of knipholone (**1a**) and 6'-*O*-methylknipholone (**1b**) presented here can, in principle, likewise be adopted for the synthesis of the other respective atropo-enantiomeric product (*ent*-**1a** or *ent*-**1b**). Analogously, the concept should be easily applicable to the synthesis of the other phenylanthraquinones and -anthrones described in the literature,^[2–4] and, furthermore, to the preparation of unnatural analogues with possibly even better antimalarial activities. This work is presently under investigation.

Experimental Section

Compound **13**: A mixture of **12** (1.00 g, 1.51 mmol), palladium(II) acetate (203 mg, 910 μmol), triphenylphosphane (475 mg, 1.81 mmol), and sodium pivalate (375 mg, 3.02 mmol) were dried in vacuo (10^{-2} mbar) for 1.5 h at 60 °C, and then dry *N,N*-dimethylacetamide (40 mL) was added. The orange-colored suspension was degassed three times and heated under argon for 4.5 h at 130 °C. After cooling to room temperature, the dark brown suspension was diluted with ethyl acetate, washed sequentially with 2*N* HCl and saturated aqueous NaCl solution, dried (Mg_2SO_4), and concentrated in vacuo. After flash chromatography on silica gel (dichloromethane/ethyl acetate 100:2), **13** (597 mg, 1.03 mmol, 68%) was obtained as a red solid, which was crystallized from dichloromethane/petroleum ether. M.p. 138 °C; IR (KBr): $\tilde{\nu}$ = 2950, 1710, 1660, 1190, 1100 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ = 1.40–1.56 (m, 12 H; $\text{CH}(\text{CH}_3)_2$), 3.67 (s, 3 H; OCH_3), 3.87 (s, 3 H; OCH_3), 4.64 (sept, J = 6.1 Hz, 1 H; $\text{CH}(\text{CH}_3)_2$), 4.77 (sept, J = 6.1 Hz, 1 H; $\text{CH}(\text{CH}_3)_2$), 6.35 (d, J = 2.3 Hz, 1 H; H-3' or H-5'), 6.53 (d, J = 2.3 Hz, 1 H; H-3' or H-5'), 7.12 (d, J = 9.2 Hz, 1 H; H-7), 7.80 (d, J = 8.9 Hz, 1 H; H-6), 7.94 (s, 1 H; H-2); ^{13}C NMR (63 MHz, CDCl_3): δ = 19.23 ($\text{CH}(\text{CH}_3)_2$), 21.88 ($\text{CH}(\text{CH}_3)_2$), 22.36 ($\text{CH}(\text{CH}_3)_2$), 55.75 (OCH_3), 57.69 (OCH_3), 73.11 ($\text{CH}(\text{CH}_3)_2$), 73.30 ($\text{CH}(\text{CH}_3)_2$), 93.79, 96.37, 102.53, 110.18, 116.67, 121.30, 123.62, 125.60, 128.02, 128.73, 133.02, 137.89, 139.21, 152.44, 155.61, 155.86, 156.85, 160.41, 161.75, 180.07 (C=O), 184.03 (C=O); MS (70 eV): m/z (%): 582/580 (5/5) [M^+], 509/507 (9/6) [$M^+ - \text{C}_4\text{H}_9\text{O}^+$], 467/465 (15/11) [$M^+ - \text{C}_8\text{H}_{19}^+$], 183 (100); elemental analysis (%): calcd for $\text{C}_{29}\text{H}_{25}\text{O}_8\text{Br}$ (581.42): C 59.91, H 4.33; found: C 59.66, H 4.25.

Compound (*P*)-**15**: The solvent was removed in vacuo from a solution of (*S*)-**14** (1.0 M in toluene, 360 μL , 360 μmol) and the residue was dissolved under argon in dry THF (1 mL). This solution was treated with a solution of the BH_3 –THF complex (1.0 M in THF, 480 mL) and stirred for 30 min at room temperature. After dropwise addition of a solution of the lactone **13** (69.8 mg, 120 μmol) in dry tetrahydrofuran (1 mL) at 0 °C the solution was stirred for 1 h at this temperature, then water (1 mL) and 2*N* HCl (1 mL) were added and the aqueous phase was thoroughly extracted with ethyl acetate. The combined organic phases were dried (MgSO_4) and the solvents were removed in vacuo. After flash chromatography of the residue on silica gel (dichloromethane/ethyl acetate 7:3), (*P*)-**15** (56.9 mg, 97.2 μmol , 81%) was obtained as a yellow solid (96% *ee*). Crystallization from dichloromethane/diethyl ether/*n*-hexane yielded yellow crystals (45.6 mg, 77.9 mmol, 65%; > 99% *ee*). M.p. 122–124 °C; $[\alpha]_D^{20}$ = –28 (c = 0.01 in methanol); IR (KBr): $\tilde{\nu}$ = 3120 (br., OH), 2950, 1660, 1570, 1190, 1090 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.37–1.44 (m, 12 H; $\text{CH}(\text{CH}_3)_2$), 3.59 (s, 3 H; OCH_3), 3.76 (s, 3 H; OCH_3), 4.33 (d, J = 13.7, 1 H; CHHOH), 4.42 (d, J = 13.7, 1 H; CHHOH), 4.55 (sept, J = 5.8 Hz, 1 H; $\text{CH}(\text{CH}_3)_2$), 4.67 (sept, J = 5.8 Hz, 1 H; $\text{CH}(\text{CH}_3)_2$), 6.12 (d, J = 1.8 Hz, 1 H; H-3' or H-5'), 6.20 (d, J = 1.8 Hz, 1 H; H-3' or H-5'), 6.97 (d, J = 8.8 Hz, 1 H; H-7), 7.43 (s, 1 H; H-2), 7.60 (d, J = 8.8 Hz, 1 H; H-6); ^{13}C NMR (63 MHz, CDCl_3): δ = 21.88 ($\text{CH}(\text{CH}_3)_2$), 21.98 ($\text{CH}(\text{CH}_3)_2$), 55.06 (OCH_3), 55.57 (OCH_3), 62.76 (CH_2OH), 72.73 ($\text{CH}(\text{CH}_3)_2$), 73.46 ($\text{CH}(\text{CH}_3)_2$), 91.32, 94.05, 105.66, 109.82, 118.94, 121.31, 122.43, 124.61, 128.01, 135.62, 137.44, 138.41, 147.96, 154.94, 155.78, 155.84, 157.21, 160.73, 182.40 (C=O), 186.23 (C=O); MS (70 eV): m/z (%): 586/584 (54/54) [M^+], 543/541 (44/39) [$M^+ - \text{C}_3\text{H}_6^+$], 495/493 (20/19) [$M^+ - \text{CH}_2\text{O}^+$], 453/451 (100/100) [$M^+ - \text{C}_5\text{H}_{17}\text{O}_2^+$]; elemental analysis (%): calcd for $\text{C}_{29}\text{H}_{25}\text{O}_8\text{Br}$ (585.45): C 59.50, H 4.99; found: C 59.59, H 4.74.

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High-Temperature Synthesis of an Open-Framework Compound, $\text{Na}_2\text{Cs}_2\text{Cu}_3(\text{P}_2\text{O}_7)_2\text{Cl}_2$ (CU-4), by Molten-Salt Methods**

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Porous materials have stimulated much interest for their applications in catalysis, ion-exchange, separation, sensor, and molecular recognition.^[1] Transition metal containing microporous (TMCM) solids have attracted particular attention because of their unique functions, such as redox catalysis,^[2]

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magnetic ordering,^[3] and cathodic electrolysis,^[4] attributed to the utility of d electrons. Traditionally, the porous solids are prepared by low-temperature, hydrothermal (or solvothermal) methods. Conventional synthesis using organic as well as organometallic templates have given some insights into tailoring porous structures.^[5, 6] Reaction mechanisms through which the pore structures are constructed, however, remain uncertain.

Prior to this study, we reported a series of new TCM compounds synthesized by employing molten-salt methods at high temperatures well above those commonly employed in hydrothermal syntheses.^[7] This compound series was designated as CU-2 (Clemson University no. 2) and contains large channels filled with a water-soluble salt.^[8] The large pore is built around a column of close-packed $(\text{K,Cs})^+/\text{Cl}^-$ ions in a squarelike lattice with a cross section of roughly $6 \times 6 \text{ \AA}$. For instance, for CU-2-CuPO, the chloride ions are bonded to the Cu^{2+} ions and, in turn, direct the orientation of otherwise square-planar CuO_4 in the construction of the Cu-P-O micropore structure.

Further studies on the “salt templating” effect have resulted in a new solid derived from different combinations of alkali metal chlorides, namely, $\text{Na}_2\text{Cs}_2\text{Cu}_3(\text{P}_2\text{O}_7)_2\text{Cl}_2$. This is the second example of a new family of open-framework compounds prepared by a conventional high-temperature, solid-state route. This new open-framework solid is designated as CU-4 and can be considered as structurally related to CU-2. Herein we report the synthesis and structure of CU-4 and compare it with CU-2. This work reaffirms the utility of molten salts for the high-temperature synthesis of microporous solids.

Crystals of the $\text{Na}_2\text{Cs}_2\text{Cu}_3(\text{P}_2\text{O}_7)_2\text{Cl}_2$ phase were grown at 750°C by employing the salt CsCl. Compared with an idealized composition of CU-2-CuPO, $\text{K}_2\text{Cs}_3\text{Cu}_3(\text{P}_2\text{O}_7)_2\text{Cl}_3$, the current compound contains the smaller Na^+ ion and less cesium chloride. The new phase can also be synthesized at 550°C in air by using stoichiometric amounts of the corresponding materials.^[9]

With respect to the Cu-P-O framework, the CU-4 structure contains 8-ring and 16-ring micropores (Figure 1), which are $5.3 \times 5.3 \text{ \AA}$ and $4.9 \times 17.2 \text{ \AA}$, respectively, measured from copper to copper.^[10] CU-2 and CU-4 have the same connectivity (Figure 2), thus one phase can be converted to the other by a chemical modification. For instance, the CU-2 phase can be prepared by an ion-exchange reaction of CU-4 by using the KCl/CsCl eutectic salts at 600°C .

The CsCl salt resides in the small channel. As in the CU-2 structure, the CsCl salt exists in a linear array of $\text{Cs}^+/\text{Cl}^-/\text{Cs}^+$; the Cs–Cl distance is $3.31 \text{ \AA}$ ($\equiv \frac{1}{4}c$). Each chlorine atom Cl(1) is bonded to four copper atoms Cu(1) ($\text{Cu(1)–Cl(1)} 2.862(1) \text{ \AA}$).

The 16-ring channel, which shows an unusually elongated window (Figure 1), is composed of eight CuO_4 and eight P_2O_7 polyhedra. The two different polyhedral units are alternately arranged and interconnected through vertex-sharing oxygen atoms (Figure 3). The 8-ring window is constructed in the same fashion with half as many CuO_4 and P_2O_7 units. The planes of the square-planar CuO_4 units all face the center of the pores. The axial positions of each unit are occupied by the

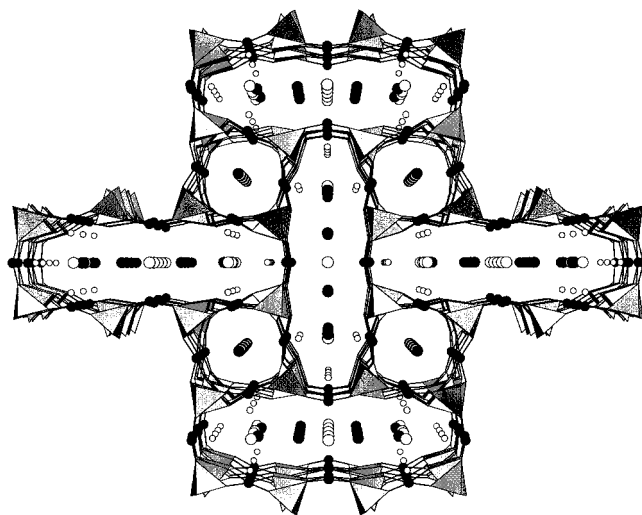


Figure 1. Projected view of the $\text{Na}_2\text{Cs}_2\text{Cu}_3(\text{P}_2\text{O}_7)_2\text{Cl}_2$ framework. The alternating CuO_4 (ball-and-stick) and P_2O_7 (polyhedral) units are interlinked through corner-sharing oxygen atoms. The mixed-salt contains Na^+ (small open circle), Cs^+ , and Cl^- (nonbonded solid and open circles, respectively) ions.

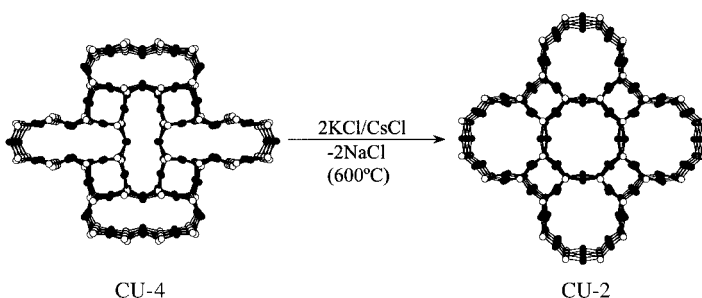


Figure 2. Microporous structures of CU-4 (left) and CU-2 (right). The frameworks are outlined by interconnecting copper metal (solid circles) and phosphorus cations (open circles). The oxygen atoms, as well as the salt, are omitted for clarity.

Cl^- ions residing in the channels. In $\text{Cu(1)O}_4\text{Cl}_2$, for example, the Cu(1) atom forms long bonds to two Cl atoms, namely, $2.86 \text{ \AA}$ to Cl(1) in the 8-ring, and $3.00 \text{ \AA}$ to Cl(2) in the 16-ring. Both these distances are significantly longer than $2.54 \text{ \AA}$ (derived from the sum of the Shannon radii of six-coordinate Cu^{2+} ($0.87 \text{ \AA}$) and Cl^- ($1.67 \text{ \AA}$)).^[11] Also, as shown in the side view of CU-4 (Figure 3b), the copper atoms shared between the neighboring 16-rings, Cu(2) and Cu(3), are stacked alternately along the channel (*c* axis). These copper atoms are each five-coordinate, surrounded by four O atoms and a Cl atom; the Cu–Cl bond lengths are shorter than those mentioned above for Cu(1), that is, $2.44 \text{ \AA}$ for Cu(2)–Cl(4) and $2.60 \text{ \AA}$ for Cu(3)–Cl(3). This indicates a stronger Cu–Cl interaction, and gives rise to the “indented” structure at the waist of the elliptical framework (Figure 2). Taking into account the short Cu–Cl bonds, the elliptical pore can be alternatively viewed as a fused structure made of two 9-rings sharing a common Cu–Cl–Cu bond.

The formation of the large pore is likely attributed to the incorporation of multiple salts. In the elliptical pore, ions form an ordered lattice $[\text{Na}_2\text{CsCl}]^{2+}$ (Figure 4). Cl(2) is tetrahe-

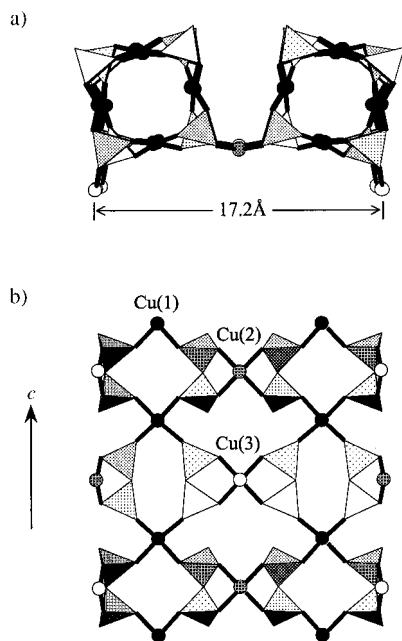


Figure 3. a) A partial structure of two large (half) and two small (full) micropores viewed along the channel, and b) a side view of the large pore in CU-4. The P_2O_7 units are drawn in fused PO_4 tetrahedra and three independent Cu^{2+} ions are labeled (see text for details).

drally coordinated to three Na and one Cs, that is $\text{Cl}(2)\text{Na}(1)_2\text{Na}(2)\text{Cs}(2)$ (Figure 4), while $\text{Cl}(3)$ and $\text{Cl}(4)$ are octahedrally coordinated to four Cs and two Cu atoms (not shown), that is, $\text{Cl}(3)\text{Cs}(2)_4\text{Cu}(3)_2$ and $\text{Cl}(4)\text{Cs}(2)_4\text{Cu}(2)_2$. $\text{Cs}(3)$ primarily interacts with oxide ions since the corresponding $\text{Cs}(3)\text{--Cl}(2,3)$ distances are long (4.69 and 4.56 Å). The two Na(1) ions reside above and below the plane of the $[\text{Na}_2\text{CsCl}]^{2+}$ lattice. Each is directly bonded to the chloride ions $\text{Cl}(2)$ ($\text{Na}(1)\text{--Cl}(2)$ 2.72 and 2.75 Å). In any event, the $[\text{Na}_2\text{CsCl}]^{2+}$ ionic lattice is tightly bonded to the $[\text{Cu}_3(\text{P}_2\text{O}_7)_2]^{2-}$ covalent framework judging from the short Cu–Cl distances mentioned above (2.44 and 2.60 Å) at the waist of the elliptical ring. This explains why the new compound does not behave like the CU-2 phase in terms of the ion-exchange properties in aqueous solution.

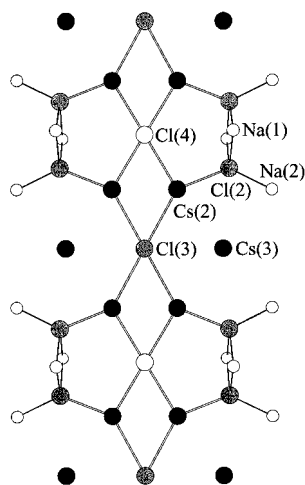


Figure 4. The ball-and-stick model of the $[\text{Na}_2\text{CsCl}]^{2+}$ lattice in the large pore (see text for details).

It should be noted here that porous solids containing large elliptical channel structures have been synthesized exclusively by employing organic templating agents. This is attributed to the anisotropic nature of the long-chain organic molecules and, of course, the versatility of the host lattice. The most studied mixed-metal phosphates, for example, have demonstrated a wide variety of elliptical channel structures.^[12] To the best of our knowledge, the title compound represents

the first open-framework structure that possesses large elliptical channels in the absence of organic templates.

In summary, the isolation of CU-4 has demonstrated the utility of molten salts in tailoring large open-framework structures. The CU-2 and CU-4 phases, in fact, are the first copper-based TMCM solids that contain channels circumscribed by 16-rings and have free diameters larger than 10 Å. We speculate that a salt structure that exists at the molten state is responsible for the formation of the porous framework. It is possible that an intermediate species, such as a Cu–Cl phase, also exists. Our preliminary differential thermal analysis studies of the reaction mixture^[13] show an exotherm at about 380 °C; that is, below the melting points of CsCl (645 °C) and P_2O_5 (580–585 °C). This low-temperature thermal event may correspond to the formation of a precursor phase. In light of the functions of salt, we anticipate that more new phases with even larger pore diameters are yet to come. Moreover, the use of molten-salt methods would allow the search of microporous solids in a temperature regime at which thermally stable phases are commonly found.^[14]

Experimental Section

Crystals of CU-4 were grown by employing a molten-salt reaction in a fused silica ampoule under vacuum. Na_2O (1.0 mmol, 86%, Alfa), CuO (3.0 mmol, 99.999%, Strem), P_2O_5 (2.0 mmol, 98+%, Aldrich), and CsCl (1.0 mmol, 99%, Aldrich) were mixed and ground in a nitrogen-blanketed dry box. The reaction mixture was heated up to 750 °C at 3 K min^{−1}, kept at that temperature for five days, then slowly cooled to 400 °C at 0.1 K min^{−1}, and finally furnace-cooled to room temperature. Colorless, transparent column crystals (65% yield) were obtained along with some light blue crystals of $\text{Na}_4\text{Cu}_3(\text{PO}_4)_8$ and an unidentified yellow-greenish powder, according to the powder X-ray diffraction patterns.

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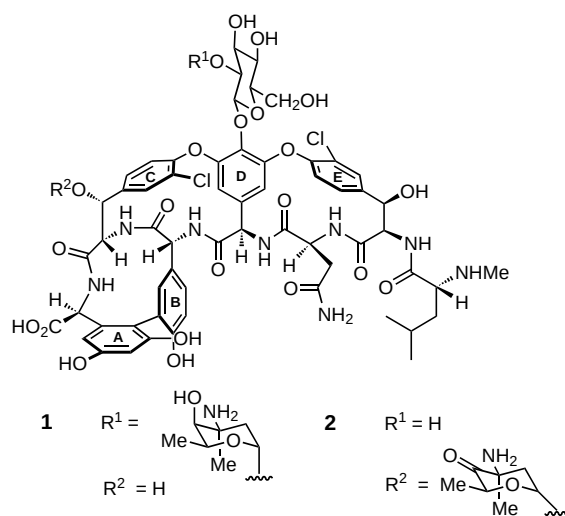
12.7 Å, in which the CsCl and mixed KCl/CsCl salt reside, respectively. The salt can be removed by washing at room temperature to give the microporous compound $\text{Cs}_2\text{Cu}_3(\text{P}_2\text{O}_7)_2 \cdot 8.5\text{H}_2\text{O}$.

- [9] Using a stoichiometric mixture of $\text{Na}_2\text{O}/2\text{CsCl}/3\text{CuO}/2\text{P}_2\text{O}_5$, reactions by both slow cooling and quenching were studied after heating at 550 °C for a day. The quenched reaction gave a high-yield product (ca. 80 %) of CU-4, while the slow-cooled reaction gave a mixture of the CU-4 phase (ca. 50 %) and unknown products. The thermogravimetric analysis results show that the CU-4 phase decomposes at ~560 °C, and further studies suggest that the temperature window in which the CU-4 phase exists is ca. 500–550 °C.
- [10] Crystal data of $\text{Na}_2\text{Cu}_3(\text{P}_2\text{O}_7)_2 \cdot 2\text{CsCl}$: colorless column crystal ($0.53 \times 0.18 \times 0.14\text{ mm}^3$), $M_r = 921.2$, tetragonal $P4_2/mnm$ (no. 136), $a = b = 15.868(2)$, $c = 13.238(2)$ Å, $V = 3333.1(8)$ Å³, $Z = 8$, $\rho_{\text{calc}} = 3.671\text{ g cm}^{-3}$, $\mu = 89.24\text{ cm}^{-1}$. Data collection: Nicolet R3mV diffractometer, ω -2 θ scan mode, $\text{MoK}\alpha$ ($\lambda = 0.71073$ Å) radiation, $T = 295\text{ K}$. A total of 2119 unique reflections measured, of which 1715 ($F > 4.0\sigma(F)$) were used for the structure solution. Lorentz, polarization and empirical absorption corrections based on three azimuthal scans ($2\theta = 18.19^\circ$, 22.01° , 24.72°) were applied to the intensity data (transmission factors: 0.43–0.62). The SHELXTL-Plus software package was used for crystal structure solution and refinement. The structure was solved by direct methods using the SHELXS-86 program and refined on $|F|$ by least-squares, full-matrix techniques. Final $R/R_w = 0.032/0.040$, GOF = 1.14 for 145 parameters. The final Fourier difference synthesis showed minimum and maximum peaks of -1.49 and $+1.88\text{ e Å}^{-3}$. 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-411491. TEXSAN: Single Crystal Structure Analysis Software, Version 1.6b, Molecular Structure Corp., The Woodlands, TX, 1993; "Scattering Factors for Non-Hydrogen Atoms": D. T. Cromer, J. T. Waber, *International Tables for X-ray Crystallography*, Vol. IV, Kynoch Press, Birmingham, 1974, Table 2.2A, pp. 71–98; G. M. Sheldrick in *Crystallographic Computing 3* (Eds.: G. M. Sheldrick, C. Krüger, R. Goddard), Oxford University Press, London, 1985, pp. 175–189; G. M. Sheldrick, SHELXS-93, Göttingen, Germany, 1993.
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The Biosynthesis of Vancomycin-Type Glycopeptide Antibiotics—New Insights into the Cyclization Steps**

Daniel Bischoff, Stefan Pelzer, Alexandra Hölzel, Graeme J. Nicholson, Sigrid Stockert, Wolfgang Wohlleben, Günther Jung, and Roderich D. Süssmuth*

Over recent years, vancomycin (**1**) (Scheme 1)^[1] has emerged as an antibiotic of last resort against infections of methicillin-resistant *Staphylococcus aureus* (MRSA) strains.^[2] The antibiotic activity of the vancomycin-related glycopeptides is based on the high specificity of the aglycon cavity



Scheme 1. Structures of the glycopeptide antibiotics vancomycin (**1**) and balhimycin (**2**).

towards the N -acyl-D-Ala-D-Ala-peptide motif of bacterial cell-wall precursors.^[3] Besides its pharmaceutical significance, work on the total synthesis of vancomycin has attracted the attention of synthetic chemists on account of the highly challenging stereochemical requirements encountered in the synthesis of the tricyclic aglycon. Chemical and biological aspects of glycopeptide antibiotics have been extensively reviewed recently.^[4]

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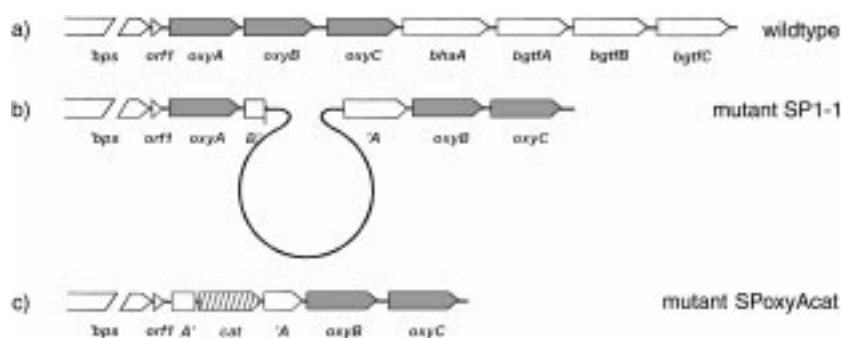
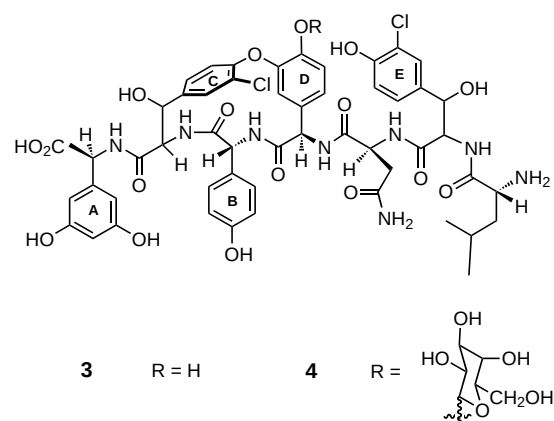


Figure 1. a) Gene organization of a part of the balhimycin biosynthetic gene cluster from *A. mediterranei* wildtype. b) The gene inactivation mutant SP1-1 after integration of plasmid pSP1.5Pst.^[8] c) The *oxyA* gene replacement mutant SPoxyAcat. ('*bps*'=part of a peptide synthetase gene; *orf1*=Orf with unknown function; *oxyA*–*C*=oxygenase genes; *bhaA*: halogenase gene; *bgtfA*–*C*: glycosyltransferase genes; *A*'/*A*'=parts of the *oxyA* gene; *B*'=part of the *oxyB* gene; *cat*=chloramphenicol resistance gene)

The aim of our investigations was to reveal the order of the oxidative bridging in the aromatic side chains during the biosynthetic formation of the aglycon unit. Sequence homology studies indicated^[5] that the aglycon ring system, which includes one biaryl bond and two diaryl ether bridges, is possibly formed from a linear precursor peptide by the action of three oxygenases (*oxyA/B/C*). This was previously confirmed for balhimycin (**2**), a glycopeptide antibiotic of the vancomycin type produced by *Amycolatopsis mediterranei* DSM 5908 (Scheme 1).^[6] The inactivation of oxygenase genes resulted in a mutant (SP1-1; Figure 1), from which the two peptides SP-1134 and SP-969 were isolated and suggested to be linear precursor peptides of the aglycon.^[7, 8] However, the sequence of the oxidation steps still remains elusive. Therefore we have continued our studies of the oxygenase genes by constructing an *oxyA* gene replacement mutant bearing a chloramphenicol resistance gene (*cat*) (Figure 1). The correct gene replacement event was proven by means of Southern hybridization. From this mutant we were able to isolate for the first time peptides with only one diaryl ether bridge (Scheme 2).

The culture filtrate of this mutant (SPoxyAcat) showed no antibiotic activity. From the supernatant, two compounds (SP-1132 **3** and SP-1294 **4**) were isolated by adsorption chroma-



Scheme 2. Structures of SP-1132 (**3**) and SP-1294 (**4**).

tography and preparative RP-HPLC. Structural characterization was achieved by means of ES-quadrupole MS and tandem MS experiments, ES-FTICR-MS, Edman degradation, 2D NMR spectroscopy, and amino acid and sugar analysis by GC-MS.

Molecular masses of 1132.2984 Da (**3**) and 1294.3512 Da (**4**) were determined by FTICR-MS. Both compounds showed the characteristic isotopic pattern for two chlorine atoms (Figure 2a). Chiral amino acid analysis revealed that L-Asn, D-Leu, D-4-hydroxyphenylglycine (Hpg), and L-3,5-dihydroxyphenylglycine (Dpg) are constituents of **3** and **4**. The primary peptide sequence ¹Leu-²Cht-³Asn-⁴–⁵Hpg-⁶–⁷Dpg was determined by Edman degradation for both compounds. No amino acid was

detected in cycles 4 and 6, which suggests that ⁴Hpg and ⁶Cht are connected by a diaryl ether bridge. The sugar analysis of **4** by GC-MS revealed the presence of galactose (Gal).

ES-MS/MS experiments (Figure 2b) and 2D NMR experiments (Tables 1 and 2) confirmed these results, and we were able to elucidate the structure of SP-1132 (**3**; Scheme 2). ¹H and ¹³C NMR chemical shifts were assigned by means of TOCSY, P.E. (primitive exclusive) COSY, NOESY, HSQC,

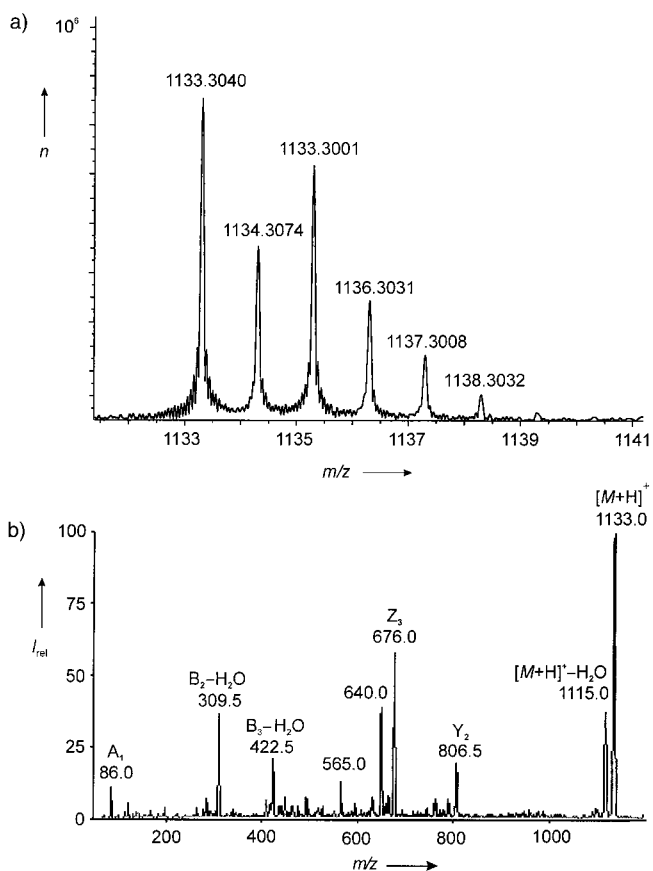


Figure 2. Mass spectrometric data of SP-1132 (**3**). a) High-resolution ES-FTICR mass spectrum with the characteristic isotope distribution pattern. b) ES-MS/MS daughter-ion spectrum with the assignments of fragments.

Table 1. ¹H and ¹³C NMR shifts of peptide SP-1132 (**3**) ([D₆]DMSO, 305 K).

	N/C' δ [ppm]	α δ [ppm]	β δ [ppm]	Others δ [ppm]
¹ Leu		3.60	1.36	γ: 1.45, δ: 0.77/0.76
	168.7	51.0	39.7	γ: 23.3, δ: 21.4/22.7
² Cht	8.51	4.49	4.66	OH ² : 5.58, 2: 7.31, OH ⁴ : 10.02
	169.4	58.5	71.9	1: 133.7, 2: 128.4, 4: 152.2, 3: 119.1
				5: 6.84, 6: 7.07
				5: 115.9, 6: 126.8
³ Asn	8.32	4.71	2.57/2.45	δ: 7.35/6.90
	170.1	49.7	37.4	γ: 171.6
⁴ Hpg	7.91	5.48	–	2: 6.57, OH ⁴ : 9.42
	168.1	54.1	–	2: 114.2, 4: 145.6, 1: 128.3, 3: 146.3
				5: 6.84, 6: 6.72
				5: 116.3, 6: 120.5
⁵ Hpg	8.51	5.22	–	2,6: 7.22, 3,5: 6.78, OH ⁴ : 9.57
	168.1	56.6	–	2,6: 129.6, 3,5: 115.4, 4: 157.3, 1: 126.3
⁶ Cht	6.48	4.59	5.32	OH ² : 5.55, 2: 7.68
	167.6	58.6	71.8	1: 140.1, 2: 128.8, 3: 125.2, 4: 149.9,
				5: 7.20, 6: 7.39
				5: 123.4, 6: 125.0
⁷ Hpg	8.86	5.13	–	2,6: 6.25, OH ^{3,5} : 9.34, 4: 6.15
	171.7	56.3	–	2,6: 105.4, 3,5: 158.4, 4: 102.1, 1: 139.2

and HMBC spectroscopic analysis. The sequence of the aglycon was reflected in numerous interresidue cross-peaks observed in the NOESY ($H_{i+1}^N \leftrightarrow H_i^a$) and the HMBC ($H_{i+1}^N \leftrightarrow C_i'$) spectra. The position of the sugar moiety of **4** was determined by NOE interactions between H1'-Gal and both H5- and H6-⁴Hpg as well as by an HMBC connectivity between H1'-Gal and C4-⁴Hpg. The molecular formulae of C₅₂H₅₄Cl₂N₈O₁₇ (**3**) and C₅₈H₆₄Cl₂N₈O₂₂ (**4**) deduced from the NMR experiments are in agreement with the molecular formulae determined by high-accuracy FTICR-MS measurements for **3** (relative error: 1.5 ppm) and **4** (relative error: 3.0 ppm).

Table 2. ¹H and ¹³C NMR shifts of peptide SP-1294 (**4**) ([D₆]DMSO, 305 K).

	N/C', δ [ppm]	α, δ [ppm]	β, δ [ppm]	Others, δ [ppm]		
¹ Leu		3.59	1.35	γ: 1.44, δ: 0.76/0.75		
	168.5	50.7	39.6	γ: 23.1, δ: 21.2/22.3		
² Cht	8.47	4.48	4.65	OH ² : 5.58, 2: 7.30, OH ⁴ : 10.00		
	169.2	58.2	71.7	1: 133.6, 2: 128.2, 4: 152.2, 3: 118.9		
				5: 6.84, 6: 7.07		
				5: 115.7, 6: 126.7		
³ Asn	8.32	4.73	2.58/2.46	δ: 7.35/6.90		
	170.0	49.5	37.1	γ: 171.5		
⁴ Hpg	8.04	5.53	–	2: 6.62		
	167.7	54.0	–	2: 114.0, 1: 132.2, 3: 149.0, 4: 144.9		
				5: 7.20, 6: 6.85		
				5: 118.7, 6: 120.4		
⁵ Hpg	8.58	5.23	–	2,6: 7.21, 3,5: 6.78, OH ⁴ : 9.56		
	167.7	56.5	–	2,6: 129.4, 3,5: 115.3, 4: 157.1, 1: 126.1		
⁶ Cht	6.49	4.61	5.32	OH ² : 5.55, 2: 7.69		
	167.5	58.4	71.7	1: 140.3, 2: 128.7, 3: 125.0, 4: 149.6		
				5: 7.21, 6: 7.39		
				5: 123.2, 6: 125.1		
⁷ Dpg	8.85	5.12	–	2,6: 6.25, OH ^{3,5} : 9.33, 4: 6.15		
	171.4	56.0	–	2,6: 105.2, 3,5: 158.3, 4: 102.0, 1: 139.0		
	1'	2'	3'	4'	5'	6'
Gal	5.57	3.85 ^[b]	3.85 ^[b]	3.84 ^[b]	3.97	3.55/3.39
	99.6	69.0 ^[b]	69.0 ^[b]	68.2 ^[b]	72.1	59.9
OH	–	4.49 ^[a]	4.76 ^[a]	4.67 ^[b]	–	4.51

[a] Assignment arbitrary. [b] Assignment ambiguous.

Compounds SP-1132 (**3**) and SP-1294 (**4**) are the first examples of singly bridged peptides that were isolated from a glycopeptide antibiotic producing organism. No linear peptides such as SP-1134 or SP-969 were detected in the culture filtrate of the mutant SPoxyAcat. The stereochemistry of the amino acids, and the chlorination and β-hydroxylation patterns of **3** and **4** are identical to those of the linear peptide SP-1134. Of the two possible atropisomers of the C-O-D ring, only the naturally occurring one has been observed.^[9] This means that the oxygenase (either intact oxyB or oxyC) specifically recognizes and quantitatively converts the linear precursor peptide into the naturally occurring atropisomer. Galactose is bonded to ⁴Hpg in **4** as the result of an unspecific glycosylation, as galactosylation has so far not been observed in balhimycin derivatives. The results herein support the hypothesis that β-hydroxylation and chlorination occur before the oxidative ring formation of the aglycon, and that glycosylation and N-methylation occur subsequently.^[7,8,10,11] We consider that the formation of the C-O-D ring system is the first ring-closure reaction in the oxidative bridging of the aglycon biosynthesis, and this is the subject of our current investigations.

Experimental Section

The SPoxyAcat-Mutant of *Amycolatopsis mediterranei* DSM 5908 was grown in a liquid culture supplemented with erythromycin (50 μg mL⁻¹), and yielded SP-1132 (6.3 mg L⁻¹) and SP-1294 (3.2 mg L⁻¹). Peptides were purified by XAD-16 chromatography and then subjected to preparative HPLC (Nucleosil C18, 5 μm, 250 × 20 mm, Grom, Herrenberg, Germany).

ES-MS and ES-MS/MS experiments were performed on an API III TAGA 6000E triple-quadrupole mass spectrometer (Perkin–Elmer Sciex, Thornhill, Canada). High-resolution mass spectra were measured on an APEX II FTICR-MS instrument (4.7 T, Bruker Inc., Bremen, Germany) in the positive-ion mode with ES ionization. The resolution was 21 000 (SP-1132) and 65 000 (SP-1294), respectively. NMR spectroscopy experiments

were carried out on an AMX600 NMR spectrometer (Bruker, Karlsruhe, Germany) equipped a 5 mm triple-resonance probehead with z -gradients. Edman degradation was performed on a Hewlett–Packard 241 protein sequencer equipped with a biphasic column detector (Hewlett–Packard, Waldbronn, Germany). For amino acid analysis with GC-MS (HP 5973/HP 6890, Agilent Technologies, Waldbronn, Germany), the peptides were hydrolyzed under vacuum (6 N HCl containing 5% phenol, 110 °C, 24 h) and derivatized with methanol/HCl (2 N, 110 °C, 15 min), trifluoroacetic anhydride (110 °C, 10 min), and then BSTFA/HMDS/pyridine (4:1:4, 80 °C, 30 min; BSTFA = *N,O*-bis(trimethylsilyl) trifluoroacetamide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane), and analyzed by GC-MS on fused silica capillaries (25 m $\times$ 0.25 mm) coated with either L-Chirasil-Val or Lipodex E (30%) in PS255 (film thickness d_f = 0.13 μ m). For sugar analysis, SP-1294 was subjected to methanolysis (HCl (0.65 N) in methanol/methyl acetate (4:1), 70 °C, 16 h). The trimethylsilyl derivatives were prepared by using BSTFA/pyridine (1:1, 80 °C, 30 min), and analyzed by GC-MS on an HP 1-MS fused silica capillary (30 m $\times$ 0.25 mm; d_f = 0.25 μ m, Agilent Technologies).

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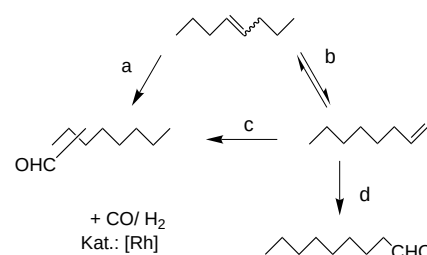
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New Phosphorus Ligands for the Rhodium-Catalyzed Isomerization/Hydroformylation of Internal Octenes

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The synthesis of plasticizers is closely related to the *n*-regioselective hydroformylation of olefins. World-wide, propene is an important feed stock in the rhodium-catalyzed synthesis of *n*-butanal. The use of higher internal olefins, for example di-*n*-butene from fraction II of the refining process, offers a very interesting and financially attractive alternative that is also used industrially. In these processes the use of unmodified cobalt catalysts and cobalt–phosphane complexes is dominant. At 80–350 bar and 160–190 °C regioselectivities of around 50% with regard to the desired terminal hydroformylation product are achieved, this can be increased to over 80% by modifying the catalyst with a suitable phosphine ligand.^[1]

The development of a catalyst that delivers high activities and selectivities under mild conditions is not only of industrial importance, Scheme 1 illuminates the scientific problems with



Scheme 1. Isomerization and hydroformylation of (Z)/(E)-4-octene.

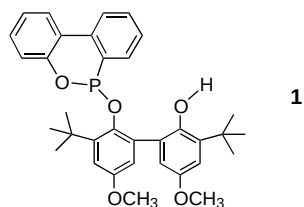
the example of 4-octene as a substrate. The catalyst and the reaction conditions must be coordinated so that a dynamic kinetic control of the reaction, based on isomerization to the thermodynamically less stable terminal olefin (step b) occurs and that this olefin rapidly undergoes the final *n*-regioselective hydroformylation step (d). The formation of the isomeric aldehydes (a, c) is thus suppressed.

Recently van Leeuwen et al. reported that with xantphos-type diphosphines rhodium catalysts gave *n*-nonanal in 86% regioselectivity from (E)-4-octene.^[2] The low isomerization activity of the catalyst however, resulted in turnover frequen-

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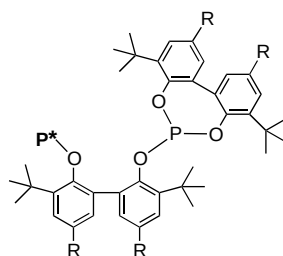
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cies of only 15 h⁻¹ (112 h⁻¹ for 2-octene) and thus no effective control of the reaction. The phosphonite system (Rh/1) that we reported recently is less selective than van Leeuwens catalyst, however, under comparatively

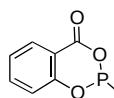
mild conditions (20 bar/140 °C) it can compete with the unmodified cobalt catalyst in terms of selectivity and activity.^[3]

New developments in the rhodium-catalyzed oxo reaction (hydroformylation) of long-chain internal olefins have to show a clear improvement in the *n*-selectivity and a catalytic activity of practical use. Herein we report results that emphasize the astounding potential that π -acid bidentate ligands of unsymmetrical structure have in the hydroformylation of isomers of *n*-octenes.

The ligands 2–7 were synthesized. Their most important structural feature, apart from the 2,2'-dioxidiphenyl frag-

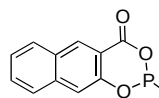


P* =



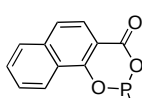
R = OMe

2



R = *t*Bu

5



3

4

6

7

ment, known from the work of the firm UCC, is an *O*-acylphosphite moiety. These types of 3-aryloxy-1,3,2-dioxaphosphine-4-ones are readily prepared from the reaction of the corresponding 2-hydroxyaryl carboxylic acid with PCl₃ and subsequent treatment with phenols.^[4, 5]

Preliminary attempts to employ the new hybrid ligands in the hydroformylation of 1-octene at 100 °C and 50 bar and with a Rh:P ratio of 1:10 (40 ppm Rh) gave *n*-selectivities with 2 and 3 of 87.4 and 79.0 %, respectively, with an aldehyde yield of around 80 % and complete isomerization of the remaining olefins. Impressively this desired isomerization activity can be used at higher temperatures for the hydroformylation of internal olefins. Table 1 summarizes the results and enables a comparison with 1. A substrate mixture containing up to 94 % internal olefins was used. The reactions were carried out at 130 °C and under a constant pressure of synthesis gas of 20 bar.

Most noteworthy are the selectivities near an *n*/*iso* ratio of two and the accompanying high catalytic activities. Thus at rhodium concentrations of 1 mmol L⁻¹ near to quantitative conversion occurs and at the same time there is very little

Table 1. Hydroformylation^[a] of isomers of *n*-octene^[b] with the bidentate ligands 2–7 and the phosphonite 1.^[c]

Ligand	Yield [%] ^[d]	<i>n</i> -Nonanal [%] ^[e]	ROH [%] ^[f]	TOF [h ⁻¹] ^[g]
2	94	63.9	0.2	> 4600 ^[h]
3	95	64.2	0.2	4310
4	96	69.0	0.3	4448
5	95	67.3	0.1	3119
6	93	67.9	0.1	3324
7	95	68.5	0.2	3336
2 ^[i]	83	64.1	0.2	4751
1 ^[i]	52	47.8	1.4	1320

[a] Experiments were performed in a 200 mL autoclave with *c*(*n*-octene)₀ = 1.68 M at 130 °C, 3 h in toluene under a constant pressure of 20 bar CO/H₂ (1/1) with [Rh(acac)(cod)] as the catalyst precursor (acac = acetylacetonate, cod = cycloocta-1,5-diene). *c*(Rh) = 1.07 mM, Rh:P:*n*-octene = 1:10:1570. [b] 3.3 % 1-octene, 48.4 % (*Z*)/(*E*)-2-octene; 29.2 % (*Z*)/(*E*)-3-octene, 16.4 % (*Z*)/(*E*)-4-octene, 2.1 % octene structural isomers, 0.6 % octane. [c] See ref. [3]. [d] Total aldehyde determined by gas chromatography using toluene as the internal standard. [e] Proportion of total aldehyde. [f] Total alcohol, with respect to olefin added. [g] Turnover frequency in (mol aldehyde)(mol catalyst)⁻¹ h⁻¹ at 20 % conversion, calculation based on the gas consumption; this was determined with a gas-flow meter from Fa. Bronkhorst, Holland, (Hitec gas-flow meter). [h] Measurement limit of the gas-flow meter. [i] *c*(Rh) = 0.107 mM, *t* = 6 h, *T* = 130 °C (2) and 140 °C (1).

hydrogenation activity towards the aldehyde. Significant substrate hydrogenation cannot be proven because the amount of octane found in the reaction solution corresponds to that present in the starting mixture. The maximum selectivity, 69 % *n*-nonanal, is obtained with ligand 4. Comparison of the results clearly shows the influence of the substituents at the periphery of the ligand; *tert*-butyl groups in the 5,5' position counteract the increasing selectivity with increasing steric bulk caused by the 3-aryloxy-1,3,2-dioxaphosphine-4-one unit.

The results presented here impressively demonstrate, for the first time, the possibility of mainly *n*-selective isomerization/hydroformylation of long-chain internal octenes through rhodium compounds, accompanied by catalytic activities that can be used in practice. This can be achieved through the presence of modifying bidentate ligands and under milder conditions than those of the cobalt catalysis.^[6]

Looking back on the results obtained with the catalyst system Rh/1 this clearly shows that the demand for a simultaneous increase in *n*-selectivity and activity can be satisfied. We imagine that the title reaction here will become a recognized synthetic method in the near future. Also with the 3-aryloxy-1,3,2-dioxaphosphine-4-ones presented here we have introduced a new class of ligands that, to the best of our knowledge, has not yet found use in homogeneous catalysis and has potential for use in other metal catalyzed reactions including stereoselective processes.

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 [5] The new compounds were obtained as a mixture of diastereomers and were fully characterized. The experimental details are given in the Supporting Information.
 [6] Industrial di-*n*-butene was also used consisting of a mixture of internal and structural isomers of octene. For the individual ligands the selectivities towards conversion into terminal aldehydes are comparable to the values given in Table 1.

A Sol–Gel Route to B₄C**

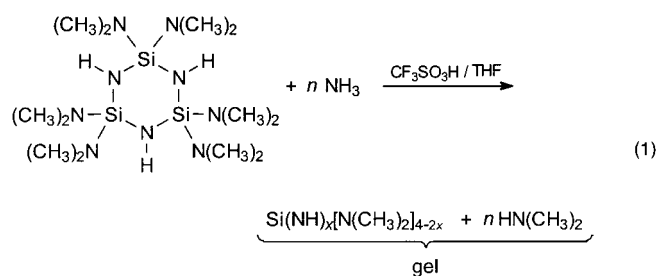
Edwin Kroke,* Karl W. Völger,
Alexander Klonczynski, and Ralf Riedel

The classic oxide sol–gel process based on hydrolysis reactions of alkoxides or halides has been examined in detail over several decades.^[1] A continuously increasing number of publications indicates that sol–gel processing as a method to produce oxide materials is still gaining importance.^[2] In contrast, there have been very few reports on non-oxide sol–gel systems.^[3] A sol–gel route to B/(C)/N materials was found in the 1980s by Paine and Narula et al. which is based on “silazanolyse” of *B*-trichloroborazenes with hexa- (HMDS) or heptamethyl disilazane. This sol–gel system was used to prepare B/C/N xerogels, aerogels, and hexagonal boron nitride (h-BN).^[4] The crystallization behavior and the oxidation resistance of the products were investigated^[5] and molecular model compounds were synthesized and structurally characterized.^[6] The results were summarized in a review article and compared with classical routes to boron nitride.^[7]

In 1997 it was discovered that chlorosilanes RSiCl₃ (with R = H, Cl, alkyl, aryl) form gels in pyridine-catalyzed reactions with bis(trimethylsilyl)carbodiimide.^[8] Later, this sol–gel process was extended to dichlorosilanes and functionalized chlorosilanes.^[9] Monodisperse spherical particles,^[10] Si/C/N coatings and membranes,^[11] bulk Si/C/N samples, and pure SiC powder were produced.^[12] It is remarkable that this “sol–gel process” is analogous to the oxide system in terms of phenomenological, chemical, physical, and spectroscopic characteristics.^[3, 13]

Several attempts to prepare gels from chlorosilanes and HMDS or other silazanes were not successful.^[14] Similarly, for carbides or nitrides of elements other than Si, as well as further non-oxide materials such as sulfides, selenides, borides etc., there are very few examples of sol–gel processes known.^[3] Most attempts to synthesize non-oxide gels resulted in the formation of solid precipitates.

Recently the first example of a sol–gel process based on ammonolysis has been discovered by Bradley et al., starting from a dialkylamino-substituted cyclic trisilane Si/(C)/N gels were prepared [Eq. (1)].^[15]



B/C/N materials are of interest for several reasons. Novel graphitic ternary phases of these elements may provide materials with properties intermediate between graphite and h-BN.^[16] Similarly, sp³-hybridized B/C/N materials are considered as promising ultra-hard phases combining the properties of diamond and cubic boron nitride (c-BN).^[17]

Boron carbide (B₄C) ranks next to diamond in its hardness.^[18] It is produced on an industrial scale by classical carbothermal reduction of B₂O₃ in electric arc furnaces. Dense materials are obtained either by pressureless sintering or hot pressing at 2100–2250 °C. B₄C is used for armor plating, blasting nozzles, as mechanical seal faces, and for grinding and cutting tools. The natural presence of the ¹⁰B isotope together with chemical inertness and stability under irradiation makes B₄C valuable as a neutron absorber. Because of its ability to generate an electromotive force (EMF) which increases with temperature B₄C has been studied for space power generation and used for high-temperature thermocouples.

In our search for ternary B/C/N phases we examined the reactions of BCl₃ and *B*-trichloroborazene with bis(trimethylsilyl)carbodiimide. It turned out that BCl₃ forms solid, insoluble, and infusible products, which contained either residual chlorine or significant amounts of silicon, depending on the reaction conditions. In contrast, *B*-trichloroborazene (B₃N₃H₃Cl₃) reacts with bis(trimethylsilyl)carbodiimide in THF, toluene, or even without any solvent to form non-oxide gels. The xerogels obtained after ageing and drying are practically free of chlorine or oxygen and contain only small amounts of silicon.

The FT-infrared (IR) and Raman spectra clearly indicate the presence of the carbodiimide unit showing the characteristic vibration at 2180 cm^{−1} and 1530 cm^{−1}, respectively.^[19] In addition the typical bands for N–H and B–N bonds were observed. Only very weak C–H and Si–CH₃ vibration bands at 2980 cm^{−1} and 1250 cm^{−1} were observed. This corresponds well with the elemental analysis, given in Table 1, that indicate

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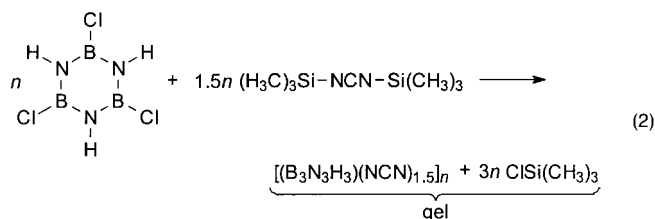
Table 1. Results of elemental analyses [mass %] of the xerogel and the amorphous and crystalline pyrolysis products. The measurements were performed by Analytisches Labor Pascher, Remagen-Bandorf (Germany).

Product	B	C	N	Si	H	O	Cl	Σ	Molecular formula
xerogel (150 °C/10 ⁻² Torr/1 h)	19.5	19.1	49.5	5.4	3.8	1.2	0.3	98.8	BC _{0.88} N _{1.96} Si _{0.11} H _{2.09} O _{0.04} (BCN ₂ H ₂)
amorphous product (1200 °C/Ar/2 h)	34.9	8.9	49.7	4.7	< 0.3	1.8	< 0.1	< 100.4	BC _{0.23} N _{1.1} Si _{0.05} H _{0.09} O _{0.03} (B ₄ CN ₄)
crystalline product (2000 °C/He/4 h)	78.3	21.0	n.d. ^[a]	n.d. ^[a]	n.d. ^[a]	n.d. ^[a]	n.d. ^[a]	99.3	BC _{0.24} (B ₄ C _{0.97}) (B ₄ C)

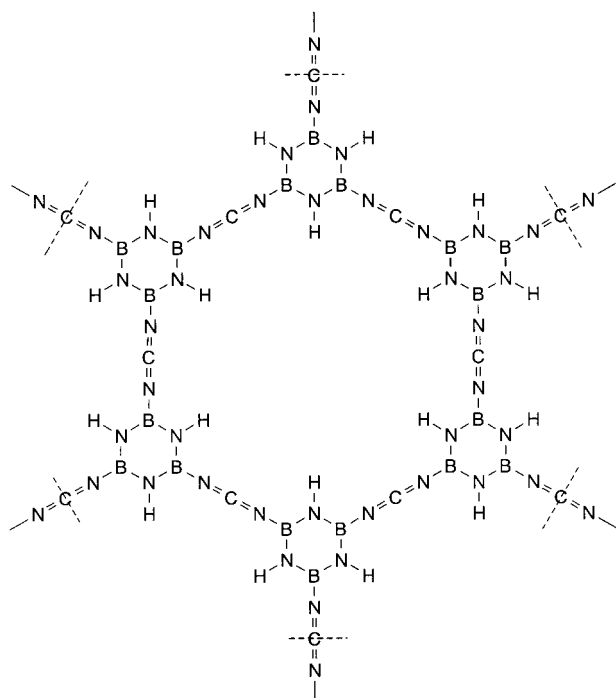
[a] n.d.: not determined.

only minor amounts of Si(CH₃)₃ end groups are present in the network.

An idealized reaction is depicted in Equation (2) and a proposed structure of the polymeric network is given in



Scheme 1. X-ray diffraction studies confirmed that an amorphous xerogel is present. The solid-state ¹¹B NMR spectrum shows a broad resonance signal centered at $\delta = 15$ which was attributed to boron atoms coordinated by three N atoms, two from the borazene ring and one from a carbodiimide group.



Scheme 1. Idealized structure of the polymeric carbodiimide borazene network forming the B/C/N gels.

Nitrogen adsorption measurements, analyzed according to the Brunauer–Emmett–Teller (BET) model, indicate that the xerogel has a surface area of 85 m² g⁻¹. This is significantly less than the values of 500–1000 m² g⁻¹ reported for the Si/N xerogel of Bradley et al. and of many porous oxide xerogels.

The xerogel was pyrolyzed in dry Argon using a heating rate of 100 °C h⁻¹. According to thermogravimetric mass spectrometry (TGA-MS) investigations two major ceramization steps occur. Around 200–300 °C methane is formed causing a mass loss of about 10%. Larger amounts of nitrogen, as well as methane are formed between 600 and 1000 °C causing another mass loss of about 40%. This corresponds well with the elemental analysis of the pyrolysis product obtained at 1200 °C (see Table 1). The composition of this amorphous material is close to that of B₄CN₄, which is located on the BN–C and B₄C–N tie-lines in the ternary B/C/N compositional diagram (Figure 1). The carbon content of this substance is relatively low compared to the molecular and polymeric precursor derived B/C/N materials normally investigated. Usually BC_xN phases with $x \geq 2$, for example BC₂N, BC₃N, or BC₄N are prepared and characterized.^[16, 17, 20]

Annealing the amorphous B₄CN₄(Si_{0.2}) at 2000 °C causes the formation of nitrogen and small amounts of volatile silicon-containing species to give pure crystalline B₄C (see Table 1 and Figure 1) as shown by TGA, X-ray diffraction, and elemental analysis. A detailed investigation of the pyrolysis and crystallization process will be published elsewhere.

Here we have reported preliminary results on a carbodiimide-based sol–gel synthesis of B/C/N polymers. These materials are almost free of oxygen, chlorine, and silicon, a remarkable result since often significant amounts of end groups such as, Cl- and (CH₃)₃Si- are trapped when three-dimensional networks formed by polycondensation reactions. Pyrolysis of the xerogel at 1200 °C provides an amorphous B₄CN₄ material, which is an interesting precursor for high-pressure/high-temperature experiments to obtain novel graphitic or sp³ hybridized crystalline B/C/N phases. Furthermore, the xerogel can be transformed into pure B₄C at 2000 °C.

Experimental Section

All manipulations were performed under inert atmosphere using glove box and/or Schlenk techniques. *B*-trichloroborazene^[21] and bis(trimethylsilyl)-carbodiimide^[22] were synthesized according to the literature methods.

In a typical experiment bis(trimethylsilyl)carbodiimide (1.24 mL) was added to freshly sublimed *B*-trichloroborazene (0.5 g) dissolved in dry

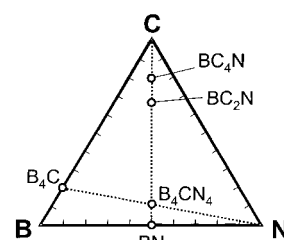


Figure 1. Compositional diagram for the ternary B/C/N system. The amorphous B₄CN₄ produced at 1200 °C is located on the intersection of the C–BN and B₄C–N tie lines.

toluene (1 mL). The clear solution was heated to 45 °C. After 0.5 h the mixture became cloudy and after 16 h a gel had formed. The product was stored at 45 °C for 30 days. During this ageing period no significant syneresis (contraction) was observed. The gel was dried at 150 °C/10⁻² Torr. Analogous reactions with a tenfold amount of starting materials were also successful.

In a similar experiment *B*-trichloroborazene (3.9 g) and bis(trimethylsilyl)carbodiimide (9.5 mL) were dissolved in dry THF (50 mL). After 2.5 h reflux the content of the flask suddenly solidified to form a monolithic colorless gel body. The gel was dried at 140 °C/10⁻² mbar/2.5 h and 190 °C/10⁻² mbar/0.5 h. Owing to the short ageing period this xerogel contained significant amounts of chlorine (4.75 mass%) and silicon (6.3 mass%).

In other variants *B*-trichloroborazene (0.5–1.5 g) was dissolved in toluene (5–10 mL) or an excess of bis(trimethylsilyl)carbodiimide and stored at 45 °C. The mixtures formed a gel after 1–3 days depending on the concentration. After an ageing period of 2–40 days the gels were dried at 150 °C/10⁻² Torr.

The xerogels were pyrolyzed in Quartz Schlenk tubes under argon at 400, 600, 800, 1000, and 1200 °C for 2 h using a heating rate of 100 °C h⁻¹. Further annealing at 1600 and 1800 °C in Ar and at 2000 °C in He was performed in a graphite furnace. Heating rates of 600 °C h⁻¹ up to 1200 °C followed by 300 °C h⁻¹ and holding times of 4 h were applied.

The yield of the xerogels, based on the amount of *B*-trichloroborazene and the idealized structure depicted in Scheme 1, was 110–125 %, which is because of residual trimethylsilyl end groups. The yield of the B/C/N material obtained at 1200 °C was 58–61 % based on the xerogel. Using this amorphous product as a reference the ceramic (boron carbide) yield at 2000 °C is 56 %.

The xerogels and pyrolysis products were investigated using FT-IR (Perkin-Elmer FTIR 1750, KBr pellets), Raman (Bruker IFS 55), and ¹¹B NMR spectroscopy (Bruker MSL 400 spectrometer, external standard: (CH₃CH₂)₂O · BF₃, 128.28 MHz) as well as nitrogen absorption measurements (Quantachrome Autosorb-3B), elemental analysis (see Table 1), X-ray diffraction (STOE STADI-P-diffractometer, CuK_α), and TGA-MS (Netzsch STA 429 coupled with a mass spectrometer Balzers QMG 420).

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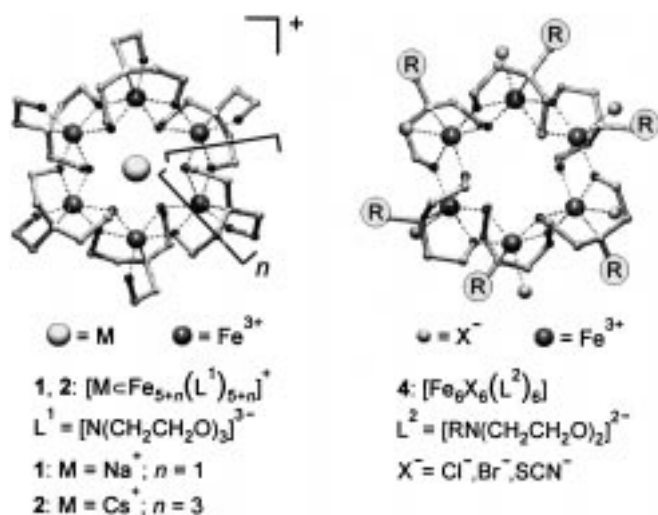
Metallacoronates or One-Dimensional Polymers through Self-Assembly—Influence of Templates and Hydrogen Bonding on Product Formation**

Rolf W. Saalfrank,* Ingo Bernt, and Frank Hampel

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

Design and synthesis of supramolecular inorganic structures with novel properties have provided exciting new possibilities.^[1] We reported on the template-mediated self-assembly of six- and eight-membered iron coronates [Na ⊂ Fe₆(L¹)₆]⁺ (**1**) and [Cs ⊂ Fe₈(L¹)₈]⁺ (**2**).^[2] They were prepared from triethanolamine (H₃L¹), iron(III) chloride, and sodium hydride or cesium carbonate, respectively (Scheme 1). A common feature of complexes **1** and **2** is that the ethanolato μ₁-O donors solely function as ligands for the coordinative saturation of the iron centers, whereas the ethanolato μ₂-O donors are structure-determining. Consequently, reaction of N-substituted diethanolamines **3** (H₂L²)

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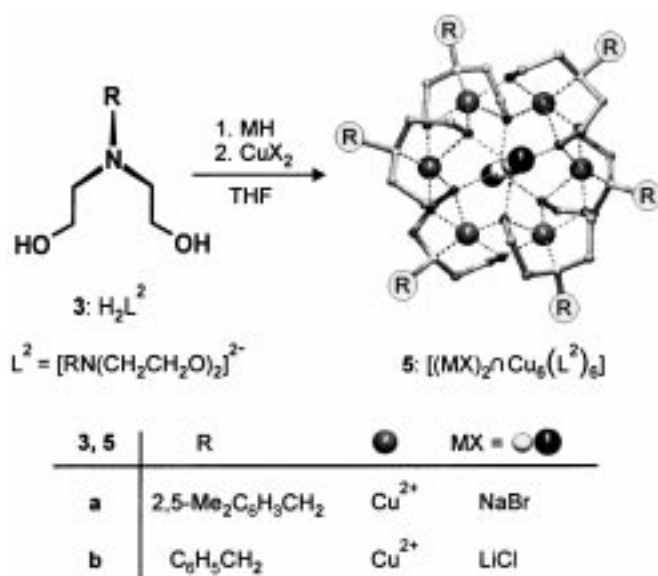


Scheme 1. Schematic representation of the metallacoronates **1** and **2** and the metallacoronands **4**.

($\text{L}^2 = [\text{RN}(\text{CH}_2\text{CH}_2\text{O})_2]^{2-}$) with calcium hydride, iron(III) chloride, and sodium bromide or sodium rhodanide yielded the unoccupied neutral iron cryptands $[\text{Fe}_6\text{X}_6(\text{L}^2)_6]$ **4** ($\text{X} = \text{Cl}^-$, Br^- , NCS^- ; Scheme 1).^[2c]

Like in **1** and **2**, in **4**, the μ_2 -O donors of the *N*-alkyldiethanolamine ligands are structure-determining. Completion of the octahedral coordination sphere at iron and charge compensation is achieved by the halogenato or pseudo-halogenato co-ligands. By changing from hexacoordinating iron(III) to pentacoordinating divalent metal ions it should be possible to synthesize neutral unoccupied metalacrowns of the type $[\text{M}^{\text{II}}(\text{L}^2)_6]$ with *N*-alkyldiethanolamine ligands alone.

To prove this hypothesis, we allowed *N*-(2,5-dimethylbenzyl)iminodiethanol (**3a**; H_2L^{2a}) to react with sodium hydride and copper(II) bromide and obtained the blue material **5a** (Scheme 2). For an unambiguous characterization, we carried out an X-ray crystallographic structure analysis of **5a**



Scheme 2. Synthesis of copper coronate **5**.

(Figure 1).^[3] As expected, **5a** is present in the crystal as a cyclic hexanuclear copper(II) complex of composition $[(\text{NaBr})_2 \cap \text{Cu}_6(\text{L}^{2a})_6]$. The six copper centers of the centrosymmetric $[\text{Cu}_6(\text{L}^{2a})_6]$ framework are located in the corners of

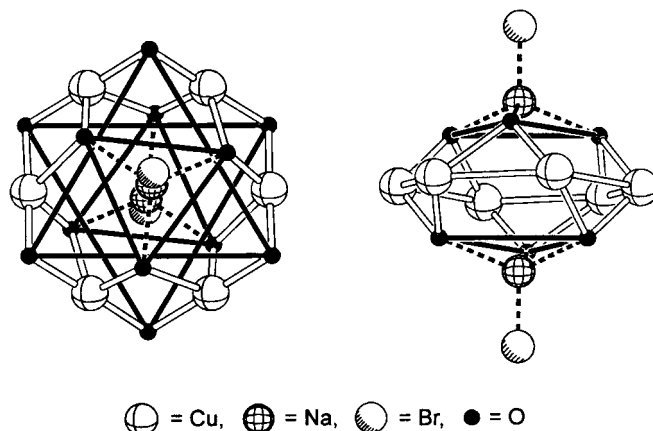


Figure 1. Left: View along the C_3 axis of the $[\text{Cu}_6\text{O}_{12}]$ core of **5a** with two exohedrally coordinated sodium bromide guests. The small triangles highlight the μ_3 -oxygen atoms and the larger triangles the μ_2 -oxygen atoms. Right: View perpendicular to the C_3 axis; μ_2 -oxygen atoms are omitted for clarity.

a regular hexagon. The mean Cu–Cu distance is 3.05 Å. The square-pyramidal coordination sphere of the copper ions is composed of one nitrogen donor, two μ_2 -oxygen donors, and two μ_3 -oxygen donors. (L^{2a})²⁻ acts as a tridentate tritopic ligand and links three copper(II) ions with each other. The twelve oxygen donors of **5a** are located in the corners of two pairs of equilateral triangles, which are rotated 60° relative to each other. One set of triangles comprises the μ_3 -oxygen donors and one set comprises the μ_2 -oxygen donors. The trigonal planes are located parallel and equidistant in pairs above and below the plane generated by the copper ions and share a common C_3 axis (Figure 1, left).

In contrast to the aforementioned ferric wheels **1** and **2**, no endohedral cation inclusion is observed for **5a**. Instead, two sodium ions are found exohedrally bound to the outer faces of the copper wheel through three of the six μ_3 -oxygen atoms, each. The tetragonal coordination spheres of the sodium ions are completed by bromide ions, giving cluster **5a** the shape of a molecular gyroscope (Figure 1, right; Figure 2). The sodium and bromide ions are located on the molecular C_3 axis. The distance between Na^+ and Br^- is remarkably short (2.81 Å; sum of ionic radii: 2.95 Å).^[4]

Provided that the core of **5** is flexible, it might be possible, that further templates besides sodium bromide are suitable for the formation of the $[\text{Cu}_6(\text{L}^2)_6]$ acceptor. Consequently, we allowed *N*-benzyliminodiethanol **3b** (H_2L^{2b}) to react with lithium hydride and copper(II) chloride and isolated **5b** as a blue powder. The X-ray structure analysis of a single crystal of **5b** revealed^[3] that $[(\text{LiCl})_2 \cap \text{Cu}_6(\text{L}^{2b})_6]$ (**5b**) is basically isostructural to **5a**. Two lithium chloride guests are bound on opposite μ_3 -O faces of the copper wheel. In contrast to **5a** the μ_3 -oxygen atoms in **5b** are tilted more towards the center of the $[\text{Cu}_6(\text{L}^2)_6]$ torus, leading to tighter cavities to

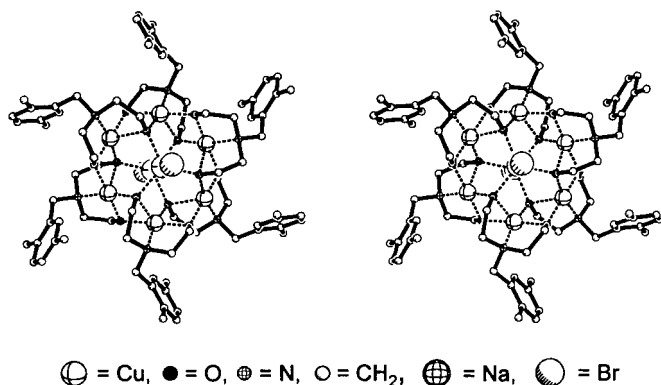


Figure 2. Stereoview of **5a** in the crystal along the molecular C_3 axis (PLUTON representation; hydrogen atoms are omitted for clarity).

accommodate the smaller guests. Like **5a**, cluster **5b** resembles a molecular gyroscope. In **5b**, two polar chloride ions form the tips of the gyro and the unpolar benzyl substituents the disk-shaped torso. The remarkable polar anisotropy results in a noteworthy crystal packing of **5b**. In the crystal, the copper wheels are arranged coplanar in layers, which are separated by 11.09 Å. The interstitial void is terminated by the chloride tips of the exohedral adducts **5b** and is occupied by solvent molecules (Figure 3).

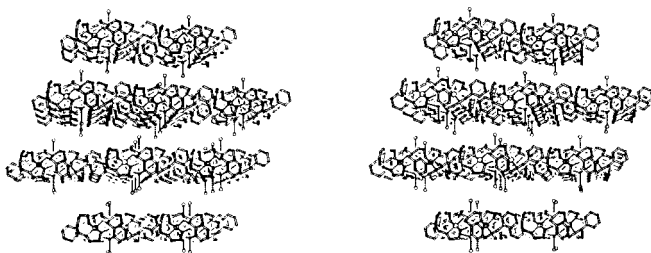
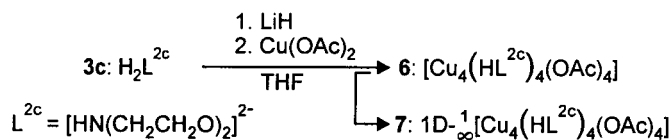


Figure 3. Stereoview of the crystal packing of **5b** along the a axis, showing the layers of the interdigitated planar cupric wheels and the chloride ions pointing towards the interstitial voids (PLUTON representation; solvent molecules and hydrogen atoms are omitted for clarity).

Investigation of the hexa- and octanuclear ferric wheels $[\text{Na} \subset \text{Fe}_6(\text{L}^1)_6]^+$ (**1**) and $[\text{Cs} \subset \text{Fe}_8(\text{L}^1)_8]^+$ (**2**) has revealed that the formation of distinct host molecules from a virtual pool of acceptor systems is determined by the presence of appropriate guests.^[5] Nevertheless, it is not necessarily the templating effect of the cation alone that determines the product. This was evident when copper(II) acetate was treated with diethanolamine **3c** and lithium hydride. After work-up, a blue powder was isolated, which according to a single-crystal X-ray structure analysis was the one-dimensional coordination polymer $1\text{D-}^\infty[\text{Cu}_4(\text{HL}^{2c})_4(\text{OAc})_4]$ (**7**) rather than a hexanuclear copper wheel.^[6] The structure of **7** becomes clear if one assumes the formation of the self-complementary tetranuclear building blocks $[\text{Cu}_4(\text{HL}^{2c})_4(\text{OAc})_4]$ (**6**) and their linkage through hydrogen bonds (Scheme 3).

In module **6** four copper centers are linked in an alternating way by two μ_2 - and two μ_3 -oxygen atoms in an *antitricyclo*[4.2.0.0^{2,5}]octane-like fashion. Two $(\text{HL}^{2c})^-$ ligands (outer ligands) coordinate to the two outer copper centers



Scheme 3. Synthesis of polymeric strands **7**.

by one nitrogen, a μ_1 -oxygen, and a μ_2 -oxygen donor. Whereas, the second pair of $(\text{HL}^{2c})^-$ ligands (inner ligands) coordinate to the two inner copper centers through the nitrogen and the μ_3 -oxygen donors alone; the ethanol arm does not participate in the coordination. The square-pyramidal coordination geometry at the inner and outer copper centers is completed by four acetate ligands. The ideal conformation necessary for the polymerization of the self-complementary building block **6** is stabilized by additional intramolecular hydrogen bonds. The modules **6** polymerize to give **7** through formation of $\text{NH-}\mu_2\text{-O-HO}$ hydrogen bonds (Figure 4).^[7] In the crystal, two sets of parallel strands of **7** are packed in equidistant alternating layers, which are rotated approximately 40° relative to each other (Figure 5).

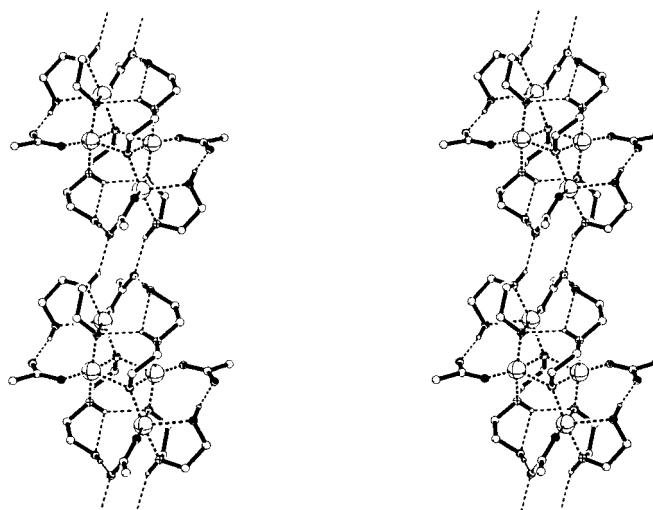


Figure 4. Stereoview of a single strand of the 1D polymer **7**, which shows the linkage of the self-complementary building block **6** through hydrogen bonds (PLUTON representation; hydrogen atoms are omitted, except those involved in hydrogen bonds).

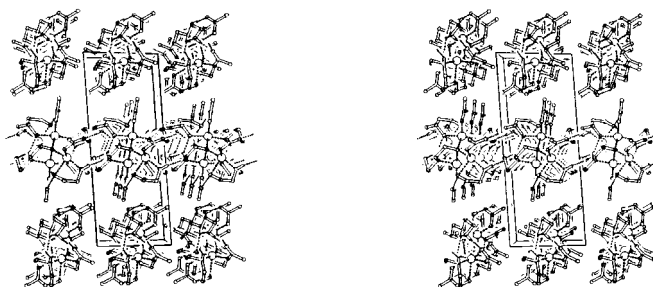


Figure 5. Stereoview of the crystal packing of **7** along the b axis, which shows two sets of alternating layers of parallel 1D strands. (PLUTON representation; solvent molecules and hydrogen atoms omitted for clarity).

We have shown that for the rational design of supramolecular systems a multitude of effects such as the denticity of the ligands, the coordination geometry of the metal centers, the influence of the templates as well as the possibility of hydrogen bonding have to be considered. Nevertheless, accurate predictions of self-assembly processes are possible, if one approaches the unknown territory in a stepwise manner from a safe camp.

Experimental Section

General method: *N*-(2,5-dimethylbenzyl)iminodiethanol (**3a**) (4 mmol, 0.89 g) (for **5a**), *N*-benzyliminodiethanol **3b** (4 mmol, 0.78 g) (for **5b**), or diethanolamine **3c** (4 mmol, 0.42 g) (for **6**) were added to a suspension of sodium hydride (9 mmol, 0.22 g) (for **5a**) or lithium hydride (9 mmol, 0.07 g) (for **5b** and **6**) in anhydrous tetrahydrofuran (60 mL). After the mixture had been stirred for 1 h at 20 °C, copper(II) bromide (4 mmol, 0.89 g) (for **5a**), copper(II) chloride (4 mmol, 0.54 g) (for **5b**), or Cu(OAc)₂ · H₂O (4 mmol, 0.80 g) (for **5a**) were added. The reaction mixture was stirred for four days at 20 °C and the blue precipitate was subsequently collected on a glass frit. In the case of **5a** and **6** the solid was extracted with dichloromethane (100 mL). After partial evaporation of the solvent, diethyl ether was added and blue crystals were obtained after two days. In the case of **5b** the solid was extracted with dimethyl sulfoxide (20 mL); chloroform (20 mL) and pentane (20 mL) were added, and upon standing for three days at 20 °C deep blue crystals were obtained. The micro-analytical data for **5a** and **5b** deviate from theory due to crystal solvents and are not recorded here.

5a · 9CH₂Cl₂: yield: 0.55 g (31 %), blue, rhombic crystals from dichloromethane/diethyl ether (1/1), m.p. > 240 °C (decomp); IR (KBr): $\tilde{\nu}$ = 2963, 2868, 1630 cm⁻¹; FAB-MS (3-nitrobenzyl alcohol-matrix): *m/z*: 1139 [Cu₄(L^{2a})₄]⁺.

5b · 6CHCl₃ · LiH: yield: 0.45 g (29 %), blue, rhombic crystals from chloroform/dimethyl sulfoxide (1/1) by diffusion of pentane, m.p. > 240 °C (decomp); IR (KBr): $\tilde{\nu}$ = 2848, 1639 cm⁻¹; FAB-MS (3-nitrobenzyl alcohol matrix): *m/z*: 1027 [Cu₄(L^{2b})₄]⁺.

6 · 2CH₂Cl₂: yield: 0.84 g (78 %), deep blue, rhombic crystals from dichloromethane/diethyl ether (1/1). Elemental analysis (%): calcd for Cu₄C₂₄H₃₂N₄O₁₆: C 31.79, H 5.78, N 6.18; found: C 31.69, H 6.07, N 5.93; m.p. > 220 °C (decomp); IR (KBr): $\tilde{\nu}$ = 2924, 2875, 1584, 1403 cm⁻¹; FAB-MS (3-nitrobenzyl alcohol matrix): *m/z*: 788 [Cu₄(HL^{2c})₄(OAc)₂]⁺.

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[3] X-ray crystal structure analyses: X-ray data were collected on a Nonius Kappa CCD area detector using MoK α radiation (λ = 0.71073 Å). Semiempirical absorption corrections were employed. The structures were solved by direct methods with SHELXS-97^[8] and refined with full-matrix least-squares against F^2 with SHELXL-97^[9]. Hydrogen atoms were attached in idealized positions and refined by using the riding model. **5a**: C₇₈H₁₁₄Br₂Cu₆N₆Na₂O₁₂ · 9CH₂Cl₂; M_r = 2679.11; triclinic, $P\bar{1}$; crystal size 0.30 × 0.10 × 0.10 mm³; a = 14.349(3), b = 15.534(3), c = 15.604(3) Å; α = 64.34(3), β = 87.60(3), γ = 65.68(3)°; V = 2817.2(10) Å³; T = 173(2) K; Z = 1; ρ_{calcd} = 1.578 Mg m⁻³; section of the reciprocal lattice $-17 < h < 17$, $-16 < k < 18$, $-18 < l < 18$; Θ = 2.54–25.03°; 17129 reflections observed, 9905 unique; 8206 reflections with $I > 2\sigma(I)$; $R1$ = 0.0544, $wR2$ = 0.1420 [$I > 2\sigma(I)$]; $R1$ = 0.0674, $wR2$ = 0.1525 (all data); largest difference peak and hole: 1.564/–0.859 e Å⁻³. **5b**: C₆₆H₉₀Cl₂Cu₆Li₂N₆O₁₂ · 6CHCl₃ · 1LiH; M_r = 2349.61; rhombohedral, $R\bar{3}$; crystal size 0.20 × 0.20 × 0.20 mm³; a = b = 16.2876(5), c = 33.2846(9) Å; V = 7646.9(4) Å³; T = 173(2) K; Z = 3; ρ_{calcd} = 1.527 Mg m⁻³; section of the reciprocal lattice $-17 < h < 19$, $-19 < k < 19$, $-39 < l < 38$; Θ = 2.50–25.02°; 10793 reflections observed, 2994 unique; 2191 reflections with $I > 2\sigma(I)$; $R1$ = 0.0484, $wR2$ = 0.1364 [$I > 2\sigma(I)$]; $R1$ = 0.0754, $wR2$ = 0.1467 (all data); largest difference peak and hole: 0.884/–0.472 e Å⁻³. **6**: C₂₄H₃₂Cu₄N₄O₁₆ · 2CH₂Cl₂; M_r = 1076.71; triclinic, $P\bar{1}$; crystal size 0.30 × 0.30 × 0.25 mm³; a = 8.7582(2), b = 12.1347(2), c = 21.6381(4) Å; α = 88.9647(11), β = 85.6537(10), γ = 69.9782(10)°; V = 2154.38(7) Å³; T = 173(2) K; Z = 2; ρ_{calcd} = 1.658 Mg m⁻³; section of the reciprocal lattice $-11 < h < 11$, $-13 < k < 15$, $-28 < l < 28$; Θ = 2.01–27.51°; 16651 reflections observed, 9790 unique; 7759 reflections with $I > 2\sigma(I)$; $R1$ = 0.0365, $wR2$ = 0.0870 [$I > 2\sigma(I)$]; $R1$ = 0.0556, $wR2$ = 0.0958 (all data); largest residue: 1.034/–0.578 e Å⁻³. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-153792 (**5a**), CCDC-153793 (**5b**), and CCDC-153791 (**6**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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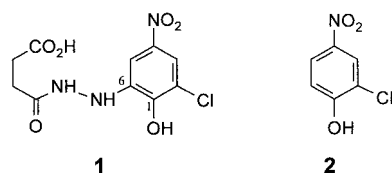
Stephanosporin, a "Traceless" Precursor of 2-Chloro-4-nitrophenol in the Gasteromycete *Stephanospora caroticolor***

Martin Lang, Peter Spiteller, Veronika Hellwig, and Wolfgang Steglich*

Dedicated to Professor Siegfried Hünig on the occasion of his 80th birthday

The carrot truffle, *Stephanospora caroticolor* (BERK.) PAT., is a rare Gasteromycete. It occurs in deciduous forests and mixed wooded areas in loamy, calcareous soil. The fruit bodies are tubers of 1 to 3 cm in diameter that mature underground. They may be recognized by their bright orange appearance on places where the soil is partially removed. The interior of the mushroom (gleba) is also intensively orange colored.

Extraction of the fruit bodies of *St. caroticolor* with methanol gives a yellow solution in which two pigments **1** and **2** (Scheme 1) can be detected by HPLC.^[1] Compound **2**



Scheme 1. Chloronitroarenes from *St. caroticolor*.

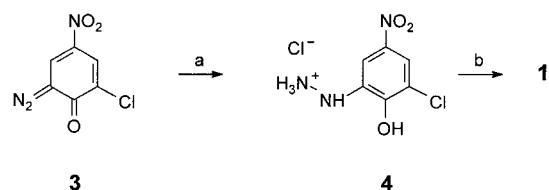
was identified as 2-chloro-4-nitrophenol from the spectroscopic data and by direct GC/MS comparison.^[2] Analysis of the extract by atomic absorption spectroscopy (AAS) and UV/Vis spectrometry indicate that **2** occurs mainly as its potassium salt, which explains the yellow color of the solution. 2-Chloro-4-nitrophenol (**2**) is a fungicide^[3a] which was used previously for seed protection^[3b] and the conservation of leather.^[3c] The compound has not yet been described as a natural product.

2-Chloro-4-nitrophenol (**2**) was always present in the raw extracts of fruit bodies that were either stored in the refrigerator, dried, or crushed before extraction. The amount of **2** can exceed 2% of the dry weight. In contrast, the extraction of young uninjured fruit bodies with methanol immediately after harvesting yields only pigment **1**, which must be isolated instantly by preparative HPLC in order to avoid decomposition to **2**.

The ¹H NMR spectrum of **1** shows only two doublets (⁴J(H,H) = 3 Hz) in the aromatic region. Thus, in comparison to **2**, the pigment must bear an additional substituent at C6. In addition, a CH₂CH₂ group can be recognized which, according to the HMBC spectrum, is flanked by two COX groups. The

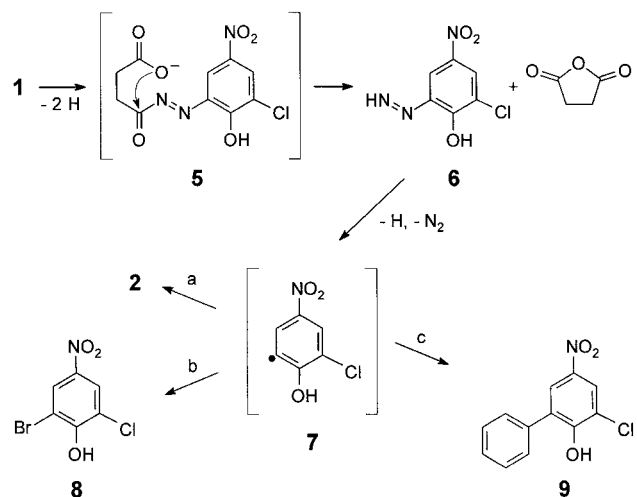
molecular mass of **1** was determined as *M_r* = 303 (ref. to ³⁵Cl) by LC/(–)-ESI-MS.^[4] The key ion at *m/z* 116 indicates that one of the carbonyl groups of the succinic acid unit is present as an amide. These facts allow the structure **1** to be deduced for the pigment, for which the name stephanosporin is proposed (Scheme 1). Like the phenol **2**, stephanosporin is present in the mushroom mainly in the form of its potassium salt, which explains the orange color of the fruit bodies.

Structure **1** was confirmed by synthesis (Scheme 2). It started from 6-chloro-4-nitro-1,2-quinone-2-diazide^[5a] (**3**), which had already been prepared by Griess.^[5b] Reduction of **3** with tin(II) chloride afforded the hydrochloride salt of 2-chloro-6-hydrazino-4-nitrophenol (**4**) which underwent reaction with succinic anhydride and triethylamine to furnish stephanosporin (**1**).



Scheme 2. Synthesis of stephanosporin (**1**). a) SnCl₂, HCl, HOAc, 0 °C, 77 %; b) succinic anhydride, NEt₃, MeOH, 25 °C, 70 %.

The oxidative transformation of stephanosporin (**1**) into 2-chloro-4-nitrophenol (**2**) is an enzymatic process induced by injury of the fruit body. It may be explained by a reaction cascade which starts by oxidation of **1** to the acyldiazene **5**. Intramolecular attack of the carboxylate ion at the activated carbonyl group^[6, 7a] then leads to the formation of succinic anhydride and 2-chloro-6-diazenyl-4-nitrophenol (**6**). Compounds of this type are known to decompose into nitrogen and an aryl radical by a one-electron transfer mechanism.^[8] In the last step, the radical **7** is converted into 2-chloro-4-nitrophenol (**2**) by abstraction of a hydrogen atom (Scheme 3, route a).



Scheme 3. Generation of 2-chloro-4-nitrophenol (**2**), 2-bromo-6-chloro-4-nitrophenol (**8**), and 3-chloro-5-nitro-2-biphenylol (**9**) from stephanosporin (**1**): a) enzymatic in the mushroom, or CAN (3 equiv), MeOH, 5 min, RT, 77 %; b) CAN (3 equiv), CBrCl₃/MeOH 2/1, 5 min, RT, 59 %; c) CAN (3 equiv), benzene/MeOH 2/1, 5 min, RT, 20 %. Concentration of **1** 25 mM each. CAN = cerium(IV) ammonium nitrate.

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The same degradation can be achieved *in vitro* by oxidation of **1** with salts such as cerium(IV) ammonium nitrate, iron(III) nitrate, or manganese(III) acetate in methanol or tetrahydrofuran.^[9] In these cases, succinic anhydride was detected by GC/MS. When the oxidation was carried out in the presence of bromotrichloromethane (route b), 2-bromo-6-chloro-4-nitrophenol (**8**) was obtained, while benzene (route c) furnished 3-chloro-5-nitro-2-biphenylol (**9**). These results are in accordance with the intermediate formation of an aryl radical (Scheme 3). The loss of the side chain in stephanosporin is comparable with the use of "traceless" hydrazide anchors in solid-phase synthesis.^[10]

Since 2-chloro-4-nitrophenol (**2**) has antibiotic properties, its enzymatic generation from precursor **1** by injury of the fruit bodies may serve the mushroom as a defense mechanism. It is interesting that *N*-aryl-*N'*-succinylhydrazines of the stephanosporin type have been patented as fungicides.^[11, 12] Moreover, an *N*-succinylphenylhydrazine group plays a crucial role in the action of the antibiotic spinamycin.^[7]

In addition to **1** and **2**, *St. caroticolor* contains 4-hydroxyacetanilide (paracetamol), 4-amino-2-chlorophenol, and 4-nitrophenol. The compounds were identified by GC/MS analysis and by comparison with authentic samples. Further investigations are required to clarify their possible role in the biosynthesis of **1**.

Interestingly, we have also found 4-nitrophenol and traces of 2-chloro-4-nitrophenol in the orange-yellow resupinate fruit bodies of *Lindtneria trachyspora* (BOURD. & GALZ.) PIL.^[13] This observation supports Oberwinkler and Horak's^[14] inclusion of *Stephanospora* and *Lindtneria* into their own family Stephanosporaceae. It is unknown, however, whether the nitrophenols in *Lindtneria* are generated from "traceless" precursors.

Experimental Section

Isolation of 1 (dipotassium salt): Two fruit bodies of *St. caroticolor* were detected on September 10th 1999 in a mixed forest near the Pupplinger Au, Wolfratshausen (Oberbayern). The fruit bodies (fresh weight approximately 3 g) were extracted instantly with MeOH (20 mL). The extract was pre-purified by solid-phase extraction (RP18) and the solvent removed *in vacuo*. The residue was dissolved in MeOH (0.5 mL) and purified by preparative HPLC (column: 25 × 2 cm, 7 μm, RP18) using MeOH/H₂O as the solvent system (linear gradient: from 100 % water to 100 % MeOH in 40 min); *R*_f = 15.9 min; yield: about 3 mg. LC/(-)-ESI-MS: *m/z* (%): 304 (28), 302 (100) [*M* - H]⁻; LC/(-)-ESI-MSMS (parent ion *m/z*: 302, 20 eV): *m/z* (%): 302 (0.2) [*M* - H]⁻, 266 (9) [*M* - H - HCl]⁻, 202 (28) [2-chloro-6-hydrazino-4-nitrophenol - H]⁻, 186 (10), 156 (9) [2-chloro-6-hydrazinophenol - H]⁻, 154 (9), 116 (100) [succinic acid monoamide - H]⁻, 98 (16) [succinimide - H]⁻; ¹H NMR (600 MHz, CD₃OD, reference: δ = 3.31, 25 °C): δ = 2.59 (m, 2H, CH₂CO₂⁻), 2.60 (m, 2H, CH₂CONH), 7.42 (d, ⁴*J*(H,H) = 3.0 Hz, 1H, H5), 7.79 (d, ⁴*J*(H,H) = 3.0 Hz, 1H, H3); ¹³C NMR (151 MHz, CD₃OD, reference: δ = 49.0, 25 °C): δ = 30.8 (CH₂CO₂⁻), 32.0 (CH₂CONH), 106.0 (C5), 119.7 (C3), 121.2 (C2), 135.7 (C4), 140.8 (C6), 158.9 (C1), 174.8 (CONH), 178.1 (CO₂⁻). **2** (potassium salt): *R*_f = 30.5 min.

4: A solution of SnCl₂ · 2H₂O (6.77 g, 30.0 mmol) in concentrated hydrochloric acid (7 mL) was added dropwise at 0 °C to a solution of **3**^[5a] (2.99 g, 15.0 mmol) in acetic acid (15 mL) and concentrated hydrochloric acid (15 mL). The precipitated product was filtered off, washed several times with half concentrated hydrochloric acid, and then with diethyl ether. Drying the product in a vacuum yielded 2.77 g of **4** (11.5 mmol, 77 %) as a greyish brown solid. Decomposition on heating: ¹H NMR (300 MHz, CD₃OD, 25 °C): δ = 7.88 (d, ⁴*J*(H,H) = 2.6 Hz, 1H), 8.00 (d, ⁴*J*(H,H) =

2.6 Hz, 1H); ¹³C NMR (75 MHz, CD₃OD, 25 °C): δ = 109.3, 120.3, 121.5, 136.3, 141.8, 149.2.

1: Triethylamine (0.46 mL, 3.3 mmol) was added dropwise to a stirred solution of succinic anhydride (0.330 g, 3.30 mmol) and 2-chloro-6-hydrazino-4-nitrophenol hydrochloride (**4**; 0.720 g, 3.00 mmol) in MeOH (7 mL). The mixture was then acidified with 2N HCl and diluted with water (15 mL). After several hours, the yellow precipitate was filtered off, washed with water, and dried *in vacuo*. Yield: 0.638 g (2.10 mmol, 70 %). M.p. 191–194 °C (decomp); UV/Vis (MeOH) λ_{max} (ε): 226 (11 925), 258 (12 579), 312 (4738), 351 nm (3751, sh); ¹H NMR (300 MHz, CD₃OD, 25 °C): δ = 2.63 (m, 4H, CH₂CH₂), 7.55 (d, 1H, ⁴*J*(H,H) = 2.5 Hz, H5), 7.71 (d, 1H, ⁴*J*(H,H) = 2.5 Hz, H3); ¹³C NMR (75 MHz, CD₃OD, 25 °C): δ = 29.5 (CH₂CO₂H), 29.7 (CH₂CONH), 106.5 (C5), 116.8 (C3), 120.5 (C2), 140.3 (C6), 142.3 (C4), 147.2 (C1), 174.6 (CONH), 176.0 (CO₂H); elemental analysis calcd for C₁₀H₁₀ClN₃O₆: C 39.55, H 3.32, Cl 11.68, N 13.84; found: C 39.55, H 3.31, Cl 11.47, N 13.70.

1 (dipotassium salt): A 1.0M solution of KOtBu in THF (0.55 mL, 0.55 mmol) was added dropwise to **1** (76 mg, 0.25 mmol) in dry THF (1 mL). The red precipitate was filtered off, washed several times with THF and once with EtOH, and dried *in vacuo*. Yield: 86 mg (0.23 mmol, 90 %). The spectroscopic data were in accordance with those of the natural compound.

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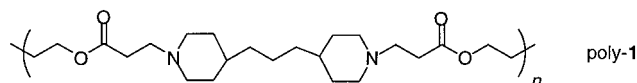
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pH-Responsive Polymer Microspheres: Rapid Release of Encapsulated Material within the Range of Intracellular pH**

David M. Lynn, Mansoor M. Amiji, and Robert Langer*

Microparticles formed from biodegradable polymers are attractive for use as delivery devices, and a variety of polymer-based microspheres have been employed for the sustained release of therapeutic compounds.^[1, 2] However, for small-molecule, protein, and DNA-based therapeutics that require intracellular administration and trafficking to the cytoplasm, there is an increasing demand for new materials that facilitate triggered release in response to environmental stimuli such as pH.^[3] Following endocytosis or phagocytosis, for example, the pH within endosomal compartments is reduced and foreign material is degraded upon fusion with lysosomal vesicles.^[4] New materials that release molecular payloads rapidly upon changes in pH within the intracellular range and facilitate escape from hostile environments could have a broad-reaching impact on the administration of therapeutic compounds for intracellular targets.^[3, 4]

We recently reported the synthesis of poly(β -amino ester) **1**.^[5] The solubility profile of this hydrolytically degradable polymer is directly influenced by solution pH. Specifically, the



solid, unprotonated polymer is insoluble in aqueous media in the pH range 7.0 to 7.4, and the transition between solubility and insolubility occurs at a pH near 6.5. Based on the differences between extracellular and endosomal/lysosomal pH (7.4 and 5.0–6.5, respectively), we hypothesized that microspheres formed from poly-**1** might be useful for the encapsulation and release of compounds in the intracellular pH range. Choy et al. recently reported that inorganic clays

can enhance the trafficking of oligonucleotides to the cytoplasm by dissolution of the inorganic matrix within acidic intracellular environments.^[6] This work demonstrates that new materials incorporating such pH/solubility profiles could have an impact on localized intracellular delivery. Herein, we report that microspheres formed from poly-**1** release their encapsulated contents rapidly and quantitatively in the range of intracellular pH values. The size distribution of the spheres considered here (4–6 μm) renders them suitable for delivery to phagocytotic cells such as macrophages, and preliminary evidence suggesting the internalization and processing of poly-**1** microspheres by macrophages is presented.

The encapsulation of water-soluble therapeutic compounds within polymer microspheres is often achieved by employing a double emulsion process.^[7] The double emulsion process is well established for the fabrication of microspheres from hydrophobic polymers such as poly(lactic-co-glycolic acid) (PLGA), a biodegradable polymer conventionally employed in the development of drug delivery devices.^[2] Preliminary experiments demonstrated the feasibility of the double emulsion process for the encapsulation of water-soluble compounds using poly-**1**. Rhodamine-conjugated dextran was chosen as a model for subsequent encapsulation and release studies for several reasons: 1) rhodamine is fluorescent, thus allowing loading and release profiles to be determined by fluorescence spectroscopy, 2) loaded microspheres could be used to monitor cell uptake directly by confocal microscopy, and 3) the fluorescence intensity of rhodamine is relatively unaffected by pH values within the physiological range.^[8]

Microspheres encapsulating labeled dextran were fabricated from poly-**1** and compared to controls formed from PLGA. The size distributions of microspheres formed from poly-**1** correlated well with the distributions of PLGA microspheres within the range of 5–30 μm , and average particle sizes could be controlled by variations in the experimental parameters, such as homogenization rates and aqueous/organic solvent ratios.^[7] In early experiments, microspheres formed from poly-**1** aggregated extensively during centrifugation and washing steps, and scanning electron microscopy (SEM) images revealed clusters of spheres that appeared to be physically joined or “welded” (data not shown). The observed aggregation was related to the removal of the stabilizing poly(vinyl alcohol) (PVA) employed in the double emulsion procedure (see Experimental Section), as suspensions isolated using 0.5% PVA solutions could be centrifuged/washed as many as four times with no observed aggregation.

We considered the possibility that residual solvent contained within poly-**1** microspheres could contribute to the observed aggregation. Although isolation was carried out below the glass transition temperature (T_g) of poly-**1** ($T_g = 49.8^\circ\text{C}$),^[9] this parameter does not apply directly under the conditions to which the microspheres are exposed during fabrication and isolation. In the later stages of the “hardening” process, for example, the microspheres may be assumed to contain residual CH_2Cl_2 or small amounts of water that could act to increase the tackiness of the polymer matrix. Extended drying times and the application of a dynamic vacuum to ensure complete removal of the organic solvent

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prior to centrifugation did not eliminate particle aggregation. However, aggregation could be essentially eliminated if centrifugation and washing were conducted at reduced temperatures (4 °C). Aqueous suspensions of poly-1 microspheres isolated under these conditions consisted primarily of single, unaggregated microspheres, as determined by optical and fluorescence microscopy. Microspheres in the range of 4–6 μm were essentially free of cracks, holes, and other defects, as determined by SEM (Figure 1).

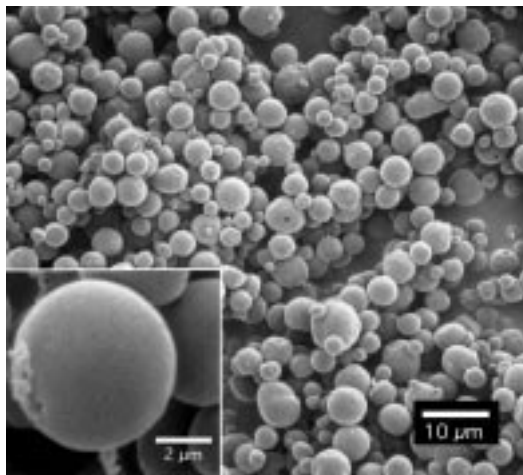
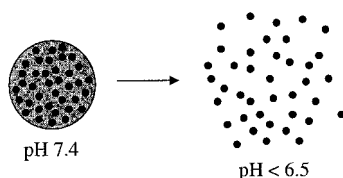


Figure 1. SEM image of rhodamine/dextran-loaded microspheres fabricated from poly-1.

Poly-1 microspheres suspended at pH 7.4 remained intact and stable toward aggregation (by visual inspection), but the spheres dissolved instantly when the pH of the suspending medium was lowered to between 5.1 and 6.5 (Scheme 1). The



Scheme 1.

release of labeled dextran from poly-1 microspheres was determined quantitatively by fluorescence microscopy (Figure 2). The release profile at pH 7.4 was characterized by a small initial burst in fluorescence (7–8%) which reached a limiting value of about 15% after 48 h. This experiment demonstrated that the degradation of poly-1 was relatively slow under these conditions and that 85–90% of encapsulated material could be retained in the polymer matrix for suitably long periods of time at physiological pH values.

The application of poly-1 microspheres to the triggered release of encapsulated drugs in the endosomal/lysosomal pH range was examined by conducting a similar experiment in which the pH of the suspension medium was changed from 7.4 to 5.1 during the course of the experiment. As shown in Figure 2, the microspheres dissolved rapidly when the suspension buffer was exchanged with acetate buffer (0.1M,

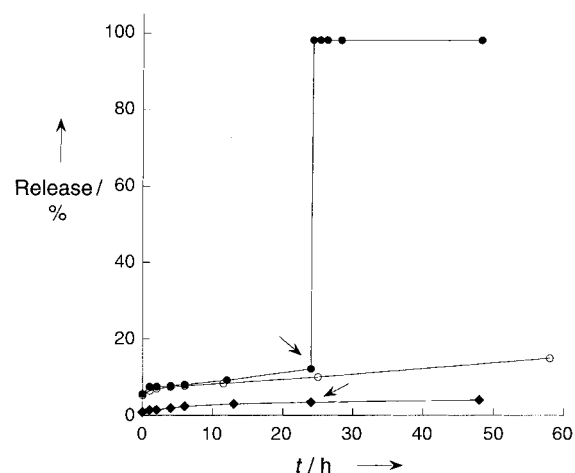


Figure 2. Release profiles of rhodamine/dextran from poly-1 and PLGA microspheres at various pH values ($\circ$, poly-1 (pH 7.4); $\bullet$, poly-1 (pH 7.5/5.1); $\blacklozenge$, PLGA (pH 7.4/5.1)). The arrows indicate the points at which HEPES buffer (pH 7.4) was exchanged with acetate buffer (pH 5.1) (HEPES = 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid).

pH 5.1), and resulted in instantaneous and quantitative release of the labeled dextran remaining in the polymer matrices. By contrast, the release from dextran-loaded PLGA microspheres did not increase for up to 24 h after the pH of the suspending medium was lowered (Figure 2). Figure 3 shows fluorescence microscopy images of a sample of dextran-loaded microspheres at pH 7.4, and a sample to which a drop of acetate buffer was added at the upper right edge of the microscope coverslip. The rapid release of rhodamine-conjugated dextran was visualized as streaks extending from the dissolving microspheres in the direction of the diffusion of

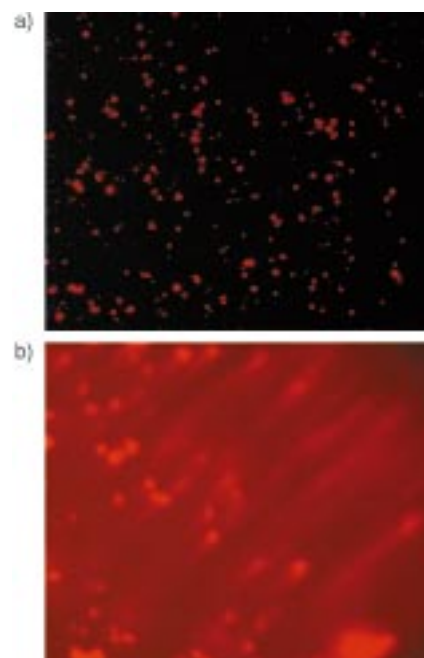


Figure 3. a) Representative fluorescence microscopy image of rhodamine/dextran-loaded poly-1 microspheres suspended in HEPES buffer (pH 7.4). b) Sample of loaded poly-1 microspheres at pH 7.4 after addition of acetate buffer (pH 5.1). The direction of diffusion of acid is from the top right to the bottom left of the image (elapsed time: ca. 5 s).

added acid and an overall increase in background fluorescence.

Both cell membrane translocation and escape from acidic intracellular vesicles represent substantial obstacles to efficient delivery by endocytosis or phagocytosis.^[4] One recent approach to facilitating endosomal and/or lysosomal escape is the incorporation of weak bases, or “proton sponges”, which are believed to buffer acidic endosomal environments and disrupt membranes by increasing the internal osmotic pressure within the vesicle.^[10] Poly-1 microspheres release encapsulated material in the endosomal pH range through a mechanism (dissolution) that involves the protonation of amines in the polymer matrix. Thus, it is possible that poly-1 microspheres could also incorporate a membrane-disrupting means of endosomal escape and prolong the lifetimes of hydrolytically unstable therapeutics.

The microspheres investigated in this current study fall within the size range commonly used to target delivery to macrophages,^[1c] and we have initiated particle uptake experiments employing the P388D1 macrophage cell line. The confocal microscopy image in Figure 4a demonstrates that particles formed from poly-1 can be internalized by phagocytosis and suggest that particle rupture occurs more readily (Figure 4b, taken 18 h after particle addition) inside the cell than for PLGA microspheres (no particle rupture observed after 18 h, data not shown).

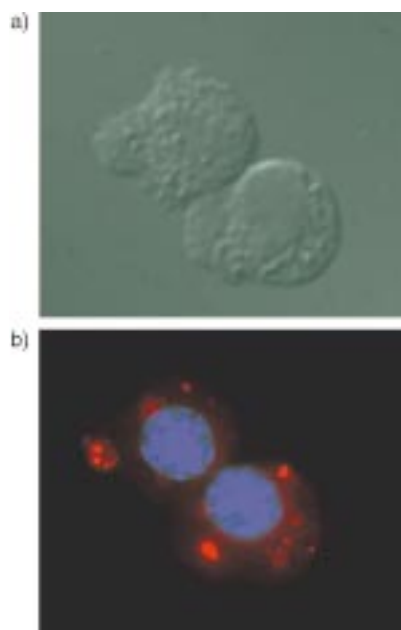


Figure 4. Confocal microscopy images of P388D1 macrophages 18 h after addition of poly-1 microspheres. a) Differential interference contrast image of fixed cells, and b) overlayed confocal microscopy images (red = rhodamine/dextran; blue = DAPI nuclear stain).

The proof-of-concept experiments described above demonstrate that poly-1 can be used to encapsulate a water-soluble polymer, retain the material at extracellular or cytoplasmic pH values, and release the encapsulated contents in the range of endosomal/lysosomal pH values. Preliminary data also suggest that these microspheres can be internalized

and “digested” by macrophages. The incorporation of degradable, pH-sensitive materials such as poly-1 could be useful in the design of new DNA-based vaccine formulations targeted to macrophages, several of which currently employ PLGA as an encapsulating material.^[11] To this end, we are pursuing studies related to the encapsulation of DNA employing poly-1. The incorporation of additional design criteria (for example, smaller particle sizes, surface characteristics, targeting moieties) may yield particles useful for the targeting of smaller, somatic cells that internalize particles by endocytosis. Such particles could represent an important addition to the arsenal of materials applied to intracellular drug delivery, such as pH-responsive polymer/liposome formulations.^[3]

Experimental Section

Fabrication of microspheres: The optimized procedure for the fabrication of microspheres was conducted in the following general manner: An aqueous solution of rhodamine-conjugated dextran (200 μ L of a 10 μ g μ L⁻¹ solution, $M_n \approx 70$ kD) was suspended in a solution of poly-1 in CH_2Cl_2 (200 mg of 1 in 4 mL of CH_2Cl_2 , $M_n \approx 10$ kD), and the mixture was sonicated for 10 s to form a primary emulsion. The cloudy pink emulsion was added directly to a rapidly homogenized (5000 rpm) solution of poly(vinyl alcohol) (50 mL, 1% PVA (w/w)) to form the secondary emulsion. The secondary emulsion was homogenized for 30 s before adding it to a second aqueous PVA solution (100 mL, 0.5% PVA (w/w)). Direct analysis of the microsphere suspension using a Coulter microparticle analyzer revealed a mean particle size of approximately 5 μ m. The secondary emulsion was stirred for 2.5 h at room temperature, transferred to a cold room (4 °C), and stirred for an additional 30 min. The microspheres were isolated at 4 °C by centrifugation, resuspended in cold water, and centrifuged again to remove excess PVA. The spheres were resuspended in water (15 mL) and lyophilized to yield a pink, fluffy powder. Characterization of the lyophilized microspheres was performed by optical, fluorescence, and scanning electron microscopies as described in the text.

Confocal microscopy imaging: P388D1 macrophages were seeded onto fibronectin-coated cover slips in a 6-well cell culture plate at an initial seeding density of 200 000 cells per well, and the cells were incubated overnight. Poly-1 microspheres and PLGA microspheres encapsulating rhodamine-labeled dextran (average diameter = 4–6 μ m) were added to each well to give final microsphere concentrations of 5 and 10 μ g mL⁻¹. Samples were incubated for 18 h, washed three times with PBS buffer, and fixed with formalin. Each cover slip was mounted on a glass slide using mounting medium containing DAPI as a nuclear stain, and the samples were analyzed by confocal microscopy.

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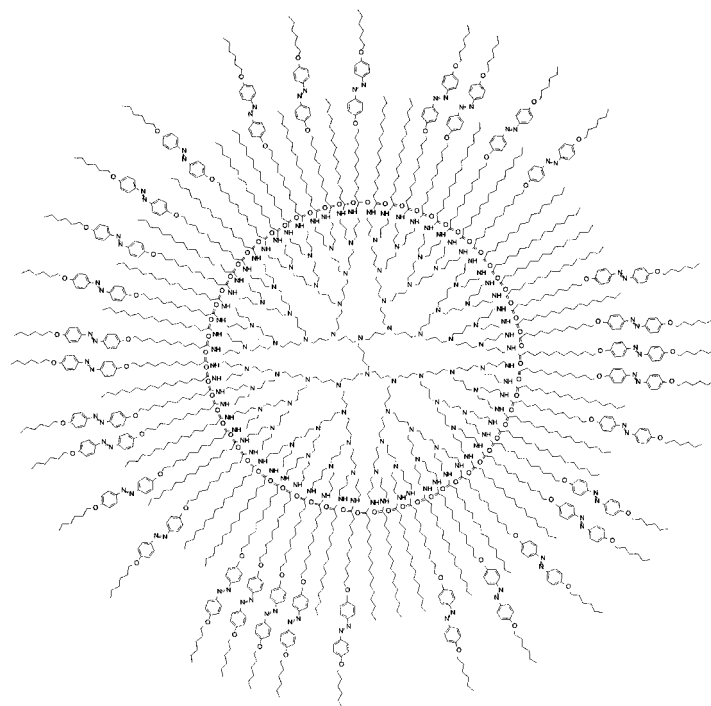
Merging of Hard Spheres by Phototriggered Micromanipulation**

Georg C. Dol, Kenji Tsuda, Jan-Willem Weener, Marcel J. Bartels, Theodor Asavei, Thomas Gensch, Johan Hofkens, Loredana Latterini, Albert P. H. J. Schenning, Bert W. Meijer, and Frans C. De Schryver*

Amphiphilic dendrimers, namely those that carry both hydrophobic and hydrophilic regions within one molecule, tend to self-assemble into a large variety of different aggregates depending on their structure. The dendritic amphiphiles investigated so far include unimolecular micelles,^[1] bolaamphiphiles,^[2] dendronized polymers,^[3] super-amphiphiles,^[4] and various other AB and ABA block copolymers.^[5] Poly(propyleneimine) dendrimers modified with aliphatic end groups proved to be extremely flexible. Protonation of the amine core (for example, by water) resulted in these dendrimers acting as amphiphiles in which all (64 for the fifth generation) the aliphatic tails point to one side while the dendrimer core adjusts its conformation to form a nearly flat structure.^[1f] Recently, the use of photoresponsive (dendritic) building blocks, obtained through the incorporation of azobenzene units, led to the formation of photo-switchable monolayers, whose macroscopic properties could be completely controlled by irradiation.^[6] Here we describe

how the use of amphiphilic azobenzene-modified dendrimers can give rise to the formation of photoresponsive supramolecular assemblies. With the aid of micromanipulation techniques, these well-defined supramolecular aggregates of dendrimers were subsequently used as secondary building blocks in the formation of even larger objects, with dimensions in the micrometer regime. Consequently, the structures ultimately obtained are the result of tuning at three different length scales.

We will focus on the fifth generation azobenzene-containing alkyl-modified poly(propyleneimine) dendrimer **1** (Scheme 1), an amphiphilic blockcopolymer with a random



Scheme 1. Schematic representation of azobenzene-modified dendrimer **1**, to illustrate the random character of the attachment of the azobenzene and palmitoyl units at the rim of the dendrimer.

shell structure that carries on average 32 azobenzene groups and 32 palmitoyl groups.^[7] Although a statistical distribution of the two different groups is obtained, as determined by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) analyses, which implicates a random positioning of these groups, the dendritic scaffold remains monodisperse.

Dendrimer **1** is molecularly dissolved in organic solvents such as tetrahydrofuran (THF) or chloroform, and displays reversible *cis*–*trans* isomerization upon excitation with light with a wavelength of 365 nm. Injection of concentrated solutions of **1** in THF into water (pH 1–8) at 333 K results directly in the formation of opalescent solutions containing vesicles. These vesicles were subsequently investigated by transmission microscopy (TM), scanning fluorescence microscopy (SFM), confocal scanning fluorescence microscopy (CSFM),^[8] atomic force microscopy (AFM),^[9] scanning electron microscopy (SEM), and cryo-transmission electron microscopy (Cryo-TEM).^[10] Transmission microscopy reveals

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the existence of micrometer-sized spherical objects (Figure 1a) that are also visible as bright circular features by SFM using blue light (420–488 nm) for excitation (Figure 1b). The diameters of these objects estimated by both techniques are identical and are all in the 400 nm–20 μm range. Samples containing different size distributions of vesicles could be obtained by microfiltration through regen-

erated cellulose membrane filters with various pore sizes (0.45, 1, 5 μm).

The AFM and SEM images taken on isolated vesicles obtained from drop-cast, aqueous solutions still show the existence of spheres and oblates in the absence of water (Figure 1c–e), thus confirming the self-stabilizing character of the assemblies. Consecutive AFM scans on the same giant vesicle yielded identical images without significant alteration of the topographic properties. Additional evidence for the stability of these vesicles was obtained by monitoring the change in the turbidity of the vesicle dispersion at $\lambda = 625$ nm on the addition of ethanol. An enhanced stability, relative to that of polymerized vesicle dispersions, was concluded from the observation that the vesicles were stable up to at least 30 vol % of added ethanol.^[11]

Cryo-TEM and small-angle X-ray scattering revealed the existence of vesicles with a multilaminar, onionlike architecture, from which a bilayer thickness of 5 nm could be estimated (Figure 1f). An interdigitated bilayer structure is proposed (Figure 1g) in which the polar dendrimer part faces the aqueous phase in a highly flattened conformation.^[7] Computational modeling yielded a length of 32 Å for an alkyl chain containing a *trans*-azobenzene unit and 22 Å for a fully extended palmitoyl chain, and, hence, confirms this arrangement. Additional information on the interdigitated layer structure and stacking of the azobenzene moieties was obtained from the absorption and emission spectra of the vesicles.^[12–14] A fraction of the azobenzene units within the giant vesicles could be isomerized from the *trans* to the *cis* conformation (360 nm, 2 mW cm^{−2}), which indicates that the bilayer structure has sufficient free volume.

CSFM measurements taken on giant vesicles in water confirmed their globular nature and showed there was fluorescence in all the nodal planes through the objects. This latter observation indicates the vesicles are solid spheres, since a series of CSFM images along the axis of the irradiating light gives direct access to the three-dimensional shape of the object as well as the distribution of the fluorescence intensity.^[15, 16]

Micromanipulation of the vesicles formed by compound **1** is readily achieved by optical trapping.^[17] In this technique, an object is forced to stay near to the focal point of a highly focused, nonabsorbed beam of light.^[18–21] Figure 2a displays the TM image which shows a trapped vesicle (encircled), and two vesicles that are immobilized by simple deposition on the surface of the cover glass. In the next images the microscopy stage is moved to the left, and consequently one of the immobilized vesicles hits the trapped vesicle (Figure 2b). The momentum of the immobilized vesicle is large enough to force the trapped vesicle from its original position in a billiardlike fashion. The force acting is in the range of several piconewtons.^[22–24] Figure 2c clearly shows the displacement of the formerly trapped vesicle, its position is now on the far left of the image. The vesicles still behaved like hard spheres when the microscopy stage was moved at a lower velocity. In these experiments (results not shown) the immobilized vesicle slightly lifted the trapped vesicle. This effect could be observed in the TM image as a change in the contrast of the trapped vesicle. Additional translation of the microscopy

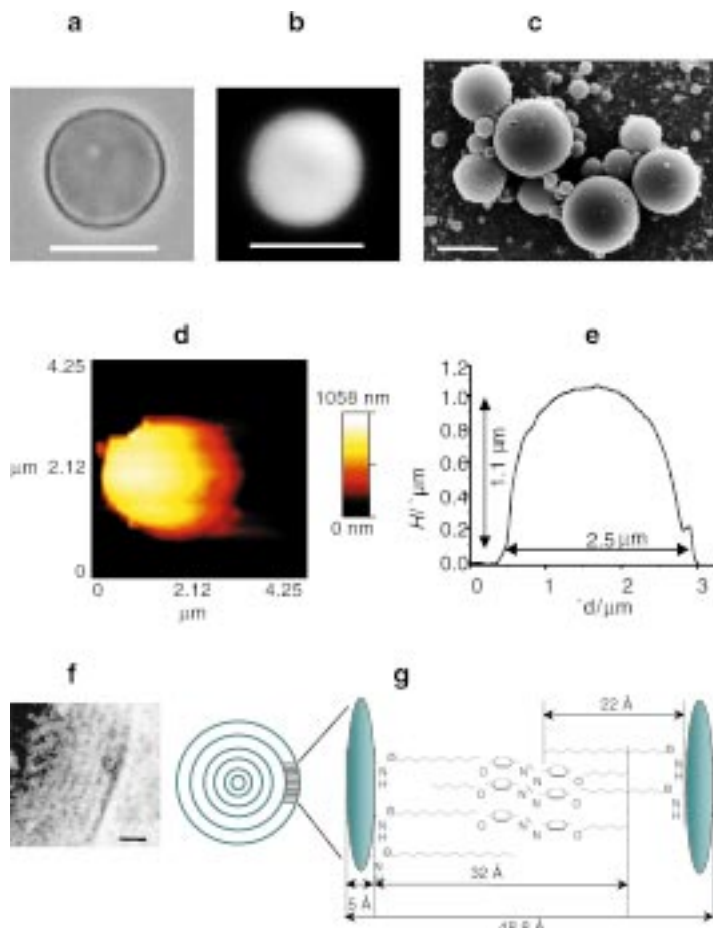


Figure 1. a) Representative TM image of a giant vesicle, which illustrates the spherical structure of the aggregate. A $100\times$, 1.3 N.A. oil immersion lens was used in the microscope for imaging. The size of the scale bar is 5 μm . b) CSFM image of the vesicle depicted in (a). The fluorescence originates from stacked azobenzene moieties in the bilayer structure (see (g) for a schematic representation). The size of the vesicle obtained from CSFM (5 μm) is identical to that of the TM image in (a). The power of the light (420 nm) was $P_{420} = 25$ kW cm^{−2}. c) SEM image of a solvent-cast vesicle solution, which shows vesicles of several sizes. The size of the scale bar is 5 μm . d) Noncontact-mode AFM image of a single vesicle deposited on glass. The image was recorded in the noncontact detection mode using an AFM microscope (Lumina, Topometrix Inc.) with amplitude detection (a commercially available high resonance frequency cantilever was used). The shadow observed on the right of the AFM image is an imaging artifact along the scanning direction (left-to-right). The AFM tip cannot follow the profile at the back edge of the structure because of the sharp topography of the object. e) AFM height profile of the vesicle. The height profile shows that the vesicles residing on the glass surface deform. The width is now roughly twice the height (2 and 1 μm , respectively). f) Cryo-TEM image of a vesicle revealing a clear layered structure. The layer spacing is approximately 5 nm (see also (g)). The size of the scale bar is 12 nm. g) Schematic representation of the interdigitated bilayer based on small-angle X-ray and Cryo-TEM measurements. Additional data from fluorescence measurements proved the presence of stacked azobenzene moieties.^[6]

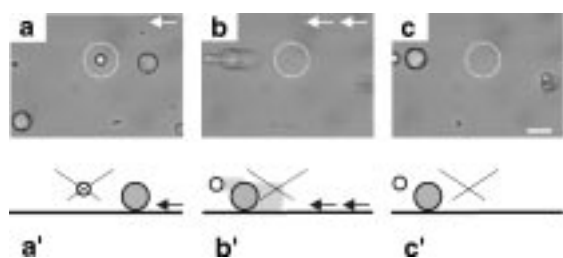


Figure 2. a) TM image of a trapped vesicle (encircled) and two immobilized vesicles. Movement of the sample stage to the left, results in a concurrent motion of the immobilized vesicles. b) On translation of the stage at a high velocity, the trapped vesicle is forced from the trap in a billiardlike fashion. c) This TM image clearly shows the displacement of the previously trapped vesicle. In all images, the dashed circle indicates the position of the trapping beam. a')–c') are schematic representations of the events in (a)–(c). The size of the scale bar is 10 μm . A $100\times$, 1.3 N.A. oil immersion lens was used with $P_{1064} = 25 \text{ MW cm}^{-2}$ from a Nd-YAG laser.

stage resulted in a shift of the immobilized vesicle concurrent with the movement of the stage, whereas the trapped vesicle regained its original position. The behavior displayed in both these experiments is remarkably different from that of giant unilaminar vesicles investigated thus far which merge upon close contact,^[25] whereas the vesicles of compound **1** act like hard spheres. The hard-sphere behavior of the vesicles is proposed to result from the unique character of the dendritic building blocks, which can be viewed as oligomeric, head-group-polymerized entities (Figure 1g).

Partial merging of the vesicles can be achieved by local irradiation at the interface of two “touching” vesicles with light with a wavelength of 420 nm (Figure 3). Figure 3a displays two separated vesicles from which the one in the center is optically trapped and therefore bright, while the deposited vesicles, being out of the confocal plane, are seen as opaque. In Figure 3b, the immobilized vesicle is forced against the trapped vesicle. After irradiation with light with a wavelength of 420 nm, both vesicles move concurrently with the cover glass (Figure 3c). Separation of the two vesicles by trapping the top vesicle and movement of the sample stage proved impossible, even when a trapping power of 250 MW cm^{-2} was used. The CSFM images of the product displayed fluorescence in every nodal plane, including the interface of the two vesicles (Figure 3d). Presumably, irradiation with light with a wavelength of 420 nm leads to local disruptions of the bilayer through isomerization of azobenzene,^[12] which induces fusion of the outer bilayers of the two vesicles (Figure 3e).

A similar approach was applied to merge small vesicles ($<500 \text{ nm}$), which were obtained after filtering the parent dispersion through a filter with a pore size of $1 \mu\text{m}$. In this case, the highly focussed infrared beam forces the vesicles to accumulate near the focus of the beam which results in a very high, local concentration of vesicles in the optical trap.^[26–28] In accordance with the hard-sphere behavior of the vesicles, the formation of larger

structures did not occur, as evident by transmission microscopy. However, rod-shaped architectures could be obtained upon simultaneous irradiation with light having a wavelength of 420 nm (Figure 4a–4d). The largest rods found were $11 \mu\text{m}$ in length with a diameter of $1 \mu\text{m}$, which suggests that at least 10 vesicles were involved in the construction process. The size of the rods depends strongly on the irradiation time used (Figure 4e). The mechanical strength of the rods was tested by pulling the trapped end of a rod, which had been fixed with one end at the surface, until the rod was fully stretched. On further extension, the rod did not rupture, it just sprang from the trap. The rods could be fused to obtain larger rods using a similar strategy. This building process could be repeated several times to yield structures up to $20 \mu\text{m}$ in length.

We have shown that irradiation with focussed laser light having a wavelength of 420 nm introduces morphological changes in vesicles of compound **1** as a result of photoisomerization of the azobenzene moieties.^[12] These changes at the interface of two vesicles presumably lead to interdigitation of the outer layers, and in this fashion a superstructure consisting of several vesicles can be formed. In order to verify this hypothesis we performed similar micromanipulation experiments with two reference compounds: 1) dendrimers functionalized with palmitoyl chains only and 2) dendrimers functionalized entirely with azobenzene-containing alkyl chains. Merging was not observed in manipulation experi-

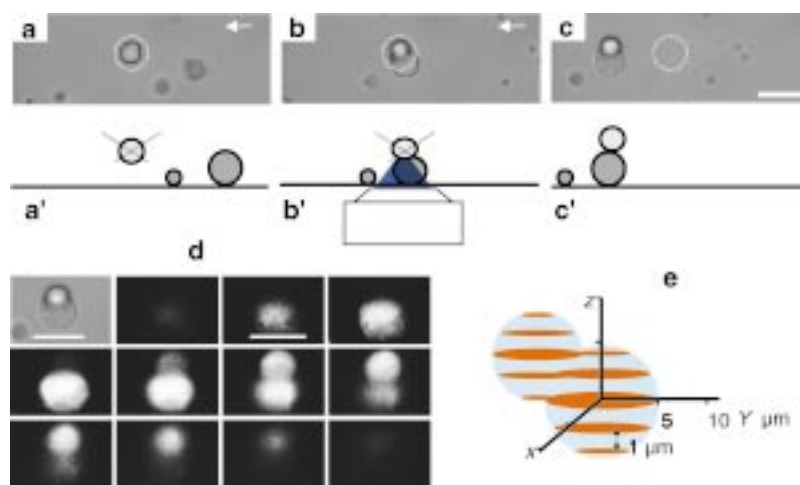


Figure 3. a) TM image of a trapped vesicle (central) floating above the surface of the cover glass, the others are immobilized on the surface. b) Movement of the sample stage to the left results in translation of the immobilized vesicles concurrent with the stage, whereas the trapped vesicle holds its position. The vesicles were kept in this position, and subsequently, the blue light was focussed at the interface of the contact pair. After irradiation for 10 min both lasers were blocked. c) The sample stage was moved to the right, which induced movement of both the immobilized vesicle and the previously trapped one, which proved that the vesicles had merged. The size of the scale bar is $10 \mu\text{m}$. a')–c') are schematic representations of the merging experiment. d) TM image (top left) and CSFM z slices, recorded after the merging experiment depicted in a)–c). The presence of fluorescence through the complete scan illustrates the existence of ordered azobenzene units within the multilaminar giant vesicle. The fluorescence at the interface of the merged vesicles is evidence for effective interdigitation of the outer layers of the vesicles. The size of the scale bars is $10 \mu\text{m}$, the thickness of each z slice is $1.5 \mu\text{m}$ and $P_{420} = 25 \text{ kW cm}^{-2}$. The apparent height is approximately $20\text{--}23 \mu\text{m}$. By using a calibration factor of $0.667 \mu\text{m}$ per z slice, a diameter of $13\text{--}15 \mu\text{m}$ is obtained, which is in good agreement with the estimated value from the individual vesicle dimensions. e) Cartoon of the CSFM experiment in (d), the red disks represent the confocal z slices.

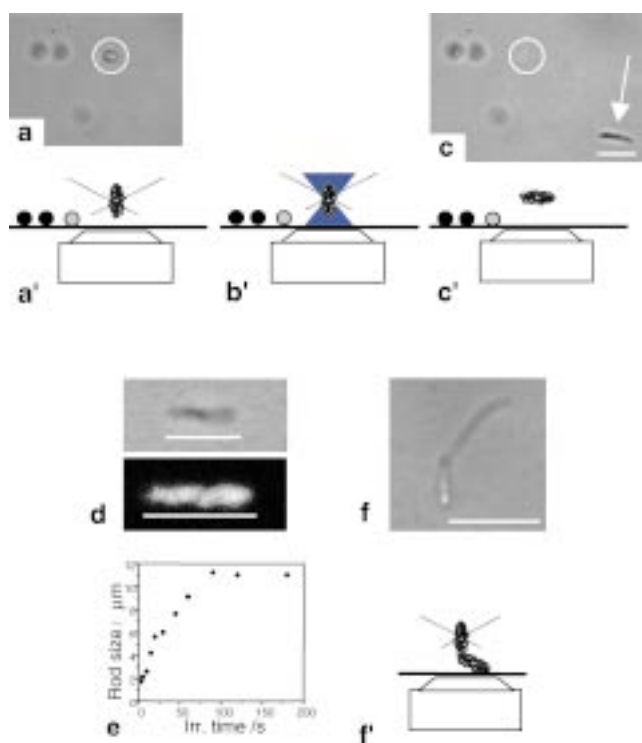


Figure 4. a), c) TM images, and schematic representations (a')–(c') of a merging experiment with small vesicles. In (a), many small vesicles are trapped, and the 420 nm wavelength laser is used subsequently to irradiate the vesicles (schematically represented in (b')). After irradiation both lasers were blocked, and the newly formed rod moves through the solution. The size of the rod is subsequently determined from the image in (c). The arrow points to the formed rod and the open circle indicates the position of the laser beams. In the cartoons (a')–(c'), the crossed, dashed lines indicate the focus of the trapping beam. d) Top: TM image, bottom: SFM image of a merging product. The size of the scale bars is 3.5 μm. Merging: $t_{\text{irr},420} = 30$ s. e) Plot of the irradiation time (t_{irr}) with light having a wavelength of 420 nm versus the size of the formed rods. The largest rod size found was approximately 11 μm. f) TM image and cartoon of a second merging experiment. The rod was attached onto the surface by descending the focus of the trapping beam until the lower part of the rod was in contact with the surface, thus inducing a fixation after a few seconds. Subsequent irradiation with light (420 nm) triggered a second rod to merge with the head of the immobilized one. The size of the scale bar is 5 μm, $t_{\text{irr},420} = 60$ s (twice). The same conditions were used in all experiments ($P_{420} = 25 \text{ kW cm}^{-2}$ and $P_{1064} = 25 \text{ MW cm}^{-2}$).

ments carried out with vesicles prepared from either of these reference dendrimers. In the first case this is the consequence of the absence of photoactive groups, whereas in the vesicles prepared from the second dendrimer the increased order reduces the free volume, and hence photoswitching is hampered. Although a precise molecular picture of the merging of **1** is still lacking, the following experiments show strong evidence for the necessity of a photoinduced process together with a local heating arising from the absorption of the infrared light by the overtone of water to obtain enough flexibility (the system is significantly below its glass-melting temperature T_g) for merging. Trapping the vesicles with IR laser light alone without irradiation at 450 nm does not lead to merging. In addition, performing the experiments in D_2O , where the local heating by IR absorption is absent as a result of a frequency shift of the overtone, also does not lead to merging on simultaneous irradiation with IR and UV light.

These results show that by careful design of the dendritic molecule the physical properties of the self-assembled structure can be tuned in such a way that phototriggered micro-manipulation and merging of hard spheres is possible. This possibility leads to the bottom-up synthesis of micrometer-sized objects through a combination of covalent synthesis and supramolecular organization followed by micromanipulation.

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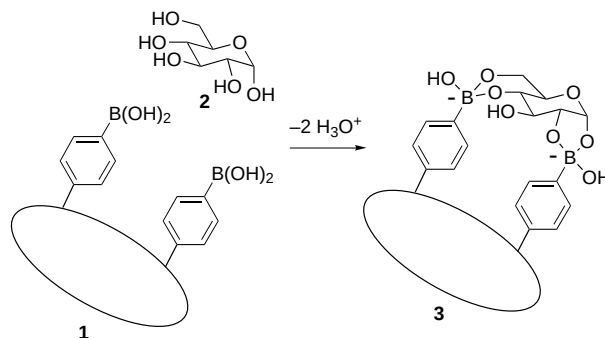
Computer-Guided Design in Molecular Recognition: Design and Synthesis of a Glucopyranose Receptor**

Wei Yang, Huan He, and Dale G. Drueckhammer*

The design of compounds which are capable of specific recognition of molecules and ions is a long-standing challenge in organic chemistry. In addition to its fundamental interest, this work is of increasing practical value in the development of chemosensors for compounds of biological and environmental importance^[1] and is a key element of biomimetic catalysis.^[2] The specific binding of one compound from a complex

mixture generally requires the interaction of multiple functional groups of the receptor with complementary functionality of the guest compound.^[3, 4] Good affinity and selectivity requires the precise placement of the recognition elements of the receptor in the proper position and orientation for optimal complementarity to the guest. Nature uses proteins (enzymes, antibodies, and other protein-based receptors) as a basis for specific receptors. Efforts to achieve specificity and affinity in smaller synthetic molecules has relied primarily on intuition for the identification of molecular scaffolds that would permit proper orientation of the functionality for molecular recognition. We envisioned that the computer program CAVEAT, developed by Bartlett and co-workers and previously utilized for the design of enzyme inhibitors and conformationally constrained peptides, could serve as a valuable tool for the discovery of molecular backbones for the orientation of functional groups for molecular recognition.^[5, 6] Described here is the demonstration of a CAVEAT-based design approach in the development of a glucopyranose receptor incorporating precisely positioned arylboronic acid groups as recognition elements.

Arylboronic acids have long been known to form stable complexes with sugars and other diols in aqueous solution.^[7] Numerous arylboronic acids have been prepared and studied as sugar receptors, and those incorporating fluorescent aryl groups have been explored as fluorescence-based sugar sensors.^[8–15] Of particular interest are glucose sensors for potential application in the maintenance of blood glucose levels in persons with diabetes.^[16, 17] However, the simple arylboronic acids form stable complexes with a variety of sugars and thus are not useful as specific receptors or sensors for a single sugar. Compounds have been prepared that contain a pair of arylboronic acid groups in somewhat flexible structures which form two cyclic boronates with a single sugar molecule.^[11–14] These bis-boronic acids, while not designed for complexation with a specific sugar, have demonstrated somewhat enhanced, though still modest, selectivity. A glucopyranose receptor **1** containing a pair of precisely positioned phenylboronic acid groups was chosen as an initial target for receptor design using CAVEAT (Scheme 1). The large oval structure in **1** represents a polycyclic organic framework to be identified using CAVEAT. Since glucopyranose **2** can form cyclic boronates between the α -1,2 and 4,6-hydroxy groups,^[14, 18] the receptor was designed to incorporate arylboronic acid groups in the proper relative position to form a



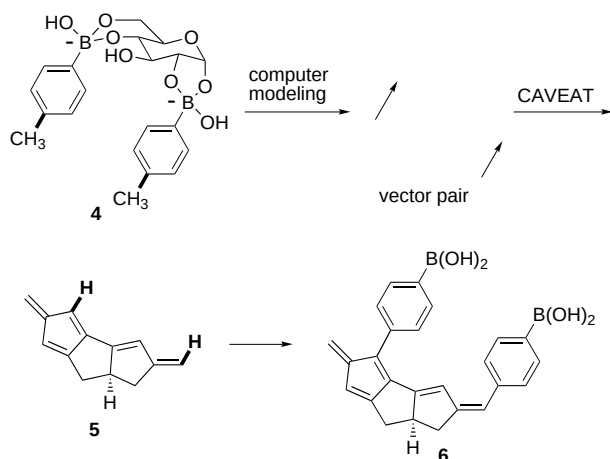
Scheme 1. Complex formation between glucose and a bis-arylboronic acid.

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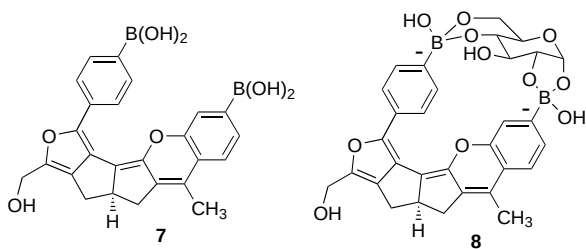
complex represented by structure **3**. This is in contrast to the simple arylboronic acids and the bis-arylboronic acids which form complexes in aqueous solution with the α -furanose form of glucose.^[14, 15]

The design approach for the receptor **1** is illustrated in Scheme 2. Initially a conformational search of the bis-*p*-tolylboronate derivative of glucose, namely **4**, was performed



Scheme 2. Computer-based design of a glucopyranose receptor.

using AM1-SM2, a semiempirical method incorporating an aqueous solvation model.^[19] This search was followed by geometry optimization using HF//6-31G* to predict the lowest energy conformation of **4**. The resulting computer-generated structure was used to define a pair of vectors corresponding to the methyl–aryl bonds (in bold) of **4**. The program CAVEAT was then used to identify polycyclic organic structures having substituent bonds to the polycyclic framework matching the vector pair. TRIAD, a computer-generated collection of 4×10^5 tricyclic hydrocarbons, was used as the database for the search.^[5] This search identified about 300 structures having substituent bonds closely matching the vector pair defined by the computer-generated model of **4**. After elimination of most of the structures because of the presence of several chiral centers and/or highly strained and unusual ring systems, compound **5** was chosen as the lead structure, primarily because of its apparent ease of synthesis. The C–H bonds of **5** in bold correspond to the vectors defined by **4**. Simple replacement of these hydrogen atoms with phenylboronic acid groups leads to the prospective glucose receptor **6**. The structure was further modified to arrive at the structure **7**. One significant modification in arriving at structure **7** from **6** is the replacement of the fulvene ring with the more stable



and synthetically accessible but isosteric furan ring. The other major modification is the introduction of a bridging oxygen atom to avoid the out of plane twisting caused by the interaction of the two hydrogen atoms for which the oxygen was substituted. More minor changes are the introduction of a hydroxymethylene group on the furan ring for increasing water solubility and for possible derivatization for further solubility enhancement, and the introduction of a methyl group on the pyran ring, a substitution which was dictated by the availability of the commercially available starting material **9** (see Scheme 3) bearing this extra methyl group. Geometry optimization of **7** using HF//6-31G* showed that its lowest energy conformation matched very well with the bis-phenylboronate glucose complex **4**. Likewise, geometry optimization of the glucose complex **8** by the same method indicated almost no change in the conformation of the receptor **7** and no accompanying increase in strain upon glucose binding. The superimposed structures of **7** and **8** (Figure 1) give a root mean square deviation (RMSD) of 0.279 Å for common atoms. On the basis of these positive results, the synthesis of the designed glucose receptor **7** was undertaken.

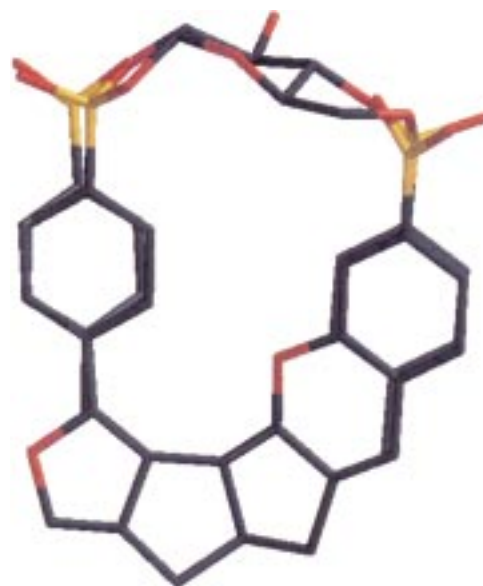
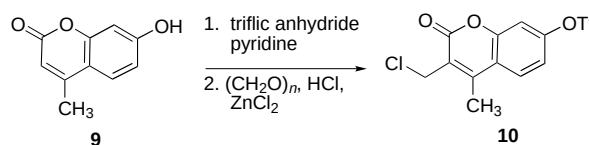
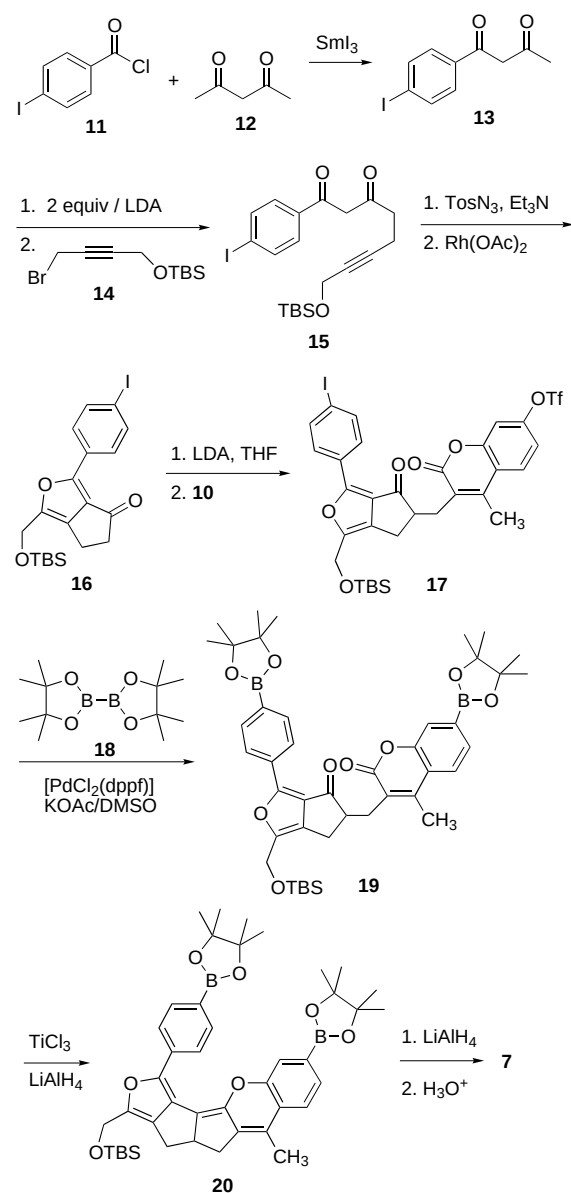


Figure 1. Superposition of the energy-minimized structures of the glucose receptor **7** and the glucose complex **8**.

The right side of **7** was derived from compound **10**, which was prepared as shown in Scheme 3. Commercially available 7-hydroxy-4-methylcoumarin (**9**) was converted into the triflate derivative followed by reaction with paraformaldehyde and HCl to introduce the chloromethylene group at C3 and give **10**.^[20, 21] The synthesis of **7** is shown in Scheme 4.



Scheme 3. Synthesis of the right side of the glucopyranose receptor. Tf = trifluoromethanesulfonyl.



Scheme 4. Synthesis of the glucopyranose receptor **7**. LDA = lithium diisopropylamide; TBS = *tert*-butyldimethylsilyl; Tos = toluene-4-sulfonyl; Ac = acetyl; dppf = 1,1'-bis(diphenylphosphanyl)ferrocene; DMSO = dimethyl sulfoxide.

Reaction of *p*-iodobenzoyl chloride (**11**) with 2,4-pentanedione (**12**) and samarium iodide gave the diketone **13**.^[22] Formation of the dienolate of **13** followed by reaction with the bromide **14**, which was prepared in two steps from 2-butyne-1,4-diol,^[23] gave **15**. Conversion of **15** into the diazo compound by reaction with tosyl azide followed by a rhodium-catalyzed cyclization gave **16**.^[24] Deprotonation of **16** adjacent to the carbonyl group followed by alkylation of the resulting enolate with **10** resulted in the formation of **17**. Reaction of **17** with the diboron diester **18** using a palladium catalyst gave the protected bis-boronic acid **19**.^[25, 26] An intramolecular McMurry reaction between the ketone and lactone carbonyl groups produced **20**.^[27, 28] Deprotection of the boronic acids and the primary alcohol gave the glucose receptor **7** in racemic form.^[29]

The formation of a complex with glucose was initially analyzed by ¹H NMR spectroscopy and mass spectrometry. The receptor **7** was combined with 1.8 equivalents of NaOD and 0.5 equivalents of D-glucose in CD₃OD. Only 0.5 equivalents of glucose were used in an effort to observe complex formation with only the preferred enantiomer of **7** and thus avoid the spectral complexity of diastomeric complexes. The resulting sample was used for both mass spectral and ¹H NMR analysis. The electrospray ionization (ESI) mass spectrum showed large peaks at *m/z* 301.12 for the dianionic tetradeuterated complex **8** (C₃₁H₂₄B₂O₁₁D₄, *M_r* = 602) and at *m/z* 603.25 for the corresponding protonated monoanion. Smaller peaks were observed at *m/z* 249.01 for the dianionic heptadeuterated boronate form of **7** (C₂₅H₁₇B₂O₉D₇, *M_r* = 497) and at *m/z*: 498.72 for the corresponding protonated monoanion. Importantly, no peaks were observed at *m/z* 321 or 643, which correspond to the dianionic and protonated monoanionic forms, respectively, of a complex of glucose with only one of the boronic acid groups of **7**. Such a complex would be 40 mass units (two equivalents of D₂O) larger than **8**. Interestingly, no peaks were observed that corresponded to complete or partial exchange of the boronic acid OH groups in complex **8** or the free receptor **7** with OCD₃ from the solvent.

The 300 MHz ¹H NMR spectra obtained within a few minutes of mixing **7** and glucose showed complete disappearance of the peaks corresponding to free glucose, with substantial shifts of these protons mostly downfield, which is indicative of complex formation. No further changes were observed in the spectra taken 4 and 16 h after mixing, which indicated that complex formation was complete within a few minutes and that no isomerization of the initially formed complex occurred.^[14] The protons of the glucose moiety in the complex were assigned using chemical shift predictions generated using ACD/Labs software. Coupling constants were measured and compared to the coupling constants for 1,2;4,6-di-*O*-benzylidene glucopyranose and 1,2;5,6-di-*O*-isopropylidene glucofuranose (Table 1). The coupling constants between H5 and the protons on C6 are not included, as they are dependent upon the conformation of the C5–C6 bond and not necessarily indicative of the ring form. A similar comparison of coupling constants has been used in the assignment of the structures of other boronate complexes of glucose.^[14] The coupling constants, most notably *J*_{2,3} and *J*_{3,4}, are clearly consistent with complex formation with the pyranose form of glucose, as expected on the basis of the receptor design and computer modeling studies.^[30] The NMR and mass spectral results confirm the formation of complex **8** as predicted by computer modeling studies.

Table 1. ¹H-¹H Coupling constants for the glucose moiety of complex **8** and related reference compounds.

Compound	<i>J</i> _{1,2}	<i>J</i> _{2,3}	<i>J</i> _{3,4}	<i>J</i> _{4,5}
8	6.3	7.8	8.0	8.8
pyranose ^[a]	4.9	6.4	9.4	9.2
furanose ^[b]	3.6	0	2.8	6.8

[a] 1,2;4,6-Di-*O*-benzylidene- α -D-glucopyranose. [b] 1,2;5,6-Di-*O*-isopropylidene- α -D-glucofuranose.

Fluorescence experiments were conducted to evaluate the affinity of **7** for glucose and its selectivity for glucose versus other common sugars. Profiles of the changes in fluorescence versus concentrations of glucose, galactose, mannose, and fructose at pH 7.5 are shown in Figure 2.^[31] Glucose exhibited

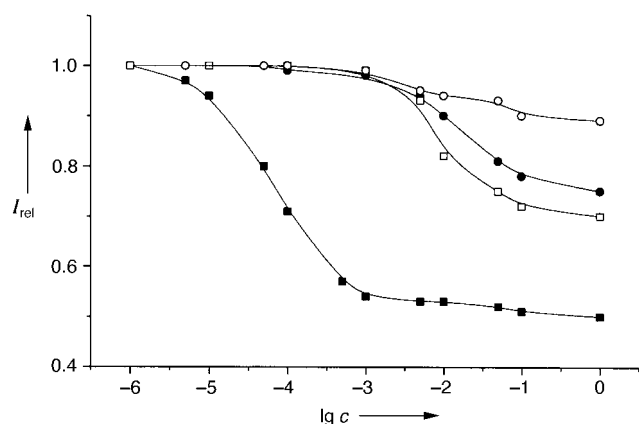


Figure 2. Relative fluorescence intensity I_{rel} of **7** as a function of the saccharide concentrations $\lg c$ at 25 °C with 1.0×10^{-5} M of **7** in 30% MeOH/aqueous phosphate buffer at pH 7.5. $\lambda_{\text{ex}} = 375$ nm, $\lambda_{\text{em}} = 447$ nm. ■ D-glucose, □ D-galactose, ● D-mannose, ○ D-fructose.

a 400-fold greater affinity than any of the other sugars for **7**, with an apparent dissociation constant for the complex of 2.5×10^{-5} M.^[32] The dissociation constants for the galactose and mannose complexes were 1.0×10^{-2} and 1.6×10^{-2} M, respectively. The dissociation constant for the fructose complex appears similar to the latter two, although the change in fluorescence intensity was too small for an accurate determination. The selectivity is attributed to the fact that only glucose is believed to form a bidentate complex involving both of the boronic acid groups of the receptor. The degree of selectivity observed is unprecedented in receptors based on boronic acid; the apparent previously most selective glucose sensor exhibits a 12-fold and 25-fold selectivity versus fructose and mannose, respectively.^[12] The maximum change in the fluorescence intensity was also much greater with glucose, with a 50% decrease in the intensity observed at saturating glucose concentrations, while a change of less than a 30% was observed for the other sugars.

Apparently both enantiomers of **7** form glucose complexes with similar binding constants: the fluorescence curve of Figure 2 shows no evidence for two discernable binding constants and the 50% decrease in fluorescence is too large to be attributed to complex formation with only half of the racemic **7**. This proposal is supported by computational evaluation of the glucose complexes with both enantiomers of **7** and the fact that the two phenyl boronic acids and their point of attachment to the rigid structure are almost coplanar and parallel.

Work is underway to further explore the potential application of **7** and derivatives thereof as fluorescence-based glucose sensors. In addition to the practical application of **7**, this work demonstrates a novel computer-based design approach for molecular recognition that uses the computer program CAVEAT. It is anticipated that this general approach may

find use in the design of receptors for the recognition of a wide range of molecules and ions.

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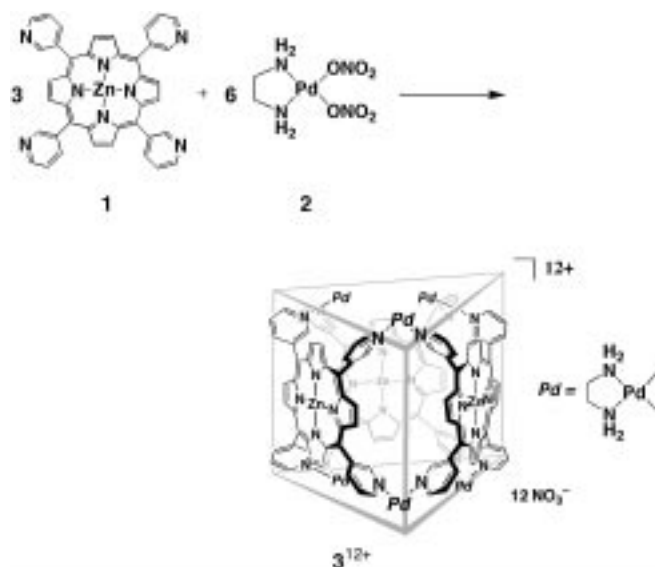
- [23] **14** was prepared by reaction of 2-butyne-1,4-diol with 1.0 equiv *tert*-butyldimethylsilyl chloride and imidazole to form the mono-TBS protected derivative followed by reaction with triphenylphosphane and carbon tetrabromide.
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- [29] Compounds **20** and **7** were characterized by high- and low-resolution mass spectra, respectively, in addition to ^1H NMR analysis.
- [30] Computer-based modeling also predicts that glucofuranose should not form a stable complex with both boronic acid groups of **7**.
- [31] Values of I_{rel} versus c were fitted to the equation $c = [(I_{\text{rel}} - 1)/\Delta\epsilon]/K\{[7]_{\text{init}} - (I_{\text{rel}} - 1)/\Delta\epsilon\} + (I_{\text{rel}} - 1)/\Delta\epsilon$ using Origin 5.0. The curves of Figure 2 were generated using B-spline fitting.
- [32] The reported values are apparent dissociation constants as the reactions involve uptake or release of hydroxide ions on complex formation and dissociation, respectively, and the apparent equilibrium constants are thus pH dependent.^[8]

A Porphyrin Prism: Structural Switching Triggered by Guest Inclusion**

Norifumi Fujita, Kumar Biradha, Makoto Fujita,* Shigeru Sakamoto, and Kentaro Yamaguchi

Porphyrin assemblies play an essential role in biological systems for oxygen transport,^[1] electron transfer, and energy migration and conversion.^[2] In this regard, designing molecular assemblies with porphyrin units is a promising approach for constructing artificial functional systems. Both covalent^[3] and noncovalent^[4] syntheses of polyporphyrins have offered some novel classes of compounds with respect to their structures and functions. Here, we report a porphyrin-based

hollow framework which is expected to open up a new area of porphyrin chemistry based on host–guest interactions. Our strategy employed here is the molecular paneling^[5] of a pyridine-functionalized porphyrin by metal coordination. A prismlike hollow structure is quantitatively assembled from three porphyrin ligands and six $[\text{Pd}^{\text{II}}(\text{en})]^{2+}$ (en = ethylenediamine) building blocks (Scheme 1). The spatially fixed



Scheme 1. Self-assembly of porphyrin prism 3^{12+} .

porphyrin ligands surround a large hydrophobic cavity which can accommodate neutral organic molecules, such as pyrene and perylene, in an aqueous solution. Though metal-linked porphyrinic square arrays have been reported by several groups,^[6] the porphyrin cores in the arrays seem to adopt cofacial rather than perpendicular conformations and provide no distinct hollow structures capable of guest inclusion. Quite recently, a Pd^{II} -linked porphyrin cage which bound diamines was reported by Shinkai and co-workers.^[7]

The ligand designed here is the (3-pyridyl)-functionalized porphyrin **1**. This square panel-like ligand can be hinged by $[\text{Pd}^{\text{II}}(\text{en})]$ units at two opposite ridges of the square, and hence is anticipated to give a discrete porphyrin box structure.^[8] Thus, the treatment of porphyrin ligand **1** with **2** (2 molequiv) in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ at 80°C gave a purple homogeneous solution after one day. ^1H NMR spectroscopic analysis showed the formation of a single product, which was isolated as a violet precipitate in 96% yield by adding acetone to the solution. After exchange of NO_3^- with PF_6^- ions, the structure of the product was assigned as 3^{12+} by coldspray-ionization mass spectrometry (CSI-MS)^[9] and NMR analyses. The CSI mass spectrum displayed prominent peaks corresponding to $[M - n(\text{PF}_6^-) + m(\text{CH}_3\text{CN})]^{n+}$, ($n = 3-9$, $m = 0-16$)^[10] (see Supporting Information). Interestingly, one NO_3^- ion was not exchanged by an PF_6^- ion even when the complex was treated with a large excess of NH_4PF_6 . The unexchanged NO_3^- ion was strongly trapped by the prism 3^{12+} . This was clearly evidenced by exact mass measurement.^[11] For example, the highest peak at m/z 567.7613 (7^+ charge) corresponds to $[M - 6\text{PF}_6^- - \text{NO}_3^- + 7\text{CH}_3\text{CN}]^{7+}$ (calcd 567.7561) and not

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

to $[M - 7\text{PF}_6^- + 5\text{CH}_3\text{CN}]^{7+}$ (calcd 567.8879), although both of them would show the same m/z value (568) by low resolution CSI-MS. The ^1H NMR spectrum fully agreed with the D_{3h} structure of $\mathbf{3}^{12+}$ with all-equivalent pyridyl groups and two inequivalent pyrrole units (singlets at $\delta = 9.01$ and 8.89; Figure 1).

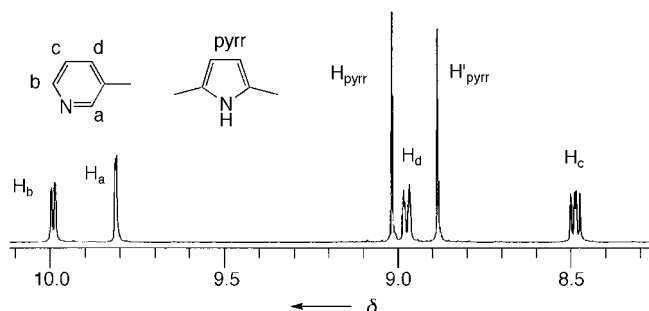


Figure 1. ^1H NMR spectrum (500 MHz, aromatic region) of $\mathbf{3}^{12+} \cdot 12\text{NO}_3^-$ in $\text{D}_2\text{O}/\text{CD}_3\text{CN}$ (1/1) at 300 K, 1.67 mM.

There are two possible conformations for the D_{3h} porphyrin prism structure: one with Pd centers at the apical positions of the prism (conformation **A**) and another one with the Pd centers at the equatorial positions (conformation **B**). Struc-

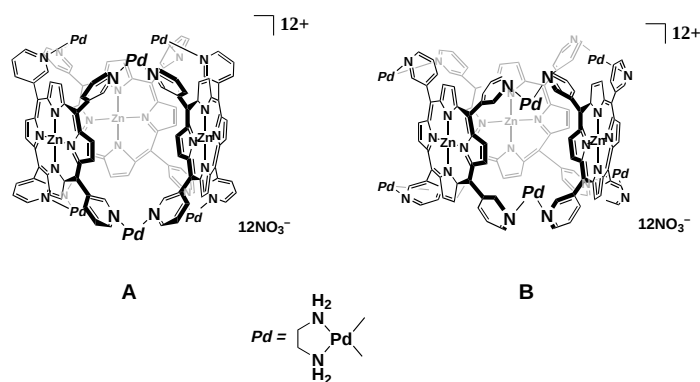


Figure 2. The X-ray crystal structure of $\mathbf{3}^{12+} \cdot 12\text{NO}_3^-$. The water molecules on the Zn^{2+} centers are omitted for clarity.

ture optimization of $\mathbf{3}^{12+}$ by using the Cerius² program^[12] revealed that **A** was more stable than **B** by 67.6 kcal mol⁻¹. In fact, conformation **A** was confirmed by an X-ray crystallographic analysis. A single crystal of $\mathbf{3}^{12+} \cdot 12\text{NO}_3^-$ was obtained by slow diffusion of ethanol into an aqueous solution of $\mathbf{3}^{12+} \cdot 12\text{NO}_3^-$ (8.3 mM) at 23 °C for one week. The crystal structure of $\mathbf{3}^{12+} \cdot 12\text{NO}_3^-$ (Figure 2) clearly demonstrated that the three porphyrin-based ligands were hinged by six palladium atoms at the apical positions of the prism structure. The bite angles of Py-Pd-Py were close (83–91°) to the ideal value of 90°, while the pyridine rings were twisted by 48–73° with respect to the porphyrin planes. The shortest Pd...Pd distance was approximately 9 Å.

The D_{3h} conformation (**A**) of the prism dramatically changed upon the addition of pyrene, as monitored by NMR spectroscopy. Thus, powdered

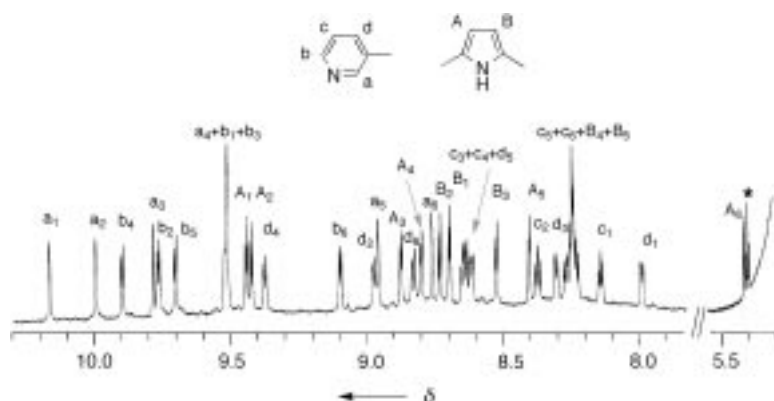


Figure 3. ^1H NMR (800 MHz) spectrum of the pyrene complex of $\mathbf{3}^{12+} \cdot 12\text{NO}_3^-$. The coupled pairs of pyrrole protons (A_1-B_1 , A_2-B_2 , ..., A_6-B_6) were assigned. The B_6 proton is missing because of overlap with the H_2O signal at $\delta = 5.0$. Six correlated pairs $b_1-c_1-d_1$, $b_2-c_2-d_2$, ..., $b_6-c_6-d_6$ were assigned for the 3-Py protons, while correlations with a_1-a_6 were not assigned. The * denotes the pyrene resonances.

located in six different environments, where each pyrrole was desymmetrized. These NMR observations fully agree with the C_2 symmetry.

We suggest that the guest binding triggered the apical-to-equatorial flipping of two Py-Pd-Py hinges at a diagonal position, thus providing C_2 -symmetrized conformation C (Figure 4). This transformation was strongly supported by a

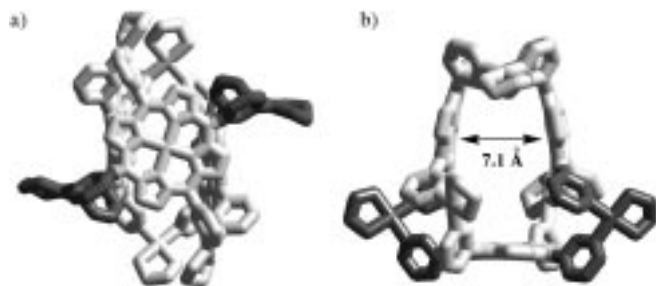


Figure 4. Optimized structure of the pyrene complex of $3^{12+} \cdot 12NO_3^{-}$ (conformation C): a) side view and b) top view. The pyrene molecule exists inside the cavity, but is omitted for clarity.

refinement using the Cerius² program. Two porphyrin faces are almost parallel to each other in the refined conformation C with an interplane distance of approximately 7.1 Å, which is an ideal distance to bind an aromatic ring in the cavity. The conformational change was also triggered by other large aromatic guests such as perylene and triphenylene. Small aromatic compounds such as benzene were also included by **3**, but the host conformation was not changed.

The UV/Vis spectrum of the pyrene complex of $3^{12+} \cdot 12NO_3^{-}$ shows the Q-band to be dramatically red-shifted by about 13 nm relative to the empty prism $3^{12+} \cdot 12NO_3^{-}$. This observation suggests that there is a strong π - π interaction between the aromatic rings of the host and the guest molecules. Photophysical properties are currently under investigation.

Experimental Section

$3^{12+} \cdot 12NO_3^{-}$: Zinc 5,10,15,20-tetra(3-pyridyl)-21H,23H-porphyrin (**1**; 1.10 g, 1.62 mmol) was treated with $[Pd(en)(NO_3)_2]$ (**2**; 0.939 g, 3.23 mmol) in a mixture of water and acetonitrile (1/1, 324 mL) at 80 °C for 1 day. The addition of acetone (2.5 L) to the resulting purple solution precipitated a purple powder which was separated by centrifugation and dried in vacuo to give $3^{12+} \cdot 12NO_3^{-}$ (1.95 g, 0.515 mmol, 96%). M.p. > 480 °C; ¹H NMR (500 MHz, CD_3CN/D_2O (1/1)): δ = 9.99 (d, J = 5.7 Hz, 12H), 9.81 (s, 12H), 9.01 (s, 12H), 8.97 (d, J = 8.1 Hz, 12H), 8.89 (s, 12H), 8.49 (dd, J = 8.1, 5.7 Hz, 12H), 3.56–3.51, 3.48–3.42 (m, 24H); ¹³C NMR (125 MHz, CD_3CN/D_2O (1/1)): δ = 153.856 (CH), 150.585 (CH), 149.439 (Cq), 149.226 (Cq), 144.948 (CH), 141.199 (Cq), 131.944 (CH), 131.510 (CH), 124.940 (CH), 114.231 (Cq); IR (KBr): 1578, 1364, 1192, 1059, 995, 797, 718 cm^{-1} ; UV/Vis (H_2O) λ_{max} (ϵ [$cm^{-1}M^{-1}$]): 322 (49460), 422 (424600), 561 (31200), 601 nm (9620). An aqueous solution of $3^{12+} \cdot 12NO_3^{-}$ (100 mg, 0.026 mmol in 40 mL of water) was poured into an aqueous solution of saturated NH_4PF_6 . The violet precipitate was separated by centrifugation, washed with water three times, and then dried in vacuo to give $3^{12+} \cdot 11PF_6^{-} \cdot NO_3^{-}$ (102 mg, 0.021 mmol, 81%). Elemental analysis (%) calcd for $C_{122}H_{120}F_{66}N_{37}O_{31}Pd_4Zn_3 \cdot 23H_2O$: C 30.99, H 3.27, N 10.13; found: C 30.86, H 2.89, N 9.79.

Crystal data for $3^{12+} \cdot 12NO_3^{-}$: The single crystal of $3^{12+} \cdot 12NO_3^{-}$ was prepared by the slow diffusion of ethanol into an aqueous solution of $3^{12+} \cdot 12NO_3^{-}$ (8.3 mM) at 23 °C for 1 week. Triclinic, space group $P\bar{1}$, a =

20.6267(14), b = 20.7442(14), c = 28.1631(19) Å, α = 72.8840(10), β = 74.0620(10), γ = 66.2070(10)°, V = 10369.3(12) Å³, Z = 2, ρ_{calcd} = 1.452 gcm^{-3} , 23102 unique reflections out of 36032 with $I > 2\sigma(I)$, $1.10 < \theta < 25.00^\circ$, final R factors R_1 = 0.1068, wR_2 = 0.2985. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157344. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Preparation and Properties of Polymer-Wrapped Single-Walled Carbon Nanotubes**

Alexander Star, J. Fraser Stoddart,* David Steuerman, Mike Diehl, Akram Boukai, Eric W. Wong, Xin Yang, Sung-Wook Chung, Hyeon Choi, and James R. Heath*

Since the discovery^[1] of single-walled carbon nanotubes (SWNTs) in 1993, it has become increasingly apparent that SWNTs, on account of their novel, structural, mechanical, and electronic properties, constitute a form of carbon with potential applications in many fields.^[2] The remarkable

electronic properties of SWNTs render them attractive candidates^[2, 3] for use as the wiring components for nanoscale devices and circuitry. Many SWNT-based devices, such as field-effect transistors^[3] and chemical sensors,^[4] have been demonstrated. One major problem—from the standpoint of manipulating and processing SWNTs—is the insolubility of SWNTs in all solvents. Although considerable progress has been made on the open-end^[5, 6] and side-wall^[7] modifications of SWNTs using covalent chemistry, it has so far not been possible to establish an efficient means of handling and manipulating NTs without risking their partial destruction. Thus, it seems attractive to explore supramolecular approaches, that is, noncovalent modifications, since 1) they will not disrupt the extended π networks of SWNTs and 2) they could open up the possibilities of being able to organize NTs into ordered networks.

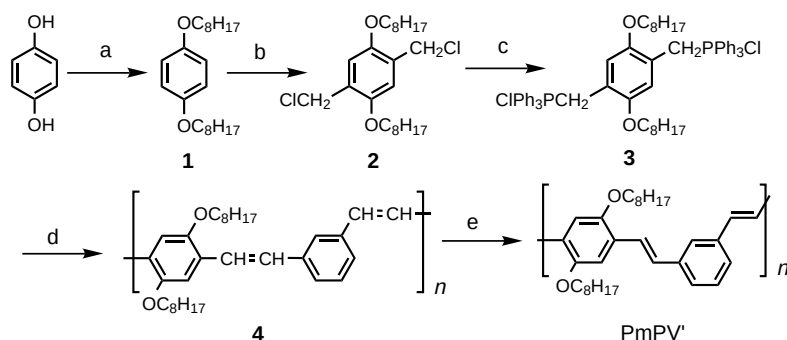
Molecules of high molecular weight that can either thread themselves onto or wrap themselves around the surfaces of SWNTs have attracted our attention as potential noncovalent modifiers of NTs that could disrupt the van der Waals interactions that cause SWNTs to aggregate into bundles. Polymers are appealing candidates to host the complexation of SWNTs since, given an appropriate structure, they can wrap themselves around SWNTs. Indeed, polymer–NT materials have been reported.^[8] Composite materials based on conjugated luminescent polymers, such as poly(metaphenylenevinylene) (PmPV), filled with NTs exhibit^[9] properties which are enhanced relative to those of the individual components. For example, NT/PmPV composites have exhibited nearly eightfold increases in electrical conductivity compared with just the polymer, and without impairment of the photo- and/or electroluminescence properties of the polymer.^[9] Here we report on an efficient synthesis of a substituted PmPV, followed by the characterization of SWNT/PmPV' complexes using UV/Vis and ¹H NMR spectroscopies. We then utilize AFM, optical, and electronic measurements of single, isolated SWNT/PmPV' structures as a means to analyze quantitatively these systems.

Our preparation of the substituted PmPV^[10] is summarized in Scheme 1. We have found that SWNTs can be suspended in solutions of PmPV' in CHCl₃. The UV/Vis absorption spectra (Figure 1) were obtained from a dilute solution (0.06 mg mL^{−1}) of the polymer and the SWNT/PmPV' complex in CHCl₃. Two major absorption bands were observed for PmPV', with λ_{max} values of 329 and 410 nm. These bands broaden in the complex, presumably as a result of π – π interactions between the SWNTs and the fully conjugated PmPV' backbone. Moreover, the SWNT/PmPV' complex yields a spectrum with broad absorptions around 650 and 900 nm. These wavelengths correspond roughly to the band-to-band transitions of pure SWNTs.^[7c] While the polymer is bright yellow, the complex possesses a deep green color. The ¹H NMR (360 MHz, CDCl₃) spectrum of the SWNT/PmPV' complex reveals (Figure 2a) significant broadening and small shifts in the resonances for the protons on the polymer, and even the TMS standard is broadened. This broadening arises most likely from the presence of conducting SWNTs, as well as from the presence of the ferromagnetic particles that are catalysts for the SWNT synthesis. Nevertheless, this broadening is not

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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. The synthesis of PmPV'. a) $\text{C}_8\text{H}_{17}\text{Cl}$ (2 equiv), K_2CO_3 , DMF, 90°C , 71%; b) HCHO , HCl , dioxane/ H_2O , $60-70^\circ\text{C}$, 77%; c) Ph_3P (2 equiv), DMF, reflux, 83%; d) isophthalaldehyde (1 equiv), NaOEt , EtOH/THF , 60%; e) I_2 (cat.), PhMe , reflux, 100%.

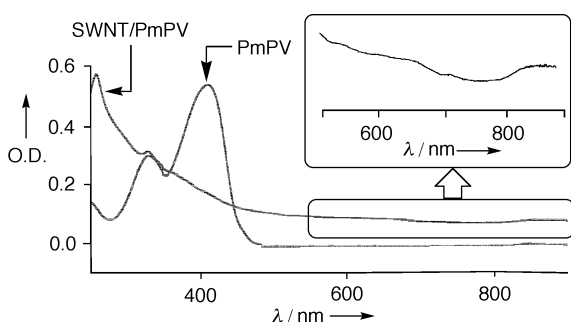


Figure 1. UV/Vis spectra (Cary 100 Bio, Varian, quartz cell) of PmPV' and the SWNT/PmPV' complex.

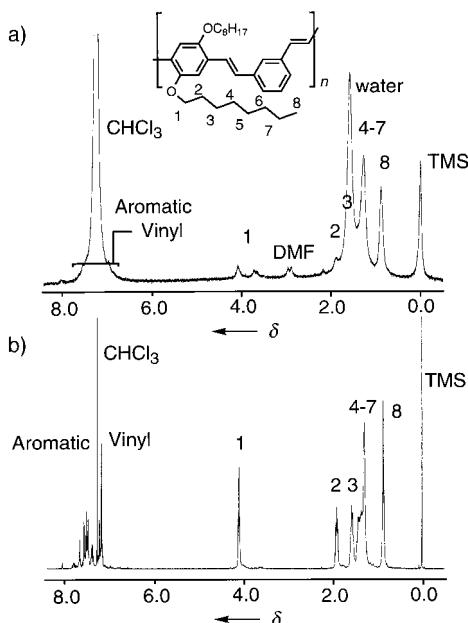


Figure 2. ^1H NMR spectra of a) the SWNT/PmPV' complex and b) PmPV' recorded in CDCl_3 (360 MHz).

completely uniform, which indicates that some chemical information is retained in the spectra of the SWNT/PmPV' complex. For example, the signals for the aromatic and vinyl protons on the PmPV' backbone, as well as the protons of the octyloxy chains that are closest to the aromatic groups, are the most broadened features. In addition, the peak intensities corresponding to the protons on the octyloxy chains that are closest to the aromatic rings are greatly reduced relative to

those of the protons that are toward the middle or terminus of those chains. Similar phenomena have been observed previously^[6b] when long alkyl chains were attached covalently to chemically modified SWNTs. All the spectroscopic evidence supports the notion that PmPV' wraps itself around the SWNTs, such that the phenylene rings and vinyl units that constitute the polymer backbone come close to the NTs' surfaces, presumably^[11] as a result of $\pi-\pi$ interactions. Such an arrangement leaves the octyloxy chains attached to the polymer backbone able to wiggle around in solution.

Noncontact AFM images of the SWNT/PmPV' samples, investigated as a function of PmPV' concentration, also indicated that the polymer enters into significant noncovalent bonding interactions with the SWNTs. Three of these AFM images prepared from samples that were spin-coated onto mica wafers are shown in Figure 3. Nanotubes prepared from DMF solutions (Figure 3a) are characterized by regions of thick, aggregated SWNT ropes that have an average height of about 7.1 nm. The surface coverage of these SWNTs was inhomogeneous, with tubes localized only at isolated regions of the wafer. Well separated SWNT bundles are observed for the PmPV'/SWNT solutions (Figure 3b and c). The surface coverage becomes highly uniform as the polymer concentration increases. This apparent increase in coverage can be attributed to the polymer breaking up the ropes into suspensions of smaller ropes, and, indeed, the average diameter of the SWNT bundles decreases. At the lowest polymer concentrations studied the distribution of tube widths is broadened relative to the pure SWNT samples, but at higher concentrations this distribution narrows as the polymer breaks up the SWNT bundles into smaller diameter ropes (Table 1). For the highest polymer per nanotube concentration sample studied there is a large excess of polymer in solution. If it is assumed that all the tubes in this solution are single SWNT strands and that the polymer covers all the available area of the tubes there is still an approximately 50% excess of polymer molecules in solution. Nevertheless, even at this concentration, more polymer clearly helps disperse more tubes. The implication is that there is either an equilibrium between bound and excess polymer, or that excess of polymer is somehow needed to support SWNTs dispersed in CHCl_3 .

When traditional characterization tools of UV/Vis and NMR spectroscopies are applied to SWNT/PmPV' solutions, the results are difficult to interpret and less informative than when they are applied to simpler systems. This situation arises from the heterogeneous character of the solution: it contains not just various diameters, lengths, and electrical types of tubes and ropes, but also both bound and free polymer. One way to avoid the problems associated with characterizing such a heterogeneous sample is to carry out measurements on single PmPV'-wrapped SWNT structures. In fact, both SWNTs and PmPV' have certain useful characteristics that can be exploited in the chemical analysis of the single structures. PmPV' has uses^[12, 13] as a photonic material: it can harvest light, and, when properly doped, PmPV' devices can exhibit photovoltaic

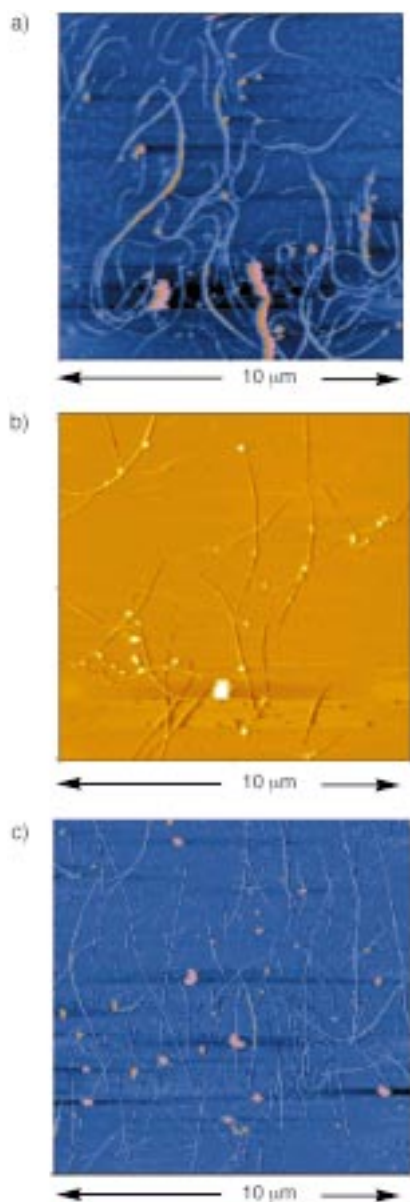


Figure 3. AFM images of bare and PmPV'-wrapped SWNTs: a) SWNTs prepared from 0.32 mg of SWNTs in 5 mL of DMF; b) solution containing 0.32 mg of SWNTs with 0.2 mg of PmPV' in 5 mL of CHCl_3 ; c) solution containing 0.24 mg of SWNTs with 1 mg of PmPV' in 5 mL of CHCl_3 .

Table 1. Statistics of SWNT heights as determined by AFM images taken from samples with various polymer concentrations. The solution that contained no PmPV was DMF-based, while all the other solutions were CHCl_3 -based.

SWNT [mg]	0.32	0.32	0.32	0.24
PmPV' [mg]	0	0.2	0.6	1.0
average diameter [nm]	7.1	6.0	5.8	3.4
standard deviation	3.9	4.7	4.0	2.4

responses. In addition, PmPV' also has distinctive UV/Vis absorption and fluorescence spectra. Finally, the high aspect ratio of SWNTs that makes them relatively easy to locate and image using AFM, also makes them ideal candidates for bridging across electrodes for charge-transport measurements. Hence, we conclude our discussion here by describing

two more experiments: 1) the photoconductivity response of a single polymer-wrapped SWNT bundle and 2) two-photon fluorescence (2PF) measurements of single SWNT/PmPV' bundles, correlated with AFM structural measurements. These experiments indicate that the polymer is, in fact, in intimate electrical contact with the NTs, and that the polymer wraps around bundles of tubes, rather than wrapping around individual tubes which then aggregate to form ropes. Although neither experiment explicitly interrogates the extent of the PmPV' wrapping, the results of both experiments are consistent with at least a high level, if not complete, coverage of the SWNT bundle by the PmPV'.

SWNT/PmPV' photovoltaic devices were fabricated by spin coating a dilute solution of polymer-coated SWNTs in CHCl_3 onto a silica substrate that was pre-patterned with Au microelectrodes (200 nm diameter widths and 1 μm electrode spacing). AFM measurements revealed that a single SWNT bundle bridged the two electrodes. This device was mounted onto the cold finger of an immersion cryostat equipped with optical access ports. Filtered light from a quartz-halogen lamp was directed through a monochromator and then onto the device. A small bias was applied and the photoresponse of the device was measured by cycling the light. Such measurements were carried out as a function of temperature, wavelength, and applied bias. Control experiments on unwrapped SWNT devices yielded no photodependent response. The photoresponse of a SWNT/PmPV' device at 375 nm excitation is shown in Figure 4. If we correlate the photoinduced current

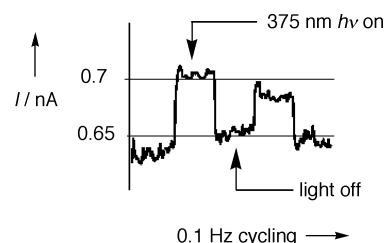


Figure 4. The performance of a PmPV'-wrapped SWNT photovoltaic device measured at 10 K. The excitation wavelength was 375 nm (slightly less than 1 mW focused to 0.2 cm^2 , with a device area of approximately $5 \times 10^{-11} \text{ cm}^2$), and a +0.025 V bias was applied to the device. Room temperature yielded a similar response if a +0.005 V bias was applied.

increase (ca. $4 \times 10^8 \text{ e s}^{-1}$) with the photon flux onto the SWNT/PmPV' structure ($7 \times 10^5 \text{ photons s}^{-1}$) we find that the polymer is not harvesting the light, but rather the photo-excited polymer is "gating" the SWNT device, and so the signal from an absorbed photon is greatly amplified. This means that the polymer, in the excited state, has a dipole moment that alters the local electric field at the surface of the SWNT bundle. It was possible, by measuring the photo-induced increase in current through the tube as a function of excitation wavelength, to map out the absorption spectrum of the polymer. The critical result here is that these measurements do indicate that the polymer is in intimate electrical contact with the SWNT bundle.

Optical experiments, correlated with structural measurements, were also carried out on single PmPV'-wrapped SWNTs and used to interrogate the general morphology of

the SWNT/PmPV' structure. To this end, we have correlated the two-photon fluorescence (2PF) intensity with the diameter of various SWNT/PmPV' structures. Unwrapped SWNT ropes exhibited no 2PF signal. Silica substrates were pre-patterned with micron-sized gold alignment markers, and dilute SWNT/PmPV' solutions were deposited onto the wafer by spin coating. AFM analysis revealed both SWNT structures and polymer particles, but the polymer particles could be removed selectively by exhaustive washing with CHCl_3 . The positions of the SWNT/PmPV' structures were recorded with respect to alignment markers (Figure 5a) using non-contact AFM. Such measurements also yielded the height (diameter) of the SWNT bundles at various positions along

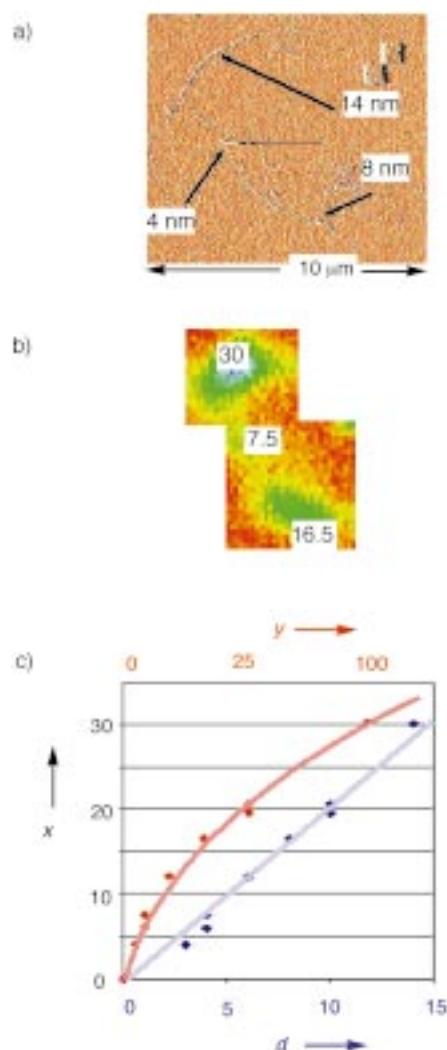


Figure 5. a) Atomic force micrograph of a polymer-wrapped SWNT bundle. The diameter of the SWNT varies in the three significant sections labeled in the image. At the top right of the image is an alignment marker. b) 2PF image of the same SWNT with the various signal strengths (relative to background) of the fluorescence signal indicated. c) A correlation of the two plots (and other similar data) presented in two ways. The blue curve represents the fluorescence intensity plotted against the diameter of the SWNT bundle while the red curve is the fluorescence intensity plotted versus the square of the radius of the SWNT bundle. Only the blue curve is linear, which indicates that the PmPV wraps only around the exterior of the SWNT bundle, and that PmPV-wrapped SWNT structures do not further aggregate to form larger diameter ropes. (x: 2PF signal; d: diameter of the SWNT bundle; y: (bundle diameter)²).

their length. The wafers were then mounted onto the illumination stage of a custom built, scanning nonlinear optical microscope capable of approximately $1 \mu\text{m}^2$ spatial resolution.^[14] Both 2PF images and second harmonic generation (SHG) images were simultaneously recorded, while various filters, polarizers, and beam splitters were employed to isolate the two signals at separate detectors. Both images were utilized. The alignment markers were detected by SHG, and the SWNT/PmPV' structures were detected by 2PF (Figure 5b). We correlated the diameter of a SWNT structure with the magnitude of the 2PF signal for a number of SWNT/PmPV' structures from both the AFM and the 2PF measurements (Figure 5c). These data distinguish between the two polymer-wrapping possibilities. If the individual SWNT strands within a bundle are wrapped, then the 2PF signal from the bundle should scale as the square of the bundle diameter, since the volume of the bundle is effectively filled with PmPV'. However, if the polymer just wraps around the surface of the bundle, then the 2PF signal should scale linearly with the bundle diameter. It is clear from Figure 5c that the scaling is linear, and hence that the polymer wraps around the already aggregated bundle.

This last issue is important in the context of using polymers as a chemical means of separating the various different SWNT types. Finally, returning to our initial motivation, the experiments reported here do indicate that the electrical properties of SWNTs are largely unperturbed by the associated polymer. It appears that PmPV may provide a useful route toward "functionalizing" the SWNTs without destroying their electrical character.

Experimental Section

PmPV': The synthesis of the polymer **4** was achieved in five steps starting from hydroquinone, which is O-alkylated with octyl chloride and K_2CO_3 in DMF at 90°C . The resulting 1,4-bis(octyloxybenzene) (**1**) was chloromethylated with HCl and HCHO in dioxane/water at $60-70^\circ\text{C}$. The resulting 1,4-bis(chloromethyl)-2,5-dioctyloxybenzene (**2**) was then heated under reflux with PPh_3 in DMF. Multiple Wittig condensations were used to polymerize the resulting bis(triphenylphosphonium salt) **3** with isophthalaldehyde using NaOEt in dry EtOH/THF to afford a polymer **4**, which was converted into its pure *trans* isomer (PmPV) by refluxing in PhMe in the presence of a catalytic amount of I_2 . The polymerization reaction under different conditions produces both low and high molecular weight polymers. The molecular weights of the polymers were determined as 9200 and 150000 in THF by using size-exclusion chromatography (SEC). The SEC system was calibrated by using polystyrene standards prior to use. Low molecular weight polymer: ^1H NMR (360 MHz, CDCl_3): δ = 7.64 (s, 1H), 7.50 (m, 4H), 7.37 (t, J = 7.5 Hz, 1H), 7.21 (s, 1H), 7.16 (s, 3H), 4.09 (t, J = 6.5 Hz, 2H), 1.90 (p, J = 6.5 Hz, 2H), 1.55 (p, J = 6.5 Hz, 2H), 1.35 (m, 8H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (90 MHz, CDCl_3): δ = 151.0, 138.3, 128.5, 126.9, 125.7, 124.0, 111.1, 69.8, 31.8, 29.4, 26.3, 22.7, 14.1.

Preparation of the SWNT/PmPV' complex for spectroscopic analysis: The SWNTs were obtained as a surfactant-stabilized water suspension (from Tubes@Rice). The nanotube sheets were typically made by vacuum filtration of around 1.5 mL of an approximately 4 mg mL^{-1} nanotube suspension through a poly(tetrafluoroethylene) filter (Gelman, 25 mm in diameter, 0.2 μm pores). The nanotube sheet (formed over the clear funnel area, which was 15 mm in diameter) was washed with deionized water (5 mL) and then MeOH (5 mL) to remove residual NaOH and surfactant, respectively. These sheets were allowed to dry under vacuum at room temperature overnight before being peeled from the filter. The typical nanotube sheet weighed about 6 mg. It was then resuspended by sonication (2.5 h) in DMF in a water bath (Branson model 1510, 40 kHz). The DMF

was then removed by high vacuum and a chloroform solution of polymer PmPV' was added (5 mg in 5 mL). Sonication for 2 h gave a stable suspension that was filtered prior to spectroscopy.

Preparation of the SWNT/PmPV' material prior to AFM: Aliquots of Triton X-100 SWNTs (from Tubes@Rice) were purified by centrifugation at 14000 rpm in MeOH. The purified tubes were re-suspended in fresh MeOH by shaking, and then they were vacuum filtered over a 0.2 mm PTFE filter and washed with MeOH and 18 MQ H₂O to form a nanotube mat. A portion of the mat weighing 6–7 mg was sonicated in DMF using a bath sonicator while stepwise adding the DMF until a total volume of 25 mL was obtained. The DMF/NT stock solution was sonicated for a period of 6 h. Measured aliquots of the stock solution were transferred to round-bottom flasks and the DMF was removed by rotary evaporation. Each flask contained between 0.24–0.32 mg of SWNTs. 5 mL of CHCl₃ containing between 0.2–1.0 mg of dissolved PmPV were added to these flasks. The SWNT/PmPV' mixtures were sonicated for 15 mins. After sonication, one drop of the SWNT/PmPV' solution was placed on a freshly cleaved 1 cm² mica wafer, and subsequently washed with 5 drops of CHCl₃ while spinning it at 750 rpm to wash off the excess of the polymer. AFM images were collected in noncontact mode.

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T_h-Symmetric Nanoporous Network Built of Hexameric Metallamacrocycles with Disparate Cavities for Guest Inclusion**

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Growing interest in the rational design and construction of nanoporous structures^[1] is motivated principally by the potential exploitation of the resulting cavities and channels in nanotechnology, including shape- and size-selective catalysis, molecular recognition, ion exchange, separation, and optoelectronic applications.^[2] Rapid growth and breakthroughs in this field rely on, to a large degree, mastery of the novel synthetic protocol in the construction of organized supramolecular systems, namely self-assembly of multiple building blocks in a single step into large aggregates of molecules through noncovalent interactions.^[3] On the other hand, difficulties were often encountered in the generation of porous networks, such as the control of cavity size and geometry, the prevention of network interpenetration, and

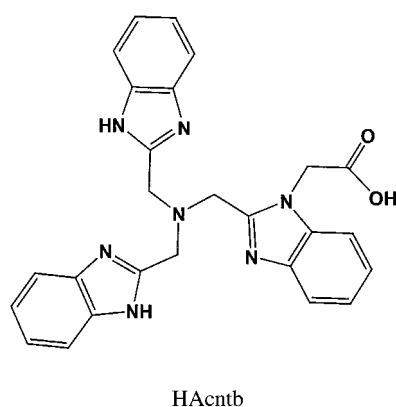
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the irreversible collapse of an open network upon the removal of absorbates.^[1a, 4]

Recent advances in molecular architecture^[5–7] have pointed the way to a promising strategy for overcoming these drawbacks. For instance, noninterpenetrating networks may be formed by using large molecular aggregates as secondary building blocks. In an earlier study, $[\{M(\text{CO})_3(\mu_3\text{-OH})\}_4]$ ($M = \text{Mn, Re}$) clusters were used to assemble super-diamondoid networks to a lower level of interpenetration.^[8] More recently, large inorganic clusters have been exploited to generate open, noninterpenetrating networks of nanoscale porosity.^[9, 10]

Our investigation of metal complexes with tripodal ligands has revealed that C_3 -symmetric tris(2-benzimidazolylmethyl)-amine (ntb) can encapsulate lanthanide(III) and silver(I) ions to afford large hexafunctional hydrogen-donor building blocks,^[11] which were further assembled to form doubly interpenetrating three-dimensional (3D) stereoisomeric networks^[11a] or rhombohedral networks with large cavities.^[11b] These findings prompted us to utilize even larger molecular aggregates as subunits to fabricate nanoporous networks. To achieve this goal, we employed the branched unsymmetric tripodal ligand N -[N' -(carboxymethyl)benzimidazol-2-ylmethyl]- N,N -bis(benzimidazol-2-ylmethyl)amine (HAcntb),



which was derived from ntb by attachment of one acetic acid group. Reaction of its sodium salt $\text{Na}(\text{Acntb})$ with an equal molar amount of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in ethanol afforded $[\text{Cu}_6(\text{Acntb})_6](\text{ClO}_4)_6 \cdot n\text{H}_2\text{O}$ ($1 \cdot 6\text{ClO}_4 \cdot n\text{H}_2\text{O}$), which crystallized as beautiful green octahedra from slow evaporation of the reaction mixture. The elemental analysis results showed that the number of solvated water molecules in the stoichiometric formula of the complex varied according to the condition of crystallization. A freshly prepared sample in aqueous ethanol may incorporate as many as 38 water molecules, while that recrystallized from a nonaqueous solvent medium usually contains less. In any event the IR spectral data indicated that the framework of the complex remains unchanged although the guest molecules may vary, and FAB mass spectrometry confirmed the presence of the $[\text{Cu}(\text{Acntb})]^+$ basic unit in all cases.

Crystallographic analysis revealed a nanometer-sized cationic hexanuclear metallamacrocyclic $[\text{Cu}_6(\text{Acntb})_6]^{6+}$ (**1**); the linkage between two adjacent $[\text{Cu}(\text{Acntb})]^+$ components is shown in Figure 1. Each copper(II) ion is coordinated by three

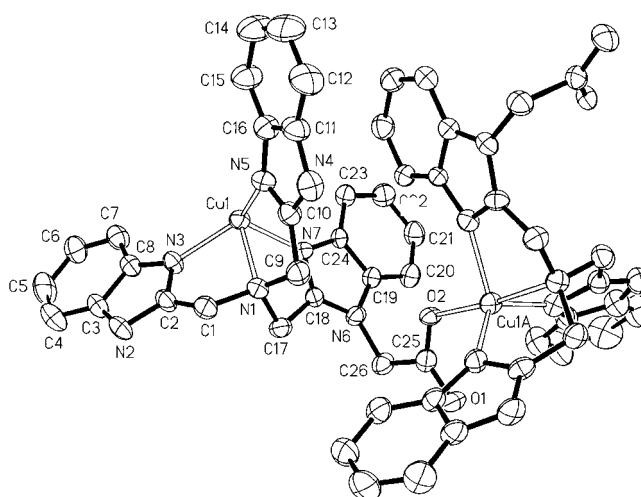


Figure 1. Linkage between two adjacent $[\text{Cu}(\text{Acntb})]^+$ units showing the bridging mode of the monodentate Acntb^- ligand and the coordination geometry about a copper(II) ion. The atoms are drawn as thermal ellipsoids at the 30% probability level.

imino-nitrogen atoms and the apical amino-nitrogen atom of an Acntb^- ligand, and the branching acetate group functions as a monodentate bridge between adjacent $[\text{Cu}(\text{Acntb})]^+$ units, thus generating a hexameric macrocycle with a crystallographic $\bar{3}$ axis passes through the center of the hexamer. Viewing down the $[1\bar{1}1]$ direction, **1** resembles a nanoscale wheel of diameter 23.3 Å with six fan-blade-like benzimidazole rings (Figure 2). The remaining twelve benzimidazole

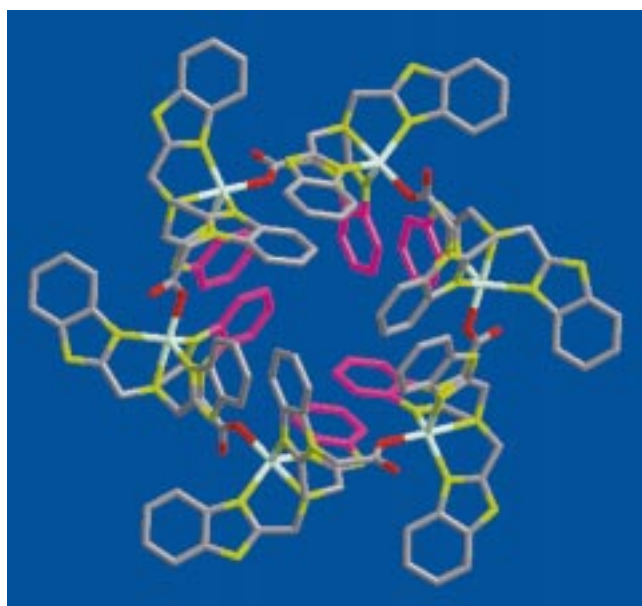


Figure 2. A view of the hexanuclear metallamacrocyclic nano-wheel $[\text{Cu}_6(\text{Acntb})_6]^{6+}$ (**1**).

rings wrap inward around the $\bar{3}$ axis, affording a hydrophobic cavity with a smallest diameter of 6 Å. The $[\text{Cu}_6(\text{Acntb})_6]^{6+}$ giant wheel has a vaulted core with a thickness of 12 Å, looking somewhat like a “flying saucer” when viewed from the side.

The distinguishing feature of **1** is that it is conformationally rigid, with all six noncoordinated carboxylato oxygen atoms and twelve amino NH groups involved in hydrogen bonding. For each $[\text{Cu}_6(\text{Acntb})_6]^{6+}$ molecule, six abducent NH groups belonging to fringe benzimidazole rings form donor bonds with the carboxylato O atoms of six neighboring molecules, while the six carboxylato O atoms are arranged alternately above and below the wheel to form acceptor hydrogen bonds with another six neighbors. Thereby a total of twelve $\bar{3}$ symmetry-related N–H $\cdots$ O hydrogen bonds (N $\cdots$ O 2.840 Å) generate an open, three-dimensional cationic network with T_h symmetry (Figure 3). Huge octahedral voids

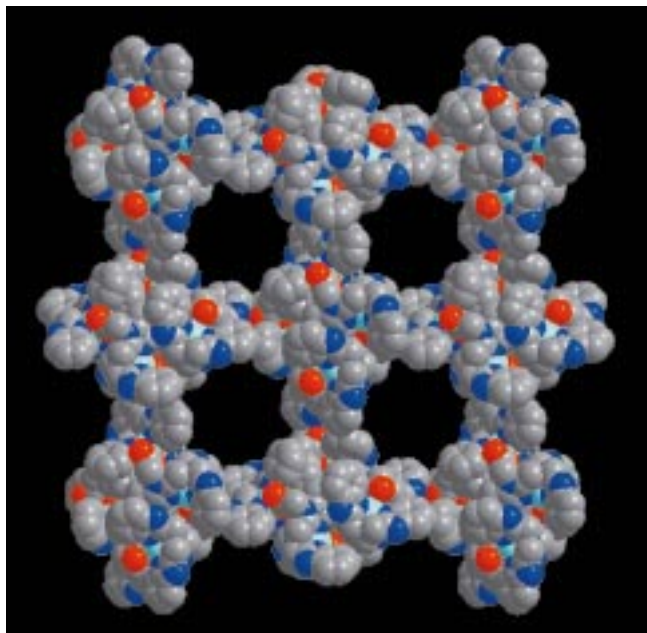


Figure 3. Space-filling diagram of the 3D network viewed along [100]. All guest molecules are omitted for clarity.

with estimated dimensions of $11 \times 11 \times 14$ Å are formed, in which another six NH groups provide a hydrophilic environment to accommodate the guest molecules. In total 26 water molecules and six perchlorate anions are located within each cavity, which has essential windows for inclusion and escape of guest molecules. Calculation using the PLATON program^[12] suggests that the effective volume for inclusion is about 8886 Å³, comprising 42 % of the crystal volume. Since the macrocyclic aggregate itself has an empty intramolecular hydrophobic cavity, selective inclusion of different guests by molecular recognition should be possible.

The possibility of exchanging the solvent water molecules in the cavity for other organic molecules of different polarity was also investigated. The IR spectrum of a freshly prepared complex that had been soaked in chloroform for several hours did not show any difference from the original complex, and the elemental analysis suggested that the stoichiometric formula remained unchanged.^[13] However, after the complex was recrystallized in acetone/ethanol (1:20), a new stretching carbonyl band appeared at 1697 cm^{−1}, and elemental analysis also indicated inclusion of the acetone molecules.^[14] This

finding may be attributed to the fact that acetone, being a stronger hydrogen-bond acceptor than chloroform, can easily replace water molecules in the void. Thermogravimetric analysis (TGA) of $(\mathbf{1} \cdot 6 \text{ClO}_4 \cdot 38 \text{H}_2\text{O})$ showed two continuous weight losses (total about 15 %) in the range 26–160 °C, followed by another (about 14 %) in the range 200–280 °C, corresponding to respective liberation of solvated water molecules and perchlorate anions. The major weight loss (about 60 %) occurred in the range 340–580 °C, which may correspond to complete destruction of the network. This study indicated that the guest water molecules can escape from the cavity even at low temperature. However, the complete liberation of water molecules over an extended range of 134 °C is suggestive of complex interactions between host and guest, or even between different guest molecules.

To the best of our knowledge nanoporous structures assembled with large molecular architectures as building blocks are seldom investigated.^[15] The present study provides the first example of a hydrogen-bonding sustained T_h -symmetric, open network constructed from nanosized metal-lamacrocylic molecules. Precise self-assembly of the hexameric aggregate **1** is facilitated by the branch-functionalized tripodal ligand Acntb[−], whose deliberately positioned hydrogen-bond donors and acceptors effectively prevent network interpenetration. The formation of multiple directional hydrogen bonds between the conformationally rigid metal-lamacrocylics consolidates the 3D network. Another feature that makes this kind of synthetic strategy commendable is the concomitant generation of both intra- and intermolecular host cavities,^[16] allowing possible fine-tuning of molecular recognition characteristics and selective enclosure of different guest molecules.

Experimental Section

1: $\text{Cu}(\text{ClO}_4)_2 \cdot 6 \text{H}_2\text{O}$ (0.019 g, 0.05 mmol) dissolved in EtOH (5 mL) was added to a solution of Na(Acntb) (0.024 g, 0.05 mmol) in EtOH (50 mL). The color turned green rapidly and the resulting mixture was stirred for 2 h. After filtration, the solution was left standing for several days to afford a green crystalline product. IR (KBr): $\tilde{\nu}$ = 3387, 3061, 1625, 1544, 1498, 1476, 1451, 1385, 1278, 1115, 1085, 747, 626 cm^{−1}; FAB-MS: m/z : 528 $[\text{Cu}(\text{Acntb})]^+$, 628 $[\text{Cu}(\text{Acntb})(\text{ClO}_4)]^+$; elemental analysis indicated the stoichiometric formula of $[\text{Cu}_6(\text{Acntb})_6](\text{ClO}_4)_6 \cdot 38 \text{H}_2\text{O}$, calcd for $\text{C}_{156}\text{H}_{208}\text{Cl}_6\text{N}_{42}\text{O}_{74}\text{Cu}_6$ (%): C 42.11, H 4.71, N 13.22; found: C 42.04, H 5.06, N 13.07. Single crystals suitable for X-ray diffraction analysis were obtained from recrystallization of the complex in dry ethanol, which contained less water molecules.

Crystal data for $\mathbf{1} \cdot (\text{ClO}_4)_6 \cdot 26 \text{H}_2\text{O}$: $[\text{Cu}_6(\text{Acntb})_6](\text{ClO}_4)_6 \cdot 26 \text{H}_2\text{O}$, M_r = 4233.39, cubic, space group $Pa\bar{3}$ (no. 205), a = 27.656(2) Å, V = 21 153(3) Å³, Z = 4, crystal size 0.22 × 0.16 × 0.16 mm³, 61 885 reflections measured, final $R1$ = 0.0616 and $wR2$ = 0.1549 for 2299 observed ($I > 2\sigma(I)$) reflections. The perchlorate anion is orientationally disordered with half-site occupancy. Anisotropic thermal factors were assigned to all the non-hydrogen atoms, while isotropic hydrogen atoms of Acntb[−] were included in structure factor calculation. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155221. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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- [14] IR (KBr): $\tilde{\nu}$ = 3432, 3067, 1697, 1626, 1543, 1498, 1476, 1452, 1386, 1278, 1114, 1088, 748, 628 cm^{-1} ; elemental analysis (%) found: C 46.12, H 4.85, N 13.22, possibly corresponding to $[\text{Cu}_6(\text{Acntb})_6](\text{ClO}_4)_6 \cdot 22\text{H}_2\text{O} \cdot 6(\text{CH}_3\text{COCH}_3)$, calcd: C 46.34, H 4.74, N 13.04.
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Toward Fully Synthetic Homogeneous Glycoproteins: A High Mannose Core Containing Glycopeptide Carrying Full H-Type 2 Human Blood Group Specificity**

Zhi-Guang Wang, Xufang Zhang, Michael Visser, David Live, Andrzej Zatorski, Ulrich Iserloh, Kenneth O. Lloyd, and Samuel J. Danishefsky*

Carbohydrate domains in the context of glycolipids and glycoproteins carry significant messages. The definition of the full scope and impact of oligosaccharide-based bioinformatics, falls within the scope of the rapidly growing field of glycobiology.^[1] The sorting out of the diverse effects of glycosylation on phenomena ranging from protein folding^[2] to cascades with a bearing on fertilization,^[3] inflammation,^[4] and metastasis,^[5] constitutes a major challenge to glycobiology.^[6] Other phenomena that are communicated in the "grammar" of carbohydrate structure include aberrant glycosylation patterns, associated with tumorigenesis, and blood typing.^[7] The most widely known of the carbohydrate-centered serology systems, the ABO classification, is based on structural patterns of cell-surface glycoproteins on erythrocytes.^[8]

From the perspective of chemistry, one of the issues complicating molecular level understanding of the consequences of glycoarchitecture is the phenomenon of heterogeneity. While the various carbohydrate domains present on a glycoprotein may be isolated and purified, this tends to be feasible only after detachment of the oligosaccharide ensemble from its macromolecular setting. One method for dealing with the issue of the inhomogeneity of glycoproteins is through synthesis—either chemical, enzymatic, or a combination of both.^[9]

A long-term goal of our laboratory has been the development of methodology and strategies which would enable the synthesis of complex oligosaccharides bearing the inherent information in a context that simulates the natural glycoprotein setting. As will be shown below, advances in the field are

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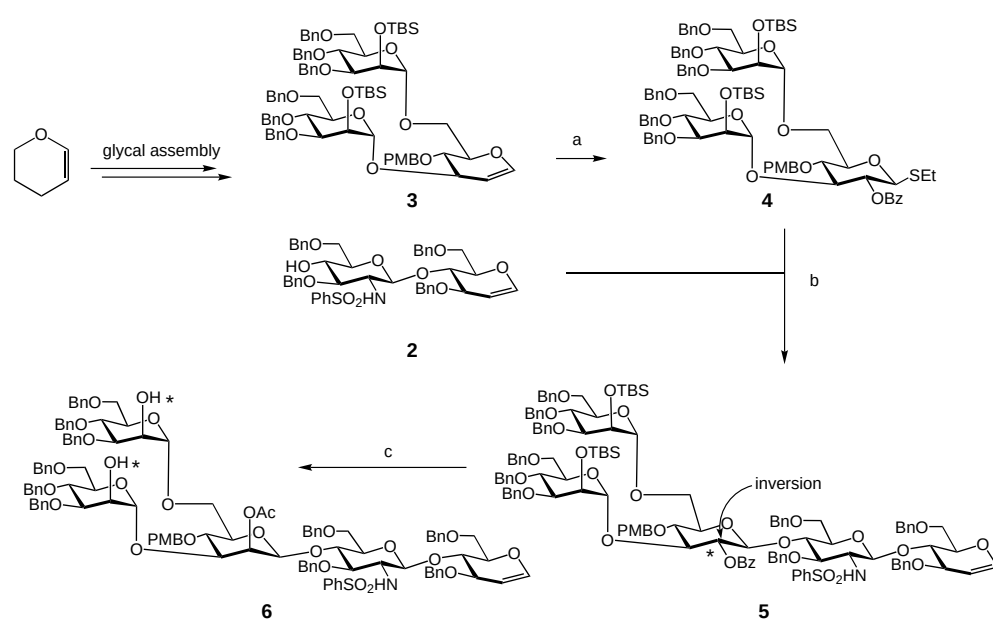
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such that a construction is now possible. Our specific focus in this project was a maximally convergent, stereospecific synthesis of a homogeneous *N*-acetylglucosamine glycopeptide bearing an *N*-linked bidomainal high-mannose core, connected through lactosamine spacers to sectors carrying the carbohydrate-encoded information.^[10] For this demonstration, we focused on the total synthesis of a glycopeptide construct that presents human H-type2 specificity in a naturally occurring, glycan-like setting. Herein, we describe a solution to this problem in the context of the synthesis of **1** (see Scheme 5).

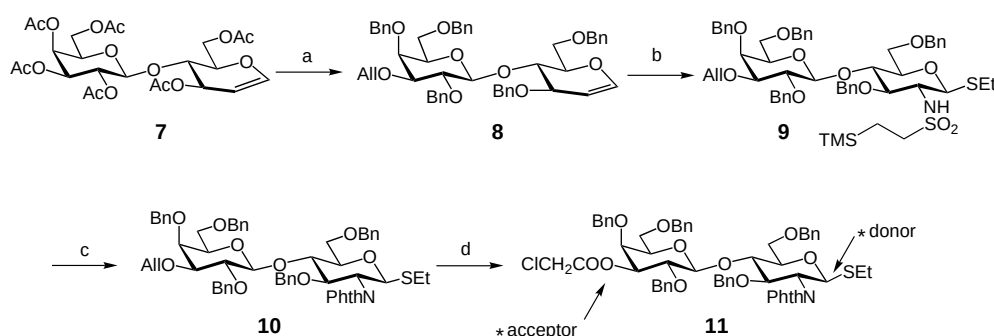
Glycal assembly logic had been used for the large-scale syntheses of **2** and **3** (Scheme 1).^[11, 12] Unfortunately, coupling of **2** with the glycal epoxide directly available from **3** occurs, at best, in poor yield. A body of chemistry to deal with just such a contingency had been developed (see **3** → **4** → **5**).^[13] System **5** had been organized such that a C-2 hydroxyl group in the C ring (see asterisk in **5**) could be exposed from a unique benzoate. Epimerization of the resultant alcohol (by oxidation/reduction),^[14] followed by acetylation at C-2 and deprotection of the unique ring D and ring E silyl ethers, gave rise to **6** with defined acceptor sites at the two “wing” mannose units (see asterisks in **6**).

We next concerned ourselves with fashioning the lactosamine spacer region, which characteristically intervenes between the bifurcated high mannose core sector and the bioinformation domains. For the purposes of this work, we focused on interpolation of an acetylglucosamine element on each wing of the mannose sector. Herein, we use the two-directional mannose building block **11** (see Scheme 2) as a single insertion unit in the two branching domains. However, the chemistry described here could be extended to the building of longer spacer sectors by controlled homocoupling of **11**.

Our synthesis of **11** commenced with peracetylated lactal **7**. This was converted into **8**, which bears a unique allyl protecting group at C-3' (Scheme 2).^[15] Following chemistry that we had developed with this type of application on the



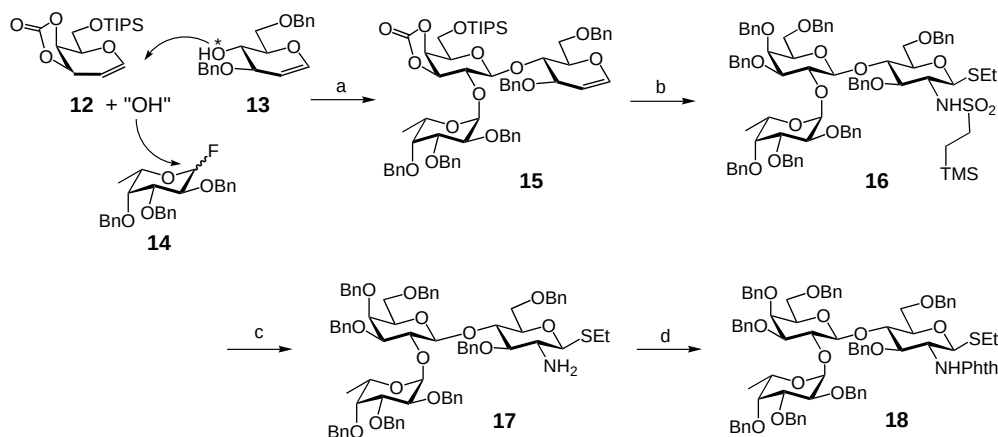
Scheme 1. Synthesis of core pentasaccharide **6**. a) 1. DMDO/CH₂Cl₂; 2. EtSH/TFA/CH₂Cl₂, 75 % (two steps); 3. BzCl/Py/DMAP, 90 %; b) MeOTf/CH₂Cl₂/DTBP, 75 %; c) 1. LiAlH₄/THF/−20 °C → 0 °C; 2. Dess–Martin periodinane/CH₂Cl₂/22 °C; 3. L-selectride/THF/22 °C; 4. Ac₂O/Py/DMAP/CH₂Cl₂, 82 % (four steps); 5. TBAF/THF, 77 %. Bn = benzyl, Bz = benzoyl, DMAP = 4-dimethylaminopyridine, DMDO = dimethyl dioxirane, DTBP = 2,6-di-*tert*-butylpyridine, PMB = *para*-methoxybenzyl, Py = pyridine, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tf = triflate = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.



Scheme 2. Synthesis of lactosamine building block **11**. a) 1. NH₃/MeOH; 2. Bu₄Sn/C₆H₆; 3. allyl bromide/Bu₄NBr; 4. BnBr/NaH/DMF, 50 % (four steps); b) 1. IDCP/TMSCH₂CH₂SO₂NH₂, 83 %; 2. EtSH/LiHMDS/DMF, 85 %; c) 1. CsF/DMF, 90 °C, 94 %; 2. phthalic anhydride/Py/22 °C; 3. Piv₂O, then Ac₂O, 100 % (two steps); d) 1. Ph₃RuCl/DABCO/THF; 1N HCl, 74 %; 2. (ClCH₂CO)₂O, DMAP/DTBP, 97 %. All = allyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMF = dimethylformamide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, IDCP = iodonium dicollidine perchlorate, Phth = phthaloyl, Piv = pivaloyl, TMS = trimethylsilyl.

horizon, *trans* diaxial addition of iodonium 2-(trimethylsilyl)ethanesulfonamide (SES) to the glycal double bond was followed by thiolysis, which triggered migration of the sulfonamide from C-1 → C-2 with concurrent ejection of iodide from C-2 to form **9**.^[16] Deprotection of the nitrogen and phthaloylation^[17] (to form **10**), followed by deallylation and reprotection at C-3, afforded **11**, which was equipped with activatable donor and acceptor sites (marked by asterisks in Scheme 2).

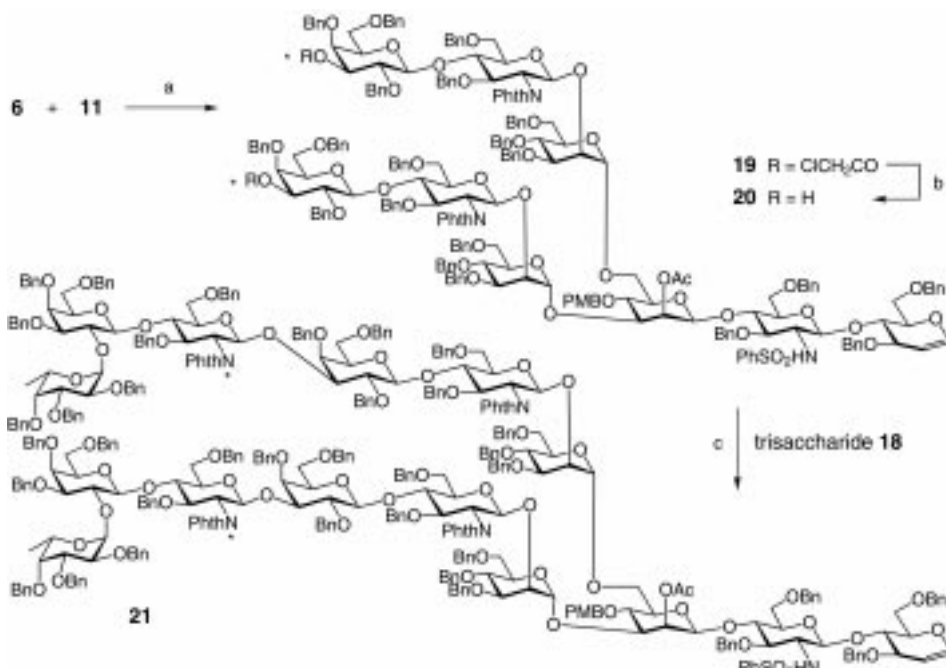
A concise fashioning of the H-type antigen is shown in Scheme 3. The galactal donor system **12** was actuated by strict α -face epoxidation. The α -epoxide coupled to **13**, notwithstanding the hindered nature of its acceptor site (marked with an asterisk). The C-2' alcohol specifically unveiled in the coupling step serves as the acceptor site for the L-fucosyl



Scheme 3. Synthesis of "wing" trisaccharide **18**: a) 1. DMDO/CH₂Cl₂; 2. ZnCl₂; 3. SnCl₄/AgOTf/DTBP/CH₂Cl₂, 50 % (three steps); b) 1. TBAF/THF; 2. BnBr/NaH/DMF, 81 % (two steps); 3. IDCP/TMSCH₂CH₂SO₂NH₂; 4. EtSLi/DMF/−40 °C–0 °C, 75 % (two steps); c) CsF/DMF/100 °C, 5 days, 65 %; d) 1. phthalic anhydride/Py/22 °C; 2. Ac₂O, 97 % (two steps). TIPS = triisopropylsilyl.

donor **14**. This glycosylation leads to the α -L-fucoside **15**. The glycal found in **15** was advanced to **18** (through **16** and **17**) with chemistry previously developed on simple systems with such applications in mind.

We next turned to the assembly of these carefully crafted subunits. The program commenced with twofold coupling of **6** with **11** (Scheme 4). Fortunately, this goal could be accomplished in good yield to produce the 9-mer **19** through an apparently stereospecific sulfonamidoglycosylation reaction, modulated by the neighboring phthalamido linkages.^[18] The two positionally defined acceptor sites (marked with asterisks) of the nonasaccharide were unveiled as shown. Fortunately, coupling of **20** with H-type donor **18** occurs at each of the lactosamine moieties, again under mediation by methyl triflate, to afford 15-mer glycal **21**.



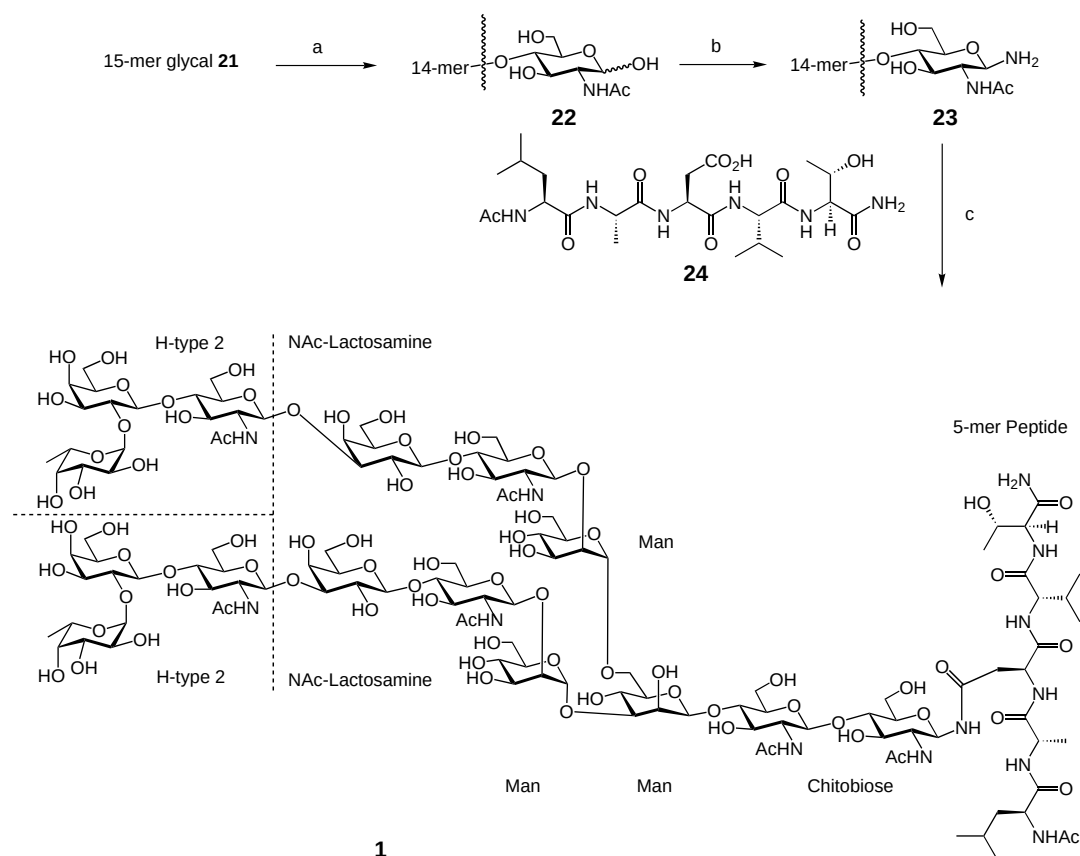
Scheme 4. Synthesis of the protected 15-mer glycal **21**. a) MeOTf/CH₂Cl₂/Et₃O/DTBP, 62 %; b) (NH₄)₂C=S/EtOH/NaHCO₃, 99 %; c) trisaccharide **18**/MeOTf/CH₂Cl₂/Et₃O/DTBP, 78 %.

Much planning and trial and error research went into accomplishing the global deprotection of the 15-mer (Scheme 5). The four phthaloyl groups of **21**, as well as the hindered acetate on the C ring, were deprotected concurrently. We next carried out the iodosulfonamidation of the glycal linkage at the reducing end of the 15-mer. This addition was followed by hydrolytic rearrangement (a four-step sequence). The critical massive deprotection step could now be realized. Thus, 37 benzyl groups and the sulfonamido function were all reductively cleaved through the agency of sodium/

ammonia.^[19] Remarkably, the terminal hemiacetal linkage was sufficiently robust such that there was no detectable reduction to an alditol under these conditions. Furthermore, selective acetylation of the lone amino function in the A ring was readily achieved in the polyhydroxyl substrate system. This remarkable sequence led to the free hemiacetal **22**, which was, in turn, converted into **23** by ammonolysis of the masked aldehyde.^[20] In the concluding step, the polyhydroxyl glycosylamine **23** coupled with differentiated pentapeptide **24** to produce the desired β -glycosyl N-linked glycopeptide target system **1** (m/z : calcd 3305 [M^+]; found 3328 [$M+Na$]⁺).^[21]

While the yield of this compound may appear modest, detailed NMR spectroscopic analysis fully corroborates that compound **1** meets the standard of homogeneity while displaying its H-type2 serological determinant in the context of an N-acetyllactosamine glycopeptide. The availability of such an advanced N-linked glycopeptide provides excellent opportunities for probing glycoarchitecture and its biological consequences. As seen in Figure 1, the ¹H NMR spectrum (800 MHz) of the 15-mer oligosaccharide system linked to the 5-mer peptide is extremely well resolved and suggestive of structural order. Detailed analysis of mutual conformational effects between the oligosaccharide and peptide domains using high level NMR spectroscopic techniques will be reported separately.

In addition to the critical nuclear magnetic resonance spectroscopic and mass spectrometric measurements that support our structural claim on behalf of compound **1**, it was



Scheme 5. Synthesis of the fully synthetic and homogeneous 15-mer glycopeptide **1**. a) 1. $\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2/\text{EtOH}$; 2. $\text{Ac}_2\text{O}/\text{Py}/\text{DMAP}$, 85 % (two steps); 3. $\text{IDCP}/\text{NH}_2\text{SO}_3\text{Ph}$, 74 %; 4. $\text{LiHMDS}/\text{AgOTf}/\text{THF}/\text{H}_2\text{O}$, 63 %; 5. $\text{Na}/\text{NH}_3/\text{THF}$; 6. $\text{Ac}_2\text{O}/\text{MeOH}$, 46 % (two steps); b) $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$, 90 %; c) peptide **24**/HOBt/HBTU/DIPEA/DMSO, 20 %.^[21] DIPEA = diisopropylethylamine, DMSO = dimethyl sulfoxide, HBTU = *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, HOBt = 1-hydroxy-1*H*-benzotriazole, Man = mannose.

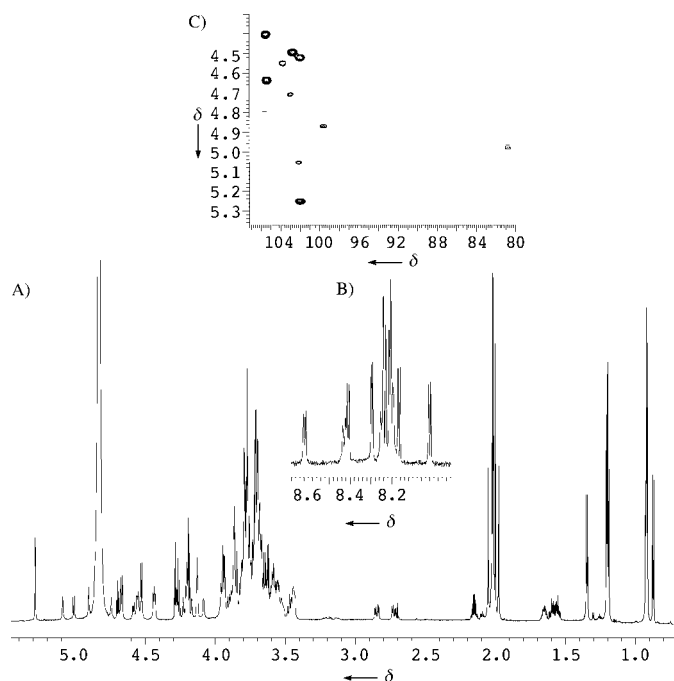


Figure 1. A) ^1H NMR (800 MHz) spectrum of **1** in D_2O at 20°C and pH 3.7 (phosphate buffer). B) Section of the spectrum of **1** in H_2O at 5°C and pH 3.7 (phosphate buffer) showing the secondary NH signals of amides from the peptide backbone, side chain, and GlcNAc sites. C) The anomeric region of the ^1H - ^{13}C HMQC spectrum at 800 MHz of **1** in D_2O at 20°C and pH 3.7 (phosphate buffer).

of interest to establish that the H-type constructs, so presented, maintain functionality. Indeed, the presence of operational H-type2 blood group determinants in the synthesized product was confirmed by demonstrating its reactivity with an antibody against H-type2 determinants (mAbSA) in an enzyme-linked immunosorbent assay (ELISA; Figure 2). This antibody is highly specific for H-type2 blood group determinants and does not react with H-type1, Le^a , or Le^x structures.^[22, 23]

This synthesis serves to illustrate the current reach of the glycal assembly method. More broadly it shows the extra-

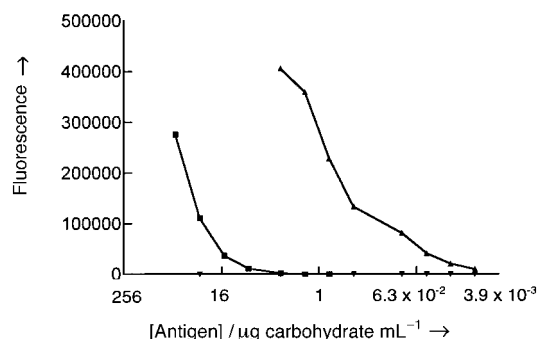


Figure 2. Reactivity of glycopeptide **1** (■), H-type2 active mucin (▲) as a positive control, and Le^a/Le^x -active mucin (▼) as a negative control with the antibody against H-type2 determinants (mAbSA) as determined with an ELISA. The mucin preparations have been previously described (see ref. [22]).

ordinary progress in the field of oligosaccharide and glycopeptide synthesis. Given the extendibility of this chemistry to virtually any type of saccharide presentation and the capacity, in principle, for ligation of the pentapeptide construct to larger polypeptide or protein domains,^[24] the synthesis of sequence-defined homogeneous glycopeptides, and thence glycoproteins, is at hand. Studies directed toward reaching fully functional glycoproteins by total synthesis are underway.

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Enhanced Physical Properties in a Pentacene Polymorph

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Pentacene is a highly promising material for application in thin film transistor devices because of its recently reported high mobilities and good semiconducting behavior.^[1] For this reason, we have carried out a program to grow single crystals of unusually high purity and crystalline perfection to study the intrinsic properties of organic semiconductors. We have produced millimeter-sized crystals with electrically active impurities at concentrations of the order of 10¹³ cm⁻³ (or one impurity molecule per 10⁸ pentacene molecules) by using a vapor-phase deposition technique. Such crystals were used for

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Total Synthesis of Azinomycin A**

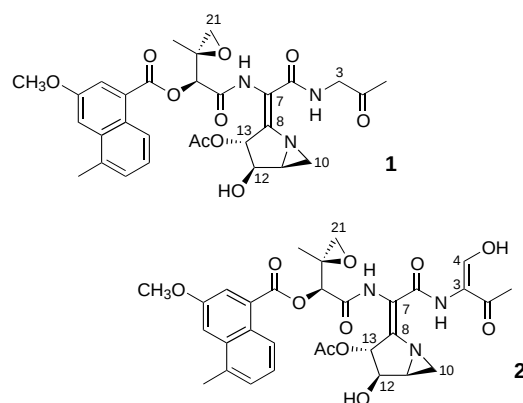
Robert S. Coleman,* Jing Li, and Antonio Navarro

The azinomycins A and B (**1** and **2**; Ac = acetyl) are a functionally complex family of antitumor agents isolated from fermentation broths of *Streptomyces griseofuscus*.^[1] These natural products are of synthetic interest because of the unprecedented and densely functionalized aziridino[1,2-*a*]pyrrolidine ring system; additional attention has been focused on these agents because of their potential as lead compounds for the design of novel chemotherapeutic agents.^[2] To date, and despite considerable effort from a number of laboratories,^[3] the total synthesis of these challenging targets has not been achieved. Herein, we describe an asymmetric total synthesis of azinomycin A (**1**) that represents the first entry into this family of natural products.

The azinomycins exhibit cytotoxicity against at sub-microgram per milliliter concentrations, but, more important, these agents show antitumor activity in mouse models that is comparable to that of mitomycin C.^[4] Unfortunately, a detailed evaluation of the scope of the biological activity of the native agents has been prevented by the poor availability and significant instability of the agents, factors that have similarly impeded synthetic efforts.

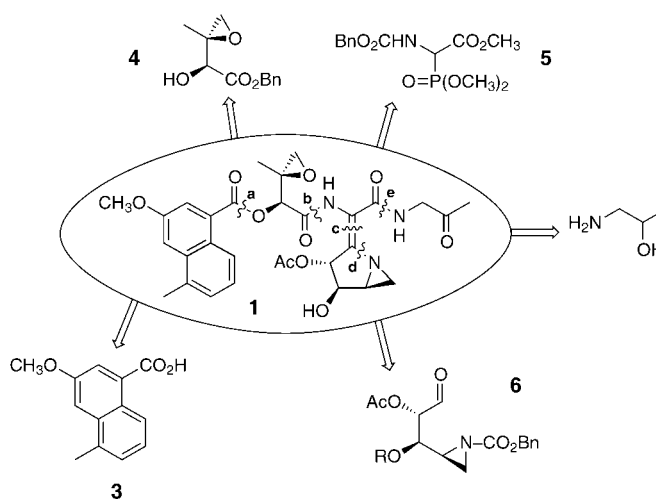
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The azinomycins are one of a small set of molecules that interact with DNA in the major groove.^[5] Azinomycin B (**2**) forms a covalent interstrand cross-link^[6] between suitably disposed purine bases in the duplex sequence 5'-d(PuNPY)-3', but the structural origin of the sequence selectivity and binding affinity are incompletely defined. We have recently described a computationally based model^[7] that explains the experimentally observed cross-linking of azinomycin B (**2**).^[8]

We now report the asymmetric total synthesis of azinomycin A (**1**) that is based on a convergent and modular synthetic plan (Scheme 1). By the five disconnections at ester, amide,



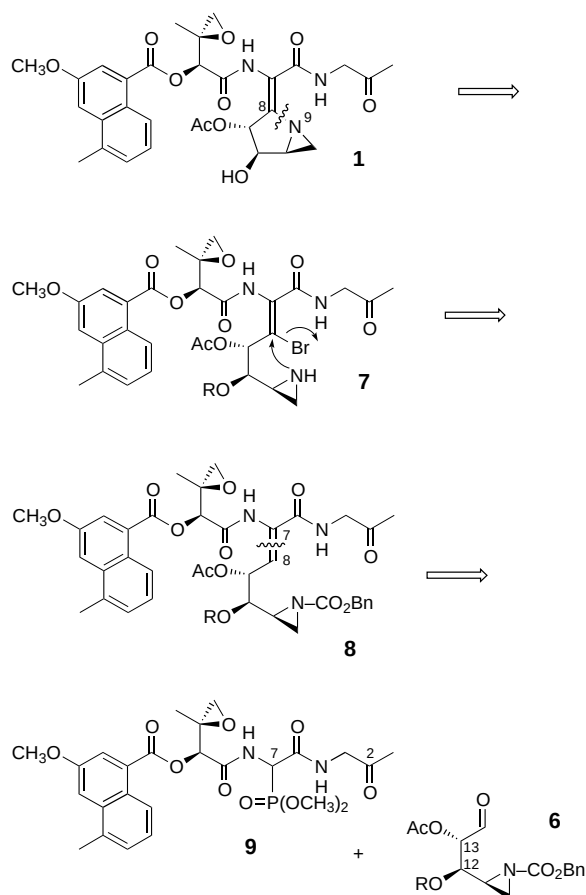
Scheme 1. Modular and convergent synthetic strategy. Bn = benzyl.

olefin and C–N bonds, a–e, we arrive retrosynthetically at five simple fragments: 1) naphthoic acid **3**,^[2a] 2) epoxyalcohol **4**,^[9] 3) glycine phosphonate **5**,^[10] 4) aziridine carbaldehyde **6**,^[11, 12] and 5) 1-amino-2-propanol. The ordering of steps a–e was not predetermined, although we had established the necessity of introducing the reactive azabicyclic system (bond d) as the penultimate step. The most relevant variable was the timing of the C7–C8 dehydroamino acid olefination of aldehyde **6** (bond c) with respect to amide bond formations b and e. In other words, would the dehydroamino acid be introduced before or after elaboration of the amide/ester backbone?

Olefination of aldehydes such as **6** with glycine-based phosphonates is problematic due to the proximal C13 acetyl group.^[13] However, having the acetate installed prior to olefination avoided problematic protecting group manipulations on advanced dehydroamino acid systems.^[13b] We viewed the strategy of bringing the “top half” of the molecule into the olefination reaction intact (bond c) as more advantageous than the complementary strategy of building the C7–C8 dehydroamino acid double bond before incorporating the left (bond b) and right portions (bond e), since this strategy minimized transformations on systems bearing the reactive aziridine ring. In the end, **1** was synthesized by formation of bonds a and e first, followed by bonds b, c, and finally d (Scheme 1).

The most important step requiring stereochemical control is the intramolecular addition–elimination reaction sequence of **7** to form the azabicyclic ring system of **1** (Scheme 2). Stereocontrol in the bromination of **8** is critical to constructing the *E*-olefin of **1**, because the addition–elimination reaction sequence of **7** is stereospecific.^[13] The C7–C8 double bond of **8** was formed by an olefination reaction^[14] between aldehyde **6**^[11] and the phosphonate “top piece” **9**. This synthetic strategy is direct, but it relies on a complex, high-risk olefination reaction between **6** and **9** as the convergent step.

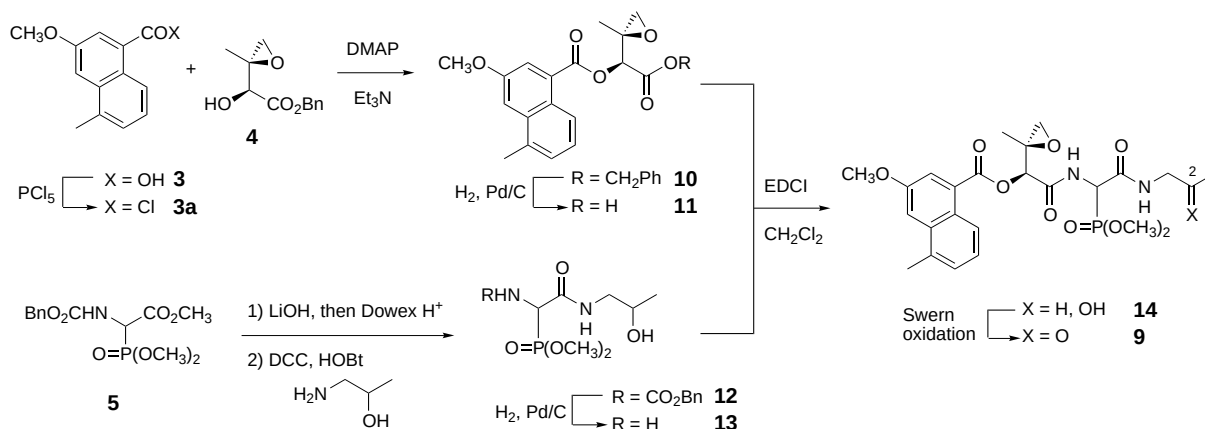
Phosphonate **9** was constructed in a convergent fashion by a series of ester and amide bond formations (Scheme 3). Naphthoic acid **3** (X = OH), most effectively prepared according to Shibuya and co-workers,^[2a] was activated as the acid chloride **3a** (X = Cl; PCl₅, Et₂O, reflux, 2 h) and coupled under standard conditions (DMAP, Et₃N, CH₂Cl₂, 0 °C, 4 h) with enantiomerically pure epoxyalcohol **4**, prepared by Sharpless kinetic resolution,^[9] to afford **10** (88%). Hydrogenolysis of the benzyl ester of **10** (1 atm H₂, 10% Pd/C, MeOH, 2 h, 25 °C) afforded unstable epoxyacid **11** (> 99%), which was coupled directly with the aminophosphonate **13**. This, in turn, was prepared from glycine phosphonate **5** by saponification (LiOH, THF/MeOH/H₂O, 25 °C, 30 min) to afford the crude acid in quantitative yield after acidification with Dowex H⁺. The acid was coupled with (±)-1-amino-2-propanol using dicyclohexylcarbodiimide (HOBt, CH₂Cl₂, 0–25 °C, 24 h) to afford **12** (86%). Hydrogenolysis of the benzyl



Scheme 2. Retrosynthetic analysis of the azabicyclic system.

carbamate of **12** (1 atm H₂, 10% Pd/C, MeOH, 25 °C, 2 h) afforded amine **13** (> 99%). Coupling of acid **11** and amine **13** using ethyl(3-dimethylaminopropyl)carbodiimide (HOBt, CH₂Cl₂, 0–25 °C, 9 h) afforded the fully elaborated “top half” phosphonate **14** in good yield (79%).

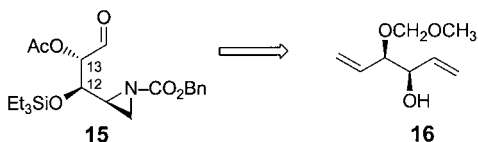
At this point, we dealt with the issue of the C2 oxidation state by synthesizing ketone **9** by Swern oxidation of alcohol **14** (DMSO, (COCl)₂, Et₃N, CH₂Cl₂, –78 °C, 83%). The



Scheme 3. Synthesis of the intact phosphonate “top piece”. DMAP = 4-dimethylaminopyridine, DCC = dicyclohexylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole, EDCI = ethyl(3-dimethylaminopropyl)carbodiimide.

avoidance of synthetic manipulations subsequent to dehydroamino acid introduction outweighed potential problems with a competing, intramolecular olefination.

The other partner in the Wadsworth–Horner–Emmons olefination reaction was aldehyde **15** (Scheme 4), which was prepared in a high yielding sequence of reactions from



Scheme 4. Origin of the azabicyclic precursor aldehyde.

unsymmetrically protected 1,5-hexadiene-3,4-diol **16**, available using Brown's diisopinylcamphylborane reagent,^[15] as described previously.^[11a,c] For the present work, we used a triethylsilyl ether for protection of the C12 hydroxy group of **15** (azinomycin numbering) rather than the previously described *para*-methoxybenzyl ether; the C13 acetyl group was carried through the synthesis intact.

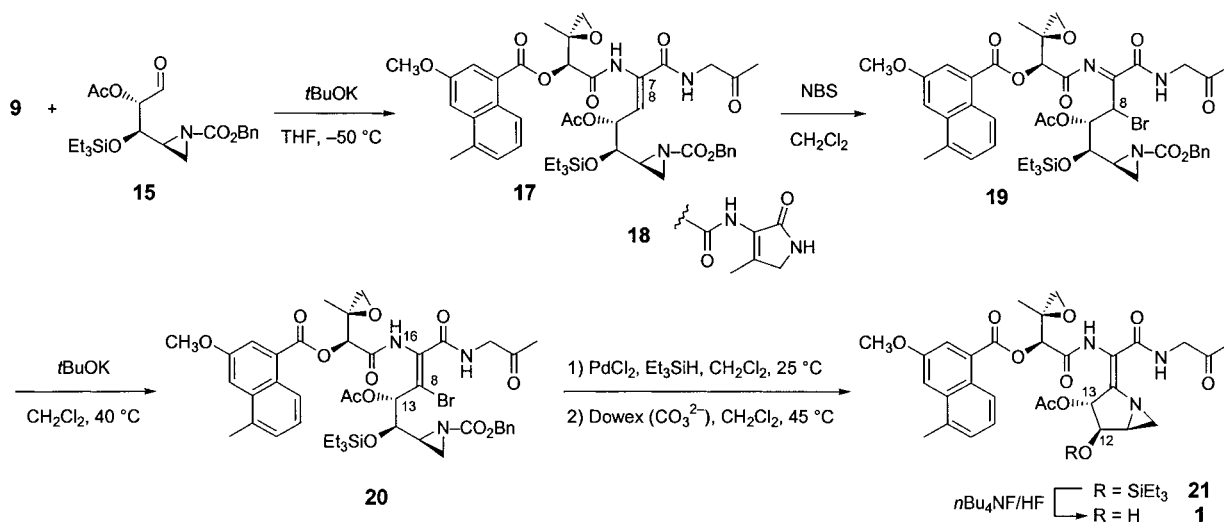
Wadsworth–Horner–Emmons olefination of aldehyde **15** with the phosphonate **9** bearing the C2 carbonyl group (Scheme 5) proceeded smoothly using potassium *tert*-butoxide at low temperature (THF, -50°C , 18 h). The (*Z*)-dehydroamino acid **17** could be isolated as the major product of the reaction with the minor *E* isomer in a modest yield (40%), which thereby completed formation of the entire azinomycin skeleton. The low yield for this transformation was more than offset by the sheer simplicity of the approach to this advanced intermediate, particularly with regard to the successful avoidance of protecting group manipulations and oxidations subsequent to olefination, which have proven to be the downfall of other approaches to **1** and **2**. To our satisfaction, intramolecular olefination of the phosphonate anion onto the C2 ketone of **9** to afford **18** proved to be a minor reaction pathway ($\leq 5\%$).

Introduction of the vinyl bromide necessary for pyrrolidine formation proved to be problematic, despite the extensive

previous work on simple model systems.^[16] The initial bromination of **17** (Scheme 5) proceeded smoothly using *N*-bromosuccinimide in the presence of a silica gel catalyst (CH_2Cl_2 , 25°C , 30 min) to afford the isolable α -bromoimine **19** (75%). Unfortunately, previously defined conditions to effect tautomerization to the vinyl bromide (*E*)-**20** (that is, 2,2,6,6-tetramethylpiperidine, 25°C , 18 h), or the use of other amine bases (for example, DABCO, DMAP, Et_3N), gave the undesired isomer (*Z*)-**20** as the sole vinyl bromide product, and was often accompanied by products resulting from hydrolysis of the imine C=N bond (DABCO = 1,4-diazabicyclo[2.2.2]octane). Alkoxide bases (*t*BuOK, CH_2Cl_2 , 40°C , 18 h) proved more effective at providing the correct vinyl bromide (*E*)-**20**,^[17] but it was always formed as a separable mixture with the undesired (*Z*)-vinyl bromide. The configuration about the stereogenic double bond of (*E*)-**20** was assigned by correlation with spectral data of related systems,^[18] and by the observation of a reciprocal nuclear Overhauser enhancement between C13-H and N16-H (C13-H $\rightarrow$ N16-H: 7.1%; N16-H $\rightarrow$ C13-H: 8.7%).

Selective removal of the aziridine *N*-benzyl carbamate of **20** (Scheme 5) using a palladium-catalyzed, silane-mediated process (Et_3SiH , PdCl_2 , Et_3N , CH_2Cl_2 , 25°C , 50 min)^[19] afforded the corresponding free aziridine (50% yield of isolated product), without complication from reduction of other functional groups in the molecule (that is, the vinyl bromide and olefin).^[20] Cyclization was effected upon warming in the presence of Dowex anion exchange resin (CO_3^{2-} form, CH_2Cl_2 , 45°C , 18 h) to afford 12-*O*-triethylsilyl azinomycin A (**21**), stereospecifically and as a single stereoisomer (64%).^[21] Final removal of the C12 hydroxy protecting group with *n*Bu₄NF/HF/pyridine^[22] (THF, 25°C , 50 min, 95%) afforded unstable azinomycin A (**1**),^[23] identical with an authentic sample by ^1H NMR and thin layer chromatography (silica gel; EtOAc, 5% MeOH/ CHCl_3 , and acetone), and thereby completed the total synthesis of a natural product that has proven to be among the most elusive of synthetic targets.

As we anticipated from previous studies^[24] and from observations made during isolation of the azinomycins from



Scheme 5. Olefination, bromination, pyrrolidine introduction, and completion of the total synthesis of azinomycin A. NBS = *N*-bromosuccinimide.

their natural source,^[25] the synthetic material proved unstable. This instability is largely, if not exclusively, a result of the C12-hydroxy group of **1**, since the penultimate intermediate 12-*O*-triethylsilyl azinomycin A (**21**) possessed a greater degree of stability towards isolation. Not surprisingly, one of the major pathways of reactivity of **1** is ring opening of the aziridine by nucleophilic attack at C10. The instability of the natural products has prevented their study as chemotherapeutic agents, and overcoming this will require further work to understand both the mechanism by which the instability is manifested and to construct structurally and functionally related agents for more detailed biological evaluation.

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Immunosensing by a Synthetic Ligand-Gated Ion Channel**

Samuel Terrettaz, Wolf-Peter Ulrich, Remo Guerrini, Antonio Verdini, and Horst Vogel*

Cell signaling is often mediated by pore- and channel-forming membrane proteins, whose function can be controlled either by changing the transmembrane electrical potential or by the binding of ligands. Although the structure of most native membrane channels is unknown at a molecular level, it is rather attractive to copy this principle of biological signaling by incorporating synthetic ligand-gated ion channels (SLICs) into an electrically insulating lipid bilayer tethered chemically to a gold electrode. The newly designed SLICs should change their transmembrane ion conductance by selectively binding an analyte.^[1] By this intrinsic amplification of a binding reaction it should be possible to develop highly sensitive biosensing devices. Recent studies have shown that molecular reactions of proteins in tethered lipid membranes can be measured with high sensitivity, either optically or electrically.^[2]

Figure 1 shows an example of a new class of SLIC molecules made of branched polypeptides. Conceptually, a SLIC comprises a ligand-binding and a channel-forming region. As a ligand-binding region we have chosen a peptide, the repetitive NANP sequence,^[3] which is recognized by a specific monoclonal antibody. The NANP sequence is the major B-cell epitope of the circumsporozoite protein of *Plasmodium falciparum*, the cause of human malaria.^[4] The channel-forming part is built by four melittin peptide segments that are chemically attached to the branched spacer. The melittin sequence was chosen because of its well-known channel-forming properties.^[5] The SLICs were directly attached to a sensing gold electrode through a sulfur-bearing peptide spacer in order to create a robust device. The direct chemical tethering of the protein has the advantage of fixing its orientation in the supported lipid bilayer. A synthetic thiolipid^[2f, 6] containing a sulfur-terminated spacer of similar length as that of the SLIC and the phospholipid POPC were

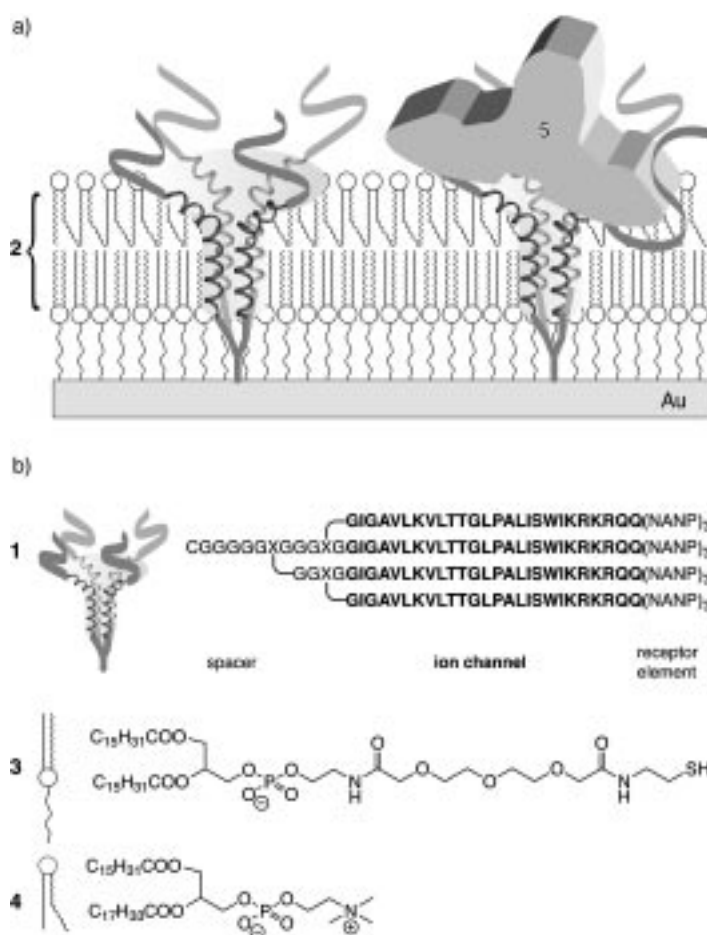


Figure 1. a) Schematic view of a synthetic ligand-gated ion channel (SLIC) in a tethered lipid bilayer (2). The SLICs and the thiolipids were covalently attached to the gold surface through terminal SH groups. The gating of an ion channel by the binding of an antibody molecule (5) is schematically illustrated. b) Amino acid sequence of the SLIC (1) in one-letter-code. X is used for the amino acid ornithine, which allows the synthesis of branched polypeptides. The SLIC is shown to traverse the bilayer as a four-helix bundle formed by the hydrophobic melittin parts (bold regions). Chemical formulas of the synthetic thiolipid (3) and of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC; 4) are also depicted.

added sequentially to build a lipid bilayer (Figure 1). The supported molecular layer on the gold surface was characterized at every stage of formation by surface-sensitive techniques: 1) infrared (IR) spectroscopy provided details about the structural organization of the layers, 2) surface plasmon resonance (SPR) was used to measure the surface concentration of each component of the supported molecular layer, and 3) impedance spectroscopy (IS) showed that an initial tethered monolayer of thiolipids increased the electrical insulation of the supported bilayer substantially.

Reference IR spectra were first recorded from bulk SLIC samples on CaF₂ plates (Figure 2a). Deconvolution of the amide I and II bands of the SLIC on CaF₂ reveals there is a large content of α -helix that compares well with pure melittin, both in frequency and relative intensity.^[7] Hence the α -helical structure of melittin is preserved in the SLIC.

Reflectance absorbance (RA) spectra (Figure 2, spectra (b)–(d)) of the tethered thiolipid/SLIC layers on gold proved that the SLICs were not replaced by the thiolipid

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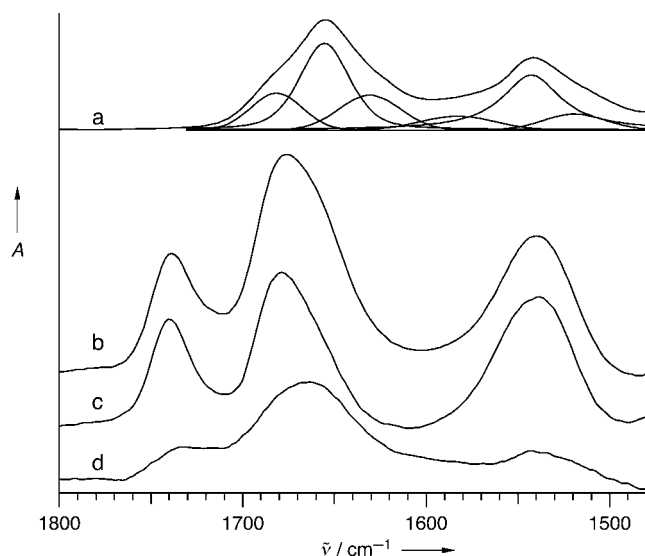


Figure 2. IR spectroscopy of the SLIC. Transmission spectrum of bulk SLICs on CaF_2 (a). The maximum of the amide I band is located at 1655 cm^{-1} . Curve fitting shows that this component accounts for 57% of the total amide I absorbance. In the RA spectrum of the mixed thiolipid/SLIC layer on gold (b) the amide I and II modes of the peptide are obscured by the strong amide I and II modes of the thiolipid (c). In the difference spectrum (d) the spectral contribution of the thiolipid has been subtracted from the spectrum of the mixed layer. For the subtraction, the thiolipid spectrum was weighted by a factor of 0.85 to account for the lower lipid content in the mixed layer. This factor was derived from the estimated 10 to 20% surface coverage determined by SPR. The subtraction leads to an almost complete extinction of the lipid ester band at 1738 cm^{-1} .

during layer formation. The orientation of the melittin subunits can be deduced from the ratio of the intensities of the amide I:II bands of the SLICs. This is possible because the major components of amide I and II transition moments of α -helical peptides are orthogonal, and on metal surfaces only p-polarized light can be absorbed.^[8] Intensity ratios of 0.1:1 or 5.7:1 have been previously reported for helix orientations parallel or perpendicular to the surface, respectively.^[8] An intensity ratio of amide I:II of greater than 3:1 was measured for the α -helical moieties of the SLIC (Figure 2, spectrum (d)). This value confirms the preferentially perpendicular orientation of the melittin moieties with respect to the surface.

The binding of the Sp3E9 antibody to a pure layer of SLICs was monitored by SPR (Figure 3 (a)). As a consequence of efficient rebinding at the surface, only a small amount of antibody could be desorbed by washing with buffer (b).^[9] A rapid dissociation was however induced by the competitive binding of the free antigen C(NANP)₆Y (c). Although, as seen previously,^[10] not all surface-bound antibodies could be displaced under these conditions, the true nonspecific adsorption measured using bovine IgG was negligible. The amount of bound Sp3E9 at saturation scaled with the SLIC content in mixed layers of lipids and SLIC. The binding of the antibody Sp3E9 did not induce any remarkable change in the electrical impedance spectra of tethered lipid bilayers with molar thiolipid:protein ratios smaller than 200:1 (data not shown). At these high surface concentrations of SLICs the tethered lipid bilayers are not sufficiently electrically blocking. There-

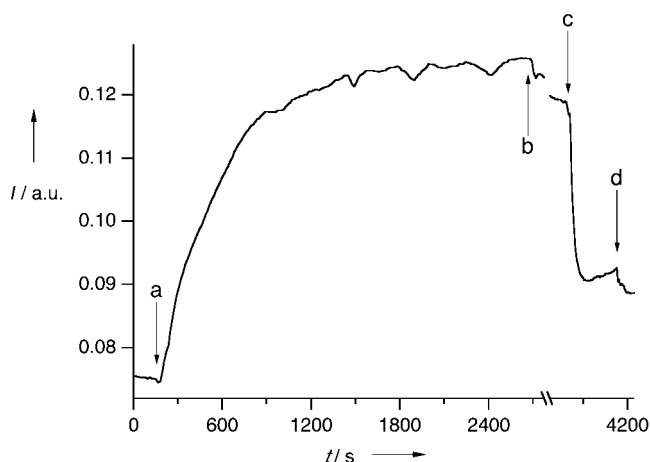


Figure 3. Change of the SPR signal of a gold film covered by a SLIC monolayer after adding 10^{-7} M antibody Sp3E9 to the aqueous phase (a), washing with buffer (b), adding of 10^{-3} M competitive ligand C(NANP)₆Y (c), washing with buffer (d). The change of reflectivity at (b) originates from a shift of the SPR resonance angle of 0.72° as a result of bound antibodies at a surface concentration of 1 antibody per 81 nm^2 .

fore, the charging current of the large interfacial (double-layer) capacitance dominates the impedance spectra at all frequencies.

Increasing the thiolipid:protein ratio to approximately 2200:1 increased the membrane resistance R_M sufficiently so that the charging current of the membrane dominated the intermediate frequency range. The resistances of the solution, of the membrane, and of the interface (charge transfer) were then well separated in the impedance spectra (Figure 4). This spectral behavior is typical of supported lipid bilayers on electrodes.^[2c-e] Accurate values of R_M were calculated with the

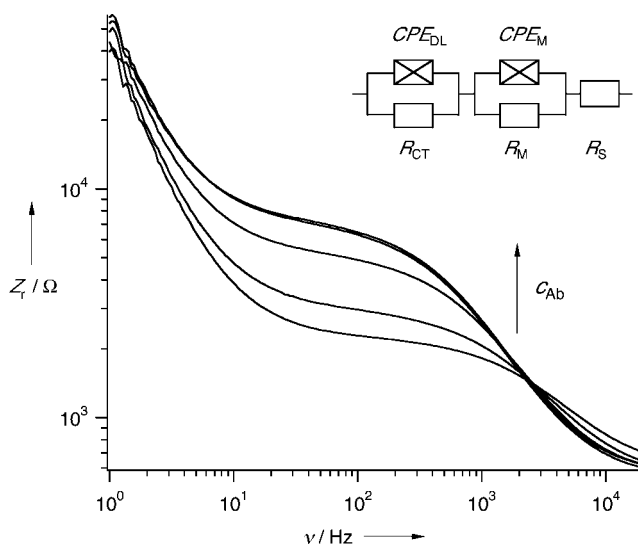


Figure 4. Real part of the impedance spectra of a lipid bilayer containing SLICs at various concentrations of antibody (from bottom to top): 0 , 10^{-9} , 3×10^{-9} , 10^{-8} , and $3 \times 10^{-8}\text{ M}$. The resistances of the interface (charge-transfer, R_{CT}), the membrane (R_M), and the electrolytic solution (R_S) are spectrally well resolved; distributed elements (CPE_{DL} and CPE_M) are used for a very accurate fit of the dielectric properties of the interface and of the membrane, respectively. The increase of R_M as a function of the antibody concentration in the bulk solution is seen at frequencies between 10 Hz and 1 kHz.

equivalent circuit of Figure 4. Here, the important finding is the increase in the value of R_M in the presence of nanomolar concentrations of the antibody Sp3E9 in the bulk solution. Figure 5 shows the time course of the corresponding admit-

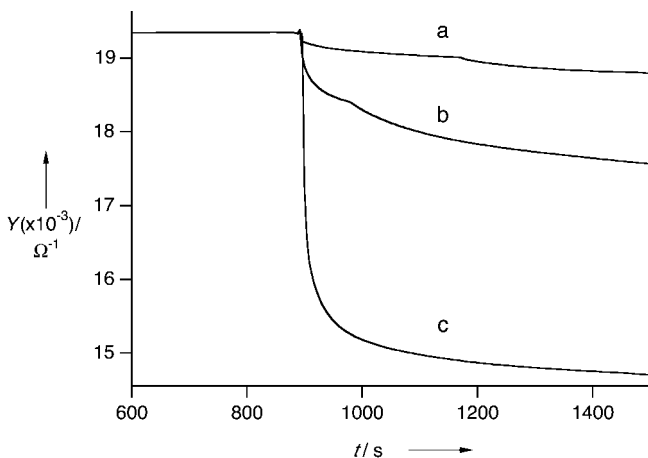


Figure 5. Electrical admittance (measured at 180 Hz) of a tethered lipid bilayer containing SLICs after the addition of buffer containing 3×10^{-7} M IgG (a), 3×10^{-9} M Sp3E9 (b), and 3×10^{-8} M Sp3E9 (c).

tance at various antibody concentrations. Unspecific adsorption of IgG at even a hundredfold higher concentration than used for Sp3E9 (Figure 5, spectrum (a)) was much smaller than the specific binding of Sp3E9 (Figure 5, spectra (b) and (c)). The major part of the response could be reversed by washing with buffer, since the fraction of rebound antibodies Sp3E9 was very small at this low density of surface-bound antigens.^[9]

The modulation of the R_M value with the antibody concentration in the electrolyte is plotted in Figure 6. The binding curve indicates some cooperativity and is best fitted by a Hill function with a dissociation constant of 2.4×10^{-9} M and a Hill coefficient of 2.1. From a comparison of the values of R_M measured before and after a buffer wash the reversibility of the response is shown to be always larger than 50%. The reported relative effect of antibody binding is large: the

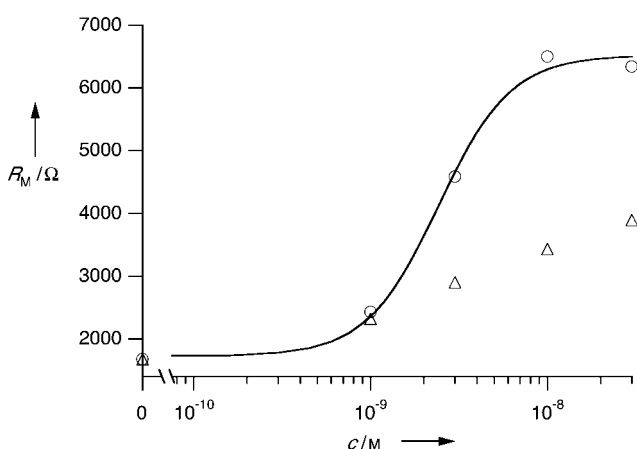


Figure 6. Electrical resistance R_M of the tethered lipid bilayer containing SLICs after antibody binding at different bulk concentrations c of Sp3E9 before (○) and after (△) washing with buffer.

membrane resistance increases by almost a factor of four at saturation. The absolute increase of approximately 4500 Ω is however limited by the number of defects in the lipid layer. The values of R_M obtained after complete antibody binding are indeed very close to the limiting values measured for the pure lipid bilayers. The complete blocking of 1% of the surface-bound SLIC is sufficient to account for the reported effect.^[11] Enhanced sensitivity is therefore expected with membranes having higher electrical resistances. Measurements on smaller electrodes would be useful if smaller changes in conductance need to be detected.

In conclusion, the gating of an artificial receptor was monitored for the first time by impedance spectroscopy in tethered lipid bilayers. Subnanomolar concentrations of antibody were detected by modulation of the channel activity. The principle of gating by an antibody is particularly attractive because of its general character, and thus opens new possibilities for immunosensing.^[12]

Experimental Section

The branched polypeptides (SLICs) and $C(NANP)_6Y$ were assembled by linear solid-phase peptide synthesis on Wang resin following the Fmoc/Bu strategy (Fmoc = 9-fluorenylmethoxycarbonyl). The polypeptides were cleaved from the resin by treatment with a mixture of trifluoroacetic acid (88%), water (2%), and triisopropylsilane (10%). The crude products were prepurified by size-exclusion chromatography on Sephadex G50 Superfine using 50% acetic acid as the eluant. The fractions containing the target products were pooled and purified by RP-HPLC on a Vydac C_{18} column. The molecular weights were controlled by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MW: 17155 Da for the SLIC). The thiolipid N -(14'-sulfanyl-1',11'-dioxo-3',6',9'-trioxa-12'-azatetradecyl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine^[2f] and the competing antigen $C(NANP)_6Y$ ^[10] were synthesized as described earlier. 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine was obtained from Avanti Polar Lipids (Alabaster, AL), and the bovine IgG from Sigma (St. Louis, MO). The monoclonal antibody Sp3E9 was a generous gift from H. Matile (Hoffmann – La Roche, Switzerland); it was raised in mice against the synthetic peptide $(NANP)_{40}$ as described elsewhere.^[13]

A 45-nm thick film of gold was prepared by evaporation through a metallic mask on a glass slide silanized with (3-trimethoxysilyl)propylthiol. Sulfur-bearing molecules were self-assembled on gold directly in the measurement cells and the layer formation was monitored in situ by SPR and IS. In order to prepare layers with a thiolipid:protein ratio smaller than 200:1, SLIC molecules were adsorbed by spreading small unilamellar vesicles composed of POPC and SLIC followed by a detergent or methanol wash. SLIC monolayers with a thiolipid:protein ratio of 2200:1 were produced by prior self-assembly of SLIC at a low concentration (10^{-8} M) in buffer. The surface-immobilized SLICs were first integrated into a tethered lipid monolayer by adding thiolipids from a detergent solution. The lipid bilayer was then completed by an external POPC monolayer by using a dilution method from detergent^[2a] or a methanol^[14] solution. Antibody binding to the sensor surface was measured under constant antibody concentration in the bulk as described earlier.^[10]

SPR measurements were performed on a home-made reflection apparatus.^[2a] Organic molecules adsorbed at the gold surface led to a shift of the resonance angle, which was used to calculate their optical thickness. Assuming a refractive index of $n=1.45$, an experimental shift of 1° corresponded to a thickness of 6.4 nm. The mean molecular area of the adsorbed proteins was calculated with a refractive index increment of $0.18 \text{ g}^{-1} \text{ cm}^3$.^[2e]

Infrared spectra were recorded using a Bruker IFS28 spectrometer equipped with a HgCdTe detector. Spectra were background-corrected using the respective bare supports and presented at 4 cm^{-1} resolution with triangular apodization. Absorbance spectra of SLICs as bulk solid samples

were obtained in transmission mode by drying methanolic solutions of the SLICs on precleaned CaF₂ windows. Reflectance absorbance spectra were recorded at an angle of incidence of 85° using p-polarized light. The amide I and II bands were deconvoluted by applying a curve-fitting procedure based on the Levenberg–Marquardt algorithm using a combination of Gaussian and Lorentzian line shapes. Initial guesses for the curve fitting were determined from second-derivative spectra.

IS was done in an electrochemical cell comprising a membrane-covered gold electrode and a counter/reference Ag/AgCl electrode in 0.1M KCl/5 mm sodium phosphate buffer, pH 7.4. The surface area of the gold disk electrode was 3.34×10^{-2} cm². No direct current voltage was applied. A sinusoidal potential of 10 mV amplitude (root mean square) was applied to the cell at 199 successive frequencies equally spaced on a logarithmic scale from 1 to 20 KHz. The resulting current was recorded by a phase-sensitive lock-in amplifier to calculate the complex impedance and admittance. Details on the interpretation of IS spectra can be found in the Supporting Information.

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Super-“Amphiphobic” Aligned Carbon Nanotube Films**

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Carbon nanotubes (CNTs) are of tremendous interest for both fundamental and applied research^[1–6] since they show unique properties. Wettability is an important factor for a material. Ebbesen and co-workers have studied the wettability of CNTs in detail and found they could be wet and filled by different substances.^[7] In order to assess the properties of CNTs easily, it is highly desirable to prepare aligned carbon nanotube (ACNT) films in which the nanotubes are perpendicular to the substrate surface and densely packed with a fairly uniform length and diameter. To the best of our knowledge, no attention has been paid to the wettability of ACNT films.

In general, the wettability of solid surfaces is controlled by the chemical composition and the geometrical structures of the surfaces, and it is usually enhanced by surface roughness,^[8–12] especially by fractal structures.^[12] Recently, super-hydrophobic or super-lipophobic surfaces, that is, those with a contact angle for water or oil, respectively, that is higher than 150°, ^[8, 12c] have attracted much interest for practical applications. These surfaces have been commonly prepared through the combination of surface roughening and the lowering of the surface energy. However, few reports have concerned super-“amphiphobic” surfaces,^[13] which have both super-hydrophobic and super-lipophobic properties. Öner and McCarthy reported that super-hydrophobic surfaces with a micrometer-scale post structure could be prepared by photolithography and made hydrophobic using silanization reagents.^[14] As the structure of ACNT films is similar to that of these super-hydrophobic surfaces, the films are expected to show special wettability features. Here we report that the nanostructured ACNT films show super-“amphiphobic” properties, namely, the contact angles for both water and oil are larger than 160°.

In a previous paper we demonstrated that honeycombl-like ACNTs could be prepared by pyrolysis of metal phthalocyanines.^[14] The approach used herein for the preparation of ACNT films is similar to that reported previously, namely ACNT films are prepared by pyrolysis of metal phthalocyanines.

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cyanines $\text{FeC}_{32}\text{N}_8\text{H}_{16}/\text{YC}_{32}\text{N}_8\text{H}_{16}$ (abbreviated as FePc/YPc) on quartz glass plates (see Experimental Section). The length of the aligned nanotubes can be varied over a wide range (up to several tens of micrometers) in a controllable fashion by changing the experimental conditions (for example, the pyrolysis time, flow rate). Figure 1 a shows a typical scanning

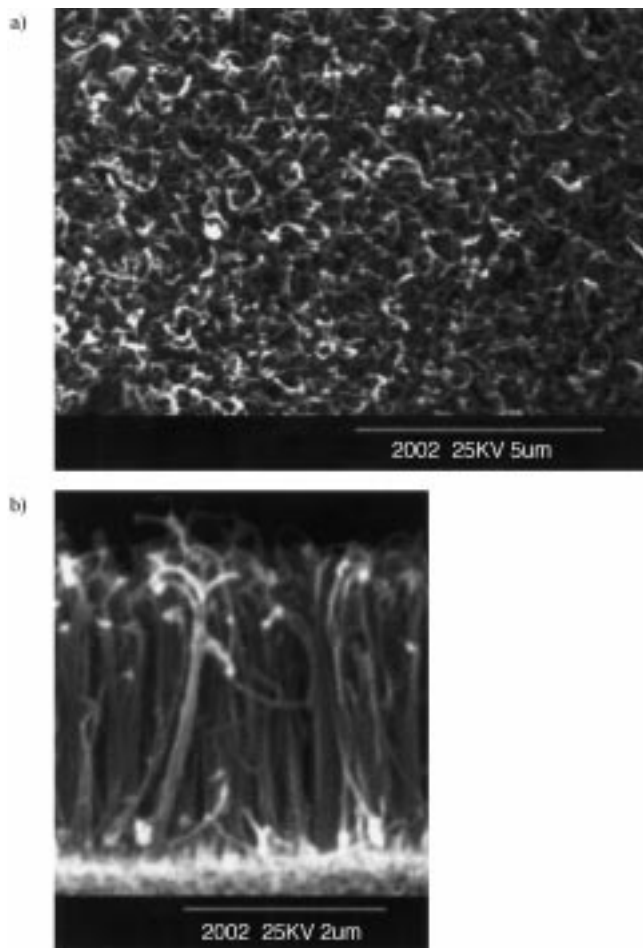


Figure 1. Scanning electron microscopy images of aligned carbon nanotubes peeled off from the quartz substrate. a) Top view of aligned nanotubes obtained by the pyrolysis of metal phthalocyanines. b) Cross-sectional view of aligned nanotubes.

electron microscopy (SEM) image of the top view of the ACNT films, where the aligned nanotubes produced are almost free from pyrolytic impurities (for example, carbon particles and other carbonaceous materials). Depending on the experimental conditions, we can prepare ACNTs with different morphologies, such as those with a bent top end or a vertical top end. ACNTs with a bent top end are shown in Figure 1 a. Figure 1 b shows the cross-sectional image of the ACNT films in which the as-synthesized nanotubes align almost normal to the substrate surface, and the alignments are densely packed with fairly uniform length (ca. $3\ \mu\text{m}$) and external diameter (ca. $60\ \text{nm}$). The as-grown ACNT films are super-hydrophobic and super-lipophilic. The contact angles (CAs) for water and rapeseed oil are 158.5 ± 1.5 and $0 \pm 1.0^\circ$, respectively. The shape of a water droplet on the film is shown in Figure 2 a. However, the CA for water on a film of carbon

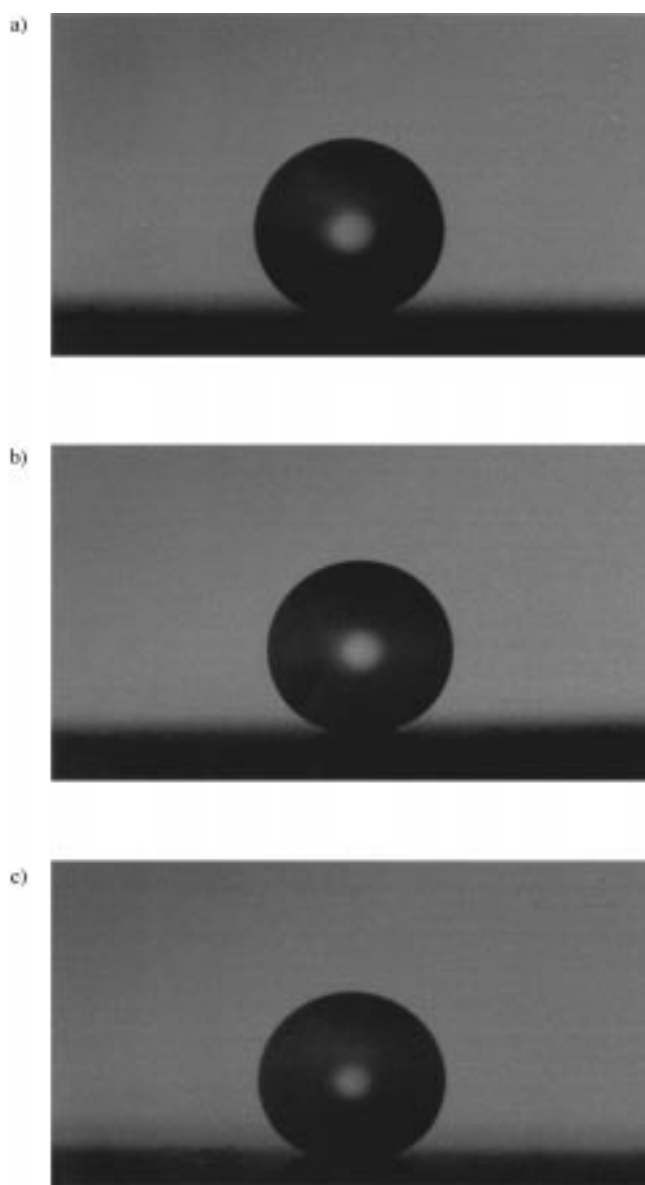


Figure 2. Shapes of water and rapeseed oil droplets (about $1.5\ \text{mm}$ diameter) on the aligned carbon nanotube films: a) a water droplet on the untreated film; b) a water droplet on the treated film; c) a rapeseed oil droplet on the treated film.

nanotubes lying flat on a surface is $136.5 \pm 7.0^\circ$,^[15] which shows that the aligned structure of the ACNT film is responsible for the super-hydrophobic properties.

A low free energy surface is required for a super-lipophobic surface to be obtained, and this can be realized by modifying the ACNT films with fluorinated compounds. Since the surface of ACNTs is rather inert, it is very difficult to modify the surface directly. A hot concentrated mixture of H_2SO_4 and HNO_3 (1:1, v:v) was employed to oxidize the ACNTs for further chemical modification. The contact angle for water on the ACNT film was $128 \pm 3.0^\circ$ after oxidation. It has been reported that some functional groups, such as hydroxyl and carboxyl, can be realized on the surface of CNTs through chemical oxidation treatments.^[16] This possibility indicates that the oxidized ACNT film contains these hydrophilic groups, which result in the severe decrease in the contact

angles for water. Hence, the oxidized films were modified through immersion in a methanolic solution of hydrolyzed fluoroalkylsilane. After this modification the ACNT film contains fluoroalkylsilane groups, which repel both water and oil. The chemical composition of the treated ACNT film was measured by X-ray photoelectron spectroscopy (XPS). The C, F, Si, O, N, S concentrations are 49.7, 36.2, 1.3, 12.1, 0.2, and 0.5 atom %, respectively. The obtained film mainly consists of carbon and fluorine, and thus indicates that the ACNT film was fluorinated. The CAs for water and rapeseed oil on the film were 171 ± 0.5 and $161 \pm 1.0^\circ$, respectively. Hence the film shows both super-hydrophobic and super-lipophobic properties, namely it is a super-“amphiphobic” surface. The water droplets move spontaneously and do not come to rest, even when there is little or no apparent tilt of the surface ($<1^\circ$), while the rapeseed oil droplets remain pinned in one place. The shapes of the water droplet and rapeseed oil droplet on the treated ACNT film are shown in Figures 2b and 2c, respectively. It is clear by comparing Figures 2a and 2b that the water repellency is improved remarkably through fluorination.

Liquids have very large contact angles on ACNT films, and the films are sufficiently rough that the liquid may trap air so as to give a composite surface effect. In this case, a roughness factor r , which is defined as the ratio of the actual surface area of a rough surface to the projected area, may be introduced into the Cassie and Baxter equation. The relationship between the contact angle of the flat surface θ and that of the suitably rough surface θ_r is expressed by Equation (1),^[9]

$$\cos \theta_r = rf_1 \cos \theta - f_2 \quad (1)$$

in which f_1 and f_2 are the fractions of the nanotubes and air on the ACNT films, respectively. Equation (1) indicates that the contact angle θ_r increases with an increasing fraction of air (f_2). We can roughly estimate f_1 and f_2 from known contact angles. Carbon nanotubes can be thought of as graphite sheets with a hexagonal lattice that have been wrapped up into seamless cylinders.^[17] The contact angle θ for water on a flat graphite surface is 86° ,^[18] and the contact angle θ_r for water on ACNT films is $158.5 \pm 1.5^\circ$. In contrast, the water contact angle θ_r on an ACNT film after fluoroalkylsilane modification was $171 \pm 0.5^\circ$ and the contact angle θ on fluoroalkylsilane-coated plane glass was 108° .^[10a] By using these values f_1 and f_2 are calculated to be 0.06 and 0.94, respectively. These values reveal that the very large fraction of air and the very small fraction of carbon nanotubes on the treated ACNT films cause super-“amphiphobic” properties. Tadanaga et al.^[10b] previously reported that the CA for water on super-water-repellent Al_2O_3 -coated films was 165° and the f_2 value was 0.92. It is clear that the fraction of air on the treated ACNT films is larger than that on Al_2O_3 -coated films. We further predict, from fractal theory,^[12] that the CA will be close to 180° on the surface of single-walled ACNT films after fluoroalkylsilane treatment.

In conclusion, the aligned structure of ACNT films and the very large fraction of air on the films determine the super-hydrophobic properties, while ACNT films with a fluoroalkylsilane coating show super-“amphiphobic” properties. From

the view-point of practical applications, carbon nanotubes can be prepared on patterned surfaces,^[5, 19] and this further increases the fluidity of liquids on the surfaces. On the other hand, the anisotropic dewetting properties might be realized by the substrate structure if ACNT films could be prepared on micrometer-size striped surfaces.^[20] This would allow the controlled manipulation of the behavior of surfaces and the design of a new type of microfluidic device (for example, DNA chips),^[21] nonwetting liquid transfer, liquid microchannels, and liquid microtracks.^[20] These kinds of devices are different from normal microfluidic devices which are based on a single hydrophilic or hydrophobic property. Also further study of this issue might open up new perspectives in the study of fundamental problems of interfacial science and in the design of physical systems with prescribed properties.

Experimental Section

ACNT films were prepared by pyrolysis of metal phthalocyanines FePc/YPc containing both the metal catalyst and carbon source required for the nanotube growth. The pyrolysis of FePc/YPc was performed under Ar/ H_2 at $600\text{--}900^\circ\text{C}$ on quartz glass plates in a flow reactor consisting of a quartz glass tube and a furnace fitted with independent temperature controllers. The resulting ACNT films appeared on the quartz glass plates as a black layer. After drying the ACNT films in vacuum, they were treated with a hot concentrated mixture of H_2SO_4 and HNO_3 (1:1, v:v) for 2 h to generate functional groups, such as hydroxyl and carboxyl, on the surface of the carbon nanotubes. The treated samples were then rinsed with pure water and dried in a vacuum again. The ACNT films were then treated with a methanolic solution of hydrolyzed heptafluorooctyltrimethoxysilane ($(\text{CF}_3(\text{CF}_2)_7\text{CH}_2\text{CH}_2\text{Si}(\text{OCH}_3)_3$; 1.0 wt %) for 3 h and subsequently heated at 140°C for 1 h.

Contact angles were measured with an optical contact angle meter at ambient temperature. Water droplets or oil droplets (1–2 mm diameter) were dropped carefully onto the ACNT films and the average value of five measurements made at different positions of the same sample was adopted as the contact angle. The ACNT samples were examined by SEM (Hitachi s-530) to characterize their morphology. XPS analyses of the samples were performed on a VG ESCALAB 220-IXL spectrometer using an $\text{Al}_{K\alpha}$ X-ray source (1486.6 eV). The energy scale was internally calibrated by referencing to the binding energy (E_b) of the C_{1s} peak of a carbon contaminant at 284.6 eV.

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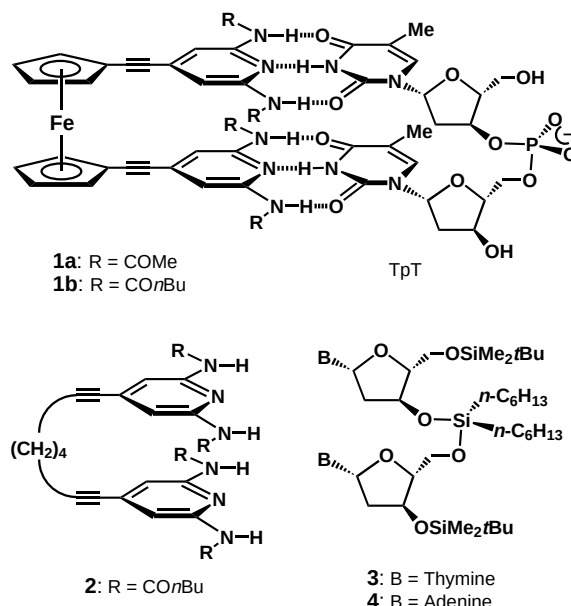
Specific Binding and Separation of Dinucleotides by Ferrocene-Modified Artificial Receptors

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Short oligonucleotides and their derivatives have significant biological activities; for example, they act as antitumor and antiviral agents.^[1] Hence, efficient syntheses and simple purification methods of such oligomers on a mg-scale are important.^[2,3] Although many artificial receptors for nucleobase and nucleoside derivatives have been reported,^[4] the selective recognition of native oligonucleotides by these receptors remains to be developed.^[5] Herein we show the strong binding of designed ferrocene-modified artificial

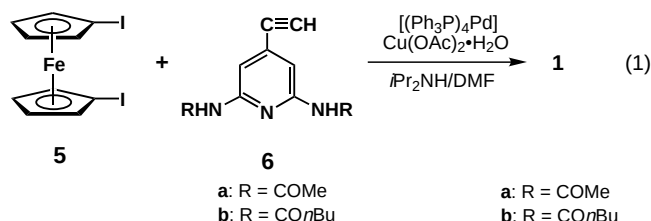
receptors for dinucleotides and demonstrate the highly selective extraction of the dinucleotides into nonpolar solvents by using the receptors.

As a starting point for this project, we chose thymidyl(3' → 5')thymidine (TpT) as a target dinucleotide because the synthetic recognition site for thymine was already developed and successfully tethered to a ferrocene skeleton.^[6] The molecular design of the dinucleotide receptors **1** (Scheme 1) for TpT was based on the inter-ring spacing



Scheme 1. A multipoint hydrogen-bonded complex between dinucleotide receptor **1** and TpT. Analogues **2**, **3**, and **4** were also investigated.

between two cyclopentadienyl (Cp) rings in ferrocene (0.33 nm),^[7] which is almost the same as the distance between stacked base pairs in DNA.^[8] Thus, when two diamidopyridine moieties (a hydrogen-bonding site for thymine)^[9] are connected to the Cp rings of ferrocene through linear ethynediyl spacers, the entropic disadvantages of the receptors during the complexation must be limited to the restricted free rotation of the Cp rings and of the diamidopyridine side chains. This might play a role in the increasing affinities of **1** for TpT. The dinucleotide receptors **1** were synthesized by the Sonogashira reaction between 1,1'-diiodoferrocene (**5**) and 2,6-diamido-4-ethynylpyridines **6** [Eq. (1)].



The recognition abilities of the artificial receptors **1** were first investigated in homogeneous solutions by the use of lipophilic TpT analogue **3** (Scheme 1),^[10] to obtain detailed information of the complexation. Receptor **1a** (5.0×10^{-4} M)

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was treated with one equivalent of **3** in CDCl_3 , and the mixture showed several characteristic changes in the ^1H NMR spectrum: the signals for the NH protons of both **1a** (from $\delta = 7.58$ to 9.97) and **3** (from $\delta = 7.87$ and 7.89 to 11.40 and 11.60 , respectively) had been shifted downfield, thus reflecting the formation of a multipoint hydrogen-bonded complex.^[6] The absorption spectra of **1a** at 298 K changed upon the addition of **3** in CHCl_3 under the relatively dilute conditions required for assessing the association constant. When **3** was added incrementally to a solution of **1a**, a decrease (at 316 , 359 , and 456 nm) and an increase (at 380 nm) in the absorbance of **1a** were observed, with several isosbestic points (Figure 1a). From these changes, a 1:1 stoichiometry was confirmed, and the association constant K_a was estimated to be $1.2 \times 10^5\text{ M}^{-1}$ by using an iterative least-squares curve-fitting analysis.^[11] Thus, the change in free energy of the complexation ($\Delta G_{298} = -29.0\text{ kJ mol}^{-1}$) is, to the best of our knowledge, one of the highest values for artificial receptors for thymine–thymine dinucleotide derivatives.^[12]

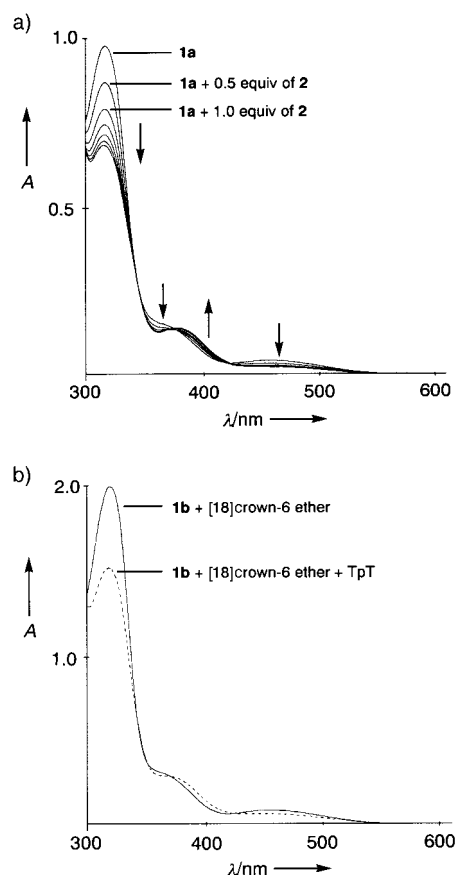


Figure 1. Electronic absorption spectra: a) **1a** ($2.5 \times 10^{-5}\text{ M}$) in the presence of **3** (0.5–3.0 equiv). b) **1b** ($5.0 \times 10^{-5}\text{ M}$) in the presence of TpT ($5.0 \times 10^{-5}\text{ M}$) and [18]crown-6 ether ($1.0 \times 10^{-4}\text{ M}$) in CHCl_3 .

Native dinucleotides are essentially insoluble in CHCl_3 and CDCl_3 . Thus, their extraction into such nonpolar solvents containing the receptors would demonstrate the high recognition efficiency of the receptors. The ammonium salt of native TpT was readily solubilized in CDCl_3 by the addition of almost one equivalent of **1b** in the presence of [18]crown-6

ether, and the molar ratio of TpT/**1b** was determined to be approximately 1, as judged from the integration of the ^1H NMR spectrum (Figure 2). A control experiment without

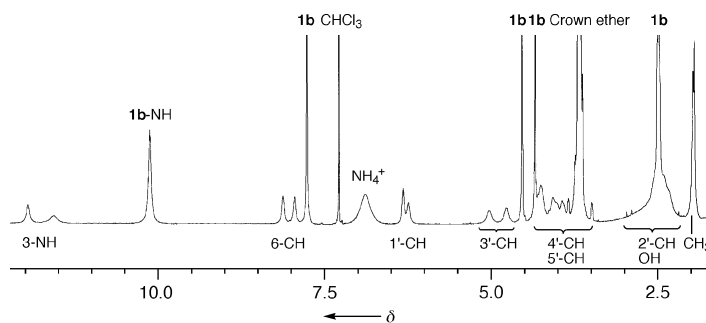


Figure 2. ^1H NMR (400 MHz, CDCl_3 , 25°C , $(\text{CH}_3)_4\text{Si}$) spectrum of the complex between TpT and **1b**. A suspension of TpT ($7.7 \times 10^{-3}\text{ mmol}$), **1b** ($7.0 \times 10^{-3}\text{ mmol}$), and [18]crown-6 ether ($1.4 \times 10^{-2}\text{ mmol}$) in CDCl_3 (0.7 mL) was stirred at 25°C for 1 h. The suspension was filtered, and the filtrate was analyzed directly by ^1H NMR spectroscopy. The signals for receptor **1b** are labeled in the spectrum. Assignments of the TpT signals (depicted below the spectrum) are based on those for **3**. Two sets of signals for the nucleoside residues of TpT cannot be distinguished.

1b revealed that no extraction occurred, which shows that the crown ether only plays a role in the capture of the ammonium counteranion. On the other hand, **2** (a flexible analogue of **1**; Scheme 1) and lipophilic dApdA analogue **4** (an antisense strategy) showed much lower extractabilities than **1b** ($\text{TpT}/\mathbf{2} \leq 0.3$ and $\text{TpT}/\mathbf{4} \leq 0.2$) under identical experimental conditions. The flexible linkages of **2** and **4** may result in lower extractabilities than that of **1** because of the expected entropic loss during the complexation (see above). In the ^1H NMR spectrum of the extracted solution, the signal for the NH proton of **1b** was shifted downfield from $\delta = 7.58$ to 10.12 , and the amide NH protons of the native TpT gave rise to signals at $\delta = 11.58$ and 11.91 , which are almost the same chemical shifts as those of the amide NH protons of the bound lipophilic TpT analogue **3** (see above). The absorption spectrum of **1b** showed similar changes to those observed for **1a** and **3** after the extraction (Figure 1b). Furthermore, the complex of achiral **1b** and chiral TpT showed a characteristic induced circular dichroism (ICD) in the visible region of the spectrum of **1b** ($\Delta\epsilon_{326} = 3.46$; $\Delta\epsilon_{384} = -0.61$; $\Delta\epsilon_{430} = 0.23$; $\Delta\epsilon_{510} = 0.61$). The ICD, which reflects the twisted orientation of the two hydrogen-bonding sites of **1b**, suggests that the Cp rings of the ferrocene modulator can rotate to give optimal hydrogen bonding to the two nucleobase residues of the dinucleotide. The NMR, UV, and CD spectroscopic data obtained from the extraction experiments are extremely important and show that the hydrogen-bonding interaction of the receptors may be a major driving force even in the recognition of native TpT (Scheme 1).

Attempts were made to extract the other native dinucleotides into CDCl_3 containing **1b** to assess the specificity of the hydrogen-bonding interaction of **1**. We could not detect any traces of dApdA, dCpdG, TpdA, and even pT under identical experimental conditions. The specific affinity of **1b** to TpT was further demonstrated by the selective extraction of TpT from a mixture of various nucleotides, including TpT. A

mixture of eight dinucleotides and four mononucleotides was added to a solution of **1b** in CHCl_3 . The suspension was filtered, and the filtrate was re-extracted with water. HPLC analysis revealed that only TpT existed in the aqueous phase (Figure 3), whereas **1b** remained unchanged in the CHCl_3 phase and could be reused without any loss of extraction ability. Excellent selectivity was also observed between

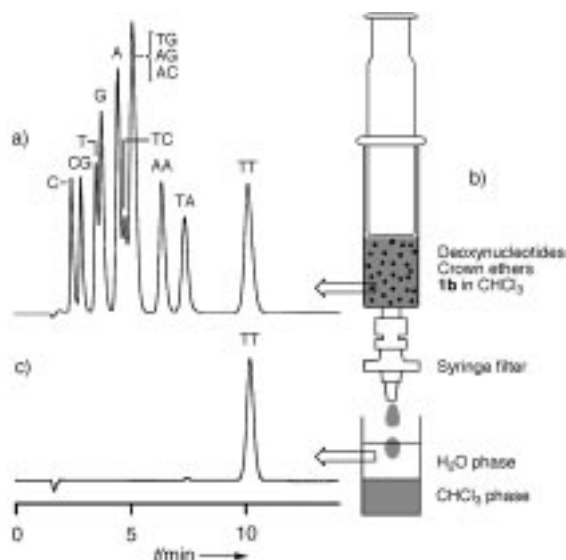


Figure 3. HPLC analyses (column: ODS; eluent: $n\text{Bu}_4\text{NBr}$ (5 mM) + K_2HPO_4 (20 mM) in CH_3CN buffer (6% v/v); flow rate: 1.0 mL min^{-1} ; temperature: ambient; detection: UV 254 nm). The suspension of a mixture of eight dideoxynucleotides (ammonium salts: $1.1 \times 10^{-3}\text{ mmol}$), four monodeoxynucleotides (sodium salts of 5'-monophosphate: $2.2 \times 10^{-3}\text{ mmol}$), [18]crown-6 ether (for the capture of the ammonium cation; $2.0 \times 10^{-3}\text{ mmol}$), [15]crown-5 ether (for the capture of the sodium cation; $4.0 \times 10^{-3}\text{ mmol}$), and **1b** ($1.0 \times 10^{-3}\text{ mmol}$) in CHCl_3 (0.2 mL) was stirred at 25°C for 1 h. a) A small quantity of the suspension was added to H_2O , and the H_2O solution was analyzed by HPLC. The rest of the suspension was filtered, and the filtrate was added to H_2O (0.1 mL). The mixed phases were stirred at 25°C for 10 min, and b) the H_2O phase was separated by centrifugation. c) The solution in H_2O was analyzed by HPLC, and by ^1H NMR spectroscopy.

oligomers of thymidine: only negligible if any extractions of pT (monomer), TpTpT (trimer), or TpTpTpT (tetramer) were observed. These extraction experiments clearly showed that the artificial receptors can perfectly distinguish one particular dinucleotide from other mono- and higher oligomeric nucleotides. Furthermore, the extracted TpT, after evaporation of the water, was found to be very pure by ^1H NMR spectroscopic analysis. HPLC purification of nucleotides usually uses various buffer solutions as eluents, so the removal of the buffer agents of inorganic and organic salts is essential to obtain pure nucleotides. The results clearly illustrated the practicability of our receptors: pure dinucleotides can be obtained from mixtures simply by mixing with the receptors, followed by filtration and reextraction.

We also found that the ferrocene linkage was remarkably effective as a modulator of two hydrogen-bonding sites for dinucleotide receptors. There are many synthetic recognition motifs for other nucleobases; these motifs have different recognition strengths and properties, and can easily be

connected to ferrocene and other modulator molecules. Thus, the present system demonstrates a new general strategy for the development of practical receptors, each with a unique recognition ability for various di- and oligonucleotides.

Experimental Section

A solution of **5** (162 mg, 0.37 mmol),^[13] **6a** (400 mg, 1.84 mmol),^[6] $[\text{Pd}(\text{Ph}_3\text{P})_4]$ (35 mg, 30 μmol), and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (6.0 mg, 30 μmol) in $i\text{Pr}_2\text{NH}$ (4.0 mL) and N,N -dimethylformamide (4.0 mL) was stirred at 100°C for 2 h. After removal of the solvent, the residue was poured into water and extracted with CHCl_3 . The CHCl_3 extract was evaporated and purified by chromatography (silica gel; eluent, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 20:1) to give **1a** (172 mg, 0.28 mmol, 76%). M.p. $170\text{--}171^\circ\text{C}$; IR (KBr): $\tilde{\nu} = 3169, 2212, 1684\text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3 , 25°C , $(\text{CH}_3)_4\text{Si}$): $\delta = 7.84$ (brs, 4H), 7.74 (brs, 4H), 4.58 (s, 4H), 4.39 (s, 4H), 2.23 (s, 12H); ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$, 25°C): $\delta = 169.22, 150.29, 133.66, 109.64, 90.51, 85.65, 72.73, 71.39, 65.66, 24.10$; FAB-MS (3-nitrobenzyl alcohol matrix): m/z (%): 617 (100) $[\text{MH}^+]$. The reaction of **5** (109 mg, 0.25 mmol) and **6b** (300 mg, 1.00 mmol)^[6] in a manner similar to that described for **1a**, led to the formation of **1b** (94 mg, 0.12 mmol, 48%). M.p. $94\text{--}95^\circ\text{C}$; IR (KBr): $\tilde{\nu} = 3286, 2214, 1676\text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3 , 25°C , $(\text{CH}_3)_4\text{Si}$): $\delta = 7.93$ (brs, 4H), 7.61 (brs, 4H), 4.59 (t, $J = 1.5\text{ Hz}$, 4H), 4.37 (t, $J = 1.5\text{ Hz}$, 4H), 2.39 (t, $J = 7.4\text{ Hz}$, 8H), 1.75–1.68 (m, 8H), 1.46–1.37 (m, 8H), 0.96 (t, $J = 7.4\text{ Hz}$, 12H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): $\delta = 171.52, 149.39, 136.45, 111.14, 92.87, 84.96, 73.31, 72.32, 65.06, 37.49, 27.37, 22.31, 13.80$; FAB-MS (3-nitrobenzyl alcohol matrix): m/z (%): 785 (100) $[\text{MH}^+]$.

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Rectification by a Monolayer of Hexadecylquinolinium Tricyanoquinodimethanide between Gold Electrodes**

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In memory of Sukant Kishore Tripathy

Rectification by Langmuir–Blodgett (LB) monolayers and multilayers of the ground-state zwitterionic molecule hexadecylquinolinium tricyanoquinodimethanide ($C_{16}H_{33}Q-3CNQ$, **1**) was first reported by Sambles, Ashwell, and co-workers between a Pt electrode on one side and a Mg pad (protected by Ag) on the other side,^[1] and also with intervening monolayers of insulating aliphatic acids.^[2] The rectification was confirmed with Al electrodes on both sides of monolayers and multilayers.^[3] The mechanism of rectification was clarified,^[3] and it was suggested that the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of **1** were involved in the enhanced current observed in the forward direction.^[3] Not all junctions rectify.^[4] The rectification was measured in the temperature range 370 to 105 K,^[5] and ancillary spectroscopic and electrochemical data were secured.^[6]

In accordance with the seminal paper in this field of Aviram and Ratner,^[7] it was suggested^[3] that the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of **1** were involved in the asymmetric shape of the observed current–voltage characteristics.^[3] The asymmetry can be ascribed to the intervalence transfer band between the HOMO and LUMO, appropriately shifted by the applied electrical potential, and coupled to levels in the Al electrodes. The optical absorption at 570 nm (2.17 eV) in films of **1** can be ascribed to the HOMO–LUMO gap, or in slightly different language, to the transition from the ground state (dipole moment 43 ± 8 D)^[3] to the first electronic excited state (dipole moment between 3 and 9 D).^[6] The results have been reviewed elsewhere.^[8, 9]

A persistent question was whether the oxides of Al or Mg were in any way involved in the rectification process.^[8, 9] We now present experimental proof that rectification occurs also when monolayers or multilayers of **1** are placed between oxide-free gold electrodes.

Working with organic monolayers sandwiched between metal electrodes is difficult. It is easy to transfer one or more monolayers onto a metal electrode, but it is not simple to deposit a metal layer on top of an organic layer without damaging it. Sambles' original method was to use Mg vapor, which, in his experience, damaged an organic film the least. Our improvement was to cryocool the glass|Al|LB film

assembly to 77 K, and thus prevent, or at least reduce, damage to the organic film when Al was evaporated on top of it.^[3] The technique did not work in our laboratory with Au. Recently, Okazaki and Sambles showed that, by letting a low pressure of Ar (4×10^{-3} Torr) into the evaporator during Au deposition and by blocking the direct path from the Au source to the target with baffles, only Au atoms that had scattered off Ar atoms several times could reach the organic multilayer.^[10]

Two glass samples (A and B; $50 \times 50 \times 0.4$ mm) with a root-mean square (r.m.s.) roughness of $2.3 \text{ \AA}$ (measured by X-ray reflectivity) were washed with isopropanol and then xylene. A thickness of 50 nm of Au was evaporated onto the hydrophobic glass from a Mo boat in an Edwards E306 evaporator. To ensure that the Au surface stayed hydrophilic, the samples were immediately placed under pure water (resistivity $18 \text{ M}\Omega\text{cm}$), and left under water until a monolayer (for sample A) or a nine-layer multilayer (for sample B) of freshly prepared $C_{16}H_{33}Q-3CNQ$ was transferred (Z-type, with transfer ratios of 100% or even above) from a monolayer of $C_{16}H_{33}Q-3CNQ$ held at the air–water interface at a surface pressure of 25 mNm^{-1} in a NIMA Model 622 film balance at 12°C in a HEPA-filtered room in darkness. As before,^[3] the LB layers were dried in a vacuum desiccator over P_2O_5 for three days to remove any entrapped water between the layers.

Two hydrophobic contact masks were prepared from thin perforated sheets, in one case an Al/Mg alloy, and in the other case a phenolic resin. After removing gross asperities by polishing, the masks were coated with an approximately $50 \text{ }\mu\text{m}$ layer of partially methoxylated poly(dimethylsiloxane) resin (General Electric Cat. No. GE 5060) by immersion in a 3% w/w solution in toluene, followed by removal of excess liquid, and evaporation of the solvent on a perfectly level surface. Samples A (with a single monolayer of $C_{16}H_{33}Q-3CNQ$) and B (bearing nine monolayers of $C_{16}H_{33}Q-3CNQ$) were placed in the Edwards evaporator on top of a Cu cryosurface; sample A faced the gold evaporation boat, but the direct trajectory of Au atoms was blocked by a copper strip, while sample B faced away from the boat. The cryosurface was cooled to 77 K using liquid nitrogen. Gold from a Mo boat was evaporated under an Ar pressure of between 8×10^{-4} and 2×10^{-3} Torr, at a rate of 0.02 nms^{-1} for the first 200 nm, and then 0.1 nms^{-1} for the next 400 nm, until the quartz thickness monitor recorded a nominal Au thickness of 600 nm. The Au pads that formed through the holes in the mask were much thinner: they were measured to be 17 nm thick by using a Sloan Dektak II profilometer. The r.m.s. roughness was measured by atomic force microscopy as 1 nm for the top of a pad and 0.4 nm for the bottom Au layer.

The measuring electronics were modified from the earlier procedure.^[3] The same voltage source (Hewlett–Packard Model 3245A) and multimeter (Hewlett–Packard Model 3245A) were connected by a National Instruments IEEE-488 GPIB interface board to a Gateway 2000 Model P5-60 microcomputer. The computer control program was written using a Borland Delphi (Inprise Corp.) compiler. The multimeter, sample, and all signal lines, except for some low-impedance high-level lines, were enclosed in a Faraday cage. Selected Au pads were contacted through a terminal droplet of Ga/In eutectic, which did not wet the gold (Figure 1). All

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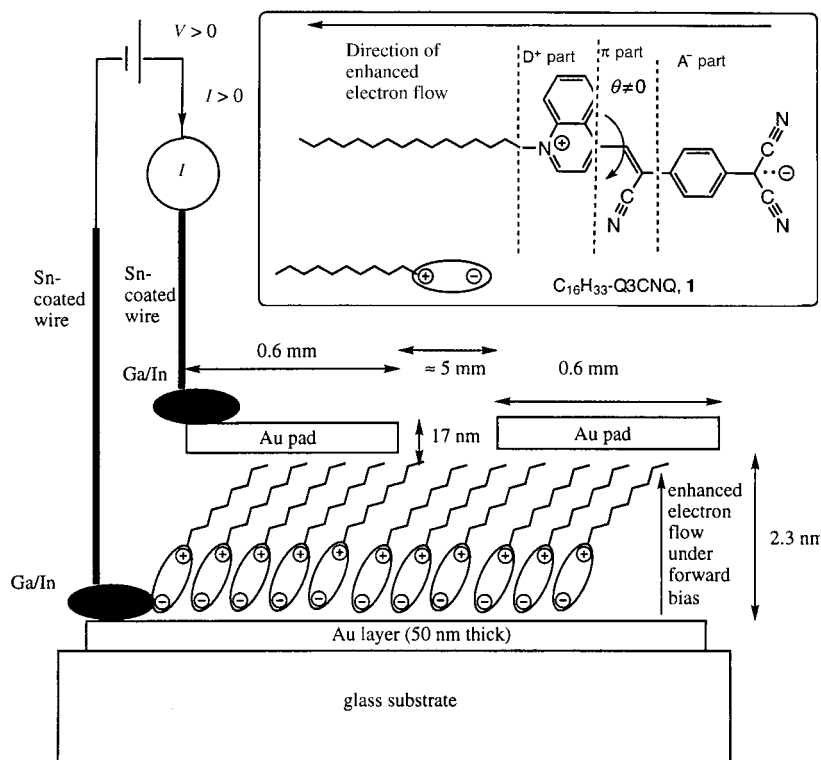


Figure 1. Depiction of a LB monolayer of **1** sandwiched between Au electrodes (top pad area: 0.6 to 1 mm²) and with electrical contacts attached to the Au electrodes. Inset: Chemical structure of the ground-state zwitterionic molecule C₁₆H₃₃Q-3CNQ (**1**) and a diagrammatic depiction. The direction of the enhanced electron flow is also shown.

measurements were performed at room temperature. The procedures followed here preclude the formation of any oxide on the Au electrodes.

Figure 2 shows the results for pad g1 on top of a single monolayer of C₁₆H₃₃Q-3CNQ: the rectification lasts for six cycles, with the enhanced currents under positive bias decreasing in cycles three to six, and the currents at maximum

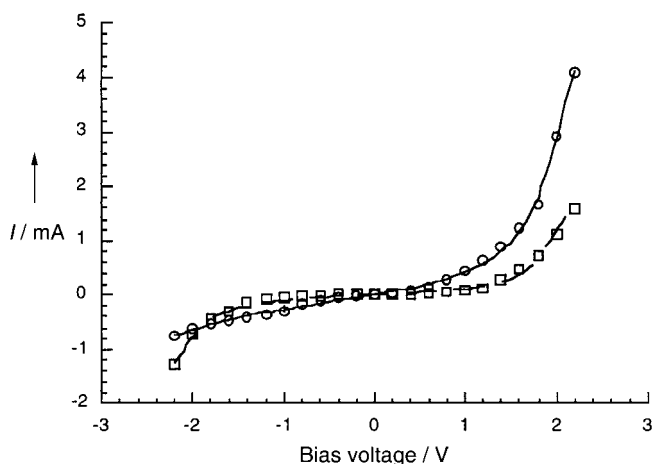


Figure 2. Current–voltage plots for sample A (pad g1) covering one monolayer of C₁₆H₃₃Q-3CNQ, and fitted to equation: $I = a[\tan^{-1}[bc + bdV] - \tan^{-1}[bc - b(1-d)V]]$,^[15, 16] where I and a are in mA, V and c are in V, and R = Pearson's coefficient of fit. Cycle 1: circles and solid line; $a = 2.24 \pm 0.11$, $b = 4.52 \pm 0.22$, $c = 1.31 \pm 0.03$, $d = 0.37 \pm 0.01$, $R = 0.9991$. Cycle 6: squares and dashed line; $a = -0.68 \pm 0.04$, $b = 7.80 \pm 0.54$, $c = 1.01 \pm 0.01$, $d = 0.48 \pm 0.00$, $R = 0.9970$.

negative bias becoming more negative in cycles two to six. Given the measured cross-sectional area of 50 Å² molecule⁻¹^[3] and a pad area of 0.283 mm², the maximum forward current (4.08 mA at 2.2 V) for the first cycle corresponds to a current of 4.5×10^4 electrons molecule⁻¹ s⁻¹. This maximum current is much larger than the 0.33 electrons molecule⁻¹ s⁻¹ reported between Al electrodes (with their partial oxide covering)^[3] or the 35 electrons molecule⁻¹ s⁻¹ reported for an improved Al electrode design.^[11] The rectification ratio at 2.2 V is $RR = [I(\text{at } 2.2 \text{ V}) / |I(\text{at } -2.2 \text{ V})|] = 4.08 \text{ mA} / 0.759 \text{ mA} = 5.39$. The minimum nominal resistance is $2.2 / 0.004088 = 538 \Omega$ at 2.2 V and 2900 Ω at -2.2 V.

Pad g2 of sample A (Figure 3) gave a higher RR value of $0.747 \text{ mA} / 0.0628 \text{ mA} = 11.9$; the current was somewhat smaller; the nominal resistance was 2945 Ω at 2.0 V; and short circuits developed in the third cycle.

Multilayers yielded, as expected, much smaller currents. Pad g22 of sample B (Figure 4) with nine Z-type monolayers gave an initial rectification ratio $RR = 1.0305 \mu\text{A} / 0.0523 \mu\text{A} = 19.7$ for the first cycle, which decreased to $RR = 0.6032 \mu\text{A} / 0.3727 \mu\text{A} = 1.61$ in the fifth cycle. Another pad (not shown) gave an initial rectification ratio of 4.34, which decreased to 0.85 on the third cycle.

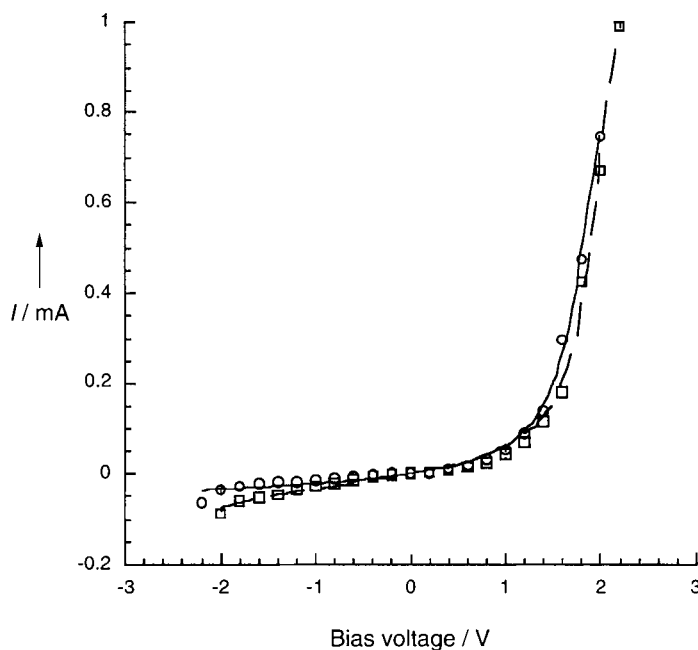


Figure 3. Current–voltage plots for sample A (pad g2) covering one monolayer of C₁₆H₃₃Q-3CNQ, and fit to the equation: $I = a[\tan^{-1}[bc + bdV] - \tan^{-1}[bc - b(1-d)V]]$,^[15, 16] where I and a are in mA, V and c are in V, and R = Pearson's coefficient of fit. Cycle 1: solid line and circles; $a = 0.36 \pm 0.02$, $b = 4.17 \pm 0.70$, $c = 1.69 \pm 0.20$, $d = 0.08 \pm 0.10$, $R = 0.9981$. Cycle 2: dashed line and squares; $a = 0.43 \pm 0.02$, $b = 6.52 \pm 0.71$, $c = 1.32 \pm 0.08$, $d = 0.33 \pm 0.04$, $R = 0.9978$.

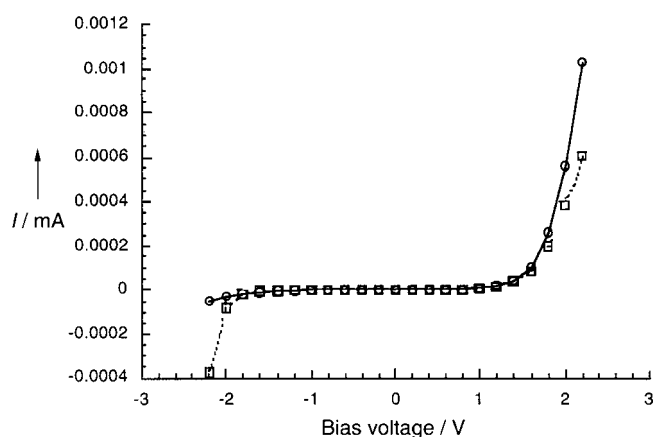


Figure 4. Current–voltage plots for sample B (pad g22) covering nine monolayers of $C_{16}H_{33}Q-3CNQ$. Cycle 1: solid line and circles; cycle 5: dashed line and squares.

Several conclusions can be drawn:

- 1) The rectification, first reported between unsymmetrical electrodes^[1] and confirmed between symmetrical Al pads,^[3] is definitely molecular in origin, and not attributable to oxide effects.
- 2) The currents through an oxide-free gold pad of macroscopic dimensions are large, because most molecules under the Au pad may be involved in the rectification.
- 3) Although LB films develop conducting defects when vacuum-coated with hot Au vapor, this is mediated by temperature-induced changes of structure.^[12, 13]
- 4) Mechanical damage to LB films, which arise from the use of a contact mask, is avoided by the use of a hydrophobic elastomer.
- 5) The currents decrease during successive cycles, presumably as the molecules reorient in the monolayer;^[3] this may be related to the damage known to occur in monolayers of long aliphatic chains as a result of the passage of hot electrons.^[14]
- 6) We should consider a chemical basis for the change in film conductivity: since the first reduction is electrochemically reversible in solution, no damage occurs on adding one electron to the LUMO (which is concentrated on the 3CNQ part of the molecule),^[6] however, oxidizing the molecule in solution is electrochemically irreversible.^[3] The large current at negative bias in the last cycle suggests that the number of molecules conducting is not decreasing dramatically; therefore the molecular reorientation mentioned above is more likely (and may be prevented if a polymerized monolayer were fabricated).
- 7) Multilayers show rectification but the currents are smaller, because the current must somehow cross the several insulating hexadecyl tails required for LB film assembly.
- 8) The bias at which enhanced electron flow occurs can be estimated visually from Figure 2 as around 2 V, while this bias was estimated as between 1 and 1.3 V with Al electrodes (Table 1 of ref. [3]); this difference in bias agrees with the difference of 1.1 eV between the work functions of Au (5.3 eV) and Al (4.2 eV).
- 9) The direction of larger conductivity in the forward direction agrees with what was established with mono-

layers of $C_{16}H_{33}Q-3CNQ$ sandwiched between Al electrodes,^[3] and therefore with a modification^[3] of the two-level Aviram–Ratner model.^[7]

- 10) Recent theoretical analyses of molecular conduction,^[15, 16] have suggested that conduction asymmetry of the type observed may also arise from processes dominated by a single molecular level. The current I as a function of the bias voltage V is given, approximately, by:^[15]

$$I = (2I_0/\pi) \{ \tan^{-1}[\theta^{-1}(pV - V_0)] - \tan^{-1}[\theta^{-1}((1-p)V + V_0)] \} \quad (1)$$

where I_0 is the saturation current, θ is a tunneling gap coupling parameter, eV_0 is the zero-bias energy difference between the dominant level and the Fermi level, and the parameter p gives the fractional position of the “center of gravity” of the molecular energy level within the gap.^[15] Equation (1) closely resembles a similar equation derived independently (Equation (21) of ref. [16]). Figures 2 and 3 show excellent fits to Equation 1. The fits yield $V_0 = 1.31$ and 1.01 V (Figure 2), and 1.69 and 1.32 V (Figure 3). The average over many data sets (more than reported here) is $V_0 = 1.31 \pm 0.25$ eV.^[17] These curve-fit estimates are smaller than the $V_0 = 2.0$ V estimated visually (see point 8 above).

- 11) The $I-V$ curves change upon successive cycles: the forward current at $V > 0$ becomes smaller, and the current at $V < 0$ becomes more negative. These observations seem to argue against some irreversible chemical reaction, and suggests that the molecules “turn around” with increased exposure to large potentials ($V = 2.3$ V across a monolayer 2.3 nm thick^[3] corresponds to an electric field of 1 GV m⁻¹).
- 12) The Aviram–Ratner proposal assumes enhanced current beyond a certain threshold voltage, and a constant current plateau, or saturation, somewhat above this threshold voltage: this enhanced current involves inelastic tunneling.^[7] In contrast, the current through an appropriately substituted triphenylenethiol at low temperatures was recently found at Yale University to have a relatively narrow peak at the threshold voltage: the device Au|bithiol|Au thus exhibits negative differential resistance over a narrow range above the threshold voltage.^[18] This enhanced current occurs only at potentials close to resonance with a localized excited state, and may be the result of elastic tunneling at resonance. Thus, the Aviram–Ratner proposal^[7] allows inelastic tunneling at and above the threshold voltage and a current plateau; in contrast, the Yale results^[18] suggest elastic tunneling at the threshold voltage, and a narrow peak. In the data reported here, no maximum in the current (peak or plateau) was found within the potential ranges used, but a plateau was seen in subsequent work.^[17]

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Nondestructive Data Processing Based on Chiroptical 1,2-Dithienylethene Photochromes**

Elisa Murguly, Tyler B. Norsten, and Neil R. Branda*

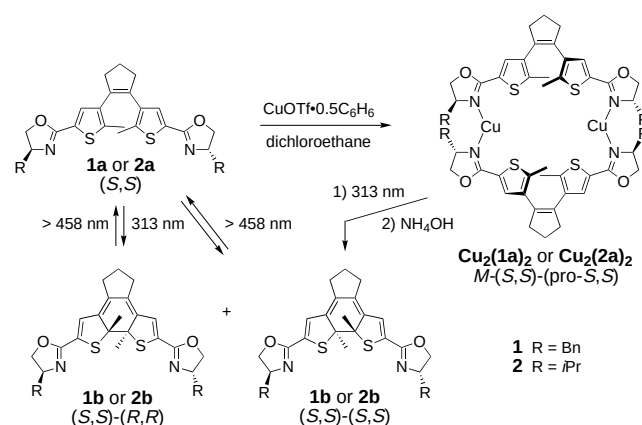
The viability of photochromic 1,2-dithienylethene derivatives in optical device applications stems from their striking display of advantageous photochromic properties such as thermal irreversibility and fatigue resistance.^[1] Their application to erasable memory media requires that both photochromic states be detected in the readout event in a facile and noninvasive manner. Typically, the readout event relies on the use of UV/Vis spectroscopy to record the spectral changes near the absorption bands corresponding to the two photochromic states. However, these are the same absorptions that induce the ring-opening and ring-closing reactions. Thus, sampling near these photoactive absorption bands inevitably causes partial switching of the photochrome and erases the stored information. This problem can be circumvented by

developing photochromic systems that employ gated mechanisms^[2] or systems that, upon photoisomerization, display variations in their optical properties such as refractive index,^[3] luminescence,^[4] or optical rotation.^[4f, 5] It is the detection of these accompanying changes that may ultimately lead to effective nondestructive information processing systems.

Recording changes in optical rotation is a particularly promising alternative for nondestructive readout, because the detection can often be performed outside the photoactive spectral regions. To enhance the readout signal in order to use this technique, two conditions must be satisfied: 1) the photochromes should exhibit significantly contrasting optical rotating strengths between their two states, and 2) the photochromic reactions should maximize the formation of only one stereoisomer.

The closed forms of 1,2-dithienylethene derivatives are chiral, making them excellent candidates for incorporation into chiroptical devices; however, the ring-closing reactions inevitably yield racemates. The presence of stereogenic centers appended to the thiophene rings can induce stereo-differentiation in the photocyclization reaction,^[5d, 6] but the restrictive conditions needed to ensure high stereoselection limit the use of the existing systems.^[5d, 6a] Inspired by several recent examples in which remote stereogenic centers guide the creation of metallohelicates in a stereochemically pure form,^[7] we began to explore the unique properties of self-assembled helicates in stereoselective photochromic transformations, with the goal of realizing a nondestructive write–read–erase system.

Herein we report the self-assembly of double-stranded stereochemically pure copper(I) helicates from chiral ligands **1** and **2** (Scheme 1). The chiral discrimination event that occurs



Scheme 1. Formation of ring-closed products **1b** or **2b** from photochromes **1a** or **2a** and their complexes with copper.

when the chiral oxazoline auxiliaries on the periphery of the individual strands are brought into close proximity translates through the 1,2-dithienylethene backbone and ultimately dictates the handedness of the helicates. This preorients the thiophene rings with respect to each other so that photocyclization yields a single diastereomer. The dramatic changes in optical rotation that accompany the stereoselective photochromic process can be recorded in a nondestructive manner.

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

Both (*R,R*)- and (*S,S*)-enantiomers of photochromic bis(oxazolines) **1a** and **2a** were prepared from the known 1,2-bis-(5-chloro-2-methyl-3-thienyl)cyclopentene.^[8] Copper(I) complexes were prepared by adding an equimolar amount of ligand **1** or **2** in deoxygenated dichloroethane to the benzene complex of copper(I) trifluoromethanesulfonate ($\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$) under argon. Care was taken when handling the copper(I) reagent to ensure a moisture and oxygen free atmosphere to minimize the oxidation of the metal. With the exception of single crystals grown for X-ray analysis, no attempts were made to isolate the copper(I) complexes.

The electrospray mass spectra of dichloromethane solutions of freshly prepared mixtures of ligand **1a** and $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ shows peaks at m/z 579.1 and 641.1, which correspond to free ligand **1a** and a mixture of the coordination compounds $\text{Cu}_2(\textbf{1a})_2$ and $\text{Cu}(\textbf{1a})$, respectively. The isotopic abundance of the peak at m/z 641.1 shows the typical half-peak separation of a doubly charged species, which confirms the presence of the binuclear complex $\text{Cu}_2(\textbf{1a})_2$. The isotopic distribution pattern verifies the presence of $\text{Cu}_2(\textbf{1a})_2$ along with mononuclear $\text{Cu}(\textbf{1a})$. The ratio of $\text{Cu}_2(\textbf{1a})_2$ to $\text{Cu}(\textbf{1a})$ increases when the solutions are concentrated. This observation clearly emphasizes the need to control the concentration when generating the coordination compounds, a condition that's importance will be illustrated in further studies.

Single crystals of both (*R,R*)- and (*S,S*)-enantiomers of $\text{Cu}_2(\textbf{1a})_2 \cdot (\text{OTf})_2$ that were suitable for X-ray crystallographic analysis were obtained by layering hexane upon freshly prepared dichloromethane solutions of the copper(I) complexes. The crystal structure (Figure 1) highlights the role of the metal centers in the self-assembly process. The resulting solid-state architecture is the anticipated stereochemically pure binuclear double helix. The bis(monodentate) oxazoline ligands coordinate to the metal centers. The two chiral auxiliaries are brought close together and can thus influence the stereochemistry of the helicate. In all cases, (*S,S*)-**1a**

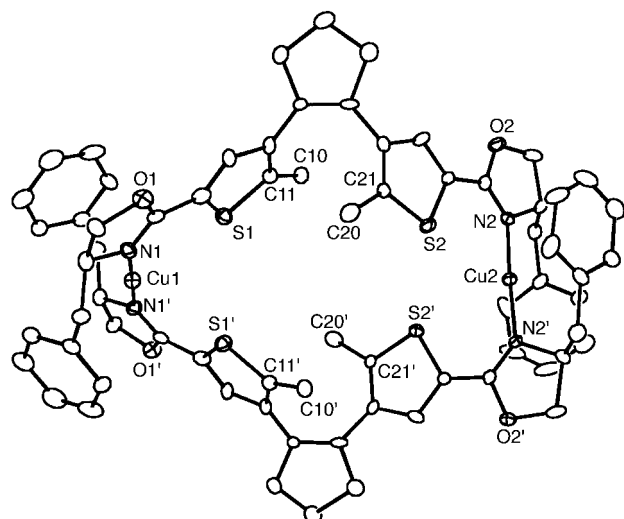


Figure 1. The structure of the copper(I) complex (*S,S*)- $\text{Cu}_2(\textbf{1a})_2$ in the crystal. All nonheteroatomic hydrogen atoms and counterions have been removed for clarity. The thermal ellipsoids are drawn at the 20% probability level. The structure of the (*R,R*)-enantiomer is a perfect mirror image.

generated solely the *M* helix and (*R,R*)-**1a** generated solely the *P* helix. The helical handedness, in turn, biases the relative orientation of the methyl groups on the thiophene heterocycles (C10, C10', C20, and C20') and sets the carbon atoms involved in forming the new single bond in the photoinduced ring closure (C11, C11', C21, and C21') as pro-(*S,S*) for the *M* helix and pro-(*R,R*) for the *P* helix.

The UV/Vis spectra of the open (**1a**) and closed (**1b**) isomers of the benzyl-substituted photochrome, and the corresponding copper(I) complexes that are generated in situ are shown in Figure 2, with the wavelengths of maximum

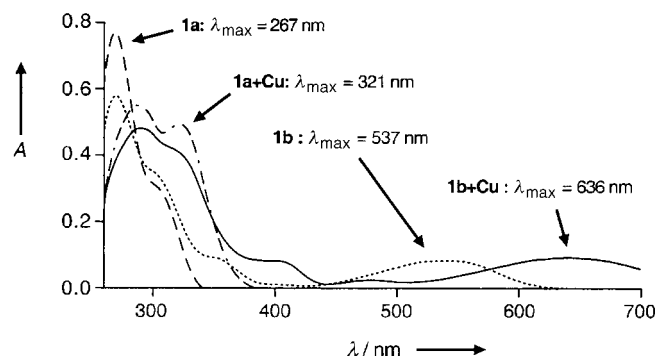


Figure 2. UV/Vis absorption spectra of photochromes **1a** and **1b** with and without $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ (1 equiv). All spectra were measured in dry deoxygenated dichloroethane ($3.5 \times 10^{-5}\text{M}$).

absorption (λ_{max}) labeled for comparison. The ring-closed isomer was produced by irradiating a dichloroethane solution of an equimolar mixture of **1a** and $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ with a hand-held (313 nm)^[9] lamp. After irradiating for two minutes, the photostationary state was formed, which showed 90% conversion to the closed isomer by ^1H NMR spectroscopic analysis. Subsequent irradiation of the closed isomer at wavelengths greater than 458 nm^[9] restored the spectrum to its original trace by regenerating the open isomer quantitatively. As expected, the spectral characteristics of both (*R,R*)- and (*S,S*)-enantiomers were identical.

Irradiation of the open isomer (*S,S*)-**1a** at 313 nm also produced characteristic shifts of the signals in the ^1H NMR spectrum. Of particular importance is the resonance assigned to the C-H protons on the thiophene rings, which appears as a singlet at $\delta = 7.65$ in **1a** and as two singlets of nearly equal intensity at $\delta = 6.47$ and 6.48 for the corresponding ring-closed product **1b**. These two singlets (Figure 3) are clearly a result of the formation of the two diastereomers in the conrotatory ring-closing reaction of the 1,2-diarylethene photochrome (i.e. (*S,S*)-(*R,R*) and (*S,S*)-(*S,S*)). The relative integrations of the two singlets indicate that both diastereomeric products are formed to nearly the same extent in the photocyclization reaction. When the photocyclization reaction of **1a** was repeated in the presence of copper(I), a major stereoisomeric product was formed with a diastereoselectivity of 86%, as shown by the nonequivalent signals in the ^1H NMR spectrum (Figure 3). This stereoselectivity can be best justified by the existence of the helical binuclear complex $\text{Cu}_2(\textbf{1a})_2$ in solution.

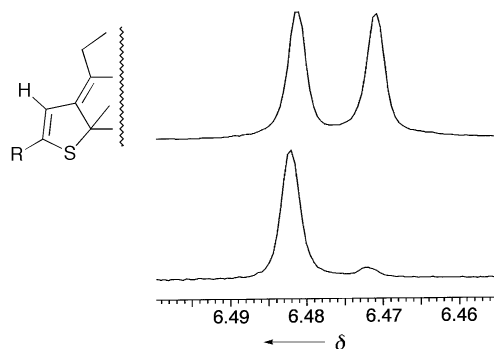


Figure 3. ^1H NMR (500 MHz, CD_2Cl_2) spectra of the C-H protons in **1b** generated from **1a** without $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ (top trace) and **1b** generated from **1a** with $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ after washing with NH_4OH to remove the metal (bottom trace).

The results of the stereoselective ring-closing reactions are shown in Table 1. We attribute the increase in diastereoselectivity as the concentration was increased (entries 1–3) to the predominance of the binuclear complex $\text{Cu}_2(\text{1a})_2$ at

Table 1. Conversions and diastereoselectivities in the photochromic processes.^[a]

Entry	Photochrome	Concentration [M]	Conversion [%] ^[b]	de [%]
1	(<i>S,S</i>)- 1a + Cu(I)	0.001	95	98
2		0.0001	94	86
3		0.00001	85	14
4	(<i>R,R</i>)- 1a + Cu(I)	0.0001	92	89
5	(<i>S,S</i>)- 2a + Cu(I)	0.0001	70	55
6	(<i>R,R</i>)- 2a + Cu(I)	0.0001	79	49

[a] In a typical reaction, the ligand and $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ were mixed in deoxygenated dichloroethane and exposed to 313-nm light for 20 minutes. After washing with excess NH_4OH to remove the metal, the conversions and *de* values of the products were measured by ^1H NMR spectroscopy in CD_2Cl_2 . [b] Based on the disappearance of the open isomers.

higher concentrations.^[10] The high degree of diastereoselectivity at 10^{-3}M is accompanied, however, by a coinciding increase in the amount of photochemical degradation. The diastereoselectivities were also lower when the photocyclization reactions were repeated with the isopropyl ligand **2a** (entries 5 and 6). We attribute this to the formation of a less robust coordination compound. Whether this difference in stability is a result of steric and/or electronic factors is currently under investigation.

The optical rotary dispersion (ORD) spectra of the photochromic reactions are shown in Figure 4. In the presence of copper(I), both the open and closed isomers **1a** and **1b** strongly rotate light throughout the UV/Vis spectrum. There are several spectral regions where the differences in rotation between copper(I) complexes of **1a** and **1b** are dramatic and provide potential nondestructive regions for read-out. For example, the angles of optical rotation at 450 nm and 475 nm can be regulated by toggling between the copper(I) complex of **1a** and the corresponding complex of **1b** by alternate irradiation at 313 nm and at wavelengths greater than 458 nm (Figure 5), which demonstrates the utility of this system for reversible data processing. This detection method

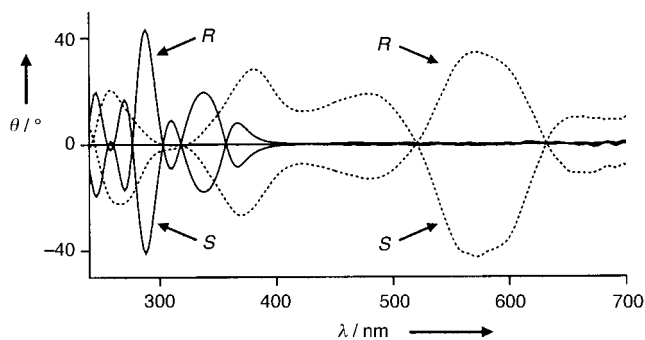


Figure 4. ORD spectra of **1a** with $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ (—) and **1b** with $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ (....). All spectra were measured in dry deoxygenated dichloroethane ($2.8 \times 10^{-4}\text{M}$).

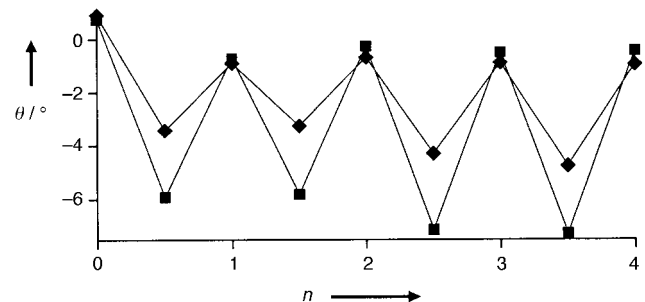


Figure 5. Modulated optical rotation at 450 nm (♦) and 475 nm (■) of a dichloroethane solution of **1a** with $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ ($2.8 \times 10^{-4}\text{M}$) during alternating irradiation at 313 nm at wavelengths greater than 458 nm (*n* = number of cycles).

is noninvasive as illustrated by the lack of variation in the UV/Vis spectrum upon extended irradiation at 475 nm.^[11]

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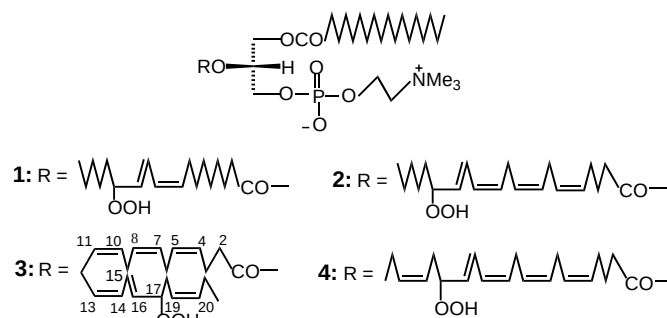
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- [9] Standard lamps used for visualizing TLC plates (Spectroline E-series, 470 $\mu\text{W cm}^{-2}$) were used to carry out the ring-closing reaction of **1a** to **1b** and **2a** to **2b** with and without copper(I). The ring-opening reactions were carried out by irradiation with a 150-W tungsten source, which was equipped with a 458 nm cutoff filter to eliminate higher energy light.
- [10] This was already suggested by the results of the ESMS studies.
- [11] The monochromator of a fluorescence spectrophotometer (1-mm slit) was employed (65-W Xenon lamp).

Synthesis and Stability of Phosphatidylcholines Bearing Polyenoic Acid Hydroperoxides at the *sn*-2 Position**

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Lipid peroxides, including phospholipid hydroperoxides, have been known to exist in mammalian blood in very low concentrations, which increase during some physiological dysfunctions and aging. Although they are generally considered to have detrimental effects, some reports have described possible beneficial actions of them both in vivo and in vitro.^[1] Gonzalez et al. found that administration of a fish oil (menhaden) diet to mice with transplanted human breast

cancer significantly reduced the size of the tumors, and showed the involvement of lipid peroxidation products.^[1a] Such a diet also significantly protected mice against a strain of the malaria parasite that is resistant to the antimalarial drug chloroquin.^[1b] Unfortunately, the nature of the lipid peroxidation products that are responsible for such beneficial effects remains largely unknown. Pure, well-defined lipid peroxides for the necessary biological studies can best be obtained by synthesis. We previously synthesized two phospholipids bearing hydroperoxides of linoleic and arachidonic acids at the *sn*-2 position (PC-LA-OOH (**1**) and PC-AA-OOH (**2**) in Scheme 1, respectively),^[2] where PC refers to phosphatidylcholine, and LA-OOH and AA-OOH denote linoleic and arachidonic acid hydroperoxides, and studied their inducement of cell death in normal and cancer cells.



Scheme 1. Phosphatidylcholine hydroperoxides.

The major polyunsaturated fatty acid components in fish oil are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). However, there has been no report on the synthesis of phospholipids bearing DHA or EPA hydroperoxides. These ω -3 fatty acids are known to be very unstable due to their high degree of unsaturation with all-*cis* unconjugated double bonds, and it was considered that the synthesis of their corresponding phospholipid hydroperoxides PC-DHA-OOH (**3**) and PC-EPA-OOH (**4**) by the method we established for **1** might be very difficult. However, with only slight modification, we have now found that it is possible. Typically, the synthesis of **3** (Scheme 2) was achieved by dicyclohexylcarbodiimide (DCC)-mediated esterification of lysophosphatidylcholine **8** with peracetal acid **7**, followed by deprotection of the hydroperoxy group. Compound **8** with *R* configuration was prepared as described previously,^[2a] and **7** was synthesized according to Scheme 2.

Docosahexaenoic acid was converted by soybean lipoxygenase to an optically active hydroperoxide, which for easier purification by column chromatography was converted to methyl ester **6** ($[\alpha]_D^{20} = -3$, $c = 1.67$ in CHCl_3)^[3] followed by protection of the labile hydroperoxy group to give a peracetal methyl ester, which was hydrolyzed by lipase PS (Amano) to give the desired peracetal acid **7**. In the new experimental procedure, omitting the azeotropic removal of residual water from **7** was important for maintaining its structural integrity, while the use of excess DCC facilitated the esterification to give the desired phospholipid **9**. Hydrolytic removal of the

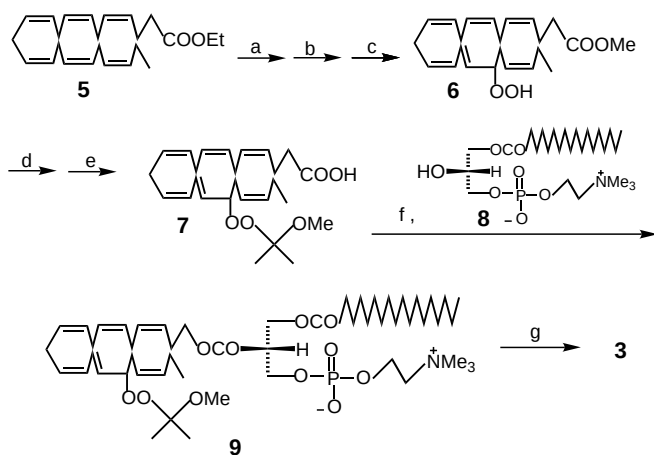
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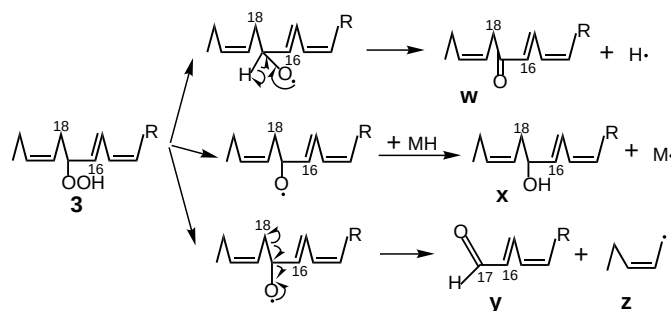


Scheme 2. Synthesis of **3**. a) 1.5 N LiOH, RT; b) O₂, lipoxygenase, borate buffer (pH 9), 0–4 °C, 6 h; c) diazomethane; d) 2-methoxypropene, PPTS, THF, RT; e) lipase, RT; f) DCC, DMAP, CHCl₃, RT; g) THF/AcOH/H₂O (4:2:1). DMAP = dimethylaminopyridine, PPTS = pyridinium *p*-toluene sulfonate.

peracetal group afforded the target compound **3**, which was purified by reversed-phase HPLC. Its structural integrity was confirmed by its molecular ion peak at m/z 866.6 [$M+H$]⁺ in the electrospray mass spectrum (ES-MS) and by ¹H NMR spectroscopy (see Experimental Section). Coloration with potassium iodide further confirmed the presence of the hydroperoxy group, whose assignment at C17 of DHA was based on the known regiospecificity of soybean lipoxygenase I, which oxidizes fatty acids at the $\omega-6$ position,^[4] and confirmed by the predominant loss of a C₅ fragment during the decomposition of the compound (vide infra). Chemical shifts and coupling constants (³*J* = 15 Hz for *trans*, and 11 Hz for *cis*) of the protons of the conjugated diene region confirmed the olefin structure depicted for **3**. Compound **4** was prepared in the same way and confirmed by its molecular ion peak at m/z 840.6 [$M+H$]⁺ and a ¹H NMR spectrum very similar to that of **3**.

The stability of these compounds is critical for their convenient use in biological studies. We examined the stability of the more highly unsaturated **3** by ¹H NMR spectroscopy and ES-MS, which not only gave simple spectra but could also give information on the major decomposition products. In the structure of **3**, the chemically most labile part is the allylic hydroperoxy group, the weak O–O bond of which is prone to homolytic cleavage, which is expected to be followed by other chemical transformations to produce a ketone **w**, an alcohol **x**, or an aldehyde **y** (Scheme 3).

The NMR signals of the olefinic protons in **6** and in **3** are well characterized for the conjugated diene system at the 14-, 15- and 16-positions, and for the unconjugated systems at the positions 4, 5, 7, 8, 10, 11, 19, and 20 (δ = 5.42, broad), with the signal for H13 overlapping with those of the latter group. However, upon formation of **w** or **y**, the resulting conjugated olefin–carbonyl π -bond systems introduce new and distinct signals in between those for H14, H15, and H16, whose intensities decrease thereby. Thus, decomposition could be easily detected and its extent estimated by the intensity of the signals for the conjugated olefinic protons relative to those of



Scheme 3. Homolytic decomposition of **3**. MH refers to an organic compound with readily abstractable hydrogen atoms (such as those of the methylene groups between the remaining unconjugated double bonds in **3**).

the stable glycerol or choline moieties. New molecular ion peaks in the ES-MS spectrum indicate the kind of decomposition products being formed. When a solution of **3** in chloroform or deuteriochloroform (15 mM) without a radical-scavenging antioxidant was stored at –20 °C, the ¹H NMR and ES-MS data remained surprisingly unchanged, even after three weeks. Moreover, in the presence of a trace of the antioxidant butylated hydroxytoluene (BHT), which can be readily removed when necessary,^[5] it was even more stable, and the NMR and ES-MS data were unchanged even after three months. However, when kept at room temperature (ca. 30 °C) without BHT, it degraded much faster, and after 3 d there were considerable changes in the NMR spectrum, with an estimated loss of about 40 % of **3**. After one week, decomposition was almost complete, and the signals for H14, H15, and H16 disappeared from the NMR spectrum. The main peak in the ES-MS spectrum of this decomposition product was at m/z 780.6 (100 %), which is 86 amu less than that for **3** at m/z 866.6 (40 %). Since its daughter ion at m/z 184 confirmed the presence of the glycerophosphocholine moiety, it must have been formed by the loss of a C₅H₁₀O fragment from the DHA-OOH moiety, which is in agreement with the hydroperoxy group being at C17 (vide supra) and cleavage between C17 and C18 to produce aldehyde **y**. A peak at m/z 850.6 (65 %), for alcohol **x**, was the second most prominent, while a peak for ketone **w** could not be identified. This differs from our previous report on the decomposition of **1** and similar observations for **2**, for which the major decomposition product corresponded to ketone **w**.^[6] A possible explanation for this is that bond cleavage between C17 and C18 of the DHA-OOH moiety in **3** is favored because the presence of a double bond at C19 leads to formation of a stable allylic radical **z** (Scheme 3), as opposed to the unstable alkyl radical that would form from **1** or **2**. At the present stage, where the true chemical species involved in the beneficial effects of fish oils and their oxidation products are not yet identified, information on the in vitro decomposition products from such phospholipid hydroperoxides as **3** may play an important role in mechanistic studies of their activities.

In summary, two new phospholipid hydroperoxides were synthesized from DHA and EPA, and the stability of the former is sufficient for storage and for use in biological studies.

Experimental Section

3: All reactions were carried out in the presence of a small amount of BHT and, except for the lipoxygenase-catalyzed hydroperoxidation, under a nitrogen atmosphere. Methyl peracetal acid **7** was prepared from DHA as previously described for linoleic acid,^[2a] and isolated by flash column chromatography, followed by drying over MgSO_4 . After filtration, the solvent was evaporated at below 30°C , and the resulting **7** (ca. 0.15 g, 0.4 mmol) dissolved in ethanol-free chloroform, followed by the addition of DCC (0.2 g, 0.9 mmol), dimethylaminopyridine (0.012 g, 0.09 mmol) and lyso-PC **8** (0.15 g, 0.3 mmol). The reaction mixture was stirred at room temperature for 48 h, and the product purified on a silica gel column ($\text{CHCl}_3/\text{MeOH}/\text{NH}_3$ (aq.) 60:30:1 to 50:30:3) to give phospholipid **9** (0.09 g, 30% from **8**), which was then dissolved in THF/AcOH/ H_2O (4:2:1) and stirred for 24 h, which achieved complete deprotection of the hydroperoxy group. The product thus obtained was purified by reversed-phase chromatography (ODS, $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$, 4.5:100:5) to give high-purity **3** as a resinous solid (0.065 g, 7% from **5**). ^1H NMR (500 MHz, CDCl_3): δ = 0.88 (t, 3H; ω - CH_3), 0.95 (t, 3H; ω' - CH_3), 1.26 (m, 32H; $\text{OCO}(\text{CH}_2)_{16}\text{CH}_3$), 2.03 (m, 2H; $\text{H}21'$), 2.28 (m, 1H; one proton of $\text{C}18'$), 2.39 (m, 4H; $\text{H}2'$ and $\text{H}3'$), 2.46 (m, 1H; one proton of $\text{C}18'$), 2.87 (m, 4H; $\text{H}6'$ and $\text{H}9'$), 2.98 (m, 2H; $\text{H}12'$), 3.28 (s, 9H; $\text{N}(\text{CH}_3)_3$), 3.72 (m, 2H; $\text{OCH}_2\text{CH}_2\text{N}$), 3.97 (m, 2H; CH_2OP), 4.18 (m, 1H; one proton of $\text{OCH}_2\text{CH}(\text{OR})\text{CH}_2\text{OP}$), 4.30 (m, 2H; $\text{OCH}_2\text{CH}_2\text{N}$), 4.38 (m, 2H; $\text{H}17'$, one proton of $\text{OCH}_2\text{CH}(\text{OR})\text{CH}_2\text{OP}$), 5.24 (brs, 1H; $\text{OCH}_2\text{CH}(\text{OR})\text{CH}_2\text{OP}$), 5.42 (m, 9H; $\text{H}4'$, $\text{H}5'$, $\text{H}7'$, $\text{H}8'$, $\text{H}10'$, $\text{H}11'$, $\text{H}13'$, $\text{H}19'$, $\text{H}20'$), 5.64 (dd, J = 15, 8 Hz, 1H; $\text{H}16'$), 6.10 (t, J = 11 Hz, 1H; $\text{H}14'$), 6.58 (dd, J = 11, 15 Hz, 1H; $\text{H}15'$); ES-MS: found: m/z : 866.6; calcd for $[\text{C}_{48}\text{H}_{84}\text{NO}_{10}\text{P} + \text{H}^+]$: m/z : 866.6.

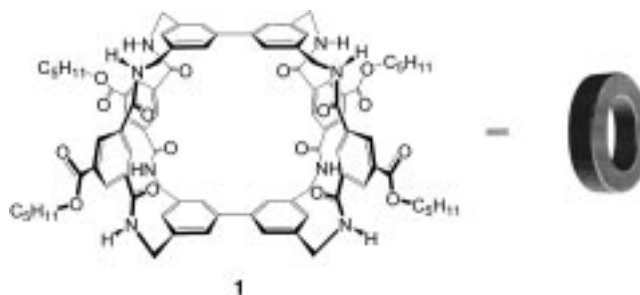
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Gel-Phase MAS NMR Spectroscopy of a Polymer-Supported Pseudorotaxane and Rotaxane: Receptor Binding to an “Inert” Polyethylene Glycol Spacer**

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The combination of magic-angle spinning (MAS) and high-resolution probe technology has provided chemists with a powerful technique for obtaining solutionlike ^1H NMR spectra of resin-bound samples.^[1] As previously described, we have been successful in applying gel-phase MAS spectroscopy to the study of metal–ligand interactions at the solid–liquid interface.^[2] Following this success, we set out to extend our understanding of other interactions, such as those between the tricyclic polyamide receptor **1** and carbohydrates. However, during the course of this study, we discovered an unexpected phenomenon which led to the synthesis of a resin-bound rotaxane as described below.



Macrocycle **1** is a good receptor for octyl pyranosides.^[3] Therefore, a galactose residue was attached onto ArgoGel resin through the primary hydroxide group, so that **1** would bind to the sugar unit and allow us to study the binding between the solid and liquid interfaces. ArgoGel resins contain highly flexible polyethylene glycol (PEG) chains (30–40 units) appended to a 1% cross-linked polystyrene bead; the flexibility of these PEG chains allows us to obtain solutionlike NMR spectra using MAS techniques. An NMR titration was performed to investigate for possible binding between **1** and the solid-supported galactoside. However, this titration unexpectedly showed a splitting of the PEG reso-

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nance (Figure 1). Since the binding between the macrocycle and the sugar is reversible, there might be a possibility that the macrocycle could dissociate from the sugar unit into the PEG

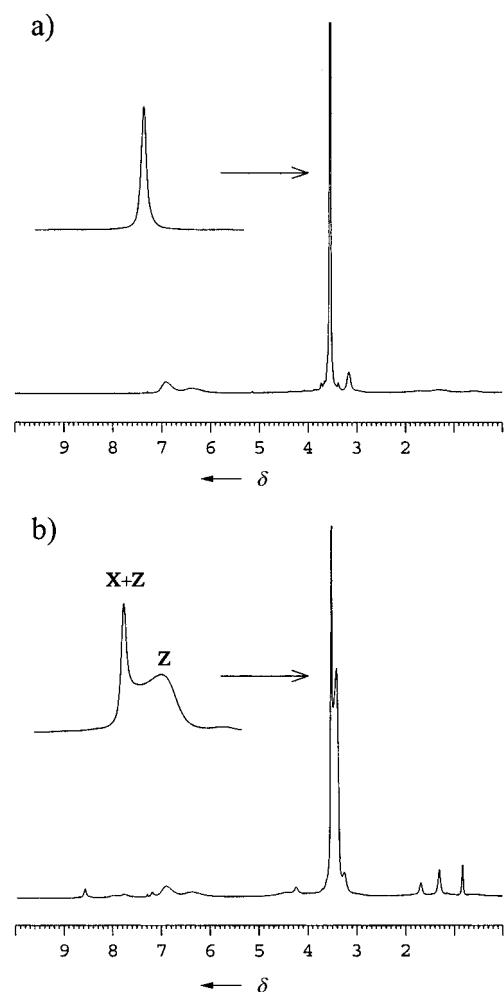
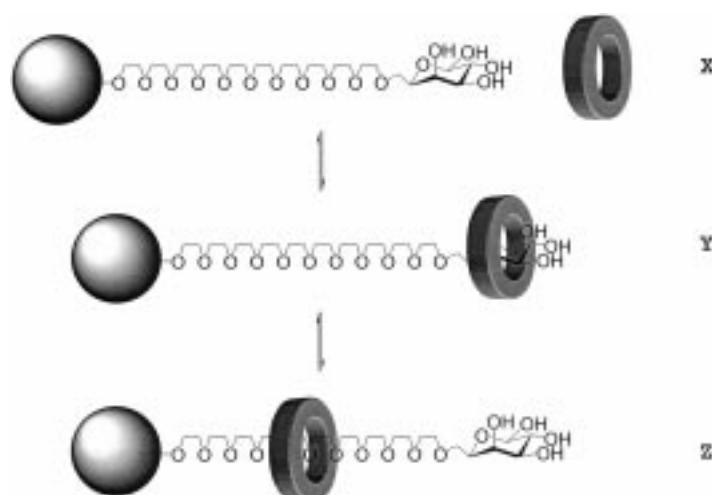


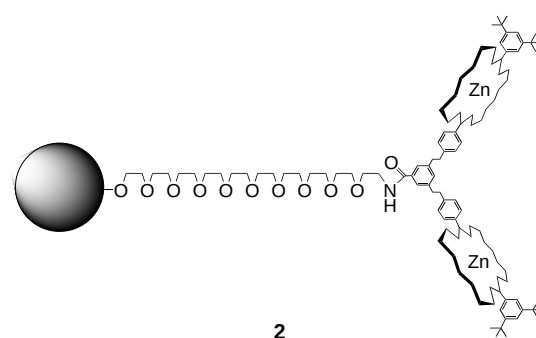
Figure 1. 400 MHz ^1H MAS NMR spectra of galactoside terminated beads (a) the and after addition of one equivalent of **1** (b). A splitting of the PEG resonance is observed. **X** and **Y** correspond to the combination of free PEG chain and sugar-bound macrocycle, and **Z** corresponds to the threaded macrocycle.

chain of the ArgoGel, thus resulting in threading (Scheme 1). Harada and co-workers^[4] and Wenz and Keller^[5] have observed a similar threading of α -cyclodextrin onto PEG chains. However, another possibility was that **1** might bind to the side of the PEG chain, with the ring current from **1** thus causing an upfield shift of the PEG resonance.

Three control experiments were carried out to explore the possibility of threading: 1) Porphyrin-terminated ArgoGel beads **2** were titrated with **1**, and showed no significant changes in the PEG resonance. This result suggests both that the porphyrin dimer attached to the end of the PEG chain acts as a stopper, thus preventing **1** from threading, and that **1** does not bind to the PEG chain on the side. 2) Unfunctionalized ArgoGel-Cl beads were titrated with **1**, and gave a broadened and upfield-shifted ($\Delta\delta = 0.6$ ppm) PEG resonance. Upon addition of glucoside, the resonance for the PEG chain sharpened and shifted towards the original chemical shift.



Scheme 1. Proposed binding modes of receptor **1** to galactosyl beads.



These observations indicate that **1** was threaded around the PEG chain in the first instance which caused a broadening and a change in the chemical shift. This effect was then reversed by the addition of octyl glucopyranoside. Since **1** is known to be a good receptor for sugars, the presence of glucoside causes **1** to dethread from the PEG chain, so that the broadened and upfield-shifted PEG resonance moved downfield and sharpened (Figure 2). 3) An NMR titration between hexaethylene glycol and **1** was carried out in solution, and a binding constant of approximately 9000 M^{-1} was observed. This value indicates that polyethylene glycol does bind to **1**. The NOESY spectrum of the 1:1 mixture of **1** and galactosyl beads showed NOE cross-peaks between the galactosyl proton and the aromatic protons of **1**. These experiments suggested that the three proposed modes **X**, **Y**, and **Z** in Scheme 1 do co-exist. The splitting of the PEG resonance shown in Figure 1b might arise from slow exchange between the bound, unbound, and threaded macrocycle, or from some of the PEG chains being inaccessible as a result of cross-linking, a process that might occur during chemical modification.

To further support our interpretation and demonstrate the analytical power of gel-phase MAS NMR we prepared the porphyrin-stoppered rotaxane **3** as shown in Scheme 2. The ^1H MAS NMR spectrum showed resonances of porphyrin dimer and **1**, but most importantly the splitting of the PEG resonance was once again observed. The outer aromatic protons of **1** were now inequivalent as a result of the large ring current of the porphyrin stopper making one side of the

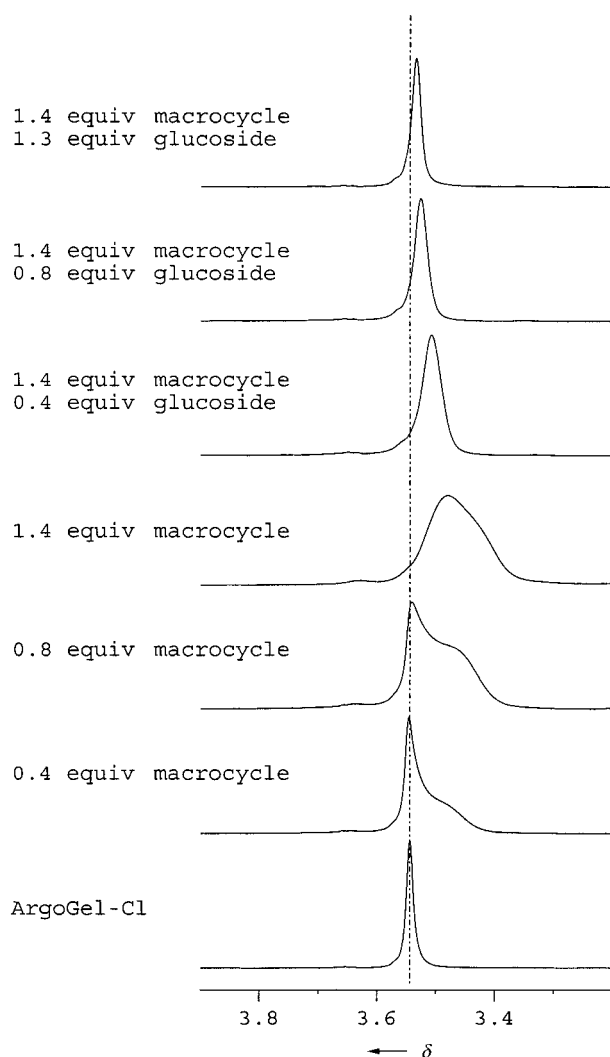
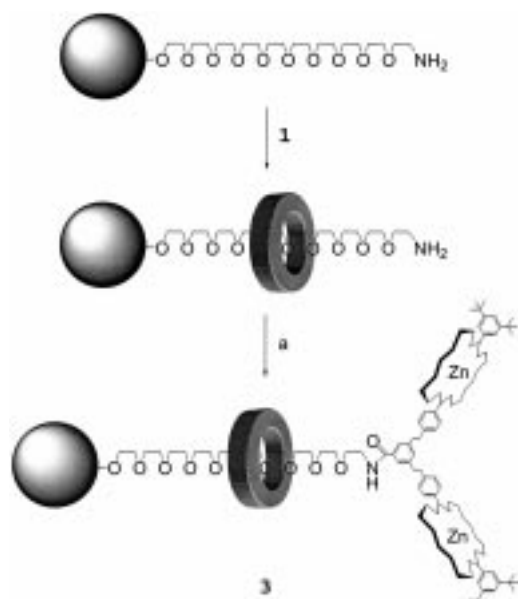


Figure 2. Control experiment showing the competition between the PEG chain of ArgoGel and octyl glucopyranoside for macrocycle **1**.



Scheme 2. Synthesis of porphyrin-stoppered rotaxane. a) Porphyrin dimer, TBTU, and (*i*Pr)₂NH in chloroform.

macrocycle different from the other. The COSY MAS NMR spectrum allowed assignment of the pentyl side chains of **1** and the NOESY spectrum gave NOE cross-peaks between the PEG chain and the aromatic protons of **1** and between the PEG chains and the pentyl groups of **1** (Figure 3). Since the beads were extensively washed with chloroform and methanol, no free macrocycle should be trapped inside the beads. In any case, we would not expect to detect NOEs between the PEG chains and the free macrocycle. We conclude that **1** is held on the PEG chain as a rotaxane and stoppered by the porphyrin dimer.

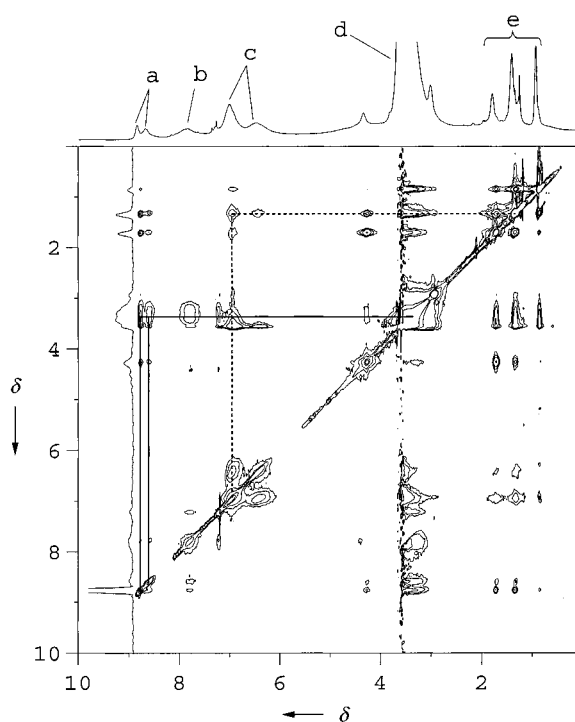


Figure 3. NOESY MAS NMR spectrum of porphyrin-stoppered rotaxane **3** showing NOE cross-peaks between the PEG chain and the outer aromatic protons of **1** (solid line), and between the polystyrene backbone of the ArgoGel and the pentyl side chain of **1** (dotted line). The 1D spectrum shown on the F2 axis is the ¹H MAS NMR spectrum of **3**, and the 1D spectrum shown inside the box is a cross-section taken from the NOESY experiment at $\delta = 8.87$. Resonances a correspond to the inequivalent outer aromatic protons of **1** (see text), and resonances b, c, d, and e correspond to the other aromatic protons of **1**, the polystyrene backbone of ArgoGel, PEG, and the pentyl side chains of **1**, respectively.

In conclusion, we have successfully used MAS NMR spectroscopy to confirm the possibility of a tricyclic polyamide receptor threading around the PEG chain of ArgoGel. This observation has led us to the synthesis of a solid-supported rotaxane. Further study, using different macrocycles and stoppers, is currently underway.

Experimental Section

NMR spectra were acquired at room temperature on a Bruker DRX400 spectrometer using a Bruker HR MAS probe. Rotors containing a suspension of the beads in a mixture of CDCl₃ and CD₃OD (92:8) were spun at 4 kHz. One-dimensional spectra were obtained using 64 scans and titrations were carried out using 10 μ L injections of **1** (ca. 0.2 equiv). NOESY MAS NMR spectra were obtained at room temperature with

suppression at the PEG resonance (70 dB), a 200 ms mixing time, 32 scans, and 512 increments.

The solution-state NMR titration between hexaethylene glycol and **1** was carried out at room temperature by monitoring the inner aromatic proton of the spacer unit. The results showed that the stoichiometry corresponds approximately to a 1:1 binding model.

Galactosyl beads: 1,2:3,4-Di-*O*-isopropylidene-D-galactopyranose (ca. 50 equiv with respect to the loading of ArgoGel-Cl) was treated with sodium hydride (ca. 100 equiv) in tetrahydrofuran. After filtration of the mixture, the filtrate was added to ArgoGel-Cl (0.41–0.45 mmol g⁻¹) and shaken for 2 days. The resulting beads were washed and deprotected with a mixture of trifluoroacetic acid and water (9:1, 2 mL). Washing the beads with tetrahydrofuran, methanol, and chloroform afforded the galactosyl beads.

2: A solution of a rigid porphyrin dimer^[6] (50 mg) and palladium on carbon (50 mg) in tetrahydrofuran (25 mL) was stirred under hydrogen for 24 h. Filtration of the mixture through celite and removal of the solvent afforded a flexible porphyrin dimer. A mixture of ArgoGel-NH₂ (13 mg, 0.41–0.45 mmol g⁻¹), flexible porphyrin dimer (30 mg), TBTU (4 mg), and diisopropylamine (3 mg) in a mixture of *N,N*-dimethylformamide (1 mL) and dichloromethane (0.5 mL) was shaken for 4 days. The solvent was then removed by filtration and the beads were washed extensively with dichloromethane and methanol.

3: A mixture of the flexible porphyrin dimer (22 mg), TBTU (5 mg), and diisopropylamine (3 mg) in chloroform (1 mL) was added to a mixture of **1** (12 mg) and ArgoGel-NH₂ (15 mg) in chloroform (1 mL). The resulting mixture was shaken for 1 day. The solvent was then removed by filtration and the beads were washed extensively with dichloromethane and methanol.

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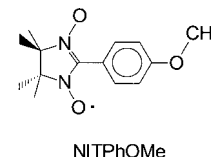
Cobalt(II)-Nitronyl Nitroxide Chains as Molecular Magnetic Nanowires**

Andrea Caneschi, Dante Gatteschi,* Nikolia Lalioti, Claudio Sangregorio, Roberta Sessoli, Giovanni Venturi, Alessandro Vindigni, Angelo Rettori, Maria G. Pini, and Miguel A. Novak

The observation of slow magnetic relaxation in molecular clusters is now considered as one of the most important achievements of molecular magnetism of the last few years.^[1] In fact systems like Mn₁₂, Fe₈ have provided unique opportunities for the investigation of molecular magnetic hysteresis,^[2] quantum tunneling of the magnetization,^[3, 4] and of phase interference (Berry phase).^[5] All these features depend on slow magnetic relaxation.

While clusters can be considered as zero-dimensional materials, in principle slow relaxation of the magnetization can also be expected in one-dimensional (1D) materials, as suggested by Glauber in 1963.^[6] However, to date, it has not been possible to observe this behavior because no suitable experimental system has been produced. In fact the conditions to be met to observe slow magnetic relaxation in 1D materials are rather stringent: 1) the ratio of the interaction within the chain, *J*, and that between chains, *J'*, must be rather high, larger than 10⁴; 2) the material must behave as a 1D Ising ferro- or ferrimagnet.

We have now found that slow relaxation of the magnetization and hysteresis effects which are not associated with three-dimensional (3D) order can be observed in [Co(hfac)₂(NITPhOMe)] (**1**; hfac = hexafluoroacetylacetonate, NITPhOMe = 4'-methoxyphenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide). We want to show that these findings provide an experimental confirmation of Glauber's prediction.



Complex **1** consists of alternating Co(hfac)₂ and radical moieties arranged in 1D arrays with a helical structure arising from the trigonal crystallographic

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lattice (Figure 1).^[7] Similar structures have been reported for manganese(II) analogues,^[8] and the role of supramolecular interactions for determining the helical arrangement were

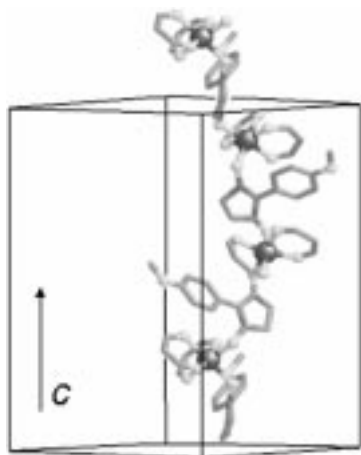


Figure 1. A simplified view of the content of the unit cell of **1**. Large dark spheres represent the metal ions. For the sake of clarity the hydrogen, fluorine, and most of the methyl carbon atoms are omitted. Compound **1** crystallizes in the $P3_1$ space group with $a = b = 11.294 \text{ \AA}$ and $c = 20.570 \text{ \AA}$. The trigonal space group leads to stacking interactions between the phenyl ring of the radical and two adjacent hfac molecules thus giving an asymmetric “sandwich structure” with the planes forming angles of $10.1/9.6^\circ$ and distances of $3.6/3.9 \text{ \AA}$. Each trigonal chain is surrounded by other six equivalent chains with $11.289 \text{ \AA}$ and $10.345 \text{ \AA}$ being the shortest interchain $\text{Co}^{\text{II}}-\text{Co}^{\text{II}}$ and the shortest NO–NO contacts, respectively.

discussed.^[7] The temperature dependence of χT of **1**, (Figure 2), gives clear indications of 1D behavior, presumably of ferrimagnetic nature. The rapid increase of χT below 100 K suggests strong intrachain interactions as observed in 1D ferro- and ferrimagnets. Antiferromagnetic coupling between cobalt(II) and the NITPhOMe radical is suggested by the temperature dependence of the magnetic susceptibility of the mononuclear complex $[\text{Co}(\text{hfac})_2(\text{NITPhOMe})_2]$,^[9] in which the coordination of the central cobalt ion is essentially the same as in the chain compound. At low temperature the spin of octahedral cobalt(II) centers can be handled as an effective $S = 1/2$ spin with anisotropic g values significantly different

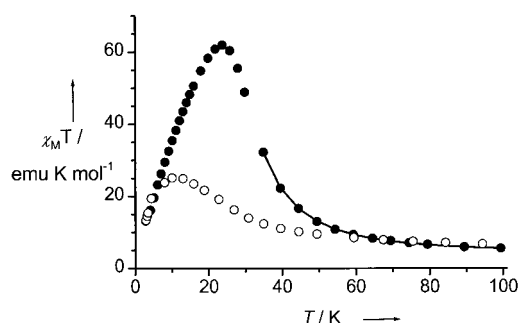


Figure 2. Temperature dependence of the ratio between magnetization and magnetic field (indicated for simplicity as a susceptibility) multiplied by the temperature and measured in 1 kOe external field parallel to the chain direction ($\bullet$) or perpendicular to it ($\circ$). The solid line corresponds to the calculated value using the alternating spins 1D Ising model (see text). The decrease observed below 30 K is field dependent and is caused by the rapid approach to saturation because of strong short-range correlation.

from 2. The chains therefore behave as 1D ferrimagnets, because of the noncompensation of the magnetic moments of the cobalt(II) center and the radical.

The susceptibility below 50 K is strongly anisotropic, as shown in Figure 2, with the trigonal axis corresponding to the easy axis of magnetization and therefore to Ising-type anisotropy. A first estimation of the exchange coupling has been obtained through a fit of the temperature dependence of χT with an Ising model, which gives $J/k_B = 220 \text{ K}$, $g_{\text{Co}} = 7.4$, $g_{\text{rad}} = 2$, where the Hamiltonian is given by Equation (1). The large value of J is in agreement with the values in the manganese(II) and nickel(II) analogues.^[7, 10]

$$\mathcal{H} = \sum_i J(\mathbf{S}_{2i}^z \mathbf{S}_{2i+1}^z + \mathbf{S}_{2i}^z \mathbf{S}_{2i-1}^z) - \mu_B H^z \sum_i (g_{\text{Co}} \mathbf{S}_{2i}^z + g_{\text{rad}} \mathbf{S}_{2i-1}^z) \quad (1)$$

The alternating current (ac) magnetic susceptibility of **1** is strongly frequency dependent below 17 K . The in-phase susceptibility, χ' , goes through a maximum, and the out-of-phase component, χ'' , becomes different from zero also going through a maximum (Figure 3). These results indicate that the

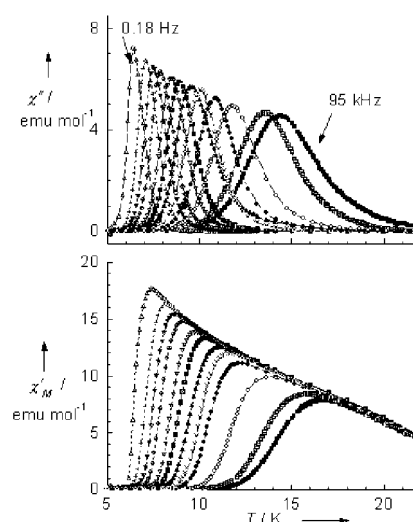


Figure 3. Temperature dependence of the real (bottom) and imaginary (top) component of the ac susceptibility measured in zero applied static field and with the oscillating field ($0.5\text{--}2 \text{ Oe}$) applied along the chain direction. The frequency of the oscillating field varies in the range $0.18\text{--}95 \text{ kHz}$. The lines are only a guide.

relaxation of the magnetization in this temperature range becomes slow on the time scale of the experiment ($2 \mu\text{s} - 1 \text{ s}$). The frequency dependence rules out a 3D transition, and suggests a thermally activated mechanism. In fact, over the wide frequency range investigated ($0.18\text{--}95 \text{ kHz}$) τ has exponential behavior [Eq. (2)] as observed in superparamagnets^[11] and spin glasses.^[12] The best-fit parameters are $\tau_0 = 3.0(2) \times 10^{-11} \text{ s}$, $\Delta/k_B = 154(2) \text{ K}$. The value of τ_0 is close to that expected for the relaxation time of octahedral cobalt(II) centers. The entire magnetization, of both the cobalt and radical sublattices, experience the same blocking temperature, as suggested in that χ' goes to zero for temperatures below the peak in χ'' , and indeed χ' and χ'' almost describe a semicircle in the Cole–Cole plot.^[13, 14]

$$\tau = \tau_0 \exp(\Delta/k_B T) \quad (2)$$

The strong frequency dependence of the relaxation time and the physically reasonable value of τ_0 , without introducing any scaling factor, rule out the possibility that the system is a spin glass.^[12] Further, since a spin glass demands the presence of disorder, this is difficult to reconcile with the single-crystal nature of the sample. The model developed by Glauber for Ising ferromagnetic chains predicts that the reversal of the spins becomes more difficult on lowering the temperature because the short-range correlation along the chain favors the parallel alignment of the spins.^[6] An Arrhenius behavior is predicted for the relaxation time, with the height of the barrier corresponding to the nearest-neighbor exchange interaction J . The experimental barrier Δ/k_B , is indeed close to the J coupling constant estimated from analysis of the magnetic susceptibility using the Ising model.

Static measurements of the magnetization parallel to the trigonal axis, obtained by cooling in zero field and then applying a field, show the onset of irreversibility around 6 K. The field-cooled magnetization shows a plateau below this temperature typical of a complete freezing process. The isothermal magnetization has a hysteretic behavior when the external magnetic field is applied parallel to the trigonal axis (Figure 4) while no hysteresis can be observed when the field is applied in the trigonal plane.

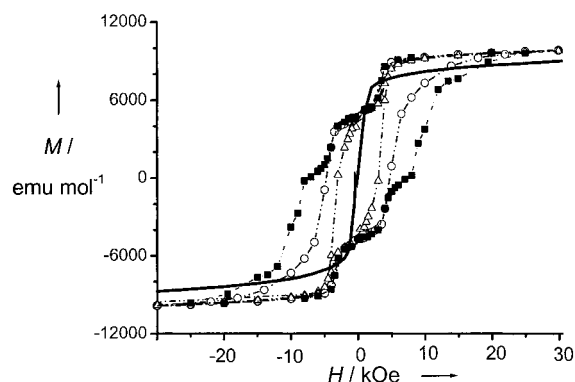


Figure 4. Hysteresis loops measured on a single crystal of **1** by applying the field parallel to the chain axis at 2.0 K (■), 3.0 K (○), 4.5 K (△), and at 2.0 K perpendicular to it (—).

The magnetization at the highest field (60 kOe) and 1.8 K is $1.90 \mu_B$ parallel to the trigonal axis and $1.72 \mu_B$ perpendicular to it. These values seem to suggest that the anisotropy of the chains is small even if the slow dynamics are associated with the Ising anisotropy of the exchange interaction. In fact, the helical arrangement of the anisotropy tensors of the individual cobalt spins reduces the bulk anisotropy if the easy axis of the cobalt(II) ions is not parallel to the trigonal axis.^[15] That the anisotropy axes of cobalt spins are not parallel to each other could also be responsible of the reversible steps in the hysteresis loop observed for $H \approx \pm 4$ kOe.

Molecular magnets are providing new types of magnetic behavior, which are not easily observed in traditional magnets. This is particularly true for nanosized species, because the presence of large nonmagnetic organic moieties can relatively easily provide confinement of the magnets in zero, one, and two dimensions.

The unique feature of **1**, its highly one-dimensional nature, allowed us to record for the first time the slow relaxation of the magnetization in the paramagnetic phase of a 1D compound, a process predicted theoretically almost forty years ago.^[6] The different magnetic behavior of the manganese(II) derivative, which orders ferrimagnetically at 4.6 K,^[7, 8] is because of the almost negligible anisotropy of the manganese(II) centers. The anisotropy of the cobalt–radical exchange interaction in the chain gives a barrier for the reorientation of the magnetization. This, combined with the smaller spin of cobalt(II) compared to manganese(II) centers, determines slow relaxation of the magnetization before the weak interchain dipolar interaction can induce three-dimensional magnetic order.

1D magnetic systems are well known to be able to show long-range order only at 0 K. The research in molecular magnetism of the last two decades therefore has been characterized by strong efforts to efficiently connect magnetic chains in 3D networks to observe bulk magnetism. We have shown here that magnetic bistability and the related *memory* effect can indeed be observed in a 1D material without requiring any interchain interaction.^[16] These results may open exciting new perspectives including that of storing information in a single magnetic polymer as well as in the novel class of 1D materials where ionic structures are obtained inside carbon nanotubes.^[17]

Experimental Section

Crystals of **1** were prepared as reported in ref. [7]. The crystals were checked on an Enraf Nonius CAD4 four-circle diffractometer. The axis of the helical chains is easily recognized as it corresponds to the elongation axis of the crystals, which have the shape of hexagonal rods. Magnetic measurements were performed by using a Cryogenic S600 SQUID magnetometer equipped with the ac option. High frequency ac susceptibility measurements have been performed on a home-built susceptometer. A single crystal of **1**, of approximate weight 1 mg, was used for the static magnetic measurements, while samples containing around 10 iso-oriented single crystals for a total weight of about 4–6 mg were employed for the ac susceptibility measurement.

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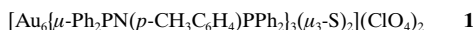
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- [15] In **1** the cobalt ion occupies a general position thus lacking the trigonal symmetry. Its easy axis of magnetization can therefore be at any angle from the trigonal axis and the comparison with the mononuclear compound^[9] suggests that this angle can be as large as 50°.
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A Novel Polynuclear Gold–Sulfur Cube with an Unusually Large Stokes Shift**

Vivian W.-W. Yam,* Eddie C.-C. Cheng, and Nianying Zhu

The luminescence properties of polynuclear transition metal complexes with a d¹⁰ closed-shell electronic configuration have attracted much attention over the past few decades.^[1] In view of the wide applicability of d¹⁰ transition metal chalcogenides in semiconducting materials, photovoltaics, and nanomaterials, and their intriguing optical behavior, their spectroscopic and photophysical properties are worthy of exploration. With our recent success in making soluble polynuclear copper(II), silver(II), gold(II), zinc(II), cadmium(II) and mercury(II) complexes with unsubstituted chalcogenide and chalcogenolate ligands and rich luminescence behavior,^[2] we hope that, by systematic variation of the metal, chalcogen, and ancillary ligands, insights into the spectroscopic properties, the nature of the excited states, and the structure–property relationship can be obtained. This is particularly important, as many of the transition metal chalcogenides and chalcogenolates are insoluble, and this renders their structures and photophysical properties less amenable to study. Owing to the recent growing interest in the aurophilic nature

of gold(II) centers and the scantiness of gold(II) chalcogenide aggregates,^[3–5] we launched a program to investigate this class of compounds. A number of soluble dodecanuclear and decanuclear gold(II) sulfido complexes with bridging diphosphane ligands have been successfully synthesized by us.^[2c,d] These complexes have the formulas [Au₁₂(μ-dppm)₆(μ₃-S)₄](PF₆)₄ (dppm = bis(diphenylphosphanyl)methane) and [Au₁₀{μ-Ph₂PN(*n*Pr)PPh₂}₄(μ₃-S)₄](PF₆)₂ and possess novel structures and interesting photophysical behaviors. Here we report an unprecedented hexanuclear gold(II) sulfido complex with bridging diphosphane ligands, namely, **1**, which has unusual photophysical properties.



Reaction of H₂S with a suspension of [Au₂{Ph₂PN(*p*-CH₃C₆H₄)PPh₂}]Cl₂ in ethanol/pyridine followed by metathesis reaction with LiClO₄ and recrystallization from acetone/dichloromethane/diethyl ether yielded **1** as colorless crystals in 50% yield. It was characterized by elemental analysis, positive-ion FAB mass spectrometry, positive- and negative-ion ESI mass spectrometry, and ¹H and ³¹P NMR spectroscopy.^[6]

The structure of the complex cation of **1** in the solid state was determined by X-ray crystallography.^[7] The cation is hexanuclear, and the Au₆S₂ unit is arranged in a distorted heterocubane structure with the two sulfur atoms at opposite apices of the cuboid. Figure 1 shows a perspective drawing of

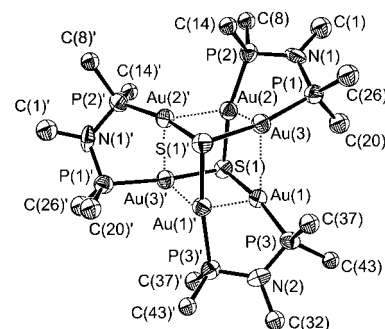


Figure 1. Perspective drawing of the structure of the complex cation of **1** in the crystal. Only the *ipso*-C atoms of the aromatic rings are shown for clarity. Thermal ellipsoids are drawn at the 30% probability level.

the cation. Each sulfur atom is bonded to three gold(II) centers in a μ₃ bridging mode, and the two Au₃S units are interconnected by three diphosphanylamin ligands. Noticeable gold–gold interactions are present, and the Au⋯Au distances range from 2.939(3) to 3.3775(18) Å. The Au–S and Au–P bond lengths of 2.325(8)–2.346(8) and 2.256(9)–2.272(8) Å, respectively, and the P–Au–S angles of 168.4(3)–178.5(3)°, which are distorted from ideal linear geometry, are not uncommon.^[2c–e, 8–10] The Au–S–Au angles at the μ₃-S atoms are in the range of 92.13–95.66° and thus deviate only slightly from the ideal 90° expected for bonding involving the sulfur 3p orbitals. The P–N–P angles are very close to 120°, indicative of sp² hybridization at the N center. Unlike other polynuclear gold(II) sulfido complexes with bridging diphosphane ligands,

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such as $[\text{Au}_{12}(\mu\text{-dppm})_6(\mu_3\text{-S})_4](\text{PF}_6)_4$ and $[\text{Au}_6(\mu\text{-dppf})_3(\mu_3\text{-S})_2](\text{OTf})_2$ (dppf = 1,1'-bis(diphenylphosphanyl)ferrocene), in which the sulfur atoms of the SAu_3 pyramids are adjacent to each other in an open structure,^[2c, 4d] **1** assumes a *closo*-cuboidal structure in which the two sulfur atoms of the SAu_3 pyramids are further apart and occupy opposite corners of the cuboid. This configuration is assumed to be more sterically demanding. However, it is likely that the presence of $\text{Au}\cdots\text{Au}$ interactions in the complex together with the small bite angle of the diphosphane ligands may overcome the steric effects and give rise to the observed structure.

The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of **1** in $[\text{D}_6]\text{acetone}$ shows a sharp singlet at $\delta = 82.7$. The presence of only one ^{31}P environment is in line with the D_3 symmetry of the molecule, in which the C_3 symmetry axis passes through the two sulfur atoms, and each of the three perpendicular C_2 axes bisects the diphosphane ligands.

The photophysical data of **1** are summarized in Table 1. The electronic absorption spectrum of **1** shows two absorption shoulders and a low-energy absorption band. With reference

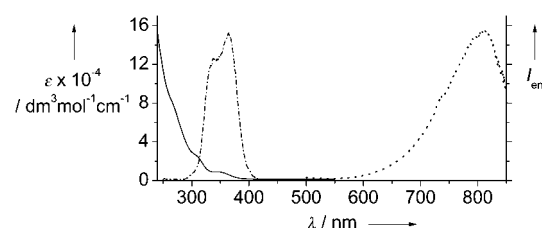


Figure 2. Electronic absorption (—, ϵ) spectrum, and emission (••••, I_{em}) spectrum with excitation at 365 nm, and excitation spectrum (---, I_{ex}), monitored at 810 nm, of **1** in dichloromethane solution at 298 K.

and the emission maximum in fluid solutions at room temperature (810 nm). Such an abnormally large Stokes shift may suggest that the excited-state structure is highly distorted from that of the ground state. When compared with the orange emission observed in solid **1** at room temperature ($\lambda_{\text{em}} = 635$ nm), the red shift for the luminescence in solution ($\lambda_{\text{em}} = 810$ nm in dichloromethane) can be ascribed to the larger structural changes that may occur in solution than in the rigid lattice of the solid. Blue shifts in emission energy upon lowering the temperature have also been observed in the solid state, and more prominently in fluid solutions, and may be attributed to rigidochromic effects, similar to those observed in the tetranuclear copper(I) cubane clusters reported by the groups of Vogler and Ford^[11] and the gold(I) thiolato complexes by Eisenberg et al.^[9] The increased rigidity of the system in the glass state compared to that in fluid solutions would restrict the extent of the distortions in the excited state and hence give rise to a smaller red shift in the emission energy. Alternatively, attribution of the large red shift to the rearrangement or decomposition of the complex in solution, or solvent–exciplex formation was not favored, in view of the establishment of the identity of **1** in solution by positive-ion ESI-MS, as well as the lack of solvent dependence in the emission energy of **1** in methanol and dichloromethane (see Table 1).

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Table 1. Photophysical properties of **1**.^[a]

Medium (<i>T</i> [K])	Emission λ [nm] (τ_0 [μs])	Medium (<i>T</i> [K])	Emission λ [nm] (τ_0 [μs])
solid (298)	635 (14.3, 2.5) ^[a]	CH_2Cl_2 (77)	562 (23.2, 3.2) ^[a]
solid (77)	603	MeOH (298)	808 (3.1)
CH_2Cl_2 (298)	810 (3.6)	EtOH/MeOH (4/1) (77)	564 (37.6)

[a] Absorption λ_{max} [nm] in CH_2Cl_2 (ϵ [$\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$]): 264 sh (83 280), 304 sh (24 290), 346 (6320). [b] Biexponential decay.

to previous spectroscopic studies on related polynuclear gold(I) compounds,^[2c–e, 8, 9] the low-energy absorption at 346 nm, which is absent in the gold(I) precursor complex $[\text{Au}_2(\text{Ph}_2\text{PN}(p\text{-CH}_3\text{C}_6\text{H}_4)\text{PPh}_2)\text{Cl}_2]$, is likely to originate from a ligand-to-metal charge transfer transition modified by $\text{Au}\cdots\text{Au}$ interactions (LMMCT; $\text{S} \rightarrow \text{Au}$). The higher-energy absorption shoulders, which are also found in the electronic absorption spectra of the corresponding ligand $\text{Ph}_2\text{PN}(p\text{-CH}_3\text{C}_6\text{H}_4)\text{PPh}_2$ and the gold(I) precursor complex $[\text{Au}_2(\text{Ph}_2\text{PN}(p\text{-CH}_3\text{C}_6\text{H}_4)\text{PPh}_2)\text{Cl}_2]$, are assigned to the diphosphane intraligand and the metal-perturbed intraligand transitions, respectively. Excitation of the hexanuclear complex in the solid state with visible light at room temperature and at 77 K results in intense orange emission. The radiative lifetimes in the microsecond range are suggestive of a triplet parentage. Excitation bands of **1** in dichloromethane solution at 298 K (monitored at 810 nm) are observed at about 333 and 365 nm, which closely resemble that of the low-energy absorption bands, indicative of their similar origin (Figure 2). The emission is therefore tentatively assigned to originate from the triplet states of a ligand-to-metal charge-transfer character that are mixed with metal-centered (ds/dp) states modified by $\text{Au}\cdots\text{Au}$ interactions (LMMCT; $\text{S} \rightarrow \text{Au}$). Assignments based on similar grounds were made for related gold(I) sulfido and thiolato complexes.^[2c–e, 8–10] An energy difference of about 1.87 eV (15052 cm^{-1}) was observed between the lowest energy excitation maximum (365 nm)

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- [6] **1**: Elemental analysis calcd (found) for $[\text{Au}_6\{\text{Ph}_2\text{PN}(\text{CH}_2\text{C}_6\text{H}_4)\text{PPh}_2\}_3\text{S}_2](\text{ClO}_4)_2 \cdot 2\text{CH}_2\text{Cl}_2$: C 37.52 (37.49), H 2.82 (2.52), N 1.38 (1.34). Positive-ion FAB-MS: ion cluster at m/z 2772 $[\text{M} - \text{ClO}_4]^+$; positive-ion ESI-MS: ion cluster at m/z 2772 $[\text{M} - \text{ClO}_4]^+$, m/z 1336 $[\text{M} - 2\text{ClO}_4]^{2+}$; negative-ion ESI-MS: ion cluster at m/z 99 $[\text{ClO}_4]^-$; ^1H NMR (500 MHz, $[\text{D}_6]\text{acetone}$, 298 K): δ = 2.02 (s, 9H, CH_3), 6.16 (d, 6H, J = 8.3 Hz, o -H of NAr), 6.61 (d, 6H, J = 8.3 Hz, m -H of NAr), 7.28–7.31 (m, 24H, PPh_2), 7.43–7.46 (m, 18H, PPh_2), 7.65–7.74 (m, 18H, PPh_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, $[\text{D}_6]\text{acetone}$, 298 K): δ = 82.7.
- [7] Crystal data for **1**: $\text{C}_{93}\text{H}_{81}\text{Au}_6\text{Cl}_2\text{N}_3\text{O}_8\text{P}_6\text{S}_2$, M_r = 2871.25, cubic, space group $I2_13$ (No. 199), a = 36.465(4) Å, V = 48487(9) Å³, Z = 12, ρ_{calcd} = 1.180 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 5.576 mm⁻¹, $F(000)$ = 16248, T = 301 K. 43 580 reflections measured, of which 8604 were unique (R_{int} = 0.1570) and were used in all calculations. Final R = 0.0842 (for observed data with $I > 2\sigma(I)$). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155449. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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First Diastereomerically Controlled Aggregation of L-Cysteinato Cobalt(III) Octahedra, Assisted by Silver(I) Ions

Takumi Konno,* Takashi Yoshimura, Kazumi Aoki, Ken-ichi Okamoto, and Masakazu Hirotsu

During the past decade considerable progress has been made in the design and creation of supramolecular systems.^[1] While the majority of supramolecular species have been constructed from organic ligands and metal ions by spontaneous self-assembly, our strategy is to use metal thiolate

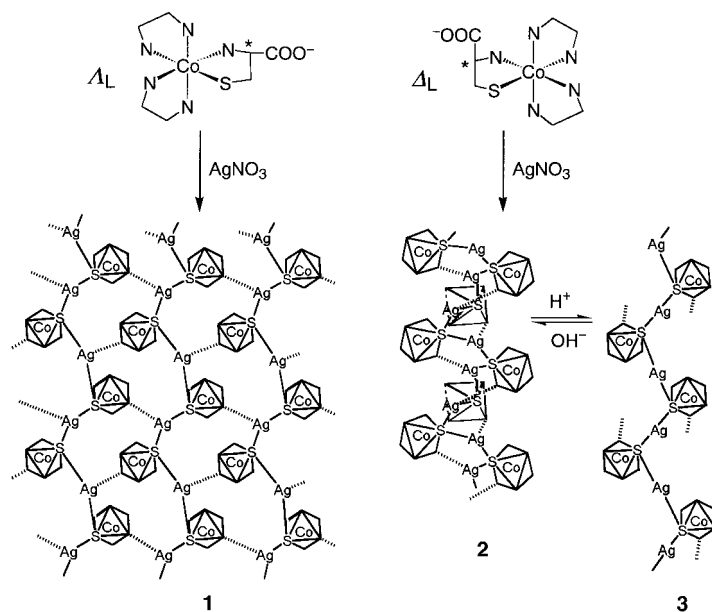
complexes as building blocks which can aggregate by forming S-bridged structures with a variety of metal ions.^[2] In particular, we are interested in the aggregation of tris(chelate)-type octahedral complexes with simple bidentate *N,S*-thiolate ligands such as 2-aminoethanethiolate ($\text{aet} = \text{NH}_2\text{CH}_2\text{CH}_2\text{S}^-$) and *L*-cysteinate ($\text{L-cys} = \text{NH}_2\text{CH}(\text{COO}^-)\text{CH}_2\text{S}^-$), with the aim of creating chiral supramolecular architectures.^[3] To date, a number of chiral aggregates based on the octahedral $[\text{M}(\text{aet})_3]$ unit ($\text{M} = \text{Co}^{\text{III}}$, Rh^{III} , Ir^{III}) with three thiolate donors, such as trinuclear $[\text{Co}^{\text{III}}\{\text{M}(\text{aet})_3\}_2]^{3+}$,^[4] pentanuclear $[\text{Ag}^{\text{I}}\{\text{M}(\text{aet})_3\}_2]^{3+}$,^[5] and octanuclear $[\text{Zn}^{\text{II}}\text{O}\{\text{M}(\text{aet})_3\}_4]^{6+}$,^[6] as well as analogous aggregates based on the $[\text{M}(\text{L-cys-}N,S)_3]^{3-}$ unit, have been prepared, and their unique stereochemical, spectroscopic, and redox properties have been extensively studied. In contrast, the aggregation of octahedral complex units with a single thiolate donor has been studied far less; only a few trinuclear and tetranuclear species such as $[\text{Co}(\text{aet})(\text{en})_2]^{2+}$ or $[\text{Co}(\text{SCH}_2\text{COO})(\text{en})_2]^+$ ($\text{en} = \text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$) have been reported.^[7]

To expand the range of chiral supramolecular architectures based on octahedral complex units with thiolate donors, it is desirable to find the key factors that control their aggregation by studying the fundamental $[\text{Co}^{\text{III}}(\text{thiolato-}S)(\text{amine-}N)_5]$ system. We therefore started by investigating the aggregation of $[\text{Co}(\text{aet})(\text{en})_2]^{2+}$ and $[\text{Co}(\text{L-cys-}N,S)(\text{en})_2]^+$ assisted by metal ions. Recently, we found that the reaction of racemic $[\text{Co}(\text{aet})(\text{en})_2]^{2+}$ with AgNO_3 in a 1:1 ratio gives an S-bridged $\text{Co}^{\text{III}}\text{Ag}^{\text{I}}$ coordination polymer having a one-dimensional infinite zigzag chain structure, namely, $\{[\text{Ag}\{\text{Co}(\text{aet})(\text{en})_2\}](\text{NO}_3)_3\}_\infty$.^[8] Interestingly, the chain structure discriminated the chiral configuration (Δ or Λ) of $[\text{Co}(\text{aet})(\text{en})_2]^{2+}$ to give exclusively the enantiomeric $(\Delta\text{-Co}^{\text{III}}\text{Ag}^{\text{I}})_\infty$ and $(\Lambda\text{-Co}^{\text{III}}\text{Ag}^{\text{I}})_\infty$ chains, which separate from one another as homochiral crystals. Given this result, we expected that similar $(\text{Co}^{\text{III}}\text{Ag}^{\text{I}})_\infty$ chiral chain structures would be formed on using the Δ_L or Δ_L diastereomer of $[\text{Co}(\text{L-cys-}N,S)(\text{en})_2]^+$ instead of racemic $[\text{Co}(\text{aet})(\text{en})_2]^{2+}$. Indeed, we found that the reactions of Δ_L - or Δ_L - $[\text{Co}(\text{L-cys-}N,S)(\text{en})_2]^+$ with AgNO_3 lead to the formation of fascinating chiral supramolecular structures, which are markedly dependent on whether the Δ_L or Δ_L diastereomer is used (Scheme 1).

Treatment of a dark brown aqueous solution of Δ_L - $[\text{Co}(\text{L-cys-}N,S)(\text{en})_2](\text{ClO}_4)$ with AgNO_3 in a 1:1 ratio at room temperature gave a dark red solution, from which red plate crystals of **1** were isolated by adding an aqueous solution of NaNO_3 . The electronic absorption spectrum of **1** in water is characterized by an intense S-to-Co charge-transfer (CT) band at 288 nm and a first d–d absorption band at 497 nm. The disappearance of a distinct shoulder at ca. 560 nm in the first d–d band of the starting material Δ_L - $[\text{Co}(\text{L-cys-}N,S)(\text{en})_2]^+$ is indicative of coordination of the thiolate S atom to an Ag^{I} ion.^[7b, 8] Plasma emission spectral analysis indicated that **1** contains Co and Ag atoms in a 1:1 ratio, and the elemental analysis was consistent with the 1:1 stoichiometry of $[\text{Co}(\text{L-cys})(\text{en})_2](\text{NO}_3) \cdot \text{AgNO}_3$.

The crystal structure of **1**, determined by X-ray analysis, revealed the presence of an asymmetric unit consisting of one octahedral Δ_L - $[\text{Co}(\text{L-cys-}N,S)(\text{en})_2]^+$ unit and one Ag^{I} ion

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Scheme 1. Synthesis of **1**, **2**, and **3**.

(Figure 1a), besides two nitrate anions.^[10] In the complex cation of **1**, the thiolate S atom of each octahedral Δ_L -[Co(L-cys-N,S)(en)₂]⁺ unit is bound to two Ag^I ions to form a one-dimensional zigzag (Co^{III}Ag^I)_∞ chain structure (Co–S 2.263(3), Ag–S 2.501(3) and 2.511(3) Å). This chain structure

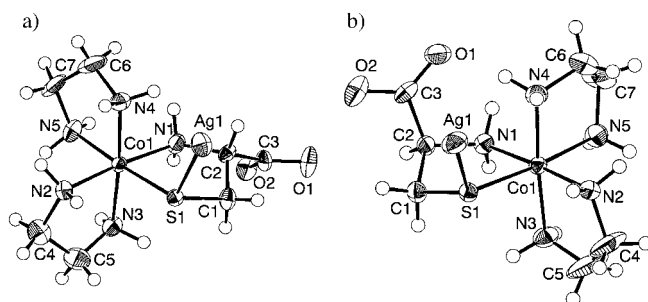


Figure 1. ORTEP plots of the complex cations (asymmetric units) of **1** (a) and **2** (b).

resembles that found in $[\text{Ag}\{\text{Co}(\text{aet})(\text{en})_2\}](\text{NO}_3)_3$ ∞ (Co–S 2.287(2), Ag–S 2.532(2) and 2.546(2) Å).^[8] However, the S–Ag–S angle in **1** deviates significantly from 180° (149.62(7)°); in contrast the S–Ag–S angle in $[\text{Ag}\{\text{Co}(\text{aet})(\text{en})_2\}](\text{NO}_3)_3$ ∞ is 173.14(6)°. A detailed inspection of the extended structure of **1** revealed that the COO⁻ group of each Δ_L -[Co(L-cys-N,S)(en)₂]⁺ unit, which adopts an equatorial orientation, chelates an Ag^I ion of the adjacent zigzag chain (Ag–O2 2.490(8), Ag–O1 2.598(1) Å; O1–Ag–O2 51.1(3)°). Thus, the (Co^{III}Ag^I)_∞ chains are connected with one another by Ag–O bonds to form a two-dimensional extended sheetlike structure composed of cyclic Co^{III}Ag^I units (Figure 2).

A similar 1:1 reaction of the Δ_L diastereomer of [Co(L-cys-N,S)(en)₂]⁺ with AgNO₃ produced dark red prismatic crystals of **2**. While the absorption spectrum of **2** in water is very similar to that of **1**, its CD spectral feature is significantly

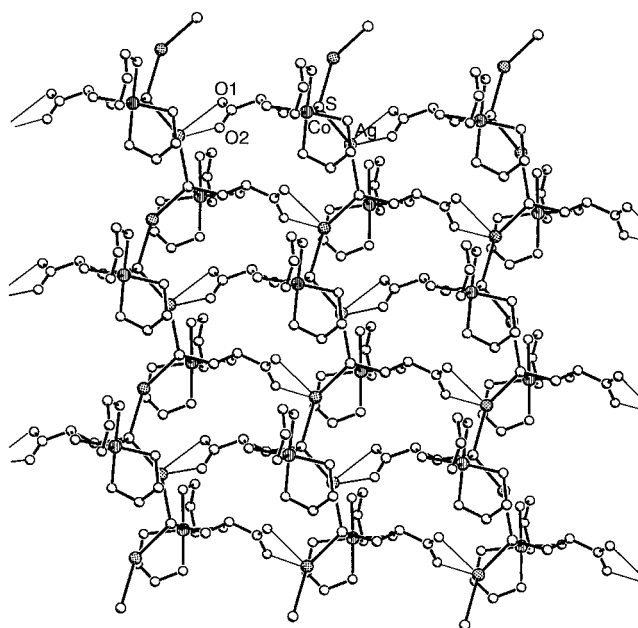


Figure 2. View of the complex cation of **1**. Hydrogen atoms are omitted for clarity.

different, especially in the d–d absorption band region, and this reflects a difference in configuration at the Co^{III} ion. Along with the elemental and plasma emission spectral analyses, which were in good agreement with the formula for the 1:1 adduct Δ_L -[Ag{Co(L-cys-N,S)(en)₂}] (NO₃)₂, the structure of **2** was established by X-ray analysis.^[10] As shown in Figure 3, the complex cation of **2** is a one-dimensional helical coordination polymer consisting of asymmetric Δ_L -[Ag{Co(L-cys-N,S)(en)₂}]²⁺ units. The thiolate S atom of each octahedral Δ_L -[Co(L-cys-N,S)(en)₂]⁺ unit is bound to two Ag^I ions to form an infinite (Co^{III}Ag^I)_∞ chain (Co–S 2.251(2), Ag–S 2.550(2) and 2.553(2) Å), as in the case of **1**. However,

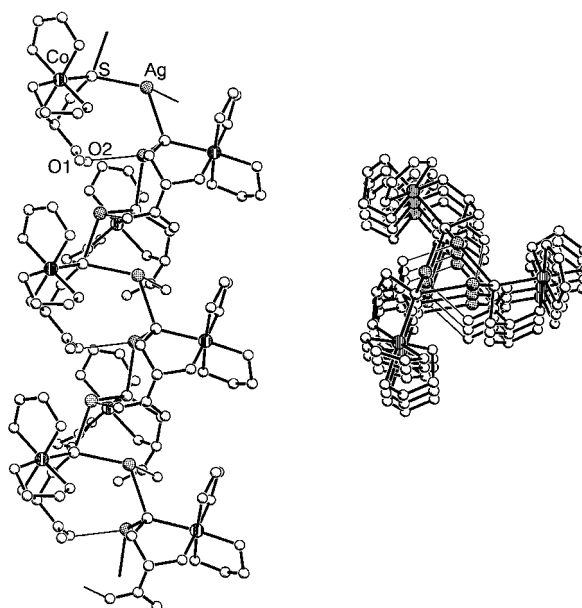


Figure 3. Side view (left) and top view (right) of the complex cation of **2**. Hydrogen atoms are omitted for clarity.

each Ag^{I} ion is weakly coordinated by the COO^- group of the $\Delta_{\text{L}}\text{-[Co(L-cys-N,S)(en)}_2\text{)]}^+$ unit attached to the same chain ($\text{Ag}-\text{O}2.539(6) \text{ \AA}$), besides the two S atoms of two different $\Delta_{\text{L}}\text{-[Co(L-cys-N,S)(en)}_2\text{)]}^+$ units, so that the chain forms a left-handed helical structure around the crystallographic 3_2 screw axis. In contrast to **1**, the COO^- group of the $\Delta_{\text{L}}\text{-[Co(L-cys-N,S)(en)}_2\text{)]}^+$ unit in **2** adopts an axial orientation (Figure 1b), which is responsible for the remarkable difference in aggregation of the octahedral $[\text{Co(L-cys-N,S)(en)}_2]^+$ units with Ag^{I} ions.

Besides their different structures, **1** and **2** exhibited different reactivity toward acid. The addition of HNO_3 to an aqueous solution of **2** produced pink microcrystalline needles of **3**, while treatment of **1** with HNO_3 in water resulted in its recrystallization. Aggregate **3** could also be prepared directly by the 1:1 reaction of $\Delta_{\text{L}}\text{-[Co(L-Hcys-N,S)(en)}_2\text{)](ClO}_4\text{)}_2$ with AgNO_3 in water followed by addition of HNO_3 . The IR spectrum of **3** exhibits a relatively sharp COO stretching band at 1732 cm^{-1} , as opposed to the broad COO stretching band centered at 1598 cm^{-1} for **2**. This IR band of **3** is characteristic of a COOH group,^[11] and elemental and plasma emission spectral analyses were in good agreement with the formula for the protonated 1:1 adduct $\Delta_{\text{L}}\text{-[Ag[Co(L-Hcys)(en)}_2\text{)](NO}_3\text{)}_3$. In the solid-state absorption spectrum (Nujol paste), **3** shows a first d–d absorption band at nearly the same position (502 nm) as **2** (499 nm). Since the $\text{Co}^{\text{III}}\text{Ag}^{\text{I}}\text{Co}^{\text{III}}$ trinuclear complex having μ_2 -thiolate donors, $\Delta_{\text{L}}\Delta_{\text{L}}\text{-[Ag[Co(L-cys)(en)}_2\text{)]}_2\text{]}^{3+}$,^[12] exhibits the first d–d absorption band at shorter wavelength of 488 nm , we believe that the S atom of each Co^{III} complex unit in **3** is bound to two Ag^{I} ions in a μ_3 -thiolate mode, as in **2**. However, the protonated COOH group of each Co^{III} unit would not coordinate to bridging Ag^{I} ion in a $(\text{Co}^{\text{III}}\text{Ag}^{\text{I}})_\infty$ chain structure. Hence we assume that **3** has a one-dimensional zigzag chain structure like that found in $[\text{Ag[Co(aet)(en)}_2\text{)](NO}_3\text{)}_3]_\infty$,^[8] rather than a helical structure, as in **2**.^[13] Interestingly, when an aqueous solution of **3** was neutralized with NaOH , red prismatic crystals of **2** were regenerated. This result obviously indicates that **3** reverts to the helical structure of **2** on changing the pH of the solution (Scheme 1).

In summary, the facile reactions of $\Delta_{\text{L}}\text{-}$ or $\Delta_{\text{L}}\text{-[Co(L-cys-N,S)(en)}_2\text{)]}^+$ with AgNO_3 gave the unique $\text{Co}^{\text{III}}\text{Ag}^{\text{I}}$ coordination polymers **1** and **2**, respectively. While **1** has a two-dimensional sheetlike structure, **2** forms one-dimensional left-handed helices.^[14] Compound **2** undergoes reversible conversion to **3**, which is assumed to have a one-dimensional zigzag structure that retains the Δ_{L} configuration of the Co^{III} complex unit. Although a variety of helical coordination polymers have been prepared from organic ligands and metal ions,^[15] only one report has appeared on the interconversion of the helical and nonhelical chain structures.^[15k] Furthermore, **2** is a rare example of heterometallic helix in which left-handed helicity is predetermined by the chiral configuration of the L-cys ligand in $\Delta_{\text{L}}\text{-[Co(L-cys-N,S)(en)}_2\text{)]}^+$. The polymeric structures in **1** and **2** are comparable with the secondary structures of proteins: the β -sheet and α -helix, respectively. Finally, the present results demonstrate that the construction of highly organized chiral molecular architectures can be achieved by the introduction of simple L-cys ligands with free

COO^- groups in an octahedral complex unit, and that their overall topology is controlled by the diastereomerism of the complex unit and conditions of reaction with Ag^{I} ions.

Experimental Section

1: An aqueous solution of AgNO_3 (0.09 g , 0.53 mmol) was added to a dark brown solution of $\Delta_{\text{L}}\text{-[Co(L-cys-N,S)(en)}_2\text{)](ClO}_4\text{)}_2$ (0.20 g , 0.50 mmol) in water (90 mL), and the mixture was stirred at room temperature for 30 min . After addition of an aqueous solution of NaNO_3 (0.50 g), the dark red reaction solution was stored at 4°C for 1 d . The resulting red crystalline product was collected by filtration and recrystallized from water by adding a saturated aqueous solution of NaNO_3 . Yield: 0.23 g (83%); elemental analysis calcd for $[\text{Ag[Co(C}_3\text{H}_5\text{NO}_2\text{S)(C}_2\text{H}_8\text{N}_2\text{)}_2\text{] (NO}_3\text{)}_2 \cdot \text{H}_2\text{O}]$: C 15.34 , H 4.23 , N 17.89 ; found: C 15.34 , H 4.28 , N 17.87 ; UV/Vis (H_2O): $\sigma_{\text{max}}/10^3$ ($\lg \epsilon$) = 20.13 (2.28), 28.6 (3.1 , sh), 34.75 cm^{-1} ($4.12 \text{ M}^{-1} \text{ cm}^{-1}$); CD (H_2O): $\sigma_{\text{ext}}/10^3$ ($\Delta \epsilon$) = 18.47 ($+2.13$), 21.11 (-0.45), 24.22 ($+1.06$), 29.04 (-1.08), 35.11 (-9.71), 41.91 cm^{-1} ($-5.75 \text{ M}^{-1} \text{ cm}^{-1}$).

2: An aqueous solution of AgNO_3 (0.07 g , 0.41 mmol) was added to a dark red solution containing $\Delta_{\text{L}}\text{-[Co(L-Hcys-N,S)(en)}_2\text{)](ClO}_4\text{)}_2 \cdot \text{H}_2\text{O}$ (0.20 g , 0.38 mmol) in water (20 mL) and a 0.25 M aqueous solution of NaOH (1.5 mL), and the mixture was stirred at room temperature for 40 min . After addition of an aqueous solution of NaNO_3 (0.33 g), the dark red reaction solution was allowed to stand at room temperature for 3 d . The resulting red prismatic crystals were collected by filtration. Yield: 0.19 g (85%); elemental analysis calcd for $[\text{Ag[Co(C}_3\text{H}_5\text{NO}_2\text{S)(C}_2\text{H}_8\text{N}_2\text{)}_2\text{] (NO}_3\text{)}_2 \cdot \frac{3}{2} \text{H}_2\text{O}]$: C 14.54 , H 4.59 , N 16.96 ; found: C 14.46 , H 4.43 , N 16.68 ; UV/Vis (H_2O): $\sigma_{\text{max}}/10^3$ ($\lg \epsilon$) = 20.00 (2.16), 28.3 (2.4 , sh), 34.84 cm^{-1} ($4.04 \text{ M}^{-1} \text{ cm}^{-1}$); CD (H_2O): $\sigma_{\text{ext}}/10^3$ ($\Delta \epsilon$) = 19.47 (-2.81), 24.66 ($+2.59$), 34.66 (-13.9), 47.51 cm^{-1} ($20.3 \text{ M}^{-1} \text{ cm}^{-1}$).

3: An aqueous solution of AgNO_3 (0.07 g , 0.41 mmol) was added to a dark brown solution of $\Delta_{\text{L}}\text{-[Co(L-Hcys-N,S)(en)}_2\text{)](ClO}_4\text{)}_2 \cdot \text{H}_2\text{O}$ (0.20 g , 0.38 mmol) in water (20 mL), and the mixture was stirred at room temperature for 40 min . After addition of a 1.0 M aqueous solution of HNO_3 (4 mL), the dark red reaction solution was allowed to stand at room temperature for 3 h . The resulting pink microcrystalline needles were collected by filtration. Yield: 0.18 g (74%); elemental analysis calcd for $[\text{Ag[Co(C}_3\text{H}_6\text{NO}_2\text{S)(C}_2\text{H}_8\text{N}_2\text{)}_2\text{] (NO}_3\text{)}_3 \cdot 2.5 \text{H}_2\text{O}]$: C 13.17 , H 4.26 , N 17.56 ; found: C 13.21 , H 4.29 , N 17.40 ; UV/Vis (H_2O): $\sigma_{\text{max}}/10^3$ ($\lg \epsilon$) = 19.98 (2.17), 28.3 (2.4 , sh), 34.84 cm^{-1} ($4.07 \text{ M}^{-1} \text{ cm}^{-1}$); CD (H_2O): $\sigma_{\text{ext}}/10^3$ ($\Delta \epsilon$) = 19.46 (-2.93), 24.66 ($+2.70$), 34.36 (-19.6), 46.95 cm^{-1} ($17.2 \text{ M}^{-1} \text{ cm}^{-1}$). This complex was also prepared by adding a 1.0 M aqueous solution of HNO_3 (1 mL) to a solution of **2** (0.09 g) in water (15 mL), and allowing the mixture to stand at 4°C for 1 d . Yield: 0.08 g (81%). When an acidic solution of **3** ($2.5 \text{H}_2\text{O}$) (0.20 g) in water (20 mL) was neutralized with a 0.25 M aqueous solution of NaOH , and the mixture was kept at 4°C for one week, red prismatic crystals of **2** formed. Yield: 0.12 g (66%).

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- [10] Crystal structure analysis: General: Rigaku AFC7S diffractometer, $T = 23^\circ\text{C}$, $\text{MoK}\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$). The structures were solved by direct methods (SIR92 for **1** and SHELXS-86 for **2**) and refined by full-matrix least-squares methods on F^2 by using SHELXL-93. Hydrogen atoms, except for those of water molecules, were placed at calculated positions but were not refined. The absolute structures for **1** and **2** were determined on the basis of the known R configuration of the asymmetric carbon atom in the L-cys ligand and were confirmed by the Flack parameters ($-0.10(6)$ for **1** and $0.03(3)$ for **2**). **1**: $\text{C}_7\text{H}_{23}\text{AgCoN}_7\text{O}_9\text{S}$, crystal dimensions $0.10 \times 0.15 \times 0.15 \text{ mm}$, orthorhombic, space group $P2_12_12_1$, $a = 8.037(4)$, $b = 8.056(3)$, $c = 26.648(6) \text{ \AA}$, $V = 1725.4(9) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 2.110 \text{ g cm}^{-3}$, $\mu = 22.75 \text{ cm}^{-1}$, $\omega/2\theta$ scan mode, $2\theta_{\text{max}} = 55.0$, 2298 reflections collected, 2296 independent reflections, 1815 observed reflections ($F > 4\sigma(F)$), 235 parameters, empirical absorption corrections based on ψ scans, max./min. transmission $0.992/0.882$, $R_1 = 0.054$ ($F > 4\sigma(F)$), $wR_2 = 0.155$ (all data), residual electron density $3.04/-1.24 \text{ e \AA}^{-3}$ (peaks larger than $1.0 \text{ e \AA}^{-3}$ were found in the vicinity of heavy atoms). **2**: $\text{C}_7\text{H}_{26.33}\text{AgCoN}_7\text{O}_{10.67}\text{S}$, crystal dimensions $0.13 \times 0.14 \times 0.60 \text{ mm}$, trigonal, space group $R\bar{3}$, $a = 24.115(3)$, $c = 8.417(3) \text{ \AA}$, $V = 4238(1) \text{ \AA}^3$, $Z = 8$, $\rho_{\text{calc}} = 1.812 \text{ g cm}^{-3}$, $\mu = 18.63 \text{ cm}^{-1}$, $\omega/2\theta$ scan mode, $2\theta_{\text{max}} = 55.0$, 2398 reflections collected, 2170 independent reflections, 2076 observed reflections ($F > 4\sigma(F)$), 268 parameters, empirical absorption corrections based on ψ scans, max./min. transmission $0.997/0.916$, $R_1 = 0.038$ ($F > 4\sigma(F)$), $wR_2 = 0.116$ (all data), residual electron density $0.84/-0.70 \text{ e \AA}^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-153429 (**1**) and CCDC-153430 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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- [12] The 2:1 reaction of $\text{A}_1\text{-[Co(L-cys-N,S)(en)}_2\text{)](ClO}_4\text{)}$ with AgClO_4 in water gave the 2:1 adduct $\text{A}_1\text{-A}_1\text{-[Ag[Co(L-cys-N,S)(en)}_2\text{)]}_2\text{](ClO}_4\text{)}_3 \cdot 4\text{H}_2\text{O}$ (**4**). X-ray analysis demonstrated that in the complex cation of **4**, the central Ag^{I} ion is coordinated by two thiolate S atoms of two octahedral $\text{A}_1\text{-[Co(L-cys-N,S)(en)}_2\text{)]}^+$ units to form an S-bridged $\text{Co}^{\text{III}}\text{Ag}^{\text{I}}\text{Co}^{\text{III}}$ trinuclear structure ($\text{Ag-S } 2.393(1)$, $\text{Co-S } 2.263(1) \text{ \AA}$; $\text{S-Ag-S } 172.39(6)^\circ$). The corresponding 2:1 adduct $\text{A}_1\text{-A}_1\text{-[Ag[Co(L-cys-N,S)(en)}_2\text{)]}_2\text{](ClO}_4\text{)}_3 \cdot 4\text{H}_2\text{O}$ (**5**) was prepared by using $\text{A}_1\text{-[Co(L-Hcys-N,S)(en)}_2\text{)](ClO}_4\text{)}_2 \cdot \text{H}_2\text{O}$ instead of $\text{A}_1\text{-[Co(L-cys-N,S)(en)}_2\text{)](ClO}_4\text{)}$. It was confirmed that **5** also has an S-bridged $\text{Co}^{\text{III}}\text{Ag}^{\text{I}}\text{Co}^{\text{III}}$ trinuclear structure, from its elemental and plasma emission spectral analyses, electronic absorption and CD spectra, and molar conductivity in water ($303 \text{ } \Omega \text{ cm}^2 \text{ mol}^{-1}$), which is in good agreement with that of **4** ($307 \text{ } \Omega \text{ cm}^2 \text{ mol}^{-1}$).
- [13] In agreement with this assumption, a noticeable difference was observed in the solid-state CD spectra (Nujol paste) of **2** and **3**, though their CD spectra in water are essentially identical; **2** exhibits a major negative CD band at 521 nm in the solid state, while the corresponding negative band of **3** appears at much longer wavelength of 551 nm .
- [14] As indicated by one of the referees, the solid-state structures of **1** and **2** would not be retained in solution; conversion to monomers and/or oligomers would result from cleavage of Ag-S and Ag-O bonds. This is suggested by the fact that the CD spectra of **1** and **2** in water are very similar to those of **4** and **5**, respectively.
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Diiron Azadithiolates as Models for the Iron-Only Hydrogenase Active Site: Synthesis, Structure, and Stereoelectronics**

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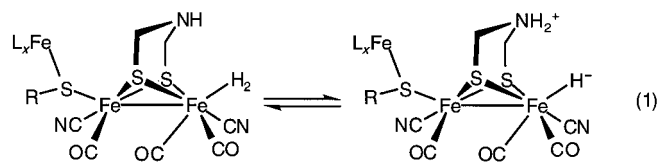
The active site of the Fe-only hydrogenases (FeH's)^[1, 2] resemble archetypal $[\text{Fe}_2(\text{SR})_2(\text{CO})_6]$ derivatives first reported by Reihlen in 1928^[3] and feature four unusual ligands: CO, CN^- , $[(\text{RS})_3\text{Fe}_4\text{S}_4(\text{SR})]$, and a unique organic dithiolate cofactor. Recent work has suggested that this dithiolate is

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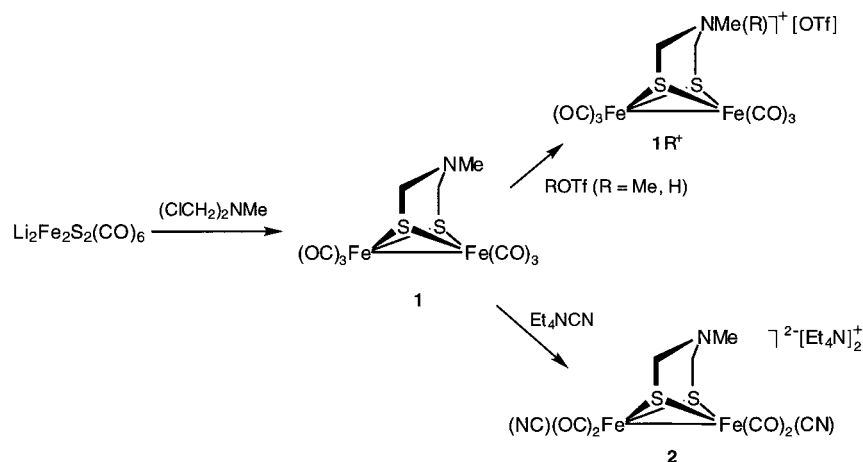
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HN(CH₂S[−])₂.^[4] An amine-containing cofactor could participate in proton transfer required in the heterolytic processing of H₂ [Eq. (1)]. Indeed, classical organometallic studies have shown that ligand-appended, noncoordinating amines facilitate the heterolytic activation of dihydrogen,^[5] a key facet of the chemistry of the hydrogenases.^[6] Herein we report diiron carbonyl derivatives of the *N*-methyl analogue of the proposed cofactor.



Treatment of Li₂[Fe₂S₂(CO)₆]^[7] with (ClCH₂)₂NMe afforded [Fe₂[(SCH₂)₂NMe](CO)₆] (**1**) as red crystals in 50% yield (Scheme 1). The NMR and infra-red (IR) spectroscopic analysis indicate that the amine is not coordinated. In the ¹H NMR spectrum the resonance signal for CH₂ splits at −60 °C consistent with slowed folding of the FeS₂C₂N ring, however, only one methyl resonance signal was observed > −80 °C. Protonation of **1** in Et₂O solution with HOTf (OTf = trifluoromethanesulfonate) precipitated orange [Fe₂[(SCH₂)₂N(H)Me](CO)₆]⁺ (**1**·H⁺). Solutions of **1**·H⁺ in MeCN are fully deprotonated by aniline but not by 4-cyanoaniline, thus placing its pK_a between 10.6 and 7.6, which is lower than that typical for a tertiary amine (pK_a 18).^[8] In the IR spectrum, the ν_{CO} pattern for **1**·H⁺ resembles that for **1**, but the bands are shifted 15 cm^{−1} to higher energy, which may be relevant to the IR spectroscopic signatures of the FeH's.^[9] The ν_{CO} pattern is identical for **1**·H⁺ and **1**·Me⁺, (an orange solid from MeOTf + **1**), indicating that the observed shifts in the ν_{CO} bands for **1**·H⁺ are not the result of proton–CO interactions nor does protonation occur at other sites, such as, the Fe–Fe bond.^[10] Protonation has no effect on the ν_{CO} bands in the *N*-methylpiperidine-4-thiolate [Fe₂(S-4-C₅H₉NMe)₂(CO)₆] because the amine is some distance from the dimetal center.^[11]



Scheme 1.

Crystallographic analysis of **1** reveals the familiar [Fe₂(SR)₂(CO)₆] framework but the details of the azadithiolate strap are noteworthy (Figure 1). Two conformers cocrystallize; in the dominant (60%) conformer the methyl group is *axial*, which is normally disfavored.^[12] For this axial conformer, the sum of angles at nitrogen is 352° versus 337° for the minor (equatorial) isomer. The C–S distance is 1.86(8) Å (average of the two conformers) versus 1.821(5) Å in the related propanedithiolate.^[13]

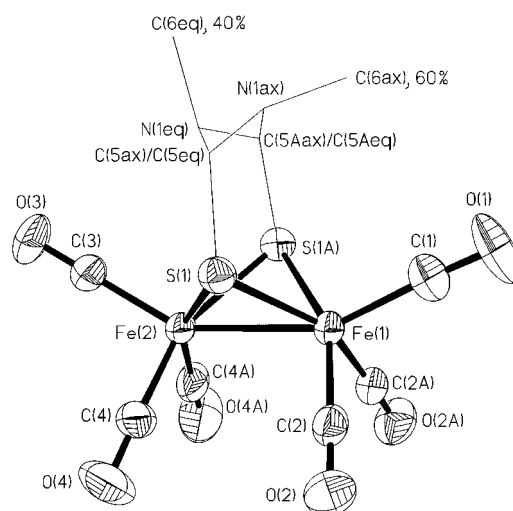


Figure 1. Structure of the axial (atoms labeled ax) and equatorial (eq) conformers of **1**. Selected bond lengths [Å] and angles [°] for the axial conformer: Fe(1)–Fe(2) 2.4924(7), Fe(1)–S(1) 2.2600(7), S(1)–C(5) 1.88(2), N(1)–C(5) 1.40(2), Fe(2)–S(1)–Fe(1) 66.96(2).

Density functional theory (DFT) calculations^[14] were carried out on the axial and equatorial conformers of **1** and the cyclic model molecules CH₂(SCH₂)₂NR (R = H and CH₃). Stabilization of the axial conformer of **1** and the models can be explained in the context of the anomeric effect, which is classically invoked to explain axial–equatorial equilibria in 1-oxo-3-azacyclohexanes.^[15] Calculations confirm that the structure of **1** results from a balance between the anomeric effect, which favors the axial methyl, and a competing steric repulsion between (CH₃)_{ax} and the carbonyl ligand lying beneath (H⋯C = 2.47 Å; H⋯O = 2.57 Å). This unfavorable nonbonding interaction is offset somewhat by a flattening of the amine, which further enhances the anomeric interaction (Figure 2). In all cases, the elongation of the C–S bond provides an easy gauge of the energetic significance of the anomeric effect (Table 1, note DFT calculated distances are slightly elongated). Replacing Me by H in **1** relieves much of the steric strain such that the axial form displays a relative stability of 5.7 kcal mol^{−1}.

Treatment of **1** with Et₄NCN following our previous protocol^[16] afforded the dicyanide complex (NEt₄)₂[Fe₂[(SCH₂)₂–

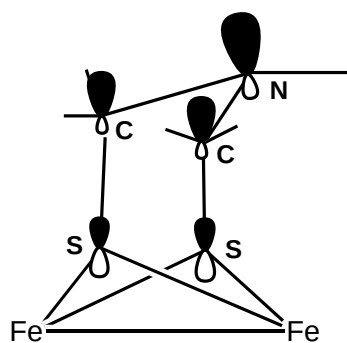


Figure 2. Orbital interactions associated with the anomeric effect in the axial conformer of $[\text{Fe}_2\{(\text{SCH}_2)_2\text{NMe}\}(\text{CO})_6]$, as indicated by DFT calculations.

Table 1. Selected results for DFT calculations on the axial (ax) and equatorial (eq) conformers of $\text{CH}_2(\text{SCH}_2)_2\text{NR}$ and $[\text{Fe}_2\{(\text{SCH}_2)_2\text{NR}\}(\text{CO})_6]$.

Compound (conformation at N)	Relative E [kcal mol $^{-1}$]	C–S [Å]	C–N [Å]	$\Sigma \chi$ at N [°]
$\text{CH}_2(\text{SCH}_2)_2\text{NH}$ (ax)	0	1.883	1.444	336.0
$\text{CH}_2(\text{SCH}_2)_2\text{NH}$ (eq)	+7.3	1.860	1.448	337.4
$\text{CH}_2(\text{SCH}_2)_2\text{NMe}$ (ax)	0	1.894	1.440	343.6
$\text{CH}_2(\text{SCH}_2)_2\text{NMe}$ (eq)	+6.9	1.853	1.454	336.1
$[\text{Fe}_2\{(\text{SCH}_2)_2\text{NH}\}(\text{CO})_6]$ (ax)	0	1.907	1.429	338.1
$[\text{Fe}_2\{(\text{SCH}_2)_2\text{NH}\}(\text{CO})_6]$ (eq)	+5.7	1.878	1.437	341.8
$[\text{Fe}_2\{(\text{SCH}_2)_2\text{NMe}\}(\text{CO})_6]$ (ax)	0	1.925	1.422	350.3
$[\text{Fe}_2\{(\text{SCH}_2)_2\text{NMe}\}(\text{CO})_6]$ (eq)	+0.8	1.866	1.445	335.7
$[\text{Fe}_2\{(\text{SCH}_2)_2\text{NMe}\}(\text{CO})_6]$ (planar)	+3.6	1.963	1.405	360.0

$\text{NMe}\}(\text{CO})_4(\text{CN})_2]$ (**2**; Scheme 1). Only the axial conformer of **2** crystallizes (Figure 3). Again the nitrogen approaches planarity ($\Sigma \chi = 347^\circ$), and the C–S bond is elongated (1.869(3) Å). Noteworthy is the similarity in the IR spectrum of **2** and the reduced H-cluster from *D. desulfuricans*.^[4] The $\nu_{\text{C=X}}$ (X = O, N) bands for the model are at 2075, 2032, 1963, 1922, 1884, 1875 cm^{-1} while for the reduced enzyme, these bands occur at 2079, 2041, 1965, 1940, 1916, 1894 cm^{-1} .

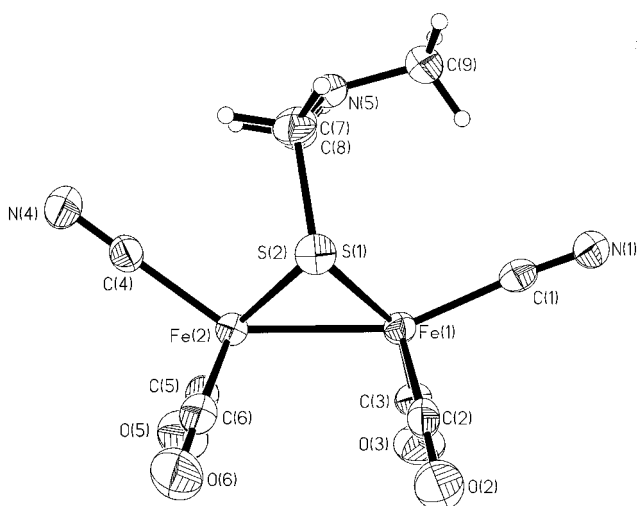


Figure 3. Structure of **2** (as Et_4N^+ salt), selected bond lengths [Å] and angles [°]: Fe(1)–Fe(2) 2.5090(6), Fe(1)–C(2) 1.745(3), Fe(1)–C(3) 1.751(3), Fe(1)–C(1) 1.940(3), C(7)–N(5) 1.424(4), Fe(1)–S(1) 2.2871(9), Fe(1)–S(2)–Fe(2) 66.49(2).

Experimental Section

1: A THF solution of $\text{Li}_2[\text{Fe}_2\text{S}_2(\text{CO})_6]$ ^[7, 17] (0.120 g, 0.349 mmol; 20 mL) at -78°C was treated with a THF solution of $(\text{CH}_2\text{Cl})_2\text{NCH}_3$ (0.054 g, 0.419 mmol; 5 mL).^[18] After 2 h, the red solution was treated with NEt_3 (0.10 mL), and allowed to warm to room temperature. Red crystals grew from cold hexane solutions, yield 0.071 g (51 %). Elemental analysis (%) calcd for $\text{C}_9\text{H}_7\text{Fe}_2\text{NO}_6\text{S}_2$: C 26.96, H 1.76, N 3.49; found: C 27.07, H 1.89, N 3.27; ^1H NMR (500 MHz, CD_3CN , 25°C): $\delta = 3.31$ (s, 4H; NCH_2S), 2.12 (s, 1H; NCH_3); IR (MeCN): $\tilde{\nu}_{\text{CO}} = 2074, 2037, 1996 \text{ cm}^{-1}$.

Protonation of **1**: An orange MeCN solution of **1** (0.043 g, 0.11 mmol; 10 mL) lightened upon acidification with one equivalent of HO_3SCF_3 , IR (MeCN): $\tilde{\nu}_{\text{CO}} = 2090, 2053, 2017 \text{ cm}^{-1}$. Treatment of $\mathbf{1} \cdot \text{H}^+$ with $4\text{-H}_2\text{NC}_6\text{H}_4\text{CN}$ (0.013 g, 0.107 mmol) resulted in no change. Treatment of $\mathbf{1} \cdot \text{H}^+$ with PhNH_2 (0.010 mL, 0.107 mmol) gave free **1** as indicated by both the color change and the IR spectrum.

Methylation of **1**: A solution of **1** (0.035 g, 0.087 mmol) in MeCN (10 mL) was treated with $\text{CH}_3\text{O}_3\text{SCF}_3$ (0.015 mL, 1.31 mmol). After 30 min, the IR bands for the starting material had disappeared. IR (MeCN): $\tilde{\nu}_{\text{CO}} = 2090, 2053, 2018 \text{ cm}^{-1}$.

2: A solution of **1** (0.10 g, 0.25 mmol) in CH_3CN (10 mL) was treated with a solution of Et_4NCN (0.073 g, 0.49 mmol) in MeCN (5 mL), causing gas evolution. After 1 h, the reaction solution was concentrated to ~ 1 mL, and the red product was precipitated with Et_2O , yield: 0.080 g (50 %). Elemental analysis (%) calcd for $\text{C}_{25}\text{H}_{47}\text{Fe}_2\text{N}_5\text{O}_4\text{S}_2$: C 45.67, H 7.20, N 10.65; found: C 45.74, H 7.23, N 10.52; ^1H NMR (500 MHz, CD_3CN , 25°C): $\delta = 3.42$ (s, 4H; NCH_2S), 3.16 (q, 16H; NCH_2CH_3), 2.47 (s, 3H; NCH_3), 1.22 (t, 24H; NCH_2CH_3); IR (MeCN): $\tilde{\nu}_{\text{CN}} = 2075, 2032$; $\tilde{\nu}_{\text{CO}} = 1963, 1922, 1884, 1875 \text{ cm}^{-1}$.

Density functional theory calculations were carried out using generalized gradient approximation (GGA), as implemented in the ADF program.^[19] The formalism is based upon the local spin-density approximation characterized by the electron gas exchange (X α with $\alpha = 2/3$) together with Vosko–Wilk–Nusair parameterization for correlation.^[20] Nonlocal corrections have been added for the exchange energy^[21] and the correlation energy.^[22] For first-row atoms, the 1s shell was frozen and described by a single Slater function. For iron and sulfur the frozen core composed of the 1s and 2s/p shells was also modeled by a minimal Slater basis. The Slater basis set for the valence shell of all nonmetal atoms is of triple- ζ quality and is supplemented with a polarization function. The 3s and 3p shells of iron are described by a double- ζ Slater basis, the 3d and 4s shells by a triple- ζ basis, and the 4p shell by a single orbital.

Crystals of **1** and **2** were mounted on glass fibers using Paratone-N (Exxon) and were analyzed on a Siemens Platform/CCD automated diffractometer at 193 K. Data were processed with SHELXTL. The structures were solved using direct methods and refined using full matrix least-squares on F^2 using the program SHELXL-93. Hydrogen atoms were fixed in idealized positions with thermal parameters 1.2 times those of the attached carbon atoms. Data were corrected for absorption on the basis of integration.

Crystal data for **1**: $\text{C}_9\text{H}_7\text{Fe}_2\text{NO}_6\text{S}_2$, $M = 400.98$, monoclinic, $C2/m$; $a = 16.246(2)$, $b = 10.0990(14)$, $c = 8.8964(12)$ Å; $\beta = 92.086(2)^\circ$; $V = 1458.7(3)$ Å ^{3} ; $Z = 4$; $\rho_{\text{calcd}} = 1.826 \text{ Mg m}^{-3}$, $F(000) = 800$, 120 parameters: $R1 = 0.0322$, $wR2 = 0.0715$, $\text{GOF} = 1.035$ for all 1410 data ($I > 2\sigma(I)$); max./min. residual electron density: $0.494/-0.348 \text{ e}^- \text{ Å}^{-3}$.

Crystal data for **2**: $\text{C}_{25}\text{H}_{47}\text{Fe}_2\text{N}_5\text{O}_4\text{S}_2$; $M = 657.50$; orthorhombic, $P2_12_12_1$; $a = 11.9403(18)$, $b = 14.043(2)$, $c = 18.862(3)$ Å; $V = 3162.8(8)$ Å ^{3} ; $Z = 4$; $\rho_{\text{calcd}} = 1.381 \text{ Mg m}^{-3}$, $F(000) = 1392$, 352 parameters: $R1 = 0.0390$, $wR2 = 0.0722$, $\text{GOF} = 0.916$ for all 5791 data ($I > 2\sigma(I)$); max./min. residual electron density: $0.327/-0.265 \text{ e}^- \text{ Å}^{-3}$.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155386 (**1**) and CCDC-155387 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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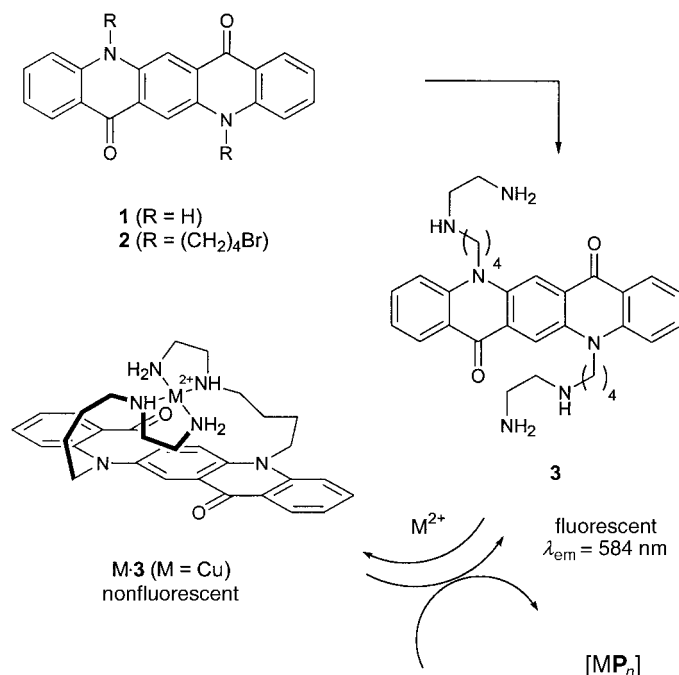
An Enzyme Assay Using pM**

G rard Klein and Jean-Louis Reymond*

The development of new catalytic methods, in particular enzymatic processes, is increasingly being followed with combinatorial and evolutionary methods, whereby sensitive assays for catalysis play an essential role.^[1–3] Most enzyme assays are based on chromogenic or fluorogenic substrates.^[1, 4, 5] In many cases, however, it is desirable to measure the reaction of a well-defined substrate of interest, and not

that of a different fluorogenic or chromogenic derivative. Such direct detection can be achieved with instrumental methods, such as HPLC and mass spectrometry,^[6] by using product-selective fluorescent sensors,^[7] or with indirect colorimetric assays based on substrate- or product-binding proteins, such as cat-ELISAs (catalytic enzyme-linked immunosorbent assays)^[8] or the QUEST method (“querying for enzymes using the three-hybrid system”).^[9] More simply, one can also measure spectrophotometrically a physico-chemical parameter that responds to the progress of the reaction, such as measuring the temperature by IR thermography,^[10] or, for reactions releasing acids or bases, the pH value of the reaction medium with pH indicators.^[11] Herein we report a new enzyme assay based on following the evolution of pM (−lg[M], where M is free metal ions) as a function of reaction time. The change in pM is recorded using an orange fluorescent metal-sensor derived from quinacridone.

The orange fluorescent sensor **3**, which is obtained from quinacridone (**1**) via dibromide **2**, responds to the presence of small concentrations of Cu²⁺ by an almost quantitative quenching of its fluorescence (λ_{em(max)} = 558 nm). The effect can be explained by formation of a macrocyclic chelate M·**3**, in which energy transfer quenching occurs due to the proximity of the quenching metal ion to the fluorophore (Scheme 1).^[12] The complex M·**3** contains a 17-membered ring. The chelate effect induced by such a large ring is expected to be weak. Indeed the macrocycle is readily broken by addition of excess metal ion, leading to the formation of an M₂·**3** complex. This suggests that other weak metal chelators,



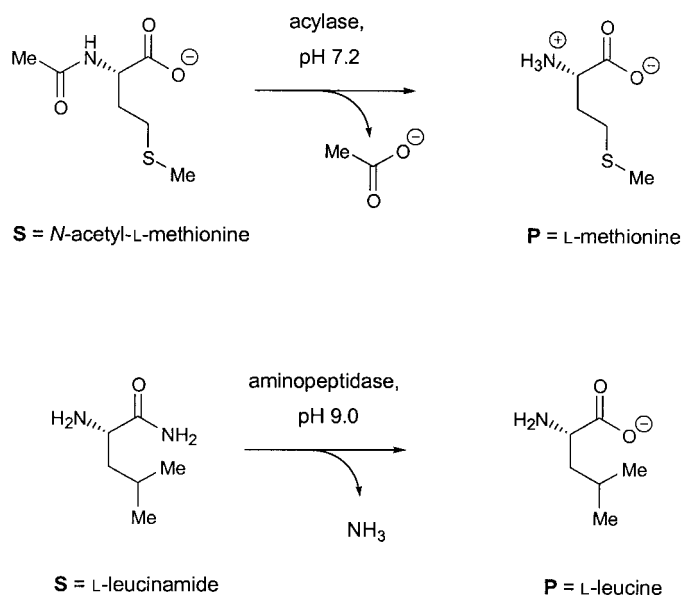
Scheme 1. Principle of the fluorescence enzyme assay using pM.

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such as simple bidentate ligands, should be able to efficiently compete with **3** for metal coordination and induce a fluorescence increase in proportion to their concentration. Such an effect should allow an enzyme-catalyzed transformation of a noncoordinating substrate **S** into a weakly chelating product **P** to be monitored (Scheme 1).

Two enzyme reactions that produce free amino acids as metal chelating products (**P**) from nonchelating amide precursors (**S**) were chosen to test our sensor concept; these were the hydrolysis of *N*-acetyl-L-methionine to L-methionine by acylase I,^[13] and the hydrolysis of L-leucinamide to L-leucine by aminopeptidase (Scheme 2).^[14] First, simulated



Scheme 2. Enzyme reactions assayed with a fluorescent pM sensor.

profiles were carried out for conversion of the amide substrates into the corresponding amino acid products in the presence of ligand **3** with Cu²⁺ or Ni²⁺ as reporter metal ions. In all cases the nonfluorescent solution of **3** containing the metal ions responded to the conversion of substrate into product by a strong increase in fluorescence (Figure 1), as expected from complexation of the metal ions by the reaction product.

The actual enzyme assays were then investigated. The reaction of acylase I was recorded at pH 7.2 in the presence of ligand **3** and Cu²⁺. The reaction of aminopeptidase was recorded at pH 9.0 with both Cu²⁺ and Ni²⁺ as reporter metal ions, since both metals induce quenching by complexation with ligand **3** at that pH. In all cases a time-dependent fluorescence increase was observed, which shows that the sensor was operative in real time (Figures 2 and 3). Indeed the apparent reaction rate increased in proportion to enzyme concentration; this indicates that the enzyme reaction itself was the rate-limiting process in the assay.

The assays were also carried out by mixing aliquots of the enzyme reactions in aqueous buffer with the sensor, consisting of metal and ligand, at fixed time intervals to measure product formation. This protocol allowed the addition of the organic solvent necessary to solubilize the sensor only after the

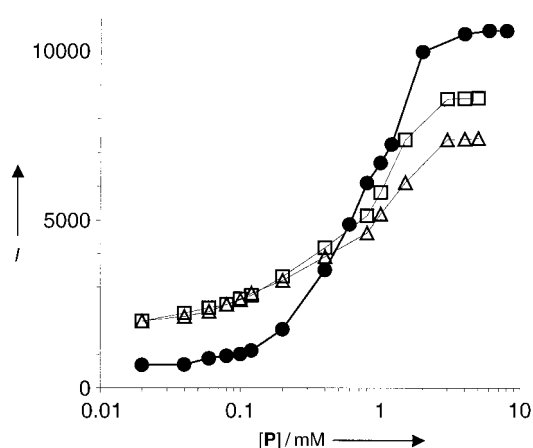


Figure 1. Fluorescence response of pM sensor **3** (1 μM) in the presence of metal ions upon simulated conversion of the following substrates **S** into products **P**: (●) *N*-acetyl-L-methionine (10 mM) into L-methionine, with Cu²⁺ (2 μM) in Bis-Tris (pH 7.2, 5 mM) and water/DMSO (60/40); (□) L-leucinamide (5 mM) into L-leucine, with Cu²⁺ (2 μM) in Tris (pH 9.0, 5 mM), and water/DMF (60/40); (△) same conditions as (□) but with Ni²⁺ (4 μM) replacing Cu²⁺. All measurements taken at 26 °C with $\lambda_{\text{em}} = 580 \pm 50$ nm ($\lambda_{\text{ex}} = 485 \pm 20$ nm). Bis-Tris = bis(hydroxyethyl)tris(hydroxymethyl)aminomethane, Tris = tris(hydroxymethyl)aminomethane.

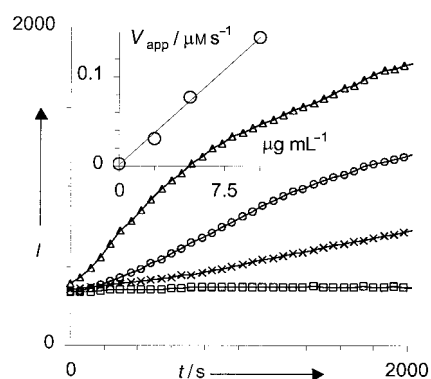


Figure 2. Fluorescence assay for acylase at pH 7.2. Hydrolysis of *N*-acetyl-L-methionine to L-methionine by acylase I is followed with ligand **3** in the presence of Cu²⁺. Main plot: Time course of fluorescence increase *I* at $\lambda_{\text{em}} = 580 \pm 50$ nm ($\lambda_{\text{ex}} = 485 \pm 20$ nm). Enzyme concentrations: Δ 10, $\circ$ 5, $\times$ 2.5, and $\square$ 0 $\mu\text{g mL}^{-1}$. Insert: replot of the apparent maximal rate in $\mu\text{M s}^{-1}$ (the steepest linear portion of each curve after conversion of the fluorescence data into product concentration according to the calibration curves in Figure 1) against enzyme concentration in $\mu\text{g mL}^{-1}$. See Experimental Section for further details.

enzyme reaction had taken place. Under these conditions, acylase I and aminopeptidase were approximately twofold and tenfold more active, respectively, than in the real-time assay. The difference in activity is most likely accounted for by the presence of cosolvent in the real-time assay, since it corresponds to the published cosolvent effect in the case of acylase I.^[13] In any event the aliquoting test, which can be conveniently applied as an endpoint measurement, can generally be used to avoid interferences between the cosolvent/pM-sensor system and the enzymes being assayed. Since the assay produces a fluorescent signal simply upon addition of the pM-sensor solution, assay throughput can easily reach several thousand samples per day by manual handling in standard 96-well microtiter plates. The assay is also suitable for ultra-high-throughput screening (UHTS, defined as

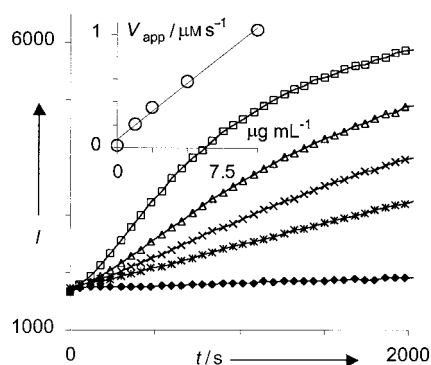


Figure 3. Fluorescence assay for aminopeptidase at pH 9.0. Hydrolysis of L-leucine amide to L-leucine by aminopeptidase is followed with ligand **3** in the presence of Cu^{2+} . Main plot: Time course of fluorescence increase I at $\lambda_{\text{em}} = 580 \pm 50 \text{ nm}$ ($\lambda_{\text{ex}} = 485 \pm 20 \text{ nm}$). Enzyme concentrations: $\square$ 10, $\triangle$ 5, $\times$ 2.5, $*$ 1.25, and $\blacklozenge$ 0 $\mu\text{g mL}^{-1}$. Insert: replot of the apparent maximal rate in $\mu\text{M s}^{-1}$ (steepest linear portion of each curve after conversion of fluorescence data into product concentration according to the calibration curves in Figure 1) against enzyme concentration in $\mu\text{g mL}^{-1}$. See Experimental Section for further details. Similar results are obtained with Ni^{2+} as the reporter metal ion.

>100 000 samples per day) if used in high-density microtiter plates (1536-wells) with the corresponding robotic liquid-handling system and plate reader.^[15]

The above experiments demonstrate a fluorescence assay for enzymes that liberate weak metal ligands, such as amino acids, as their reaction products. The assay is made possible by the absence of a strong chelate effect in the tetradentate ligand **3**, which allows these reaction products to efficiently compete for metal coordination in a useful concentration range. Ligand **3** can be considered as a pM sensor by its ability to differentiate free metal ions from weakly chelated metal ions. The fact that product sensing occurs indirectly through the pM value makes the assay applicable to a broad variety of substrates, as is the case for assays using pH indicators. Our pM assay detects structural changes otherwise difficult to measure, such as the hydrolysis of a carboxylic amide (CONH_2) to the corresponding acid (COOH). The kinetics of ligand exchange at copper and nickel are sufficiently fast for the fluorescent pM sensor to respond in real time to the reaction progress. Its usefulness is illustrated by the fact that the examples presented are the first fluorescence assays for acylase and aminopeptidase.

Experimental Section

Reagents and buffers were prepared in deionized milliQ-filtered water. Ligand **3** was diluted from a 1 mM stock solution of the trifluoroacetate salt in acetonitrile/water (1/1). *N*-acetyl methionine and L-methionine, were diluted from 0.1 M aqueous stock solutions buffered at pH 7.2 and pH 9.0, respectively; these pH values correspond to the reported optimal values for activity of the enzymes. Acylase I (from pig kidney, Fluka 01821) was diluted from a 1 mg mL^{-1} stock solution in 5 mM Bis-Tris (bis(hydroxyethyl)tris(hydroxymethyl)aminomethane) at pH 7.2. Cytosolic leucine aminopeptidase (from pig kidney, Fluka 61860) was diluted from a 1 mg mL^{-1} stock solution in 5 mM Tris (tris(hydroxymethyl)aminomethane) at pH 9.0.

Assays (0.1 mL) were followed at 26 °C in individual wells of round-bottom polypropylene 96-well microtiter plates (Costar) using a Cytofluor II Fluorescence Plate Reader (Perseptive Biosystems; filters: $\lambda_{\text{ex}} = 485 \pm 20 \text{ nm}$, $\lambda_{\text{em}} = 580 \pm 50 \text{ nm}$, gain = 65). Enzyme assays were initiated by

adding enzyme to the following solutions: acylase I: Bis-Tris (pH 7.2, 5 mM) in water/DMSO (60/40) containing ligand **3** (1 μM), CuCl_2 (2 μM), and *N*-acetyl-L-methionine (10 mM); aminopeptidase: Tris (pH 9, 5 mM) in water/DMF (60/40) containing ligand **3** (1 μM), CuCl_2 (2 μM) or NiCl_2 (4 μM), L-leucinamide hydrochloride (5 mM), and MgSO_4 (0.1 mM).

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Using an Enzyme's Active Site To Template Inhibitors**

Régis Nguyen and Ivan Huc*

The identification of substances that have a strong affinity for the surface or the active site of a protein is not a trivial task. Numerous strategies can be followed, ranging from de novo design to the systematic screening of large libraries. One approach makes use of the recognition between the target protein and building block precursors to favor the formation of a complementary substance. Thus, materials capable of selectively recognizing protein surfaces may be prepared by using the molecular imprinting technique. The protein acts as a template to kinetically generate specific recognition sites in a polymer matrix, which is formed irreversibly.^[1,2] In a related approach, namely dynamic combinatorial chemistry, an enzyme's active site may template the assembly of a complementary substance from a mixture of interconverting species (Figure 1). In this case, the precursors combine through reversible linkages. Under thermodynamic conditions, the protein selects and stabilizes the products with the highest affinity,^[3,4] which leads to their amplification and hence their identification.

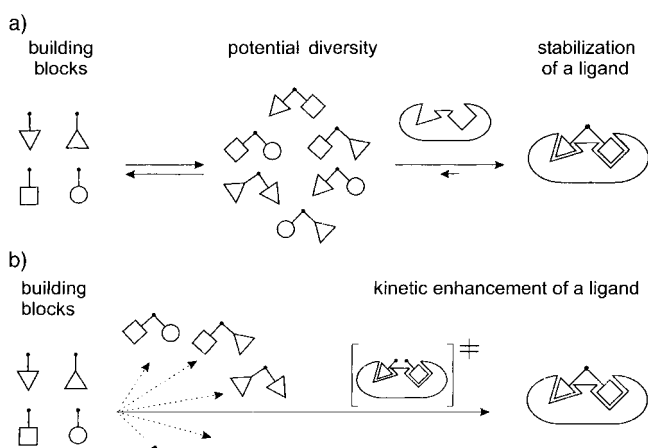


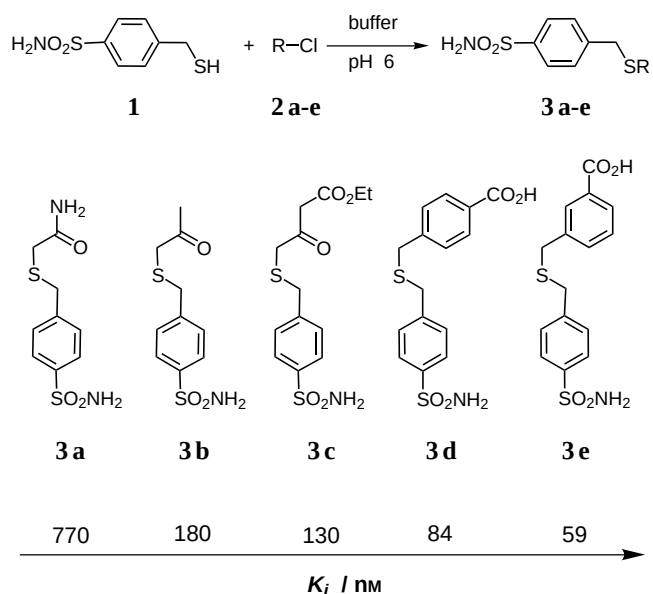
Figure 1. Casting of a ligand for a protein cavity a) from reversibly connecting components (e.g. dynamic combinatorial chemistry), b) by using an irreversible reaction between building block precursors.

Herein we show for the first time that an inhibitor can be cast by using the enzyme's active site as a template in both reversible and irreversible reactions (Figure 1).^[5]

We have previously^[4c] exploited the well-characterized binding of *para*-substituted aromatic sulfonamides to the Zn^{II} metalloenzyme, bovine carbonic anhydrase (CA II,

EC 4.2.1.1).^[6] These compounds insert into the active site of CA II, and the nitrogen atom of the sulfonamide group coordinates to the Zn^{II} center. Hydrophobic groups substituted at the *para* position to the sulfonamide group lie on a hydrophobic wall of the protein, which stands above the Zn^{II} pocket.^[6,7]

A series of inhibitors **3a–e** was prepared from α -mercaptototosylamide **1**^[8] and various alkyl chlorides **2a–e** (Scheme 1). Their inhibition of the esterase activity of CA II



Scheme 1. Alkylation of thiol **1** by using various alkyl halides **2**, to form inhibitors of CA II. The measured inhibition constants of the esterase activity of CA II are specified under each structure.

was measured by using a simple spectrophotometric assay that gives a reliable value of the affinity of the sulfonamides for the active site (Scheme 1).^[9] The inhibition constants can be ranked from 770 nM for **3a** to 59 nM for **3e** according to an increasing hydrophobicity of the substituent *para* to the sulfonamide group.

Subsequently, the ability of CA II to enhance the formation of its inhibitors was assessed in competition assays. Thiol **1** was treated with two alkyl chlorides,^[10] first in the absence of CA II, then in the presence of CA II (1 equivalent, so that **1** is bound almost quantitatively by the enzyme). The final proportions of the two thioether products measured by HPLC analysis revealed that CA II strongly favors the best inhibitor (Table 1 and Figure 2). For example, when chloride **2a** competes with **2d**, the proportion of product **3d** shifts from 50% in the absence of CA II to 92% in its presence (Table 1, entry 1). When the products have similar affinities for CA II (Table 1, entry 5), their proportions are hardly affected by the presence of the protein in the reaction medium. Despite the fact that the inhibition constants of **3a–e** extend over only one order of magnitude, the competition experiments give a good estimate of their relative affinities. Based on these results, one can expect even stronger effects for larger differences in affinities.

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Table 1. Reactions^[a] between thiol **1** (320 μ M) and two competing alkyl chlorides.

Entry	Competing electrophiles	Conc. ^[b] [equiv]	Products (K_i in nM)	Yield ^[c] (without additives) [%]	Additives (equiv)	Yield ^[b] (with additives) [%]
1	2a ClCH ₂ CONH ₂	50	3a (770)	50	CA II (1)	8
	2d <i>p</i> -ClCH ₂ C ₆ H ₄ CO ₂ [−]	12.5	3d (84)	50		92
2	2a ClCH ₂ CONH ₂	50	3a (770)	40	CA II (1)	10
	2e <i>m</i> -ClCH ₂ C ₆ H ₄ CO ₂ [−]	12.5	3e (59)	60		90
3	2a ClCH ₂ CONH ₂	500	3a (770)	46.5	CA II (1)	16
	2b ClCH ₂ CCOCH ₃	2	3b (180)	53.5		84
4	2a ClCH ₂ CONH ₂	125	3a (770)	15	CA II (1)	2
	2c ClCH ₂ COCH ₂ CO ₂ Et	1.08	3c (130)	85		98
5	2b ClCH ₂ CCOCH ₃	25	3b (180)	49	CA II (1)	43
	2c ClCH ₂ COCH ₂ CO ₂ Et	9.25	3c (130)	51		57
6	2a ClCH ₂ CONH ₂	50	3a (770)	50	− (CH ₃ CN 75 %)	70
	2d <i>p</i> -ClCH ₂ C ₆ H ₄ CO ₂ [−]	12.5	3d (84)	50		30
7	2a ClCH ₂ CONH ₂	50	3a (770)	50	CA II (1) + methazolamide ^[12] (20)	60
	2d <i>p</i> -ClCH ₂ C ₆ H ₄ CO ₂ [−]	12.5	3d (84)	50		40

[a] The reactions were carried out at 25 °C in buffered water at pH 6 (sodium phosphate 200 mM), and were complete after 48 h. [b] The initial stoichiometry of the chlorides was adjusted to compensate for large differences in reactivity. [c] The yield was determined by integrating the peaks in the HPLC chromatograms, and comparing them to an internal standard (benzoic acid). These data were reproducible within 15 % when the same batch of CA II was used.

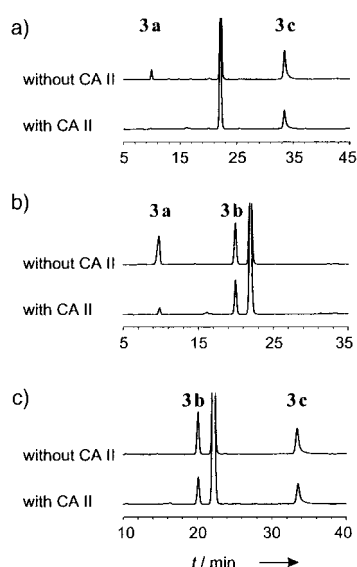


Figure 2. Selected chromatograms showing the proportions of products in reactions between **1** and two competing chlorides **2**: a) **1**+**2a**+**2c** (Table 1, entry 4), b) **1**+**2a**+**2b** (Table 1, entry 3), c) **1**+**2b**+**2c** (Table 1, entry 5). In each case, the top trace is for the reaction performed without CA II, and the lower trace is for the reaction performed with CA II (1 equivalent with respect to **1**). The peak at 22.4 min is that of the internal reference (benzoic acid). See Table 1 and Experimental Section for details.

Several control experiments were performed to establish that CA II actually operates as a template in these reactions. When the concentration of the enzyme was varied, saturation behavior was observed: the ratio of products **3d/3a** increased progressively when the amount of CA II was increased from zero to one equivalent, and leveled off at 1.5 equivalents of CA II (data not shown).^[11] When CA II was replaced by a protein that has no affinity for **1** (e.g. bovine serum albumin), or when **1** was replaced by a thiol that has no affinity for CA II (e.g. α -mercapto-*para*-toluenesulfonic acid), the proportion of products remained unchanged. More importantly, when methazolamide,^[12] a known inhibitor of CA II, was added, it competed with **1** for binding and the effect of CA II on the proportion of the products was very limited (Table 1, entry 7).

These experiments consistently show that the enzyme directs reactions of **1** only when it is bound. The possibility that the nonpolar environment of the active site may selectively enhance some reactions (medium effects or catalysis) was ruled out—when the medium polarity was decreased by adding CH₃CN, the reactions between **1** and benzylic chlorides **2d** and **2e** were clearly disfavored,^[13] whilst they are favored in the presence of CA II (Table 1, entries 1, 2, and 6).

Thus, the most likely mechanism for the observed effects is the preassociation of thiol **1** in the Zn^{II} pocket with a hydrophobic chloride against the hydrophobic wall.^[7] The reagents are brought into close proximity of each other in a ternary complex with CA II, and their reaction is favored (Figure 1). Nonhydrophobic chlorides are less strongly bound, and their reactions are not favored.

The formation of an inhibitor can be enhanced under kinetic control by the active site of the enzyme. Under thermodynamic control (e.g. when a reversible reaction is used), the reaction products may be stabilized and enhanced in a complex with the target protein (Figure 1).^[3, 4] For an irreversible reaction, the enhancement of the products is an indication that the high-energy reaction intermediates are tightly bound, and not necessarily the products. In the S_N2 reactions used herein and in model systems,^[14] the products resemble the transition states, which results in a correlation between the amplitude of the template effect and the affinity of the product for the template.

The method described herein may be useful to identify new inhibitors and to evaluate their relative affinities. Further developments include combinatorial assays where multiple reagents compete simultaneously in the reaction.

Experimental Section

In a typical assay, stock solutions of thiol **1**, chlorides **2a–c**, benzoic acid (internal standard), and CA II in an aqueous phosphate buffer (200 mM, pH 6) were prepared just before use. The desired quantities of these solutions were mixed in a screwcap vial equipped with a small magnetic stirrer bar. When necessary, the total volume was adjusted to 500 μ L. The

stirred reaction mixtures were degassed under vacuum, and purged three times with argon. Stirring was stopped, and the solutions were allowed to react at room temperature under an anaerobic atmosphere. After 48 h, a 250- μ L aliquot was removed, diluted with CH₃CN (750 μ L), and sonicated for 7 min to precipitate the CA enzyme. The suspension was centrifuged on an ultrafree-CL-Biomax membrane (PBCC 5000 UFC4 BCC25). This treatment was also applied when no CA was present. The filtrate was lyophilized and redissolved in H₂O/CH₃CN (1:1, 200 μ L). The solution was analyzed by reversed-phase HPLC with detection at 230 nm on a Waters 2690 instrument equipped with a Merck RP-Select B reversed-phase column (5 μ m, 250 $\times$ 4 mm, flow rate: 1 mL min⁻¹). A ternary solvent gradient (solvent A: 0.1% trifluoroacetic acid in H₂O; solvent B: 0.08% trifluoroacetic acid in CH₃CN; solvent C: isopropanol) was optimized so that most of the compounds used in this study have different retention times: C: constant at 2%; B: 0% during 3 min, then increased to 80% over 79 min.

The assay described above was optimized to limit side reactions such as disulfide formation, alkyl chloride hydrolysis, and trialkyl sulfonium formations. Some of these side products have been identified on the chromatograms and are mentioned below. The products **3a–e** were synthesized and characterized separately to validate their assignments on the chromatograms.

The following retention times and absorption coefficients were measured: **3a** (10 min, ϵ_{230} = 12 000 cm⁻¹M⁻¹), **3b** (20 min, ϵ_{230} = 16 000 cm⁻¹M⁻¹), **3c** (33 min, ϵ_{230} = 15 000 cm⁻¹M⁻¹), **3d** (57 min, ϵ_{230} = 23 000 cm⁻¹M⁻¹), **3e** (57 min, ϵ_{230} = 23 000 cm⁻¹M⁻¹), **2d** (40 min), **2e** (40 min), 4-hydroxymethylbenzoic acid (14 min), 3-hydroxymethyl benzoic acid (14 min), benzoic acid (22 min), α,α -tosylamide disulfide (61 min, ϵ_{230} = 23 000 cm⁻¹M⁻¹).

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Nonhazardous Direct Oxidation of Hydrogen to Hydrogen Peroxide Using a Novel Membrane Catalyst

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Hydrogen peroxide is a clean oxidizing agent that is useful for converting organic compounds into value-added products (bulk and fine chemicals), as well as for industrial and municipal waste-water treatment, and water disinfection. However, because of the high cost of its production by the standard anthraquinone process,^[1] hydrogen peroxide cannot be used for the production of bulk organic chemicals or for water treatments. Moreover, the anthraquinone method is not a green process. Hence, it is of great practical importance to develop an environmentally friendly process based on the direct oxidation of hydrogen to hydrogen peroxide. Although the formation of hydrogen peroxide in the palladium-catalyzed liquid-phase oxidation of hydrogen has been known since 1914, and several patents have been issued since then,^[2–11] this process could not be put into practice. This is mostly because of its highly hazardous nature (the explosive limits of hydrogen/oxygen gas mixtures are very wide and are further widened with increasing pressure), and/or poor

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hydrogen peroxide selectivity and yield. The readily available literature on this process is scarce, and the conversions and selectivities reported earlier are poor (maximum 8.7 % H_2O_2 selectivity with 41 % H_2 conversion at 0.65 MPa).^[12]

Our new approach, which gives a very high conversion (up to 100 %) with high H_2O_2 selectivity, involves the liquid-phase oxidation of H_2 by O_2 , without any explosion hazards: a) a composite Pd-membrane catalyst (Figure 1a) was specially designed to greatly increase the H_2O_2 selectivity, and b) the H_2 is separated from the O_2 in the liquid reaction medium in the reactor by the membrane catalyst, thereby avoiding the formation of an explosive gas mixture (Figure 1b).

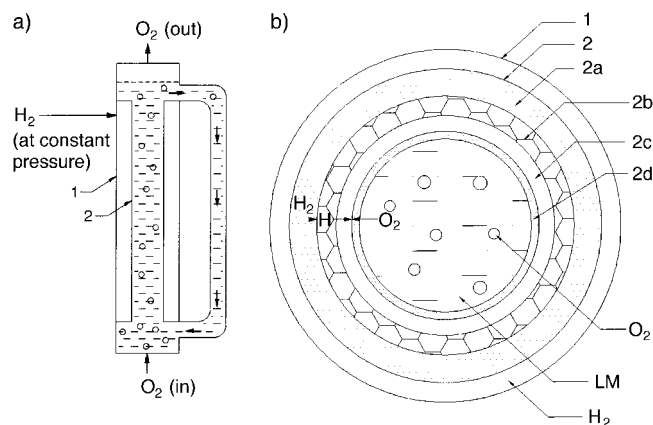


Figure 1. Schematic representation of the composite Pd-membrane catalyst and the membrane reactor for the nonhazardous oxidation of H_2 by O_2 to H_2O_2 . a) Membrane loop reactor with recirculation of the liquid medium (0.02M H_2SO_4) by gas lift. b) Cross sectional view (not to scale) of the membrane reactor and the membrane catalyst (1 = membrane reactor wall, 2 = tubular membrane catalyst, 2a = tubular membrane support with α - or γ -alumina (200 nm) deposited on the inner walls, 2b = Pd-Ag alloy film on the α - or γ -alumina, 2c = Pd film (on the Pd-Ag alloy) with or without oxidation by N_2O or H_2O_2 , 2d = hydrophobic polymer membrane permeable to gases and vapours, LM = liquid medium (0.02M H_2SO_4); area of the metallic membrane = 50 cm²).

We have observed a large increase in the H_2O_2 selectivity as a result of the deposition of a thin film of pure palladium on a stable Pd-Ag alloy/ γ - or α -alumina membrane. The selectivity is increased markedly by the bulk oxidation of the Pd film. The deposition of a thin film of a hydrophobic polymer membrane on the oxidized Pd film also causes a further small increase in the selectivity. In the Pd-based membrane reactor, H_2 gas (at constant pressure) is separated by the membrane catalyst from the aqueous liquid medium (0.02M H_2SO_4) through which O_2 gas is bubbled (Figure 1). Because of its permselectivity, only hydrogen atoms permeate through the Pd-based metallic membrane.^[13–16] At the surface of the Pd film or of the oxidized Pd film, the hydrogen atoms react with the oxygen molecules transported in the liquid medium, to form H_2O_2 :



Because of its high affinity for water, the H_2O_2 formed in this reaction [Eq. (1)] is absorbed by the aqueous liquid medium, which is recirculated over the surface of membrane catalyst in the membrane loop reactor by the gas lift (Figure 1a).

To illustrate this approach, H_2 was oxidized by treating it with O_2 in the liquid reaction medium (0.02M H_2SO_4). A novel composite Pd-based membrane catalyst (Figure 1a) was used at different stages of its preparation, in a membrane loop reactor (Figure 1b). We also used powdered Pd-containing catalysts (with or without Ag), and a mixed H_2 and O_2 gaseous feed in a three-phase stirred reactor. We then studied the decomposition of H_2O_2 over the powdered catalysts, which were stirred in the reactor.

The results of the oxidation of H_2 to H_2O_2 using the three different membrane catalysts at the different stages of their preparation are presented in Figure 2. The membrane catalyst

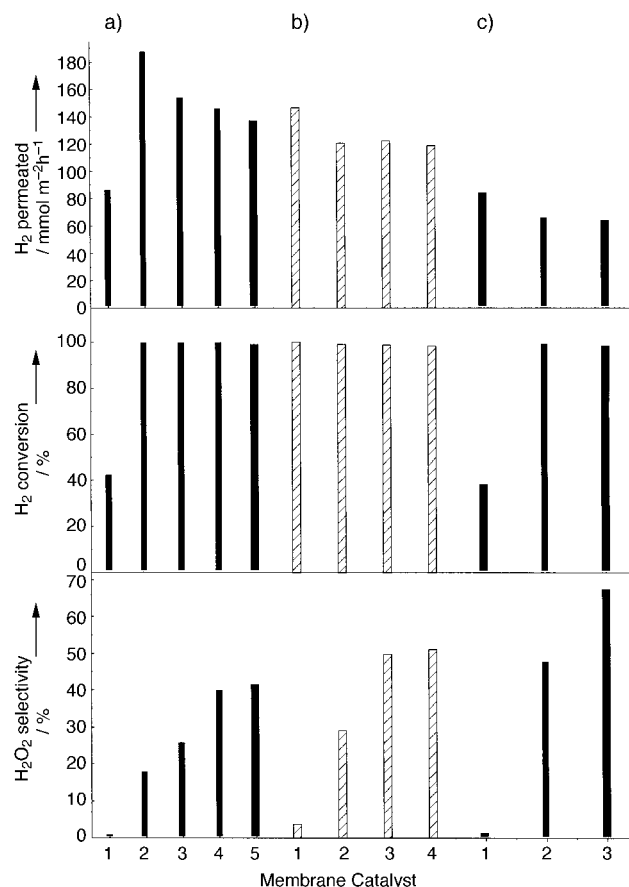


Figure 2. Beneficial effect on the H_2O_2 selectivity of: the deposition of a thin Pd film on Pd-Ag alloy membrane (deposited on α - or γ -alumina membrane support), the oxidation of the Pd film, and the deposition of a thin hydrophobic polymer membrane on the oxidized Pd film, in the oxidation of H_2 at 29 °C (H_2 pressure 243 kPa, O_2 pressure 101 kPa). 1a) Pd-Ag alloy (26.5 wt % Ag, 173.1 g m⁻²) deposited on an α -alumina membrane support, 2a) after deposition of a Pd film (0.6 μm) on the alloy, 3a) after increasing the thickness of the Pd film from 0.6 to 1.4 μm , 4a) after oxidation of the Pd film by N_2O at 250 °C for 2 h and 5a) after deposition of a thin film 0.9 μm of silicon rubber on the oxidized Pd film; 1b) for Pd-Ag alloy (10.1 wt % Ag) alloy (36.2 g m⁻², film thickness 3.3 μm (max)) deposited on γ -alumina membrane support, 2b) after deposition of Pd film (0.8 μm) on the alloy, 3b) after oxidation of the Pd film by N_2O at 250 °C for 2 h, 4b) after deposition of a thin film (0.5 μm) of polyether sulfone polymer membrane on the oxidized Pd film; 1c) for Pd-Ag (30.5 wt % Ag) alloy (54.2 g m⁻², film thickness 4.9 μm (max)) deposited on γ -alumina membrane support, 2c) after deposition of the Pd film (1.5 μm) on the alloy, 3c) after oxidation of the Pd film with concentrated H_2O_2 (30 % aqueous H_2O_2) at 80 °C for 2 h. Concentration of H_2O_2 in the liquid medium after 3 h (mmol dm⁻³): 1a) 0.09, 2a) 7.9, 3a) 9.9, 4a) 13.4, 5a) 13.5, 1b) 0.4, 2b) 8.4, 3b) 14.8, 4b) 15.6, 1c) 0.08, 2c) 8.5 and 3c) 12.3.

that contained only Pd (i.e. no Ag) lost its permselectivity for H₂ as a result of the pinholes that developed in the Pd membrane because of the formation of a brittle β -Pd hydride phase.^[17]

For comparison, H₂ was oxidized to H₂O₂ by using a mixed H₂ and O₂ gaseous feed. The H₂O₂ was also decomposed over Pd–Ag/ γ -alumina, Pd/ γ -alumina, and oxidized Pd/ γ -alumina catalysts in a stirred slurry reactor at 29 °C (Figure 3). X-ray diffraction studies of the oxidized Pd/ γ -alumina showed the presence of a PdO phase as well as a metallic Pd phase, which indicated a partial bulk oxidation of the Pd catalyst in its treatment with N₂O or H₂O₂.

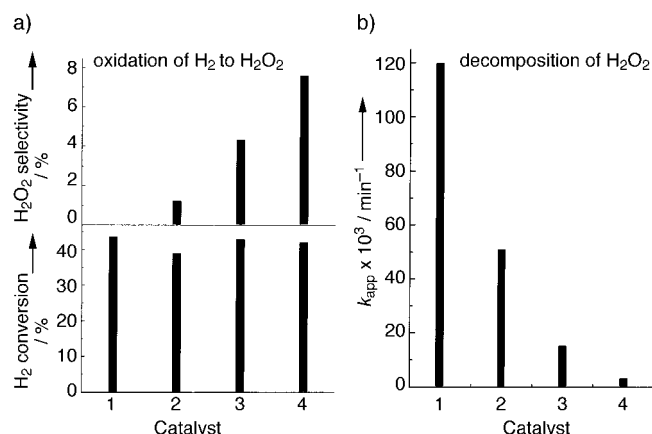
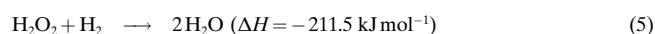
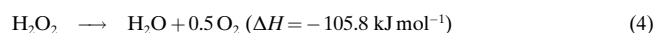
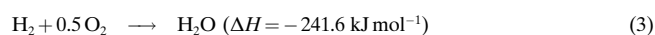
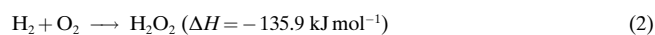


Figure 3. Results of a) direct oxidation of H₂ by O₂ to H₂O₂ by using a mixed H₂ and O₂ gas feed (1.7 vol % H₂ in O₂) and b) decomposition of H₂O₂ over the powdered Pd–Ag alloy (25 wt % Ag)/ γ -alumina (6.3 wt %; 1a and 1b), Pd/ γ -Al₂O₃ (5 wt %; 2a and 2b), oxidized (with N₂O) Pd/ γ -Al₂O₃ (5 wt %; 3a and 3b), and oxidized (with H₂O₂) Pd/ γ -Al₂O₃ (5 wt %; 4a and 4b) catalysts, stirred in a slurry reactor at 29 °C, with H₂SO₄ (0.02 M) as the reaction medium (k_a = apparent first-order rate constant).

Based on the results in Figure 2, the following observations were made: a) the membrane catalyst that contained only Pd–Ag alloy shows little or no selectivity for H₂O₂ formation; b) the H₂O₂ selectivity is greatly increased after the deposition of a Pd film, depending on its thickness; c) the H₂O₂ selectivity is increased appreciably if the Pd film is oxidized; d) the deposition of a hydrophobic polymer membrane on the oxidized Pd film also causes a further small increase in the H₂O₂ selectivity. These observations for the membrane reactor are consistent with those for the slurry reactor, which uses a similar catalyst in the form of fine particles, and a mixed feed of H₂ and O₂ gases (Figure 3a).

The reactions involved in the low temperature (25 °C) Pd-catalyzed oxidation of H₂ are:



These reactions are exothermic and thermodynamically feasible over a wide temperature range. However, the

oxidation of H₂ to H₂O₂ [Eq. (1)] is favored at lower temperatures and higher pressures, whereas the conversion of H₂O₂ [Eq. (4) and (5)] occurs more readily at higher temperatures. Therefore, the formation of H₂O₂ is preferred at lower temperatures and higher pressures.

Little or no H₂O₂ selectivity was observed for the Pd–Ag alloy, which can be attributed to its high H₂O₂ conversion activity. The H₂O₂ decomposition activity of the Pd-containing catalysts was found to be in the following order: Pd–Ag > Pd > Pd–PdO (Figure 3b). The observed H₂O₂ selectivity trend for both the membrane and slurry catalysts (Figure 2 and 3a) is consistent with this order; the lower the H₂O₂ decomposition activity, the higher the H₂O₂ selectivity. The role of the hydrophobic polymer membrane is to increase the H₂O₂ selectivity by avoiding catalytic conversion of H₂O₂ [Eq. (4) and (5)], once it is formed and absorbed by the aqueous liquid medium. The hydrophobic polymer membrane provides a barrier for returning the H₂O₂ back to the catalyst surface.

Both the selectivity and the H₂ conversion are much higher for the membrane catalyst than for the corresponding catalyst used in the slurry reactor with a mixed feed of H₂ and O₂ gases (Figure 2 and 3a). Furthermore, the H₂O₂ selectivity of the membrane catalyst (Figure 2) is much higher than that of similar Pd-containing catalysts that use a mixed feed of H₂ and O₂ gases (Figure 3a), and even at much higher pressure (> 2 MPa).^[12] The higher selectivity and conversion can be attributed mostly to the formation of H₂O₂ by the reaction of the permeated hydrogen atoms (which are more reactive than H₂ molecules) with molecular O₂ [Eq. (1)] at the catalyst surface, in the membrane process. Once the H₂O₂ is formed and absorbed by the liquid medium, its conversion is eliminated or decreased by providing a resistance for the transport of H₂O₂ back to the catalyst surface using the polymer membrane. Also, since the conversion of H₂ is complete or close to 100 %, there is no need for the separation of unconverted H₂ from the reactor effluent gas (unconverted O₂) before it is recycled in the process. The concentration of H₂O₂ in the liquid medium could be increased by increasing the reaction time and/or the H₂ pressure, while maintaining the pressure drop across the membrane catalyst well below its burst pressure. A further improvement in the selectivity by optimizing the design of the membrane catalyst and the process conditions, and also by operating the process at much higher pressures would make this environmentally friendly process much more attractive and also commercially more feasible.

Experimental Section

Pd–Ag alloy was deposited on the inner walls of an α -alumina (pore size = 200 nm) or a γ -alumina (2 nm) membrane support tube (i.d. 7 mm, o.d. 10 mm and length 250 mm; Scoete des Ceramiques Technique, France), by the electroless deposition technique described elsewhere.^[17, 18] The Pd film on the Pd–Ag alloy was also deposited by the same technique. The Pd film was oxidized by N₂O at 250 °C for 2 h, or by a solution of H₂O₂ (30 %) at 80 °C for 2 h. The hydrophobic polymer membrane on the oxidized Pd film was deposited by exposing it to a polymer solution (silicone rubber (polydimethyl siloxane)) and a cross-linking agent, trimethylol propane (C₂H₅C(CH₂OH)₃) dissolved in toluene or polyether sulfone dissolved in *N,N*-dimethylformamide, and drying in air at 80 °C for 2 h. The Pd–Ag

alloy (25 wt % Ag)/ γ -alumina (6.3 wt %) was prepared by impregnating the Pd/ γ -alumina catalyst (5 wt %, powder, Lancaster Chemicals, England) with silver nitrate and calcining at 500 °C for 4 h under helium. The oxidation of H₂ in the membrane loop reactor was carried out batchwise with respect to H₂ and liquid medium (0.02 M aqueous H₂SO₄) and continuous with respect to O₂ (50 cm³ min⁻¹) for a period of 3 h (Figure 1 a). The liquid medium (60 cm³) was recirculated continuously by the gas lift mechanism. On the other hand, the H₂ was oxidized by O₂ over the magnetically stirred powdered catalysts in a glass slurry reactor (capacity 250 cm³) at atmospheric pressure (101 kPa), by using a mixed feed of H₂ and O₂ (1.7 vol % H₂) and H₂SO₄ (150 cm³, 0.02 M) as the reaction medium. In both cases, the H₂O₂ formed in the reaction was determined by iodometric analysis. The concentration of H₂ in the reactor effluent gases was measured by an online H₂ analyzer. The amount of H₂ that permeated through the membrane catalyst was measured from a decrease in the pressure in the H₂ reservoir, from which the H₂ was supplied to the membrane reactor at a constant pressure. The H₂O₂ was decomposed over the powdered catalysts (0.2 g) by stirring in aqueous H₂SO₄ (105 cm³, 0.02 M) in the glass reactor; the initial concentration of H₂O₂ in the medium was 0.3 wt %.

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Crystal Structure of Potassium Croconate Dihydrate, after 175 Years

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Potassium croconate dihydrate, K₂(C₅O₅)·2H₂O, was isolated by Leopold Gmelin in 1824 and described as an orange-colored (*pomeranzenfarbige*) crystalline hydrate in 1825.^[1] Obtained by heating a mixture of potash and carbon and predating Wöhler's urea synthesis by three years, it thus has a claim to be the first "organic" compound to have been synthesized from inorganic precursors (for an account of early work on oxocarbon compounds, see the chapter by West.^[2]) Although some X-ray studies have been reported on other crystalline croconate salts (e.g., ammonium croconate,^[3] diethylammonium croconate,^[4] ammonium hydrogencroconate,^[5] and rubidium hydrogencroconate^[5]), the structure of the potassium salt has remained unknown until now.

We have obtained the substance by slow evaporation of an aqueous solution of commercial potassium rhodizonate K₂(C₆O₆)^[6] in air. This gave a mixture of colorless and orange-yellow needles, of which the former could be identified as potassium oxalate monohydrate,^[7] while the latter was shown by X-ray analysis to be potassium croconate dihydrate,^[8] both presumably derived from air oxidation of the rhodizonate. Apart from its historical interest, the crystal structure has some noteworthy features. It gives the first reasonably precise dimensions of the aromatic ring system and shows a remarkable stacking of the planar, doubly negatively charged croconate anions.

From the dimensions of the croconate dianion shown in Figure 1, it is evident that it does not deviate much from fivefold symmetry in the crystal environment. The slight differences among the individual distances may be real and attributable to the lower symmetry of the crystal environ-

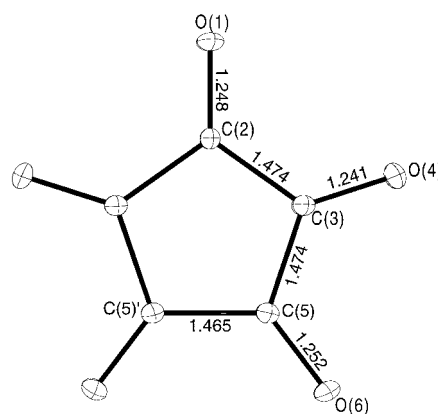


Figure 1. Bond lengths [Å] in the croconate dianion of K₂(C₅O₅)·2H₂O (estimated standard deviations are ca. 0.003 Å). The dianion has crystallographic C₂ symmetry. The oxygen atoms deviate by up to 0.076 Å from the mean plane of the carbon skeleton (planar to within 0.025 Å). The C-C-C angles are all within 0.5° of 108°, and the C-C-O angles all within 1° of 126°.

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ment. Small deviations of the atoms from the mean plane of the anion (up to 0.025 Å for C atoms, 0.076 Å for O atoms) may arise from the same cause. The most striking feature of the crystal structure is perhaps the stacking of the nearly planar, doubly negatively charged croconate anions along the short *c* axis (Figure 2). With the plane normal tilted 13° from

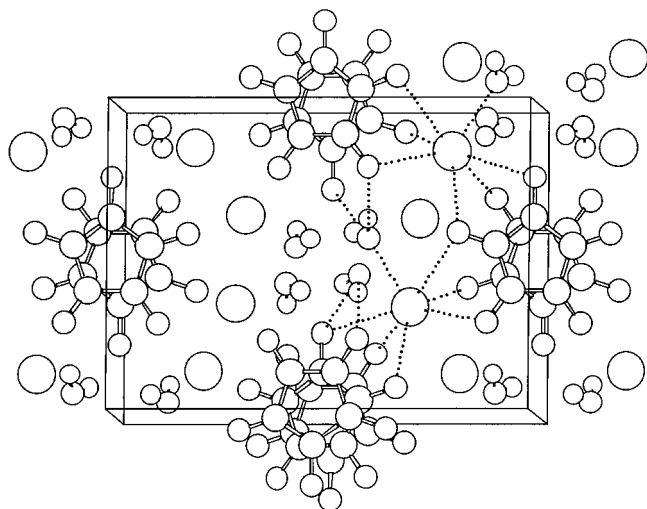


Figure 2. Crystal structure of $K_2(C_5O_5) \cdot 2H_2O$ viewed along a direction nearly parallel to the *c* axis with the *a* axis horizontal. The large circles represent potassium atoms, and dotted interactions correspond to $K \cdots O$ and $H_2O \cdots O$ distances in the range of 2.65 Å to 3.01 Å.

this axis, the interplanar spacing is only 3.30 Å, and individual interatomic distances between neighboring molecules in the stack are as short as 3.28 Å for $C \cdots C$ and 3.34 Å for $O \cdots O$. These anionic stacks are separated by a complex system of potassium cations and water molecules (Figure 2), in which each K cation is linked to six O atoms of four separate anions in two different stacks ($K^+ \cdots O$ 2.79–3.01 Å) and to the O atom of a water molecule (2.65 Å) in an irregular coordination environment. Each water molecule in turn forms hydrogen bonds to O atoms of two adjacent anions in the same stack ($O \cdots O$ 2.79, 2.88 Å), as well as being engaged in the coordination of K^+ .

None of the other crystal structures of croconate salts show this pattern; nor does the crystal structure of anhydrous potassium rhodizonate.^[9] The simple model in which the

doubly negative charge of an individual croconate anion is assumed to be localized on its peripheral oxygen atoms ($q_O = -\frac{2}{5}$) is grossly inadequate for explaining the anion stacking; it would correspond to a potential energy of more than 100 kcal mol⁻¹ per pair of anions in the stack. Models involving more localized charges, for example, on the carbon atoms or at the ring centre would be even worse. Perhaps point-charge models are inadequate to describe the observed packing. In any case, the present structure would seem to represent a challenge for advanced crystal structure modelers.

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