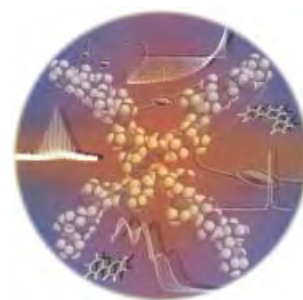


COVER PICTURE

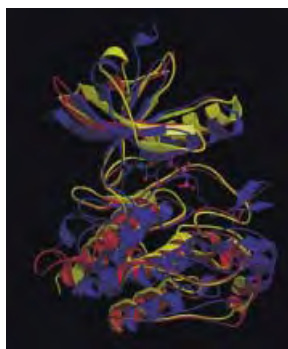
The cover picture shows the molecular modeling of a star-shaped metallo-supramolecular polymer and the schematic drawing of a linear analogue. These molecules are of great interest because of their unique properties. Metallo-supramolecular polymers emerge by the well-directed combination of polymers, the properties of which have dominated the development of materials in recent years, with supramolecular ligands, which have the ability to organize spontaneously and form unique structures on a molecular level, and transition-metal ions, which, through their physical properties bring characteristic functionalities. The well-known properties of the individual components allow the use of established methods, such as UV/Vis spectroscopy, NMR spectroscopy, and gel permeation chromatography for characterization. However, the combination also requires the application of new methods, such as analytical ultracentrifugation or MALDI-TOF mass spectrometry. More about metallo-supramolecular polymers based on bipyridine and terpyridine complexes can be found in the review by U. S. Schubert and C. Eschbaumer on p. 2892 ff.



REVIEWS

Contents

Evolution leads the way: The structure of proteins is based on a limited number of folds (see picture). Natural products have been evolutionarily selected to bind to such protein domains, therefore, they represent biologically validated starting points for the design of combinatorial compound libraries, which allow a higher hit rate despite smaller library sizes.



Angew. Chem. **2002**, *114*, 3002–3015

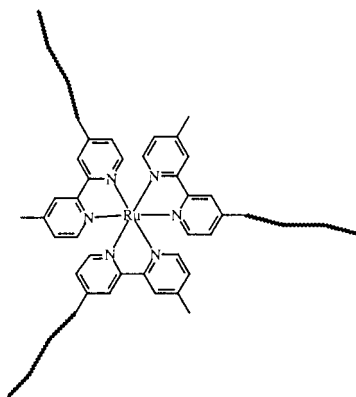
R. Breinbauer, I. R. Vetter,
H. Waldmann* 2878–2890

From Protein Domains to Drug
Candidates—Natural Products as Guiding
Principles in the Design and Synthesis of
Compound Libraries

Keywords: bioorganic chemistry •
combinatorial chemistry • natural
products • protein structures • solid-
phase synthesis

Functional architectures and “intel-ligent” materials can be constructed from polymer complexes with bipyridine (see picture) and terpyridine ligands, compounds that play an important role in modern macromolecular and supramolecular chemistry. This review provides an overview of the current status of the synthesis, characterization, and application of this class of compounds.

Angew. Chem. **2002**, *114*, 3016–3050



Ulrich S. Schubert,*
C. Eschbaumer 2892–2926

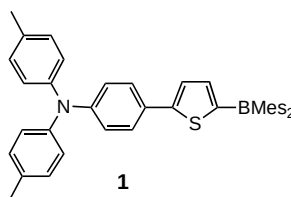
Macromolecules Containing Bipyridine and Terpyridine Metal Complexes: Towards Metallosupramolecular Polymers

Keywords: bipyridine ligands • coordination chemistry • polymers • supramolecular chemistry • terpyridine ligands

MINIREVIEW

Molecular and polymeric boron-containing systems are proving to display interesting optical and electrooptical properties. Molecules such as thiophene **1** with a donor (4-[bis(4-methylphenyl)amino]phenyl) and an acceptor (dimesitylboryl) substituent, are strongly electroluminescent, and have been incorporated into organic electronic devices.

Angew. Chem. **2002**, *114*, 3051–3056



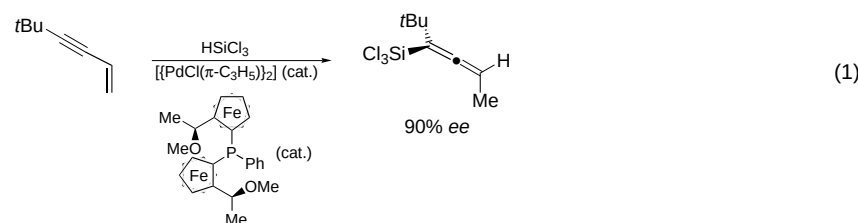
C. D. Entwistle,
T. B. Marder* 2927–2931

Boron Chemistry Lights the Way: Optical Properties of Molecular and Polymeric Systems

Keywords: amorphous materials • boron • electroluminescence • fluorescence • nonlinear optics

HIGHLIGHT

A breakthrough in the catalytic enantioselective synthesis of allenes was recently reported by Hayashi and co-workers: chiral trichlorosilyl allenes were generated with up to 90 % *ee* by palladium-catalyzed hydrosilylation of but-1-en-3-yne in the presence of a chiral ferrocenyl phosphane [Eq. (1)]. This transformation, as well as further recent highlights in enantioselective allene synthesis, are summarized in this account.



Angew. Chem. **2002**, *114*, 3057–3059

A. Hoffmann-Röder,
N. Krause* 2933–2935

Enantioselective Synthesis of and with Allenes

Keywords: allenes • asymmetric catalysis • copper • hydrosilylation • transition metals

VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly. Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.org>

Metallabenzenes and Valence Isomers: Synthesis and Characterization of a Platinabenzene

Syntheses and Crystal Structures of the New Ag-S Clusters [Ag₇₀S₁₆(SPh)₃₄(PhCO₂)₄(triphos)₄] and [Ag₁₈₈S₉₄(PnPr₃)₃₀]

Protonated Benzene: IR Spectrum and Structure of C₆H₇⁺

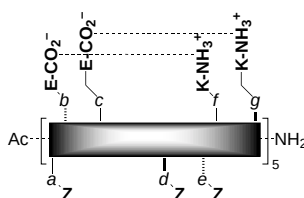
V. Jacob, T. J. R. Weakley,
M. M. Haley*

X.-J. Wang, T. Langetepe,
C. Persau, B.-S. Kang, D. Fenske*

N. Solcà, O. Dopfer*



Substitution in the outer surface of the six-helix peptide bundle improved the solubility and enhanced the anti-HIV-1 activity of SC peptides. The E and K residues at positions *b*, *c*, *f*, and *g* (see scheme) stabilize the α -helix conformation critical to inhibition; the Z residues at positions *a*, *d*, and *e* interact with the inner strand.



A. Otaka,* M. Nakamura, D. Nameki, E. Kodama, S. Uchiyama, S. Nakamura, H. Nakano, H. Tamamura, Y. Kobayashi, M. Matsuoka, N. Fujii * 2938–2940

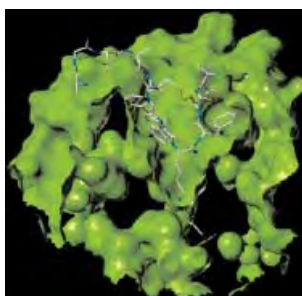
Remodeling of gp41-C34 Peptide Leads to Highly Effective Inhibitors of the Fusion of HIV-1 with Target Cells

Keywords: antiviral agents • drug design • helical structures • HIV • peptides

Angew. Chem. **2002**, *114*, 3062–3064



The salient structural features of urotensin II (U II) required for stimulation of its G-protein-coupled receptor were obtained from biological evaluation of synthetic derivatives of U II. This approach led to a plausible U-II–receptor complex (see picture), which inspired the installation of nonnatural amino acids in place of key residues. Notably, replacement of tyrosine with (2-naphthyl)-L-alanine resulted in a sixfold potency improvement compared to U II.



W. A. Kinney,* H. R. Almond, Jr., J. Qi, C. E. Smith, R. J. Santulli, L. de Garavilla, P. Andrade-Gordon, D. S. Cho, A. M. Everson, M. A. Feinstein, P. A. Leung, B. E. Maryanoff 2940–2944

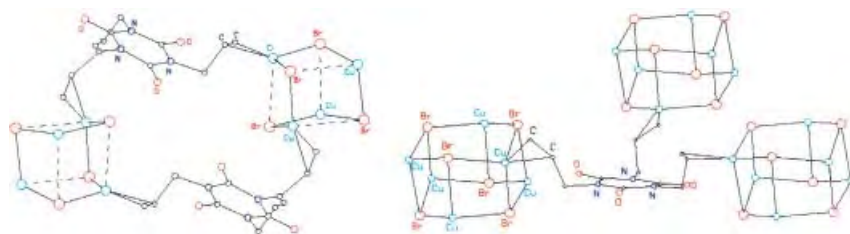
Structure–Function Analysis of Urotensin II and Its Use in the Construction of a Ligand–Receptor Working Model

Keywords: G proteins • protein models • structure–activity relationships • urotensin II • vasoactive peptides

Angew. Chem. **2002**, *114*, 3064–3068



Temperature determines the product: The reaction of triallyl-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione with CuBr at 60°C affords a copper(I)–olefin coordination polymer with a Cu₄Br₄ open cubane (left) as a connecting node; when the reaction is repeated at 90°C a Cu₆Br₆ prismane unit is formed in a coordination polymer (right).



X. Xue, X.-S. Wang, R.-G. Xiong,* X.-Z. You, B. F. Abrahams,* C.-M. Che, H.-X. Ju 2944–2946

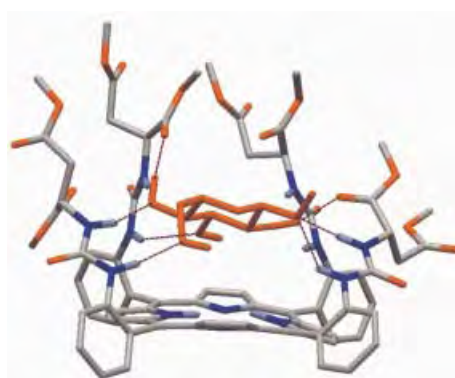
A Cluster Rearrangement of an Open Cubane (Cu₄Br₄) to a Prismane (Cu₆Br₆) in a Copper(I)–Olefin Network

Keywords: cluster compounds • copper • crystal engineering • cubanes • supramolecular chemistry

Angew. Chem. **2002**, *114*, 3068–3070



Sugar receptors: Urea-appended porphyrins were the most effective binding agent for pyranosides in chloroform and still very effective even in the presence of hydroxylic cosolvents. The combination of a rigid porphyrin skeleton and acyclic, flexible, yet preorganized polar urea groups aligned in a rigid platform (see picture) enabled three-dimensional recognition of carbohydrates.



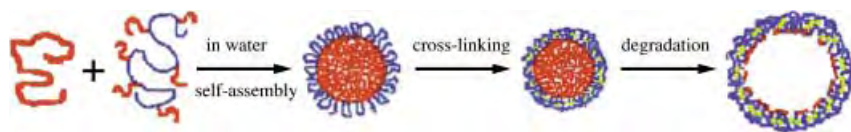
Y.-H. Kim, J.-I. Hong * 2947–2950

Molecular Recognition of Carbohydrates through Directional Hydrogen Bonds by Urea-Appended Porphyrins in Organic Media

Keywords: carbohydrates • host–guest systems • hydrogen bonds • molecular recognition • porphyrinoids

Angew. Chem. **2002**, *114*, 3071–3074

A block-copolymer-free strategy has been used to form micelles by the self-assembly of poly(ϵ -caprolactone) (PCL) and a graftlike copolymer which has a hydrophilic backbone and short PCL side-chains (see schematic representation). Affinity between the PCL homopolymer and the PCL short branches appears to stabilize the micelles. The hydrophobic polyester core can be selectively hydrolyzed by lipase to give hollow spheres, as shown by transmission electron microscopy.



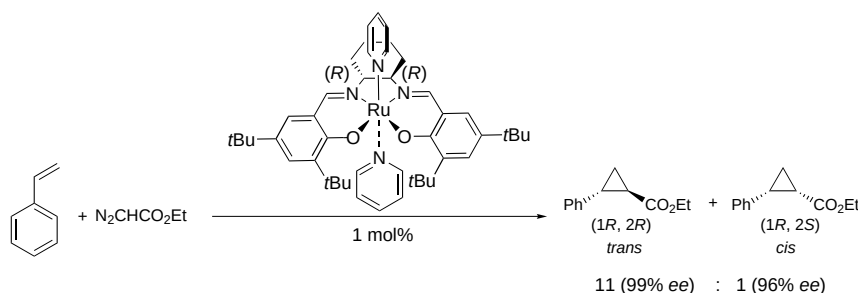
Angew. Chem. **2002**, *114*, 3074–3077

X. Liu, M. Jiang,* S. Yang, M. Chen,
D. Chen, C. Yang, K. Wu 2950–2953

Micelles and Hollow Nanospheres Based
on ϵ -Caprolactone-Containing Polymers
in Aqueous Media

Keywords: electron microscopy •
micelles • nanostructures • polymers •
self-assembly

Both electron-rich and electron-deficient olefins—such as styrene and methyl methacrylate—undergo efficient (yields >90%) cyclopropanation with ethyl diazoacetate as the carbene source to give predominantly *trans* products with exceptionally high enantioselectivity when the (salen)Ru catalyst shown is used (see scheme).



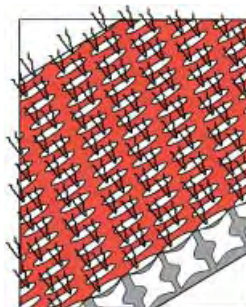
Angew. Chem. **2002**, *114*, 3077–3080

J. A. Miller, W. Jin,
S. T. Nguyen* 2953–2956

An Efficient and Highly Enantio- and
Diastereoselective Cyclopropanation of
Olefins Catalyzed by Schiff-Base
Ruthenium(II) Complexes

Keywords: asymmetric catalysis •
cyclopropanation • N,O ligands •
ruthenium

Ionic self-assembly: Oligopeptides with a small number of charged sites can be precipitated from water by complexation with oppositely charged surfactants, as exemplified here with oxidized glutathione, GSSG. These complexes are well-defined 1:1 species, dissolve in organic solvents, and form highly organized supramolecular aggregates (solution; see schematic representation) or mesophases (solid-state films). This ionic self-assembly with surfactants represents a simple access to new peptide superstructures with structural features on the nanometer scale.



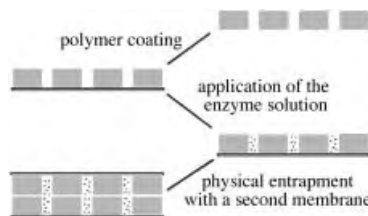
Angew. Chem. **2002**, *114*, 3081–3084

S. General, M. Antonietti* . . . 2957–2960

Supramolecular Organization of
Oligopeptides, through Complexation
with Surfactants

Keywords: nanostructures •
oligopeptides • self-assembly •
superhelices • surfactants

The conversion of enzymes into enantioselective receptors by mutagenesis opens the way for resolution of racemates by using enantioselective membranes: the transport of one enantiomer is accelerated through the membrane, while the other enantiomer diffuses across much more slowly. As an example, histidine ammonia lyase and phenylalanine ammonia lyase were rendered catalytically inactive and incorporated in artificial membranes (see figure). The facilitated transport of L-histidine and L-phenylalanine resulted in a maximum 14-fold enantiomeric enrichment.



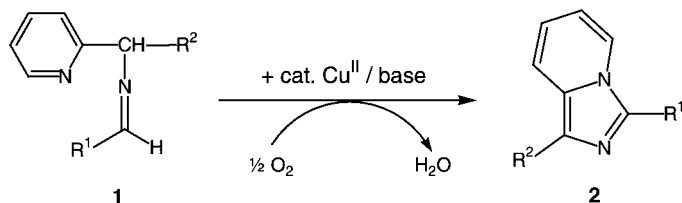
Angew. Chem. **2002**, *114*, 3094–3096

A. Skolaut, J. Rétey* 2960–2962

Use of Enzymes Deactivated by Site-
Directed Mutagenesis for the Preparation
of Enantioselective Membranes

Keywords: amino acids • chiral
resolution • enantioselective transport •
lyases • membranes

 **Starting from Schiff bases 1**, a wide variety of heterobicycles, which can be applied as pharmaceuticals or as ligands for catalysts, is accessible by copper-catalyzed oxidation with atmospheric oxygen. The scheme shows, for example, the synthesis of imidazo[1,5-*a*]pyridines **2** (R^1 = 2-hydroxy-3-methoxyphenyl, *t*Bu, 2-hydroxyphenyl, 2-aminophenyl; R^2 = 2-pyridyl, Me, phenyl).



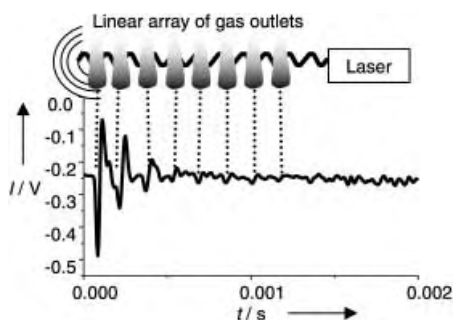
Angew. Chem. **2002**, *114*, 3104–3107

M. E. Bluhm, M. Ciesielski, H. Görls,
M. Döring* 2962–2965

Copper-Catalyzed Oxidative
Heterocyclization by Atmospheric
Oxygen

Keywords: copper • homogeneous
catalysis • metalloenzymes • oxygen •
Schiff bases

Photoacoustic parallel detection is introduced as a novel analysis technique for high-throughput experimentation in catalysis (see picture). Libraries of mixed-metal oxides were generated by a novel process based on activated carbon and thus novel CO-oxidation catalysts were discovered.



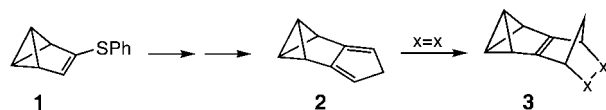
Angew. Chem. **2002**, *114*, 3096–3100

T. Johann, A. Brenner, M. Schwickardi,
O. Busch, F. Marlow, S. Schunk,
F. Schüth* 2966–2968

Real-Time Photoacoustic Parallel
Detection of Products from Catalyst
Libraries

Keywords: amorphous materials •
CO oxidation • heterogeneous catalysis •
high-throughput screening •
photoacoustics

A strong pyramidalization of the double bond in the Diels–Alder adducts **3**, as suggested by quantum-chemical calculations and NMR spectroscopic data, is probably the reason why these very reactive compounds are observable at best at low temperatures. The title compound **2**, required for preparation of **3**, was prepared in five steps from benzvalene **1**.



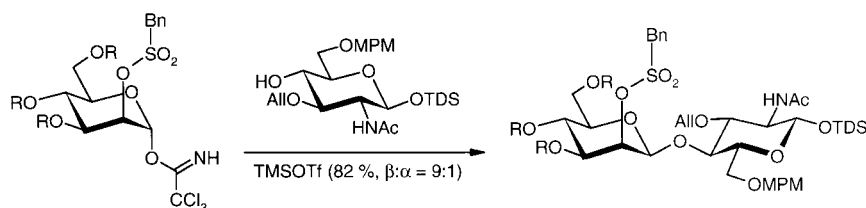
Angew. Chem. **2002**, *114*, 3091–3093

T. Fischer, U. Kunz, S. E. Lackie,
C. Cohrs, D. D. Palmer,
M. Christl* 2969–2971

1,2,3,5-Tetrahydro-1,2,3-
methenopentalene, a Valence Isomer of
Isoindene: Synthesis and Diels–Alder
Reactions

Keywords: benzvalene • cycloaddition •
Pauson–Khand reaction • polycycles •
rearrangement

An electron-withdrawing protecting group at the O-2 atom and a good anomeric leaving group at the mannopyranosyl donor are required for a new, practical approach to the production of β -linked mannopyranoside units (see scheme, MPM = *para*-methoxybenzyl, TDS = thexylmethysilyl, TMS = trimethylsilyl, All = β -D-allose, OTf = trifluoromethanesulfonate). Many attempts to solve this problem in a direct manner have failed. β -Mannopyranoside units are found, for instance, in N-glycopeptides.



Angew. Chem. **2002**, *114*, 3100–3103

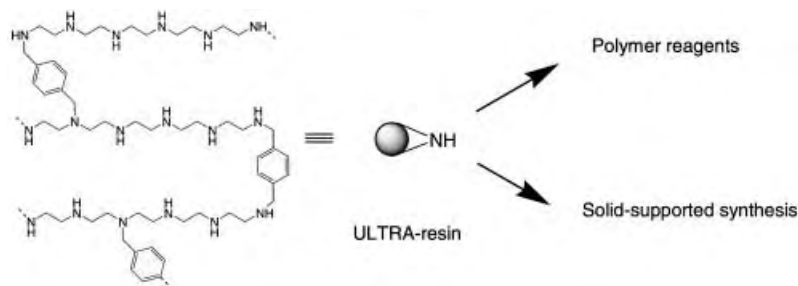
A. A.-H. Abdel-Rahman, S. Jonke,
El S. H. El Ashry,*
R. R. Schmidt* 2972–2974

Stereoselective Synthesis of β -D-
Mannopyranosides with Reactive
Mannopyranosyl Donors Possessing a
Neighboring Electron-Withdrawing
Group

Keywords: asymmetric synthesis •
C-glycosides • mannopyranosides •
protecting groups • stereoelectronic
effects



ULTRA resins (see picture), useful for making polymer reagents, heterocycles, and peptides, were prepared by thermodynamically controlled cross-linking of linear poly(ethylene imine)s with a loading of up to 15 mmol g^{-1} . During characterization, the secondary amines in the resin backbone of the novel carriers were found to be very accessible to chemical modification.



Angew. Chem. **2002**, *114*, 3087–3090

J. Rademann,* M. Barth 2975–2978

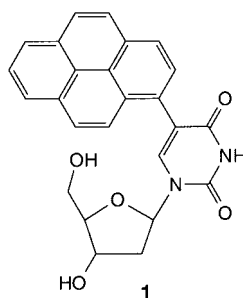
ULTRA Loaded Resins Based on the Cross-Linking of Linear Poly(ethylene imine): Improving the Atom Economy of Polymer-Supported Chemistry

Keywords: combinatorial chemistry • polymers • solid-phase synthesis • synthetic methods



Ultrafast intramolecular electron transfer results from the excitation of the pyrene-modified nucleoside **1**. The dynamics and pH dependence of this process were investigated by steady-state fluorescence and femtosecond time-resolved transient absorption spectroscopy. These studies suggest that reductive electron transfer through DNA is not coupled to protonation.

Angew. Chem. **2002**, *114*, 3084–3087

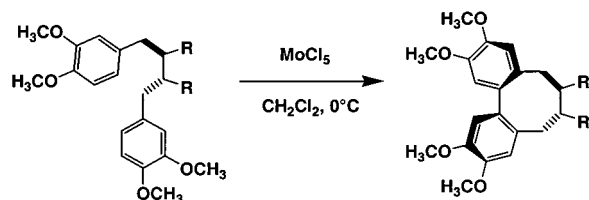


N. Amann, E. Pandurski, T. Fiebig,*
H.-A. Wagenknecht * 2978–2980

A Model Nucleoside for Electron Injection into DNA: 5-Pyrenyl-2'-Deoxyribose

Keywords: charge transfer • cross-coupling • electron transfer • nucleosides • protonation

Avoiding six-membered rings: The oxidative coupling reaction of electron-rich 1,4-diarylbutanes with molybdenum pentachloride as the sole reagent leads to the exclusive formation of eight-membered ring systems (see scheme).



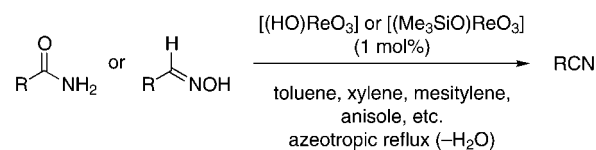
Angew. Chem. **2002**, *114*, 3103–3104

B. Kramer, A. Averhoff,
S. R. Waldvogel* 2981–2982

Highly Selective Formation of Eight-Membered-Ring Systems by Oxidative Cyclization with Molybdenum Pentachloride—An Environmentally Friendly and Inexpensive Access to 2,2'-Cyclolignans

Keywords: biaryl compounds • C–C coupling • cyclization • molybdenum • natural products

An economical and environmentally benign process for the preparation of nitriles by the dehydration of primary amides and aldoximes is catalyzed by rhenium(vii) oxo complexes such as perrhenic acid and trimethylsilylperrhenate (see scheme). The reaction proceeds at azeotropic reflux (with the removal of water) under essentially neutral conditions.



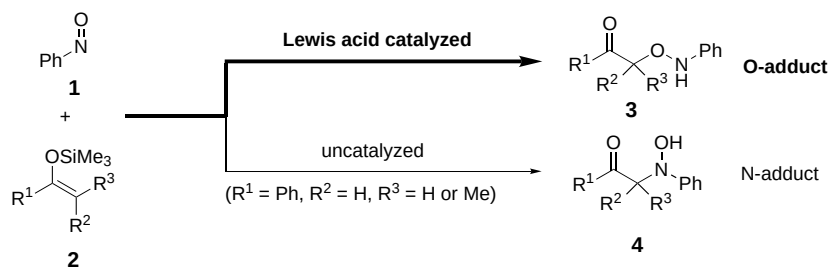
Angew. Chem. **2002**, *114*, 3109–3112

K. Ishihara, Y. Furuya,
H. Yamamoto * 2983–2986

Rhenium(VII) Oxo Complexes as Extremely Active Catalysts in the Dehydration of Primary Amides and Aldoximes to Nitriles

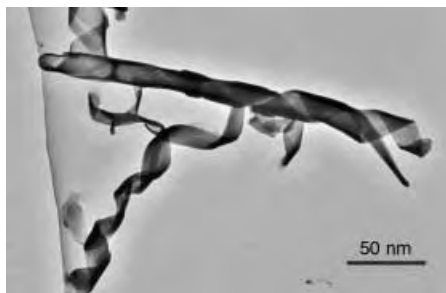
Keywords: dehydration • green chemistry • homogeneous catalysis • nitriles • rhenium

Not N-adduct but O-adduct is formed in the Lewis acid catalyzed nucleophilic addition of silyl enol ethers **2** to the N=O bond of nitrosobenzene (**1**). Various Lewis acids (e.g. alkylsilyl triflates) efficiently catalyze the formation of the aminooxy ketone (O-adduct **3**) rather than of the hydroxyamino ketone (N-adduct **4**), which is the product of the uncatalyzed reaction.



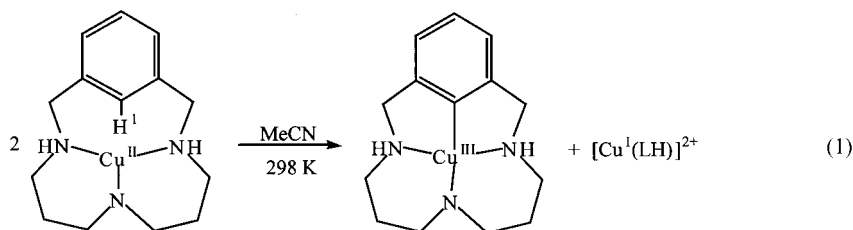
Angew. Chem. **2002**, *114*, 3112–3114

A lamellar hybrid mesostructure containing polymerizable diacetylenic groups is coassembled in the in situ synthesis of silica by acid hydrolysis and condensation of tetraethylorthosilicate (TEOS) in the presence of 1,2-bis(10,12-tricosadiyonyl)-*sn*-glycero-3-phosphatidylcholine (DC_{8,9}PC) lipid molecules. This mesostructure is subsequently twisted into high aspect-ratio tubules and ribbons with helical architecture (see picture). Interactions between the silica and lipid headgroups promote diacetylenic polymerization under conditions at which the unmineralized lipid microstructures show little or no activity.



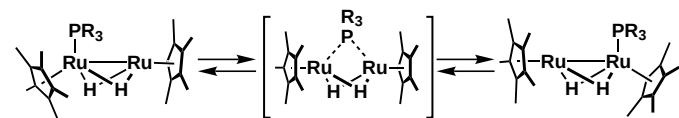
Angew. Chem. **2002**, *114*, 3114–3117

Simple triazamacrocyclic ligands react with copper(II) salts under mild conditions to give the products of intramolecular aryl C–H activation and metal disproportionation [Eq. (1)]. The novel organometallic Cu^{III} complexes thus formed are stable under protic conditions.



Angew. Chem. **2002**, *114*, 3117–3120

On the move! Novel diruthenium dihydrido $[(\eta^5\text{-C}_5\text{Me}_5)\text{Ru}]_2(\text{PR}_3)(\mu\text{-H})_2$ complexes, which were synthesized in the reaction of $[(\eta^5\text{-C}_5\text{Me}_5)\text{Ru}]_2(\mu\text{-H})_4$ with a phosphorus ligand containing no aryl substituents, undergo intramolecular migration of the phosphorus ligand between the two ruthenium centers (see scheme). Support for this result is derived from variable temperature NMR spectroscopic studies and preliminary DFT calculations.



Angew. Chem. **2002**, *114*, 3120–3123

N. Momiyama,
H. Yamamoto* 2986–2988

Lewis Acid Promoted, O-Selective,
Nucleophilic Addition of Silyl Enol
Ethers to N=O bonds

Keywords: Lewis acids • nitroso
compounds • nucleophilic addition • silyl
enol ethers • synthetic methods

A. M. Seddon, H. M. Patel, S. L. Burkett,
S. Mann* 2988–2991

Chiral Templating of Silica–Lipid
Lamellar Mesophase with Helical Tubular
Architecture

Keywords: mesoporous materials •
nanotubes • silica • surfactants •
template synthesis

X. Ribas, D. A. Jackson, B. Donnadieu,
J. Mahía, T. Parella, R. Xifra,
B. Hedman,* K. O. Hodgson,*
A. Llobet,* T. D. P. Stack* .. 2991–2994

Aryl C–H Activation by Cu^{II} To Form an
Organometallic Aryl–Cu^{III} Species:
A Novel Twist on Copper
Disproportionation

Keywords: C–H activation • copper •
macrocyclic ligands • X-ray absorption

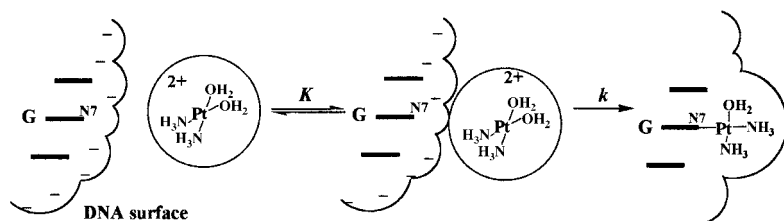
Y. Ohki, H. Suzuki* 2994–2997

Migration of a Phosphane Ligand
between the Two Metal Centers in
Diruthenium Hydrido Complexes

Keywords: hydride ligands • P ligands •
reaction mechanisms • ruthenium

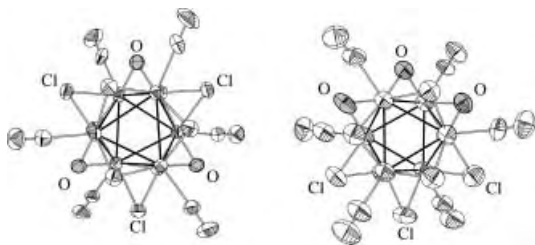


The main factor determining the sequence-selective binding of platinum complexes to DNA is the accessibility of the N7 atom of guanine (G). The rate constants observed for the reactions of *cis*-[Pt(NH₃)₂(H₂O)₂]²⁺ with DNA G residues in various sequences can be accounted for by a mathematical formula compatible with the kinetic model shown in the scheme, where the association constant *K* is determined by the molecular electrostatic potential and the rate constant *k* by the accessible area of the N7 van der Waals sphere.



Angew. Chem. **2002**, *114*, 3124–3127

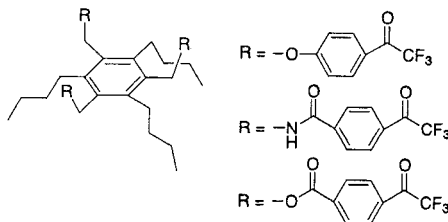
The distribution of the oxygen atoms varies in the two isomers of the [Nb₆Cl₉O₃(CN)₆]⁵⁻ ion found in the title compounds (both isomers are shown). This difference in the inner ligand sphere in turn leads to variations in the structure and physical properties of the cluster oxyhalides.



Angew. Chem. **2002**, *114*, 3128–3130



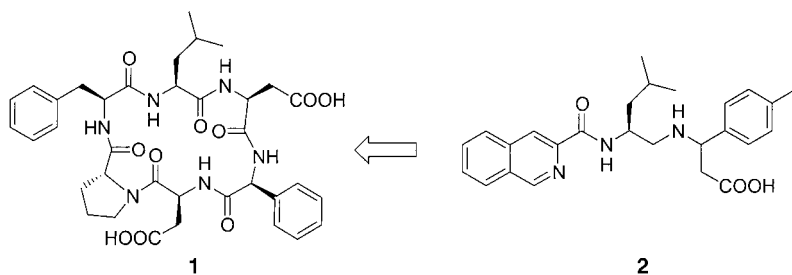
Selective sensors: Trifluoroacetophenone derivatives were synthesized with a hexasubstituted benzene ring as a preorganized spacer (see scheme) and their characteristics as ionophores were examined for use in ion-selective electrodes. The electrode membranes based on these neutral carriers combined with a cationic additive showed a monoanionic Nernstian response to underivatized phenylalanine, with excellent selectivity towards other essential amino acids and inorganic anions.



Angew. Chem. **2002**, *114*, 3131–3133



Non-peptidic compounds (e.g. **2**) derived from cyclic peptides such as **1** are able to inhibit the α4β7-integrin/MAdCAM-1 interaction. 3-Amino arylpropionic acids are valuable dipeptide mimetics. MAdCAM-1 = mucosal addressin cell-adhesion molecule 1.



Angew. Chem. **2002**, *114*, 3133–3137

V. Monjardet-Bas,
M.-A. Elizondo-Riojas,* J.-C. Chottard,
J. Kozelka * 2998–3001

A Combined Effect of Molecular
Electrostatic Potential and N7
Accessibility Explains Sequence-
Dependent Binding of *cis*-
[Pt(NH₃)₂(H₂O)₂]²⁺ to DNA Duplexes

Keywords: DNA complexes •
electrostatic interactions • kinetics •
platinum • sequence selectivity

N. G. Naumov,* S. Cordier,
C. Perrin 3002–3004

Two [Nb₆Cl₉O₃(CN)₆]⁵⁻ Isomer Anions in
Two Nb₆ Cluster Oxyhalides:
Cs₅[Nb₆Cl₉O₃(CN)₆] · 4 H₂O and
(Me₄N)₅[Nb₆Cl₉O₃(CN)₆] · 5 H₂O

Keywords: cluster compounds •
cyanides • isomers • niobium • solid-
state structures

S.-i. Sasaki, A. Hashizume, D. Citterio,
E. Fujii, K. Suzuki * 3005–3007

Trifluoroacetophenone Derivatives as
Amino Acid Selective Ionophores for the
Potentiometric Determination of
Phenylalanine

Keywords: amino acids • ionophores •
molecular recognition • sensors

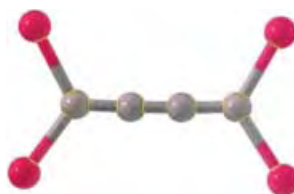
D. Gottschling, J. Boer, A. Schuster,
B. Holzmann, H. Kessler * .. 3007–3011

Combinatorial and Rational Strategies To
Develop Nonpeptidic α4β7-Integrin
Antagonists from Cyclic Peptides

Keywords: drug research • inhibitors •
integrins • peptidomimetics • medicinal
chemistry



In how many different ways can carbon and iodine combine to form a stable molecule? Here is a new possibility: the first reported iodo-cumulene. Tetraiodobutatriene (C_4I_4 ; see picture) is formed spontaneously and in good yield from diiodobutadiene (C_4I_2). In solution, however, C_4I_4 disproportionates to give hexaiodobutadiene (C_4I_6) and unknown carbon-rich by-products.



J. A. Webb, P.-H. Liu, O. L. Malkina,
N. S. Goroff* 3011–3014

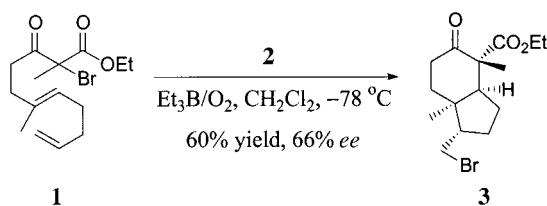
Tetraiodobutatriene: A New Cumulenic
Carbon Iodide

Keywords: addition • alkynes • carbon •
cumulenes • iodine

Angew. Chem. **2002**, *114*, 3137–3140



Various polycyclic ring skeletons (e.g. **3**) are formed from unsaturated α -bromo β -keto esters (e.g. **1**) in a Lewis acid catalyzed atom-transfer tandem radical-cyclization reaction in moderate to good yields and with excellent stereoselectivities. Furthermore, in the presence of chiral complexes such as $[Yb(Phpybox)(OTf)_3]$ (**2**), the enantioselective cyclization gave up to 84% *ee*. OTf = trifluoromethanesulfonate, pybox = 2,6-bis(2-oxazolin-2-yl)pyridine.



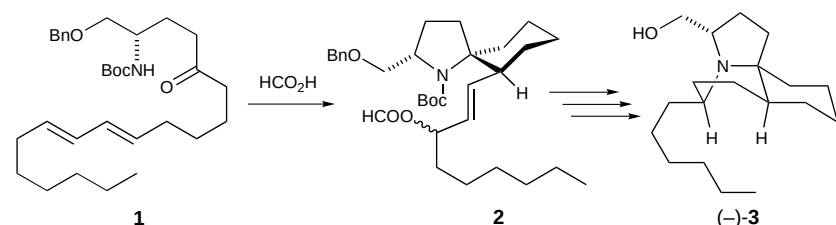
Angew. Chem. **2002**, *114*, 3140–3143

D. Yang,* S. Gu, Y.-L. Yan, H.-W. Zhao,
N.-Y. Zhu 3014–3017

Atom-Transfer Tandem Radical
Cyclization Reactions Promoted by Lewis
Acids

Keywords: cyclization •
enantioselectivity • Lewis acids •
radicals • synthetic methods

A short synthesis: The naturally occurring (–)-lepadiformine ((–)-**3**) was prepared in nine steps in 31.4% overall yield. The key step involved the formation of **2** by the spirocyclization of the *N*-acyliminium ion generated from **1**. Furthermore, HPLC analysis of the synthetic material and the natural product established the absolute configuration of **3** as 3*S*,5*R*,7*aS*,11*aS*. Bn = benzyl, Boc = *tert*-butoxycarbonyl.



Angew. Chem. **2002**, *114*, 3143–3146

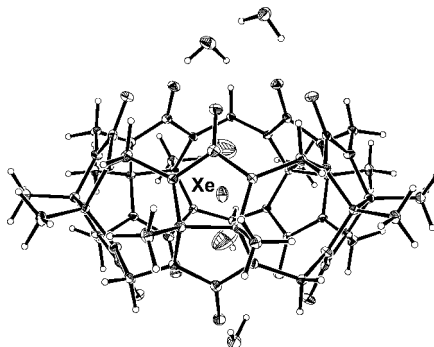
H. Abe, S. Aoyagi,
C. Kibayashi* 3017–3020

Total Synthesis of the Natural Enantiomer
of (–)-Lepadiformine and Determination
of Its Absolute Stereochemistry

Keywords: configuration determination •
natural products • spiro compounds •
total synthesis



Miniature gas jars with lids: Salt-free decamethylcucurbit[5]uril (MeCuc5) powder, absorbs N_2 , O_2 , Ar, N_2O , NO, CO, and CO_2 selectively at room temperature and desorbs at $110^\circ C$, this process can be carried out repeatedly. In contrast, all noble gases from He to Xe were encapsulated inside MeCuc5 in solution and the crystal structures of the gas inclusion complexes were determined (see picture for Xe complex).



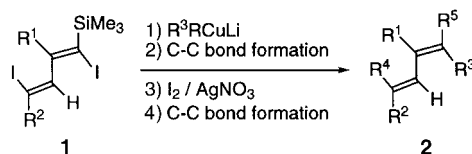
Angew. Chem. **2002**, *114*, 3146–3149

Y. Miyahara,* K. Abe,
T. Inazu 3020–3023

“Molecular” Molecular Sieves: Lid-Free
Decamethylcucurbit[5]uril Absorbs and
Desorbs Gases Selectively

Keywords: cage compounds •
cucurbiturils • gas encapsulation • host–
guest systems • inclusion compounds

Taking advantage of the presence of a silyl group at the α position in **1**, carbon–carbon bonds are formed regioselectively by the reaction of **1** with organocuprate compounds. This method is a practical and efficient approach to molecules of type **2** (R^1 – R^5 = alkyl, aryl) with a variety of substitution patterns.



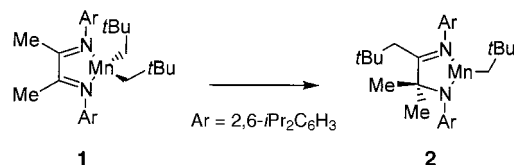
R. Nakajima, C. Delas, Y. Takayama, F. Sato * 3023–3025

Efficient and General Synthetic Approach to Pentasubstituted Conjugated Dienes Using Site-Selective Coupling of Cuprates with 1,4-Diiodo-1,3-alkadienes as the Key Reaction

Keywords: C–C coupling • cuprates • dienes • regioselectivity • synthetic methods

Angew. Chem. **2002**, *114*, 3149–3151

Ligand transformations that depend on the substitution patterns of the diimine ligands occur upon their complexation with Mn^{II} dialkyl complexes. For example the 1,3-migration of the neopentyl unit from Mn to a carbon atom and the 1,2-migration of the methyl in the putative intermediate **1** give the product **2**.



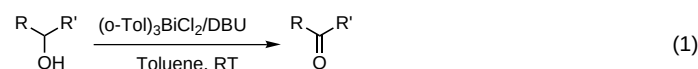
V. Rioulet, C. Copéret,* J.-M. Basset, L. Rousset, D. Bouchu, L. Grosvalet, M. Perrin 3025–3027

Reaction of “[$Mn^{II}(CH_2tBu)_2$]” with Bidentate Diimine Ligands: From Simple Base Adducts to C–C Activation of the Ligand

Keywords: C–C activation • chelates • manganese • N ligands

Angew. Chem. **2002**, *114*, 3151–3153

High efficiency and chemoselectivity as well as the facile isolation of the carbonyl products by simple workup procedures characterize a new method of alcohol oxidation. A variety of primary and secondary alcohols are oxidized to aldehydes and ketones by the combined use of tris(2-methylphenyl)bismuth dichloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under mild conditions [Eq. (1)].



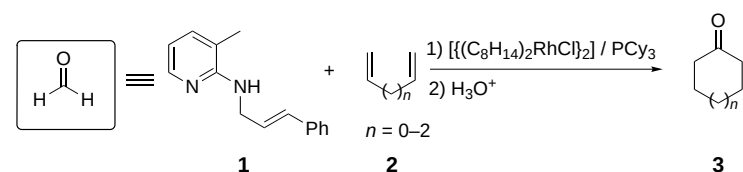
Y. Matano,* H. Nomura 3028–3031

Facile Oxidation of Alcohols to Carbonyl Compounds Using a Tris(2-methylphenyl)bismuth Dichloride–DBU Binary System

Keywords: alcohols • bismuth • carbonyl compounds • oxidation • substituent effects

Angew. Chem. **2002**, *114*, 3154–3157

Formaldehyde in disguise: The allylic amine **1** is used as a masked form of formaldehyde in the rhodium-catalyzed cyclization of dienes **2**. The reaction provides access to various cycloalkanones **3** through chelation-assisted C–H- and C–C-bond activation.



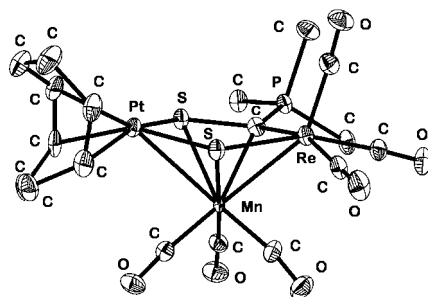
D.-Y. Lee, I.-J. Kim, C.-H. Jun * 3031–3033

Synthesis of Cycloalkanones from Dienes and Allylamines through C–H and C–C Bond Activation Catalyzed by a Rhodium(I) Complex

Keywords: C–C activation • C–H activation • cyclization • dienes • rhodium

Angew. Chem. **2002**, *114*, 3157–3159

A new ring for cymantrene: the five-membered ring of the new cymantrene analogue shown in the picture contains two sulfur atoms, two different transition-metal atoms (Re and Pt), and only one carbon atom and forms a π complex with a $\{Mn(CO)_3\}$ unit.



D. Miguel,* D. Morales, V. Riera, S. García-Granda 3034–3036

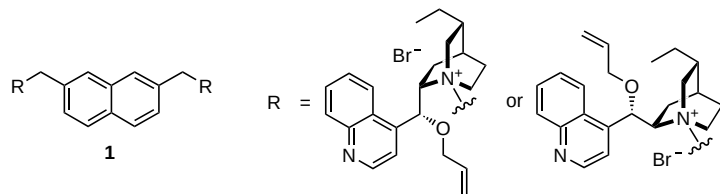
An Analogue of Cymantrene [$(\eta^5-C_5H_5)Mn(CO)_3$] That Contains a Dimetalladithiacyclopentadienyl ring

Keywords: cluster compounds • isolobal relationships • manganese • metallacycles • platinum • rhenium

Angew. Chem. **2002**, *114*, 3160–3162



A new class of naphthalene-based dimeric cinchona alkaloids **1** are very efficient and practical phase-transfer catalysts in the alkylation of a glycine derivative. The mild reaction conditions and the high catalytic efficiency (high yields and *ee* values) could make these alkaloids practical catalysts in the industrial synthetic process for natural and nonnatural chiral α -amino acids.



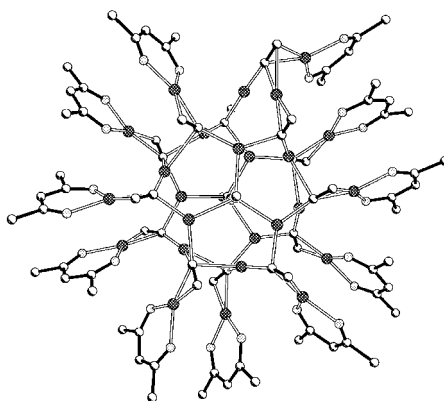
Angew. Chem. **2002**, *114*, 3162–3164

H.-g. Park,* B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew* 3036–3038

Highly Enantioselective and Practical Cinchona-Derived Phase-Transfer Catalysts for the Synthesis of α -Amino Acids

Keywords: alkylation • amino acids • cinchona alkaloids • phase-transfer catalysis • synthetic methods

A remarkably anisotropic structure is exhibited by $[\text{Cu}_{26}(\text{hfac})_{11}(1\text{-pentynyl})_{15}]$ (hfac = hexafluoroacetylacetone), the largest Cu^{I} cluster to have been isolated (see picture). A variety of copper–alkynyl bridging modes are found within the disc-shaped cluster, with all but one of the 26 Cu atoms being located in either of two “layers”. Many short $\text{Cu}^{\text{I}} \cdots \text{Cu}^{\text{I}}$ interactions can be discerned within the cluster.



Angew. Chem. **2002**, *114*, 3164–3167

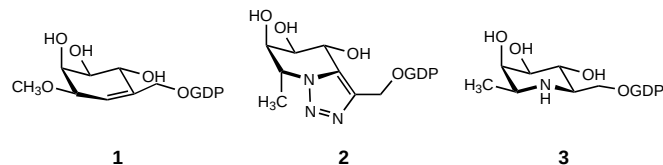
T. C. Higgs,* P. J. Bailey, S. Parsons, P. A. Tasker* 3038–3041

Facile Syntheses of Copper(I) Alkynyl Clusters Stabilized by Hexafluoroacetylacetonate (hfac) Ligands: The Structure of $[\text{Cu}_{26}(\text{hfac})_{11}(1\text{-pentynyl})_{15}]$

Keywords: alkyne ligands • cluster compounds • copper • metal–metal interactions • O ligands



Mimics of the geometry or charge of the fucose moiety of GDP-fucose in the transition state of fucosyltransferase-catalyzed reactions, compounds **1–3** are good competitive inhibitors of α -1,3-fucosyltransferases V and VI with K_i values between 6 and 13 μM . GDP = guanosine diphosphate.



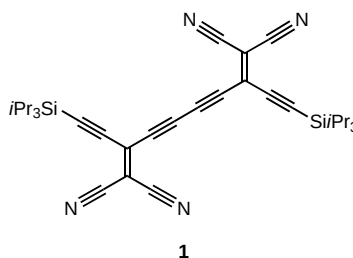
Angew. Chem. **2002**, *114*, 3167–3170

M. L. Mitchell, F. Tian, L. V. Lee, C.-H. Wong* 3041–3044

Synthesis and Evaluation of Transition-State Analogue Inhibitors of α -1,3-Fucosyltransferase

Keywords: carbocycles • enzymes • inhibitors • transition states • triazoles

Extended π -electron acceptors, such as **1**, have been constructed by the acetylenic scaffolding of a series of novel cyanoethynylethenes. Electrochemical analysis shows that acceptor strength is a function of π -electron conjugation length, and that a linear correlation exists between the electron affinities (B3LYP, 3-21G) and their first reduction potential.



Angew. Chem. **2002**, *114*, 3170–3173

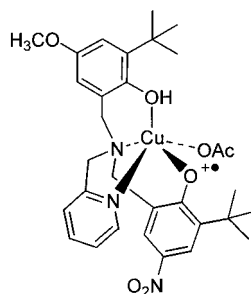
N. N. P. Moonen, C. Boudon, J.-P. Gisselbrecht, P. Seiler, M. Gross, F. Diederich* 3044–3047

Cyanoethynylethenes: A Class of Powerful Electron Acceptors for Molecular Scaffolding

Keywords: alkynes • conjugation • cyanoethynylethenes • cyclic voltammetry • electron acceptors



The axial phenol group is protonated and the equatorial phenoxyl group antiferromagnetically coupled to the cupric center in the complex $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+$ (see picture), which can be considered as both a structural and functional model of galactose oxidase. This complex reproduces the features of the enzyme chemistry. The phenoxyl radical position (equatorial versus axial) is dictated by protonation.



F. Thomas,* G. Gellon,
I. Gautier-Luneau, E. Saint-Aman,
J.-L. Pierre 3047–3050

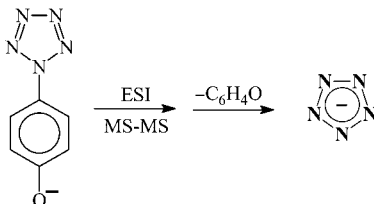
A Structural and Functional Model of Galactose Oxidase: Control of the One-Electron Oxidized Active Form through Two Differentiated Phenolic Arms in a Tripodal Ligand

Keywords: copper • enzyme models • N ligands • oxidation • radicals

Angew. Chem. **2002**, *114*, 3173–3176



The long-sought pentazolate anion, cyclo-N_5^- , the isoelectronic polynitrogen counterpart of the cyclopentadienide anion, has been experimentally detected for the first time. Using electrospray ionization mass spectrometry and carefully selected collision voltages, the aryl substituent in the *para*-pentazolyphenolate anion can be removed selectively without breaking the nitrogen–nitrogen bonds of the pentazolate anion (see scheme), thus delineating a synthetic method for the bulk synthesis of N_5^- .



A. Vij,* J. G. Pavlovich, W. W. Wilson,
V. Vij, K. O. Christe * 3051–3054

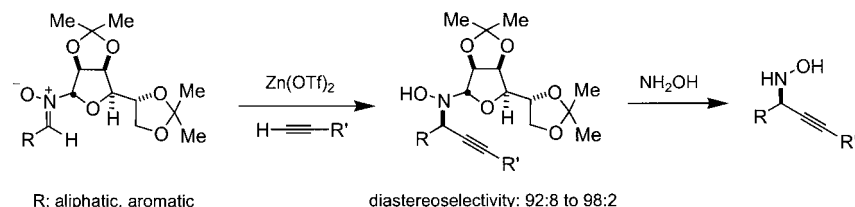
Experimental Detection of the Pentaazacyclopentadienide (Pentazolate) Anion, cyclo-N_5^-

Keywords: mass spectrometry • nitrogen • pentaazacyclopentadienide anion • pentazolate anion

Angew. Chem. **2002**, *114*, 3177–3180



In situ generation of nucleophilic alkynilides by using substoichiometric amounts of $\text{Zn}(\text{OTf})_2$ (OTf = trifluoromethanesulfonate) followed by removal of the chiral auxiliary enables the direct use of a wide range of terminal acetylenes in the synthesis of optically pure propargylic *N*-hydroxylamines (see scheme).



R. Fässler, D. E. Frantz, J. Oetiker,
E. M. Carreira * 3054–3056

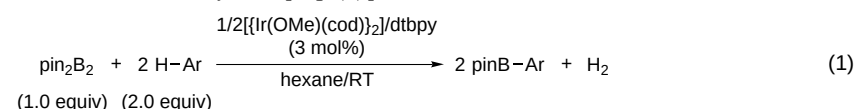
First Synthesis of Optically Pure Propargylic *N*-Hydroxylamines by Direct, Highly Diastereoselective Addition of Terminal Alkynes to Nitrones

Keywords: acetylides • diastereoselectivity • glycosylnitrones • hydroxylamines • zinc

Angew. Chem. **2002**, *114*, 3180–3182



Room-temperature C–H borylation using a stoichiometric amount of arenes and bis(pinacolato)diboron (pin_2B_2) is efficiently catalyzed by iridium(III) complexes generated from $[\text{Ir}(\text{OMe})(\text{cod})_2]$ (cod = 1,5-cyclooctadiene) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) in hexane, and provides the corresponding arylboronates in excellent yields [Eq. (1)].



T. Ishiyama,* J. Takagi, J. F. Hartwig,
N. Miyaura * 3056–3058

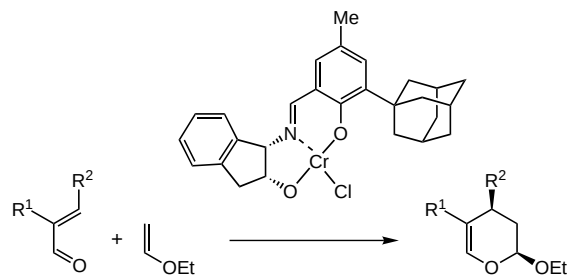
A Stoichiometric Aromatic C–H Borylation Catalyzed by Iridium(III)/2,2'-Bipyridine Complexes at Room Temperature

Keywords: arenes • boron • C–H activation • homogeneous catalysis • iridium

Angew. Chem. **2002**, *114*, 3182–3184



Straightforward access to useful synthetic intermediates is provided by this new method. Simple, α,β -unsaturated aldehydes are excellent substrates in the hetero-Diels–Alder reaction with inverse electron demand, catalyzed by Cr^{III} –Schiff base complexes (see scheme; R^1 , R^2 = alkyl or aryl) in the presence of 4-Å molecular sieves and no solvent. The resulting dihydropyrans are obtained in high enantio- (89–98% *ee*) and diastereoselectivity (>95% *de*) and yield (40–95%).



Angew. Chem. **2002**, *114*, 3185–3187



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



Accelerated publications

K. Gademann, D. E. Chavez,
E. N. Jacobsen* 3059–3061

Highly Enantioselective Inverse-
Electron-Demand Hetero-Diels–Alder
Reactions of α,β -Unsaturated Aldehydes

Keywords: asymmetric catalysis •
chromium • cycloaddition •
dihydropyran • hetero-Diels–Alder

* Author to whom correspondence should be addressed



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Bernard Valeur

J. Querner, T. Wolff 3063

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Eric Croddy, Clarisa
Perez-Armendariz,
John Hart

E. Geißler 3064

Science, Truth, and Democracy

Philip Kitcher

M. Weisberg 3064

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Shigeo Nishimura

T. Mallat 3066



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V. Wittmann 3067

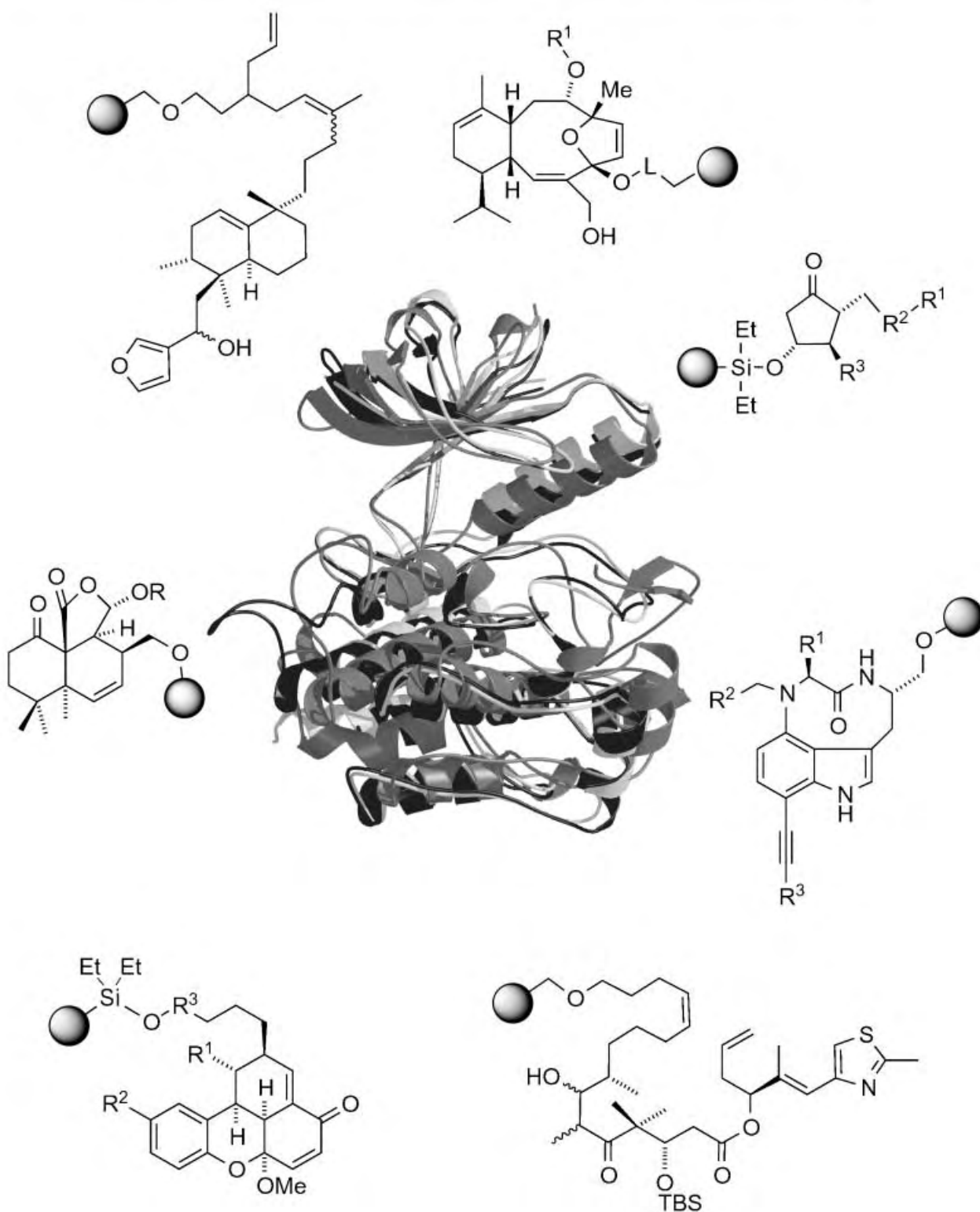
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From Protein Domains to Drug Candidates



From Protein Domains to Drug Candidates—Natural Products as Guiding Principles in the Design and Synthesis of Compound Libraries

Rolf Breinbauer, Ingrid R. Vetter, and Herbert Waldmann*

In the continuing effort to find small molecules that alter protein function and ultimately might lead to new drugs, combinatorial chemistry has emerged as a very powerful tool. Contrary to original expectations that large libraries would result in the discovery of many hit and lead structures, it has been recognized that the biological relevance, design, and diversity of the library are more important. As the universe of conceivable compounds is almost infinite, the question arises:

where is a biologically validated starting point from which to build a combinatorial library? Nature itself might provide an answer: natural products have been evolved to bind to proteins. Recent results in structural biology and bioinformatics indicate that the number of distinct protein families and folds is fairly limited. Often the same structural domain is used by many proteins in a more or less modified form created by divergent evolution. Recent progress in solid-phase organic

synthesis has enabled the synthesis of combinatorial libraries based on the structure of complex natural products. It can be envisioned that natural-product-based combinatorial synthesis may permit hit or lead compounds to be found with enhanced probability and quality.

Keywords: bioorganic chemistry • combinatorial chemistry • natural products • protein structures • solid-phase synthesis

1. Introduction

The completion of the Human-Genome Project has outlined the map for further expeditions towards providing a complete understanding of cellular processes at the molecular level. In particular, the nature, function, and amount of the proteins that are actually expressed in cells under particular conditions (proteomics), their interplay, and their interactions with supramolecular structures such as membranes and the cytoskeleton are of paramount interest. Recently, efforts have been initiated to determine the structures of all protein folds coded/expressed by the human genome by X-ray crystallography and NMR spectroscopy (structural genomics).^[1] The structural determination is crucial for an understanding of the

function of the proteins and will certainly help to achieve the ultimate goal: altering protein function by small molecules, which either selectively inhibit or activate a particular protein.^[2] Combinatorial chemistry will become the method of choice to undertake this herculean task. Herein we propose and discuss the argument that in the almost indefinite space of conceivable chemical compounds,^[3] natural products are viable, biologically validated starting points for library design. In this context, natural products are defined as all low-molecular-weight chemical compounds that are synthesized by biological organisms. Such natural-product-based libraries should permit hit or lead compounds to be found with enhanced probability and quality if these libraries are included in high-throughput screening.^[4, 5]

[*] Prof. Dr. H. Waldmann, Dr. R. Breinbauer

Department of Chemical Biology
Max-Planck-Institut für molekulare Physiologie
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)
and
Fachbereich 3, Organische Chemie, Universität Dortmund
44221 Dortmund (Germany)
Fax: (+49) 231-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de

Dr. I. R. Vetter
Department of Structural Biology
Max-Planck-Institut für molekulare Physiologie
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)

1.1. Disillusionment in Combinatorial Design

The hype of combinatorial chemistry as a tool in the pharmaceutical industry at the beginning of the 1990s has turned into a disappointment at the turn of the millennium. The original expectation that the synthesis of libraries that contain millions of compounds would produce as many or even more drug candidates as historical libraries of pharmaceutical companies and that it would thereby overcome the problem of efficient hit and lead finding has not been fulfilled.

Even worse, some of the libraries contained hardly any hit structures. Clearly the underlying structure of the individual library members was not biologically relevant. It was soon recognized that the number game would not determine the quality of a library; the quality would be determined by its “diversity”^[4] and its “drug-likeness”^[6, 7]—qualitative parameters that are now being considered in current library design.

From this disillusioning experience, an intense and urgent demand was born to find efficient and new guiding principles for a significant improvement in library quality and the quest for library types that are biologically relevant and yield high hit and lead rates. In developing new concepts and logic for meeting this demand, the central and crucial tasks are to identify compound classes that represent already biologically validated starting points in structural space, to find a synthetic

access to them that is amenable to combinatorial variation, and to design and synthesize combinatorial libraries centered on the identified underlying structural framework of these compound classes. In this Review we delineate arguments for a structure-based approach to this fundamental problem; the key feature of this approach is the use of the structural frameworks of biologically active natural products that have undergone evolutionary selection for binding to specific protein domains.

2. Protein Folding and Protein Function

Proteins can be regarded as modularly built biomolecules assembled from individual building blocks. These building

Herbert Waldmann, born in 1957, received his Dr. rer. nat. in 1985 under the supervision of Prof. H. Kunz at the University of Mainz (Germany). After postdoctoral studies at Harvard University with Prof. G. Whitesides (1985–1986) and habilitation (1991, University of Mainz) he accepted a professorship at the University of Bonn (Germany) in 1991. In 1993 he moved to the University of Karlsruhe (Germany) as a Full Professor of Organic Chemistry. In 1999 he was appointed as Director at the Max-Planck-Institut für molekulare Physiologie, Dortmund (Department of

Chemical Biology) and as Full Professor of Biochemistry at the University of Dortmund (Germany). Herbert Waldmann has been the recipient of the Friedrich Weygand Award for the advancement of peptide chemistry, of the Carl Duisberg Award of the Gesellschaft Deutscher Chemiker, the Otto Bayer Award, and the Steinhöfer Award of the Steinhöfer Foundation. His current research interests include bioorganic chemistry and natural-product synthesis as well as biocatalysis, stereoselective synthesis, and combinatorial chemistry. A major focus of the research activities is on the combination of organic chemistry, biophysics, and biology for the synthesis and biological evaluation of peptide and protein conjugates that are involved in biological signal-transduction processes. More recently, syntheses of natural products and natural-product-derived compound libraries on polymeric supports have been investigated (further information: <http://www.mpi-dortmund.mpg.de>).



H. Waldmann



I. Vetter



R. Breinbauer

Ingrid Vetter, born in 1963, studied biology in Frankfurt, Main (Germany). After completing her degree with Prof. H. Fasold/Prof. H. Rüterjans in 1987, she moved to Heidelberg (Germany) to join the group of Prof. P. Rösch. Her thesis describes NMR spectroscopic studies of adenylate kinase. In 1991, she started postdoctoral work in the field of crystallography in the group of Prof. D. Tsernoglou (EMBL, Heidelberg, Germany). After a 20-month postdoctoral stay in the group of Prof. B. Matthews (University of Oregon, Eugene, USA) she joined the Max-Planck-Institut für molekulare Physiologie, Dortmund (Germany) as a group leader in the department of Prof. A. Wittinghofer, where she is currently working. Her current research interests include the structural investigation of nuclear transport proteins and molecular modeling.

Rolf Breinbauer was born in Schärding (Austria) in 1970. He studied chemistry at the Technical University of Vienna (Austria) and the University of Heidelberg (Germany), where he completed his degree under the supervision of Prof. G. Helmchen in the field of asymmetric catalysis. During his doctoral studies (1995–1998) with Prof. M. T. Reetz at the Max-Planck-Institut für Kohlenforschung (coal research) in Mülheim an der Ruhr (Germany) his research interests focused on the synthesis and catalytic applications of transition-metal colloids. From 1998–1999 he worked as a Erwin Schrödinger fellow in the laboratory of Prof. E. N. Jacobsen at Harvard University (USA) where he studied cooperative effects in asymmetric catalysis. In 2000 he moved as a Liebig fellow to Dortmund where he leads a group in the Department of Chemical Biology at the Max-Planck-Institut für molekulare Physiologie and the Institute of Organic Chemistry at the University of Dortmund (Germany). His research interests include the development of new synthetic methods and its applications in solid-phase synthesis and combinatorial chemistry.

blocks are called “domains”, parts of the proteins that fold independently from the rest of the structure to a compact arrangement of secondary structures (such as α -helices, β -sheets, or β -turns) and that are connected through more or less complex linker peptides. The term “domain family” in this Review refers to a family of related sequences that have a common ancestor and that have developed through divergent evolution. Different sequence families (i.e. domains) can have the same fold (Figure 1), which could be regarded either as convergence caused by functional and physical constraints or as a result of divergent evolution.^[8] Domains are structurally conserved units, but can be genetically mobile.^[9]

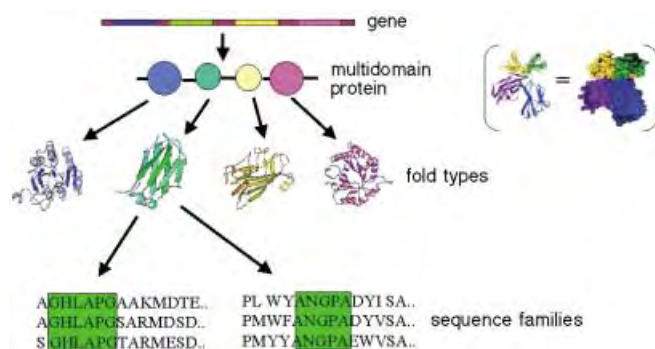


Figure 1. Modular build-up of multidomain proteins.

Although the estimate for the number of different proteins in humans range between 100 000 and 450 000, there is a common agreement that the number of domain families and—above all—of topologically distinct folds will be much smaller. At present approximately 600 fold types are known,^[10] derived by classifying all structurally characterized proteins according to their three-dimensional structure.^[11, 12] Data from the ongoing genome sequencing projects allow the number of existing folds and families in Nature to be estimated. Current estimates vary between 600 and 8000 distinct folds, and 4000–60 000 sequence families.^[12c, 13, 14]

There is an ongoing effort to understand the correlation between protein function and protein sequence.^[9a, 15] Especially the increasing amount of data from genome-sequencing projects, evaluated with the tools of bioinformatics, allow a faster recognition of patterns than the more elaborate method of structural genomics (which tries to deduce the function from structure) would be able to do by itself.^[9] Although we are still far from a deep and consistent understanding, and analysis is hampered by the small number of available X-ray structures of proteins with bound small-molecule binders,^[16] some interesting observations have been made, and the following remarks should serve to give an overview about the diversity and evolutionary relationships of ligand-binding sites in proteins.^[17]

2.1. Similar Folds Bind Similar Ligands—A Concept and Its Limitations

In many examples it has been confirmed that protein families can have similar folds even though they at first seem

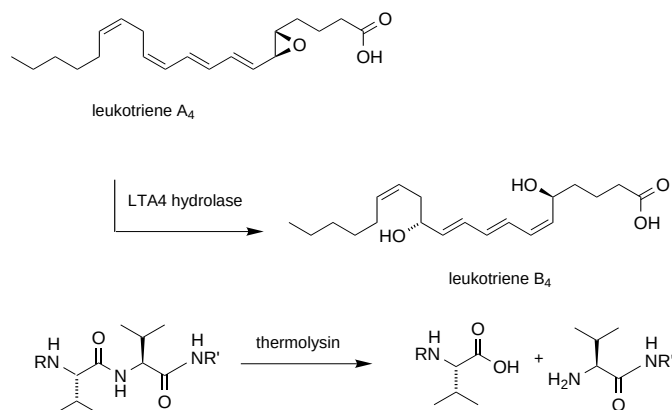
to have completely different sequences and/or catalyze quite different chemical reactions with a different arrangement of active-site residues. However, these protein families did evolve from the same ancestors and can still bind similar ligands.^[18] Since the sequence homology is sometimes weak or not recognizable, the detection of these cases is not necessarily straightforward.

A striking example is leukotriene A4 hydrolase/aminopeptidase (LTA4H), a bifunctional enzyme whose aminopeptidase functionality is combined with an additional function, namely the vinylogous hydrolysis of the leukotriene epoxide LTA4 into LTB4. Both reactions are catalyzed in the same Zn-containing active site.^[19a] In this case, the presence of some short conserved sequence elements was sufficient to prompt investigations of the relationship of this enzyme to metalloproteases.^[19e] The evolutionary relationship of the LTA4H fold (which was unknown at the time) to M1 metalloproteases would have immediately suggested that peptidase inhibitors be investigated as potential ligands. Indeed, the aminopeptidase inhibitor bestatin also inhibits LTB4 biosynthesis.^[19e] This result and the related observation that captopril, an inhibitor of the angiotensin-converting enzyme (which is also a metalloprotease), also inhibits LTA4H,^[19e] have inspired the variation of these lead structures, which led to the syntheses of molecules that inhibit LTA4H in the nanomolar range.^[19b–d] Subsequent determination of the structure of LTA4H and comparison with thermolysin, confirmed that both enzymes exhibit the same fold (Figure 2, Scheme 1). In fact, the fold structure of the catalytic domain of LTA4H is also adopted by the peptidases aureolysin, neprilysin, and elastase.



Figure 2. Overlay of the X-ray structure of LTA4H (red) and thermolysin (blue).

Empirical observations show that related sequences have similar folds. This does not mean, however, that the active sites have to be built up by sequentially homologous residues: a thorough comparative X-ray analysis of enzymes of the enolase superfamily (enolase, muconate lactonizing enzyme,



Scheme 1. LTA4 hydrolase and thermolysin exhibit the same fold and are both inhibited by bestatin, but catalyze two different reactions.

and mandelate racemase) by Petsko and co-workers led to the discovery of common features in the design of the active site. They found that the abstraction of the α proton of a carboxylic acid plays a crucial role in the overall reaction sequence.^[20] Although the residues that contain the catalytic atoms are located at different points in the protein fold and their identity and roles in catalysis vary, the position of catalytic groups relative to the substrate remains constant. Indeed, the three enzymes share some significant sequence homologies, have a similar fold, and are thus assumed to belong to the same protein family. Although they would not have been classified as belonging to the same functional target family because they catalyze different reactions, their common evolutionary relationship revealed by the similar structures would have allowed a rational lead search for ligands that would bind to the active sites with their common features.

This approach based on sequence analysis promises that in the long run the process from gene identification to lead discovery may be shortened and accelerated significantly.^[21] For instance, the analysis of a newly discovered gene by bioinformatic tools may suggest that the corresponding protein will be a multidomain protein composed of already known domains.^[22] If ligands for these domains are already known, then these can serve as starting points for the design and synthesis of libraries that target the protein product of the desired gene (Figure 3). This inhibitor development could be initiated without further information on the three-dimensional structure of the protein product, which can usually be obtained by X-ray crystallography or NMR spectroscopy, and even without further knowledge about its biological functions, binding partners, etc., which are usually obtained by biochemical and cell biological techniques.

A case in which the “similar folds bind similar ligands” approach will fail is when divergent evolution has proceeded too far, so that the similarities in the binding site are completely obscured.^[17a] However, even in those cases some similarities might remain, for example, the position of the binding site in a fold. This has led to the introduction of the term “supersites”, for example, in the ferredoxin-like fold.^[23] A potential supersite can also be observed in the cystatin-like fold (Figure 4). These similarities are thought to be the result of divergent evolution.^[24] Even if the diversity in the binding

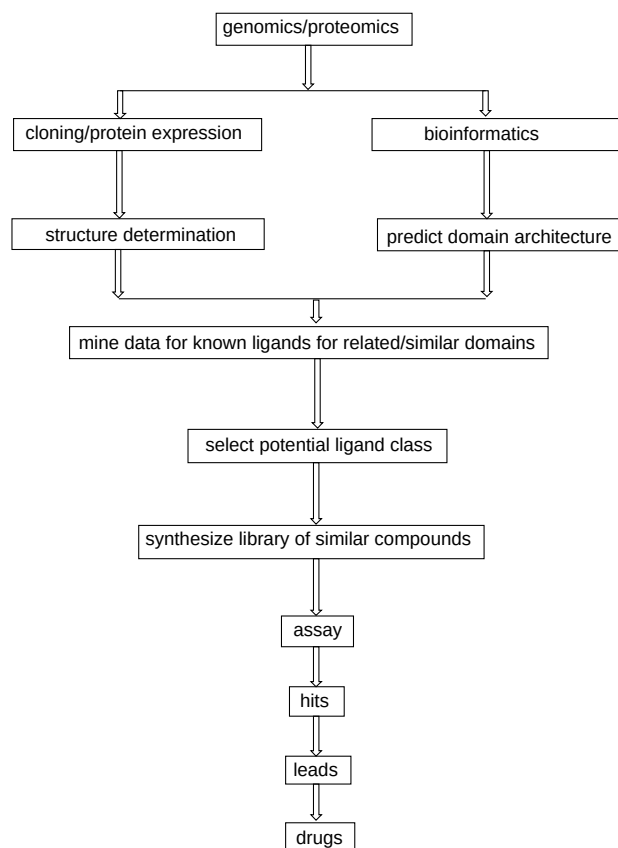


Figure 3. Influence of sequence analysis in the drug-finding process.

site cannot be addressed by a combinatorial library built around a single scaffold, the evolutionary relationship, if known, could provide hints about which other leads should be tested.

In summary, the advantage of the domain family classification over the conventional, functional classification of target families (kinases, proteases, phosphatases, etc.) is that the former can be solely derived from sequence information. This can be very helpful in the initial stages of screening when little is known about the protein. In this case, all existing ligands that bind to sequentially related proteins could be tried; in the example described above, the peptidase inhibitor bestatin could be tried against the leukotriene A₄ hydrolase.

2.2. Different Folds Bind the Same Ligand—Privileged Structures

The term “privileged structure” was originally coined by the group of B. E. Evans at Merck who recognized in their pharmacological studies of benzodiazepines,^[25] that derivatives within this compound class bind not only to benzodiazepine receptors of the central nervous system, but also to cholecystikinin receptors, although the natural substrates showed little resemblance to this compound class. A third class of unrelated receptors that bind benzodiazepines are the peripheral benzodiazepine receptors. As peptidomimetics, benzodiazepines can be assumed to have an intrinsic good

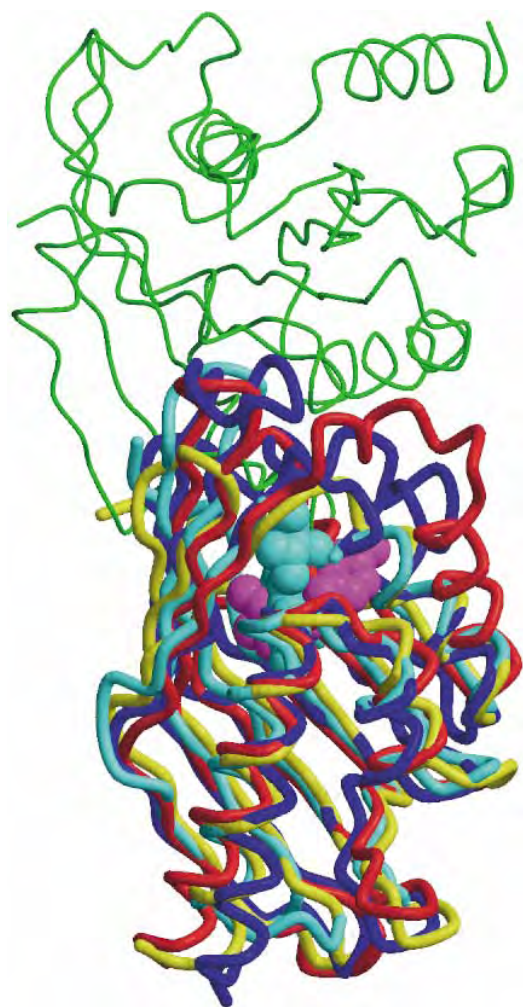


Figure 4. Proteins that embody the cystatin fold. Turquoise: Δ^5 -3-ketosteroid isomerase complexed with the reaction intermediate equilenin (PDB code 4TSU); blue: scytalone dehydratase complexed with the inhibitor carpropamid (pink; PDB code 2STD); red: naphthalene 1,2-dioxygenase β -subunit (no bound ligand; PDB code 1EG9); yellow: NTF2 complexed with Ran (green; PDB code 1A2K).

binding affinity to several proteins that bind similar regions of peptides or other proteins. According to the definition of Evans, privileged structures are a compound class that can bind to various protein-receptor surfaces.

3. Natural Compounds and Privileged Structures

Natural products very often embody privileged structures according to the definition described in Section 2.2, since they are synthesized or modified by different proteins (and thus have to bind to them), and their function might involve binding to other proteins as well. Examples include nucleotide triphosphates (NTPs), which bind (among many other proteins) to P-loop-containing NTP hydrolases (the fourth most frequent domain in the current human genome database), to protein kinases (fifth most common), to the actin-like domain, and to many others. NTPs are thus bound by a plethora of different proteins that have either similar or different folds

(Figures 5 and 6).^[26] In the cases of different folds (e.g. the P-loop-containing NTP hydrolases and the protein kinases), the similar shape and properties of the binding pockets for the nucleotide in the different scaffolds are

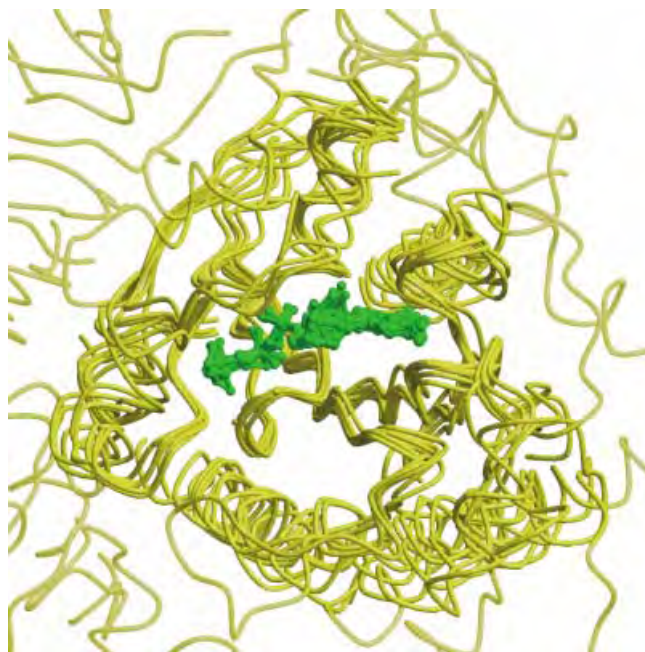


Figure 5. Overlay of the GTP-binding sites of some known X-ray structures of GTP-binding proteins, including small GTP-binding proteins, heterotrimeric G proteins, and the elongation factor Tu. The nucleotides are shown in green, the protein backbones in yellow.

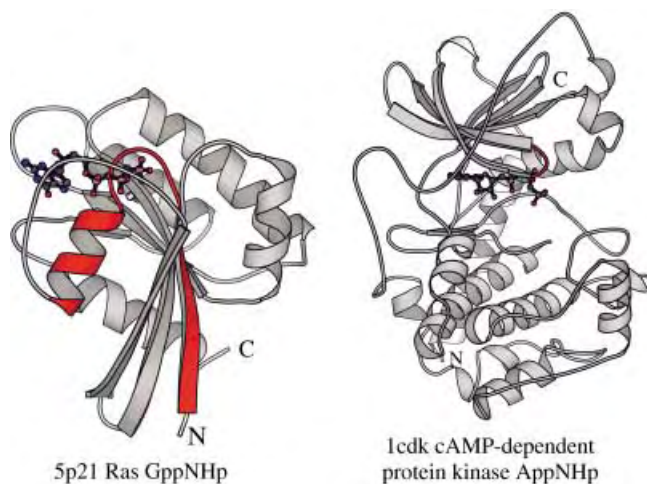


Figure 6. NTP-binding sites in two different folds: Ras (left) and protein kinase C (right).

most likely the result of convergent evolution (for instance the protein kinases and P-loop-containing NTPases both have a glycine-rich motif to bind the phosphates of the nucleotide, but have a different arrangement of glycine residues).^[27]

It is thus likely that more exploitable privileged structures such as the peptidomimetic benzodiazepine might be found among the evolutionarily selected ligands that bind to

particular binding pockets or folds that have also been selected by Nature in its effort to use modular domains to render evolution more efficient.

When looking for privileged structures among natural substances the question arises as to why natural products from different organisms have (often unexpected) effects in humans and why the hit rates in high-throughput screens determined for natural-product collections are often dramatically higher than the rates found for large classical libraries obtained from combinatorial chemistry.^[28] Two cases can be distinguished: natural products might bind by chance to particular human proteins or they were selected by evolution to bind to a protein similar to a human protein. The latter case is quite likely given the close relationship of the genomes of all organisms. Furthermore, one can assume that at least most of the substances synthesized have a purpose for the organism that produces it. Many plants synthesize alkaloids to protect themselves from being eaten by animals, especially mammals. Therefore, the alkaloids have evolved to bind to mammalian proteins and to be poisonous to the corresponding organisms. Such alkaloids include drugs such as morphine, nicotine, ephedrine, strychnine, quinine, and atropine. Other examples are the venom of snakes, frogs, or spiders which are designed to poison or to paralyze mammals. Among other targets, these poisons are active against ion channels in mammalian nerve-cell membranes.

Drugs such as cyclosporin, FK506, and rapamycin are probably synthesized for the chemical defense of the organisms that produce them.^[29] There are proteins that are homologous to the human proteins involved in immunosuppression, for example, in yeast. Therefore, it is not accidental that those substances are active against human proteins, although with a quite different functions in the end.

A given scaffold can thus be privileged in a chemical sense, that is, a scaffold with the necessary compromise of flexibility and rigidity combined with the ability to present functional groups in a favorable arrangement (e.g. biphenyl compounds). Second, and maybe additionally, it may be privileged in a biological sense in that it mimics natural compounds, which very often bind to different protein domains. An example is the protein-kinase inhibitor genistein, which is a competitive inhibitor of ATP binding by protein tyrosine kinases (PTK), but also inhibits topoisomerase II and 1-phosphatidylinositol 4-kinase and interacts with the estrogen receptor.^[30] A privileged core structure is a basis for finding good protein binders, but an optimization along this core scaffold will be necessary to improve both the binding affinity and selectivity. Not necessarily, but surprisingly often, certain natural substances exhibit already advantageous pharmacokinetic properties as well. This appears to be logical because in a biological environment (e.g. after production by a particular organism to defend itself) they must find their way to the final target protein inside other organisms. The importance of natural products in drug discovery and development is reflected by the fact that close to half of the best-selling pharmaceuticals are either natural products or derivatives thereof.^[31–33] Their role is even

more prominent in antibacterial, immunosuppressant, and anticancer drugs.

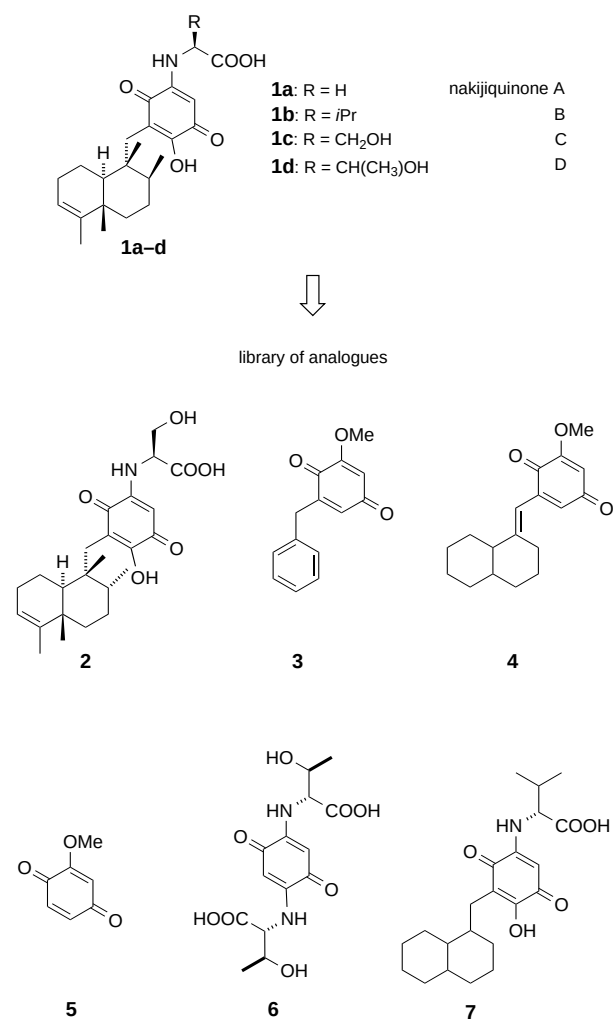
4. Biologically Validated Starting Points for Library Design

If ligand types or frameworks for certain domain families are already known from the investigation of evolutionarily related proteins, then the underlying structure of this ligand may be employed as the guiding principle for library development. Such ligands would provide targeted, biologically validated starting points in structural space for focused library development. As detailed above, natural products are such biologically validated structural entities.

Libraries designed and synthesized around the basic structure of natural products should yield modulators of protein activity with high hit rates with significantly reduced library size. Within a group of closely related protein domains, the details of the structure usually vary substantially, which provides the basis for selective binding and inhibition (e.g. in the ATP-binding sites of protein kinases). Therefore, the stereochemistry and substitution pattern of the chosen underlying framework should be varied. It is not necessary and probably even counterproductive to build up a given natural structure slavishly in every structural detail.

The structure-based concept delineated above differs in its fundamental reasoning from related approaches that focus on the creation of chemical diversity. It does not neglect this issue, however, and builds on the diversity created by Nature itself. This approach, therefore, offers the opportunity to identify new privileged structures from Nature, which may prove broadly usable for various applications in chemical biology and biomedicine.

The validity of this approach was demonstrated by Waldmann and Giannis and their co-workers.^[34] Nakijiquinones **1a–d** (Scheme 2) are the only known naturally occurring inhibitors of the Her-2/Neu receptor tyrosine kinase, which is overexpressed in about 30% of primary breast, ovary, and gastric carcinomas. In light of the concept described above a library of 56 analogues of this lead structure was synthesized and screened for its inhibitory activity against other receptor tyrosine kinases involved in cell signaling and proliferation, such as the vascular endothelial growth-factor receptors (VEGFR1–3), the Tie-2-receptor, the insulin-like growth-factor 1 receptor (IGF1R), and the epidermal growth-factor receptor (ErbB-1). Whereas none of the natural products **1a–d** exhibited significant inhibitory activity against the new set of receptor kinases, six members of the library of analogues were identified as kinase inhibitors in the low micromolar range (Scheme 2, Figure 7, and Table 1). In particular, a structural pattern emerged that may allow the Tie-2 receptor kinase to be targeted selectively, which is of paramount importance in the regulation of blood-vessel formation and therefore in cancer development. This result stresses the importance of combinatorial libraries based on natural products, in contrast to using only the natural substances by themselves. If only natural substances had been screened, this inhibitor would have been missed.



Scheme 2. Compounds **2–7** of a 56-membered library of nakijiquinone analogues.

5. Solid-Phase Synthesis of Natural-Product Libraries

Paramount to the success of this library-design approach is that efficient and reliable methods and multistep sequences for the total synthesis of natural products and their analogues on polymeric supports are available. The corresponding transformations must proceed with a degree of selectivity and robustness typical of related classical solution-phase demands imposed by the anchoring to the polymeric support.

The generation of libraries of natural-product analogues has received increasing attention during the last five years. As this subject has been reviewed just recently,^[35] we specifically want to focus on solid-phase syntheses that involve the construction of entire molecular skeletons as opposed to subsequent derivatization of preformed and then immobilized natural-product cores. We present this field with a few selected examples, which represent the state of the art of this discipline and also mark the current frontiers.

Epithilones are natural products isolated from myxobacteria, which have been found to exhibit cytotoxic activity

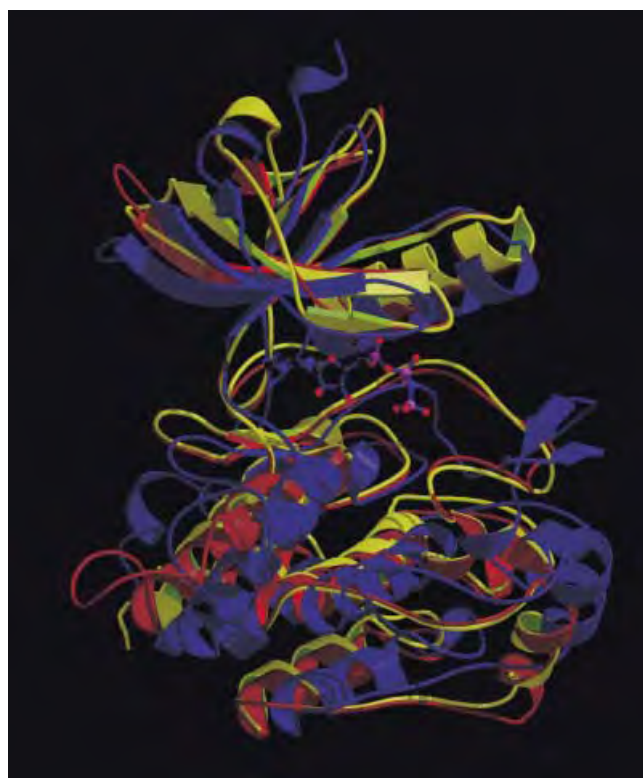


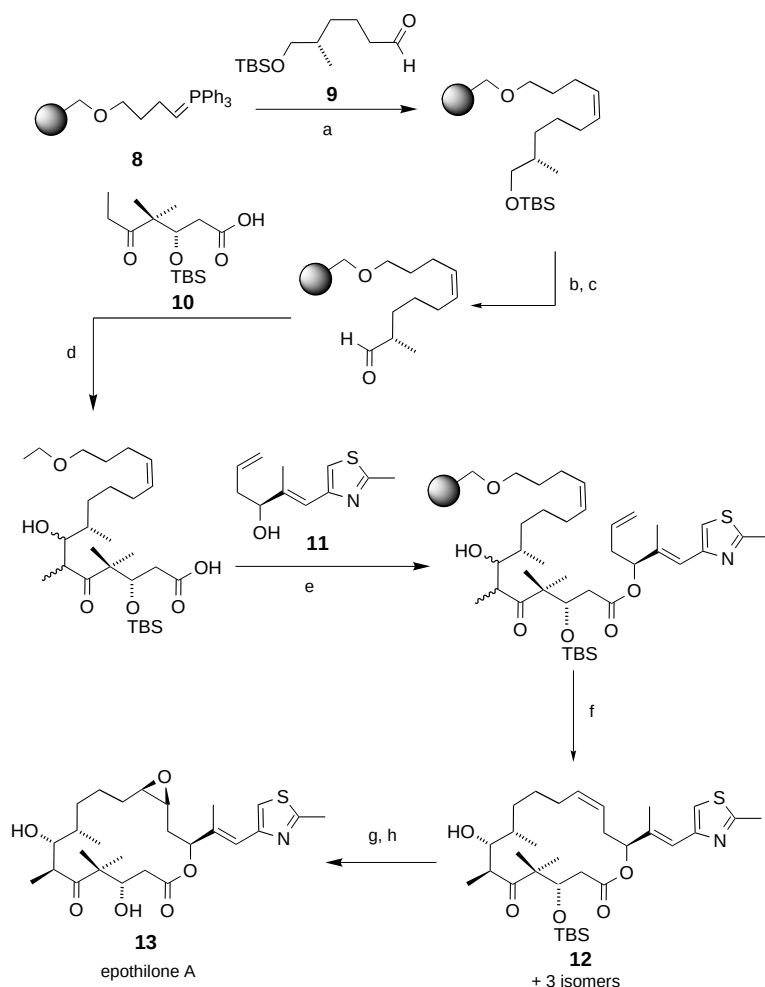
Figure 7. Overlay of receptor tyrosine kinases inhibited by the nakijiquinone-based library. Yellow: Tie-2 receptor kinase, red: VEGFR2, blue: IGF1R with a bound ATP analogue. (We thank Lars Kissau for preparing this figure.)

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

Compound	IC ₅₀ [μM] for the receptors					
	EGFR	ErbB-2	IGF1R	VEGFR-2	VEGFR-3	Tie-2
1a–d	–	–	–	–	–	–
2	–	–	–	21	–	–
3	–	–	–	–	–	18
4	–	–	–	–	–	14
5	–	29	–	8	–	–
6	–	–	6	–	3	5
7	–	–	0.5	–	–	9

against paclitaxel-resistant tumor cell lines by inducing tubulin polymerization. The successful synthesis of epithilone A by Nicolaou and co-workers represents a landmark in the synthesis of complex molecules on solid supports.^[36] A polymer-bound Wittig ylide **8** was further elaborated by olefination with **9**, aldol reaction with **10**, and esterification with **11** (Scheme 3). Following a very clever cyclo-release strategy, the acyclic precursor formed the macrocycle **12** through an olefin metathesis reaction mediated by the Grubbs catalyst. After two subsequent reactions in solution, epithilone A (**13**) was isolated. This example demonstrated for the first time the feasibility of multistep natural-product synthesis on solid supports. In a subsequent paper, Nicolaou et al. prepared a library of further analogues, which helped to establish structure–activity relationships of this compound class.^[36b]

Prostaglandins play a prominent role in a wide variety of physiological processes and exhibit a very subtle structure–



Scheme 3. Total synthesis of epothilone A on a solid phase by Nicolaou et al.: a) **9**, THF, 0 °C, 3 h; b) 10% HF·pyridine in THF, 25 °C, 12 h; c) (COCl)₂, DMSO, Et₃N, −78 °C→RT; d) **10**, LDA, THF, −78 → −40 °C, 1 h; e) **11**, DCC, DMAP, room temperature, 15 h; f) Grubbs catalyst, CH₂Cl₂, room temperature, 48 h, 30% yield of the desired isomer; g) TFA in CH₂Cl₂ (20%); h) methyl(trifluoromethyl)dioxirane, CH₃CN, 0 °C, 2 h. DMSO = dimethylsulfoxide, LDA = lithium diisopropylamide, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid, TBS = *tert*-butyldimethylsilyl.

activity relationship, which make them a target for combinatorial chemistry of foremost interest and significance. Ellman and co-workers disclosed the solid-phase synthesis of a 26-membered library of prostaglandin E₁ analogues (**14**). After modification of the core structure **15** by a Suzuki coupling with building block **16**, the relative stereochemistry of the two carbon centers that bear the side chains was set by a diastereoselective Michael addition of the higher-order cuprate **17** across the enone **18** (Scheme 4).^[37]

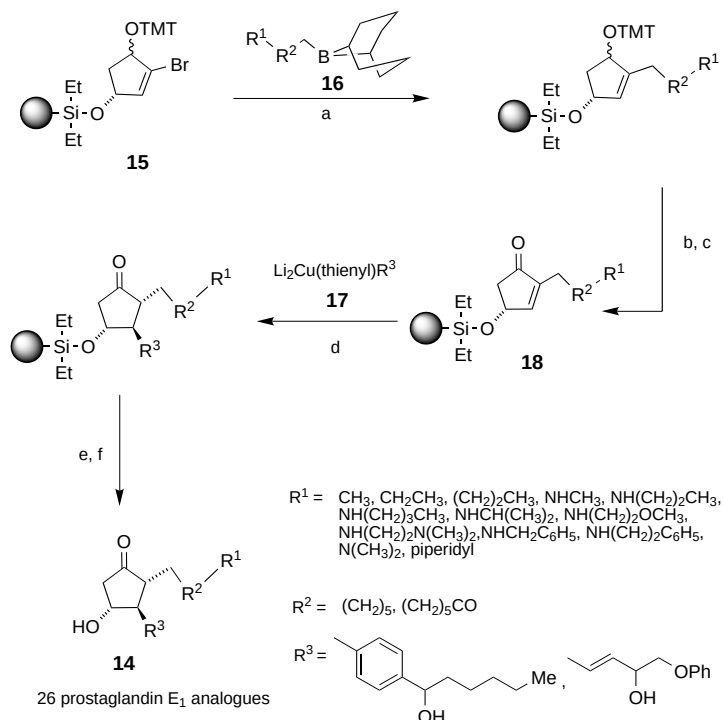
In an experimentally challenging effort, Shair and co-workers completed a biomimetic synthesis of carpanone-derived compounds **19** by a PhI(OAc)₂-mediated oxidative heterodimerization. In only three steps on a solid support, they were able to access a library of six different compounds of high structural complexity (Scheme 5). Shair and co-workers announced the preparation of a 100 000-membered library and high-throughput biological screens,

which will be received with great interest because of the biological activity of carpanone.^[38]

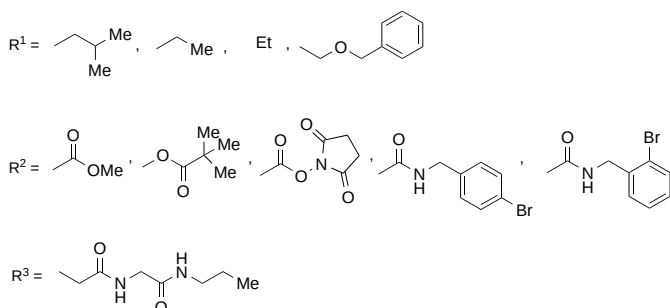
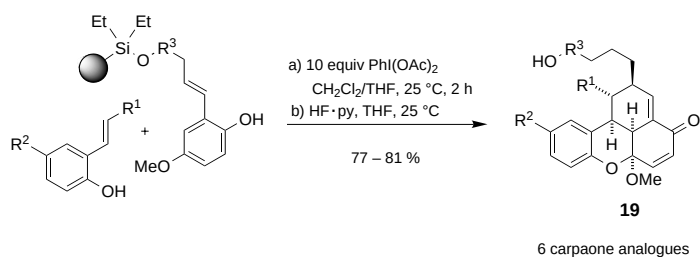
Sarcodictyins are a class of natural products that have received much attention by synthetic chemists recently owing to their structural complexity and especially because of their anticancer properties, originated by its paclitaxel-like mechanism of action in the tubulin–microtubulin interplay. Nicolaou et al. have built a library of sarcodictyin derivatives **20 a–c**. The complexity of the natural product prompted a strategy in which they prepared the core structure **21** of the target compound in solution, attached it to a solid support through an acid-labile linker, and then carried out further modifications on three different reactive entities of the core structure (Scheme 6). In their library of 22 derivatives, they identified compounds with biological activities superior than those of the parent structure and they also established a structure–activity relationship.^[39]

A similar approach of synthesizing the core structure in solution and then elaborating it on solid supports for further diversification was applied by Waldmann and co-workers in their synthesis of a 31-membered library of analogues **22** of the protein kinase C activator indolactam V (Scheme 7).^[40]

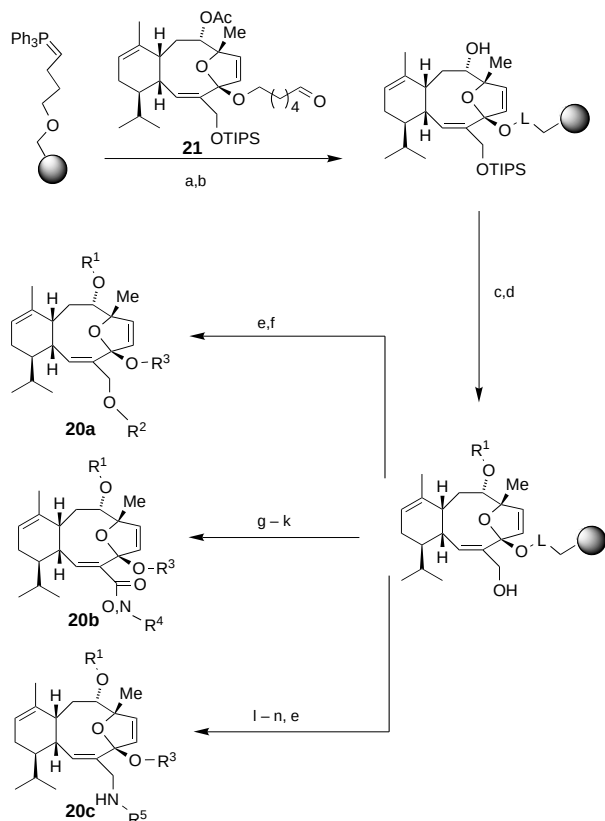
Waldmann and co-workers synthesized a library of analogues of the antitumor phosphatase inhibitor dysidiolide.^[41] A notable feature of this 11-step solid-phase reaction sequence is that a wide range of transformations with widely differing requirements



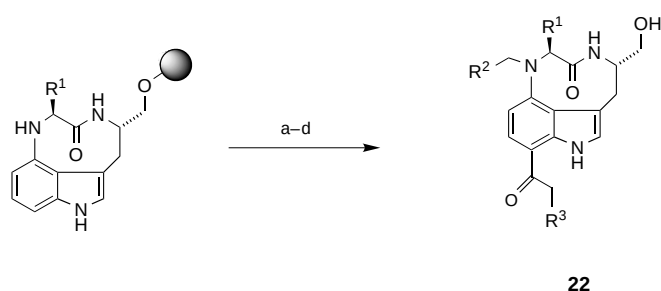
Scheme 4. Synthesis of a prostaglandin E₁ analogue library by Ellman et al.: a) [Pd(PPh₃)₄], Na₂CO₃, THF, 0 °C; b) HCOOH (1M), CH₂Cl₂, 5 min; c) Dess–Martin periodinane, CH₂Cl₂; d) THF, −78 → −20 → −78 °C, then AcOH/THF (10%); e) HF/pyridine in THF; f) TMSOMe. TMS = trimethylsilyl, TMT = trimethoxytrityl.



Scheme 5. Synthesis of a library of carpanone analogues by Shair et al.



Scheme 6. Synthesis of a library of sarcodictyin analogues by Nicolaou et al.: a) THF, $-78^{\circ}\text{C} \rightarrow \text{RT}$; b) NaOMe, MeOH; c) R^1X , Et_3N , DMF; d) TBAF, THF, 25°C ; e) R^2X , Et_3N , DMAP, CH_2Cl_2 , room temperature; f) PPTS, MeOH, room temperature; g) Dess–Martin periodinane, NaHCO_3 , pyridine, CH_2Cl_2 , room temperature; h) NaClO_2 , KH_2PO_4 , 2-methyl-2-butene, THF, THF/ $\text{tBuOH}/\text{H}_2\text{O}$ (5:5:1), 25°C ; i) HOR^4 , DEAD, Ph_3P , THF, $0 \rightarrow 25^{\circ}\text{C}$, 12 h; j) H_2NR^4 , DCC, DMAP, DMF, room temperature, 20 h; k) CSA, HOR^3 , room temperature, 15 h; l) $(\text{PhO})_2\text{PON}_3$, DEAD, Ph_3P , THF, $0^{\circ}\text{C} \rightarrow \text{RT}$, 4 h; m) Ph_3P , H_2O , THF, room temperature, 8 h; n) XR^5 , Et_3N , CH_2Cl_2 , room temperature, 10 h. DMF = *N,N*-dimethylformamide, TBAF = tetrabutylammonium fluoride, PPTS = pyridinium *p*-toluenesulfonate, DEAD = diethylazodicarboxylate, CSA = camphorsulfonic acid, TIPS = triisopropylsilyl



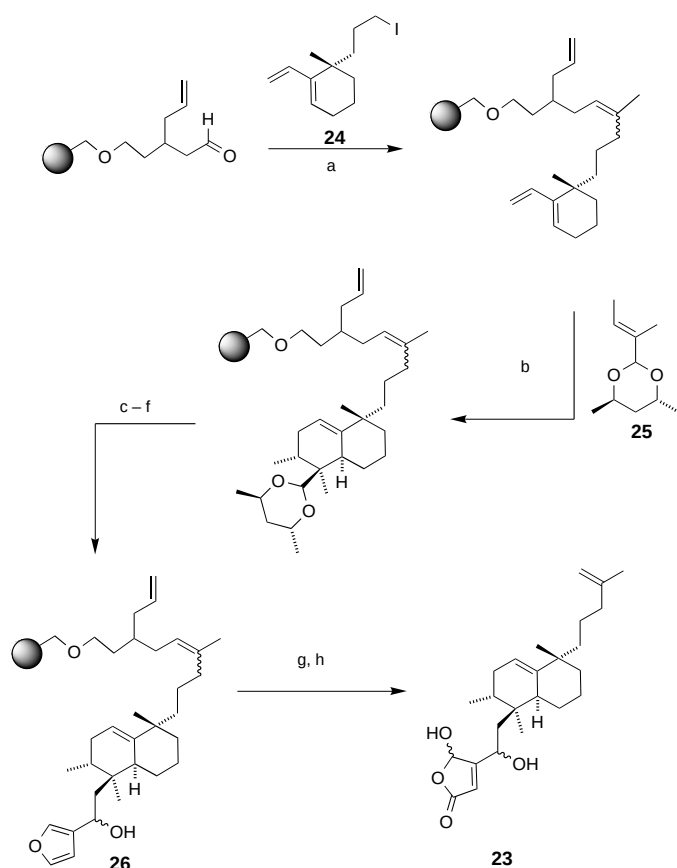
Scheme 7. Synthesis of a library of indolactam V analogues by Waldmann et al.: a) R^2CHO , $\text{NaBH}(\text{OAc})_3$, DMF/ AcOH (99:1), room temperature; b) I_2 , pyridine/1,4-dioxane, 0°C ; c) R^3CCH_3 , $[(\text{PPh}_3)_2\text{PdCl}_2]$, CuI , Et_3N , 1,4-dioxane, room temperature; d) TFA/ H_2O (95:5).

could be developed successfully. Key transformations of the synthesis are an asymmetric Diels–Alder reaction with chiral dienophile **25**, oxidative elaboration with singlet oxygen of furan **26** on a solid support, and complete cleavage of the products from the solid support by means of olefin metathesis (Scheme 8). The sequence rapidly yielded access to nine analogues of the natural product and led to the identification of a potent inhibitor of the cell-cycle-controlling phosphatase *cdc25c*, which displays a very promising selectivity pattern. Contrary to the solid-phase synthesis of many other natural product, this synthesis builds up the natural-product framework on a solid phase in several steps, rather than immobilizing an advanced intermediate generated in solution as a scaffold and varying its substitution pattern on the solid support. Thus, it convincingly demonstrated that multistep total synthesis of natural products and close analogues on polymeric supports can be achieved.

Reiser and Jauch have recently paved the way for a solid-phase library synthesis of mniopetals, a compound class that has been shown to contain inhibitors of HIV reverse transcriptase.^[42] Notable features of their synthesis are the formation of adduct **27** through a Baylis–Hillman reaction and its further elaboration by an intramolecular Diels–Alder reaction into **28** (Scheme 9).

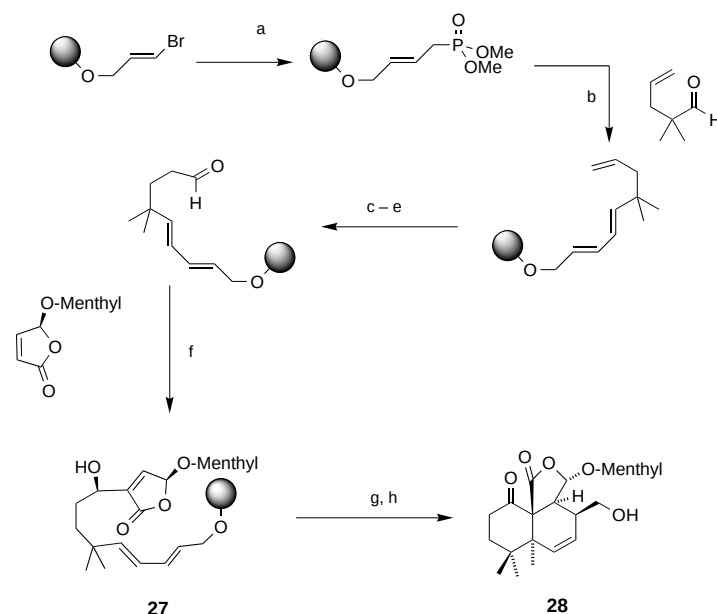
6. Alternative Approaches

The approach delineated in this article is only one new concept among others. For instance, in recent years in silico methods have gained much interest in the development of new and more efficient approaches to hit and lead identification.^[43] Among the different concepts currently under evaluation, diversity-oriented synthesis introduced by Schreiber and co-workers is conceptually related to natural-product-based library design.^[44] Diversity-oriented synthesis for chemical genetics aims at libraries of compounds with huge three-dimensional structural complexity, functionality, and diversity; in this sense, these substances can be regarded as “natural-product”-like.^[45] Whereas natural-product libraries are motivated by a biologically validated starting point in the conformational and structural space of potential protein

9 6-*epi*-dysidiolide analogues

Scheme 8. Synthesis of a library of 6-*epi*-dysidiolide analogues by Waldmann et al.: a) EtPPh_3I , $n\text{BuLi}$, **24**, THF, room temperature, 16 h, then $n\text{BuLi}$, 0°C ; b) TMSOTf , CH_2Cl_2 , -78°C , 5 h; c) PTSA , acetone, DCE, H_2O ; c) $(\text{Ph}_3\text{PCH}_2\text{OMe})\text{Cl}$, KOtBu , THF, room temperature, 2 h; d) PPTS , THF, H_2O (1%), reflux, 16 h; f) 3-bromofuran, $n\text{BuLi}$, THF, -78°C , 5 h; g) O_2 , Hünig base, bengal rose, $h\nu$, -78°C , CH_2Cl_2 ; h) Grubbs catalyst ($2 \times 10\%$), CH_2Cl_2 , room temperature, 16 h. OTf = trifluoromethanesulfonate, PTSA = *p*-toluenesulfonic acid, DCE = 1,2-dichloroethane.

binders, diversity-oriented synthesis addresses an area of compound diversity around a starting point that has been chosen by its mere chemical accessibility and “natural-product likeness”, that is, structural complexity (Table 2). In Table 2, the extreme positions for both approaches are listed; however, these two approaches are intertwined and for each combinatorial library synthesized so far, elements of both can be found, with variations only in the degree of expression.



Scheme 9. Synthesis of the central building block of a mniopetal library by Jauch et al.: a) $\text{P}(\text{OMe})_3$, 90°C , 48 h; b) $-80 \rightarrow -10^\circ\text{C}$, 12 h; c) 9-BBN (4 equiv), room temperature, 24 h; d) $\text{H}_2\text{O}_2/\text{NaOH}$, room temperature, 4 h; e) IBX, room temperature, 5 h; f) PhSeLi (5 equiv), $-60 \rightarrow -30^\circ\text{C}$, 12 h; g) Dess–Martin periodinane, 2,6-lutidine, CH_2Cl_2 , room temperature, 12 h; h) DDQ, room temperature, 40 min. IBX = *o*-iodoxybenzoic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 9-BBN = 9-boracyclo[3.3.1]nonane, Menthyl = (+)-menthyl.

Protein binders that would be found by screening such diversity-oriented libraries will be of complementary interest, because they might be based on scaffolds different from the known natural products. This may lead to the identification of unprecedented new scaffolds, for example, as in the discovery of benzodiazepines.

7. Conclusion and Outlook

The recent success in the generation of natural-product libraries has convincingly proven that solid-phase organic chemistry has reached a level that allows its application in natural-product synthesis. It is now possible to tackle complex synthesis targets that require double-digit numbers of individual chemical steps. Although the overall yields of the presented syntheses are highly respectable, the demand for

Table 2. Comparison of “natural-product-guided combinatorial synthesis” with “diversity-oriented combinatorial synthesis”.

Natural-product-guided	Diversity-oriented
● aims to achieve focused diversity around a biologically validated starting point in the chemistry “universe”—the diversity of these starting points is selected by nature ● synthetic methods are primarily chosen to lead to the target core structure, even if this goal requires a considerable amount of optimization ● retrosynthetic analysis will be also validated by its potential for diversity generation ● building blocks are commercially available or synthesized in solution ● parallel or split-pool synthesis ● small to middle library size	● aims to achieve maximum diversity around a spot in the chemistry “universe” chosen for its chemical accessibility and “natural-product likeness”, that is, structural complexity ● synthesis route is driven by “powerful” chemical reactions (general, high-yielding, stereoselective, bond-constructing, functional-group-tolerant, etc.) ● forward diversity-oriented synthetic design ● building blocks should be commercially available in great diversity ● encoded split-pool synthesis is preferred method ● large library size

new, efficient, and selective reactions that can be applied in solid phase synthesis is greater than ever. It can be anticipated that the ongoing progress in methodology development will have an impact in the quest for structurally more complex and more diverse libraries. A further direction for future efforts will certainly be the creation of larger libraries in which the advantages of solid-phase synthesis over synthesis in solution will justify the initial cost of optimization.^[5, 38b] The return on this additional investment in synthetic effort, which is necessary to generate combinatorial libraries of structurally diverse natural-product analogues, should result in higher and better hit rates and better leads with libraries of much smaller size than conventional random libraries.

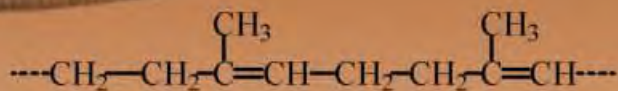
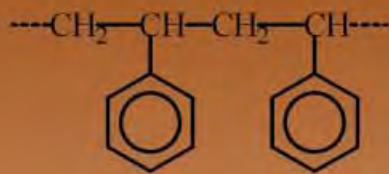
As Nature has already identified natural products as lead structures of biological relevance in the almost infinite universe of chemical structures, there are good reasons to take the effort to design combinatorial libraries based on these scaffolds. Nature has been fairly restrictive in exploiting the infinite number of possible protein structures and has allowed itself access to only a limited number of folds and domains. However, the possible variations on these scaffolds by individual amino acid side chains will ensure that the search for small-molecule ligands for these proteins remains a challenge.

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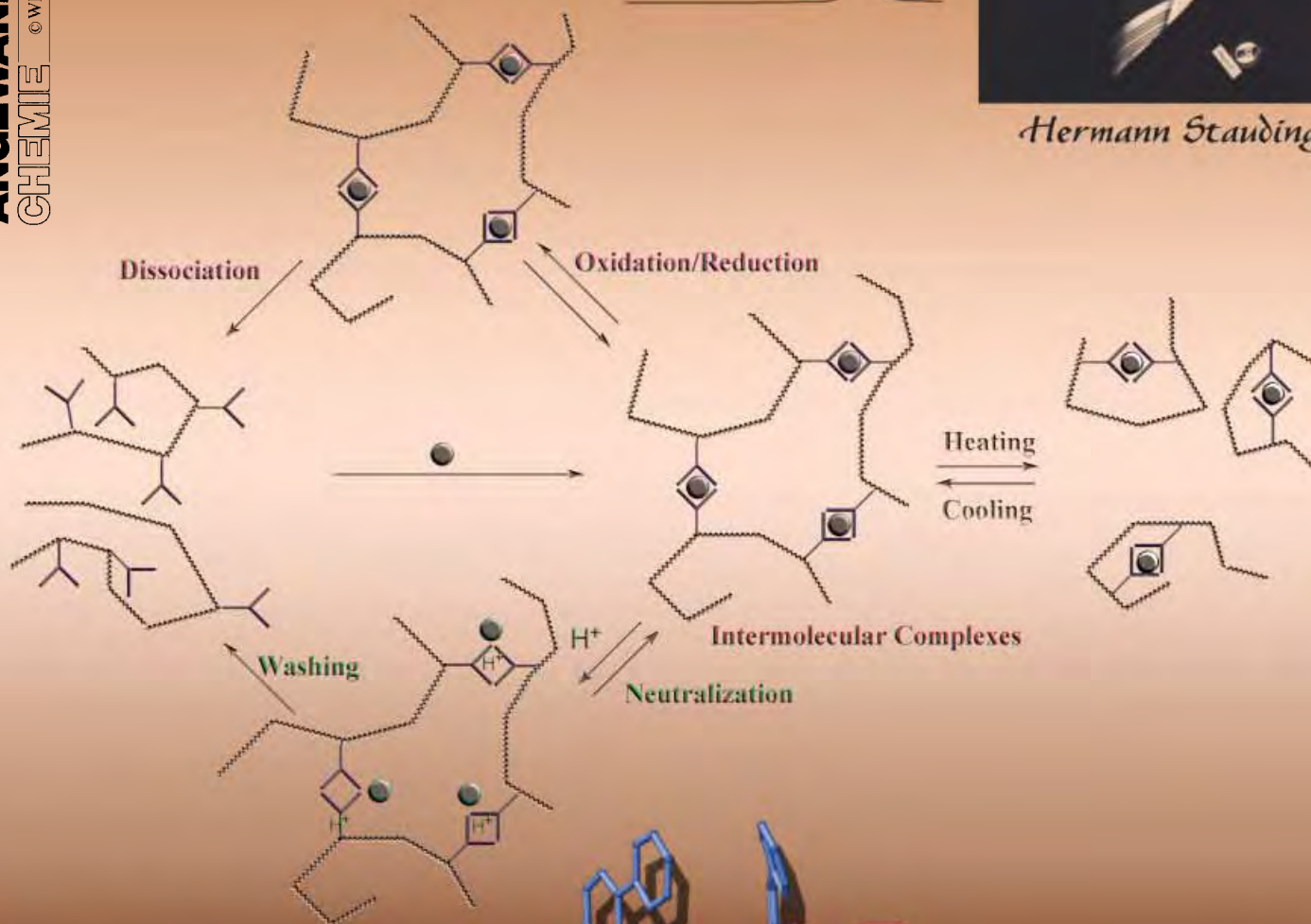
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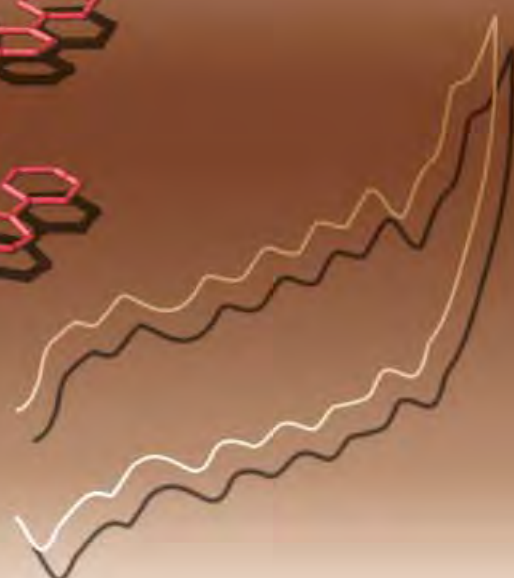
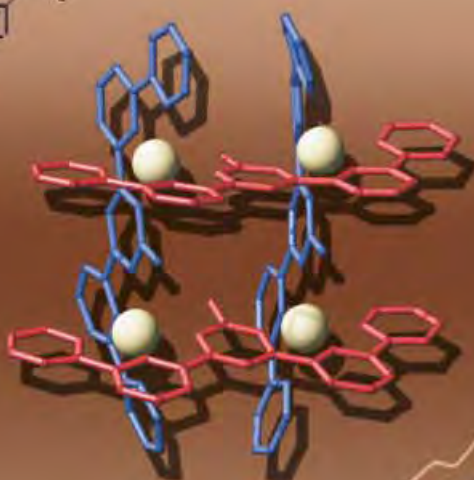
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Hermann Staudinger



Jean-Marie Lehn



Macromolecules Containing Bipyridine and Terpyridine Metal Complexes: Towards Metallosupramolecular Polymers

Ulrich S. Schubert* and Christian Eschbaumer

Dedicated to Professor Dr. Claus D. Eisenbach

The ability of a broad range of N-heterocycles to act as very effective and stable complexation agents for several transition metal ions, such as cobalt(II), copper(II), nickel(II), and ruthenium(II), has long been known in analytical chemistry. This behavior was later utilized in supramolecular chemistry for the construction of highly sophisticated architectures, such as helicates, racks, and grids. The discovery of macromolecules by Staudinger in 1922 opened up avenues towards sophisticated materials with properties hitherto completely unknown. In the last few decades, the combination of macromolecular and supramolecular

chemistry has been attempted by developing metal-complexing and metal-containing polymers for a wide variety of applications that range from filtration to catalysis. The stability of the polymer-metal complex is a fundamental requirement for such applications. In this respect, the use of bi- and terpyridines as chelating ligands is highly promising, since these molecules are known to form highly stable complexes with interesting physical properties with transition-metal ions. A large number of different structures have been designed for many different applications, but polymers based on the application of coordinative forces

have been prepared in a few cases only. Furthermore, the synthetic procedures applied frequently resulted in low yields. During the last few years, strong efforts have been made in the direction of self-assembling and supramolecular polymers as novel materials with “intelligent” and tunable properties. In this review, an overview of this active area at the interface of supramolecular and macromolecular chemistry is given.

Keywords: bipyridine ligands • coordination chemistry • polymers • supramolecular chemistry • terpyridine ligands

1. Introduction

Since 1987, when Lehn, Pedersen, and Cram received the Nobel prize for their studies in selective host-guest chemistry,^[1–3] supramolecular chemistry has become a well-known concept and a major field of today's chemical research. Starting with the development and design of crown ethers, spherands, and cryptands, modern supramolecular chemistry concerns the self-assembly^[4] of well-defined structures, similar to those in natural systems.^[5] In the same time frame, there was a blending of supramolecular systems with tailor-made macromolecules and traditional polymer chemistry. By making a supramolecular entity with a relatively large

polymer ratio, it is possible to produce on a large scale materials combining the new and interesting features and structures of supramolecular species with well-known polymeric properties. As a consequence of their polymeric nature, these materials can be, for example, spin-coated into thin films or used in bulk systems, thus reducing technical processing to common techniques used in polymer engineering. By altering the polymer part, the macroscopic properties of the material can be changed dramatically, for example, from rigid to elastic, from hydrophobic to hydrophilic, or from liquid to solid. A prominent example of the combination of hydrogen bonding and polymer chemistry is represented by the work of Meijer's research group:^[6] the creation of stable polymers built up from low-molecular-weight poly(ethylene/butylene) with telechelic 2-ureido-4[1*H*]-pyrimidinone end groups. The end groups bind each other by quadruple hydrogen bonds which results in supramolecular high-molecular-weight polymers. Since the polymerization is reversible, a strong temperature dependence of the melt viscosity was detected because of depolymerization. The current research results in this area have been summarized in a recent review.^[7]

[*] Prof. Dr. Ulrich S. Schubert, Dr. C. Eschbaumer
Laboratory of Macromolecular and Organic Chemistry
Eindhoven University of Technology
P.O. Box 513, 5600 MB Eindhoven (The Netherlands)
Fax: (+31) 40-247-4186
E-mail: u.s.schubert@tue.nl

In this review we consider the results of a different combination story: that of metal complexes (metallo-supramolecular assemblies) with polymer chemistry and materials.^[8] In view of the outstanding importance of 2,2'-bipyridine and 2,2':6',2''-terpyridine ligands (Figure 1) and metal complexes, we have limited this review to macromolecules and polymers containing these types of ligands or their metal complexes. Polymers containing the bipyridine analogue phenanthroline will not be considered here (for an overview see ref. [9]). For other general overviews concerning metal-containing polymers see, for example, refs. [9–12].

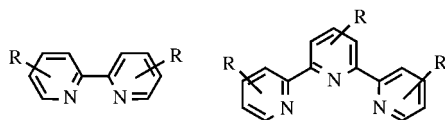


Figure 1. 2,2'-Bipyridine and 2,2':6',2''-terpyridine.

Since 2,2'-bipyridines are considered only in this review we will call them simply bipyridines and adopt the abbreviation bpy for these ligands. Bipyridines have been known since 1888 when F. Blau synthesized the first bipyridineiron complex.^[13] One year later, Blau synthesized and analyzed bipyridine by dry distillation of copper picolinate.^[14] Since the molecule consists of two identical parts, no directed coupling procedure is required for its synthesis. Therefore, unsubstituted and symmetrically substituted (in particular, 4,4'-functionalized) bipyridines are accessible in good yields. Apart from this, bipyridine–metal complexes (in particular ruthenium com-

plexes) have very interesting photochemical and other properties which, for example, makes them suitable for applications in solar energy conversion.^[15] For these reasons, scientists started in the early 1970s to insert bipyridine units into polymers, thin films, and membranes. A large part of the review is therefore devoted to this theme.

The chemistry of 2,2':6',2''-terpyridines (here simplified to terpyridine and abbreviated as tpy) is much younger than that of bipyridines. Terpyridine (Figure 1) was isolated for the first time by Morgan and Burstall in the 1930s.^[16, 17] The molecule contains three nitrogen atoms and can therefore act as a tridentate ligand and form stable complexes by chelating a broad variety of transition metal ions.^[18, 19] This property has been widely used in analytical chemistry.^[18] Nevertheless, it took almost 30 years longer than a bipyridine-containing polymer for the first example of a terpyridine-containing polymer to be published. This time difference can be attributed to the difficulty in preparing terpyridines, particularly substituted terpyridines. Overviews of metallodendrimers with complex building units other than bi- and terpyridines can be found in refs. [20, 21].

2. Macromolecules Bearing Bipyridine Units

2.1. Dendrimers and Starlike Macromolecules

In 1999, Newkome et al. published a very detailed review on metallodendrimers and metal-containing starlike macromolecules.^[20] There have been many publications on macro-

Ulrich S. Schubert was born in Tübingen (Germany) in 1969. He studied chemistry at the Universities of Frankfurt and Bayreuth and the Virginia Commonwealth University, Richmond (USA). His Ph.D. work was performed under the supervision of Professor C. D. Eisenbach (Bayreuth, Germany) and Professor G. R. Newkome (Florida, USA). In 1995 he obtained his doctorate with Prof. Eisenbach. After a postdoctoral training with Professor Lehn at the Université Strasbourg (France) he moved to the Technische Universität München (Germany) where he obtained his habilitation in 1999 (with Professor O. Nuyken). From 1999 to spring 2000 he held a temporary position as a professor at the Center for NanoScience at the Universität München (Germany). Since summer 2000 he has been a Full-Professor at the Eindhoven University of Technology. His awards include the Bayerischen Habilitations-Förderpreis, the Habilitandenpreis of the GDCh (Makromolekulare Chemie), the Heisenberg Stipendium of the DFG and the Dozenten Stipendium of the Fonds der Chemischen Industrie. The major focus of his research interests relates to organic heterocyclic chemistry, supramolecular materials, nanoscience, combinatorial material research, and tailor-made macromolecules.



U. S. Schubert



C. Eschbaumer

Christian Eschbaumer was born in 1970 at Erding (Germany). He started studying chemistry at the Technische Universität München in 1991. His diploma thesis dealt with the synthesis of functionalized terpyridines as building blocks for heavy-metal-complexing polymers. In 1998 he started working on his Ph.D. thesis at the Technische Universität München in the group of Prof. U. S. Schubert with a project entitled "Metallo-Supramolecular Polymers—On the Way to New Materials". From July 2000 he continued his work at the Technische Universität Eindhoven, where he defended his thesis in March 2001. In October 2000 he joined the Memory Products Division of Infineon Technologies (Erlangen/Germany).

molecules with bipyridines attached only to the outermost sphere of the molecule to saturate the free coordination sites of a metal complex (for example, in ref. [20, 21]). In this review, only selected dendrimers and some starlike molecules are discussed. We will divide this part into two sections. Dendrimers with bipyridine–metal complexes within its core are discussed followed by starlike molecules containing either complexed or free bipyridine ligands at the surface.

The work of Newkome et al. fits just in between these two sections.^[22] They incorporated a 5,5''-diamino-functionalized bipyridine through ester binding onto the backbone of two molecules (Figure 2). The addition of a bis(bipyridine)ruthenium(II) complex resulted in systems in which tris(bipyridine)ruthenium(II) complexes are bound within the inner sphere of the dendrimer, but do not act as branching units. These systems consist of the same core, but their surfaces differ.

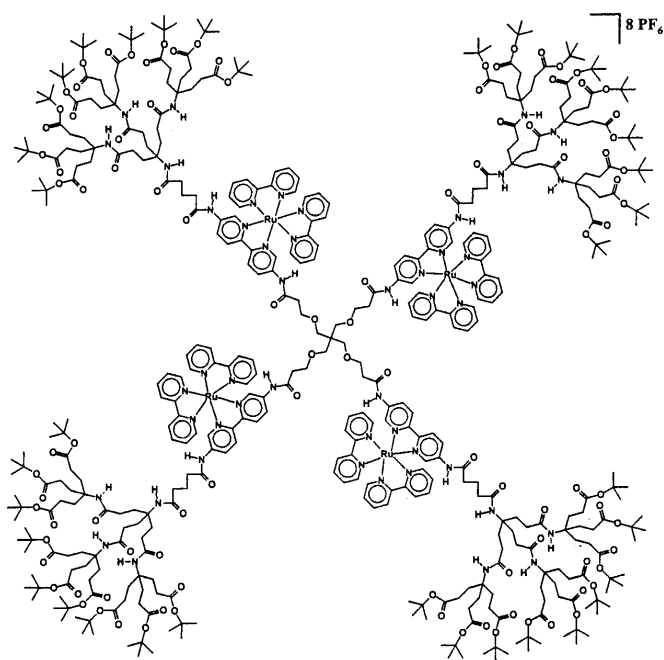


Figure 2. The dendrimer synthesized by Newkome et al. contains metal complexes within the inner sphere of the molecule.^[22]

Dendrimers containing a bipyridine–metal core are rare. In 1991, Beer et al. reported a starlike system with a tris(bipyridine)ruthenium(II) core and six benzo- or azacrown ether units on the surface (Figure 3).^[23] The alkynyl- or vinyl-linked systems are electropolymerizable and produce films capable of recognizing alkali and alkaline-earth metal cations (as shown by spectroscopic methods). The ligand-centered (MLCT) emission maximum of both the monomer and polymer films were shifted to lower wavelengths in the presence of these ions. A typical value for the shift in the spectrum of a monomeric complex is 16 nm (from 686 to 670 nm).

Vögtle, De Cola, and Balzani et al. also used a convergent strategy to assemble five different types of dendrimers up to the third generation with bipyridineruthenium complexes forming the core.^[24–26] The aim of this work was the design of

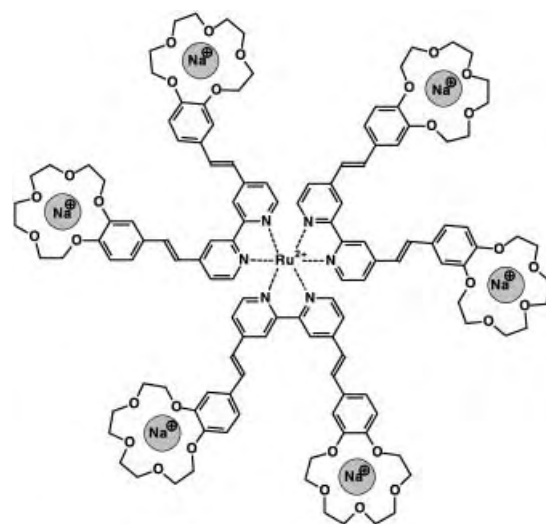


Figure 3. Alkali and alkaline-earth metals can be recognized by the benzocrown ether with a $[\text{Ru}(\text{bpy})_3]$ core synthesized by Beer et al.^[23]

photoactive and redox-active dendrimers by the incorporation of bipyridine complexes. The large dendritic complexes exhibited more-intense emission and a longer excited state lifetime than common $[\text{Ru}(\text{bpy})_3]$ complexes. For example, the excited-state lifetime of the dendrimer with 54 peripheral methyl ester units in aerated acetonitrile solution is longer than 1 μs . The structures of the dendritic ruthenium complexes have been deduced by using NMR spectroscopy and MALDI-TOF mass spectrometry. Another example of a dendrimer with a tris(bipyridine)ruthenium(II) core was reported by Constable et al.^[27, 28]

In 1997, Marvaud and Astruc presented starlike macromolecules containing either benzene or $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}^{\text{II}}(\eta^6\text{-C}_6\text{R}_6)]$ ($\text{R}=\text{CH}_3$) as the core and pyridine, bipyridine, terpyridine, or the corresponding ruthenium complexes at the surface.^[21] A divergent approach (Figure 4) was used for constructing the molecules. The characterization of molecules with up to 12 positive charges was performed by NMR spectroscopy and also by MALDI-TOF and electrospray mass spectrometry. Further evidence for the presence of terminal Ru complexes was obtained by electrochemical measurements, where the $\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$ redox systems gives a single and reversible anodic wave at +0.82 and +0.79 V (versus the ferrocene/ferrocenium couple (Fc/Fc^+)).

Some innovative work in this direction has been reported by Abruña's research group with their poly(amidoamine)-based dendrimers containing pendant bipyridine- or terpyridineruthenium complexes (see Section 3.1).^[29–31] The research groups of Puddephatt, Achar, and Catalano chose a divergent route to synthesize organoplatinum or mixed organoplatinum/palladium dendrimers.^[32–36] The dendrimers were built up converting a four-coordinate, square-planar platinum(II) center into a six-coordinate, octahedral platinum(IV) center by oxidative addition of an aryl bromide to the repeat unit. Figure 5 shows an organoplatinum dendrimer with four arms in which transition metal ions are present in every layer of the dendrimer except in the core. Up to 12 ferrocene units have been incorporated in one macromolecule.^[36]

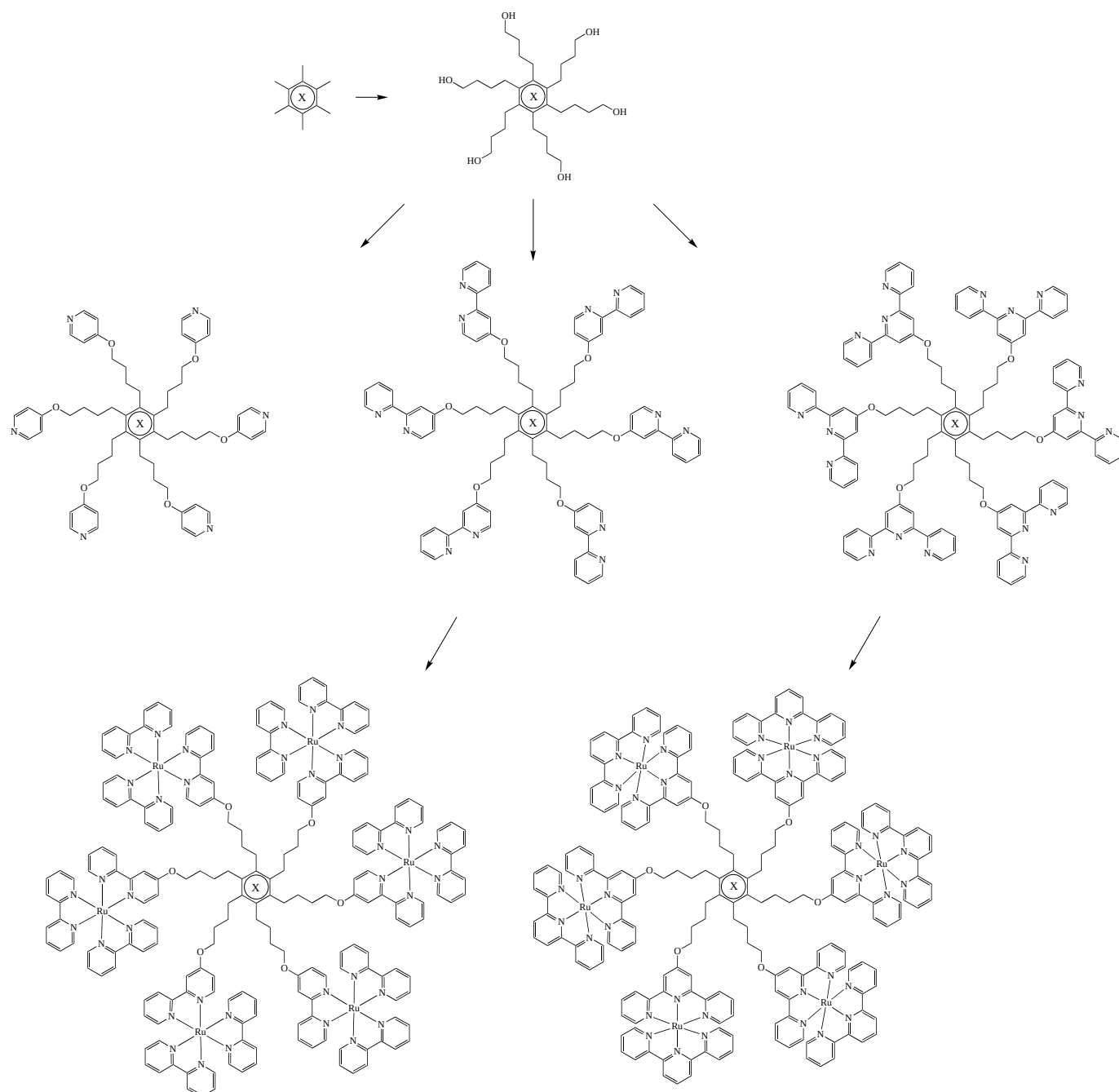


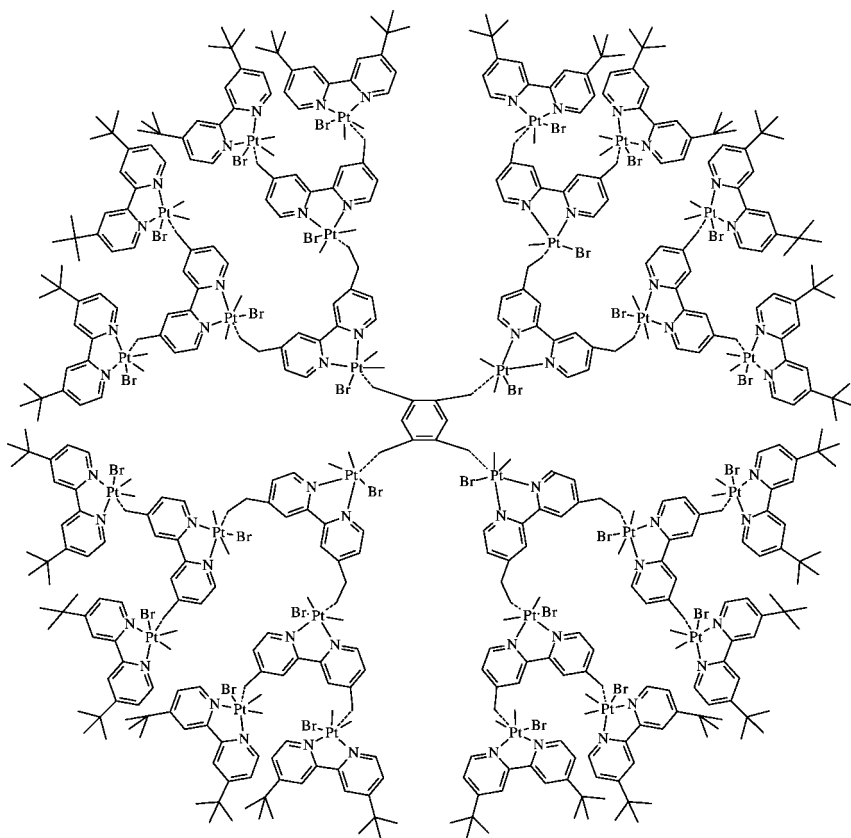
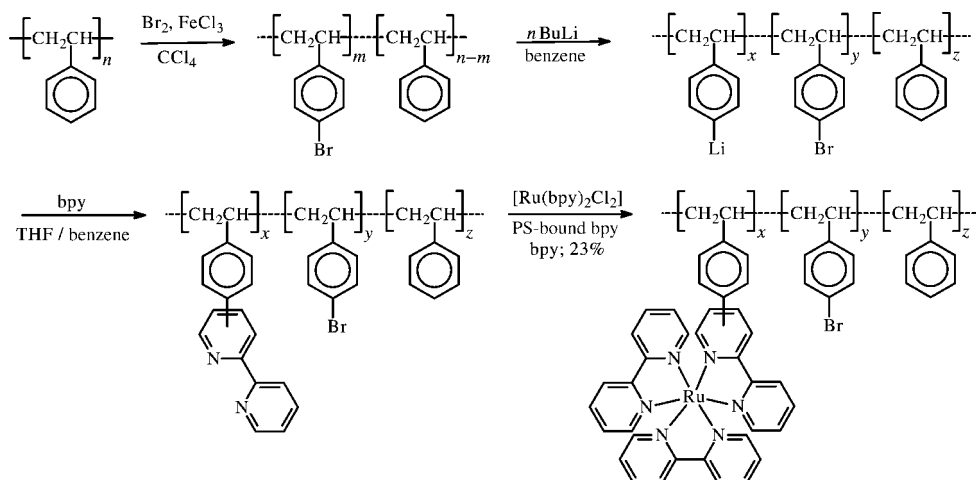
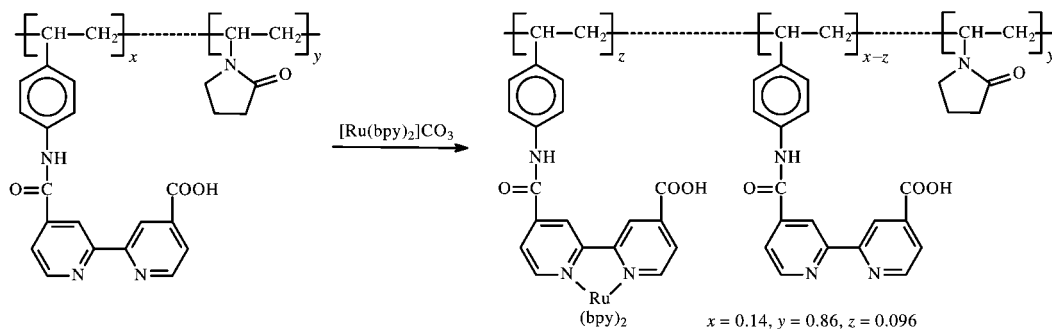
Figure 4. Synthesis of $[\text{Ru}(\text{bpy})_3]$ -terminated macromolecules with a metallocene core ($\text{X} = \text{Fe}(\eta\text{-C}_5\text{H}_5)^+$) by Marvaud and Astruc.

2.2. Polymers with Bipyridine Units in the Side Chain

Kaneko et al. presented their first studies on polymers with covalently bound bipyridines in 1980.^[37, 38] They targeted the preparation of a heterogeneous photocatalyst for the decomposition of water by solar irradiation. The polystyrene backbone was radically polymerized, then brominated, lithiated, and finally treated with bipyridine in different molar ratios (Figure 6). The resulting modified polymers were characterized by IR and UV/Vis spectroscopy. The photochemical reduction of methyl viologen revealed the existence of three components in the polymer with lifetimes τ of the excited state $[\text{Ru}(\text{bpy}_3)]^{2+*}$, ranging from 7 to 474 ns.^[39] The rate

constant k_1 for the transition from the excited state complex to methyl viologen MV^{2+} was determined to be around $10^8 \text{ L mol}^{-1} \text{ s}^{-1}$, as in monomeric complexes.

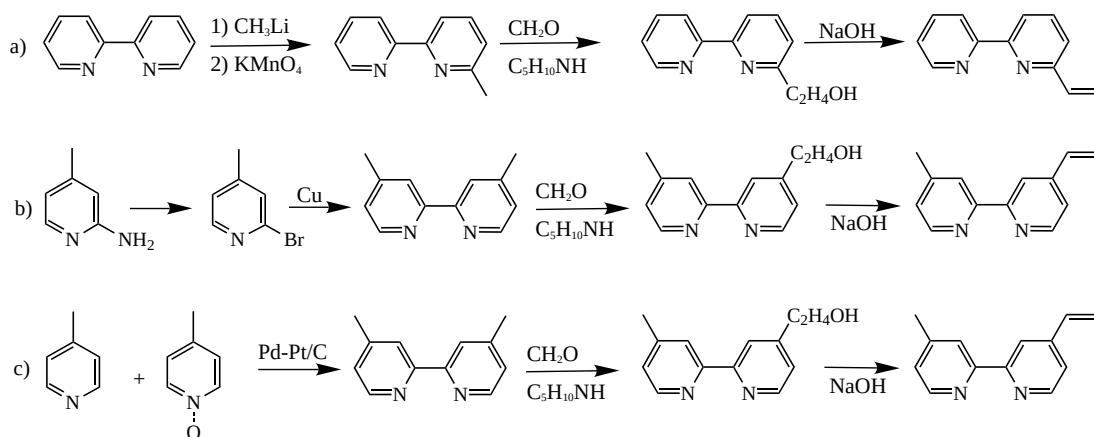
As a next step, Kaneko et al. prepared *p*-aminostyrene-*N*-vinylpyrrolidone copolymers with pendant tris(bipyridine)-ruthenium(II) complexes (Figure 7).^[40] Again, the polymer backbone was synthesized first. Afterwards it was treated with 2,2'-bipyridine-4,4'-dicarboxylic acid to form the corresponding amides. Ruthenium complexes were obtained by subsequent reaction of the polymer with $[\text{Ru}(\text{bpy})_2\text{CO}_3]$. In 1982, Kaneko et al. also investigated the copolymerization of 4-methyl-4'-vinylbipyridine with styrene,^[41] followed by analogous work with a variety of other co-monomers such as

Figure 5. Organoplatinum dendrimer with four dendrons.^[33, 34]Figure 6. Synthesis of the first polymers with pendant $[\text{Ru}(\text{bpy})_3]$ complexes.^[37, 38]Figure 7. *p*-Aminostyrene-*N*-vinylpyrrolidone copolymers with pendant $[\text{Ru}(\text{bpy})_3]$ complexes.^[40]

acrylic acid, methyl methacrylate, and *N*-vinylpyrrolidone.^[42–46] A lifetime τ of 430 ns and a rate constant k_1 of $10^8 \text{ L mol}^{-1} \text{ s}^{-1}$ were determined for the excited states of the complexes. The influence of the anionic and cationic pendant groups on the quenching of the photoexcited state were later studied.^[42–45]

Another contribution aimed at the photochemical conversion of solar energy was made by Sumi et al.^[47] They synthesized 6-vinylbipyridine and 4-methyl-4'-vinylbipyridine (Figure 8a, b), and used free-radical polymerization to prepare the corresponding homopolymers. While poly(4-methyl-4'-vinylbipyridine) was insoluble because of cross-linking, poly(6-vinylbipyridine) was soluble in common organic solvents. After complexation with different transition metal chlorides, poly(6-vinylbipyridine) became soluble in water and insoluble in THF, while the cross-linked poly(4-methyl-4'-vinylbipyridine) swelled to a voluminous gel. In an alternative monomer synthesis, Pd-catalyzed coupling of pyridine-*N*-oxide was used instead of copper catalysis to prepare 4-methyl-4'-vinylbipyridine (Figure 8c).^[48] The poly(4-methyl-4'-vinylbipyridine) produced from this monomer was found to be soluble in common organic solvents.

First investigations on the use of bipyridine–metal complexes as templates for polymeric matrices were carried out by Gupta and Neckers in 1982.^[49] The idea was to copolymerize divinylbenzene and metal complexes of 4'-methyl-4-vinylbipyridine in variable quan-

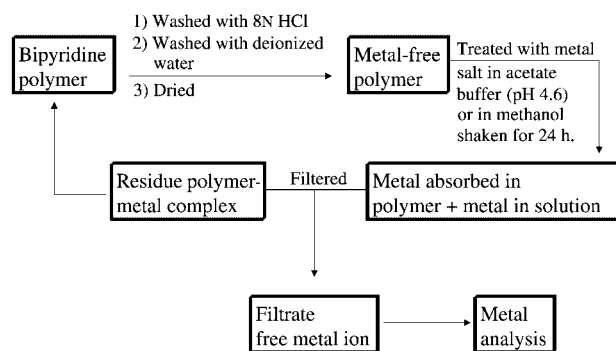
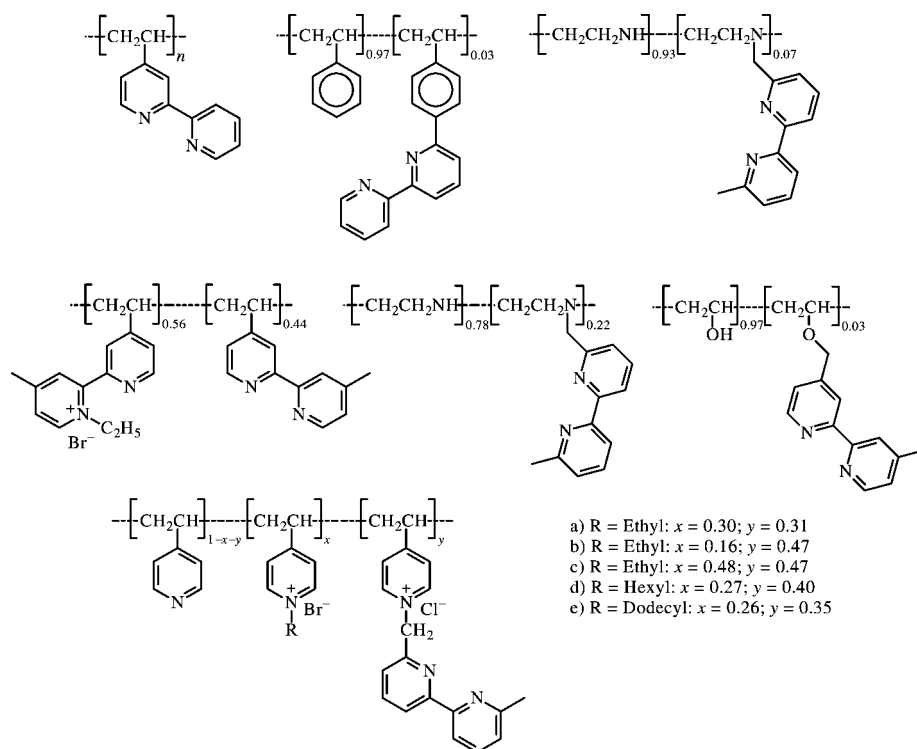
Figure 8. Vinyl-substituted bipyridines as monomers for radical polymerization.^[47, 48]

ties, to remove the metal ion, and then to measure the selectivity of the polymer for the metal ion (Figure 9). This system demonstrated some template effect but on a too small a scale to be of relevance for practical applications.

In 1982, Kelly and Tinnemans et al. reported on the photo- and electrochemical properties of polymer-bound bipyridine-ruthenium and bipyridine-tungsten complexes. The copolymers were prepared from 6-styrenebipyridine and styrene, methyl methacrylate, or maleic anhydride and treated with ruthenium or tungsten ions.^[50] In contrast to the results from the studies of Kaneko et al., the authors detected that the rate of production of methyl viologen MV^+ was only slightly greater in the presence of the Ru^{II} complexes than in their absence, which suggests that the different sites of attachment might be responsible for the results. In 1984, Fischer investigated the preparation of bipyridines with long-chain substituents by deprotonation of 4,4'-dimethylbipyridine with lithium diisopropylamide (LDA), and then addition of bromododecane or poly(vinylbenzyl chloride).^[51]

In their search for polymeric catalysts for the hydrolysis of organophosphate esters, Pitt et al. used a different synthetic approach to 4-methyl-4'-vinylbipyridine.^[52] Starting with commercially available 4,4'-dimethylbipyridine, they applied an *N*-oxide route via the monochloro- and the mono(methyl-enetriphenyl)phosphonium chloride to yield the monovinylene-functionalized bipyridine. Homopolymerization yielded a white non-cross-linked product that was soluble in organic solvents. Derivatization of commercially available poly(ethyleneimine), poly(vinyl alcohol), and poly(4-vinylpyridine) was also used to incorporate the bipyridine into the polymer side chain.^[52, 53] A variety of polymeric amines was later investigated (Figure 10), and the

catalytic activity of the polymer-metal complexes in the solvolysis of organophosphorus esters studied.^[54] The highest activity was exhibited by copper(II) complexes of polymers

Figure 9. Sorption studies on polymers imprinted with metal complexes.^[49]Figure 10. Polymers and their complexes as catalysts for the hydrolysis of organophosphate esters.^[52, 53, 54]

containing the bipyridine group. At pH 7.6 and at a concentration of $3.7 \times 10^{-3} \text{ mol L}^{-1}$, these catalysts reduced the half-life of diisopropyl fluorophosphate from 800 to 9 min.

Meyer et al. synthesized a series of redox-active $[\text{Ru}(\text{bpy})_3]$ polymers containing chromophores absorbing light in the visible region or organic energy transfer reagents (derivatized anthracenes).^[55] They used the nucleophilic displacement of chloro substituents from poly(*m(p)*-(chloromethyl)styrene-*stat*-styrene) with alkoxide or carboxylate nucleophiles, under concomitant formation of amide and ether linkages (Figure 11). In the case of pendant bipyridine complexes, the corresponding unsymmetrically functionalized tris(bipyridine)ruthenium(II) complex was used as a nucleophile. In later work, tris(bipyridine)ruthenium(II) complexes and tris(bipyridine)osmium(II) complexes were attached to a polystyrene backbone. The type and length of the linkage as well as the molar ratios of the polystyrene and the pendant complexes were varied. A large difference in the ability of the ether and amide linker to promote intrastrand energy transfer was detected.^[56–61] The electrogenerated chemiluminescence of these polymers in SiO_2 sol–gel/polymer composites was later studied.^[62, 63] The sols were spin-coated onto an indium-tin-oxide (ITO) electrode and studied spectroscopically. While similar MLCT absorption spectra were detected ($\lambda_{\text{max}} = 458 \text{ nm}$) in solution, the emission spectra of dry films were blue-shifted compared to those obtained in water or ethanol. The lifetime of the emissions in solution and film varies between 294 and 648 ns.

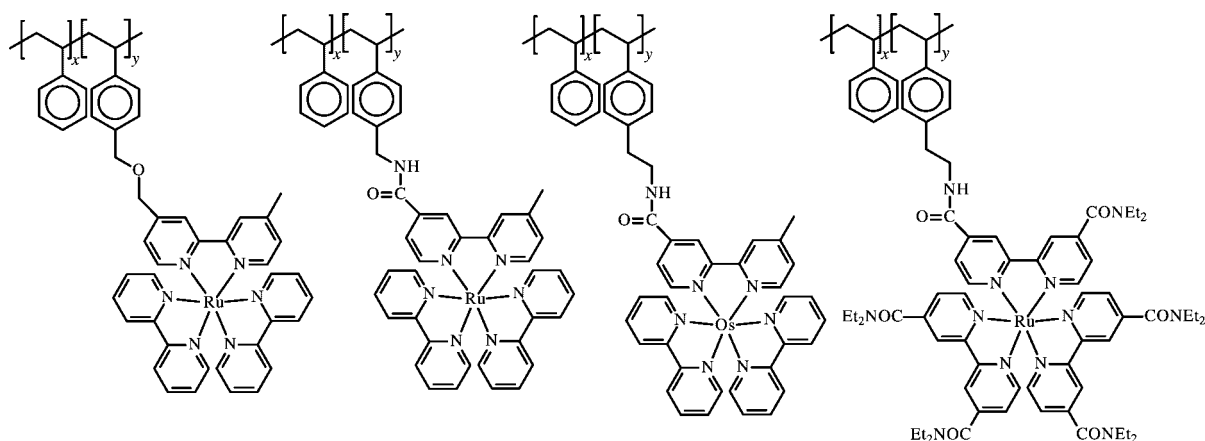


Figure 11. Polystyrene-bearing pendant bipyridineruthenium or -osmium complexes for the study of energy transfer.^[55, 56, 57–61]

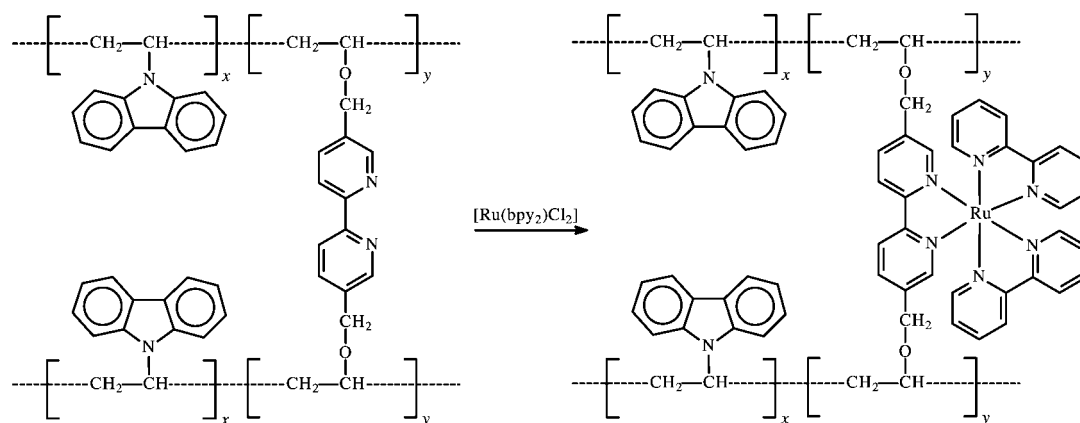


Figure 12. Synthesis of a new photoactive polymer–ruthenium complex.^[64]

A partially cross-linked polymer based on poly(*N*-vinylcarbazole vinyl alcohol) with bipyridineruthenium lumino-phores was reported by Farah and Pietro in 1999 as a new material for electroluminescence.^[64] Poly(*N*-vinylcarbazole vinyl alcohol) was cross-linked in a post-polymer modification by reaction with butyllithium and 5,5'-dibromomethylbipyridine. The resulting moiety was treated with bis(bipyridine)-ruthenium to obtain the corresponding polymer–ion complex shown in Figure 12. An investigation of the thermal and photochemical behavior demonstrated that the material was thermally stable up to 300°C and exhibited emitted light at 590 nm upon radiation at the maximum absorption of 400 nm. The electroluminescence properties reported of poly(phenylenevinylene) with pendant bipyridine- or terpyridineruthenium complexes was reported by Chan and Wong (see Figure 57, Section 3.3).^[65]

Newkome and Yoneda prepared homopolymers from 5-vinyl-6,6'-dimethylbipyridine,^[66] a monomer not commonly used (Figure 13), and copolymers of the corresponding acrylate-functionalized bipyridine with styrene.^[67] The polymers were treated with metal ions and the resulting complexes characterized by NMR and IR spectroscopy. The polymeric Pd^{II} complexes were later shown to be effective in the

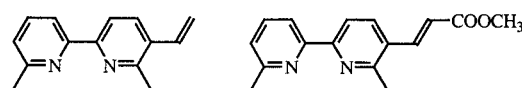


Figure 13. Unusual monomers prepared by Newkome and Yoneda.^[66, 67]

catalytic hydrogenation of simple olefins such as (*E*)-cinnamic acid.

Polystyrene-bound 2,2'-bipyridine–metal complexes were synthesized by Lei et al. and characterized by IR, X-ray, and photoelectric spectroscopy, by thermogravimetry, differential thermal analysis, inductively coupled plasma atomic emission spectrometry, and elemental analysis. The metal complexes were covalently attached to the polymer through the bipyridine and the free coordination sites on the metal ions were saturated with bipyridine, oxime, or phenanthroline units (Figure 14). The complexes were found to act as catalysts, in the absence of solvent, in the oxidation of alkyl benzenes and cyclohexene in the presence of molecular oxygen. Reaction rates of 3.57×10^4 to $3.83 \times 10^5 \text{ mL min}^{-1} \text{ mol}^{-1}$ and a selectivity of oxidation to the ketone and alcohol ranging from 79 to 100% were detected. The alcohol/ketone molar ratio of the products can be adjusted by employing additives or by varying the pH value of the reaction.^[68–72]

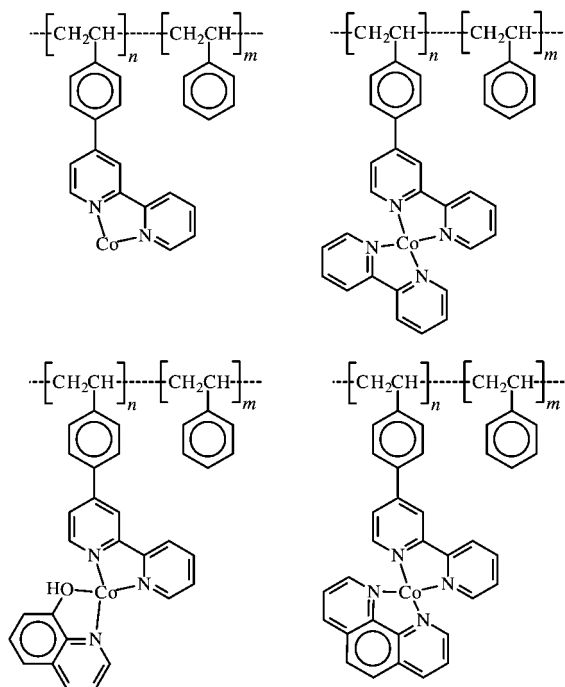


Figure 14. Polymeric catalysts prepared by Lei et al. for the oxidation of cyclic alkenes.^[68]

A polymer-bound palladium catalyst for the synthesis of acetylene-terminated resins has been synthesized by Trumbo and Marvel from palladium diacetate and single-crystalline polyethylene containing pendant bipyridine units.^[73] However, the authors found that the synthesized materials were unsuitable as supported catalysts for the planned reaction because of leaching, nonrecyclability, and low yields.

The preparation of a series of copolymers of 2-hydroxyethyl methacrylate and 4-vinylpyridine or 4-methyl-4'-vinylbipyridine was reported by Miller and Lewis.^[74–78] The addition of a solution of FeSO_4 or CuCl_2 to such polymers led to the formation of a hydrogel of cross-linked polymers. The

mechanism and kinetics of the formation and the influence of the metal ions were also studied. Chujo et al. also published results on the formation of hydrogels from polyoxazoline-containing pendant bipyridine units.^[79, 80] The addition of Co^{III} and Fe^{II} ions gave rise to noncovalent cross-linking and a swelling of the polymer. The Fe^{II} -containing gel was stable for several days at ambient temperature, but dissolved in hot water within 30 min. The stability of the Co^{III} -containing gel was lower than that of a Ni^{II} -containing gel, but higher than that of a Fe^{II} -containing gel. After reduction of the Co^{III} ions to Co^{II} , the polymer–ion complex was too labile to be handled as a hydrogel in water (Figure 15).

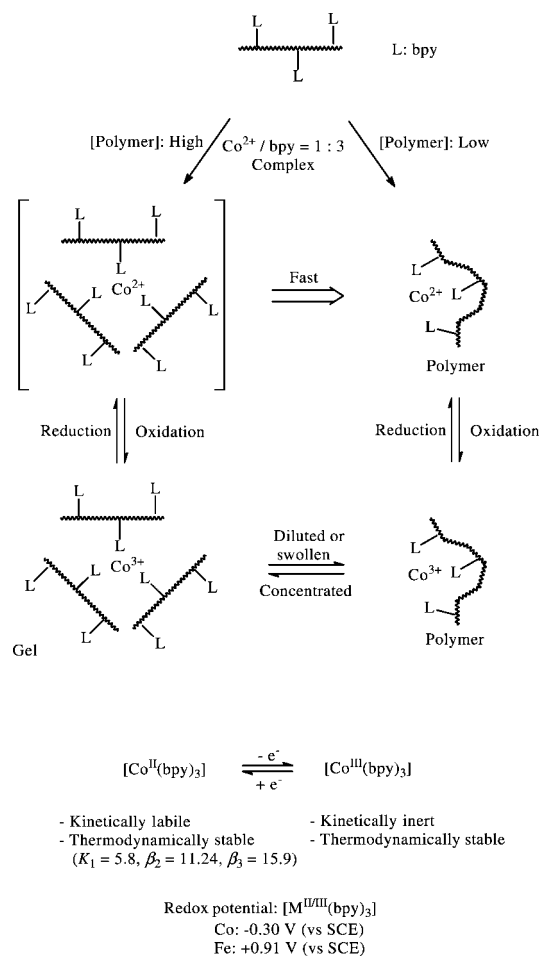


Figure 15. A thermally as well as oxidatively reversible hydrogel designed by Chujo et al.^[79, 80]

Stimuli-responsive polymer gels as novel materials with sensor, actuator, and processor functions were investigated by Yoshida et al.^[81–83] They copolymerized (Figure 16) the temperature-responsive *N*-isopropylacrylamide with bis(bipyridine)(4-methyl-4'-vinylbipyridine)ruthenium(II). Immersing the system in a $\text{Ce}^{\text{IV}}/\text{Ce}^{\text{III}}$ solution induced the oscillatory Belousov–Zhabotinsky reaction,^[84] and the gel swelled and deswelled periodically at a constant temperature without external stimuli. Depending on the composition of the environment, the chemical energy is transduced into mechanical energy and vice versa to drive the oscillation with a period of about 5 min.

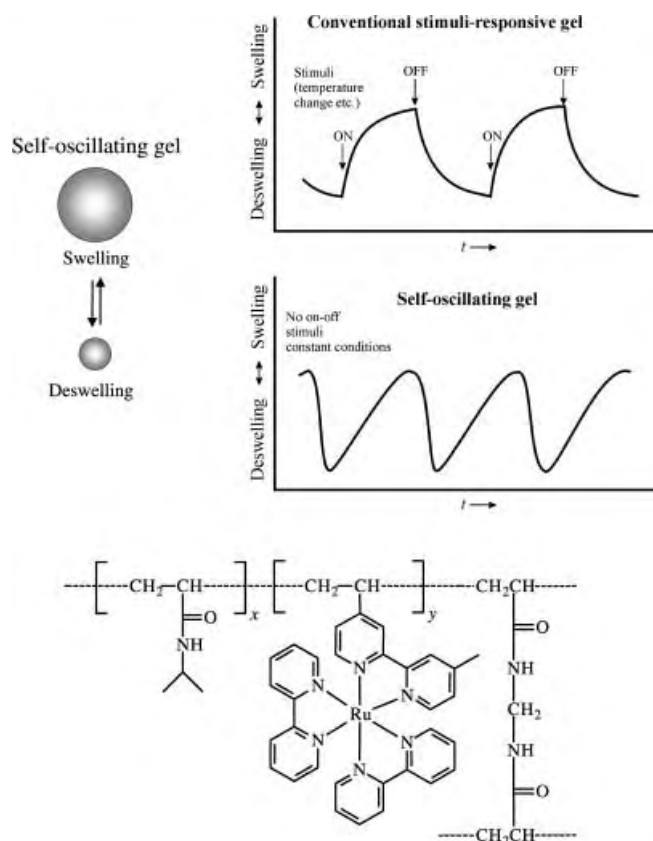


Figure 16. Self-oscillating gels based on *N*-isopropylacrylamide and co-polymerized bipyridineruthenium complexes.^[81]

Using a similar material, the tris(bipyridine)ruthenium(II) complex of *N*-isopropylacrylamide-*co*-(2-(4-(4'-methylbipyridyl))ethylacrylate), Miyashita et al. studied the electron-transfer quenching of the complex by methyl viologen as a function of temperature.^[85] They determined the rate constant to be four to five times higher in the globular state than in the coil state. This result is in contrast to a similar experiment with a pyrene-labeled probe. This could mean that in the globular state the hydrophilic ruthenium complexes are placed at the interface of the hydrophobic polymer matrix and therefore are more easily accessible for the methyl viologen quencher (Figure 17). Later Miyashita and co-workers formed Langmuir–Blodgett films of these materials and investigated the photoelectrochemical response of a monolayer prepared on ITO.^[86–89] A typical anodic photocurrent of 20 nA was determined upon irradiation of the film in the presence of an electron donor.

Bartsch et al. recently described 26 chelating copolymers for heavy-metal-ion sorption.^[90] The copolymers were prepared by free-radical copolymerization of chelating monomers, such as 4-methyl-4'-vinylbipyridine, 2-vinylpyridine, or 4-vinylpyridine, with a dimethacrylate cross-linker (Figure 18). The bipyridine-containing polymers were shown to exhibit very efficient metal-ion sorption and were highly selective for Cu^{II} over Co^{II} and Ni^{II} ions and for Hg^{II} over Cd^{II} ions.

In 1995, Antonietti et al. presented microlatex dispersions with a surface of approximately 120 m² per gram of polymer

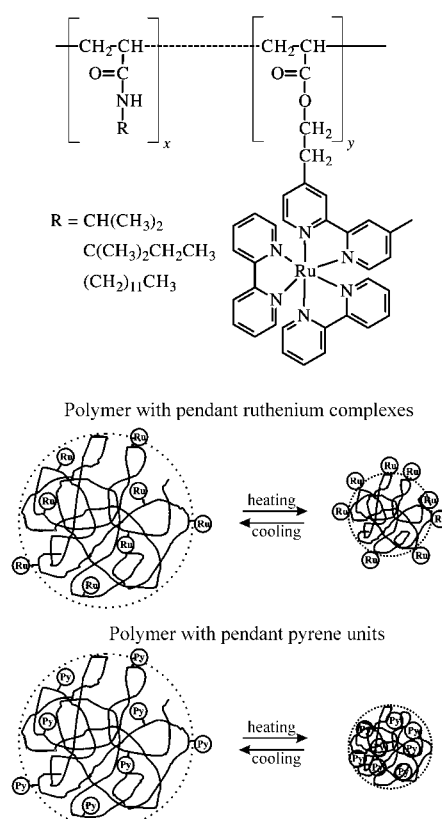


Figure 17. Top: A thermoresponsive polymer with pendant ruthenium complexes; bottom: in the globular state the hydrophilic ruthenium complexes are placed at the surface of the pyrene units within the polymer matrix.^[85–88]

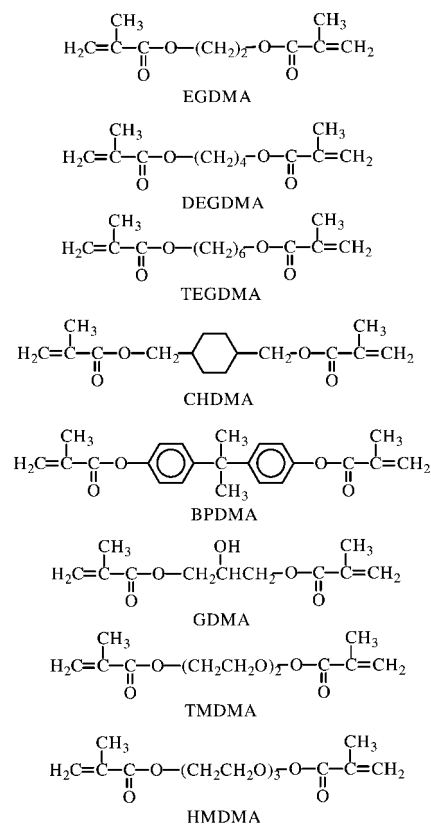


Figure 18. The different dimethacrylate cross-linking units for the preparation of chelating monomers for metal sorption.^[90]

functionalized with bipyridine.^[91] The polymers were synthesized by radical copolymerization of styrene and 10% (w/w) of 6'-methylbipyrid-6-ylmethyl methacrylate or 4-(6'-methylbipyrid-6-ylmethoxy)butyl methacrylate (Figure 19) and a cross-linking unit. Complexation experiments with transition-metal ions revealed that most of the bipyridine units were located at the latex surface and were accessible in the binding process.

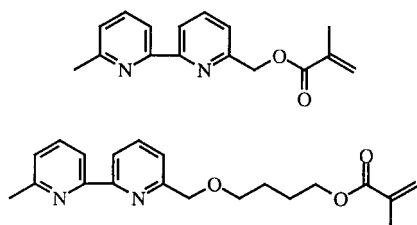


Figure 19. Methacrylate-functionalized bipyridine ligands for the preparation of metal-complexing microlatex dispersions.^[91]

A system completely different to those shown above was presented by Lindsell et al. in 1999,^[92] in which they investigated polydiacetylenes with bipyridine ligands in the side chain as systems with nonlinear optical properties (Figure 20).

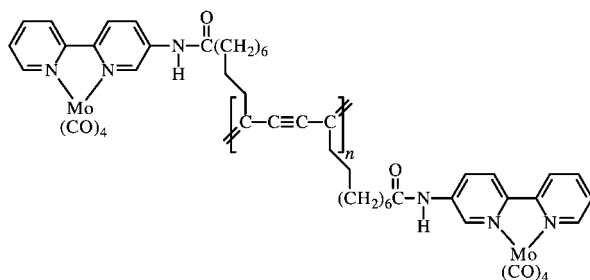


Figure 20. Functionalized poly(diacetylenes) for nonlinear optics.^[92]

The monomers were synthesized by reaction of carboxy-functionalized 1,3-diynes and 5-aminobipyridine to obtain the corresponding amides. Polymerization was achieved by UV or γ irradiation at room temperature, and resulted in an insoluble material. The addition of metal ions resulted in the corresponding polymeric ruthenium(II) and molybdenum(0) complexes becoming soluble. Their linear absorption coefficients were determined to be 25.8 cm^{-1} for the Ru^{II} -complex and 33.2 cm^{-1} for the Mo^0 -containing polymer. Their nonlinear absorption coefficients were determined to be -6.5 and -8.5 cm GW^{-1} , respectively.

2.3. Polymers with Bipyridine Units in the Polymer Backbone

Yamamoto et al. published several papers on polymers with bipyridines in the polymer backbone.^[93–104] In earlier approaches, 5,5'-dihalogeno-substituted bipyridines were reacted in the presence of nickel(0) catalysts, which resulted in rather low-molecular-weight polymers ($\bar{M}_w = 3800$; degree of polymerization (DP) = 21) that were only partially soluble in

formic acid.^[93–95] In contrast to the uncomplexed polymer, metal-containing oligomers ($\bar{M}_w = 1500$) were demonstrated to be soluble in water.^[102] The soluble polymeric platinum or ruthenium complexes can act as photocatalysts for H_2 evolution from aqueous media.^[101, 102] The polymeric complexes can also transfer the photoactivated energy to other molecular parts of the systems and thus cause emission of light from other parts of the molecules (Figure 21, top).^[99] Evidence for this energy transfer was demonstrated by the absorption at 350 nm, which was assigned to the poly(bipyridine) unit, and the fluorescence emission at 640 nm, which was assigned to the Ru^{II} complex. The degree of polymerization was increased to 65 ($\bar{M}_w = 21\,000$) by changing to 6,6'-dihexyl-substituted bipyridines; these polymers remained soluble.^[97, 98] The steric effects of the alkyl groups resulted in the π conjugation being shortened in these systems.

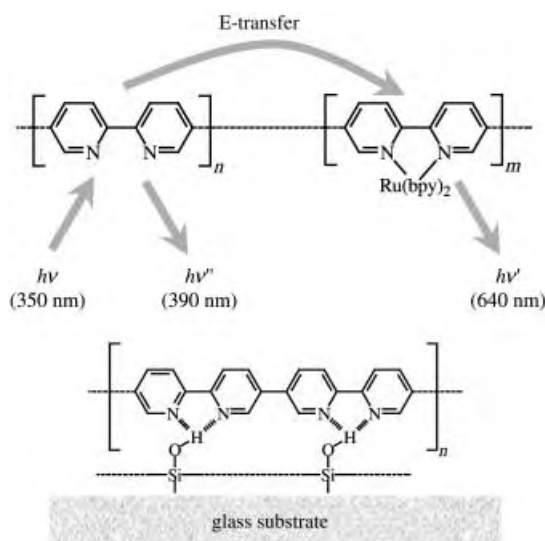


Figure 21. Top: transfer of the photoactivated energy to other molecular parts; bottom: coordination of bipyridine units to Si-O-H groups.^[93–96, 98–103]

Copper complexes of polymers composed of 6,6'-dimethyl-substituted and 6,6'-dihexyl-substituted bipyridines were synthesized and investigated with respect to their optical and electrochemical properties.^[100] A film of poly(bipyridine) molecules vacuum-deposited on a glass substrate has the molecules oriented parallel to the surface of the substrate (Figure 21, bottom). The coordination of poly(bipyridine) to the substrate is proposed to explain such an orientation.^[98]

In 1985, Sassoon described a two-electrolyte system for energy storage based on tris(bipyridine)ruthenium compounds and a *N,N,N,N*-tetraalkyl-*p*-phenylenediamine derivative bound covalently to a poly(3,3-ionene) polyelectrolyte (Figure 22).^[105] An inhibition of more than five orders of magnitude in the photochemical properties of the system were found relative to the reverse electron-transfer reaction between $[\text{Ru}(\text{bpy})_3]$ and the radical cation of *N,N,N,N*-tetraalkyl-*p*-phenylenediamine.

In 1997, Wasielewski and Wang published a sophisticated approach to metal-ion-sensitive polymers,^[106] in which they chose a partially conjugated polymeric system consisting of oligo(*p*-phenylenevinylene) segments that were covalently

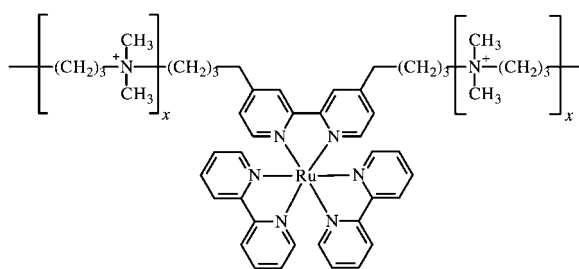


Figure 22. Covalent binding of a photosensitizer to a polyelectrolyte by Sassoon.^[105]

connected to bipyridines at their 5,5'-positions by a Wittig-type reaction. As shown in Figure 23, two polymers with different segment ratios were synthesized. The transoid conformation of the free bipyridines means there is a dihedral angle of approximately 20° between the pyridine planes. The corresponding metal complexes have been formed, and the optical behavior of the free polymer and the polymer–ion complex has been compared. Since the twisted conformation is forced into a planar one upon metal complexation and the partially conjugated polymer is therefore transformed into a fully conjugated polymer, different physical properties are obtained (Figure 24). The addition of Pd^{II} ions to the polymer shown in Figure 23 (top) shifts the absorption maximum of the uncomplexed polymer from 455 to 564 nm. Different absorption maxima were obtained with different metal ions, with the shift ranging from 38 to 112 nm. Chen et al. studied the effects of π conjugation on the photophysics and excitation dynamics of these polymers.^[107] Relative to the homopolymers, they demonstrated blue shifts in their absorption and emission spectra, spectral diffusion in stimulated emission, and enhancement in their photoluminescence quantum yields and lifetimes. The ionochromic effects and structures of the metalated polymers were recently published.^[108]

Yu et al. utilized Heck-coupling reactions to synthesize photorefractive copolymers based on *p*-phenylenevinylene and tris(bipyridine)ruthenium or tris(bipyridine)osmium complexes for nonlinear optics.^[109, 110] A variety of polymers with slightly different substituents to enhance the solubility were reported. While most polymers were synthesized by Heck coupling of iodo-substituted tris(bipyridine)ruthenium complexes with *p*-phenylenevinylene or other iodo-substituted co-monomers (Figure 25), there has been one approach utilizing the Horner–Wadsworth–Emmons reaction of free bipyridine ligands and metal complexation after polymerization (Figure 26). Klemm et al. also used the Heck-coupling procedure for the preparation of conjugated organic polymers.^[111, 112]

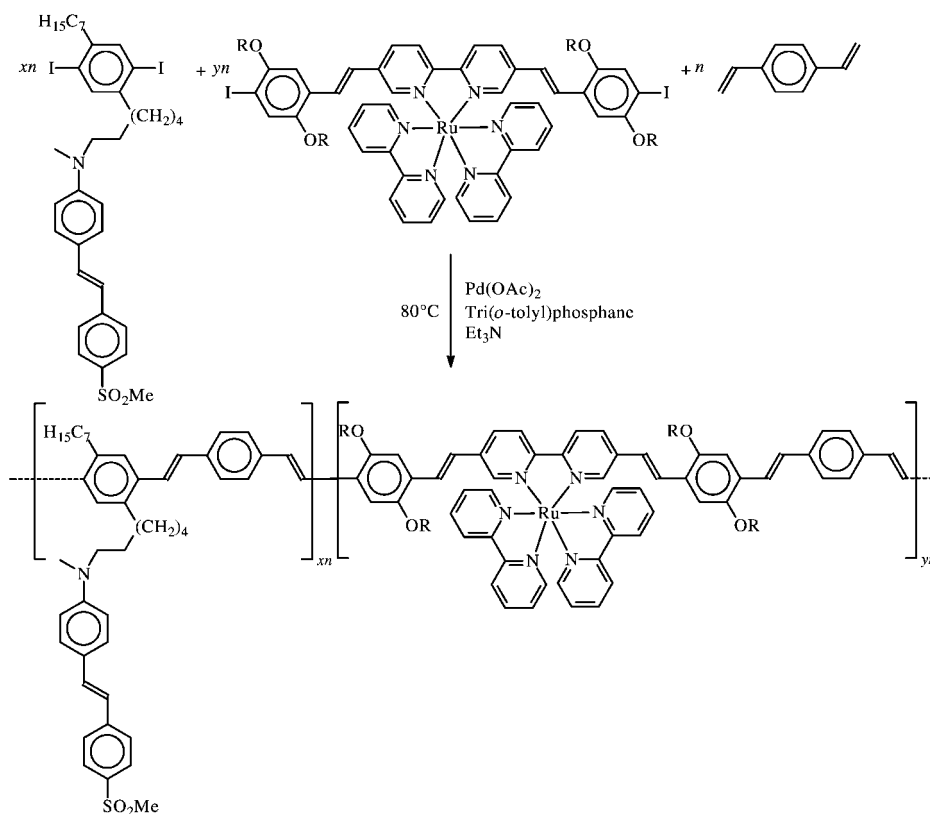
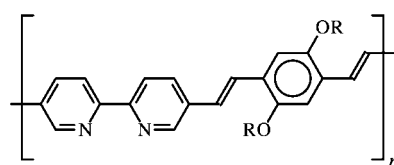


Figure 25. Heck coupling of alkenes with aryl iodides.^[110]



R = 2-ethylhexyl

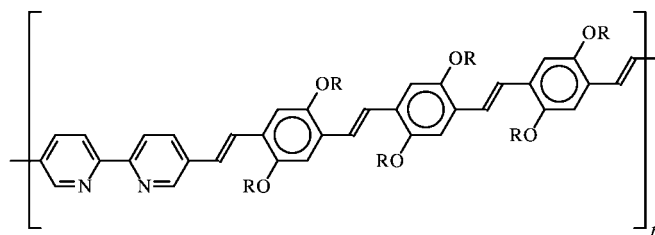


Figure 23. Partially conjugated ion-sensitive polymers.^[106]

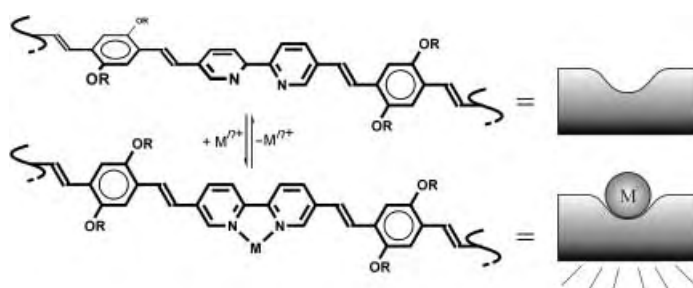


Figure 24. Chelating a metal ion forces the bipyridine group from a twisted conformation into a planar one and enables full conjugation of the polymer.^[106]

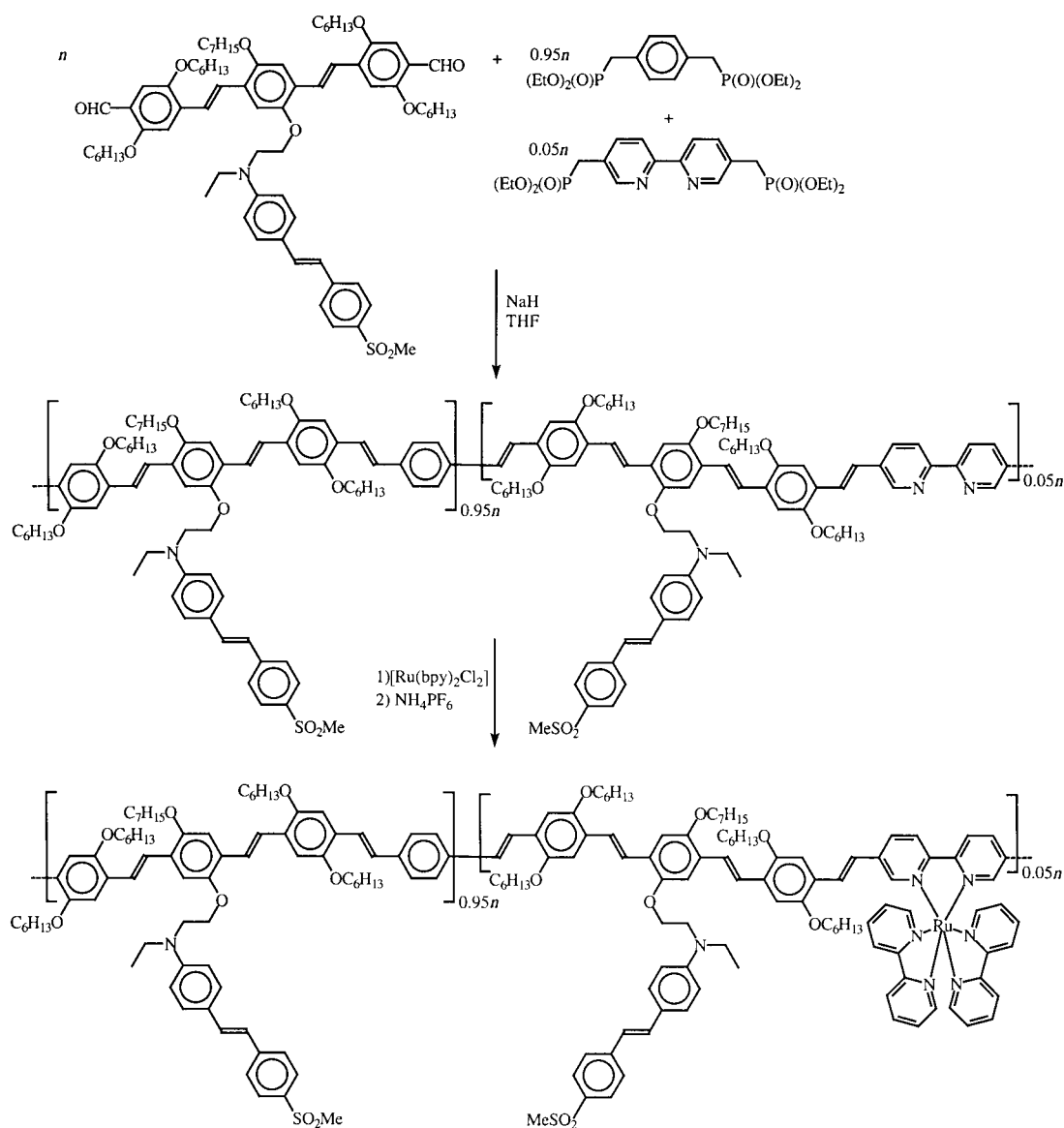


Figure 26. Horner–Wadsworth–Emmons reaction for the synthesis of photorefractive polymers.^[110]

The reaction of 5,5'-dibromobipyridine and substituted phenyldiacetylenes provided conjugated polymers with a rigid backbone and molecular weights up to $23\,000\text{ g mol}^{-1}$ (Figure 27 a). The polymers were characterized by NMR and UV/Vis spectroscopy, gel permeation chromatography (GPC), and vapor-pressure osmometry. Fluorescence quantum yields ϕ_{fl} between 71 and 96% make these new compounds potential candidates for light-emitting diode (LED) or laser-dye applications. The corresponding polymeric metal complexes have not yet been prepared. Conjugated polymers comprising the arylene–ethylene architecture have also been published by Schanze et al. (Figure 27 b).^[113–115] Similar to the system described by Wasielewski and Wang (Figure 23),^[106] the transoid bipyridine was forced into a cisoid conformation upon complexation and, therefore, the conjugation in the polymer was extended. For this purpose, instead of chelating the polymer after polymerization, bipyridinerhenium(i) complexes were polymerized. Spectroscopic studies revealed fluorescence at 435 nm (2.85 eV) in all the polymers at

298 K, with the fluorescence being quenched with increased molar fractions of Re^{II} in the polymer.

In 1986, Evers and Moore were the first to prepare bipyridine-containing poly(benzobisoxazole)s and poly(benzobisthiazole)s^[116] when they copolymerized bipyridine-4,4'-dicarboxylic acid chloride with terephthalic acid and 4,6-diamino-1,3-benzenediol dihydrochloride or 2,5-diamino-1,4-benzenedithiol. The polymers were essentially unaffected at 316°C and displayed thermo-oxidative stability for 200 h. Chan et al. later reported the synthesis and physical properties of a series of poly(benzobisoxazole)s and poly(benzobisthiazole)s containing bipyridine derivatives.^[117, 118] These polymers were synthesized by polycondensation of bipyridine-4,4'-dicarboxylic acid or bipyridine-5,5'-dicarboxylic acid and diaminobenzenediols in poly(phosphoric acid) (Figure 28). The polymers exhibited thermal stabilities up to 650°C in a nitrogen atmosphere and up to 590°C in air. Polymers containing bipyridine-5,5'-dicarboxylic acid demonstrated a lyotropic liquid-crystalline phase in methanesulfonic acid;

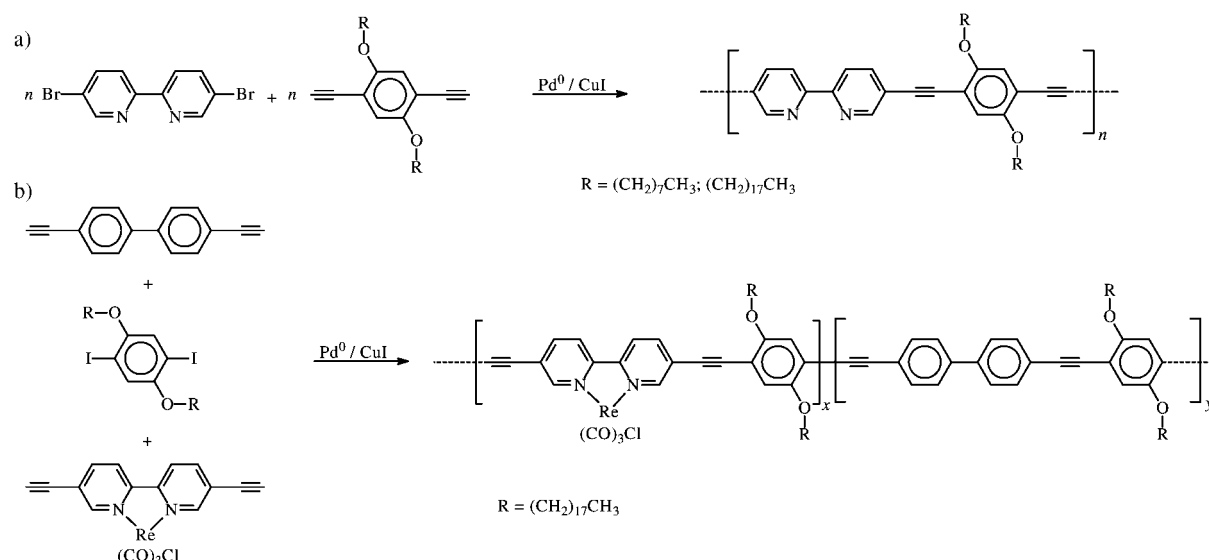


Figure 27. Conjugated polymers based on bipyridine and aryl diacetylene a) ref. [111, 112]; b) ref. [113].

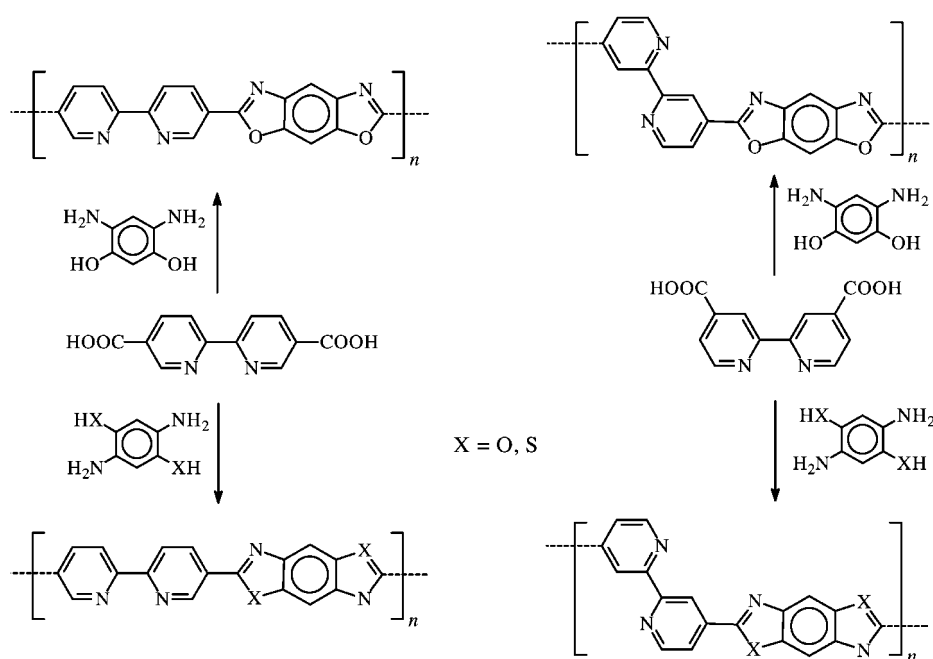


Figure 28. Poly(benzobisoxazole)s and poly(benzobisthiazole)s containing bipyridine units in the backbone.^[117]

however, the polymers containing bipyridine-4,4'-dicarboxylic acid did not demonstrate any anisotropy. The formation of polymeric ruthenium complexes increases the mobility of the charge carriers by two orders of magnitude to $10^{-5} \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$.

Rigid-rod benzobisazole polymers as well as poly(benzobisthiazole)s and poly(benzobisoxazole)s with main-chain bipyridine-5,5'-diyl units were reported by Tan et al. in 1999 (Figure 29).^[119] The polymers were doped with AgNO_3 to enhance the conductivity from 10^{-10} – $10^{-8} \text{ S cm}^{-1}$ to 10^{-5} – $10^{-4} \text{ S cm}^{-1}$. A conductivity of 25 – 42 S cm^{-1} resulted when Ag^+ was reduced to Ag^0 by NaBH_4 .

In more recent work, Chan et al. published a broad range of bipyridine-based polyamides (Figure 30a) and polyesters (Figure 30b).^[120, 121] Polyamides were synthesized by Yamazaki's method using pyridine and triphenyl

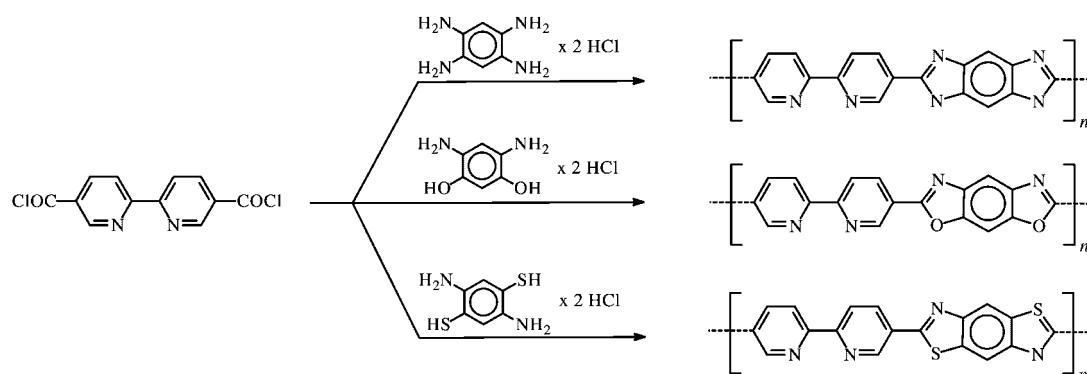


Figure 29. Synthetic route to poly(benzobisoxazole)s and poly(benzobisthiazole)s.^[119]

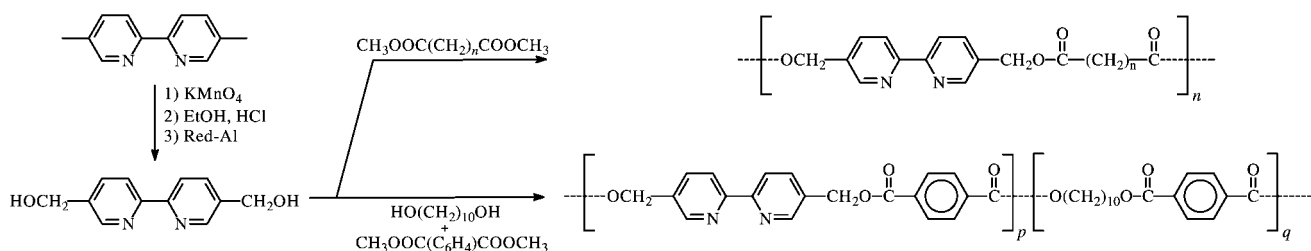


Figure 31. Liquid-crystalline polyesters showing thermotropic behavior after the addition of several molar equivalents of metal ions (FeCl_2 or CuCl_2).^[122]

concentrations of metal ions. A nematic mesophase was observed in the case of the aromatic polyesters. Two endothermic transitions at 114 and 135 °C, respectively, arising from the transition from the crystalline to the liquid-crystalline and finally to the isotropic state were observed regardless of the kind and amount of metal ions present. The structural properties of a polyester– Cu^{II} complex were examined by ESR spectroscopy. Several years later, Rubner et al. described the synthesis of a polyester similar to that synthesized by Hanabusa et al.^[122] by utilizing a modified Schotten–Baumann reaction of 4,4'-bis(hydroxymethyl)bipyridine and dodecanedioyl dichloride in THF.^[123, 124] However, since the solubility of the resulting polymer was poor, they treated bis(hydroxymethyl)bipyridine with $[\text{Ru}(\text{bpy})_2\text{Cl}_2]$ and polymerized the resulting Ru complex with dodecanedioyl dichloride to obtain a polymer with an average molecular weight of about 5500 g mol^{-1} . The polymer became soluble in acetone by using PF_6^- counterions. In contrast, when the counterions were changed to Cl^- , the new polymer was soluble only in polar solvents such as water or methanol. Light-emitting devices were produced from these materials by utilizing either a spin-coating technique or a layer-by-layer self-assembly. The spin-coated devices produced maximum luminance levels of 250–300 cd m^{-2} with an external quantum efficiency of 0.2% photons per electron. Devices based on sequentially adsorbed layers of the polyester and poly(acrylic acid) exhibited a maximum light output of 40–50 cd m^{-2} and external quantum efficiency of 1–3% photons per electron.^[123, 124]

Polyamides and polyureas with acyclic and cyclic bipyridyldiamino structures in the polymer backbone were described by Pappalardo et al. in 1987.^[125, 126] While the polymer containing the acyclic bipyridine moiety formed stable metal complexes with Co^{II} , Cu^{II} , or Ni^{II} ions, the cyclic structure exhibits a special affinity towards Cu^{II} ions (Figure 32). The polymers were characterized by NMR and IR spectroscopy and their thermal behavior was studied. The polyamides were stable at temperatures above 400 °C, while the polyureas decomposed between 300 and 400 °C. The first bipyridine-containing polyureas were reported by Zhang and Neckers in 1983.^[127–129] The polymers were prepared from 4,4'-diaminobipyridine and toluenediisocyanate. The metal-complexing abilities of the polymers, in particular with cobalt, palladium, and vanadium ions, were investigated with special attention to the catalytic activity in the hydrogenation and epoxidation of olefins and in the aldol condensation. In addition to the soluble linear polymers, insoluble cross-linked moieties were prepared. In 1985, Neckers et al. reported on polyamides and their Pd^0 and Rh^{III} complexes.^[130, 131]

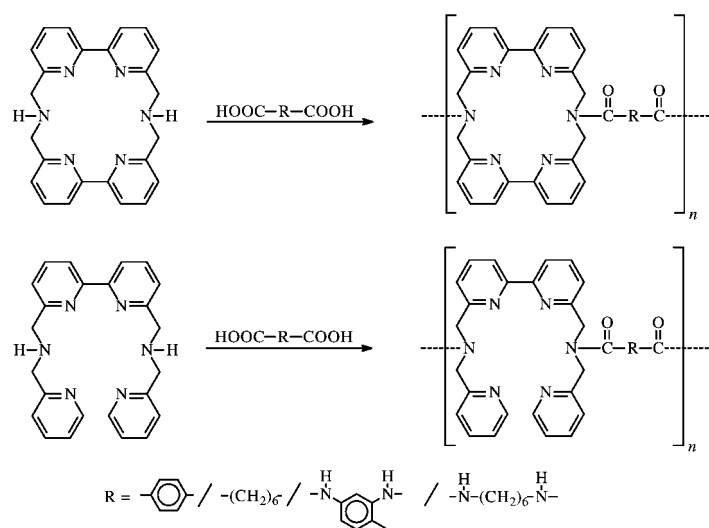


Figure 32. Polyamides and polyureas with cyclic and acyclic bis(bipyridyl) structures synthesized by Pappalardo et al.^[125, 126]

Polyimides consisting of 5,5'-diamino-bipyridine derivatives and aromatic tetracarboxylic acid anhydrides that were designed to be more heat-resistant, were described by Kurita and Williams in 1973.^[132–134] They also synthesized similar poly(amidoimide)s. In most cases, the pyridine units of the bipyridine derivatives were separated by a heteroatom or a functional group X ($\text{X} = \text{S}$, NH , or SO_2), but some were also linked together directly (Figure 33). Yang and co-workers later described polyimides consisting exclusively of 2,2'-bipyridine (Figure 33, top, $\text{X} = -$).^[135] They treated 5,5'-diaminobipyridine with three different aromatic dianhydrides, heating then effected imidization to obtain fairly thermostable polymers, for example, only a 5% weight loss occurred

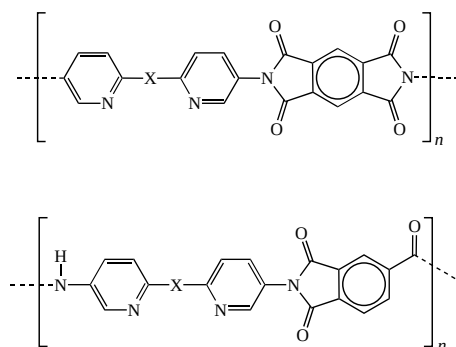


Figure 33. Polyimides and polyamideimides ($\text{X} = -, \text{S}, \text{SO}, \text{SO}_2, \text{NH}$) synthesized from 5,5'-diaminobipyridine derivatives.^[132, 133]

in the range of 480–580 °C. The polymers were treated with several different transition-metal ions, and the catalytic activity of the polymeric complexes in the condensation of benzaldehyde with acetophenone was investigated. The degree of catalytic activity for different metal ions was demonstrated to be in the order $\text{Zn}^{\text{II}} > \text{Co}^{\text{II}} > \text{Cu}^{\text{II}}$ and the yield of 1,3-diphenyl-2-propen-1-one was in the range of 6–32%. Recently, Chen et al. reported on novel polyimides (Figure 34) based on bipyridine.^[136] In addition to the synthesis, the group investigated the influence of the coordination of malenonitriledithiolatenickel on the copolymers, in particular on their thermal stability. The polymers had elevated glass transitions in the range of 270–320 °C and decomposition temperatures ranging from 370–520 °C. Majumdar and Biswas published the reaction of pyromellitic dianhydride with unsubstituted bipyridine in 1991.^[137, 138] In our mind, the presented structures are to be doubted and will not be considered any further.

In 1997, Kira and co-workers published the synthesis of poly(disilanylene-2,2'-bipyridine-5,5'-diyl) and poly(silylene-2,2'-bipyridine-5,5'-diyl) and their ruthenium complexes (Figure 35).^[139] The polymeric ruthenium complexes underwent metal-to-ligand charge-transfer excitation which resulted in photoconductivity. A photocurrent with a maximum at 470 nm of approximately 1.8×10^{-13} A was measured in a sandwich-type cell with aluminum and ITO as the top and bottom electrodes, respectively, at 6 V. The optical properties of the polymeric metal complexes were studied two years later.^[140] A noncovalent polymerization of bis(bipyridine)alkanes was carried out by Ching and Elliot in 1999.^[141] The addition of iron and cobalt ions to spin-coated films of the monomers shown in Figure 36 resulted in highly cross-linked electroactive coordination polymers. Charge-transport measurements by chronoamperometry on thin films of the Fe^{II} -containing polymer in which the alkyl linker consists of 2, 4, and 6 methylene groups shows $D^{1/2}C$ values (D = charge-

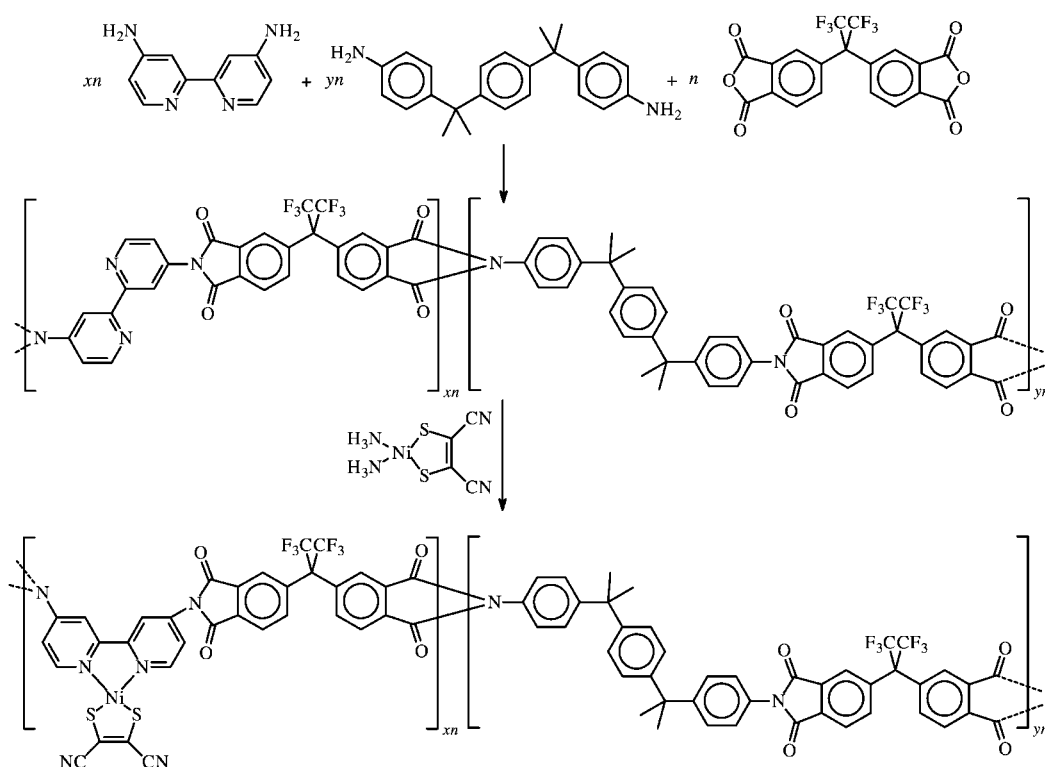


Figure 34. Copolymers based on polyimides with bipyridine units in the polymer backbone.^[136]

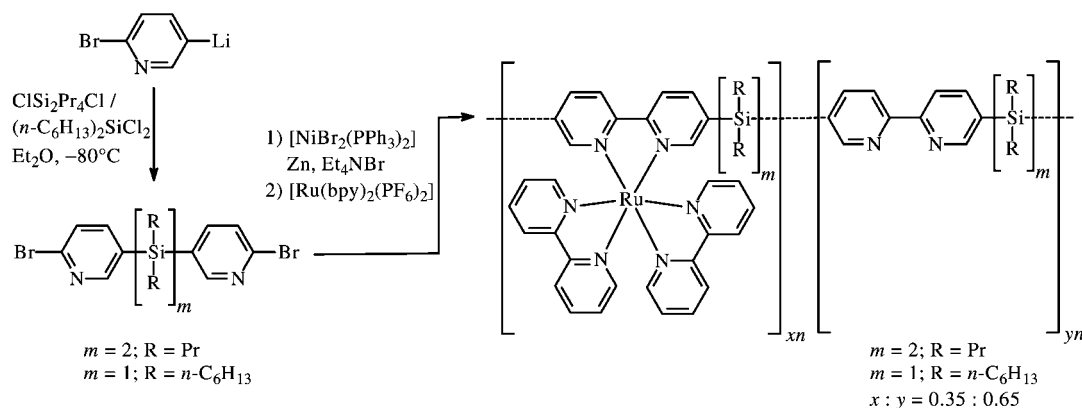


Figure 35. Synthesis of σ - π -alternating copolymers and their ruthenium complexes by Kira and co-workers.^[139, 140]

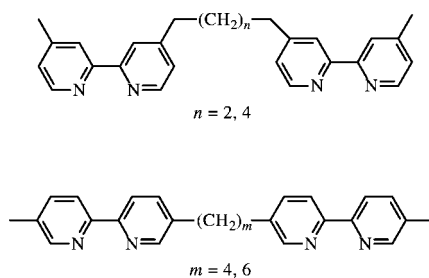


Figure 36. Coordinative polymer films were prepared by adding metal ions to the shown ligands.^[141]

transfer diffusion coefficient; C = concentration of redox sites) ranging from 9.5×10^{-8} to $2.3 \times 10^{-8} \text{ mol cm}^{-2} \text{ s}^{-1/2}$ at 298 K and follow a trend of decreasing $D^{1/2}C$ values with increasing length of the alkyl chain. No such trend was observed for the analogous systems linked through the 5-position. Attempts to prepare polymer films with other metal ions such as Ni^{II} , Cu^{II} , or Ru^{II} failed.

A special case of polymers containing bipyridine units in the polymer backbone are molecules containing only one bipyridine unit. The addition of metal ions to that moiety results in star-shaped polymers. Different approaches to these structures have been reported in the literature. Murray and co-workers treated bipyridine-4,4'-dicarboxylic acid chloride with poly(ethylene oxide) monomethyl ester ($M_w = 350$) to reveal the substituted ligand 4,4'-di(poly(ethylene oxide) methyl ether)bipyridine.^[142] The transport, ionic conductivity, and viscosity properties of the molten salt were studied after addition of cobalt perchlorate. For LiClO_4 (1.3 M), the average diffusive jump rate was about 3 s^{-1} , the average electron-hopping rate was about $2 \times 10^4 \text{ s}^{-1}$, and the rate of short-range motions of the hard metal complex core within its soft polyether shell was determined to be about 10^5 s^{-1} .

Chujo et al. synthesized bipyridines substituted on just one side with poly(ethylenoxide)s or poly(propylenoxide)s (Figure 37)^[143–145] by starting with 4,4'-dimethylbipyridine. Reaction with LDA and subsequent addition of an α -alkyl ether- ω -tosylate polymer yielded the desired polymer containing a single bipyridine unit. The addition of metal ions such as Ni^{II} , Co^{II} , or Ru^{III} yielded star-shaped structures, which were investigated by UV/Vis spectroscopy and GPC analysis. While the Ru complexes were stable against shearing forces under GPC conditions, the Ni^{II} and Co^{II} complexes dissociated. Following the current interest in metal clusters and colloids in the size range of 1–10 nm for catalytic use and as advanced materials in electronics (for example, as quantum dots), poly(ethylene oxide)-grafted palladium clusters were prepared and used in a first application.^[145]

A completely different approach towards star-shaped polymers was established by the research groups of Fraser and Schubert.^[146–155] They used metal complexes of halomethyl-substituted bipyridines as initiators for the living cationic polymerization of 2-oxazolines. The polymer growth starts from the metal complex and, depending on the substitution pattern of the complex, several different structural types are accessible (Figure 38). To obtain a higher order of structural diversity, not only 4,4'-bipyridines were utilised, but 5,5'- and

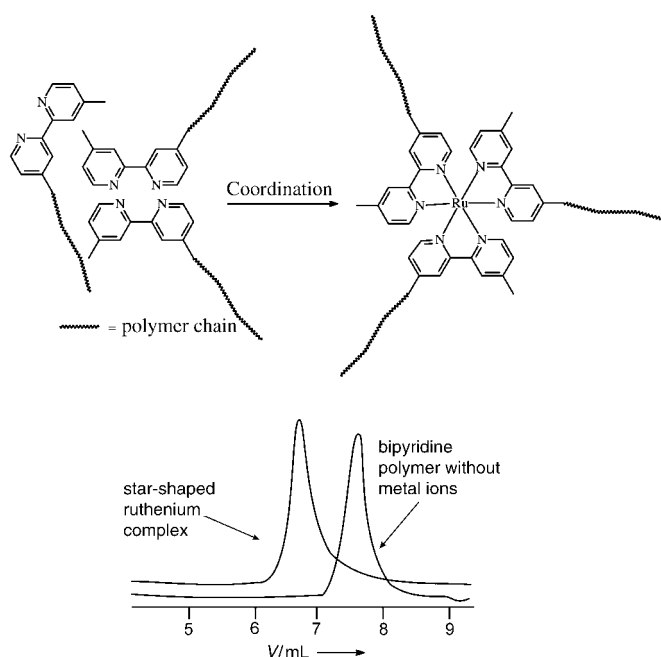


Figure 37. Top: Preparation of star-shaped polymers by the addition of metal ions to monofunctionalized bipyridine polymers; bottom: GPC analysis showed a significant shift in the molecular weight after complexation.^[143, 145]

6,6'-functionalized bipyridines were used as well. In addition, the living character of the polymerization and the accessibility of suitable monomers, for example, 2-ethyloxazoline, 2-phenyloxazoline, and 2-undecyloxazoline, allow the preparation of amphiphilic block copolymers (Figure 39). Finally, depending on the choice of a suitable termination reagent, more functionalities can be introduced into the molecules. In the case shown in Figure 39, the oxidation of the Cu^{I} ion to Cu^{II} would switch from the star-shaped molecule to a linear system since Cu^{II} ions cannot form stable complexes with 6,6'-substituted bipyridines, but is chelated by terpyridines to form very stable complexes.

The principle of initiating polymerization by supramolecular metal complexes and ligands does not only work with oxazolines. In two independent papers, Schubert and Hochwimmer as well as Wu and Fraser recently used 6,6'-substituted bipyridinecopper(I) complexes^[156] and 4-mono- and 4,4'-disubstituted bipyridines^[157] as initiators for the controlled radical polymerization of styrene (Figure 40). While we used the tris(4,4'-dimethylbipyridine)copper(II) complex as the catalyst for polymerization and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone as the solvent, Fraser's group used either 4,4'-bis(tridecyl)bipyridine or 1,1,4,7,10,10-hexamethyltriethylenetetramine and CuBr or CuCl as catalysts. Polymerization was carried out either in the bulk or in solution with anisole as the solvent. For a further extension of this method, the same research groups have recently used the so-called "co-initiator approach" with hydroxy-functionalized N-heterocyclic ligands as the co-initiator and aluminum alkoxides as efficient initiators for the ring-opening polymerization of ϵ -caprolactone and lactid acid (Figure 41).^[158–161]

The formation of well-defined structures by self-assembly is the central theme of supramolecular chemistry. Polymers with

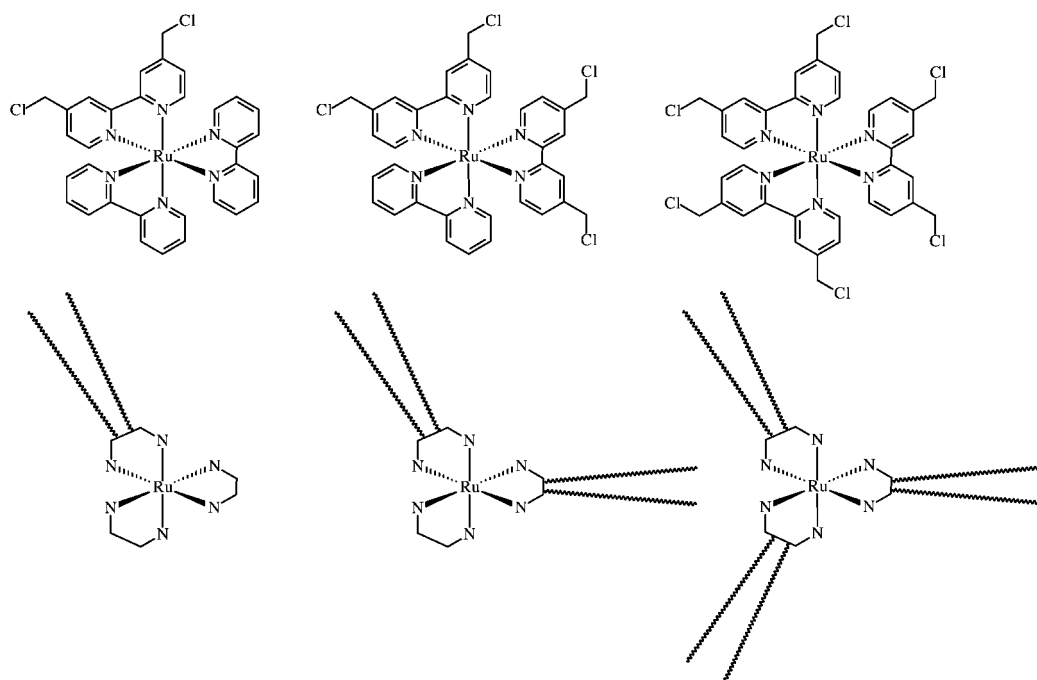


Figure 38. Different substitution patterns of the metal complex (upper row) give access to different structural types of star-shaped molecules (lower row).^[155]

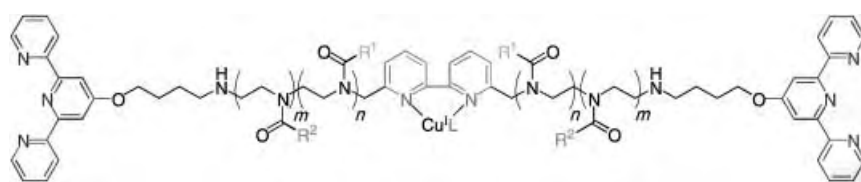


Figure 39. Amphiphilic macromolecule with two different metal-binding sites ($R^1 = \text{Et}$, $R^2 = \text{Ph}$).^[153]

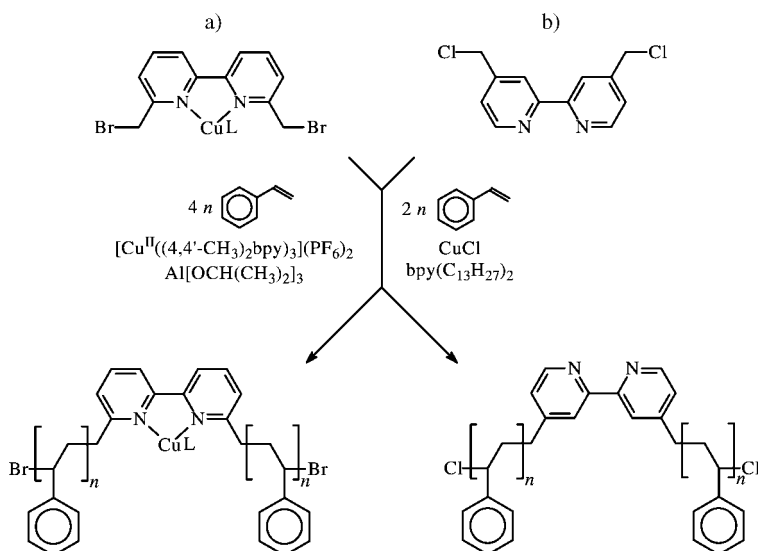


Figure 40. Synthesis of star-shaped polystyrene by using metallosupramolecular initiators and catalysts (a);^[156] and a functionalized bipyridine for initiation and CuCl/bipyridine as catalyst (b).^[157]

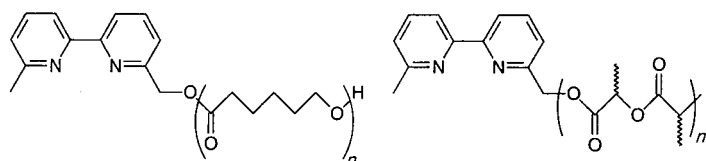


Figure 41. Introduction of metal-binding units into biodegradable polymers.^[161]

two bipyridine units connected by a short and flexible spacer belong to this area of research. In their monomeric form, these systems are already well-known in supramolecular chemistry.^[1, 4] Eisenbach et al. prepared telechelic polymers consisting of bipyridine and bis(bipyridine) end groups.^[162–172] As shown in Figure 42, both types of polymers can be elongated on addition of Cu^I or Ag^I ions by formation of the corresponding metal complexes. The bis(bipyridine)-functionalized polymers form helical structures similar to their monomeric analogues. The resulting coordination polymers were characterized in detail with respect to their mechanical properties and morphological behavior. They were shown to be microphase-separated systems in the bulk, with nano- to mesoscopic superstructures consisting of aggregates of bipyridinecopper complexes in a polyether matrix.

Hosseini and co-workers described a single-stranded helical coordination polymer (Figure 43), as a racemic mixture of left- and right-handed helices, which was obtained by self-assembly of an *exo*-ditopic ligand and silver ions.^[173] The

structure of the infinite network was established by single-crystal X-ray structural analysis. Although the structure of the coordination polymer was investigated, no information concerning the degree of polymerization was given. In this field of supramolecular chemistry, Stoddart and co-workers described a poly(bis[2]catenane) containing a combination of covalent, mechanical, and coordinative bonds, in which the coordina-

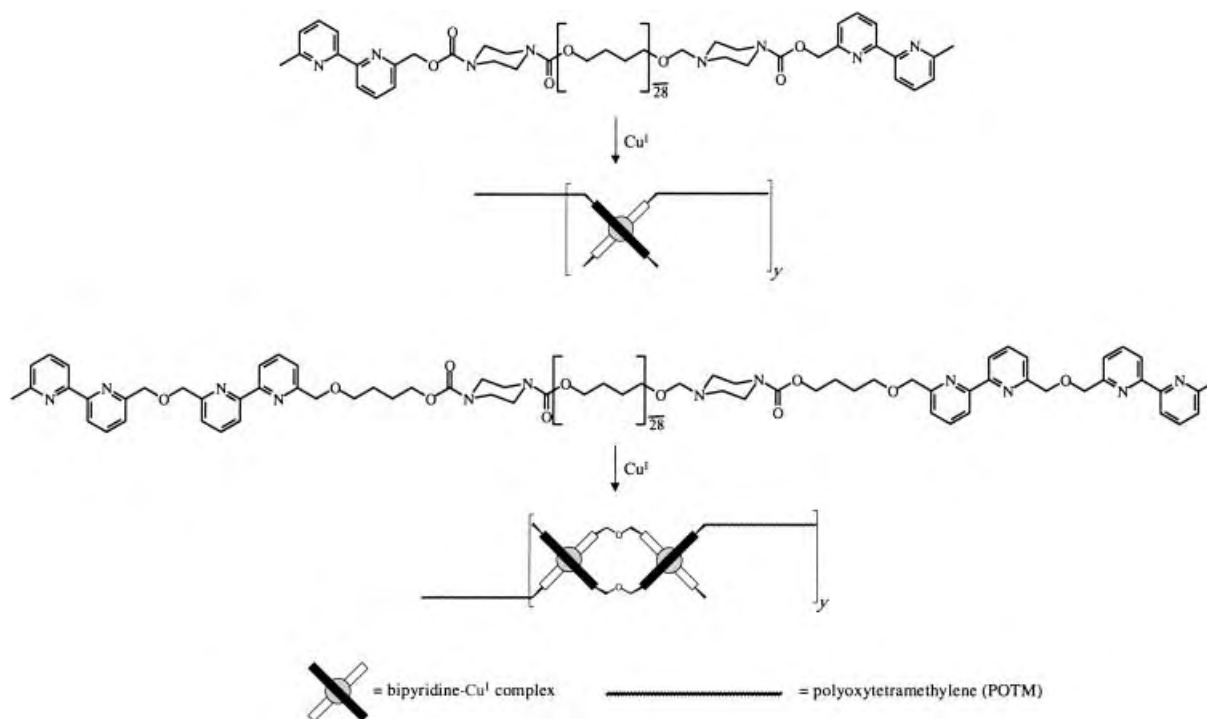


Figure 42. Synthesis of supramolecular $(\text{ABA})_n$ systems by the addition of Cu^{I} ions.^[162–172]

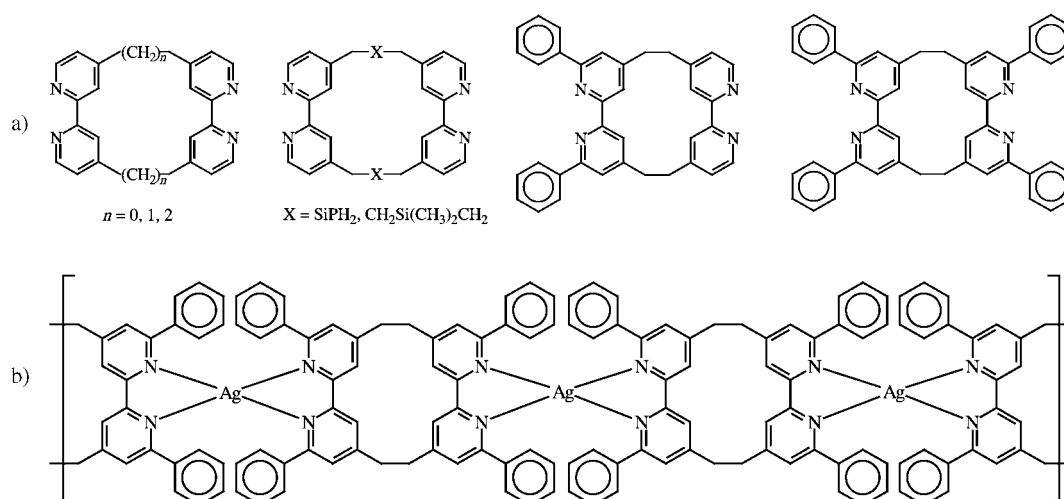


Figure 43. Helical coordination polymer (b) formed by the self-assembly of a bipyridine-based ligand (a).^[173]

tive bonds are based on bipyridine–silver interactions.^[174] The degree of polymerization was determined to be 40, which is equivalent to a molecular weight of $M_n = 150\,000 \text{ g mol}^{-1}$.

2.4. Bipyridine-Containing Resins and Beads

Pioneering efforts by Merrifield in polypeptide synthesis made the anchoring of reagents to insoluble supports, known as solid-phase synthesis, popular.^[175] In the late 1970s, Card and Neckers were the first to publish a report on bipyridines bound to polymeric supports.^[176] Bipyridines were attached after ring bromination and lithiation of polystyrene-divinylbenzene copolymer beads (Figure 44). Shaking a mixture of

the polymer and a metal salt in solution led to complexation of the metal ions, and the complexed resin could be easily removed by filtration. The amount of metal ions bound to the polymer was partially controlled by the solvent system because of the different accessibility of the chelating compound. In later works, the same research group prepared zero-valent polymeric metal complexes by chelating, for example, $[\text{Cr}(\text{CO})_4]$, $[\text{Mo}(\text{CO})_4]$, and $[\text{W}(\text{CO})_4]$.^[177–179] The catalytic activities for the hydrogenation of alkenes and alkynes based on these systems showed, for example, a turnover number greater than 2800 for the hydrogenation of 3-methyl-3-buten-2-ol.

In 1981, Drago et al. utilized Necker's polystyrene beads to investigate the activity of polymer-bound bipyridineplatinum

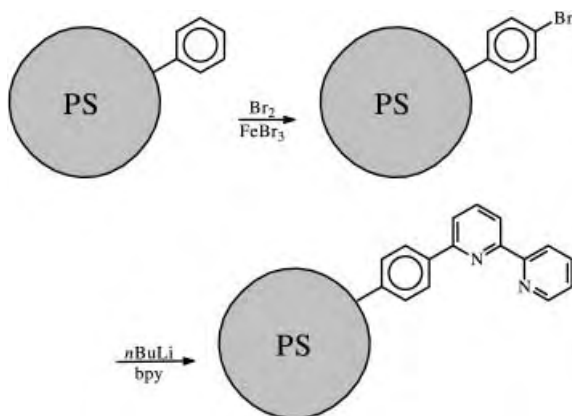


Figure 44. Polystyrene beads containing bipyridine end groups synthesized by Card and Neckers.^[176, 179]

and bipyridinerhodium complexes in the catalytic hydrogenation of olefins.^[180] Turnover numbers as large as 300 were obtained with the rhodium systems. One year later, Tsuchida and co-workers tried to overcome the reduced activity of the ligands located at the inside of the resins.^[181] As shown in Figure 45, they grafted polystyrene beads with soluble oligo(ethylene oxide) spacers to allow the same degree of solvation of the pyridine ligand as in a homogeneous solution. In this case, the beads were cross-linked with 20 mol % divinylbenzene and the complexation behavior with Cu^{II} ions was studied. An apparent formation constant of $11 \times 10^4 \text{ s}^{-1}$ was determined for the complex in water, and a stability constant of 4700 L mol^{-1} .

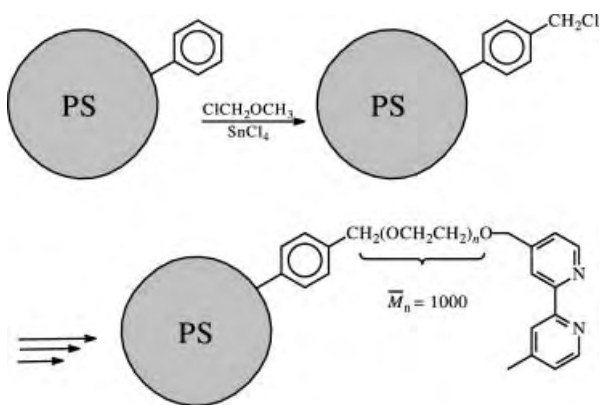


Figure 45. Grafted poly(ethylene oxide) spacers enhance the solubility of the complexing unit.^[181]

In their research towards the photochemical behavior of polymers with covalently bound tris(bipyridine)ruthenium complexes, Bourdelande and de March prepared a system with complexes directly anchored to a hydrophobic polystyrene bead.^[182] This system was far less efficient than the monomeric $[\text{Ru}(\text{bpy})_3]^{2+}$ complex with respect to photo-induced electron-transfer from the complex to methyl viologen. The authors assumed that the hydrophobicity of the polymeric backbone prevented the approach of water-solvated methyl viologen; therefore they introduced, similar to Tsuchida and co-workers (Figure 45),^[181] water-soluble tri-

(ethylene oxide) spacers.^[183] However, though they demonstrated the spectroscopic properties of the polymeric Ru^{II} -complexes to be similar to those of $[\text{Ru}(\text{bpy})_3]$, the photochemical behavior was different. Therefore, the authors concluded that the applied polymeric supports prevent the bound complexes from being useful for photoinduced electron-transfer reactions. Nakamura and co-workers prepared polymer-bound nitridomolybdenum(vi) complexes by utilizing polystyrene with pendant bipyridine units, similar to the system published by Card and Neckers (Figure 44).^[184] The polymeric metal complexes were characterized by photoacoustic and resonance Raman spectroscopy. The hydrolysis and hydrolytic reactions of the complexes, which resulted in the formation of ammonia, were investigated.

By utilizing a more sophisticated system based on colloidal titanium oxide particles, Yoshinaga et al. investigated recently the photochemical behavior of tris(bipyridine)ruthenium complexes bound covalently to these particles.^[185] The poly-(maleic anhydrides-co-styrene)trimethylsiloxane-coated titanium particles were grafted with amino-functionalized copolymers from *N,N*-dimethylacrylamide- and acrylate-modified bipyridine (Figure 46). It was suggested that in the course of the photoreaction the excited electron of the complex is transferred to methyl viologen via the titanium surface. The maximum yield of methyl viologen was 6 %, but depended on the flexibility of the bipyridine group on the grafted polymer. The quantum yield of fluorescence was less than 0.001.

Thermally stimulated self-aggregation of silica particles was reported by the same research group in 1997.^[186] The authors targeted the thermal triggering of particle aggregation by making use of temperature-dependent changes of intramolecular coordination versus intermolecular coordination of certain polymeric bipyridine-metal complexes described by Chujo in 1993.^[79, 80] For this purpose, ultrafine colloidal silica particles were coated with trimethoxysilyl-terminated poly-(acrylamide-(2-(4-(4'-methylbipyridyl))ethyl acrylate) or poly-(*N*-isopropylacrylamide-(2-(4-(4'-methylbipyridyl))ethyl acrylate) (Figure 47). A monodisperse solution of the latter system was stable for 24 h at 15 °C, as indicated by a constant absorption at 500 nm. The absorption decreased when the temperature was elevated to 35 °C. Dynamic light scattering analysis demonstrated that particles in the size range of 1.2 to 1.4 μm were formed.

3. Macromolecules Bearing Terpyridine Units

3.1. Dendrimers with Terpyridine Units

Dendritic structures represent a very special case of terpyridine-containing macromolecules. The following examples are divided into two sections: Dendrimers containing a terpyridine-metal complex inserted at the dendrimer core and dendrimers with terpyridine-metal complexes incorporated in the branching unit or attached to the surface of the molecules.

The use of metal complexes as the core of the molecule provides a convenient opportunity for a convergent synthesis of dendrimers. However, up to now only a few research

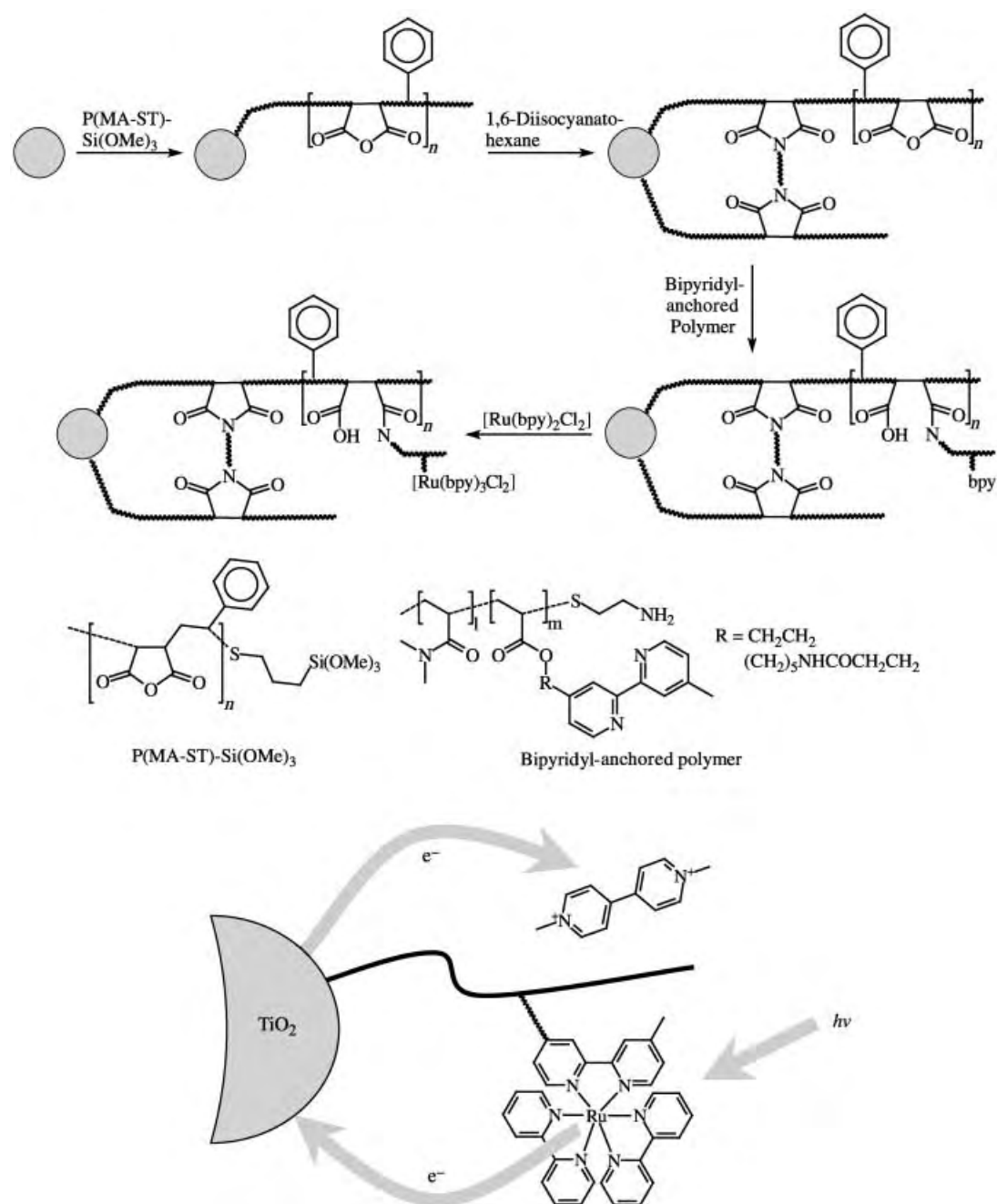


Figure 46. Top: Titanium particles modified with the polymer-grafting $[\text{Ru}(\text{bpy})_3]^{2+}$ complex; bottom: suggested mechanism of the photoreaction.^[185]

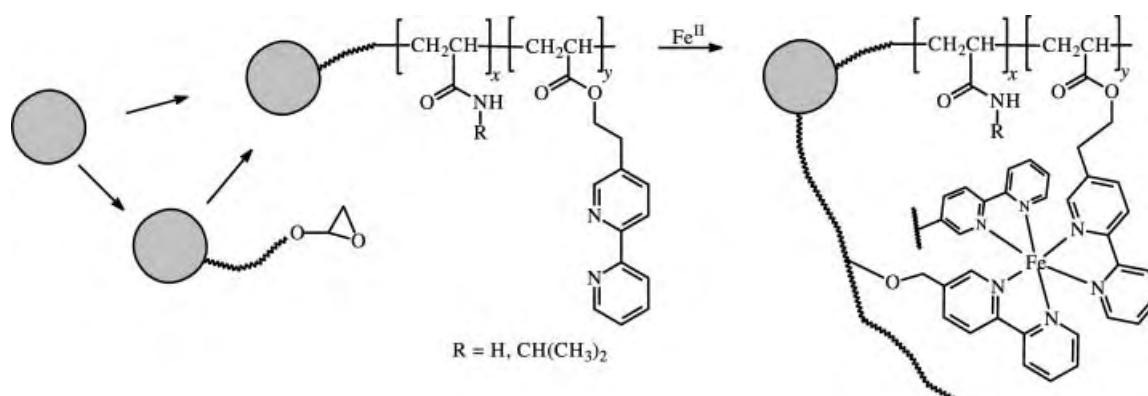


Figure 47. Self-aggregation by ligand exchange among the silica particles in response to temperature elevation.^[186]

groups have made use of this strategy. Chow et al. (Figure 48) reported the synthesis and characterization of metallodendrimers with a bis(terpyridine)iron(II) core up to the fourth generation by using benzyl ether based dendritic building blocks with propylene spacer moieties.^[187–190] Newkome et al. utilized this principle to connect two independently prepared dendrons in a process that mimicked a key and lock system (Figure 49).^[191, 192] Kimura et al. recently connected two 1,3,5-phenylene-based dendrons^[193] to form a dendrimer that exhibited one oxidation ($E_{1/2} = +1.12$ V versus SCE) and two reduction processes ($E_{1/2} = -1.28$ and -1.43 V versus SCE). A large voltage difference between the current maximum of the reduction and the oxidation wave (ΔE) indicate a slower electron transfer than in the nondendritic complex.

A special case is represented by the work of Constable et al. in which they utilized a convergent approach consisting of connecting three bipyridine-functionalized arms through the formation of the bipyridine–metal complex to build starlike molecules with a tris(bipyridine)iron(II) or tris(bipyridine)-Co(II) core and bis(terpyridine)ruthenium(II) complexes in the outer sphere.^[27, 28, 194] NMR spectroscopy and MALDI-TOF mass spectrometry were used to characterize the resulting species. In the case of the iron(II)-containing dendrimers, the most intensive peak in the MALDI-TOF spectra was exhibited at $m/z = 6330$ Da, which indicates the loss of three PF_6 counterions. For molecules containing the cobalt(II) core, the loss of two to four counterions could be detected.

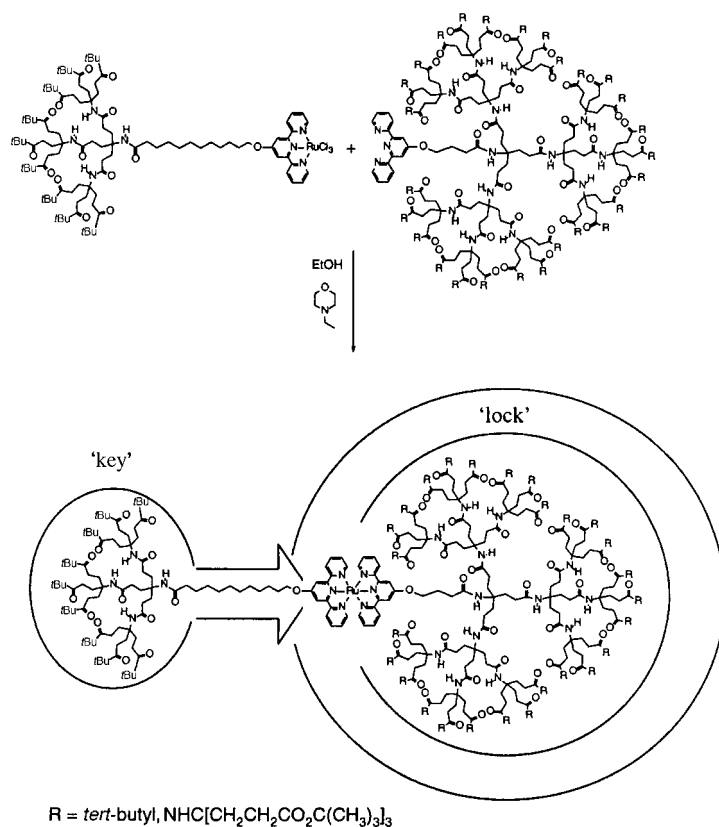


Figure 49. Lock and key system presented by Newkome et al.^[191, 192]

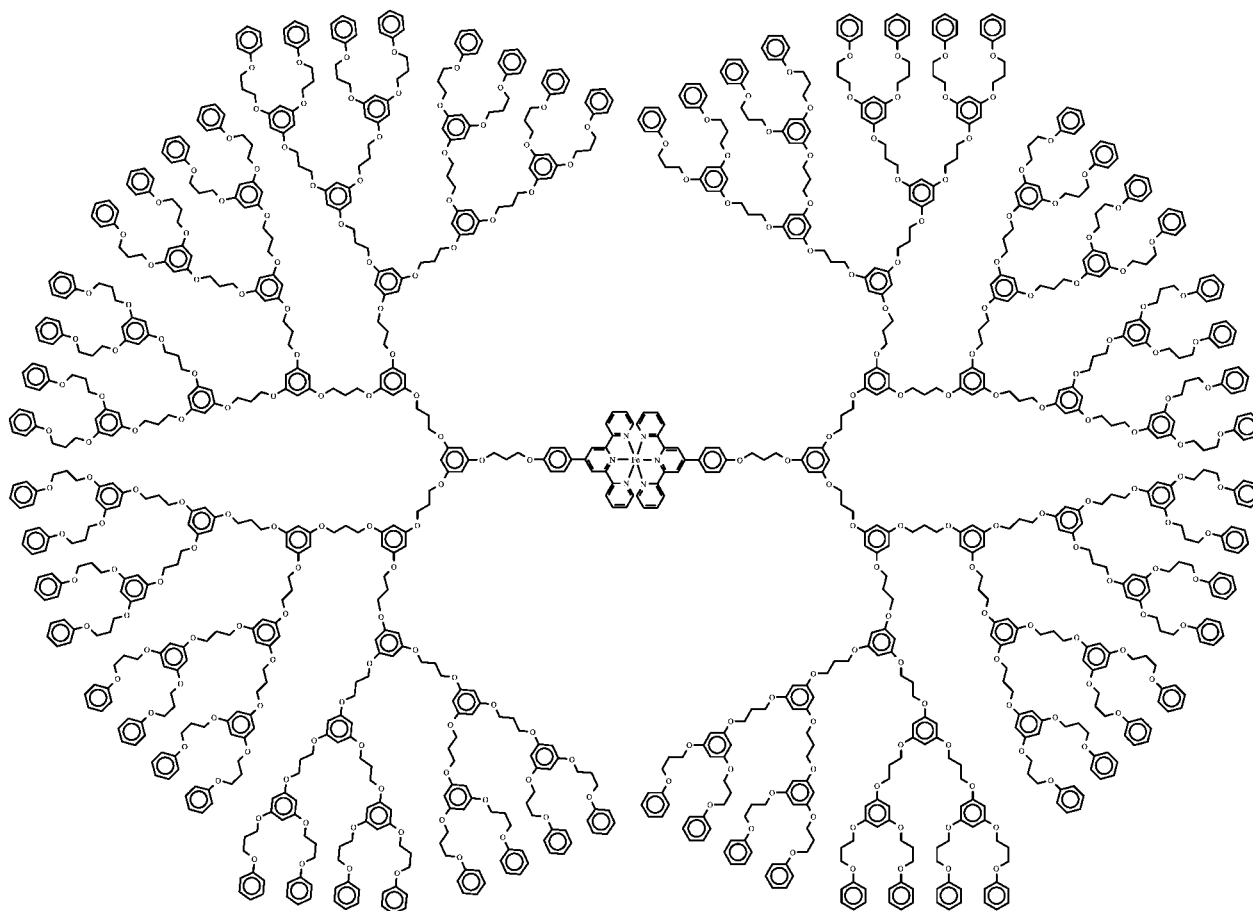


Figure 48. Benzyl ether based dendrimer with an Fe^{II} core.^[187–190]

Research on the second category, that is, starlike macromolecules with terpyridine metal complexes in the outer sphere, is being conducted by more research groups.^[21, 29–31, 194–202] Some of the published structures have already been reviewed,^[20] and therefore we will consider the most interesting and recent publications only. In 1996, Constable and Harverson presented a starlike macromolecule with 18 Ru^{II} centers and 36 positive charges.^[198] This molecule, prepared from hexakis(bromomethyl)benzene, possesses six arms, each containing three Ru centers (Figure 50). Constable and co-workers also published a “first generation” starlike system based on pentaerythritol bearing pendant [terpyridine-(4'-[2-(*tert*-butyldimethylsilyl)-1,2-carbaboranyl]-terpyr-

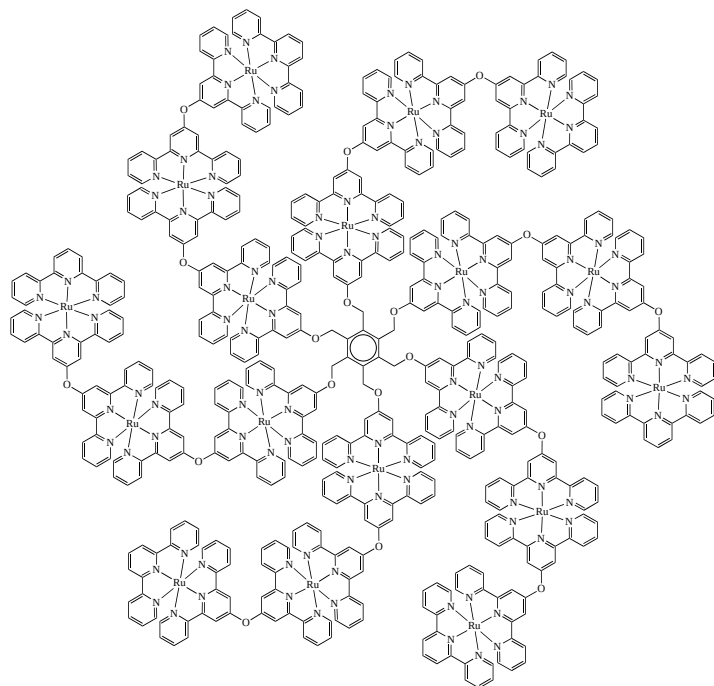


Figure 50. 18 Ru^{II} centers result in a 36-fold positively charged dendrimer.^[197, 198]

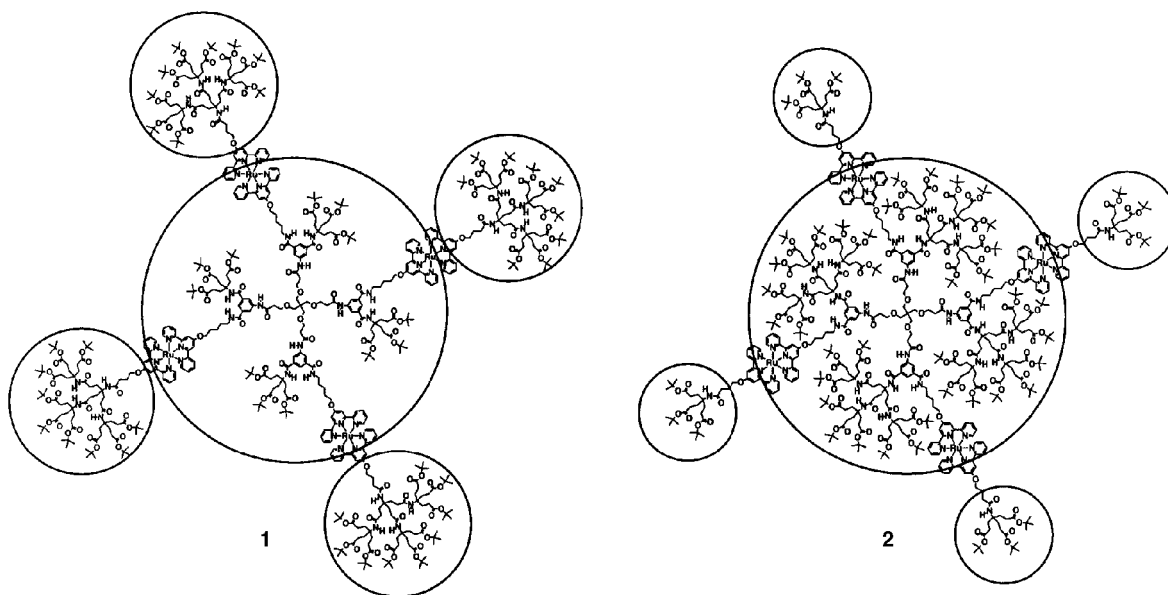


Figure 51. Isomeric metallodendrimers designed by Newkome et al.^[201]

idine]ruthenium(II) complexes.^[197] MALDI-TOF mass spectrometry was very useful for characterizing this high-molecular-weight, eightfold-charged system. In a more recent paper, the pentaerythritol core was used for assembling a second-generation hexadecanuclear metallosupramolecular system.^[199]

Tailor-made isomeric metallodendrimers have been synthesized by Newkome et al.^[201] The two dendrimers shown in Figure 51 have an identical molecular formula ($C_{597}H_{880}F_{48}N_{52}O_{136}P_8Ru_4$) and a molecular mass of 12 526 Da. The nanoscopic tetrahedral geometry of the methane molecule was mimicked by controlling the design of the macromolecular architecture. While IR, UV, NMR, and MALDI-TOF experiments of the two isomers revealed very similar results, electrochemical studies indicated that internal densities and void regions differ greatly. The voltammograms of both compounds are similar and exhibit two quasireversible waves at negative potentials that correspond to redox processes on the two terpyridine units. The $E_{1/2}$ values of the two waves of **1** ($E_{1/2} = -1.951$ ($\Delta E_p = 0.097$); -1.751 V ($\Delta E_p = 0.109$)) are slightly more negative than these of **2** ($E_{1/2} = -1.923$ ($\Delta E_p = 0.121$); -1.720 V ($\Delta E_p = 0.087$)). The additional difficulty in reducing the terpyridines of **1** could be a result of an increased inaccessibility of the counterions because of the increased dendritic character on the periphery of the molecule. In addition, the ΔE_p values for the two waves of **1** and for the most positive wave of **2** are similar to each other and smaller than the ΔE_p value for the most negative wave of **2**. This result indicates that the rate of electron transfer for one of the terpyridines in **1** is slower than that of the others.

Whereas all other published metallodendrimers utilized counterions such as Cl^- , BF_4^- , or PF_6^- , Newkome et al. introduced a neutral metallodendrimer possessing four bisterpyridineruthenium(II) linking sites.^[202] Eight internal carboxylate groups balance the

charge of the Ru^{II} centers. After dialysis, the characterization was conducted by MALDI-TOF mass spectrometry, UV/Vis, CV, and NMR spectroscopy. Only one signal for the carbon atom was detected for the internal carboxylate group in the NMR spectrum. Poly(amidoamine) dendrimers with an ethylenediamine core were presented up to the third generation by Kimura et al.^[195] and up to the fourth generation by Abruña and co-workers.^[29–31] The fourth-generation dendrimer contains 64 bis(terpyridinyl)-ruthenium(II) complexes and therefore a total of 128 positive charges. Both groups used peptide-coupling procedures for the synthesis. Abruña and co-workers demonstrated that the interfacial reaction of the terpyridine-pendant dendrimers and a bridging ligand (1,4-bis[4,4''-bis(1,1-dimethylethyl)-terpyridine-4'-yl]benzene) dissolved in CH_2Cl_2 with an aqueous solution of metal ions gave rise to ordered films on highly oriented pyrolytic graphite. STM investigations of these films (Figure 52) demonstrated highly ordered hexagonal 2D domains (in this case dend-8-tpy/ Fe^{2+}).^[31]

As part of their approach to the preparation of macromolecules with encapsulated silsesquioxanes, Murfee and Hong recently presented dendrimers up to the third generation based on an octa(diphenylphosphanyl)-functionalized silsesquioxane core.^[203–205] The third generation was built up by eight dendrons, each possessing four terpyridine molecules to which bis(bipyridine)ruthenium complexes were attached (Figure 53). The molecule thus had 64 positive charges within its outer sphere, which were balanced by PF_6^- counterions. The quantum yields of the dendrimers depended on the generation, but ranged from 0.021–0.011. The excited state lifetimes of the ruthenium(II) centers were again dependent on the generation, being 605, 890, and 880 ns (the emission wavelength was 610 nm).

3.2. Polymers with Terpyridine Units in the Side Chain

Potts and Usifer were, to the best of our knowledge, the first to incorporate terpyridine molecules into polymer chains.^[206] They homopolymerized 4-vinyl- and 4'-vinylterpyridine by free-radical polymerization, and copolymerized 4'-vinyl-terpyridine with styrene (Figure 54). The resulting polymers were all white powders with molecular masses up to $60\,000\text{ g mol}^{-1}$ (GPC (polystyrene standard)) and polydispersities in a range of 2 to 44. The addition of metal ions to these polymers resulted in insoluble polymer–metal complexes. The free polymers

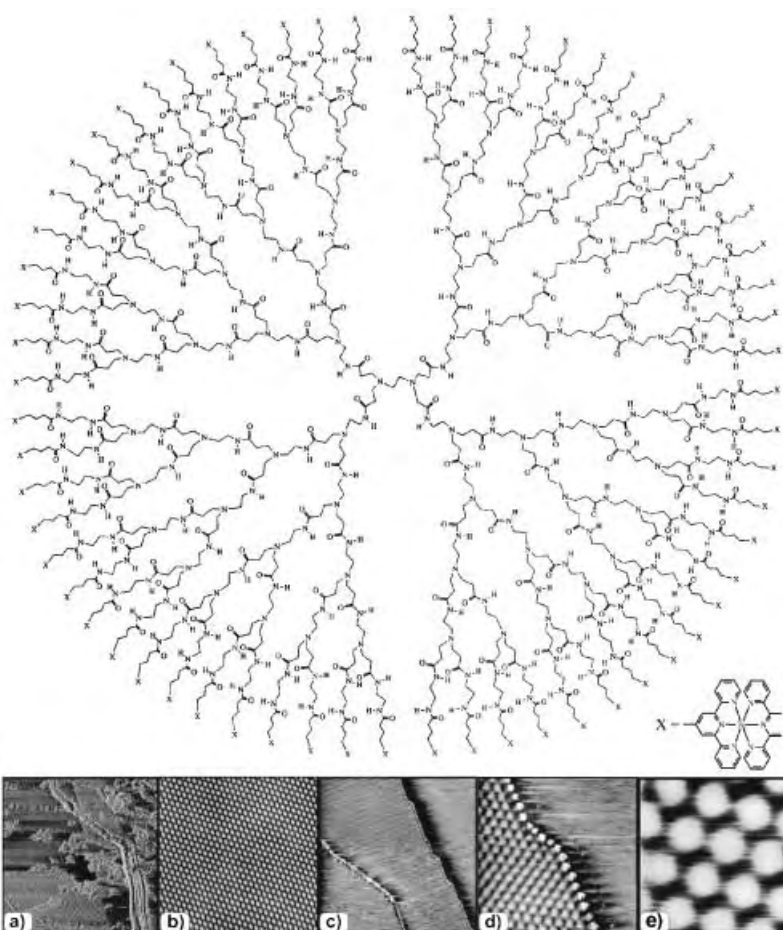


Figure 52. Top: Fourth generation of a dendrimer with pendant bipyrindine or terpyridine complexes (X); Bottom: unfiltered STM images of dend-8-tpy/ Fe^{2+} : a) 550 nm, b) 200 nm, c) 304 nm, d) 69 nm, e) 26 nm.^[29–31]

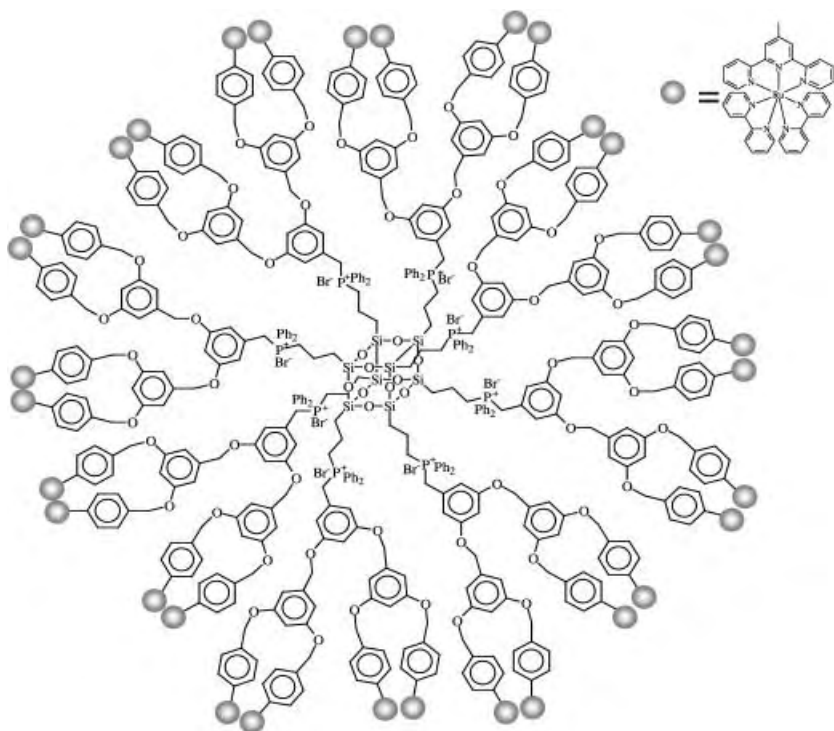


Figure 53. Third generation dendrimer based on a silsesquioxane core.^[203–205]

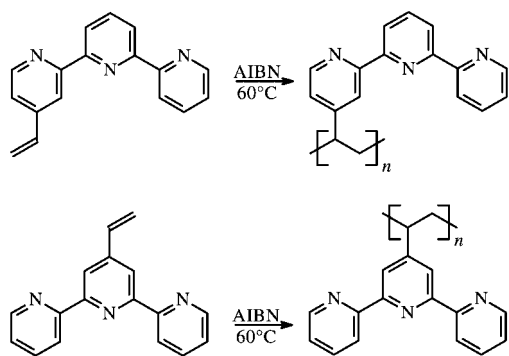


Figure 54. The first terpyridine-containing polymers prepared by radical polymerization of vinylterpyridines.^[206]

could be recovered by hot, concentrated hydrochloric acid. Attempts to homopolymerize the corresponding vinylterpyridine–metal complexes failed. In contrast, styrene copolymers were readily formed from (4'-vinylterpyridine)(terpyridine)cobalt(II) hexafluorophosphate and bis(4'-vinylterpyridine)ruthenium(II) hexafluorophosphate complexes.^[207]

A similar but more extended work has been published by Hanabusa et al.^[208, 209] in which they prepared 4'-[4-(2-acryloxyethoxy)phenyl]terpyridine and copolymerized it with styrene or methylmethacrylate (Figure 55). The average molecular weight, as determined by GPC, was 6400 g mol⁻¹ for the styrene copolymer and 15000 g mol⁻¹ for the methylmethacrylate copolymer. Later work reported on homopolymers of 4'-(4-styrene)terpyridine, and copolymers with styrene, vinyl acetate, and acrylic acid. While the homopolymers were insoluble, all three copolymers were soluble as a result of their low terpyridine content (5%). In all cases, the corresponding metal complexes were formed with CoCl₂, FeCl₂, NiCl₂, and CuCl₂. In 1998, Kimura and Hanabusa et al. introduced a fluorescing poly(*p*-phenylenevinylene) with pendant terpyridyl groups as a chemosensor for metal ions.^[210] As shown in Figure 56, polymerization was carried out by a

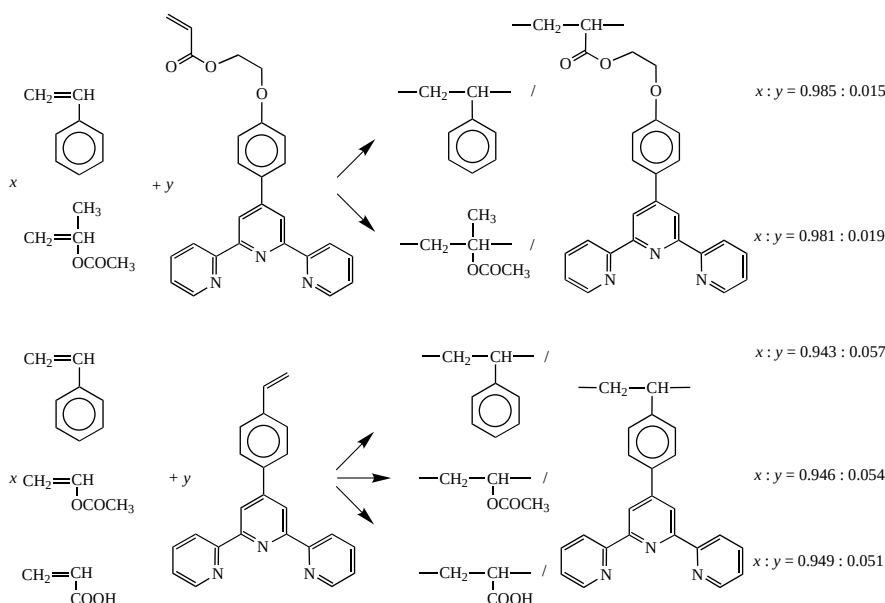


Figure 55. Copolymers with pendant terpyridine units in the side chain.^[208, 209]

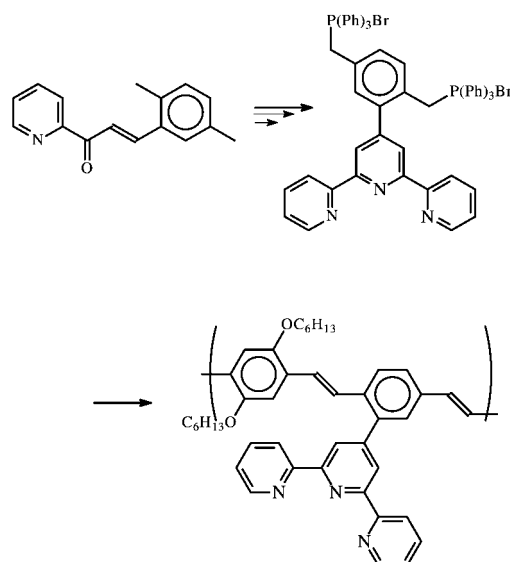


Figure 56. Preparation of conjugated polymers by using the Wittig reaction for an application as fluorescing chemosensors.^[210]

Wittig-type reaction of 2,5-bis(hexyloxy)benzene-1,4-dialdehyde and the terpyridylphosphonium salt to yield a polymer with a mass of 4000 g mol⁻¹, as determined by GPC (polystyrene standard). The fluorescence of the polymer was investigated as a function of various metal ions. The fluorescence at 524 nm was completely quenched by Fe^{II}, Fe^{III}, Ni^{II}, Cu^{II}, Cr^{II}, Mn^{II}, and Co^{II} ions, while a blue shift in the emission spectrum was caused by Pd^{II}, Sn^{II}, Al^{III}, and Ru^{II} ions. Poly(*p*-phenylenevinylene)s with pendant terpyridine ligands were recently synthesized by Wong and Chan.^[65] In contrast to the above-mentioned work by Kimura et al.,^[210] Wong and Chan did not utilize the Wittig reaction for polymerization, but copolymerized 1,4-divinylbenzene, 1,4-didodecanoxy-2,5-diiodobenzene, and an iodo-functionalized terpyridineruthenium complex in various ratios by Heck coupling (Figure 57). The polymers obtained exhibited photo- and electroluminescence at room temperature. Photocurrent measurements at 490 nm carried out on samples spin-coated onto ITO demonstrated photoconductivities of the order of 10⁻¹² Ω⁻¹ cm⁻¹. LEDs produced from these polymers exhibited a turn-on voltage of 5 V with rectification greater than 10³ at 15 V and a maximum luminance of 360 cd m⁻².

In a different approach, a dihydroxyterpyridine was treated with a commercially available bisisocyanate-functionalized prepolymer to give an AB multiblock copolymer (Figure 58).^[211] The treatment of a solution of the block copolymer with cobalt(II) acetate in chloroform immediately revealed a red-brown color. In contrast to the free polymer, which is a viscous liquid, the complexed material had rubber-like properties.

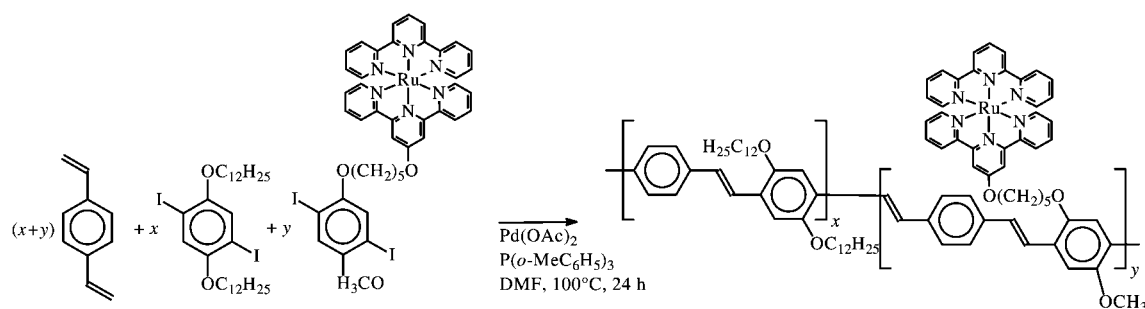


Figure 57. Light-emitting polymers with pendant terpyridineruthenium complexes.^[65]

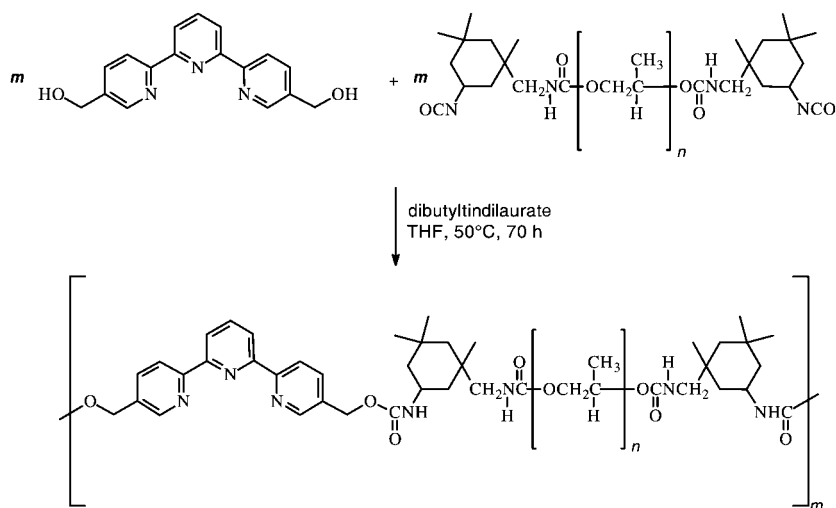


Figure 58. Copolymerization of dihydroxyterpyridine with a bisisocyanate-functionalized prepolymer.

3.3. Polymers with Terpyridine Units in the Polymer Backbone

Polymers with a terpyridine complex in the backbone are rather exceptional. In 1995, Constable discussed, in a small review, his own concept of using metallocsupramolecular principles to prepare oligomers and polymers with precoded properties by coordination to metal ions.^[212] Although the successful synthesis of a coordination polymer has not yet been reported, the presented structures give a first impression of the potential of this strategy in regard to the incorporation of distinctive physical properties. Some research groups have investigated rigid rods during their research into long-distance interaction phenomena such as electron and energy transfer or magnetic coupling of transition-metal ions.^[213] Though no polymers were formed, structures containing functionalized bis(terpyridine) units were obtained which could act as very interesting building blocks for noncovalent polymers.

The research groups of Harrimann and Ziessel are working on building photoactive wires on a molecular scale.^[214–221] In 1996, they reported on stiff ditopic ligands and oligomers derived from terpyridines bridged by an alkyne comprised of one to four ethynyl groups.^[214] These polyalkynylene chains (Figure 59) allow very fast exchange of electrons between photoactive terminals and prolong the triplet lifetimes by a factor of 3000, relative to the unsubstituted terpyridineruthenium complex. In certain cases, the

alkyne bridge undergoes reductive electropolymerization to generate molecular films which contain metal centers dispersed along a conjugated backbone. A major drawback of these rigid bridged systems is that their solubility decreases significantly as the number of acetylene groups increases. To overcome this disadvantage, Khatyr and Ziessel investigated the properties of bis(terpyridine) ligands bearing ethynylene phenylene spacers with solubilizing groups in the 2,5-positions (Figure 60).^[218] The lowest energy absorption in these compounds is shifted towards lower energy as the number of repeat units increases. The same correlation was demonstrated for the emission ($n=1$: 434 nm, $n=5$: 472 nm). This behavior demonstrates that the electronic communication along the molecular axis is improved as the number of repeat units increases.

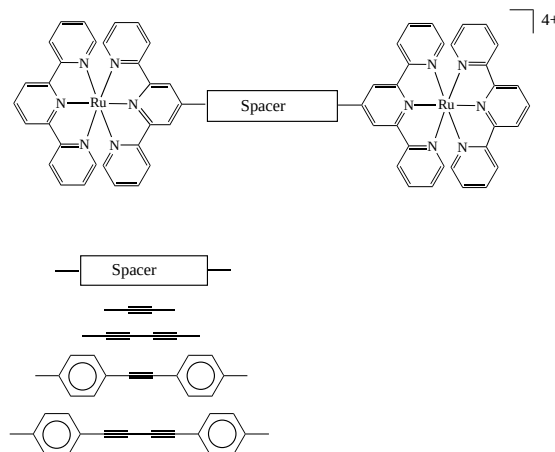


Figure 59. Stiff molecular wires prepared by Ziessel and co-workers.^[214–221]

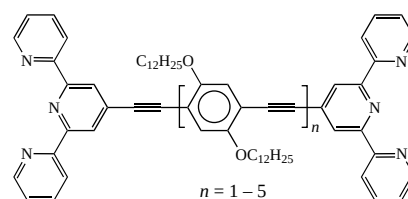


Figure 60. The solubility of the stiff ligands was enhanced by introduction of an alkyl spacer.^[218]

The research groups of Sauvage, Barigelletti, and Balzani also investigated rigid ditopic ligands for the construction of one-dimensional molecular arrays.^[222–226] To investigate the luminescence and electron-transfer properties, they prepared a ligand consisting of two 4'-(*p*-phenylene)-terpyridine end groups and a bicyclo[2.2.2]octane unit.^[224] By this method, strict control over the metal-to-metal distance (2.4 nm) could be obtained and complexes with different metal ions in one molecule could be created. The lifetime of the Ru-based moiety ($\tau = 1.1$ ns) in solution is too short to allow energy or electron transfer. The lifetime is longer ($\tau = 10.5$ μ s) in a rigid matrix at 77 K and energy transfer from the Ru-based moiety to the Os-based moiety takes place with a rate constant of 4.4×10^6 s^{−1} (Figure 61). In an earlier publication, a porphyrin was incorporated instead of the bicyclo[2.2.2]octane unit.^[223] By utilizing the different complex binding properties, molecules with different metal ions were again prepared. This approach allows the photophysical properties of porphyrin- and terpyridine–metal complexes to be combined.

Bis(terpyridyl)–transition-metal oligomers with up to three metal centers have been reported by Storrier and Colbran.^[227] Coupling the aniline group in the heteroleptic bis(4'-(4-anilino)terpyridyl)ruthenium(II) complex with 4'-(4-chlorocarboxyphenyl)terpyridine yielded an amido-linked ligand with a coordinated and a noncoordinated terpyridine domain (Figure 62). Dimers are easily accessible with this ligand by using Co^{II}, Fe^{II}, and Ru^{II} ions to connect the ligands. The application of NMR spectroscopy is of particular interest in examining these complexes, particularly the Co^{II} complex. The paramagnetic ion leads to the signals of the terpyridine

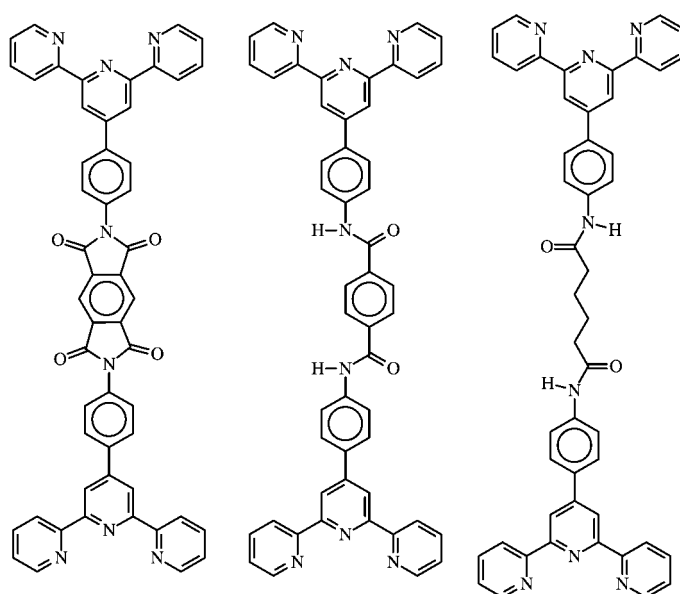


Figure 63. Organic ligands suitable for transition metal ion based non-covalent polymerization.^[228, 229]

hydrogen atoms being shifted downfield by approximately 15 to 90 ppm. Such uncomplexed entities provide interesting building blocks for metallosupramolecular polymers.^[228, 229] Starting with 4'-(4-anilino)terpyridine, the polymers were prepared by two different synthetic routes: a) by the coupling of two ligands with difunctional organic reagents (such as pyromellitic anhydride, terephthaloyl chloride or adipoyl chloride) and then treating the

new binucleating ligands (Figure 63) with metal ions, or b) pre-forming monomeric complexes of the 4'-(4-anilino)terpyridine and treating them with the same difunctional organic reagents as mentioned above. In approach b, the polymerization was quenched, and from the end groups a molec-

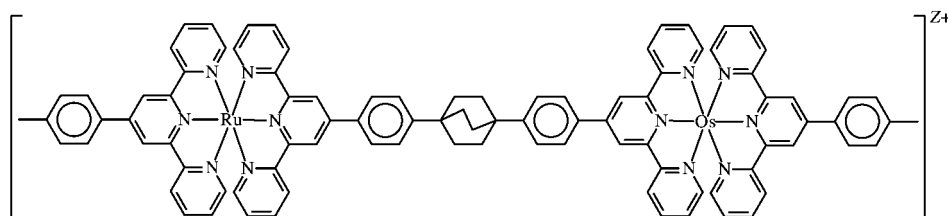


Figure 61. Two different metal ions were held at a distance of 2.4 nm in this photoactive molecule.^[222–226]

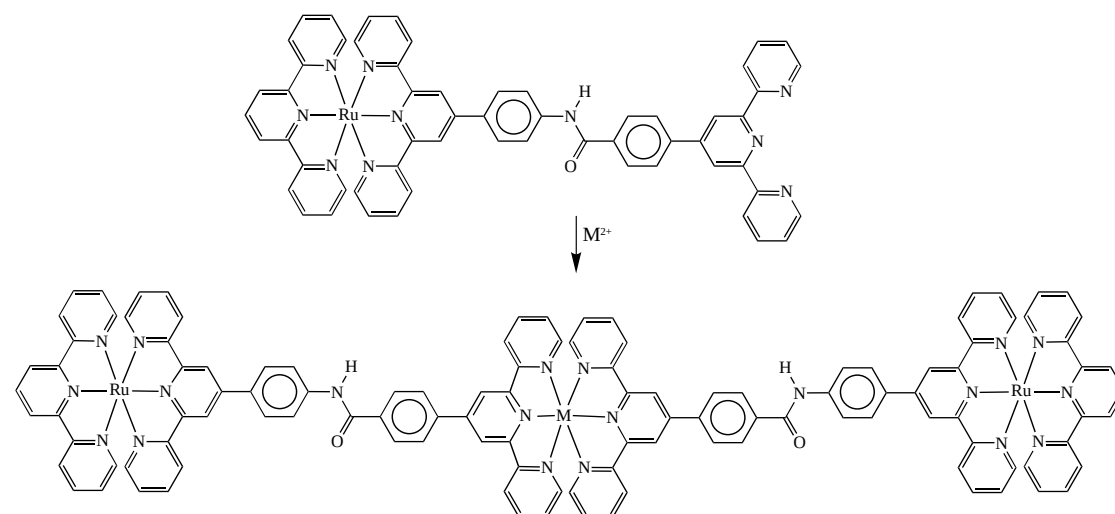


Figure 62. Linear molecules with three metal centers prepared by Colbran and Storrier.^[227]

ular weight of 18 kDa, which corresponds to a degree of polymerization of 17, was calculated. Similar results were obtained for the polymers resulting from approach a.

Möhwald, Kurth, and co-workers used analytical ultracentrifugation for the characterization of a coordinating polymer built of 1,4-bis(terpyrid-4'-yl)benzene (Figure 64), first introduced by Constable et al.,^[230] and iron(II) ions.^[231] By applying the Svedberg formula, they determined a minimum molecular mass of 14900 g mol⁻¹, which corresponds to 25 repeating units. However, this can only be considered as a very rough estimation because of uncertainty in the determination of the compound's partial specific volume.^[232]

Interesting layer-by-layer self-assembly experiments with this polymer were conducted by Kurth and Osterhout. The resulting alternating monolayers were investigated by X-ray reflectivity measurements, X-ray photoelectron spectroscopy, and surface plasmon resonance spectroscopy.^[233] A thickness of dried polymer films of 18 ± 3 Å was determined, which corresponds to a single layer (for the results obtained by utilizing monomeric terpyridine–metal complexes, see ref. [234–238]). Anisotropic thin-film materials of this metallosupramolecular polymer were produced by electrostatic binding to the amphiphile dihexadecyl phosphate.^[239] The resulting polyelectrolyte–amphiphile complex forms a stable

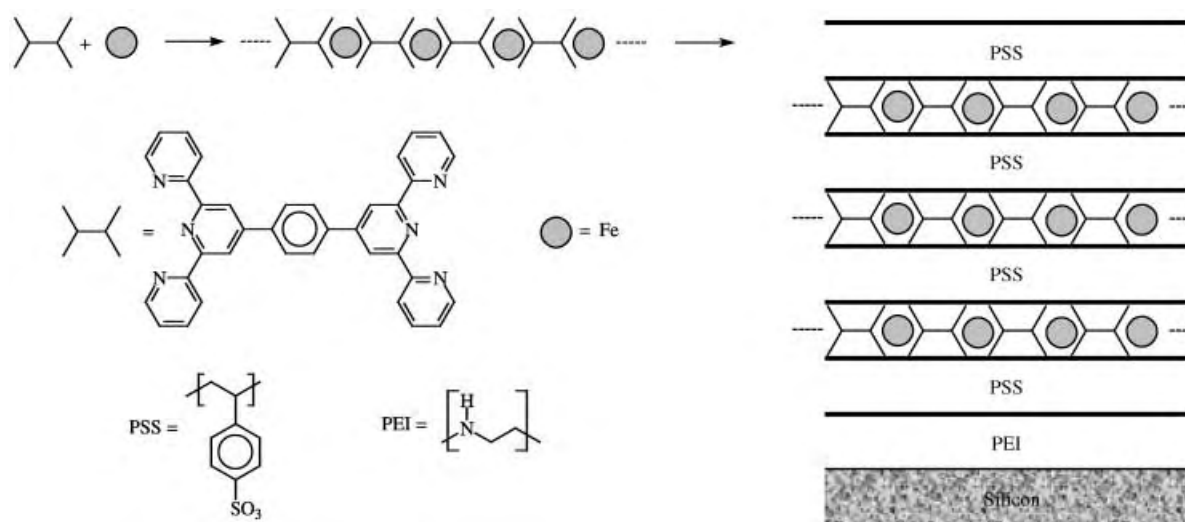


Figure 64. Linear metallosupramolecular coordination polyelectrolytes used for the formation of a superlattice by layer-by-layer self-assembly.^[233]

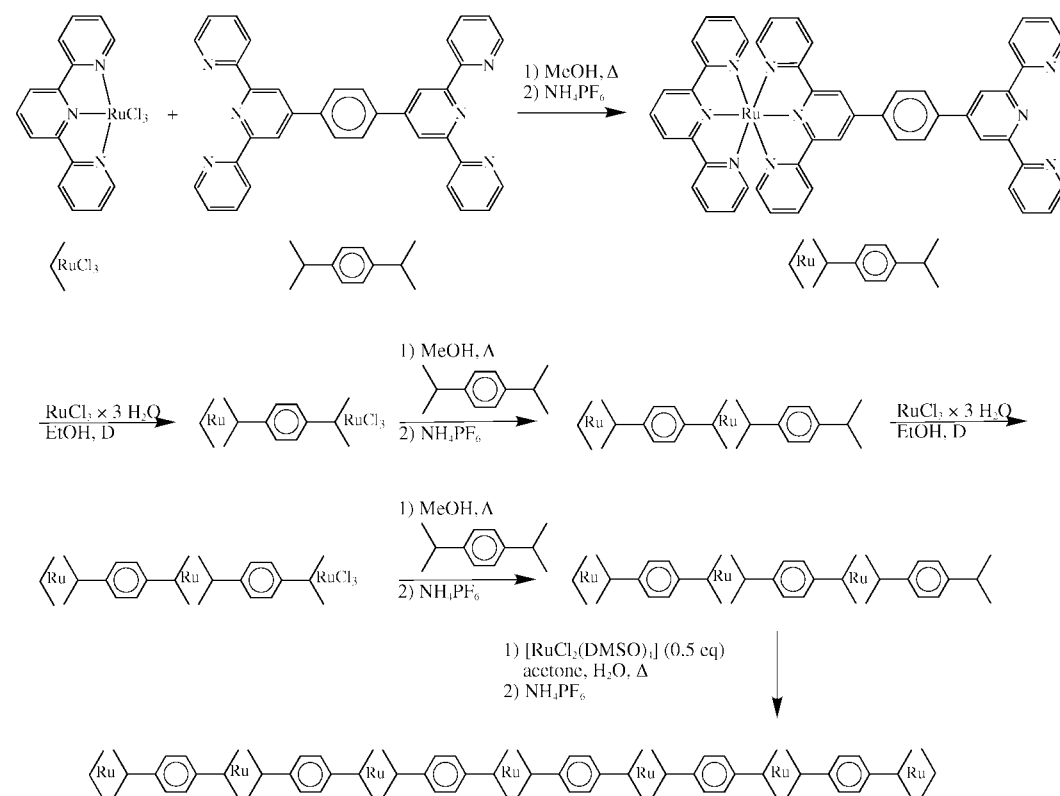


Figure 65. Synthesis of well-defined linear rods consisting of seven metal centers.^[240]

monolayer at the air–water interface that is readily transferred and oriented on solid supports by using the Langmuir–Blodgett technique. The average thickness per layer was demonstrated to be 2.8 ± 0.2 nm. The presented strategy opens a new route to materials with tailored structures and functions. The same ligand has been used by Mohler and co-workers for the controlled stepwise self-assembly of rigid rods.^[240] A well-defined linear oligomer consisting of seven metal centers was assembled by utilizing ruthenium chemistry (Figure 65). Electrospray mass spectrometry was applied to characterize the heptanuclear complex from a solution in acetonitrile.

A series of poly(*p*-phenylenevinylene) polymers and aromatic polyimides (Figure 66) were synthesized and characterized by Chan and co-workers.^[241–244] Poly(*p*-phenylenevinylene)s with the terpyridine complex in the backbone were synthesized by coupling 1,4-divinylbenzene, 1,4-dibromo-2,5-dihexybenzene, and bis[4'-(4-iodophenyl)terpyridine]-ruthenium(II) in different ratios by Heck coupling procedures.^[241] The macroscopic properties of the polymers, for

example, solubility, changed depending on the monomer ratios. The polyimides were synthesized by the copolymerization of a bis[4'-(4-aminophenyl)terpyridine]ruthenium(II) hexafluorophosphate complex with different aromatic dianhydride monomers.^[242] The electron and hole-carrier mobilities of the polyimides were demonstrated to be of the order of 10^{-4} cm² V⁻¹ s⁻¹. Single-layered LEDs were produced with an external quantum efficiency of 0.1% and a maximum luminance of 120 cd m⁻². Up to now, the most extensive study on terpyridine-based metal coordination polymers has been performed by Kelch and Rehahn in 1999^[245, 246] in which the rigid ligand was functionalized with two *n*-hexyl groups to enhance solubility (Figure 67). From endcapping experiments combined with NMR investigations, the degree of polymerization demonstrated to be at least 30, which corresponds to a molecular weight of more than 36000 g mol⁻¹. These high values were supported by viscosity measurements. The intrinsic viscosity η was determined to be approximately 300 mL g⁻¹, which is in the same order of magnitude as the intrinsic viscosities observed for poly(*p*-phenylene)s.

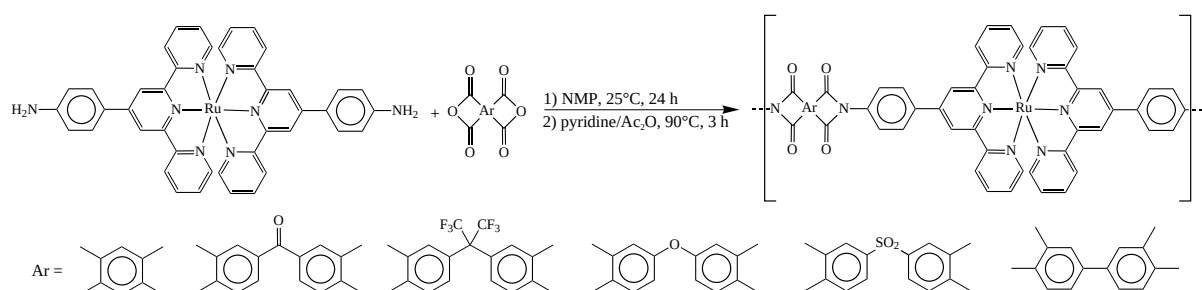


Figure 66. Novel aromatic polyimides for application in LEDs.^[241–243]

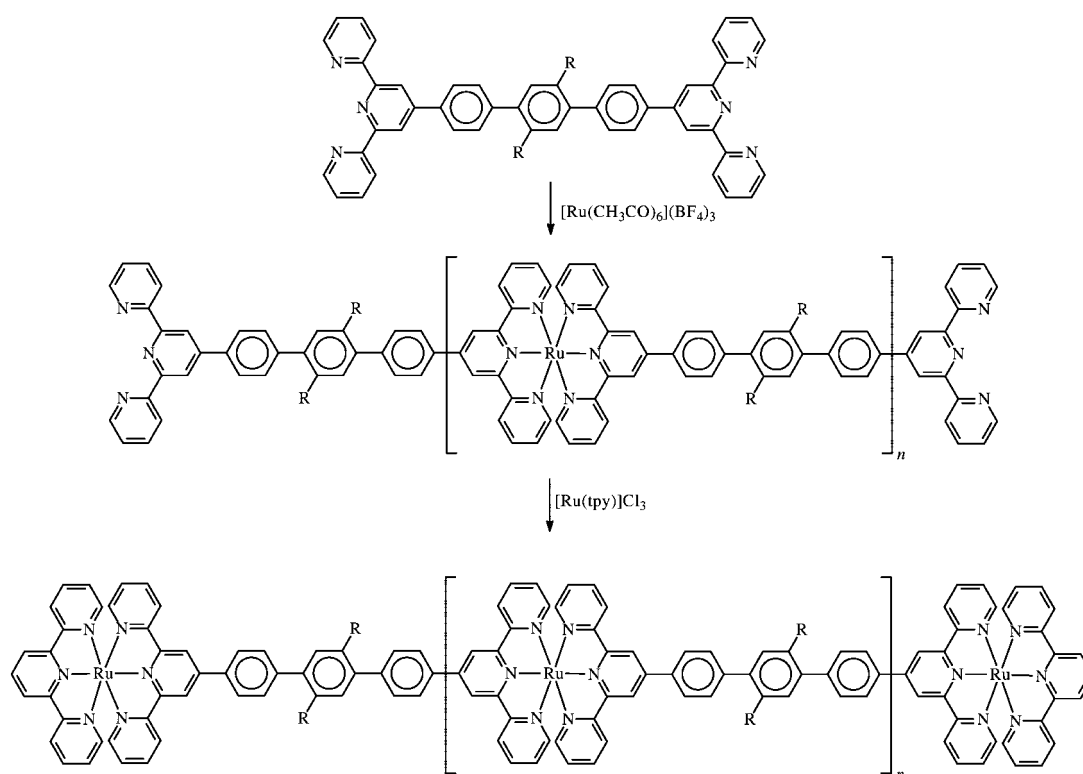


Figure 67. Rigid rodlike polymer based on terpyridine-ruthenium(II) complexes.^[245, 246]

The above described approaches utilizing long side chains to yield soluble rodlike noncovalent polymers in solution have the drawback of using rather complicated building blocks and needing coupling procedures. Recently, a different approach to this class of macromolecules was published: It was demonstrated that 4'-chloro-2,2':6',2''-terpyridine can be treated very efficiently with different hydroxy- and thiol-terminated molecules in the presence of KOH in DMSO to yield the corresponding oxo and thioethers in high yields. As a first example a α -carboxy- ω -hydroxy-functionalized poly(oxytetramethylene) prepolymer was modified in this way with only one terpyridine end unit (Figure 68).^[247, 248] The same

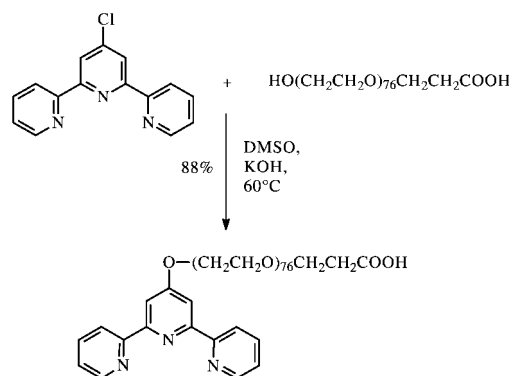


Figure 68. Synthesis of a α, ω -functionalized polymer.

strategy was then applied to the modification of other different commercially available bisfunctionalized telechelics, based, for example, on poly(oxytetramethylene) and poly(ethylenoxide) prepolymers (Figure 69).^[249–251] In all these cases, MALDI-TOF mass spectrometry proved to be a very powerful tool for the investigation of the resulting modified macromolecules. As shown in Figure 70, the complete bis-

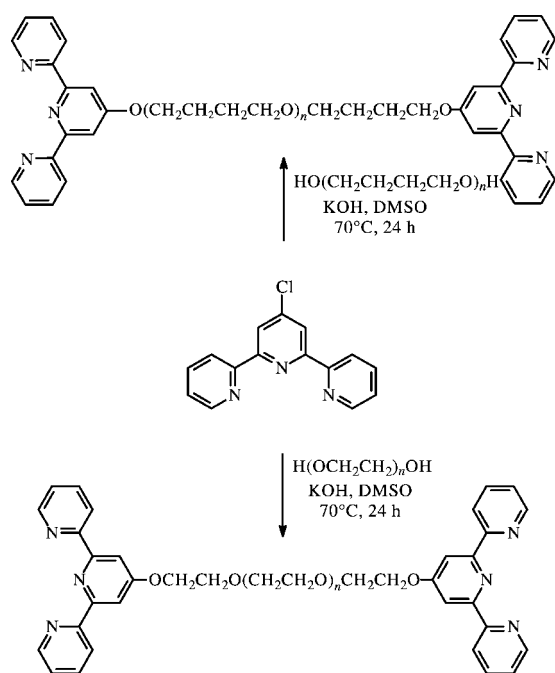


Figure 69. Different metal-complexing compounds.

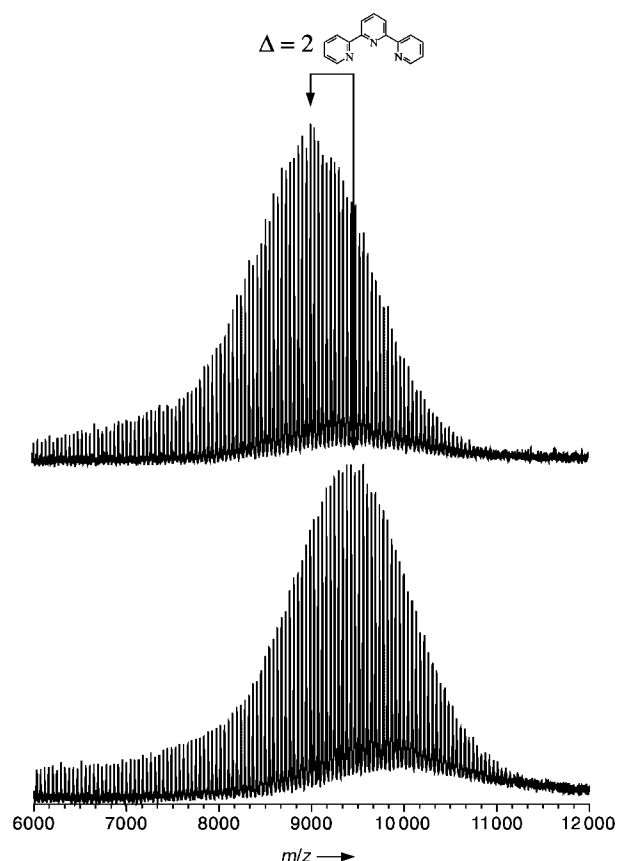


Figure 70. MALDI-TOF mass spectra of the α, ω -bis(hydroxy)-poly(ethylene oxide)₈₀₀₀ (top) and the product α, ω -bis(terpyrid-4'-yl)-poly(ethylene oxide)₈₀₀₀ (bottom; $M_n = 9380 \text{ g mol}^{-1}$); the difference in the peak maxima resembles two terpyridine units.

functionalization of the poly(oxytetramethylene) with an average molecular weight of 8000 Da can be easily proven by this technique. The difference in the molecular weights between the prepolymer (top) and the product (bottom) correlates with the complete reaction of two terpyridine units for each prepolymer. In addition, NMR, UV/Vis, and GPC results are also in good agreement with this result. The modification strategy can be easily expanded to other polymeric systems, such as polystyrene, polymethacrylate, or polysiloxanes.

The addition of octahedral coordinating transition-metal ions to terpyridine-modified prepolymers leads to a spontaneous self-assembly of two terpyridine units and therefore to a polymerization (in principle, a polyaddition reaction; Figure 71). The formation of the complexes can be reversed, for example, by changing the pH value^[252] or applying electrochemical^[253] or thermal changes.^[237] The formation of the

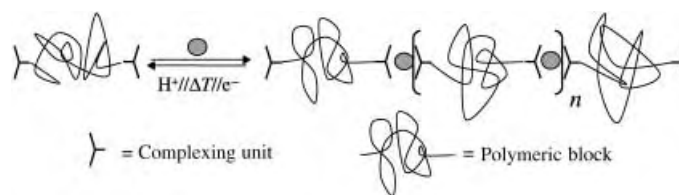


Figure 71. Schematic representation of the noncovalent polymerization.

terpyridine metal complexes and thus the noncovalent coordination polymers can easily be monitored by various techniques, such as UV/Vis and NMR spectroscopy or titration microcalorimetry.

4. Summary and Outlook

The research efforts in the field of bipyridine- and terpyridine-containing ligands and their metal complexes have strongly increased within the last few years. In particular, the central focus has shifted from analytical purposes (complexing of metal ions) to the creation of new materials and supramolecular polymers. However, this development is still at the very beginning, and the first promising results have only been published during the last two years. Certainly there will be a considerable impact of such materials in applications for nanoscience, for tailor-made polymers with tunable properties, and for life-science applications. The first examples can already be seen: such as the temperature and sheer-sensitive starlike polymers from the research group of Fraser, the thermoreversible hydrogels of Chujo et al., the oscillating systems of Yoshida et al., the promising LED devices based on bipyridine–metal complexes by Rubner et al., the stabilization of nanoparticles by coordination of bipyridines on the surface (Chujo et al.), as well as the high-molar-mass metallosupramolecular polymers based on terpyridine metal complexes (research groups of Kurth, Rehahn, Ziessel, and Schubert). A major advantage of these polymer systems over hydrogen-bonded supramolecular polymer systems is the greater stability of the bonds. The use of metal ions has the additional advantage that the chemical and physical properties of the materials can be changed without synthetic expenditure by simply changing the type of metal ions. The future developments in the synthesis and functionalization of suitable metal binding units, the advancements in living and controlled polymerizations, and the progress in modern analytical tools will surely further promote this development.

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Boron Chemistry Lights the Way: Optical Properties of Molecular and Polymeric Systems**

Christopher D. Entwistle and Todd B. Marder*

Electrooptical and electronic materials are the subject of much research interest, whereby the focus has often been on electron-rich organic molecules. In the past years, new routes to electron-deficient systems have been developed that take advantage of the fact that three-coordinate boron is isoelectronic and isostructural with a positively charged carbocation, which allows neutral, p-type materials to be synthesized directly. This minireview summarizes recent work on compounds with 3- and 4-coordinate boron as well as boron clusters, placing it in the context of prior studies by the research groups of Williams and Glowowski, Kaim, Lequan, and Marder.

1. Introduction

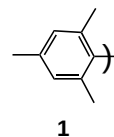
Nonlinear optical (NLO) and electrooptical (EO) properties of polymeric and molecular materials have been the subject of an explosion of interest in the past decade, with the increasing realization that traditional inorganic solid-state materials can be replaced by organic and organo-element materials which are easier and cheaper to fabricate.^[1, 2] In the search for new materials, the properties of a diverse array of boron-containing systems have been investigated, from NLO chromophores to the emitting or electron-transporting components in multilayer organic light-emitting diodes (OLEDs).

Research into new EO and electronic materials has concentrated on electron-rich organic molecules often containing nitrogen, sulfur, or selenium. Electron-deficient systems are usually arrived at by oxidative doping. As three-coordinate boron is isoelectronic and isostructural with a positively charged carbocation, an alternative strategy is to replace carbon atoms with boron, allowing neutral, p-type materials to be synthesized directly. It should be noted that

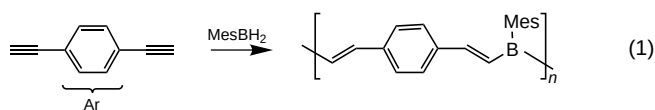
three-coordinate nitrogen is isoelectronic with a carbanion, in effect the mirror image of boron in this respect. Whilst there has been a huge amount of research aimed at exploiting this property of nitrogen to produce n-type materials, for example for hole transporters in OLEDs^[3] and for two-photon absorption,^[4] research into the analogous boron-substituted materials has been surprisingly limited. In part, this may be due to the relative lack of stability, particularly to hydrolysis, of many boron systems when compared to C- or N-based compounds. In recent years, however, a large number of boron-containing compounds which exhibit enhanced stability to moisture and oxygen have been synthesized, allowing the development of new materials with second- and third-order NLO properties. They are also under investigation for photoluminescence (PL) and electroluminescence (EL) applications, with a particular focus on the generation of blue EL for OLEDs.

2. Three-Coordinate Boron

With its vacant p_z orbital, three-coordinate boron is inherently electron deficient and is a strong π -electron acceptor. In contrast to other strong π acceptors such as the nitro group, however, three-coordinate boron is not generally inductively electron withdrawing and may well be a σ donor. The vacant p_z orbital also allows for conjugation of organic π systems with and through boron, and it has been shown that significant delocalization occurs. Kinetic stability towards air and moisture can be achieved by steric hindrance of the p_z orbital by bulky substituents. In particular, the mesityl (2,4,6-trimethylphenyl, Mes, **1**) group has been used to synthesize a great number of air-stable organoboranes.



Recently, several π -conjugated polymers containing boron in the polymer chain have been synthesized by Chujo et al.^[5] The hydroboration of aromatic and heteroaromatic diynes with mesitylborane [Eq. (1)]^[6] was employed to synthesize

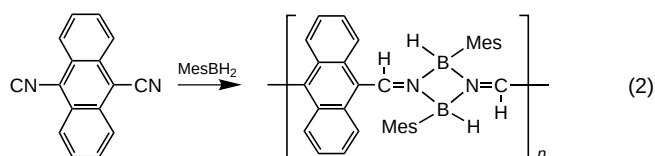


[*] Prof. Dr. T. B. Marder, C. D. Entwistle
Department of Chemistry
University of Durham
South Road, Durham DH1 3LE (UK)
Fax: (+44)191-386-1127
E-mail: todd.marder@durham.ac.uk

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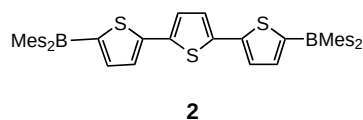
polymers of the general form shown in Equation 1 that are related to poly-*p*-phenylene vinylene (PPV), but contain boron conjugated in the main chain. Despite having relatively low molecular weights, these polymers exhibited strong PL in the blue region. With heteroaromatic diynes, the resulting polymers displayed much larger Stokes shifts resulting in green (Ar = furandiyl, thiophenediyl) or white emission (Ar = pyridinediyl). The polymer based on diethynylbenzene also displayed an unusually large third-order nonlinear optical susceptibility ($\chi^{(3)}$) of 6.87×10^{-6} esu, more than a thousand times higher than that of all-*trans*-polyacetylene as measured by degenerate four-wave mixing.^[5]

A different strategy, the polycondensation of difunctional Grignard reagents with aryldimethoxyboranes, was used to produce poly(*p*-phenyleneborane)s.^[7] All such polymers were found to be highly fluorescent in the 477–496 nm region, with sterically demanding mesityl or triptyl (2,4,6-*i*-Pr₃C₆H₂) groups on boron providing stability. Hydroboration polymerization of dicyano compounds with mesitylborane provided another class of polymers, poly(cyclodiborazane)s.^[8] For example, hydroboration polymerization of 9,10-dicyanoanthracene [Eq. (2)] produced a polymer having a broad emission in



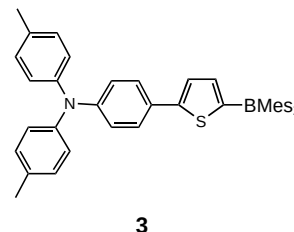
the green region (494 nm). Polymers containing both boron and the transition metals ruthenium, palladium, or platinum in the main chain have also been prepared.^[9] The absorption and fluorescence spectra of these polymers indicate a high degree of π delocalization via boron and the metal atoms. The interaction between metal and boron was highly dependent on the nature of the metal involved. Boration copolymerization of silanes and aromatic diynes^[10] or dinitriles^[8c] was used to prepare novel σ - π conjugated polymers which proved to be highly fluorescent.

Shirota et al. have investigated the properties of oligothiophenes of the form (Mes)₂B(X)_{*n*}B(Mes)₂ where X = 2,5-thiophenediyl and *n* = 2 (BMB-2T) or 3 (BMB-3T, **2**).^[11] These compounds readily formed amorphous glasses with



relatively high glass transition temperatures (T_g), and were found to have good electron-transporting properties. BMB-2T was also found to electroluminesce with $\lambda_{\text{max}} = 446$ and 472 nm. These properties were utilized in the construction of multilayer OLEDs. Both BMB-2T and BMB-3T were

incorporated as the electron-transporting layer in a green OLED with Alq₃ (q = 8-hydroxyquinolato, **10**) as the emitting layer; BMB-2T was also used as the emitting layer to construct a blue OLED. This device exhibited a maximum luminance of 1700 cd m⁻² at a driving voltage of 17 V, comparing favorably with blue OLEDs using oxadiazole- or triazole-based materials, which typically display a maximum luminance of ca. 1000 cd m⁻².^[12] The related compounds 1,3-bis(5-(dimesitylboryl)thiophen-2-yl)benzene and 1,3,5-tris[5-(dimesitylboryl)thiophen-2-yl]benzene have also been investigated, and were found to be effective electron transporters and hole blockers.^[13] The asymmetric compounds Ar₂NXB(Mes)₂ where X = (1,4-phenylene)thienyl and Ar = 4-methylphenyl (**3**) or 2-(9,9-dimethylfluorenyl) have also been shown to exhibit strong EL behavior.^[14]



A recent extension of this work has seen the tri-arylamine tris[4-[5-(dimesitylboryl)thiophen-2-yl]phenyl]-amine incorporated into photovoltaic devices.^[15]

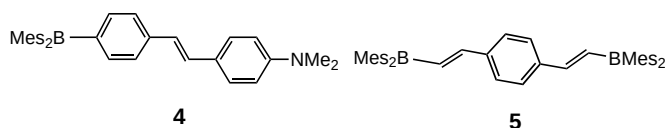
Lequan et al. have investigated the NLO properties of donor-acceptor (D-A) substituted oligothiophenes, once again using B(Mes)₂ groups as the acceptor moiety.^[16] First molecular hyperpolarizabilities (β) were measured by EFISH (electric field induced second harmonic generation), and were found to be significantly larger than for biphenyl-based systems. This was attributed to two factors: the reduced aromaticity of thiophene compared with benzene, thus increasing the delocalization of electrons from donor to acceptor; and the greater planarity of oligothiophenes due to the reduction of steric hindrance.

Polythiophenes containing 3-coordinate boron have been prepared by Corriu and Siebert et al.^[17] These polymers were intensely colored and displayed a marked bathochromic shift in absorption compared to the corresponding monomers, indicating conjugation of the π system through boron. However, the polymers had limited stability due to the lack of bulky substituents to prevent access to the vacant *p_z* orbital of boron.

Molecules and oligomers based on rigid, π -conjugated rods have attracted much attention for their NLO properties,^[18] with much of the research concerning delocalized D-A systems. These exhibit a large change in dipole moment upon excitation, a characteristic that gives rise to a large value of β .

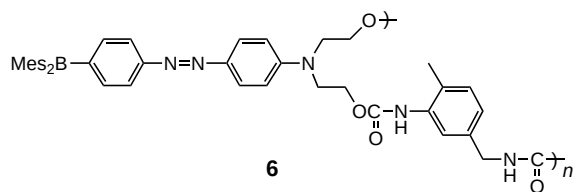
The dimesitylboryl group has also been used as the electron-accepting moiety in molecules of the form DXB(Mes)₂. Marder et al. have prepared a wide range of such molecules and investigated their second-order and third-order NLO properties;^[18] donors D included MeO, MeS, H₂N, Me₂N, Ph₂P, ferrocenyl moieties, and various conjugated alkene, alkyne, aryl or mixed π systems. In addition, they have investigated symmetric bis[B(Mes)₂] compounds.^[19] Hydroboration of terminal alkynes was used to prepare molecules with vinyl-B(Mes)₂ groups, whereas aryl and alkynyl derivatives were prepared by lithiation followed by reaction with FB(Mes)₂. Although these compounds had

unusually small ground state dipole moments, their β values, measured by EFISH, were in the range of those of the cyano or nitro acceptor analogues. For example, $\beta_{1.907\ \mu\text{m}}$ for compound **4** is 45×10^{-30} esu. The third-order NLO properties of bis[B(Mes)₂] compounds were investigated by third harmonic



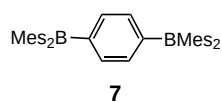
generation (THG), and it was found that the B(Mes)₂ group was superior to the nitro group for increasing γ values. Well characterized compounds such as **5** represent models for the polymers synthesized more recently.^[5, 6]

In addition, Lequan et al. have investigated the second-order NLO properties of rods where D = dimethylamino and X = biphenyldiyl (BNB) or C₆H₄N=NC₆H₄ (BNA),^[20, 21] which gave β values (EFISH) of 32×10^{-30} and 47×10^{-30} esu and UV/Vis absorption maxima of 376 and 446 nm, respectively. The greater electron delocalization in the azo compound was suggested as the cause of the differences between these compounds. A modified version of BNA was later incorporated as a side chain in polyurethane-based polymers (**6**),^[22] which were poled under an external electric



field using the corona technique,^[23] and the second harmonic of the resulting thin films examined. The magnitude of the second harmonic generation (SHG) signal was found to be strongly dependent upon the poling time, but relatively large quadratic susceptibilities were observed for these materials.

The electron-accepting properties of the B(Mes)₂ group were investigated by Kaim et al. in an electrochemical study of *p*-phenylenediboranes.^[24] These compounds were found to exhibit redox properties that were opposite in nature but



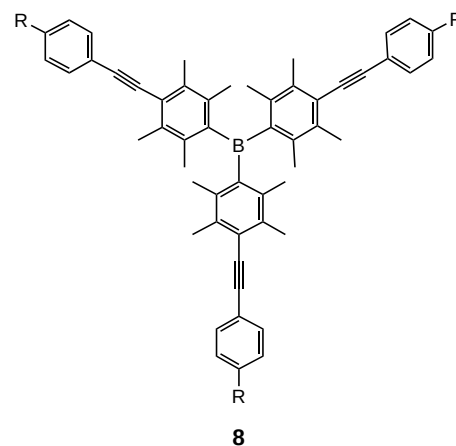
similar in magnitude to the analogous *p*-phenylenediamines, with 1,4-bis(dimesitylboryl)benzene (**7**) having two reversible electrochemical reduction steps leading to the radical anion and the dianion. This work

suggested that B(Mes)₂ should prove useful in D-A compounds, with ENDOR spectroscopy suggesting that considerable delocalization of the unpaired electron occurs in the radical. Further investigation of the electronic properties of arylboranes by cyclic voltammetry and UV/Vis spectroscopy^[25] showed that a single mesityl group was sufficient to provide stabilization of the singly reduced radical anion.

UV/Vis/near-IR spectroelectrochemistry was used to investigate the compounds **7**, 4,4'-bis(dimesitylboryl)biphenyl, and PhB(Mes)₂.^[26] The radical anions and dianions were all found to absorb strongly in the visible or near-IR region,^[18c, 27] with absorption bands of the radical anions resembling those of the analogous isoelectronic amine radical cations. Ab initio^[27] and density functional^[18a] calculations on BH₂-substituted analogues of these compounds demonstrated a quinoidal distortion of the organoboron systems upon reduction, suggesting conjugation of the boron p orbital with the organic π system. These calculations supported earlier EPR/ENDOR measurements on the radicals,^[27] thereby providing further evidence of their electronic structure.

Photochemical studies of dimesitylphenylboranes were first conducted by Williams et al.^[28] Investigation of the fluorescence quantum yields for various *para*-substituted compounds showed an increase in the quantum yield with electron-donating substituents and a marked solvatochromic dependence on the position of the fluorescence (but not absorption) maxima. This result indicated stabilization of a charge transfer excited state species having a large dipole moment by increasingly polar solvents, which could only be possible if the boron atom was capable of conjugation with the phenyl group (see also ref. [18a]). The B(Mes)₂ group was later compared to the nitro group in azo dyes.^[29] This work suggested that B(Mes)₂ was a powerful electron-withdrawing group, comparable in magnitude to the nitro group. From subsequent studies, however, it followed that B(Mes)₂ is in fact closer to the cyano group in its electron-withdrawing properties.^[25] The photophysics of some related *ortho*-substituted PhB(Mes)₂ derivatives has recently been investigated.^[30]

Tri(9-anthryl)borane has recently been prepared by Tamao et al.^[31] The anthryl group is similar to the mesityl group in that it provides kinetic stability to boron, and UV/Vis and theoretical studies demonstrated that π conjugation is extended throughout the entire molecule. Using B(Mes)₂-substituted derivatives of anthracene, starburst oligomers with multiple boron centers were prepared. Complexation of fluoride anions at boron disrupts π conjugation in these molecules, allowing them to behave as fluoride-selective chemosensors.^[32] This group has also prepared substituted tridurylboranes (**8**), which display interesting photophysical properties. Such systems offer a new approach to the

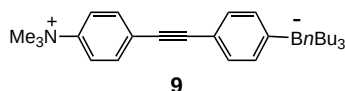


construction of electron-deficient materials, which could potentially be used in organic electronic devices.^[33]

Rigid rods containing anionic boratastilbene and (boratasyryl)stilbene units have been prepared by hydrazironeation using $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$ with an appropriate alkyne followed by transmetalation and reduction with sodium hydride.^[34] The photophysics of these compounds was found to be dependent upon solvent effects, suggested to be due to aggregation and conjugation length.

3. Four-Coordinate Boron

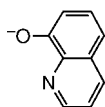
Zwitterionic borates **9** with conjugated π systems show interesting second-order NLO properties.^[35] Compared to analogous, uncharged D-A molecules, they are of



higher transparency and have much higher $\mu\beta_o$ values due to their increased dipole moments. For example, $\text{Me}_3\text{N}^+\text{C}_6\text{H}_4\text{CH}=\text{CHCH}=\text{CHC}_6\text{H}_4\text{B}^-\text{nBu}_3$ was found to have a $\mu\beta_o$ value of approximately 3250×10^{-48} esu. The large dipole moments should favor the alignment of these molecules in polymer films, thus enhancing macroscopic NLO properties. Upon excitation, these zwitterionic compounds experience a dipole change in the opposite sense to uncharged D-A molecules, with the excited state having a lower dipole moment than the ground state.

The investigation of the second-order NLO properties of borane adducts of stilbazoles and pyridines revealed^[36] that they exhibit significantly higher β values than the corresponding (uncomplexed) stilbazoles or pyridines, and values of $\mu\beta$ were also much enhanced. Recently, a theoretical study of this system has produced results in good agreement with the experimental data.^[37]

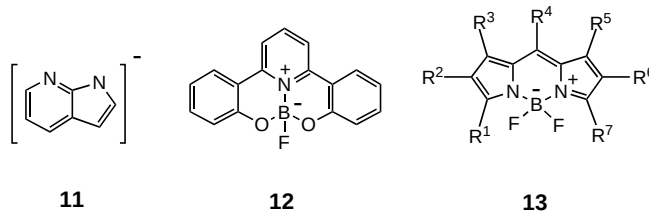
Efficient green EL from a thin film of Alq_3 ($q=8$ -hydroxyquinolato, **10**) was first reported by Tang and van Slyke in 1987,^[38] and Alq_3 has since been used extensively as the electron-transporting and emissive layers in OLEDs. Whilst OLEDs emitting in the green and red regions of the spectrum have been developed by doping Alq_3 with various dyes, the blue region has proved harder to attain by this method. In recent years, however, a number of 4-coordinate boron systems have been observed to emit in the blue region.



There have been a number of studies on boron analogues of Alq_3 . Whilst Alq_3 is octahedral, with bidentate ligands, the smaller size of boron prevents this. Compounds of the form BR_2q are tetrahedral, with a bidentate quinolato ligand,^[39] but Bq_4^- anions have monodentate coordination through oxygen.^[40] Generally, the boron compounds emit at shorter wavelengths and are more covalent in nature than their Al relatives, leading to greater stability towards air and water. The quantum efficiency of emission is higher than that of Alq_3

derivatives, and some of the compounds have also been found to have excellent electron-transporting properties.

Strong blue EL has been observed for the air-stable diborates $\text{B}_2(\mu\text{-O})\text{Et}_2(\text{azain})_2$ and $\text{B}_2(\mu\text{-O})\text{Ph}_2(\text{azain})_2$ ($\text{azain}=7\text{-azaindole anion, 11}$)^[41] and for the complexes



$\text{BPh}_2(2\text{-py-in})$ and $\text{BPh}_2(2\text{-py-aza})$ ($2\text{-py-in}=2\text{-(2-pyridyl)indole}$, $2\text{-py-aza}=2\text{-(2-pyridyl)-7-azaindole}$).^[42] A boron compound with one pyridinium and two phenolate units, $(\text{dppy})\text{BF}$ (**12**), has also been used to construct EL devices with strong emission at either 550 or 450 nm, though it is uncertain whether **2** functions as the electron-transporting or emissive material.^[43] A particularly versatile chromophore is offered by boron–dipyrin compounds **13**. These fluorescent dyes have been investigated for a variety of purposes from light-harvesting arrays to doping Alq_3 OLEDs.^[44]

4. Borane and Carborane Clusters

A number of boron cluster compounds have been investigated for their NLO properties. The molecular hyperpolarizabilities of a series of disubstituted carboranes have been studied by SHG and EFISH,^[45] but were found to be generally low. Recently, however, with the carborane ylide $12\text{-C}_7\text{H}_6^+-\text{CB}_{11}\text{H}_{11}^-$ a compound has been synthesized that displays a β value of $(236 \pm 50) \times 10^{-30}$ esu by HRS (HRS = hyper Rayleigh scattering)^[46] and was also found to be transparent below 400 nm.

Theoretical work has also suggested the potential of boranes and carboranes for second-order NLO. The structures and second-order responses for *nido*-, *conjuncto*-, and *closo*-boranes bearing tropylium and cyclopentadienyl substituents have been calculated using semiempirical methods (MOPAC AM1), as have those of the corresponding *ortho*-, *meta*-, and *para*-carboranes.^[47] Some of these clusters were predicted to exhibit surprisingly large β and $\mu\beta$ values. For example, $[(\text{C}_7\text{H}_6)\text{C}_2\text{B}_{10}\text{H}_{10}(\text{C}_5\text{Me}_4)]$ was calculated to have $\beta = 682 \times 10^{-30}$ and $\mu\beta = 12000 \times 10^{-48}$ esu. Ab initio molecular orbital calculations have also suggested that dimeric carborane anions should display NLO properties.^[48]

A recent study of some novel carborane–fullerene dyads^[49] revealed unexpectedly large β values of up to 1189×10^{-30} esu for these materials; no explanation of these properties is available at present. The potential use of carboranes in optoelectronics has received very little attention. The hafnium–carborane complex $[\text{Hf}(\eta^5\text{-C}_5\text{H}_4\text{CMe}_2)\text{CB}_{10}\text{H}_{10}\text{C}_2]$ displays both EL and mechanoluminescence.^[50]

In summary, molecular and polymeric boron-containing compounds exhibit a wide variety of useful optical properties. It is clear that some of these compounds have great potential

in the fields of linear and nonlinear optics, which should stimulate research on these systems.

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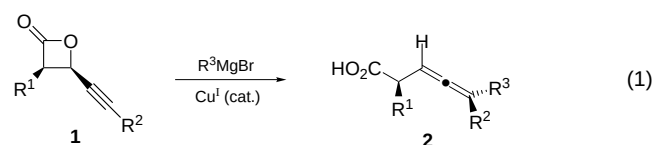
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Enantioselective Synthesis of and with Allenes

Anja Hoffmann-Röder and Norbert Krause*

In recent years, allenes have gained increasing attraction as interesting building blocks in modern organic chemistry. Their synthetic utility is not only demonstrated by an abundance of regio- and stereoselective C–C-bond-forming transformations (e.g., Diels–Alder reactions), but they are also prone to transfer their axial chirality efficiently to one or several new stereogenic centers.^[1] These characteristics, as well as the occurrence of allenic structures in a variety of natural products and pharmacologically active compounds, gave rise to ample interest in the stereoselective synthesis of allenes.^[2] In this account, we report selected developments in the enantioselective synthesis of allenes and allenic natural products in the last two years, but by no means comprehensively.

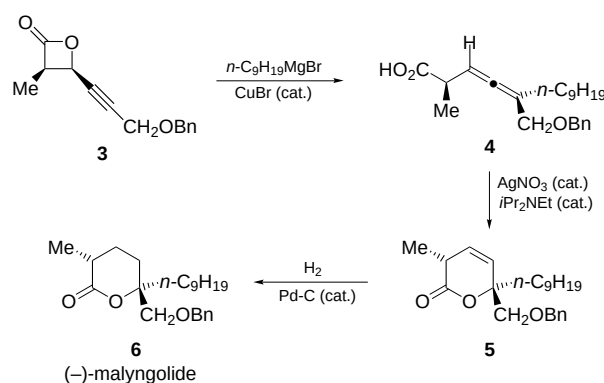
A well-established, widely applicable access to various enantiomerically enriched and pure allenes relies on the S_N2' substitution of chiral propargylic derivatives with nucleophiles, in particular with organocuprates.^[1–4] According to this principle, Wan and Nelson reported the use of optically active alkynyl-substituted β -lactones as highly reactive precursors for allenes through copper-catalyzed S_N2' -reactions with Grignard reagents [Eq. (1)].^[4] The required enantiomerically



enriched β -lactones **1** are readily accessible by condensation of propargylic aldehydes with acid halides and furnish, in a S_N2' -ring-opening process, the desired β -allenic carboxylic acids **2**. The latter were obtained in good yields and with high enantiomeric excesses, since the reaction occurs strictly *anti*-stereoselectively with complete chirality transfer from the stereogenic center of the lactone to the chirality axis of the resulting allene.

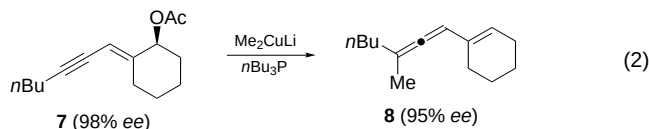
The authors showed the synthetic practicality of this reaction by using different nucleophiles (including a zinc

ester enolate) and by the stereoselective synthesis of the natural product (–)-malyngolide (**6**), which was obtained from β -lactone **3** in only 3 steps with 64% overall yield (Scheme 1).^[4]



Scheme 1. Synthesis of (–)-malyngolide (**6**). Bn = benzyl.

On the other hand, a direct access to enantiomerically enriched and pure vinylallenes was established by Krause and Purpura through 1,5-(S_N'')-substitution reaction of chiral enyne acetates with organocuprates.^[5] Although the vinyl allenes **8** were mostly formed as a mixture of *E* and *Z* isomers, high enantiomeric excesses of up to 99% could be achieved starting from the respective enantiomerically enriched enyne acetates like **7** [Eq. (2)]. In this case, the presence of tri-*n*-butylphosphane or triethylphosphite as an additional ligand

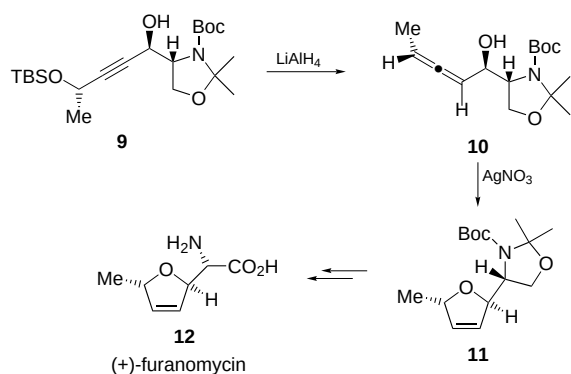


served to avoid racemization of the product by reactive copper species present in the mixture, and thus proved to be indispensable for high enantioselectivities. Since the enantioselectivity is controlled by a comparatively remote stereogenic center, this 1,5-substitution constitutes one of the few examples of “remote stereocontrol” in organocopper chemistry. Furthermore, the 1,5-substitution of chiral, nonracemic enyne acetates can be performed equally well with catalytic

[*] Prof. Dr. N. Krause, A. Hoffmann-Röder
Lehrstuhl für Organische Chemie II, Universität Dortmund
44221 Dortmund (Germany)
Fax: (+49) 231-755-3884
E-mail: nkrause@pop.uni-dortmund.de

amounts of copper salts, a fact that is of special importance both from an economic and a preparative point of view.

The high stereoselectivity of many S_N2' -substitution reactions, as well as the possibility of utilizing the generated allenic moiety for a chirality transfer in subsequent transformations (often cyclizations^[6–8]), make the sequence highly attractive for the synthesis of natural products. Thus, the formation of the α -hydroxyallene **10** and its silver-promoted cyclization to dihydrofuran **11** are key steps of the synthesis of (+)-furanomycin (**12**) described by VanBrunt and Standaert (Scheme 2).^[8]

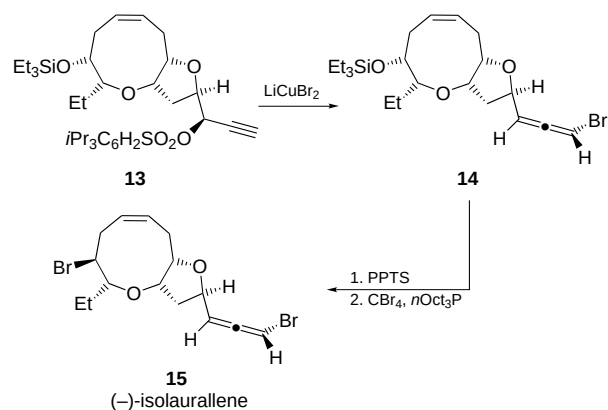


Scheme 2. Synthesis of (+)-furanomycin (**12**). TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

Starting from Garner's aldehyde, the authors prepared the propargylic silyl ether **9** by diastereoselective acetylide addition and converted this into the allenic alcohol **10** by an *anti*-stereoselective hydrometalation–elimination sequence with lithium aluminum hydride (Scheme 2). Although this transformation only gave a moderate yield, the subsequent diastereoselective cyclization to dihydrofuran **11** could be carried out with stoichiometric amounts of $AgNO_3$. Cleavage of the N,O-acetal and formation of the carboxy group finally led to (+)-furanomycin (**12**) in 12% yield over eight steps.

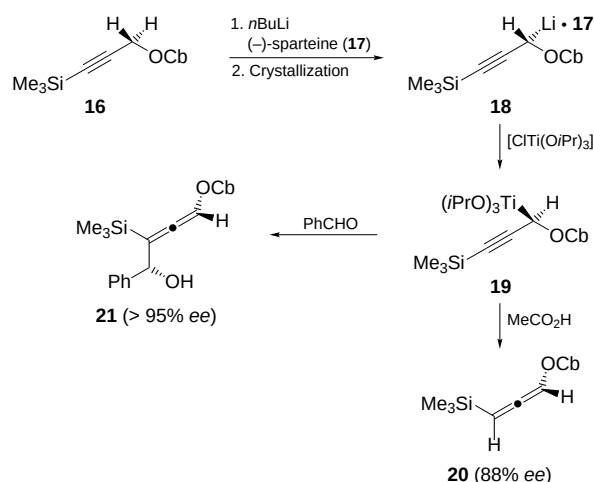
Allenes are not only important as reactive key intermediates in organic synthesis, but also in their own right as natural products and pharmacologically active compounds.^[1, 9, 10] An intriguing example of an allenic natural product is the bromoallene (–)-isolaurallene (**15**) which was isolated from marine red algae and was recently synthesized by Crimmins and Emmitte (Scheme 3).^[9] The allenic moiety is again formed in a copper-mediated S_N2' -substitution reaction by making use of a triisopropylbenzenesulfonate (trisylate) as the leaving group. The precursor **14** was obtained in 67% yield by treatment of trisylate **13** with $LiCuBr_2$ and was finally transformed into the target molecule **15** by cleavage of the silyl protecting group and introduction of the secondary bromide.

Conceptually rather different ways to enantiomerically enriched and pure allenes are based on the construction of the carbon skeleton (e.g., by enantioselective Wittig–Horner–Wadsworth–Emmons (WHWE) reactions of ketenes^[11] or on kinetic resolutions.^[12, 13] Thus, Hoppe and co-workers^[13] demonstrated that the deprotonation of prochiral secondary alkynyl carbamates **16** with *n*-butyllithium in the presence of



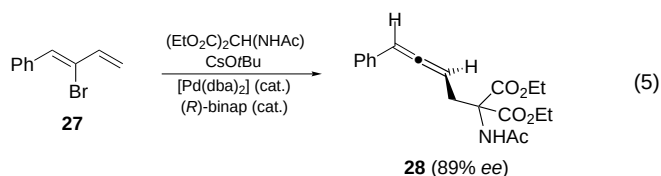
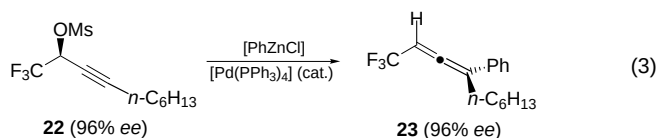
Scheme 3. Synthesis of (–)-isolaurallene (**15**). PPTS = pyridinium-*p*-toluenesulfonate.

(–)-sparteine (**17**) in pentane leads to the spontaneous crystallization of the diastereomerically pure complex **18** (Scheme 4), which could be transmetalated with $[CpTi(OiPr)_3]$ under inversion of configuration into the corresponding titanate **19**. Subsequent protonation of **19** with acetic acid or a trapping reaction with an aldehyde finally furnished the allenes **20** and **21**, respectively, with high enantioselectivities.



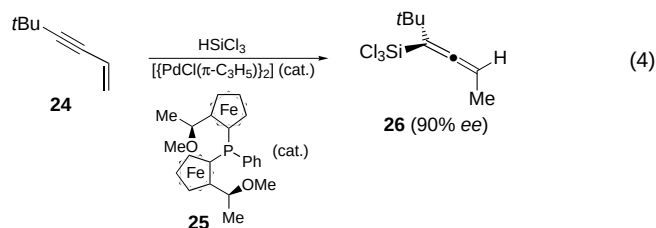
Scheme 4. Synthesis of the allenes **20** and **21** by sparteine-mediated lithiation of the alkynyl carbamate **16**. Cb = iPr_2NCO .

Besides the element copper, other transition metals (in particular palladium) can also be used to generate allenes through S_N2' substitution of chiral, nonracemic propargylic derivatives. In this case, the intermediate allenyl–Pd species, formed by oxidative addition and insertion steps, exists in equilibrium with the corresponding propargylic Pd intermediate. This equilibrium often results in a racemization of the allenic product, as observed recently by Tanaka and co-workers^[14] in a Pd^0 -catalyzed transformation of allylic alcohols into allenes. In contrast, Konno et al.^[15] were able to obtain fluorinated allenes of type **23** with high optical purity by reaction of the corresponding enantiomerically enriched propargylic mesylates **22** with organozinc reagents in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ [Eq. (3)]. Clearly, the formation of a propargylic Pd species and



subsequent racemization are efficiently prevented by the presence of the perfluorinated alkyl group.

From an (atom) economical point of view, the generation of enantiomerically pure products from achiral precursors by stereoselective catalysis with catalytic amounts of both the transition metal and the chiral ligand is particularly desirable. However, no example of such a transition-metal-catalyzed synthesis of enantiomerically pure allenes existed until recently, even though the Rh- or Ni-catalyzed hydrosilylation of butadiynes reported by Tillack et al. gave the desired chiral allenes, albeit with low enantioselectivity.^[16] The desired breakthrough in this field has now been achieved by Hayashi and co-workers, who developed two new, highly efficient catalytic allene syntheses. Thus, the palladium-catalyzed hydrosilylation of but-1-en-3-yne **24** with trichlorosilane in the presence of the chiral ferrocenyl phosphane ligand **25** gave preparatively useful stereoselectivities of up to 90 % *ee* [Eq. (4)].^[17] In this case, a sterically demanding substituent

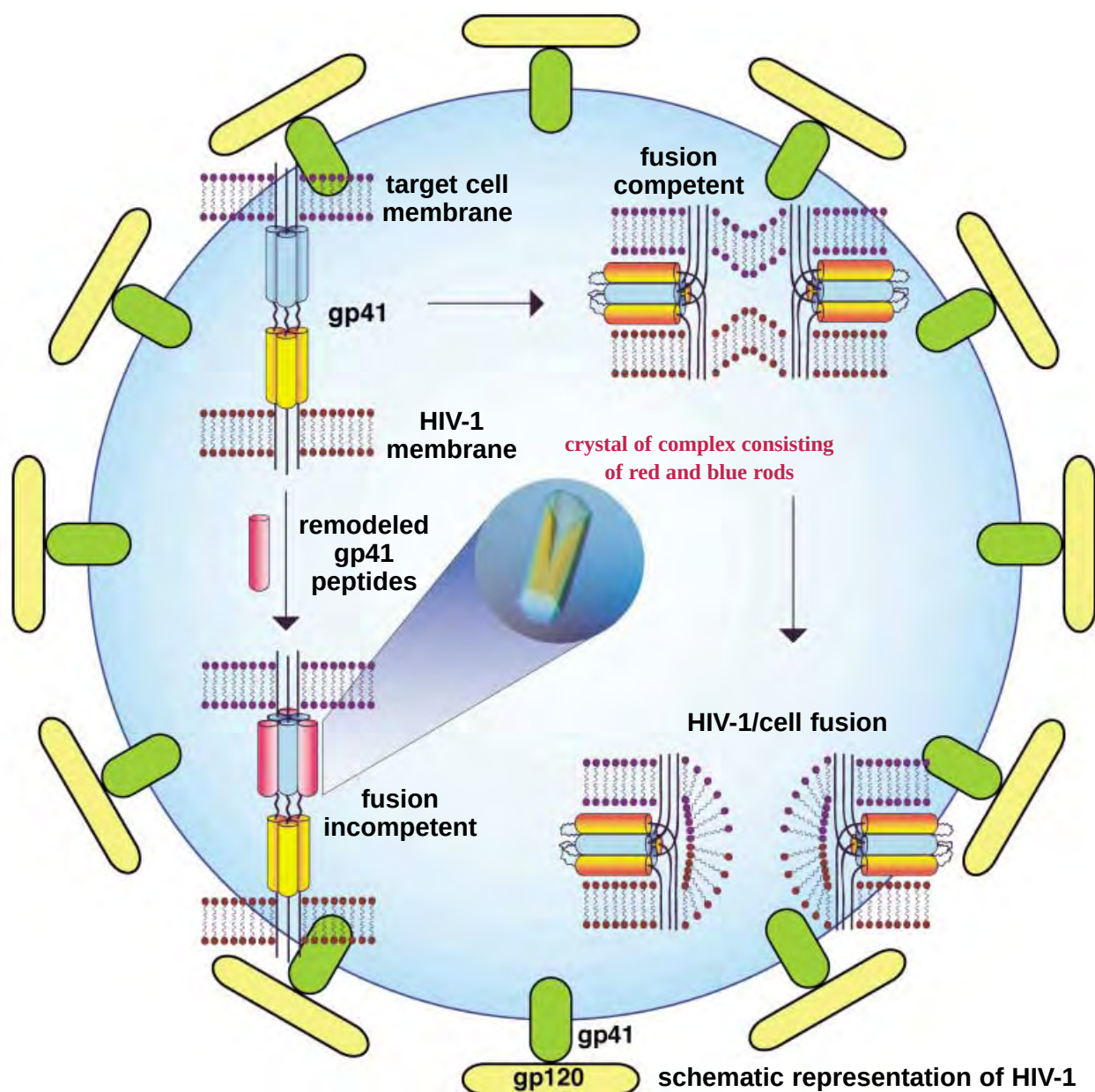


at the triple bond of the enyne **24** was found to be crucial for high enantioselectivity. Furthermore, the resulting trichlorosilanes **26** can be converted not only into allenyl trimethylsilanes, but also (with chirality transfer) into preparatively valuable chiral homopropargylic alcohols.

The second catalytic enantioselective allene synthesis, also developed by Hayashi and co-workers,^[18] relies on the palladium-catalyzed S_N2' substitution of prochiral 2-bromobuta-1,3-dienes like **27** with soft nucleophiles. In the presence of 10 mol % of (*R*)-2,2'-bis(diphenylphosphanyl)-1,1'-binapthalene (binap) as the chiral ligand, CsOtBu as base, and [Pd(dba)₂] as the precatalyst, the desired allene **28** was obtained with 89 % *ee* [Eq. (5)]. Interestingly, the presence of dibenzylideneacetone (dba) in the reaction mixture proved to be indispensable for high enantiomeric excesses.

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Promising anti-HIV-1 peptide was developed



Fusion of HIV-1 with target cells is mediated by gp41 insertion into the cell membrane, followed by six-helix bundle formation. Artificially remodeled gp41 peptides are likely to inhibit the formation of the six-helix bundle, and exhibit extremely high anti-HIV-1 activity and water solubility.

For more information see the following pages.

Remodeling of gp41-C34 Peptide Leads to Highly Effective Inhibitors of the Fusion of HIV-1 with Target Cells**

Akira Otaka,* Miki Nakamura, Daisuke Nameki, Eiichi Kodama, Susumu Uchiyama, Syota Nakamura, Hiroaki Nakano, Hirokazu Tamamura, Yuji Kobayashi, Masao Matsuoka, and Nobutaka Fujii*

The disclosure of a dynamic supramolecular mechanism involved in the fusion of HIV-1 to cells^[1] provides insights into inhibitors for blocking HIV entry into host cells. Among them, molecules targeting events involved in the formation of fusogenic trimeric hairpin structures in the envelope glycoprotein (gp41) are potential candidates for anti-HIV-1 drugs.^[2] The trimeric hairpin is formed as a bundle of six α helices, consisting of inner three-stranded coiled coils formed by the N-terminal helical region (N region) of gp41 and three outer α helices. These latter α helices, which are derived from the C-terminal membrane-proximal region (C region) of gp41,^[3] are packed antiparallel to the inner strand.

The packing of the C regions onto the inner strand brings the viral and cell membranes into close proximity, thereby prompting membrane fusion. C peptides derived from these C regions are known to prevent formation of the fusogenic structure and inhibit HIV-1 infection^[4] (Figure 1A). Among several C peptides, DP178 (T20, pentafuside)^[4a] was initially subjected to clinical trials to meet with, unfortunately, the emergence of DP178-resistant HIV-1 strains.^[4d,5] Compared to DP178, C34^[3b,4c] and T649^[4d] exhibit both potent anti-HIV activity as well as reduced susceptibility to the evolution of resistant viruses. However, C34 is less soluble in aqueous media than DP178, which might prevent C34 from being used in clinical cases. We report herein the development of highly soluble C34 variants (referred to as SC peptides) that exhibit amplified anti-HIV-1 activity.

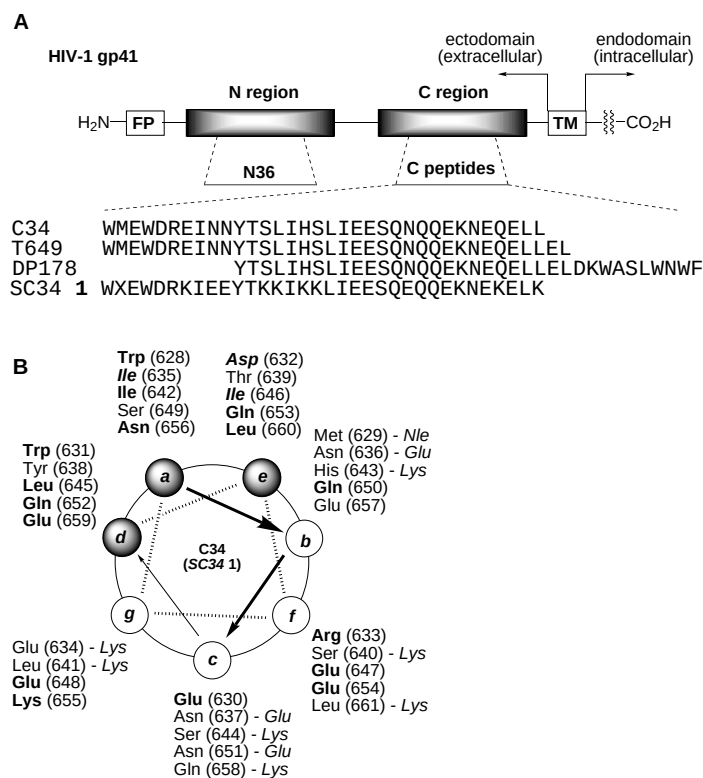


Figure 1. A) Schematic representation of HIV-1 gp41 and sequences of synthetic C peptides. Amino acids are represented by one-letter codes. Underlined letters in SC34 **1** show substituted residues (X in SC34 denotes Nle: **1a** or Met: **1b**). Listed peptides have an acetylated N terminus and a C-terminal amide. FP: fusion peptide; TM: transmembrane domain. B) Helical-wheel representation of C34 and SC34. Residues at each position are symbolized according to their conservation between HIV-1 (NL4-3 or HXB2) and SIV (Mac239):^[3b] bold: identity; bold-italic: conservative change; plain: nonconservative change; italic: amino acid replacements in SC34. Underlined Glu and Lys were changed to Lys and to Glu, respectively, in SC34EK **2**. For SC35EK **3** only Glu residues are situated in both *b* and *c* positions and only Lys residues in both *f* and *g* positions. Shaded spheres (*a*, *d*, and *e*) represent important sites for interaction with the N region (or N36). Residues are numbered starting at the first amino acid of the NL4-3 gp160.

[*] Dr. A. Otaka, Prof. Dr. N. Fujii, M. Nakamura, Dr. H. Tamamura
Graduate School of Pharmaceutical Sciences
Kyoto University
Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-4570
E-mail: aotaka@pharm.kyoto-u.ac.jp, nfujii@pharm.kyoto-u.ac.jp

D. Nameki, Dr. E. Kodama, Prof. Dr. M. Matsuoka
Laboratory of Virus Immunology
Research Center for Acquired Immunodeficiency Syndrome
Institute for Virus Research
Kyoto University, Sakyo-ku, Kyoto 606-8507 (Japan)
Dr. S. Uchiyama, S. Nakamura, H. Nakano, Prof. Dr. Y. Kobayashi
Graduate School of Pharmaceutical Sciences
Osaka University
Suita, Osaka 565-0871 (Japan)

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

Based on a helical-wheel diagram depicting the interaction of the inner coiled-coil strand formed by an N-region peptide (N36) with C34 helices^[3b] (Figure 1B), we modeled C34 according to the following concepts: firstly, maintenance of amino acid residues critical for interaction with the inner strand formed by N36 (*a*, *d*, and *e* positions); and secondly, replacement of only nonconserved residues located at solvent-accessible sites in the six-helix bundle (*b*, *c*, *f*, and *g* positions) by Glu or Lys. These should be arranged so that glutamate/lysine ion pairs can be formed between *i* and *i* + 4 positions along the C34 sequence. We expected that such replacements with Glu or Lys could enhance solubility as well as α -helicity through intrahelical salt bridges,^[6] which could stabilize the six-helix bundle crucial for anti-HIV activity.^[4c,7] Peptides SC34(Nle) (Nle = norleucine) **1a** and SC34(Met) **1b**, designed according to these principles, are summarized in Figure 1. These peptides were synthesized by standard solid-phase methods (see Supporting Information). In **1a** Met was replaced with Nle to avoid oxidation of the Met residue. The

solubility of **1a** in H₂O increased by more than 1000-fold over that of C34. The hydrophilicities of the designed molecules **1–3** relative to that of C34 were also ascertained by reversed-phase HPLC analyses (Table 1).

The inhibitory effects of **1** were determined in the multi-nuclear activation of the galactosidase indicator assay (MAGI assay).^[8] The anti-HIV-1 activities of SC peptides **1** were ten times higher than that of DP178. Furthermore, **1** exhibited strong anti-HIV-1 effects comparable to those of the parent C34 (Table 1). We also evaluated whether **1a** was active against the NL4-3_{SIM} HIV-1 variant, which is resistant to DP178.^[4d] Although DP178 showed anti-HIV activity against the wild-type HIV clone NL4-3, its anti-HIV effect decreased sevenfold against NL4-3_{SIM}. In contrast, **1a** effectively inhibited the NL4-3_{SIM} strain as well as the NL4-3 strain. These results encouraged us to develop further C peptides based on SC34 derivatives.

Among the eight *i* to *i* + 4 Glu-Lys (or Lys-Glu) intrahelical salt bridges (shown as thick and thin lines, respectively, in Table 1) introduced in the designed SC34 **1**, two pairings had Lys-Glu orientations ordered in the N to C terminus. This was due to an initial working hypothesis that conserved residues should not be substituted (Glu647, 648 are conserved residues). However, helix dipole interactions should be favorable when anionic Glu residues close to the N terminus and cationic Lys residues close to the C terminus are involved, since the positive pole of the α -helix dipole is near the N terminus and the negative pole is near the C terminus. Therefore, we speculated that reversal of the two Lys-Glu arrangements would further stabilize helix formation for SC34 based on expected interactions of these charged groups with the helix dipole. Additionally, three possible *i* and *i* + 3 Lys-Glu intrahelical interactions (represented by dotted lines in the formulas in Table 1) could possibly stabilize the helix.

These reversed derivatives (referred as SC34EK **2**) were also prepared by standard methods (see Supporting Information). MAGI analysis showed that the anti-HIV-1 activity of both SC34EK(Nle) **2a** and SC34EK(Met) **2b** was higher than that of **1**. Of note, **2a** was three times more potent than either C34 or SC34s **1**. From these results we concluded that conserved residues in the solvent-accessible face (*b*, *c*, *f*, and *g*) of SC34s (C34) could be changed unless such replacements interfered with α -helix formation. Accordingly, we synthesized five-repeats of Z-EE-ZZ-KK (SC35EK **3**), in which Z residues interact with the inner strand, and both E and K residues stabilize α -helix conformation (Z corresponds to *a*, *d*, and *e* residues in Figure 1 B). Synthetic **3** was shown by MAGI analysis to exhibit high anti-HIV-1 activity comparable to that of **2**. We observed that peptides **1–3** were not cytotoxic up to 10 μ M in MAGI cells.

Circular dichroism (CD) analyses of SC peptides **1a**, **2a**, and **3** in the absence of N36 indicate that introduction of *i* to *i* + 4 Glu-Lys (or Lys-Glu) pairs with resultant possible intrahelical salt bridges remarkably increases the helicity of SC peptides in the order **1a** < **2a** < **3**. By contrast, the parent C34 has an almost featureless spectrum. CD spectra of equimolar mixtures of N36 and SC peptides **1a**, **2a**, or **3** are typical of α -helical conformations, similar to that observed for the N36/C34 complex. Stabilities of N36/SC peptide complexes were assessed by monitoring the changes in $[\theta]_{222}$ as a function of temperature. The apparent melting temperatures (T_m) of the N36/SC peptide complexes are higher than T_m of the N36/C34 complex (Table 1). Analytical ultracentrifugation sedimentation of the N36/SC peptide (**1a**, **2a**, or **3**) complexes, over a fourfold range of peptide concentrations, indicated that each N36/SC peptide forms a six-helix complex consisting of three molecules each of N36 and SC peptide. The stability of the N36/SC peptide complex correlates to some extent with its anti-HIV activity.^[4c,7] Therefore the design of

Table 1. Anti-HIV-1 activity and physicochemical properties of the tested peptides.

Peptide ^[a,b]	EC ₅₀ ^[c] [nM]	T_m ^[d] [°C]	M_w (calcd) ^[e] [kD]	RT ^[f] [min]
C34				
Ac-WMEWDREINNYTSLIHSLEESQNQQEKNEQELL-NH ₂	0.68 ± 0.12	57.2	—[g]	28.0
SC34 1				
Ac-WXEWDRKIEEYTKKIKKLEESQEQQEKNEKELK-NH ₂	1a (X = Nle) 0.64 ± 0.20 1b (X = Met) 0.73 ± 0.12	65.2 —[g]	26.1 (25.9) —[g]	18.7 18.9
SC34EK 2				
Ac-WXEWDRKIEEYTKKIEELIKKSQEQQEKNEKELK-NH ₂	2a (X = Nle) 0.23 ± 0.11 2b (X = Met) 0.42 ± 0.06	75.2 —[g]	25.1 (25.9) —[g]	19.5 19.5
SC35EK 3				
Ac-WEEWDKKIEEYTKKIEELIKKSEEQKKNEELKK-NH ₂	0.39 ± 0.11	77.2	26.8 (26.3)	19.5
DP178	6.7 ± 2.2			

[a] Incorporated Glu(E) and Lys(K) residues are underlined. [b] Thick and thin lines represent *i* to *i* + 4 Glu-Lys and Lys-Glu arrangements, respectively. A dotted line shows an *i* to *i* + 3 arrangement modified with conversion of **1** to **2**. [c] Anti-HIV activity determined by three independent MAGI assays. EC₅₀: concentration of peptide which blocks HIV-1 replication by 50%. [d] Thermal melting temperature of 40 μ M C-peptide/N36 complex. [e] M_w : molecular mass of C-peptide/N36 complex determined by sedimentation equilibrium; calcd: calculated molecular mass of the complex consisting of three molecules each of C peptide and N36. [f] Retention time in reversed-phase HPLC analysis with linear gradient of MeCN (30–50% over 30 min) in 0.1% aqueous trifluoroacetic acid. [g] Not measured.

highly helical C peptides based on C34 proved to be a useful guide for developing highly active fusion inhibitors.

In this work we have developed soluble and highly active inhibitors of the fusion of HIV-1 with target cells based on the remodeling of a parent C34 pharmacophore by introducing *i* to *i* + 4 Glu-Lys pairs into the solvent-accessible surface of the six-helix bundle. Effects on anti-HIV-1 activity of amino acid changes in the inner-strand contact surface have been well documented.^[4e,7b] However, little attention has been paid to the effects of substitution in the outer surface of the six-helix bundle.^[7a] The α -helical SC peptides reported herein can be divided functionally into two α -helical surfaces: surfaces that interact with the inner strand where Z residues (*a*, *d*, and *e* in Figure 1 B) are located, and surfaces that are responsible for α -helix formation, which are formed by both Glu and Lys residues. Reportedly, the latter is needed for appropriate positioning of Z residues through α -helix formation. Therefore, other approaches for presenting Z functionality potentially could be used as alternatives to replacement with Glu-Lys pairs.^[9] A Z-EE-ZZ-KK repeated peptide such as **3** could serve as a scaffold to explore the interactive surfaces responsible for anti-HIV-1 activity. Finally, we have elucidated the structures of N36/SC peptide complexes using X-ray analysis in order to finetune the Z residues.

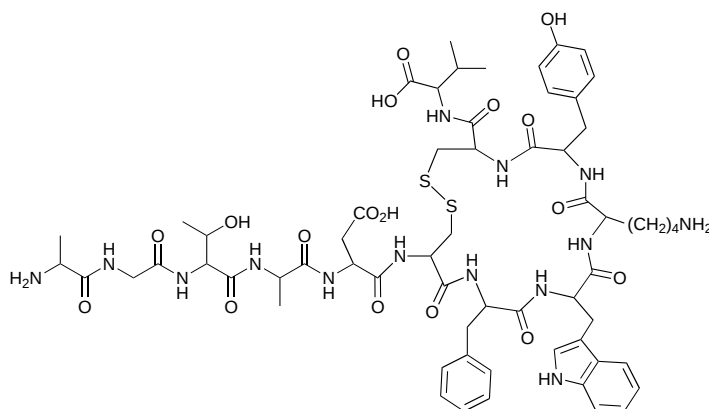
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Structure–Function Analysis of Urotensin II and Its Use in the Construction of a Ligand–Receptor Working Model

William A. Kinney,* Harold R. Almond, Jr., Jenson Qi, Charles E. Smith, Rosemary J. Santulli, Lawrence de Garavilla, Patricia Andrade-Gordon, Daniel S. Cho, Anita M. Everson, Mark A. Feinstein, Perry A. Leung, and Bruce E. Maryanoff

Urotensin II (U II) is a cysteine-linked cyclic peptide with potent vasoactive properties. Originally, this substance was isolated from the urophysis (a caudal neurosecretory organ) of the goby fish (*Gillichthys mirabilis*) as a 12-mer, AG-TADCFWKYCV (Scheme 1),^[1] but it has now been identified



Scheme 1. U II peptide from the goby fish (1).

in all classes of vertebrates. The composition of U II ranges from 11 amino acids in humans to 14 amino acids in mice, always with the conserved cysteine-linked macrocycle, CFWKYC. Recently, the U II receptor was identified^[2] as a G-protein-coupled receptor (GPCR) previously known as the GPR14 orphan receptor,^[3] which is expressed predominantly in cardiovascular tissues.

Goby U II (**1**) possesses powerful vasoconstrictor activity in fish, mammals, and humans.^[4,5] Moreover, it appears to be the most potent vasoconstrictor known,^[6] causing concentration-dependent contraction of isolated arterial rings of rats and humans with an EC₅₀ value of less than 1 nM, which means it is about ten times more potent than endothelin 1. However, the

- [*] Dr. W. A. Kinney, Dr. H. R. Almond, Jr., Dr. J. Qi, C. E. Smith, R. J. Santulli, Dr. L. de Garavilla, Dr. P. Andrade-Gordon, Dr. B. E. Maryanoff
Drug Discovery
Johnson & Johnson Pharmaceutical Research & Development
Welsh and McKean Roads, Spring House, PA 19477-0776 (USA)
Fax: (+1) 215-628-4985
E-mail: Wkinney1@prius.jnj.com
D. S. Cho, A. M. Everson, M. A. Feinstein, P. A. Leung
Drug Discovery
Johnson & Johnson Pharmaceutical Research & Development
San Diego, CA 92121 (USA)



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in vivo effects of U II can be tissue- and species-specific, and sometimes contradictory. For example, U II has also been described as a vasodilator in conscious rats.^[7] In addition, this peptide was recently reported to induce hypertrophy in cardiomyocytes^[8] and the proliferation of smooth muscle cells,^[9] which suggests a possible involvement in heart failure and atherosclerosis. The discovery of U II receptor antagonists would help to elucidate the in vivo pharmacology, as well as afford potential therapeutic agents for the treatment of cardiovascular disorders such as hypertension and heart failure.

Utilizing the techniques of peptide pharmacophore identification pioneered by others,^[10] we performed a structure–function study of U II that established its minimal active size and key structural features. This information, in conjunction with molecular modeling of the GPCR, led to the assembly of a three-dimensional structure of the U-II–receptor complex, which was used to design a more potent U II agonist.

Derivatives of goby U II were screened in a FLIPR-based calcium mobilization assay utilizing the rat receptor expressed in CHO cells^[11] as a measurement of agonist activity. Evaluation of close analogs of U II has provided clues to important structural features of the peptide molecule (Table 1). The goby U II peptide was truncated on the N terminus

Table 1. U II agonist activity of cyclic truncated and alanine-scan peptides as measured by calcium flux.

Compound	Sequence ^[a]	EC ₅₀ [nM] ^[b]
1 (goby U II)	AGTADCFWKYCV	0.17 ± 0.05 ^[c]
2	GTADCFWKYCV	0.29 ± 0.18
3	TADCFWKYCV	0.11 ± 0.05
4	ADCFWKYCV	0.16 ± 0.05
5	DCFWKYCV	0.10 ± 0.04
6	CFWKYCV	0.76 ± 0.65
7	CFWKYC	1.6 ± 0.9
8	AACFWKYCV	0.60 ± 0.10
9	ADCAWKYCV	6.5 ± 1.5
10	ADCF ~~A~~ KYCV ^[d]	> 1000
11	ADCFW ~~A~~ YCV ^[d]	> 1000
12	ADCFWK ~~A~~ CV ^[d]	67 % @ 1000 ^[e]
13	ADCFWKYCA	0.40 ± 0.20

[a] All peptides were in the cyclic form. The one-letter amino acid code is used. [b] Not corrected for peptide content, unless noted otherwise. [c] Corrected for peptide content. [d] Inactive as an antagonist at 10000 nM. [e] Percent activation at given concentration.

from the 12-mer (**1**) down to the 7-mer (**6**), and finally the valine residue was eliminated from the C terminus to give the 6-mer (**7**). Although a 10-fold reduction in potency is seen in the 6-mer, low-nanomolar agonist activity is retained. An alanine scan was applied to the 9-mer **4** to determine which amino acid residues are most important for U II receptor stimulation. Only replacement of W, K, and Y caused large changes in biological activity, suggesting the importance of the side chains of these amino acids for binding to and activating the U II receptor. Recent structure–function results on human U II are in agreement with our findings.^[12]

The significance of the conserved cyclic sequence CFWKYC was confirmed by further truncation (Table 2). Capping of the 6-mer (compound **14**) did not change the

Table 2. Effect of capping, ring removal, and D scan of 6-mer peptide on agonist activity and binding.

Compound	Sequence ^[a]	EC ₅₀ [nM] ^[b]	K _i [nM] ^[c]
7	CFWKYC	1.6 ± 0.9 ^[d]	86 ± 13
14	(Ac)-CFWKYC-NH ₂	1.6 ± 0.5	13 ± 4
15	(Ac)-SFWKYS-NH ₂ ^[e]	> 500	> 10000
16	(Ac)-FWKY-NH ₂ ^[e]	57 % @ 500	> 10000
17	(Ac)-WKY-NH ₂ ^[e]	> 500	> 10000
18	(Ac)-C(D-F)WKYC-NH ₂ ^[e]	57 % @ 500	> 10000
19	(Ac)-CF(D-W)KYC-NH ₂	26 ± 3	600 ± 30
20	(Ac)-CFW(D-K)YC-NH ₂ ^[e]	54 % @ 500	> 10000
21	(Ac)-CFWK(D-Y)C-NH ₂	37 ± 6	1000 ± 100

[a] All cysteine-containing peptides are in the cyclic form. Data corrected for peptide content unless noted otherwise. [b] Agonist activity measured by the calcium flux assay. [c] Binding as measured by displacement of [¹²⁵I]-urotensin II (rat). [d] Not corrected for peptide content. [e] Inactive as an antagonist at 300 nM.

efficacy as was previously reported.^[13] However, replacement of the cysteine residues with serine residues to give the acyclic 6-mer **15**, or further removal of amino acids, led to significantly reduced agonist activity (viz. **16** and **17**). Inversion of the configuration of a single amino acid is known to convert an agonist into an antagonist for certain cyclic peptide ligands. An example is the vasoconstrictor endothelin, which acts at a different GPCR.^[14] With the U II ligand, reduced agonist potency was seen on stereoinversion of the W and Y residues. However, the modified peptides (**18–21**) did not possess U II antagonist properties, as measured by the compounds' ability to block the response induced by U II (**1**).^[11] This result demonstrates the importance of the spatial orientation of the WKY pharmacophore for interaction with the receptor. A binding assay,^[11] measuring displacement of [¹²⁵I]-labeled rat U II from membranes containing the rat U II receptor, showed activity at higher concentrations (8- to 50-fold) for these short peptides. There appears to be a greater dynamic range in this assay, possibly because of the presence of the native ligand. These smaller peptides might have difficulties in competing with the full-length U II peptide because they have fewer interactions with the receptor, although functionally they can activate the receptor at low concentrations.

The U II receptor is related to the δ -opioid receptor with 27 % identity and 56 % homology.^[3] A working model of the latter,^[15] which is based on the X-ray structure of rhodopsin,^[16] was used as a starting point for our construction of a model of the U II receptor (rat). U II models were placed above the receptor model in various orientations and were then pulled into the receptor with a tether between the lysine nitrogen of U II and the carboxylate of Asp 130 on TM3 of the receptor, a reputed site for such ligand–amine interactions.

It is inherently problematic to establish a plausible structure of a flexible ligand complexed with a second-generation GPCR homology model. However, such a U-II–receptor complex can offer a qualitative assessment of potential interactions and serve to generate hypotheses that are testable with modified ligands. Although a solution-based structure determination using NMR spectroscopy might be more reliable, the resulting structure describes the unbound form of the ligand.^[12] The molecular modeling method probes the bound conformation of the ligand, which is more relevant

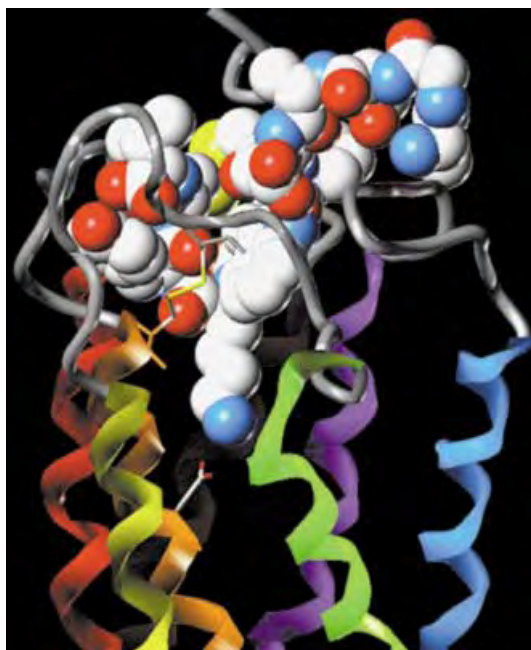


Figure 1. U II (**1**) docked into the U II receptor model.

from a drug design perspective. The docking procedure is based on two central assumptions: the “essential” lysine on the U II ligand binds to Asp 130 on TM3 (similar to many other GPCRs), and interactions between the extracellular loops and the ligand mutually restrict each other's conformations. Thus, as the lysine residue is drawn toward Asp 130, the loops of the receptor and the other parts of the ligand can adjust in a manner that could mimic a native docking process. As a consequence, only a small fraction of the conformational space had to be explored. The receptor models produced from the various starting orientations were visually examined and very few showed well-defined binding sites for the critical W, K, and Y residues of U II (Table 1). A docking model consistent with the molecular recognition of the key side chains of W, K, and Y was selected (Figure 1).

A useful avenue for improving potency and altering efficacy with other GPCR peptide ligands has been the insertion of nonnatural amino acids into the sequence. In Table 3 the capped cyclic 6-mer **14** and analogs modified by point substitution with natural and nonnatural amino acids are compared. Replacement of the Y residue with the related amino acid F maintained potency (**22**) in both the functional and binding assays. Substitution at the same position by A (**23**) drastically reduced potency, as was seen with the 9-mer peptide **12** (Table 1). The combined results with **22** and **23** indicate the primary importance of a hydrophobic group at the Y position of the ligand. The hypothesized tyrosine-binding pocket within the best model of U II (Figure 2)

suggested a bulkier side chain for the Y residue, for example, 2-naphthyl.

Introduction of (2-naphthyl)-L-alanine (2-Nal, **25**) actually improved agonist activity slightly in the calcium flux assay relative to the native Y residue, presumably due to enhanced hydrophobic interactions. However, in the binding assay a 100-fold improvement in affinity was noted. Placement of 2-Nal at the W position (**24**) significantly decreased potency in both assays. This loss of activity can be rationalized by the loss of a possible hydrogen bond linking the indole NH group on U II to the receptor. The use of 1-Nal (**26**) led to a potency comparable to that of the parent 6-mer **14**. The D-variant of **25**, **27**, did not exhibit agonist or antagonist activity. Since a large aromatic residue was tolerated at the putative tyrosine-binding site, further elongation of this residue was probed (analogues **28** and **29**). The Bip derivative was similar to the native residue in potency, while the Dpa one was not accommodated, as predicted by the model. The 2-Nal residue was also favorable in the full-length goby U II **1** leading to subnanomolar agonist **30**. Compound **30** was about equipotent to **1** in the functional assay and six-fold more potent in the binding assay ($K_i = 40$ pM), confirming the favorable inter-

Table 3. Effect of the substitution of the tyrosine and tryptophan residues of **14** and **1** with other hydrophobic groups on agonist activity, binding, and vasoconstrictor activity.

Compound	Sequence ^[a]	EC ₅₀ [nM] ^[b]	K _i [nM] ^[c]	Response [%] ^[d]
14	(Ac)-CFWKYC-NH ₂	1.6 ± 0.5	13 ± 4	11
22	(Ac)-CFWKFC-NH ₂	2.1 ± 0.3	18 ± 2	–
23	(Ac)-CFWKAC-NH ₂ ^[e]	50 % @ 1000	> 10000	0
24	(Ac)-CF(2-Nal)KYC-NH ₂ ^[f]	31 ± 6	260 ± 50	–
25	(Ac)-CFWK(2-Nal)C-NH ₂ ^[f]	0.54 ± 0.2	0.12 ± 0.05	43
26	(Ac)-CFWK(1-Nal)C-NH ₂ ^[f]	1.5 ± 0.2	6 ± 1	–
27	(Ac)-CFWK(D-2-Nal)C-NH ₂ ^[f,g]	> 1000	1700 ± 200	–
28	(Ac)-CFWK(Bip)C-NH ₂ ^[h]	1.8 ± 0.1	6 ± 1	–
29	(Ac)-CFWK(Dpa)C-NH ₂ ^[e,i]	> 1000	1600 ± 400	–
1	AGTADCFWKYCV	0.17 ± 0.05	0.26 ± 0.05	91
30	AGTADCFWK(2-Nal)CV ^[f]	0.34 ± 0.10	0.04 ± 0.02	–

[a–c] See footnotes to Table 2. [d] Vasoconstriction of isolated thoracic aorta at a fixed concentration of 30 nM ($n = 2$). [e] Inactive as an antagonist at 3000 nM. [f] Nal = naphthylalanine. [g] Inactive as an antagonist at 300 nM. [h] Bip = 4-phenyl-L-phenylalanine. [i] Dpa = 4-(2,6-dichlorobenzyloxy)-L-phenylalanine.

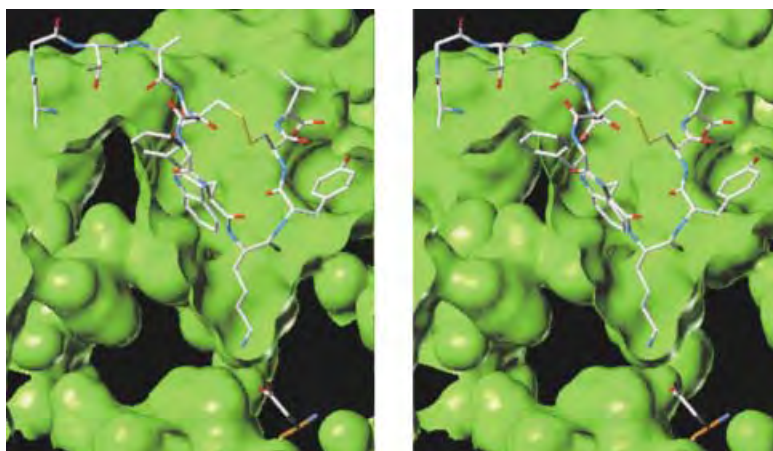


Figure 2. Modeled docking pockets for U II in its receptor. Cut-away view of the U II receptor contact surface.

action of the 2-Nal group in the tyrosine-binding pocket. The improved potency in the binding assay for analogues **25** and **30** relative to potency in the functional assay is even more striking as compared to other analogues such as **7** and **14**, which had decreased activity in the binding experiment competing with the native ligand. These results point to the beneficial impact of the 2-Nal residue on binding energy.

A selected group of peptides was evaluated for vasoconstrictor activity in a thoracic aorta smooth muscle tissue preparation (Table 3).^[11] The rank order of agonist potency at a fixed dose of 30 nM was that predicted by the FLIPR assay results. Goby U II (**1**) was most potent, followed by the 2-Nal 6-mer **25**. Compound **23** was included as a negative control. Again, 2-Nal derivative **25** was more potent than Y-containing analog **14** in this system.

In conclusion, we have conducted a structure–function analysis of the vasoactive peptide U II and employed that information in a docking strategy for the assembly of a ligand–receptor model. This three-dimensional construct has proven useful in rationalizing biological activity and predicting opportunities for potency improvement. In particular, the key W, K, and Y residues of U II, identified as being important for biological function, were found to have significant interactions with the GPCR model. A prominent feature of the receptor model is a tyrosine-binding pocket. As predicted by our working model, the 2-Nal group showed an enhanced interaction with this critical binding region, whereas larger groups were not accommodated. The 2-Nal substituted peptides **25** and **30** showed greater affinity for the receptor than U II as measured by displacement of the radiolabeled native ligand. The interplay between structure–function and molecular modeling studies proved effective as a drug design tool in a case where no tertiary structural information is known. This working model should assist efforts to design nonpeptide ligands as potential U II receptor antagonists.

Experimental Section

Modeling: Starting with a model of the δ -receptor, amino acid residues were mutated according to the homology alignment,^[3] and extracellular loops were added with the aid of the Loop–Search routine in Sybyl.^[17] The side chains and loops were energy-minimized with AMBER^[18] while restraining the backbone of the seven transmembrane (TM) helices. A computational structural analysis of U II (goby) revealed a wide range of low-energy conformations. Two of the lowest-energy structures (found by Monte Carlo conformation searches in a water-solvated model with the MacroModel program^[19]) were chosen as starting points and the U II models were placed above the receptor model (≈ 20 Å tether, see below) in orientations rotated by 30°. The Sander module of AMBER^[18] was used to place a tether between the lysine nitrogen of U II and the carboxylate of Asp130 on TM3 of the receptor. After 5 ps of thermal equilibration at 300 K (a type of simulated annealing), the tether strength (tether energy well parameters: $r_1 = 2$, $r_2 = 2.5$, $r_3 = 3.5$, $r_4 = 4.0$, $r_{k2} = 32$, $r_{k3} = 128$) was increased (0 to 32 kcal mol^{−1} Å²) over 3 ps, held at the top value for 1 ps, and then turned off for 10 ps. During this process, only the backbones of the helices were kept stationary; the ligand, extracellular loops, and side chains were free to move about and interact. The resulting complexes were selected on the basis of the structure–activity relationships available at that time (Table 1). The receptor model with the best-defined pockets for the tryptophan, lysine and tyrosine residues of the ligand was chosen as working model.

Peptides:^[20] Goby U II (**1**) was purchased from Bachem Bioscience Inc., King of Prussia, PA, USA (no. H-6950). Peptides **2–30** were prepared from

the C terminus to the N terminus by the Merrifield method on a solid resin support.^[21] Depending on whether the C terminus was desired as an amide or acid, the resin was selected from an Fmoc-amide resin or Wang resin, respectively. During the synthesis, lysine (Boc), cysteine (Trt), aspartic acid (tBu), serine (tBu), threonine (tBu), and tyrosine (tBu) all contained side chain protecting groups (given in brackets). N-acylation was done as the last step of the synthesis by using acetic anhydride. Cleavage of the peptide from the resin was achieved with 95% trifluoroacetic acid, which also removed the protecting groups. The peptide was purified prior to cyclization by reversed-phase HPLC and then cyclized directly with potassium ferricyanide in aqueous ammonium bicarbonate. Since side products, for example dimeric products, were often formed during this cyclization, the post-cyclization product was chromatographed to isolate the desired peptide. All the peptides were analyzed by electrospray mass spectrometry (Finnegan LCQ instrument) and analytical HPLC. All compounds exhibited the correct mass and most were at least 90% pure (HPLC). Peptides **14–30** were assayed for peptide content by amino acid analysis.^[11] The biological data were calculated based on the amount of pure peptide present in the sample. All unique structures (disregarding stereoisomers) within compounds **14–30** were analyzed for accurate mass by high-resolution fast-atom bombardment mass spectrometry with a Micromass Autospec E double-focusing mass spectrometer (polyethylene glycol as internal mass reference); only the D-peptides **18–21** were not analyzed by this method.^[11]

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A Cluster Rearrangement of an Open Cubane (Cu_4Br_4) to a Prismane (Cu_6Br_6) in a Copper(I)–Olefin Network**

Xiang Xue, Xi-Sen Wang, Ren-Gen Xiong,* Xiao-Zeng You, Brendan F. Abrahams,* Chi-Ming Che, and Huang-Xian Ju

The rational design and self-assembly of copper(I)–olefin coordination polymers possessing high thermal stability has been the focus of intense interest in recent times.^[1] While these materials possess many of the general features normally associated with coordination polymers, the inclusion of bridging ligands that are capable of π bonding offers the possibility of unusual and novel properties. The Cu^{I} –olefin complexes examined so far have demonstrated an ability to act as fluorescent sensors,^[1] and have potential applications in areas such as olefin separation^[2] and enantioseparation.^[3]

To the best of our knowledge, the presence of clusters, such as cubanes, within Cu–olefin coordination polymers is unknown, however there are a number of metal–organic frame-

works with clusters acting as connecting units. Such materials have demonstrated gas-storage capabilities as well as exhibiting magnetic and catalytic properties.^[4–6] The successful generation of networks incorporating olefin coordination to a copper cluster represents an exciting challenge in modern supramolecular and organometallic chemistry. With this in mind, we have studied the reactions of triallyl-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (TTT) with CuBr at different temperatures. Herein we report the synthesis, solid-state structures, and some electrochemical properties of two materials generated from such reactions.

The reaction between TTT and CuBr in methanol at 50–60 °C in a sealed tube yielded a product with the formula $[\text{Cu}_4\text{Br}_4(\text{TTT})_2]_n$ (**1**), which was examined by single-crystal X-ray diffraction.^[7] In this complex, Cu_4Br_4 clusters are linked by TTT ligands to form a polymeric chain (Figure 1). The Cu



Figure 1. The chain structure of **1** which extends in the *c* direction (Cu green, Br pink, O red, N blue, C black). The open-cubane unit is highlighted with yellow bonds. H atoms have been omitted for clarity. Typical bond lengths [Å]: Cu–Br 2.422–2.395, Cu–C 2.063–2.106, coordinated olefin C=C 1.347–1.402.

and Br atoms occupy corners of a distorted cube, however as is apparent in Figure 1, there are only 10 Cu–Br bonds in each cluster resulting in an open-cubane arrangement (a closed-cubane arrangement would have a bond along each edge). The open-cubane unit has two unique Cu^{I} atoms each being coordinated by an olefin moiety and two bromide ions in an approximate plane with the metal center. One of the unique Cu atoms is coordinated to an extra bromide ion located within the cubane unit. This third Cu–Br bond is almost perpendicular to the plane of the other donor atoms, and with a length of 2.95 Å it is considerably longer than the other Cu–Br bonds.

Only two of the three arms of the TTT ligand are involved in coordination to the cubane units. The terminal carbon atom of the third arm is disordered over two sites. As is apparent in Figure 1, small cavities within the chain exist with approximate dimensions of 5×7.5 Å. These are formed by double-ligand bridges linking neighboring cubane units (a pseudo-3D network representation of **1** can be seen in the Supporting Information).

There are many examples of cubane clusters serving as the connecting node^[8] in metal–organic coordination polymers, however, to the best of our knowledge, **1** is only the second example of olefin-based ligands linking cubane-type units in coordination polymers.^[8c]

The complex $[\text{Cu}_6\text{Br}_6(\text{TTT})_2]_n$ (**2**), was formed in the reaction between CuBr and TTT in ethanol at approximately 90 °C. The solid-state structure of **2**^[7] (Figure 2a) indicates the

[*] Prof. Dr. R.-G. Xiong, X. Xue, X.-S. Wang, Prof. Dr. X.-Z. You, Prof. Dr. H.-X. Ju
Coordination Chemistry Institute
The State Key Laboratory of Coordination Chemistry
Nanjing University
210093 Nanjing (P. R. China)
Fax: (+86)25-331-4502 or (+86)25-331-7761
E-mail: xiongrg@netra.nju.edu.cn

Dr. B. F. Abrahams
School of Chemistry
University of Melbourne
Victoria 3010 (Australia)
Fax: (+61)3-9347-5180
E-mail: bfa@unimelb.edu.au

Prof. Dr. C.-M. Che
Department of Chemistry
The University of Hong Kong
Pokfulam Road, Hong Kong (China)

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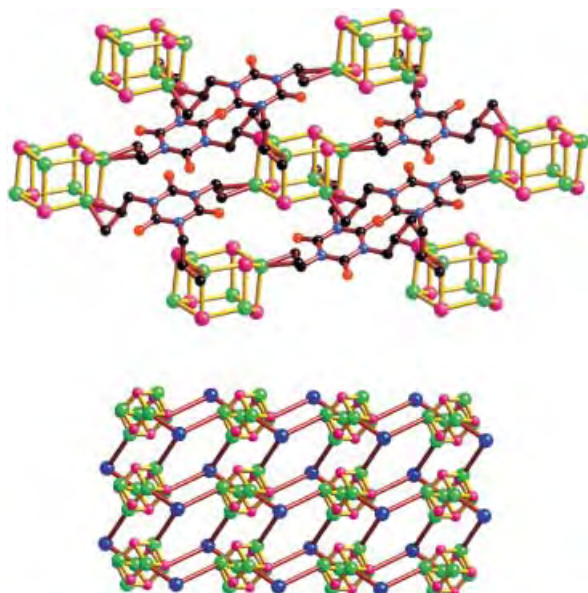
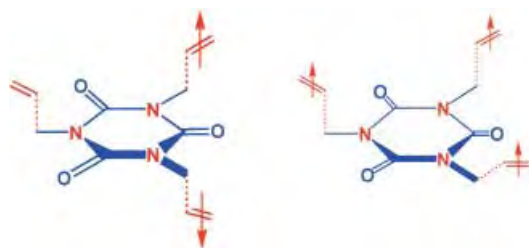


Figure 2. Top: The 2D structure of **2** which extends along the *a-b* plane (Cu green, Br pink, O red, N blue, C black). For clarity only ligands attached to the central prismane unit are shown. The prismane units are highlighted with yellow bonds. H atoms have been omitted for clarity. Typical bond lengths [Å]: Cu–Br 2.417–2.741, Cu–C 2.103–2.172, coordinated olefin C=C 1.336–1.350; bottom: an idealized representation of **2** showing the connectivity between prismane units. The blue spheres represent the tridentate TTT ligands.

presence of Cu_6Br_6 prismane clusters. Each Cu atom of the cluster is coordinated to three Br atoms and an olefin moiety, which gives rise to a slightly distorted tetrahedral coordination environment around each metal center. Each cluster is attached to six TTT ligands, each of which is attached to three prismane clusters. The resulting coordination polymer is a 2D-network (a 2D layered representation of **2** is supplied in the Supporting Information).

The tridentate bonding motif adopted by the TTT ligand in **2** contrasts with the bidentate form found in **1**. Another notable difference relates to the position of the olefin moieties relative to the triazine plane of the ligand. In **1** the olefin binding groups are on opposite sides of the triazine plane in an arrangement that may be described as *trans*. In **2**, however, all binding units are on the same side of the plane in what may be regarded as a *cis* arrangement (Scheme 1).

The incorporation of a prismane cluster into a supramolecular structure such as this is unprecedented. However, Hartl and co-workers reported a compound in which Cu_6I_6 prismane building blocks were linked intramolecularly to



Scheme 1. Illustration of the *trans*-coordinating mode in **1** (left) and the *cis*-coordinating mode in **2** (right).

form chains in which instead of C=C coordination, the Cu center is coordinated to $n\text{-}\sigma$ bound ligands.^[9] The ability of the prismane unit to link to six bridging ligands (with metal connecting centers lying at the vertices of a slightly distorted octahedron) makes this an appealing structural motif that may be useful in forming a variety of novel network structures.

Thermogravimetric analysis (TGA) of the crystalline complexes **1** and **2** showed no weight loss below approximately 200 and 265 °C, respectively, which indicates good thermal stability for these compounds, while beyond these temperatures both complexes decompose and lose their crystallinity. Interestingly, **1** can be converted into **2** in high yield by the reaction of **1** with CuBr on heating in ethanol. The conversion reaction may be a consequence of the open-cubane structure possessing a lower thermal stability than the prismane structure, which is suggested by TGA.

Electrochemical measurements at platinum and glassy carbon working electrodes gave similar results for both complexes. As seen from Figure 3, the cyclic voltammograms of both **1** and **2** displayed one redox couple with similar behaviors, indicative of a closely related structure. The anodic and cathodic peak potentials of **1** were –146 and –530 mV at 150 mV s^{-1} , respectively, while the peaks of **2** occurred at –166 and –530 mV. No peaks were observed in a solution of the ligand, which suggests that these peaks were attributed to the oxidation and reduction of the Cu^{I} centers in the complexes.

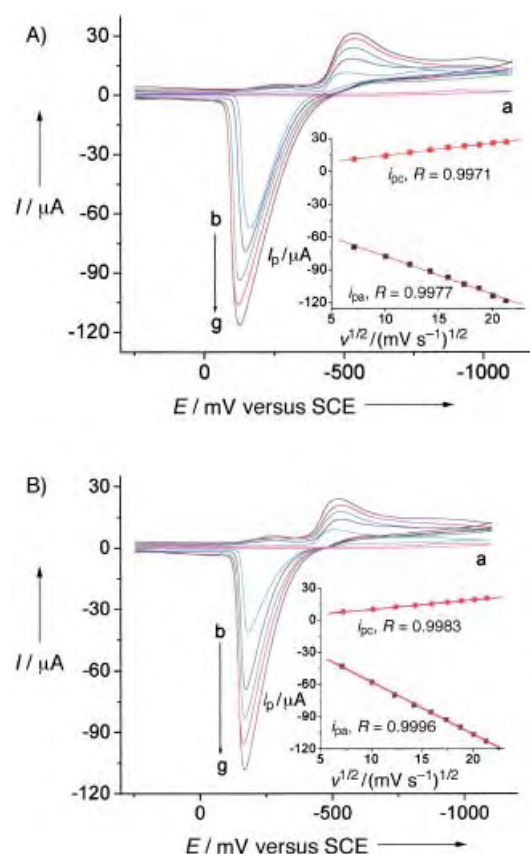


Figure 3. Cyclic voltammograms of 1.0 mM TTT in 0.1M Bu_4NClO_4 solution (CH_3CN) at 150 mV s^{-1} of 1.0 mM of **1** (A) and 0.5 mM of **2** (B) in 0.1M Bu_4NClO_4 solution (CH_3CN) at 50, 150, 250, 350, and 450 mV s^{-1} (from b to g) at a platinum disc working electrode. Insert: plots of anodic and cathodic peak currents versus $v^{1/2}$.

The single oxidation peak for both complexes indicated that all of the Cu^I centers were in the same local coordination environment.^[10] The linear relation between peak currents and the square root of the scan rate, the large difference between anodic and cathodic peak currents, and the large peak-to-peak separations all indicated that both electrode reactions were irreversible processes. The larger peak current of **1**, compared with **2**, was caused by a higher solution concentration of **1** in acetonitrile. A smaller peak-to-peak separation of **2**, compared with **1**, and the larger ratio of peak current to amount of Cu^I centers in solution indicate a more rapid electron-transfer rate in **2**, as a result of its prismane-based structure. However, the exact nature of the species in solution is unclear.

In conclusion, with a precise knowledge of their solid-state structures and facile tunability of their building blocks, the present work definitely holds great promise in the development of novel Cu–olefin supramolecular motifs containing clusters as connecting nodes.

Experimental Section

1: CuBr (2.0 mmol) and TTT (1.0 mmol) were heated in MeOH (1.5 mL) for 3 days at 50–60 °C in a sealed tube to yield colorless platelike crystals of **1** (approximately 0.4 mmol, 40 % yield). IR (KBr): $\tilde{\nu}$ = 3427(brw), 1686(s), 1457(s), 1315(w), 930(w), 764(w), 701(w), 669(w), 605(w), 544 cm^{−1}(w). Complex **1** is slightly soluble in CH₃CN.

2: CuBr (3.0 mmol) and TTT (1 mmol) were heated in EtOH (1.5 mL) for 3 days at 80–90 °C in a sealed tube to yield colorless platelike crystals of **2** (approximately 0.5 mmol, 50 % yield). IR (KBr): $\tilde{\nu}$ = 3426(brw), 2961(w), 1759(w), 1681(s), 1561(w), 1456(s), 1496(m), 1398(m), 1335(w), 1319(w), 1305(w), 1266(w), 977(w), 949(m), 930(w), 778(m), 746(w), 736(w), 695(w), 528(w), 428(w) cm^{−1}. Complex **2** is also slightly soluble in CH₃CN.

Conversion of **1** into **2**: Treatment of powdered **1** (1.0 mmol) with CuBr (1.0 mmol) in EtOH (1.5 mL) for 2 days at 80–90 °C in a sealed tube affords colorless platelike crystals of **2** (approximately 0.5 mmol, 90 % yield).

EPR spectra of the complexes are all silent, thus confirming that the oxidation state of Cu ions in both **1** and **2** is +1.

Electrochemical measurements of **1** and **2** were performed with a BAS 100 B electrochemical analyzer (Bioanalytical Systems Inc., USA) by using a standard three-electrode system comprising a saturated calomel electrode (SCE) as reference, a platinum wire as auxiliary electrode and a platinum disc (1.0 mm diameter) or glassy carbon disc (3.0 mm diameter) as working electrode. The working electrodes were polished to a mirrorlike surface with 0.3 and 0.05- μ m alumina slurries on microcloth pads (Buehler), then rinsed with water and ethanol, and sonicated in twice-distilled water. After the electrodes had been dried in heated air, they were used for electrochemical experiments in deaerated CH₃CN solutions after purging with pure nitrogen for 15 min.

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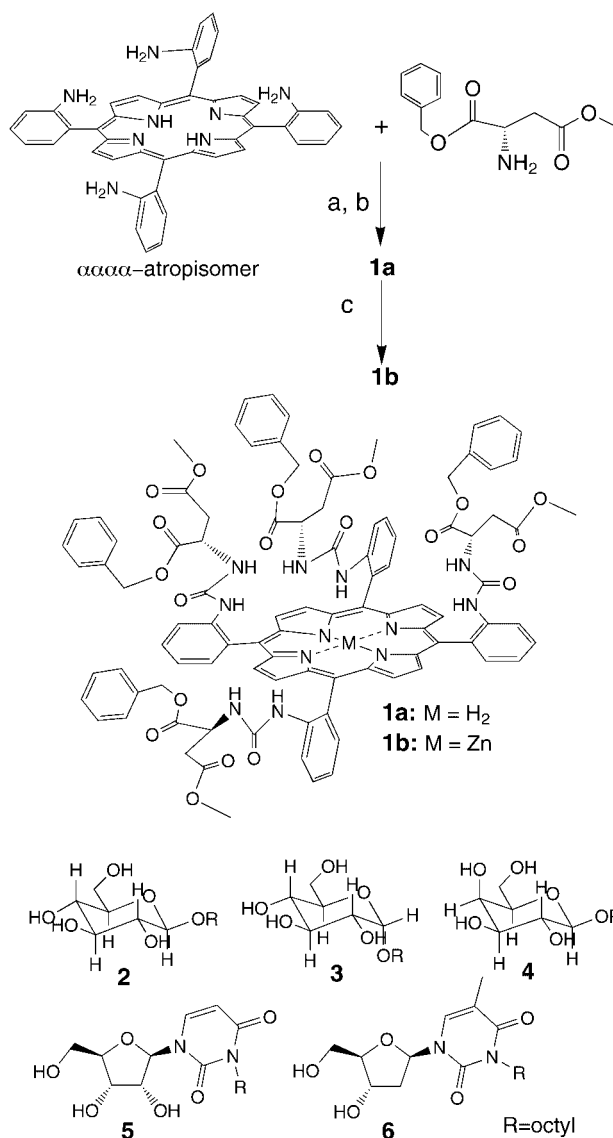
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- [7] Crystal data for **1**: C₂₄H₃₀Br₄N₆O₆Cu₄, *M_r* = 1072.34, monoclinic, space group C2/c, *a* = 21.710(19), *b* = 8.079(7), *c* = 19.000(16) Å, β = 90.000(17)°, *V* = 3333(5) Å³, *Z* = 4, ρ_{calcd} = 2.137 Mg m^{−3}, *R*₁ = 0.0708, *wR*₂ = 0.1649, μ = 7.361 mm^{−1}, *S* = 0.845. Crystal data for **2**: C₁₂H₁₅Br₃N₃O₃Cu₃, *M_r* = 679.62, monoclinic, space group P2₁/c, *a* = 10.7562(15), *b* = 7.9594(11), *c* = 20.662(3) Å, β = 96.588(2)°, *V* = 1757.3(4) Å³, *Z* = 4, ρ_{calcd} = 2.569 Mg m^{−3}, *R*₁ = 0.0337, *wR*₂ = 0.0570, μ = 10.432 mm^{−1}, *S* = 0.726. The structures were solved by direct methods using the SHELXTL program (Sheldrick, 1997).^[11] All the non-hydrogen atoms were located from the trial structure and then refined anisotropically (except for atom C3 which was found to be disordered over two sites) with SHELXTL using the full-matrix least-squares procedure. The hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent carbon atoms. The final difference Fourier map was found to be featureless. CCDC-179241 (**1**) and CCDC-179242 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).
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Molecular Recognition of Carbohydrates through Directional Hydrogen Bonds by Urea-Appended Porphyrins in Organic Media **

Yeon-Hwan Kim and Jong-In Hong*

Carbohydrate recognition through noncovalent interactions is one of the challenging goals of biomimetic and supramolecular chemistry.^[1] This is partly because of the various cellular recognition processes of oligosaccharides on the cell surfaces,^[2] and partly because of the 3D complexity, even in monosaccharide structures.^[3] X-ray crystallographic analyses of sugar–protein complexes reveal that multiple hydrogen bonds are equatorially arranged in the hydrophobic protein cavity for effective intermolecular interactions.^[4] Therefore, an effective approach to carbohydrate recognition is to surround the polar hydroxy groups of carbohydrates with complementary hydrogen-bonding receptor groups and introduce aromatic surfaces into the receptor against carbohydrate CH moieties. Despite considerable efforts in the development of artificial carbohydrate receptors, there have only been a few effective hydrogen-bonding and biomimetic carbohydrate-recognition systems in organic media reported to date.^[5,6] Here we report novel porphyrin-based carbohydrate receptors with a complementary and convergent arrangement of hydrogen-bond donor and acceptor functionality, which show unusually high affinity and selectivity toward monosaccharides in chloroform and can tolerate significant amounts of hydroxylic cosolvents, in spite of an acyclic and flexible structure without a discrete hydrophobic cavity.^[7]

Inspired by the X-ray crystal structures of protein–carbohydrate complexes, we designed receptors **1a** and **1b** (Scheme 1), in which four aspartate units are used as hydrogen-bond donors and acceptors and *aaaa*-5,10,15,20-tetrakis-(*o*-aminophenyl)porphyrin both as a π donor for CH– π interactions and as a rigid spacer for the convergent hydrogen-bonding groups (four urea groups) to be prearranged in favorable positions for sugar recognition above the porphyrin plane. These units were covalently connected by four urea linkages that were known to be strong H-bond donors. Therefore, multiple hydrogen bonds were possible in the inner cavity of the receptors. Compound **1a** was prepared by a reaction of α -benzyl- β -methyl protected aspartate and *aaaa*-5,10,15,20-tetrakis-(*o*-isocyanophenyl)porphyrin,^[8] as shown in Scheme 1.^[9a] Compound **1b** was prepared in quantitative yield by heating **1a** at reflux with Zn(OAc)₂ in a mixture of chloroform and methanol.^[9b]



Scheme 1. Synthesis of **1a** and **1b**: a) 20% phosgene in toluene, triethylamine (TEA), CH₂Cl₂; b) TEA, α -benzyl- β -methyl-aspartate, CH₂Cl₂; c) Zn(OAc)₂, CHCl₃/CH₃OH.

UV/Vis absorption spectra in chloroform, stabilized by 2% ethanol at 298 K, showed that the Soret bands of **1a** and **1b** underwent a red shift (1–2 nm) as **2–6** were bound in the inner space of the receptors (Supporting Information: Figure S1). The appearance of clear isosbestic points indicates the existence of two states, caused by the formation of a 1:1 complex. The relative binding affinities of **2–6** (**2** > **4** > **3** > **5** > **6**, with *K_a* values ranging from 700–65 000) for the receptors **1a** and **1b** depend upon the number of equatorial hydroxy groups of the guests (Supporting Information: Table S1). A higher affinity to octyl β -D-glucoside, with its all-equatorial hydroxy groups, is caused by the appropriately arranged hydrogen-bonding sites of the receptors for **2**. It turns out that the inner space of the receptors is a pool of hydrogen bonding sites in which urea NH groups, strong hydrogen-bond donors, are positioned equatorially in a convergent manner.

For comparison of the receptors with other systems, we attempted to obtain the association constants in chloroform

[*] Prof. J.-I. Hong, Y.-H. Kim
School of Chemistry, College of Natural Sciences
Seoul National University
Seoul 151-747 (Korea)
Fax: (+82)2-889-1568
E-mail: jihong@plaza.snu.ac.kr

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using fluorescence spectroscopy. On excitation at 420 nm, **1a** emits fluorescence between 620 nm and 690 nm (maximum at 649 nm). Compound **1b** emits between 540 nm and 690 nm (two maxima at 605 nm and 652 nm) on excitation at 430 nm. Addition of **2–6** to **1a** caused blue shifts (3–5 nm) with increasing emission intensity, and addition of **2–6** to **1b** led to a decrease of intensity and a slight blue shift of λ_{max} (≈ 1 nm), unless a large excess of **2–6** was added (Supporting Information: Figure S2). The fluorescence titration data for **1b** at 605 nm as a function of the change in carbohydrate concentration fit well to a 1:1 binding isotherm before addition of many equivalents of **2–6**, and similar results were also obtained for **1a** (Figure 1). The apparent association constants for the formation of the complexes of the receptors and various carbohydrates are listed in Table 1. The selectivity trend is maintained, while the K_a value for **2** is raised to the high value of $2 \times 10^7 \text{ M}^{-1}$.

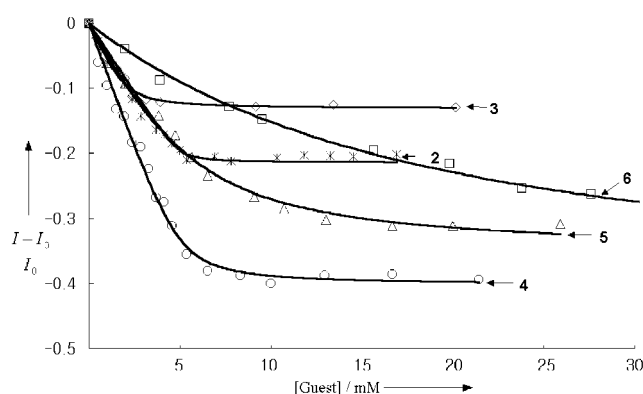


Figure 1. Experimental and calculated values for the fluorescence binding study of **1b**+(**2–6**). The solid line is the calculated curve; [**1b**] = $5 \times 10^{-6} \text{ M}$ for **2** and **4–6**, and [**1b**] = $2.0 \times 10^{-6} \text{ M}$ for **3**.

The interactions between the receptors and **2–6** were investigated by ^1H NMR spectroscopy. In CDCl_3 , the formation of the complexes through multiple hydrogen bonds was shown by the significant downfield shifts of the signals for urea NH protons and the appearance of signals arising from carbohydrate protons in an abnormal upfield region, which may be attributed to the effect of the ring current of the porphyrin plane. In ^1H NMR spectroscopic reverse titrations, it was also found that addition of **1** to **2–4** induced upfield shifts of the signals for carbohydrate CH and OH protons (Supporting Information: Figure S3). However, the ^1H NMR titration spectra in CDCl_3 indicated saturation at about one equivalent carbohydrate and the motion of signals could not

be analyzed by nonlinear least-squares curve fitting, maybe because of the large association constants in CDCl_3 . Addition of **2–6** to **1** in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (v/v, 10:1) showed distinct shifts of the other signals for **1**, despite the disappearance of the signals caused by the urea protons. This information means that complexation of pyranosides with the receptors remained effective in the presence of competing methanol and the association constants could be calculated by 1:1 nonlinear least-squares curve fitting (Table 2). The selectivity trend (**2** > **4** > **3**) was as before, and furanosides **5** and **6** were bound very weakly.

Molecular modeling revealed the plausibility of multiple hydrogen bonds in the complex of **1a** and **2**, in which all the hydroxy groups and the alkoxy oxygen of **2** were involved in the formation of hydrogen bonds as two donors ($\text{C}=\text{O}\cdots\text{HO}$) and five acceptors ($\text{urea-NH}\cdots\text{O}$), as shown in Figure S4 (Supporting Information).^[10] In addition, the porphyrin plane is below two axial CH groups of **2**; this was confirmed by the upfield shifts of the CH-proton resonance signals of **2**. The complex of **1a** and **2** ($\Delta G^\circ = -111.0 \text{ kcal mol}^{-1}$) had a lower calculated conformation energy than that of **1a** and **3** ($\Delta G^\circ = -108.8 \text{ kcal mol}^{-1}$), which shows the same anomer-selective recognition for **2** as in the experimental result.^[10]

Compound **1b** shows essentially distinct biphasic circular dichroism (CD) in the Soret region with negative Cotton effects at a short wavelength and positive Cotton effects at a longer wavelength (Figure 2). This biphasic CD seems to originate from the relative orientation of the aspartate carbonyl groups to the porphyrin^[12] because one chiral aspartate group of **1b** is situated near the porphyrin plane through the formation of intramolecular hydrogen bonds between one aspartate β -carbonyl group and urea NH groups in the alternate position. This explanation was confirmed by the low-energy conformations based on the Monte Carlo conformation search, in which all the conformations found within 5 kcal above the lowest energy conformer show the same pattern of intramolecular hydrogen bonds (Supporting Information: Figure S5).^[10] Interestingly, **1b** demonstrates chirality-specific CD signals on complexation with chiral carbohydrates; while the **1b**-L-glucoside complex gives an S-shaped CD band with decreased amplitude, **1b**-D-pyranoside complexes exhibit reversed S-shaped CD bands. We concluded that the intramolecular hydrogen bonds of the receptor were replaced by stronger intermolecular hydrogen bonds between the receptor and the guest, and therefore the relative orientations of the C–O and O–H moieties of the carbohydrate guest, which are located near the porphyrin plane, induced distinct biphasic CD spectra similar to the

Table 1. Binding constants (K_a [M^{-1}]) and free-energy change (ΔG° [kcal mol^{-1}]) calculated from fluorescence titrations of **1** with octyl pyranosides/furanosides **2–6** in chloroform^[a] at 298 K.

	2		3		4		5		6	
	K_a [b]	$-\Delta G^\circ$	K_a	$-\Delta G^\circ$	K_a	$-\Delta G^\circ$	K_a	$-\Delta G^\circ$	K_a	$-\Delta G^\circ$
1a	$2(\pm 0.05)^{[c]} \times 10^7$	9.87	$4(\pm 0.7) \times 10^6$	9.06	$9(\pm 0.4) \times 10^6$	9.51	$6(\pm 1) \times 10^5$	7.92	$2(\pm 0.3) \times 10^5$	7.25
1b	$2(\pm 0.05) \times 10^7$	10.00	$4(\pm 0.3) \times 10^6$	9.03	$5(\pm 0.8) \times 10^6$	9.17	$5(\pm 0.9) \times 10^5$	7.80	$7(\pm 0.5) \times 10^4$	6.59

[a] Used immediately after raising the pH with anhydrous K_2CO_3 , [**1a**] = $2.5 \times 10^{-6} \text{ M}$ for **2**, **3**, and **4**, $4.0 \times 10^{-6} \text{ M}$ for **5** and **6**, guest concentrations: 0.4–11 μM for **2**, 0.4–30 μM for **3**, and 0.6–11 μM for **4**, 0.6–18 μM for **5**, and 2–100 μM for **6**. [**1b**] = $5 \times 10^{-6} \text{ M}$ for **2**, **4**, **5**, and **6**, $2.0 \times 10^{-6} \text{ M}$ for **3**. Guest concentrations: 0.5–17 μM for **2**, 0.4–20 μM for **3**, and 0.5–21 μM for **4**, 1–26 μM for **5**, and 2–79 μM for **6**. [b] Calculated using custom-written nonlinear least-square curve-fitting programs implemented within Sigmaplot version 4.01. [c] Standard deviations in K_a .

Table 2. Binding constants (K_a [M^{-1}]), limiting change in chemical shift ($\Delta\delta$ [ppm]) of signals for benzylic H atoms and free-energy change (ΔG° [kcal mol $^{-1}$]) from ^1H NMR spectroscopic titrations of **1** with octyl pyranosides/furanosides **2–6** in $CD_3OD/CDCl_3$ (1:10) at 298 K.^[a]

	2			3			4			5			6		
	K_a ^[b]	$\Delta\delta$	$-\Delta G^\circ$	K_a	$\Delta\delta$	$-\Delta G^\circ$	K_a	$\Delta\delta$	$-\Delta G^\circ$	K_a	$\Delta\delta$	$-\Delta G^\circ$	K_a	$\Delta\delta$	$-\Delta G^\circ$
1a	340(9)	0.13	3.45	110(5)	0.14	2.78	140(13)	0.11	2.93	58(5)	0.11	2.40		NB ^[c]	
										> 10000 ^[d]	0.22	> 5.45	6900(1600) ^[d]	0.19	5.23
1b	150(3)	0.05	2.97	59(1)	0.05	2.41	73(3)	0.05	2.54		NB ^[c]			NB ^[c]	
										> 10000 ^[d]	0.24	> 5.45	1150(210) ^[d]	0.20	4.17

[a] **1a** is in the range 2.0–1.5 mM for titration with octyl pyranosides and in the range 0.8 to 0.7 mM for titration with octyl furanosides. The ^1H NMR spectrum of **1a** was independent of concentration within this range. Guest concentrations: 0.99–20 mM for **2**, 1.0–19 mM for **3**, 1.1–23 mM for **4**, 0.4–8 mM for **5**, and 0.4–6 mM for **6**. **1b** is in the range 1.5–1.0 mM for titration with octyl pyranosides and in the range 2.0–1.6 mM for titration with octyl furanosides. The ^1H NMR spectrum of **1b** was independent of concentration within this range. Guest concentrations: 0.79–33 mM for **2**, 2.0–33 mM for **3**, 1.2–33 mM for **4**, 0.8–16 mM for **5**, and 2.0–28 mM for **6**. [b] Standard deviations in K_a . [c] NB = No binding or very weak interaction in $CD_3OD/CDCl_3$. There is a very small chemical shift change during titration in this range and the binding constant is estimated to be $< 10 M^{-1}$. [d] In $CDCl_3$, in the range of **1a** = 1.54–2.0 mM, **1b** = 2.2–2.8 mM for titration with octyl furanosides. ^1H NMR spectra of **1** were independent of concentration within this range. Guest concentrations: 0.4–4.6 mM (for **1a**), 0.4–9.1 mM (for **1b**) of **5**, and 0.4–6.7 mM (for **1a**), 0.4–23 mM (for **1b**) of **6**.

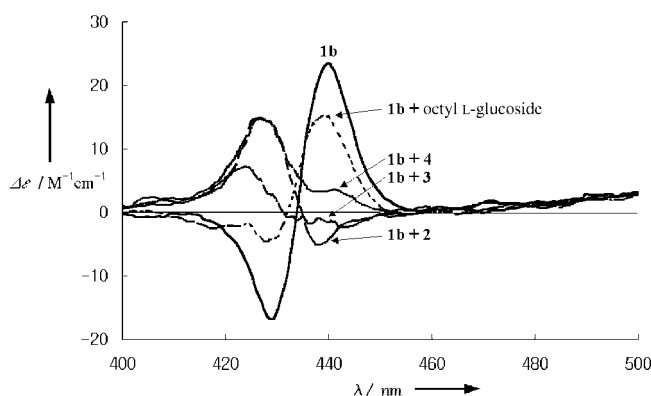


Figure 2. Circular dichroism induced in receptor **1b** by various carbohydrates in $CHCl_3$ at 25 °C. **1b** = $5 \times 10^{-6} M$, **2** = **3** = **4** = [octyl L-glucoside] = $2 \times 10^{-3} M$.^[11]

results reported by Shinkai and co-workers and Mizutani et al.^[13] Therefore, the receptors are not only effective binding agents for monosaccharides but also act as a sensitive CD probe for their chirality determination.

Finally, the extraction of native carbohydrates into non-polar organic media containing the receptor yields further valuable information about the carbohydrate recognition of the receptors. When **1b** was sonicated with an excess of carbohydrates (glucose, galactose, and mannose) in $CHCl_3$, significant quantities of the carbohydrate could be detected by ^1H NMR spectroscopy after re-extraction into D_2O . No carbohydrate was detected in a control run in the absence of **1b**, except for trace galactose. These results show that organic-insoluble carbohydrates can be transported into an organic phase by the receptor. The extractabilities or affinities of hexoses for the receptor decreased in the same order as in the binding of organic-soluble carbohydrates to the receptors: glucose > galactose > mannose.^[6a] The binding of natural carbohydrates to **1b** makes it possible that urea-appended porphyrin receptors with a well-defined hydrophobic cavity may bind them effectively, even under aqueous conditions (Supporting Information: Figure S6).

In summary, urea-appended porphyrins with convergent multiple hydrogen-bonding sites were found to be the most effective binding agent for pyranosides in chloroform among the carbohydrate receptors known to date, and still very

effective even in the presence of hydroxylic cosolvents. The current system is an excellent example of how the combination of a rigid platform (porphyrin skeleton) and acyclic, flexible, yet preorganized polar groups (urea groups), aligned in a rigid plane, enables three-dimensional recognition of carbohydrates through the formation of a hydrophobic cavity and a suitable arrangement of hydrogen bonding sites. Such results look very promising as urea groups in the *aaaa*-positions of the porphyrin can be used to create strong hydrogen-bonding motifs for carbohydrate recognition and further adjusted to act as versatile receptors by introducing polar groups with H-bond donors and acceptors and/or hydrophobic groups.

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Micelles and Hollow Nanospheres Based on ϵ -Caprolactone-Containing Polymers in Aqueous Media**

Xiaoya Liu, Ming Jiang,* Shuli Yang, Mingqing Chen, Daoyong Chen, Cheng Yang, and Kang Wu

Motivated by the great range of potential applications, the development of polymeric nanostructures has witnessed great progress in the last decade.^[1] Among the target materials, polymeric hollow nanospheres are especially interesting and are in great demand because of their ability to encapsulate large quantities of guest molecules, particularly those with functionalities within the inner cavity.^[2] The most studied procedures^[3] for preparing polymeric hollow nanospheres from block copolymer precursors involves many steps: preparing micelles in the selective solvents, cross-linking of the micellar corona, and removing the core by chemical degradation. However, further development has been limited by the preparation of block copolymers containing both cross-linkable and degradable blocks.

We have been attempting to produce polymeric micelles in which only hydrogen bonds, rather than covalent bonds, connect the core and shell.^[2c,4] As a significant advance in a “block-copolymer-free” strategy for preparing micelles, we

[*] Prof. M. Jiang, Prof. X. Liu, Prof. D. Chen
The Key Laboratory of Molecular Engineering of Polymers
Ministry of Education of China, Fudan University
Shanghai 200433 (China)
Fax: (+86) 21-6564-0293
E-mail: mjiang@fudan.edu.cn
Prof. X. Liu, S. Yang, Prof. M. Chen, Prof. C. Yang, K. Wu
School of Chemical & Material Engineering
Southern Yangtze University
Wuxi, Huihe Road 170, 214036 (China)

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report here an entirely new approach to the preparation of micelles and hollow spheres through self-assembly of a homopolymer and a random copolymer, both of which are readily attainable. The principle of the procedure is illustrated in Figure 1. The polymer pair of poly(ϵ -caprolactone) (PCL) and the graftlike copolymer MAF (formed from methacrylic acid (MAA), macro-monomer FA [$\text{CH}_2=\text{CHCOOCH}_2\text{CH}_2(\text{OCOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)_3\text{OH}$] and methyl methacrylate (MMA), see Experimental Section), which has a hydro-

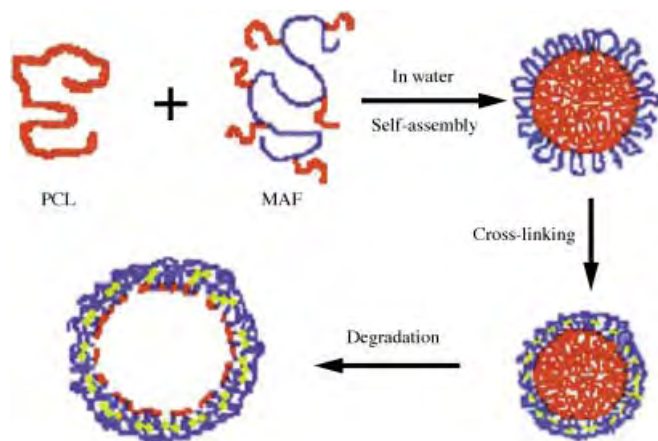


Figure 1. A schematic illustration of the processes of self-assembly, cross-linking, and degradation.

philic backbone and short PCL branches, self-assembles into micelles when a mixture of them in DMF is added to water. The PCL does not precipitate but forms a micellar core that is stabilized by the hydrophilic main chains of MAF, thus forming a shell with the PCL branches anchored to the aggregate. In this new kind of micelle, neither covalent bonds nor hydrogen bonds exist between the core and shell. The affinity between the PCL homopolymer and the short PCL branches is believed to be beneficial to the formation of the micelles. Furthermore, the micelle shell can be cross-linked chemically to form “shell-cross-linked knedel-like nanoparticles” (SCKs),^[5] the core of which can be biodegraded by an enzyme to give hollow nanospheres.

The dependence of micelle size on both the composition of MAF and the ratio of [PCL] to [MAF] was investigated by dynamic laser-light scattering (DLS). In all cases, the particles showed relatively narrow size distributions (size polydispersity ($\mu_2/\langle\Gamma\rangle^2$) was found to be in the range 0.08 to 0.16. The particle size varies considerably, depending on both the MAF and blend compositions, and ranges from 90 to 190 nm (Figure 2). The three series of particles, composed respectively of MAF-1, 2, and 3 (Table 1, see Experimental Section) show a parallel trend that the particle size increases with increasing PCL content for blends in the range of 10 to 50 wt %. This variation is understandable since the PCL aggregates are stabilized by the hydrophilic main chains in MAF. PCL precipitated out when its content exceeded 50 wt %, when the quantity of PCL branches in the MAF is not sufficient to stabilize the PCL aggregates. In addition, the results also show that for any given PCL concentration, the higher the FA content is, the smaller the respective particles

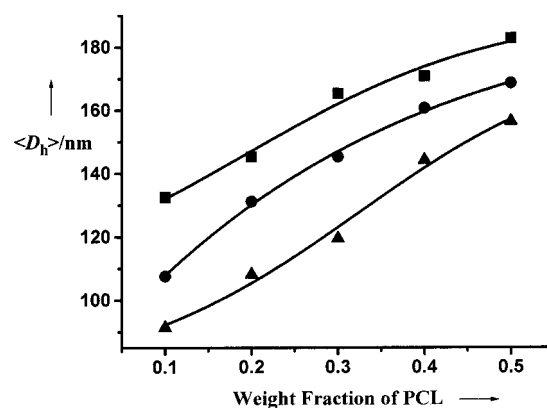


Figure 2. The average hydrodynamic diameter of the micelles of MAF-X/PCL as a function of the weight fraction of PCL. ■: MAF-1, ●: MAF-2, ▲: MAF-3.

Table 1. The molecular weight and its distribution and T_g of MAF.

Sample no.	Monomer molar ratio ^[a] MMA/FA/MAA	$M_n \times 10^{-3}$ ^[b]	M_w/M_n ^[b]	T_g [°C]
MAF-1	9.2/11.8/79.0	5.25	1.78	32.6
MAF-2	6.9/23.8/69.3	3.90	1.60	-27.7
MAF-3	6.1/34.0/59.9	4.16	1.44	-37.1

[a] Measured by ^1H NMR spectroscopy. [b] Estimated by size exclusion chromatography in DMF.

are. This observation is also reasonable as an increase in the FA content implies there is a relative increase in the short PCL branches to the homopolymer, which will certainly favor a finer dispersion of PCL aggregates.

DLS measurements show that after cross-linking, the hydrogel displays less swelling than the un-cross-linked shell. For example, for MAF-2/PCL (1:1, w/w), the average hydrodynamic diameter ($\langle D_h \rangle$) varies from 162 to 128.5 nm as a result of cross-linking.

The enzyme lipolase is a type of lipase that can selectively degrade polyesters and fats, hence it was chosen to hydrolyze the polyester core domain without affecting the cross-linked poly(methacrylicamide) structure of the main chains. Changes in the size and morphology of the SCKs upon hydrolysis of the core were studied by using a combination of DLS and transmission electron microscopy (TEM).

DLS was used to trace the process of core degradation as well as the formation of the hollow spheres. For the micelles of MAF-3/PCL (1:1, w/w), the relative intensity and average hydrodynamic diameter of the micelles of MAF-3/PCL (1:1, w/w, Figure 3) apparently follow opposite trends with reaction time, that is, the intensity gradually decreases with increasing size. This trend actually reflects that the size increase was accompanied by a decrease in the mass as the degradation proceeded. During the initial stage of the reaction (0–100 min) the intensity dramatically decreased, which indicates that an immediate and quick degradation occurs, while no distinct change in the particle size was detected. A significant increase in $\langle D_h \rangle$ from about 110 to 300 nm was observed in the period 400–1200 min, and accompanied by a slow decrease in intensity. In the final stage, neither the intensity nor $\langle D_h \rangle$ changed, which indicated that degradation of the core was

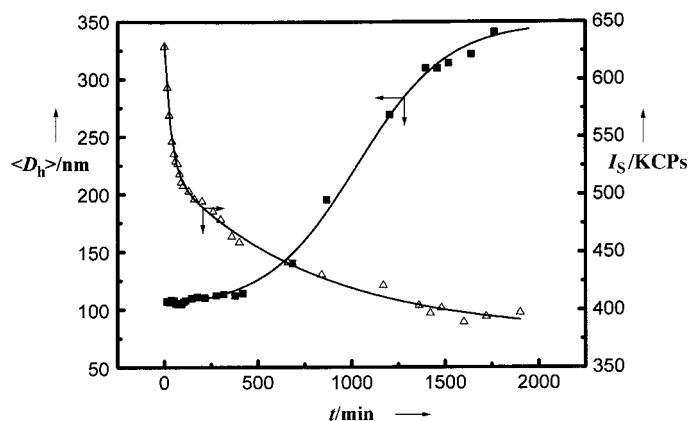


Figure 3. Average hydrodynamic diameter ($\langle D_h \rangle$) and scattering light intensity (I_s , kilo-counts per second) of the micelles MAF-3/PCL (1:1, w/w) at 25 °C as a function of degradation time.

complete. The most remarkable phenomenon, as suggested by DLS data, is the significant increase in micellar diameter from 100 to 350 nm when the mass of the particles was reduced by half. Similar behavior has been previously reported for the micelles of block copolymers on removing species contained within the micellar interior.^[3b,4f] This expansion is caused by releasing the restriction imposed by the insoluble blocks on the solvated blocks in the shell. The same phenomenon occurs here, and is indicative of the restriction on the MAF chains caused by the insoluble PCL chains in the core, even though there are no chemical bonds between them. The cross-linked shell, which contains poly(methylacrylamide) segments, can be regarded as a hydrogel that swells more extensively when the core domain fills with water after the removal of the PCL.

The TEM studies gave direct evidence of the morphologies of the micelles and hollow spheres. A typical photograph of the micelles of MAF-2/PCL (1:1, w/w) is shown in Figure 4A in which the micelles clearly display a spherical shape. Figure 4B presents the morphological details of a single micelle at a higher magnification. The micelles have a three-layer structure, with the PCL core being the major constituent of the particle. The gray outer shell is believed to be composed of the hydrophilic main chains of MAF. Interestingly, the inner shell shows much lower chain density, which can be attributed mainly to the short PCL branches. These morphological results illustrate the role of the PCL branches: they act as a “glue” between the outer shell and core by means of the affinity between the PCL homopolymer chains and branches, which are chemically identical. Although the combined thickness of the inner and outer shell is only about 10 nm while the radius of the core is as large as 45 nm, the calculated volume fraction of the shell at 47.7% is comparable to that of the core, which seems reasonable as the weight ratio of MAF to PCL is about 1:1.

The morphologies of the particles after core degradation are shown in Figure 4C and D, with all of the particles clearly displaying a hollow structure. In comparison with the particles shown in Figure 4A and B, the particles have expanded significantly to about 300 nm in diameter and a shell thickness of up to 100 nm, which is indicative of the swelling of the nanocages after removing the PCL core.

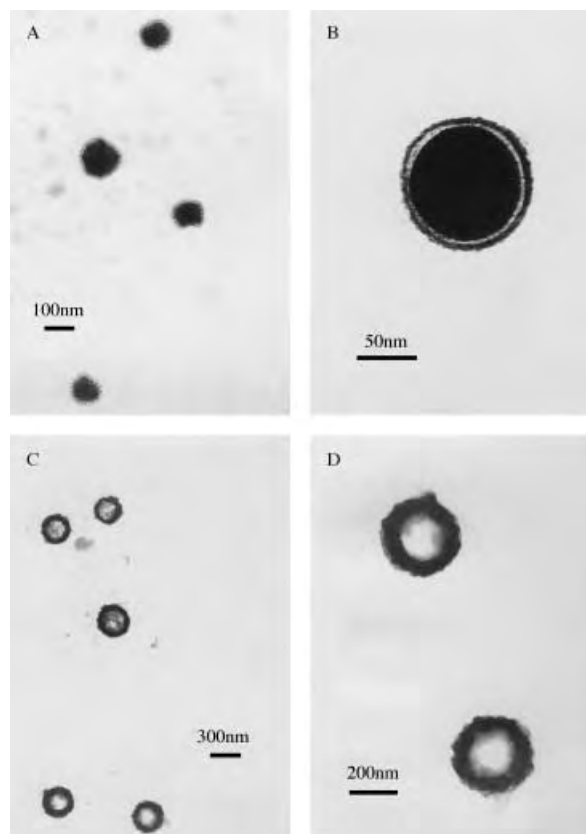


Figure 4. TEM images of MAF-2/PCL (1:1, w/w) nanoparticles before (A and B) and after (C and D) biodegradation.

In conclusion, we have succeeded in obtaining micelles and hollow nanospheres by a “block-copolymer-free strategy”. The combination of PCL and MAF led to the formation of micelles possessing a hydrophobic PCL core surrounded by a hydrophilic MAF shell. The central layer, composed of PCL branches in MAF, glues the outer shell to the core. Cross-linking of the micelles gives rise to stable shell-cross-linked nanoparticles. As this route is based on common and nonexpensive polymer products and the processing is simple, it may have great potential for further applications in fabricating supramolecular materials for various fields such as medicine, catalysis, and photoelectronics.

Experimental Section

A series of the graftlike copolymer MAF was synthesized by free-radical copolymerization of methylacrylic acid (MAA), macro-monomer FA ($\text{CH}_2=\text{CHCOOCH}_2\text{CH}_2(\text{OCOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)_3\text{OH}$, Daicel Chem. Co. Ltd.), and a small amount of methyl methacrylate (MMA) in DMF at 70 °C using 2,2'-azo-bisbutyronitrile as initiator. The products were purified by dissolution-precipitation in DMF/water three times. The copolymers are characterized by a hydrophilic main chain and hydrophobic short PCL branches. Table 1 lists the characterization data of the MAF copolymer prepared with different feed compositions. The copolymer compositions were calculated based on ^1H NMR measurements. The signals at $\delta=0.93\text{--}1.03$ for $-\text{CH}_3$ in MAA, $\delta=1.54$ for $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ in FA, and $\delta=3.52$ ppm for $-\text{OCH}_3$ in MMA were used for the calculation. The data show that varying the composition did not significantly affect the molecular weight or the distribution of the copolymers produced under similar reaction conditions. All of the copolymers have a single glass-transition temperature (T_g), which decreases as the quantity of macromer FA increases. This observation indicates

that there are no highly blocked sequences along the copolymer chains. The micellar nanospheres were prepared by dropwise addition of the various blend solutions of MAF/PCL in DMF into water, with moderate stirring. The appearance of a bluish hue signals the formation of micelles. The mixture was stirred for approximately 24 h at room temperature, and then DMF was removed by dialysis with pure water, which resulted in stable homopolymer/copolymer micelles in water. The micellar structure was locked by cross-linking the hydrophilic shell layer through condensation reactions between the carboxylic acid groups of poly(methylacrylic acid) (PMAA) and the amino groups of hexamethylenediamine in the presence of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide methiodide, which activates the carboxylic acid at room temperature.^[3a] The cross-linked product was then dialyzed with distilled water for 3 days to remove the by-products of the reaction. The success of the cross-linking was confirmed by the fact that the resultant nanoparticles maintained their integrity upon switching the medium from water to a solvent mixture containing a large proportion of DMF. DLS (Malven Autosizer-4700) studies on the cross-linked particles found that no particle aggregation had taken place, which meant that there had been almost, zero interparticle cross-linking. For conducting biodegradation of the core, an appropriate amount of dust-free lipolase solution in water (Novozymes Co.) and dilute aqueous NaOH solution was added into the SCK nanoparticulate dispersion.^[6] Typical reaction conditions: MAF-3/PCL (1:1, w/w), 50% cross-linked, $C = 2.9 \times 10^{-4} \text{ g mL}^{-1}$, pH 8–11 at 25°C. TEM imaging was performed on a Philips CM 120 electron microscope at an accelerating voltage of 80 kV. The specimens were prepared on copper grids coated with a thin carbon film.

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An Efficient and Highly Enantio- and Diastereoselective Cyclopropanation of Olefins Catalyzed by Schiff-Base Ruthenium(II) Complexes**

Jason A. Miller, Wiechang Jin, and SonBinh T. Nguyen*

Dedicated to Professor Robert H. Grubbs on the occasion of his 60th Birthday

Compounds containing the cyclopropane fragment have received considerable attention because of their frequent occurrence in natural products and their importance as valuable synthetic intermediates.^[1–3] Since the introduction of chiral cyclopropanation catalysts by Nozaki et al.,^[4] Aratani et al.,^[5] and Nakamura et al.,^[6] transition-metal-catalyzed asymmetric cyclopropanation has emerged as one of the most efficient synthetic routes to the optically pure cyclopropane fragment.^[2,7] Perhaps the most difficult aspect of these asymmetric cyclopropanations is the simultaneous control of yield and regio-, diastereo-, and enantioselectivity while maintaining functional group tolerance.^[8,9] In cyclopropanation studies of chiral copper^[10–15] and rhodium^[16–18] complexes it was found that high enantioselectivities and high diastereoselectivities usually do not go hand-in-hand unless reactions were carried out in an intramolecular manner. Further, in the case of intermolecular cyclopropanation, best enantio- and diastereoselectivities are often only achieved with large diazo esters.

Since the early 1980s, a number of ruthenium complexes have been shown to catalyze olefin cyclopropanation.^[1] In view of the advantages that ruthenium-based catalysts have over copper- and rhodium-based catalysts in functional-group tolerance and cost, respectively, the last decade has witnessed an increase in the number of reports on ruthenium-based cyclopropanation catalysts, many of which are porphyrin-based.^[19–21] Because of the well-known challenges associated with porphyrin synthesis, especially when chiral porphyrins are involved, non-porphyrin multidentate ligands have attracted a lot of attention from investigators over the last few years. In 1994, Nishiyama and co-workers employed a chiral Ru-pybox catalyst (pybox = bis(oxazolinyl)pyridine) for the cyclopropanation of styrene with *tert*-butyl diazoacetate (*t*BDA) and menthyl diazoacetate (MDA) which resulted in high enantio- and *trans*-selectivity.^[22–25] However, when the smaller—and more common—diazo ester ethyl diazoacetate (EDA) is employed in this reaction, selectivities are much lower (see Table 1, entry 9). Recently, Katsuki and co-workers

[*] Prof. Dr. S. Nguyen, J. Miller, Dr. W. Jin
Department of Chemistry
Northwestern University
2145 Sheridan Road, Evanston, IL 60208-3113 (USA)
Fax: (+1) 847-467-5123
E-mail: stn@chem.northwestern.edu

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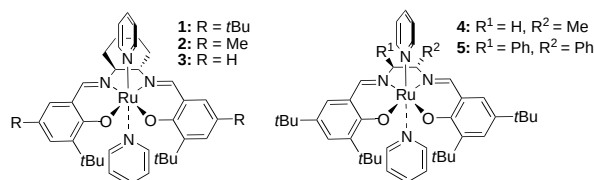
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Table 1. Asymmetric cyclopropanation of styrene with EDA catalyzed by complexes **1–5**^[a] in comparison to other catalysts. Bold-faced data indicate the best values.

Entry	[Ru] cat./ref.	Diazo ester	<i>t</i> [h]	<i>trans</i> : <i>cis</i>	Yield [%] ^[b]	<i>trans</i> (% <i>ee</i> ^[c])	<i>cis</i> (% <i>ee</i> ^[c])
1	(<i>S,S</i>)- 1	EDA	3	10.8:1	95	98 (1 <i>S</i> ,2 <i>S</i>)	96 (1 <i>S</i> ,2 <i>R</i>)
2	(<i>R,R</i>)- 1	EDA	3	10.8:1	95	99 (1 <i>R</i> ,2 <i>R</i>)	96 (1 <i>R</i> ,2 <i>S</i>)
3	(<i>S,S</i>)- 2	EDA	3	10.6:1	96	99 (1 <i>S</i> ,2 <i>S</i>)	95 (1 <i>S</i> ,2 <i>R</i>)
4	(<i>R,R</i>)- 2	EDA	3	10.6:1	94	99 (1 <i>R</i> ,2 <i>R</i>)	96 (1 <i>R</i> ,2 <i>S</i>)
5	(<i>S,S</i>)- 3	EDA	3	10.7:1	90	98 (1 <i>S</i> ,2 <i>S</i>)	95 (1 <i>S</i> ,2 <i>R</i>)
6	(<i>R,R</i>)- 3	EDA	3	10.7:1	95	99 (1 <i>R</i> ,2 <i>R</i>)	95 (1 <i>R</i> ,2 <i>S</i>)
7	(<i>R</i>)- 4	EDA	3	7.2:1	93	12 (1 <i>R</i> ,2 <i>R</i>)	25 (1 <i>R</i> ,2 <i>S</i>)
8	(<i>R,R</i>)- 5	EDA	3	3.4:1	95	> 99 (1<i>R</i>,2<i>R</i>)	> 99 (1<i>R</i>,2<i>S</i>)
9	Nishiyama ^[22]	EDA ^[d]	12–20	11.5:1	69	88 (1 <i>R</i> ,2 <i>R</i>)	78 (1 <i>R</i> ,2 <i>S</i>)
10	Katsuki ^[39]	<i>t</i> BDA	24, irradiation	1:13.3	45 ^[e]	N/A	97 (1 <i>S</i> ,2 <i>R</i>)
11	Zheng ^[34]	EDA	14	1:1.9	15 ^[f]	13 (1 <i>R</i> ,2 <i>R</i>)	0

[a] Reaction conditions: EDA (0.5 mmol), styrene (2.5 mmol), catalyst (0.005 mmol), CH₂Cl₂, 3 h. [b] GC yield with undecane as an internal standard. [c] Determined by using Supelco β-DEX series chiral GC columns (see Supporting Information for method). Absolute configuration determined from known standards. [d] Slow addition of diazo ester over 4 h is required. [e] ¹H NMR yield. [f] GC yield with diethyl adipate as internal standard.

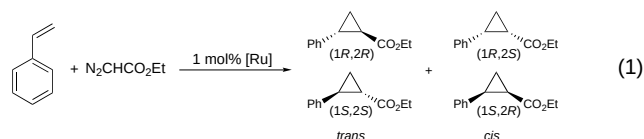
reported the use of a Ru(BINOL)-derived salcen) complex as a catalyst in the photo-induced cyclopropanation of styrene with *t*BDA (salcen = *trans*-1,2-cyclohexanedi-amino-*N,N'*-bis(salicylidene)).^[26] In spite of the high enantio- and *cis*-selectivity reported, the reaction yields for Katsuki's catalyst were generally low (Table 1, entry 10). Further, owing to photolytic conditions reaction times for Katsuki's catalysts are generally long and optimal selectivity is only reported for the more bulky *t*BDA. Recently, Munslow and co-workers reported the use of nonplanar *α-cis* ruthenium biaryldiimine complexes to cyclopropanate olefins with EDA.^[27] They reported good yields and diastereoselectivities and moderate to good enantioselectivities, however, the substrate scope was limited to styrene derivatives and tethered substrates and the ligand synthesis is quite complicated. More recently, Tang and co-workers have also reported a [Ru(pyridyldiimine)Cl₂] catalyst for the cyclopropanation of styrene with EDA.^[28] Herein, we report the high-yield syntheses of the chiral Ru-salen complexes **1–5** containing *trans*-oriented pyridine ligands (H₂salen = *N,N'*-bis(salicylidene)ethylenediamine).^[29,30] These compounds are very efficient catalysts for the asymmetric cyclopropanation of both electron-rich and electron-deficient olefins with EDA to give predominantly *trans* products with exceptionally high enantioselectivity. EDA was chosen as the test case because it is the most readily available diazoester and, because of its small size, one of the most difficult carbene precursors to employ in an enantioselective cyclopropanation reaction.



Complexes **1–5** were prepared from the reaction of the in situ prepared dilithium salt of the ligand, Li₂(salen), with [{RuCl₂(*p*-cymene)}₂], followed by the addition of excess pyridine at room temperature. Recrystallization of the dark-red crude products from toluene/hexanes mixtures afforded

the analytically pure chiral ruthenium complexes in 48–86 % yield. ¹H and ¹³C NMR (and X-ray diffraction^[31]) studies revealed that these complexes contain two molecules of pyridine axially bound to the metal center in a *trans* coordination mode. Treatment of these pyridine complexes with excess PPh₃ resulted in no reaction which implies that pyridine binds tighter to the Ru center than PPh₃.

Complexes **1–5** were employed in catalytic amounts (1 mol %) for the cyclopropanation of styrene with EDA at ambient conditions [Eq. (1)]. Diastereo- and enantioselectiv-



ity results for these reactions are listed in Table 1 (entries 1–8). The presence of dimeric side products, such as diethyl fumarate and maleate, was negligible (< 1 %) for each reaction. For the cyclohexane-based system, the *trans*/*cis* ratio was found to be at least 10.6:1 in all cases, in stark contrast to that observed for Katsuki's Ru(BINOL)-derived salcen) catalyst^[26] where high *cis* selectivity is the norm. Katsuki's work (as well as current studies in our group) shows that substitution at the 3,3'-positions of the salen ligand plays a large role in the diastereoselectivity of ruthenium(II)-salen catalysts, in contrast to that observed for the isoelectronic cobalt(III)-salen system.^[32] The *trans*/*cis* selectivity for our salen-type catalysts decreases when other backbones are used which shows that the 3,3'-substituents are not the only factors governing diastereoselectivity. Exceptionally high enantiomeric excesses of cyclopropane products were found for both *trans* and *cis* isomers (Table 1). These remarkable *ee* values can be attributed to backbone substituents and the intrinsic properties of the highly effective salen ligand structure, which has also proven to be useful in other examples of asymmetric catalysis.^[33] Interestingly, changing the substituent groups at the 5,5'-positions from H to Me to *t*Bu has little effect on the resulting product selectivity. Isolation of analytically pure catalyst is critical in our catalyst system. Zheng and co-workers have presumably generated the PPh₃ analogue of **1** in

situ but their cyclopropanation selectivities for styrene are quite low (Table 1, entry 11).^[34]

The high *trans* selectivities of our ruthenium(II)–salen catalyst for the cyclopropanation of styrene can be rationalized by a ZINDO-minimized model structure calculation, which suggests that the olefin approach to the metal carbene intermediate (above the plane, as depicted in Figure 1) leads to a *trans* geometry between the olefin's substituent with

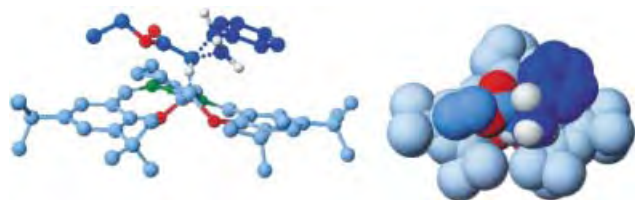


Figure 1. A ZINDO-optimized model structure of styrene as it approaches the putative (salen)Ru-EDA carbene intermediate. Left: a ball-and-stick model of this structure without a *trans* axial ligand. Right: a top-view space-filling model showing an optimal fit. A model structure with an additional *trans*-py axial ligand is given in the Supporting Information.

respect to the carbene group. This calculation supports our observations that substituents in the 5,5'-positions of the salen ligand do not significantly affect either diastereo- or enantioselectivity owing to their remote locations: the 5,5'-substituents are simply too far away from the metal carbene to influence its orientation. the 3,3'-substituents, however, are close enough to keep the singlet carbene locked in position while the olefin approaches.

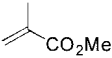
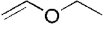
The substrate scope of our catalyst system is quite remarkable and covers a whole range of conjugated, electron-rich, electron-poor, and aliphatic olefins with good enantioselectivity (Table 2). Methyl methacrylate (MMA) proves to be the most active substrate for our system: absolutely no carbene dimer was produced when only a 5:1 olefin:EDA ratio was used. However, all other substrates

needed to be run at higher olefin concentrations to minimize carbene dimer formation. MMA is the substrate that gives the best diastereoselectivity (*trans/cis* = 100) and also shows opposite enantioselectivity from that for other olefins. These selectivities for MMA are the best observed to date.

Work carried out in the Doyle^[35,36] and Nakamura^[6,37] laboratories has shown that α,β -unsaturated carbonyl compounds and nitriles can yield racemic cyclopropanes through the decomposition of pyrazoline intermediates, which result from the noncatalyzed 1,3-dipolar cycloaddition of olefins with diazoesters. Although pyrazoline formation was a competing reaction in our ruthenium-catalyzed acrylonitrile cyclopropanation (Table 2), the enantiomeric excesses of the cyclopropane products are quite high which suggests that noncatalyzed cyclopropane formation from pyrazoline decomposition is only a minor pathway. In the case of MMA cyclopropanation catalyzed by our ruthenium–salen complexes, no evidence of the pyrazoline or olefin side-product formation normally associated with the 1,3-cycloaddition reaction^[1] was observed and stereoselectivities are excellent. Thus, the 1,3-dipolar cycloaddition pathway is unlikely under our reaction conditions (dichloromethane, room temperature). Indeed, control reactions (0.5 mmol EDA, 2.5 mmol olefin, no catalyst, 5 mL CH₂Cl₂, 3 h, room temperature) show no evidence of pyrazoline formation when MMA was used. We have also taken steps to eliminate the possibility that pyrazoline adducts can be selectively decomposed to chiral cyclopropanes by our catalyst. Methyl methacrylate and acrylonitrile–2-pyrazoline adducts were separately synthesized^[36] and then subjected to our catalyst under our typical cyclopropanation conditions. No tautomerization to 1-pyrazolines, pyrazoline decomposition, cyclopropane formation, or olefin side-product formation occurred. This leads us to believe that 1,3-dipolar cycloaddition is not a significant mechanistic pathway for our Ru^{II}–salen-type catalysts.

It is interesting to note that cyclopropanation of *trans*-piperylene with the nonsymmetrical catalyst (*R*)-**4** results in a

Table 2. Asymmetric cyclopropanation of other electron-rich and electron-deficient olefins with EDA catalyzed by complexes **1**, **4**, and **5**.^[a] Bold-faced data indicate the best values.

Olefin	[Ru] cat.	<i>trans</i> : <i>cis</i>	Yield [%] ^[b]	<i>trans</i> (% <i>ee</i>) ^[c]	<i>cis</i> (% <i>ee</i>) ^[c]
	(<i>R,R</i>)- 1	100:1	26	2 (1 <i>S</i> ,2 <i>S</i>)	Not observable
	(<i>R</i>)- 4	100:1	95	95 (1<i>S</i>,2<i>S</i>)	Not observable
	(<i>R,R</i>)- 5	100:1	53	91 (1 <i>S</i> ,2 <i>S</i>)	Not observable
	(<i>R,R</i>)- 1	1.8:1	57 ^[d]	72 (1 <i>R</i> ,2 <i>R</i>)	65 (1 <i>R</i> ,2 <i>S</i>)
	(<i>R</i>)- 4	1.6:1	93	39 (1 <i>S</i> ,2 <i>S</i>)	44 (1 <i>S</i> ,2 <i>R</i>)
	(<i>R,R</i>)- 5	1.9:1	97	89 (1<i>R</i>,2<i>R</i>)	90 (1<i>R</i>,2<i>S</i>)
	(<i>R,R</i>)- 1	2.6:1	26 ^[e]	40 (1 <i>R</i> ,2 <i>R</i>)	39 (1 <i>R</i> ,2 <i>S</i>)
	(<i>R</i>)- 4	2.1:1	74	15 (1 <i>R</i> ,2 <i>R</i>)	38 (1 <i>R</i> ,2 <i>S</i>)
	(<i>R,R</i>)- 5	1.2:1	28	58 (1<i>R</i>,2<i>R</i>)	62 (1<i>R</i>,2<i>S</i>)
	(<i>R,R</i>)- 1	4.1:1	80	69 (1<i>R</i>,2<i>R</i>)	78 (1<i>R</i>,2<i>S</i>)
	(<i>R</i>)- 4	4.4:1	84	24 (1 <i>R</i> ,2 <i>R</i>)	30 (1 <i>R</i> ,2 <i>S</i>)
	(<i>R,R</i>)- 5	3.8:1	91	68 (1 <i>R</i> ,2 <i>R</i>)	67 (1 <i>R</i> ,2 <i>S</i>)
	(<i>R,R</i>)- 1	3.1:1	30	90 (1<i>R</i>,2<i>R</i>)	18 (1 <i>R</i> ,2 <i>S</i>)
	(<i>R</i>)- 4	2.9:1	36	49 (1 <i>R</i> ,2 <i>R</i>)	26 (1 <i>R</i> ,2 <i>S</i>)
	(<i>R,R</i>)- 5	4.3:1	20	74 (1 <i>R</i> ,2 <i>R</i>)	56 (1<i>R</i>,2<i>S</i>)

[a] Reaction conditions: 0.5 mmol EDA, neat olefin (used to minimize EDA dimer formation) with the exception of MMA (2.5 mmol olefin, 0.005 mmol catalyst, CH₂Cl₂, 12 h). Reactions are over within 2–3 h. [b] GC yield using undecane as an internal standard, with the exception of ethyl vinyl ether and 1-pentene where benzyl ether was used. [c] Determined by using Supelco β -DEX series chiral GC columns (see Supporting Information for method). Tentative absolute configurations determined by chiral GC elution orders.^[40] [d] Only the terminal olefin of piperylene was cyclopropanated. [e] Pyrazoline formation was a competing reaction when acrylonitrile was cyclopropanated.^[35]

reversal of enantioselectivity in comparison to the use of (*R,R*)-**3** and (*R,R*)-**5**. This phenomenon has not been observed with any other olefin, including a variety of other conjugated olefins and olefins of similar size.^[38] The reasons for this reversal of enantioselectivity are currently being investigated.

Although the cyclopropanation of the unactivated olefin 1-pentene with our catalysts affords quantitative EDA conversion, carbene dimerization is a significant competitor to cyclopropane production. Neither slow addition of the reactants (both olefin and EDA solutions) nor changing reaction conditions (temperature, solvent, and olefin concentrations) helped to reduce dimer formation. Nevertheless, the catalyst solution remains active for long periods in the presence of excess 1-pentene: successive addition of one equivalent EDA per day over four days continues to generate 2-propyl cyclopropanecarboxylic acid ethyl ester at the same rate and diastereoselectivity each time.

In summary, our ruthenium-based salen complexes constitute an important addition to the rank of modern asymmetric cyclopropanation catalysts, as a result of their ease of synthesis, high activity/selectivity, and broad applicability to a wide range of electronically diverse terminal olefins.

Experimental Section

General procedures for the syntheses and characterizations of catalysts **1–5** and details of the calculation are available in the Supporting Information. Also included are all chiral GC methods and information regarding the characterization of cyclopropanes.

Preparation of complexes **1–5** (general procedure): Under an inert atmosphere, a THF solution (15 mL) of the salen ligand (1.5 mmol) was treated with lithium diisopropylamide (LDA; 2 mL of a 1.5 M solution of the monotetrahydrofuran complex in cyclohexane, 3.0 mmol) at 0°C. After the addition was completed, the solution was allowed to warm up to room temperature and stirred for 1 h. This mixture was then added dropwise to a solution of [$[\text{RuCl}_2(p\text{-cymene})_2]$] (460 mg, 0.75 mmol) and pyridine (1 mL) in THF (15 mL) at 0°C. The reaction mixture was allowed to stir overnight. A dark-red solution was obtained, which was subsequently evaporated in vacuo. The residue was extracted into toluene (30 mL), filtered through a cannula, and evaporated under reduced pressure. Hexanes (20 mL) was then added to the residue to precipitate a dark red solid, which was filtered through a cannula and dried under vacuum. Further recrystallization with a toluene/hexanes mixture affords analytically pure compounds.

General procedure for the asymmetric cyclopropanation of styrene with EDA: A mixture of a chiral ruthenium–salen catalyst (0.005 mmol) and the olefin (2.5 mmol) in CH_2Cl_2 (1 mL) was placed in a 25-mL round-bottomed flask under N_2 in a glovebox. A CH_2Cl_2 solution (degassed three times) of EDA (0.50 mmol in 2.5 mL total volume) and internal standard (0.50 mmol) was slowly added through a gas-tight syringe over a period of 23 min under N_2 . After the addition was complete the reaction mixture was allowed to stir for 12 h at room temperature. The solution was then passed through a short plug of silica gel to remove catalyst and washed with CH_2Cl_2 (15 mL). Samples were then analyzed by GC.

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Supramolecular Organization of Oligopeptides, through Complexation with Surfactants**

Sascha General and Markus Antonietti*

Oligopeptides are not only omnipresent in living systems but, because of their well-defined molecular structure, stereochemistry, and chemical functionality, are also ideal building blocks for a molecular tectonics or supramolecular chemistry^[1] towards chemical nanostructures with a function. Organization of such building blocks can be caused by shape and complementary functional patterns,^[2] but can also be induced by addition of a species that mediates additional weak and directed interactions, such as a transition-metal ion.^[3] However, this chemistry is still restricted to aqueous or highly polar environments, and more extended structures and materials are only produced in this way in nature.

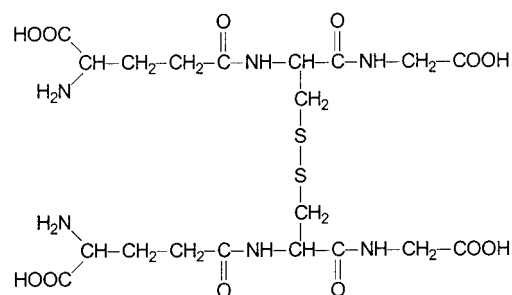
The approach presented here is complementary to such approaches: multiply charged, water-soluble oligopeptides are hydrophobized by complexation with appropriate organic counterions (in the present case simple oppositely charged surfactants and lipids) and the resulting hybrid structures act as building blocks for further, spontaneous supramolecular assembly. The complexation with organic counterions is expected to be very simple, because it is known that other organic compounds such as dye molecules^[4] and polyelectrolytes^[5] complex in a strict 1:1 stoichiometry, and the resulting product usually precipitates from water and can be isolated. Because of the amphipolar character introduced by the surfactant, the polar peptide backbone with its hydrogen-bonding system and hydrophobic tails are expected to separate into different nanophase regions. The minimization of binding and interface energy consequently results in structural complexity and a high degree of supramolecular order.

This mode of self-organization is also known from less defined polyelectrolytes, analogues with larger molecular weight and structural distributions, which form highly organized polyelectrolyte–surfactant^[6–8] and polyelectrolyte–lipid complexes,^[9] or from the hydrogen-bond-mediated supramolecular complexes between polar polymers and alkylphenols.^[10,11] Synthetic polypeptides made of a single amino acid such as poly-L-lysine, poly-L-histidine, and poly-L-glutamic acid have also been complexed with surfactants,^[12,13] mostly under preservation and sometimes stabilization of their typical α -helical structure.

Contrary to the simpler polymer–surfactant complexes, we expect the realization of new, unconventional assembly structures for the more variable and molecularly uniform oligopeptides, while their lower molecular weight should

support a more rapid equilibration and higher perfection of the resulting structures.

Herein we focus on surfactant and lipid complexation of a simple model peptide, oxidized glutathion or GSSG. GSSG is an H-shaped hexapeptide composed of two γ -GluCysGly trimers which are linked by a sulfur bridge. GSSG contains



four carboxy units and two amine groups available for complexation (depending on the pH value), is cheap and easily available in larger amounts. Glutathion has a number of cellular functions: it is important as a redox buffer, maintains the sulfhydryl status of proteins, is important for a whole range of detoxification reactions, and binds easily to xenobiotic compounds.^[14]

The synthesis of the complexes is rather simple, because all samples precipitate from aqueous solution. After washing, the residual amount of sodium and halogenide ions is very low (<0.02 weight %), which indicates a close-to-perfect complexation with 1:1 stoichiometry with respect to the charges. The complexes can be redissolved in organic solvents such as THF, unlike peptides. In dilute solution, rather large aggregates are formed, as already indicated by dynamic light scattering. Drying those solutions and characterizing the dried aggregates with AFM and TEM reveals an exciting superstructure (Figures 1 and 2).

Both complexes of GSSG with lipids and surfactants form fibers with lengths of at least a few microns. A TEM of a GSSG–Lec complex (Lec = lecithin), which develops well (because of the absence of side-chain crystallinity in this complex), is shown in Figure 1. The fibers are flexible, bundled in the middle and frayed towards the ends. Each fiber is 35–45 nm wide, displaying a height of 15 nm (see AFM, Figure 2). A close-up of the aggregates shows them to be formed by left-handed spirals. The pitch of these supercoils is 40 nm with a tilt angle of 30°; the width of the coiled ribbon is about 15 nm. The diameter and height of the fibers is by far too large to be caused by a simple aggregation structure of single GSSG–surfactant units. We assume that about ten of the complexes laterally aggregate to form a nanosized ribbon which (as a wood shaving) winds up to give a left-handed spiral (Figure 3).

It is underlined that this “spirelli”-motive is a well-known superstructure for chiral surfactants and organogelators, such as those formed by modified steroids,^[15] octylglucosides,^[16] and dodecanoylserines,^[17] which is however extended by the present systems to much larger tectonic units with higher stability. Similar superhelices made of non-natural peptide analogues were recently described by Nolte et al.,^[18,19] who

[*] Prof. Dr. M. Antonietti, Dr. S. General
Max Planck Institute of Colloids and Interfaces
14424 Potsdam-Golm (Germany)
Fax: (+49)331-567-9502
E-mail: pape@mpikg-golm.mpg.de

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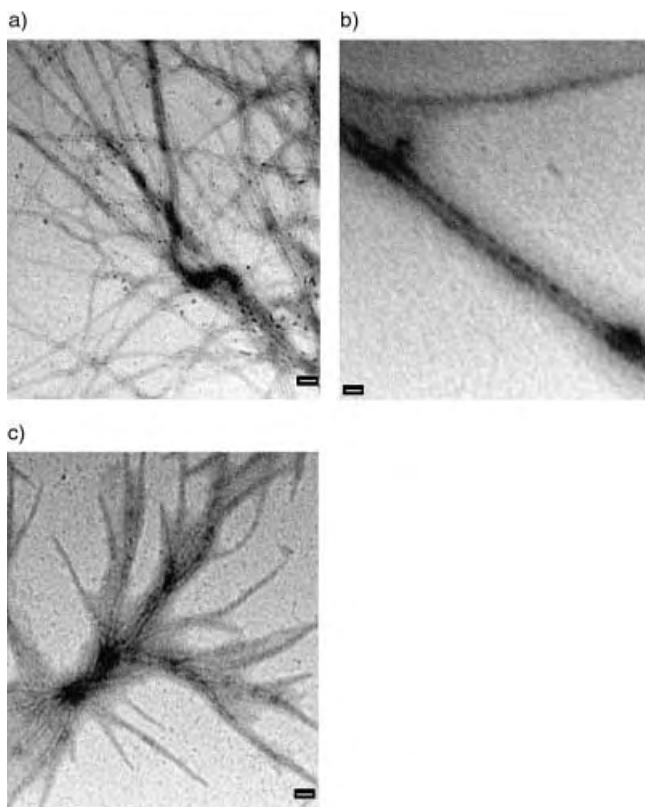


Figure 1. TEM pictures of the GSSG-lecithin aggregates in THF. Long, homogeneous, hollow tubules are formed. Scale bars: 100 (a), 40 (b), and 100 nm (c).

synthesized isocyanopeptides which also arrange via a modified β -sheet structure towards larger superhelices. The route presented here is however more simple, because we create our

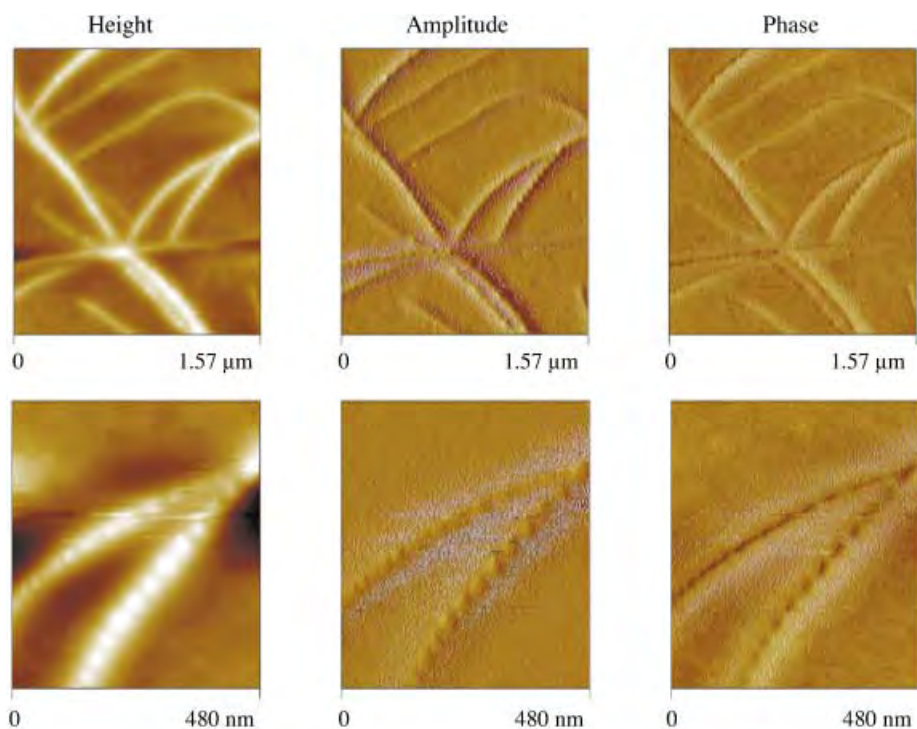


Figure 2. Tapping-AFM pictures of the GSSG-lecithin complex, different views of two selected areas; the aggregates are left-handed spirals.

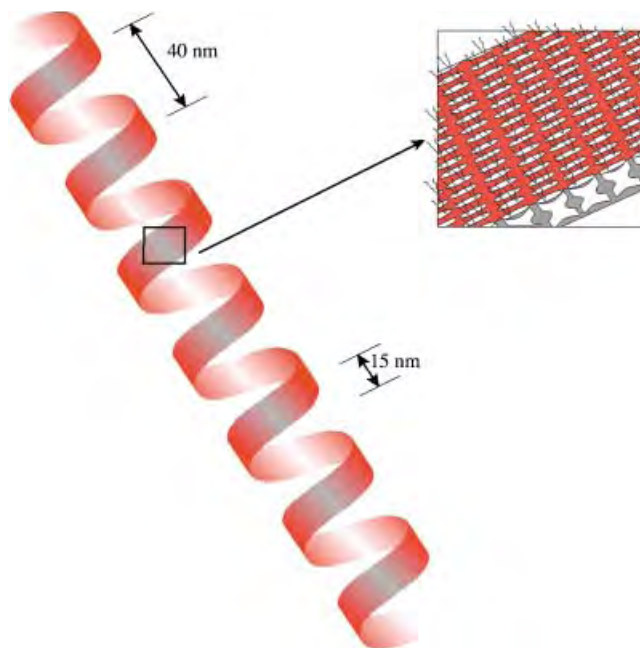


Figure 3. Schematic representation of the aggregates.

tectonic units by a primary assembly step (the “ionic self-assembly”) from two simple starting products, and the method can be easily generalized towards other peptide and surfactant units.

Evaporation of the solvent leads to transparent films which are hard but flexible and show high optical birefringence, that is, the complexes possess reasonable material properties and are much harder than bare surfactant structures or films of the corresponding peptides. The nanostructure of the GSSG-lecithin complex (two lipids per oligopeptide unit) was characterized by small-angle X-ray scattering (SAXS) measurements (Figure 4).

Measurements are taken above and below a broad enthalpic phase transition found by differential scanning calorimetry (DSC) at about 60°C, which is identified as a liquid-crystalline phase transition, since birefringence is preserved above this temperature. The formed complexes obviously exhibit high mesomorphic order on the nanometer scale. Both SAXS diffractograms are consistent with the fundamental symmetry of a lamellar, stack-of-bilayer structure, where the main scattering peak corresponds to a bilayer-to-bilayer distance of 4.76 nm. However, in the low-temperature phase there is a set of three other peaks, two of them even ahead of the main peak, which show that the unit cell is twice as large as the layer-to-layer distance and which must be interpreted as a superstructure onto the lamellae.

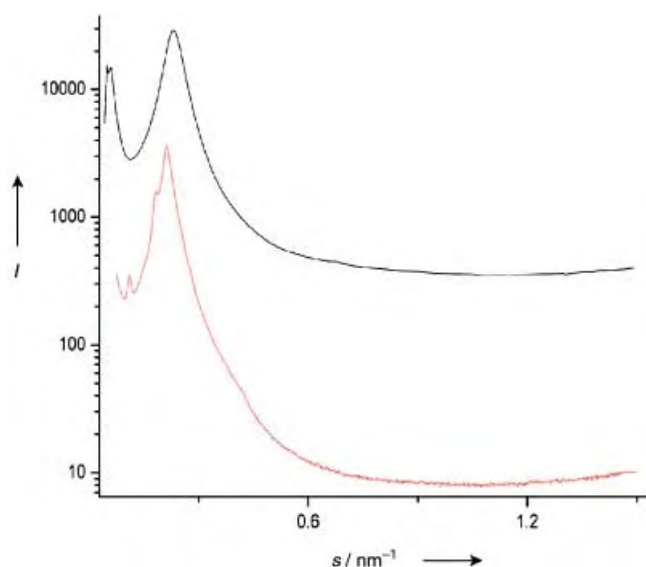


Figure 4. Small-angle X-ray scattering of solid GSSG-lecithin. Red curve: 25°C, black curve: 60°C. An evaluation of the structures with κ - ι analysis gave: $\kappa = 1.5$, $\iota = 1.7$.

From volume considerations and quantitative determination of the interface area per unit cell and the averaged curvature from the SAXS data (using the κ - ι approach, see ref. [20]), a so-called “tagliatelle” phase (a distorted hexagonal packing of one-dimensional channels in the lamellae with ABA symmetry, as depicted in Figure 5) is consistent with all experimental observations.

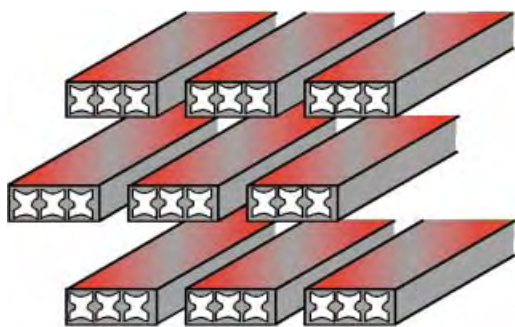


Figure 5. Schematic structural model for the solid GSSG-lipid phase. The presentation of the separating bilayers is omitted for better visualization. The peptide subphase breaks up in stripes.

The correspondence to the solution structure is obvious: it is a similar ribbon-type secondary structure which winds up to a spiral in solution and forms a layered lyotropic phase in the solid film. At higher temperature, this hexagonal ordering of the ribbons “melts away”, and statistically stacked ribbons are obtained. This structure is not specific to the lipid complex, but is also found for the double-tail surfactant. Because every GSSG unit binds four DOAC surfactants in this case (instead of two), minor differences in the superstructure arise.

The DSC trace of this complex indicates side-chain crystallinity at room temperature, which makes sample preparation more complicated; liquid crystallinity occurs only at elevated temperatures (ca. 60–80°C). The sample clears at about 250°C, which is attributed to the disintegration of the

GSSG-subphase, but sample decomposition also occurs around the same temperature.

To summarize, the simple complexation of a model oligopeptide with appropriate surfactants leads to species soluble in organic solvents which—presumably by a combination of polarity effects, packing, and the formation of hydrogen-bonding bridges—further aggregate to rather complicated, but really well-defined superstructures and lyotropic phases. This way, it is in the hand of the chemist to encode (by the appropriate choice of the starting components) at least three levels of a hierarchical ordering process, by employing a different mode of self-assembly for each hierarchy, namely ionic self-assembly for the creation of the tectonic units, H-bond formation for the build-up of the constituent secondary ribbons, and amphipolar organization for the final nanophase structures.

Experimental Section

Synthesis of the GSSG-surfactant complexes: GSSG from Sigma, dimethyldioctadecyl ammonium chloride (DOAC, Fluka Co.) and soy lecithin “Lipopur” (Lec, Lucas Meyer Co) were used as received. Deionized water (resistance > 18 M Ω) and THF (HPLC grade, Sigma Co.) were used to prepare all solutions.

For production of the 1:1 charge ratio complex, all components were prepared as 50 mM aqueous stock solutions. For the complexation of the cationic sites of GSSG with lecithin, 2 equivalents of Lec were added to 1 equivalent of GSSG stock solution, both adjusted to a pH value of 2.0. The precipitate was collected after 24 h. For the second complex, anionic complexation was performed at a pH value of 10 with four equivalents DOAC and the precipitate was collected directly. The precipitate was centrifuged and washed three times with 30 mL of water (pH 2.0 or pH 10, respectively) to remove all unbound species. The complex was then dissolved in THF and cast to form films under vacuum.

Analysis: Small-angle X-ray-scattering (SAXS) curves were recorded by using a Nonius rotating anode ($P = 4$ kW, $\text{CuK}\alpha$) with pinhole collimation and an image-plate detector system. With the image plates placed at a distance of 40 cm from the sample, a scattering-vector range from $s = 0.05$ – 1.6 nm $^{-1}$ was available ($s = 2 \sin \theta / \lambda$, scattering angle 2θ , $\lambda = 0.15418$ nm). The samples were irradiated for 24 h to reduce the noise level and to obtain a sufficiently high scattering intensity. 2D diffraction patterns were transformed into a 1D radial average of the scattering intensity.

TEM was performed with a Zeiss 912 Omega electron microscope operating at 120 kV. The diluted colloidal solutions were applied to a 400-mesh carbon-coated copper grid and left to dry; no further contrasting was applied. DSC was performed on a Netzsch DSC 200 apparatus at a scanning rate of 10 K min $^{-1}$ by applying two heating and one cooling cycle. AFM was performed with a Nano Scope IIIa microscope (Digital Instruments, Santa Barbara, USA), operating in tapping mode. The instrument was equipped with a 10×10 μm E scanner and commercial silicon tips (model TESP, the force constant was 50 N m $^{-1}$, the resonance frequency was 300 kHz, and the tip radius < 20 nm). The samples were prepared by letting droplets of diluted solutions (0.01 % w/w) in THF dry on a freshly prepared gold surface at room temperature.

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Use of Enzymes Deactivated by Site-Directed Mutagenesis for the Preparation of Enantioselective Membranes**

Alexander Skolaut and János Rétey*

Many biologically active compounds, among them drugs, have chiral structures, of which only one stereoisomer has the desired activity. Chemical synthesis of such compounds often leads to racemic mixtures, whose resolution may be a tedious and expensive procedure. Enantioselective membranes can facilitate the transport of one enantiomer of a racemate, thus constituting a simple and fast resolution method. Lakshmi and Martin incorporated enzymes into porous polymeric membranes and prevented the undesired catalytic turnover of the substrates by depriving the enzymes of their cofactors.^[1] Many enzymes do not use cofactors and thus a more general method would involve destroying the catalytic activity of the enzymes by site-specific mutagenesis, while maintaining their property to bind their substrates enantioselectively, that is, the enzymes are converted into receptors.

The enzymes histidine ammonia lyase (HAL) and phenylalanine ammonia lyase (PAL) seemed to us to be two

excellent candidates for such an endeavor. Both enzymes have a catalytically essential electrophilic group, which for almost 30 years was believed to be dehydroalanine. The recently determined X-ray crystal structure of HAL revealed that the electrophilic prosthetic group is not dehydroalanine, but rather methyldene imidazolone (MIO).^[2] Although there is currently no X-ray crystal structure of PAL, its MIO group has been identified by UV-difference spectroscopy.^[3] We prepared a number of mutants of HAL and PAL that lack the MIO group or other catalytically essential amino acid residues.^[3–6] Most of the mutants maintained their binding affinity for their substrates, but lost almost all catalytic activity. The two mutants PAL Y109F and HAL E414A were selected for incorporation into an artificial membrane.

To accelerate the transport through the membrane, the carrier molecule must be able to move freely in the whole pore volume. This movement is possible by physical entrapment between polymer films that serve as semipermeable barriers. Small molecules such as solvent or substrate molecules can diffuse through the polymer, but large molecules such as the carrier can not. The polymer film can be prepared, for example, by redox polymerization of pyrrole or its derivatives, or by polycondensation of dialkyl dichlorosilanes on the surface of a mesoporous membrane.

The quality of the synthetic polymer film can be best monitored by electron microscopy.^[7] By using this method, we found that only poly(dimethylsiloxane) polymer films that were synthesized on the surface of an alumina membrane (Anodisc membrane, Figure 1a) could be obtained in a

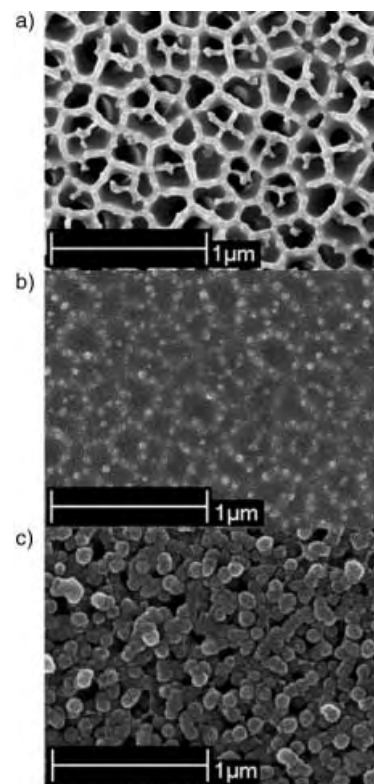


Figure 1. Electron microscope images: a) the uncoated surface of an alumina membrane (Whatman Anodisc); b) a poly(dimethylsiloxane) polymer film synthesized on the membrane surface; c) platelets of poly(pyrrole) on the surface of an alumina membrane.

[*] Prof. Dr. J. Rétey, Dr. A. Skolaut
Institut für Organische Chemie, Universität Karlsruhe
Richard-Willstätter-Allee 2, 76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4823
E-mail: biochem@ochhades.chemie.uni-karlsruhe.de

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reproducibly good quality (Figure 1 b). All other polymers or polymer/membrane combinations did not give polymer films; instead, only small polymer platelets were obtained (Figure 1 c).

The immobilization of the enzymes was carried out as follows: a small volume (<100 μL) of the concentrated enzyme solution (50 mg mL^{-1}) was applied to the uncoated side of the membrane. After the enzyme solution had entered the membrane pores it was physically immobilized with a further single-coated membrane, thus forming a membrane sandwich (Figure 2 a). Varying amounts of the protein (up to 10 mg) can be immobilized under very mild conditions by this procedure, thereby preventing denaturation and thus inactivation.

The transport experiments were carried out at optimal pH values and temperatures of the wildtype enzyme (Table 1). The membrane sandwich was mounted between the two halves of the test cell (Figure 2 b). One side of the membrane was in contact with a solution of the racemic substrate (feed side), the other with a substrate-free buffer solution (strip side). Both chambers were stirred with a magnetic stirring bar

at 250 rpm. After certain intervals, samples were withdrawn from the chambers and analyzed by reverse-phase and chiral-phase HPLC. The ratio of the transported L and D enantiomers was termed the selectivity coefficient (SF).

The first transport experiments were performed with the immobilized PAL mutant Y109F, which was about 75 000 times less active than the wildtype.^[6] Figure 3 a shows both the concentration dependence and time dependence of the selectivity. At low concentrations (0.1 mM) L-phenylalanine is transported faster and the selectivity coefficient reaches a maximum (2.5) at 30 min. Thereafter the selectivity decreases, which can be explained by the assumption that the facilitated transport takes place in both directions. It is known that PAL also accepts D-phenylalanine as substrate, albeit with lower affinity and turnover number. Simultaneously and independ-

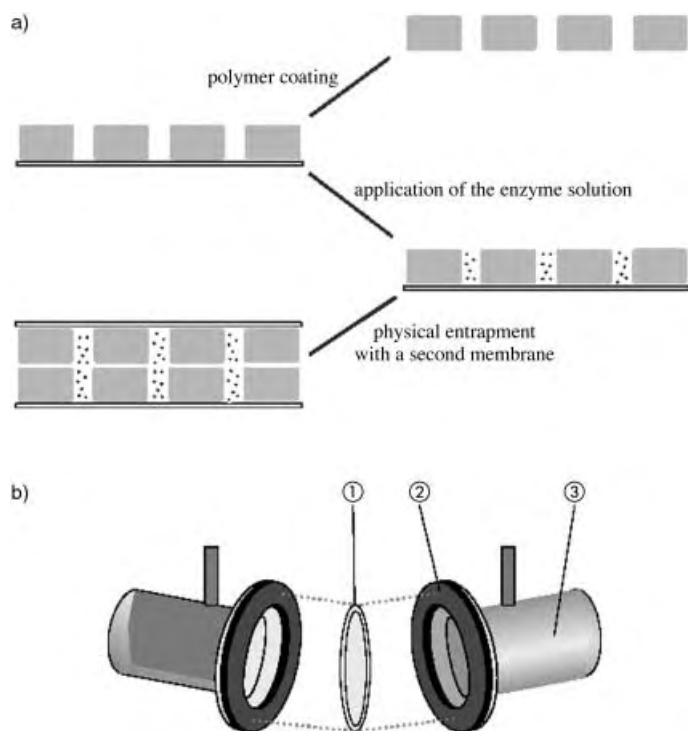


Figure 2. a) Principle of the membrane coating and immobilization process of an alumina membrane with poly(dimethylsiloxane); b) scheme of the test cell (1 = membrane, 2 = seal, 3 = chamber).

Table 1. Characteristic data of the wildtype enzyme and the inactive mutants.

Enzyme	K_m [mM]	V_{max} [U mg^{-1}]	Optimum pH	Optimum t [°C]
wildtype PAL	0.12	2.6	8.8	30
PAL Y109F ^[a]	n.d. ^[b]	0.00035	8.8	30
wildtype HAL	3.9	24.3	9.3	25
HAL E414A	6.1	0.00024	9.3	25

[a] Y109F means the amino acid at position 109 was changed from tyrosine (Y in one letter code) to phenylalanine (F). [b] not detectable.

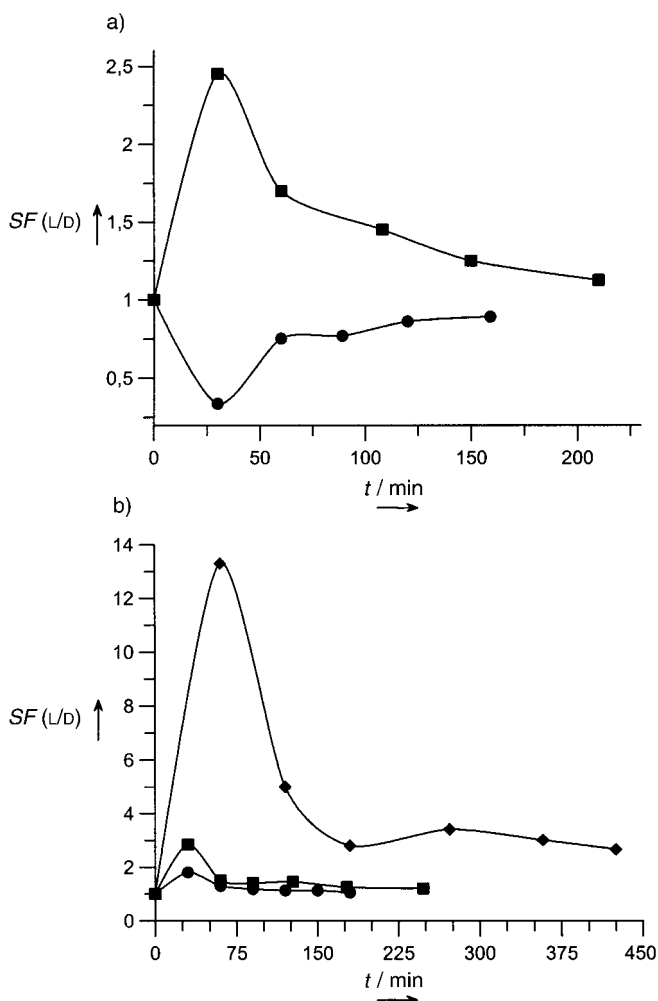


Figure 3. Time dependence of the selectivity coefficient in transport experiments: a) Anodisc membrane, 20-nm pore diameter, silane coating; PAL-Y109F at different feed concentrations of D,L-phenylalanine and protein loadings ([●] = D,L-phenylalanine (2.5 mM), protein (2.2 mg); [■] = D,L-phenylalanine (0.1 mM), protein (3.5 mg)); b) Anodisc membrane, 20-nm pore diameter, silane-coating; HAL E414A at different feed concentrations of D,L-histidine with 5-mg protein loading ([●] = D,L-histidine (2.5 mM); [■] = D,L-histidine (1.0 mM); [◆] = D,L-histidine (0.1 mM)). All substrate concentrations are those at the start of the experiments. During the first hour, 3 % of the amino acids were transported to the strip side, at the end of the experiments about 15 % of the amino acids had been transported.

ently of the carrier, a slower nonselective diffusion transport also takes place. Surprisingly, at a much higher substrate concentration (2.5 mM) in the feed, D-phenylalanine is transported faster. This unexpected result can be explained by the fact that at this concentration the D enantiomer successfully competes for the binding site of PAL and occupies it for a much longer period of time, so that little free enzyme remains available for transporting the L enantiomer. The selectivity coefficient in this case also decreases after 30 min and approaches equilibrium asymptotically.

The immobilized HAL mutant E414A behaved differently. HAL is known to be strictly enantioselective for L-histidine.^[8] Indeed, its mutant facilitated the transport of the L enantiomer at all three concentrations applied (Figure 3b). However, the selectivity coefficient in this case also reached the highest value (13.3) at the lowest concentration (0.1 mM). After 70 min the selectivity decreased, clearly for the same reason discussed for the PAL experiment. At high concentrations in the feed side, the maximum was much lower (2–3) and was reached faster (30 min.). As a control, the same membrane system without encapsulated enzyme has been also examined for its capacity to transport phenylalanine enantiospecifically. Analysis on a chiral column (see Experimental Section) showed that both enantiomers diffused through the membrane at the same rate.

Our results show that enzymes can be converted into enantioselective receptors by site-directed mutagenesis and used in an immobilized form to facilitate enantioselective transport across a membrane. The technique described herein differs from previously published methods in which enantioselective membranes that contain nonselective proteins, for example, serum albumin or other chiral materials.^[9–11] Such membranes as well as chiral chromatography columns work by binding and retarding the transport of one enantiomer, while the other enantiomer can passively diffuse or can be eluted without retardation. In our method, the transport of one enantiomer is accelerated while the other diffuses through the membrane, but much more slowly. Continuous removal of the enriched enantiomer from the permeate (strip) side could lead to resolution on a preparative scale. Whether the present method may become competitive with other established racemate separations or not, is the subject of future research.

It is the first time that not only the concentration dependence but also the time course of the enantioselectivity of the transport through an enzyme-loaded membrane are reported. A further aspect of our results is that as a consequence of the broad substrate specificity of PAL, the present membranes have the potential to resolve the racemates of a large number of aryl alanines.^[12]

Experimental Section

Membrane coating: The membrane was first equilibrated for 5 min with the vapor of dichlorodimethylsilane, and water was then applied to one side of the membrane for an additional 5 min. The coated membranes were washed for 1 min with water and dried at room temperature.

Analytical methods: the HPLC separations were run on a Hewlett Packard Series 1050 HPLC with the following columns and under the following conditions: D,L-phenylalanine: Grom Symbasic 125 × 4.6 mm equipped

with a 10 × 2.5-mm guard column, 5 μm, isocratic elution with doubly distilled water with TFA (0.1 vol %); D,L-histidine: Grom Sil ODS-O AB, 250 × 4.0 mm, 5 μm, isocratic elution with CH₃CN (20 %) and potassium phosphate buffer (pH 8.0, 10 mM, 80 %); Astec Chirobiotic T, 250 × 2.5 mm with a 10 × 2.5-mm guard column for chiral analysis.

Conditions according to the Chirobiotic handbook (Advanced Separation Technologies, Inc.).

All chromatograms were monitored at 210 nm.

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Copper-Catalyzed Oxidative Heterocyclization by Atmospheric Oxygen

Martin E. Bluhm, Michael Ciesielski, Helmar Görls, and Manfred Döring*

Although molecular oxygen is the most low-priced of all known oxidants, it is applied only rarely in synthetic chemistry. This is because the O₂ molecule has a low reactivity at moderate temperatures due to kinetic barriers, and because of its commonly poor selectivity in the oxidation of organic substrates. However, O₂ can be activated in living organisms by catalytically active metalloenzymes, showing that many selective oxidations are feasible even under very mild conditions. Therefore, metal complexes possessing similarities

[*] Prof. Dr. M. Döring, Dr. M. E. Bluhm, Dr. M. Ciesielski
Institute for Technical Chemistry (ITC-CPV)
Forschungszentrum Karlsruhe
P.O. Box 3640, 76021 Karlsruhe (Germany)
Fax: (+49) 7247-82-2244
E-mail: manfred.doering@itc-cpv.fzk.de
Dr. H. Görls
Department of Inorganic Chemistry
University of Jena
August-Bebel-Strasse 2, 07743 Jena (Germany)



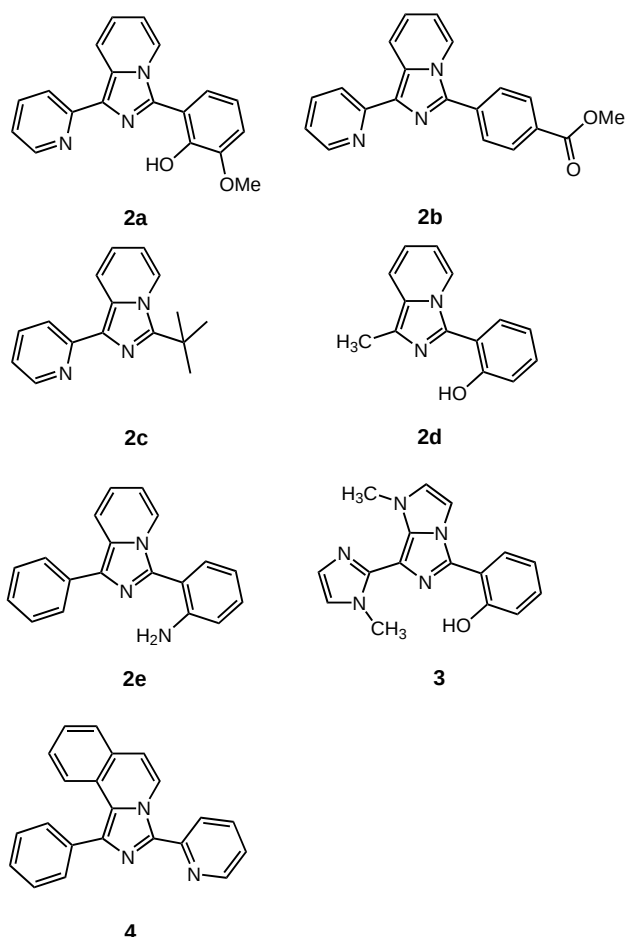
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

with the active site of copper-containing oxygenases and oxidases, for example bilirubin and sulochrin oxidase, have attracted increasing interest.^[1] To date, the transfer of the chemical reactivity of a biooxidase into a simple synthetic complex has been successful in a few cases only. Examples include amino and phenoxy ligands as mimics for the copper-containing enzyme galactose oxidase,^[2] as well as mononuclear and binuclear copper(I) complexes as models of the biological oxygenases.^[3] In addition, the oxidation of a bis(pyridine)imine ligand in vanadium(V) complexes has been described;^[4] however, this oxidation has not yet been performed in a closed catalytic cycle. Recently an oxidative heterocyclization of thiosemicarbazones to 1,3,4-oxadiazole derivatives was described,^[5] in which the reactant had to be coordinated to copper(II) ions with KBrO_3 as oxidant. Likewise, this reaction was not carried out catalytically.

Most interesting is the ecologically compatible synthesis of new heterocyclic compounds that are not easily accessible and that can be applied as pharmaceuticals or as ligands for the development of new catalysts. A series of imidazo[1,5-*a*]pyridines (**2a–e**), the imidazo[1,5-*a*]imidazole **3**, and the imidazo[5,1-*a*]isoquinoline **4** were prepared by copper-catalyzed oxidation with atmospheric oxygen.^[6] Here, we describe the synthesis of the seven heterobicycles **2a–e**, **3**, and **4** by catalytic ring closure starting from the Schiff bases **1a–g** (Scheme 1). The Schiff bases **1a–g** were prepared readily from the appropriate aldehydes and primary amines. The required amines are accessible by the reduction of the oximes with zinc.^[7] The isolation of the imine **1** is not necessary; that is the copper-catalyzed reaction of **1** was performed in situ, as shown, for example, by the synthesis of **2b**.

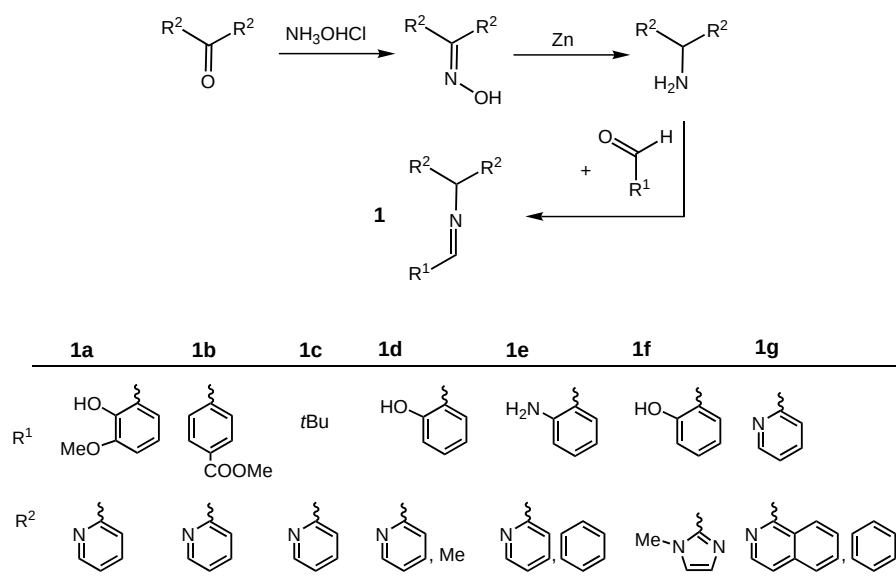
A methanolic solution of **1** and catalytic amounts of CuCl_2 and base (sodium hydroxide, triethylamine) were heated in the presence of air (Scheme 2). The Schiff base **1** undergoes an oxidative dehydrogenation after coordination to a copper(II) ion. Then, a C–N bond was generated between the imino-carbon atom and the nitrogen atom of the 2-pyridyl, 2-imidazolyl, or isoquinolyl group in **1**, leading to the formation of the five-membered heterobicycles.^[8] The copper(II) ions are regenerated after the oxidative cyclization when atmospheric O_2 is present. The oxidized, monodentate ligands **2–4** coordinate more weakly to the Cu^{II} center than the bidentate imine starting material **1** and can therefore be substituted by ligand exchange; in this way the catalysis cycle begins anew.

Neither hydroxy or amine groups at R^1 (**1a, d–f**) nor other substituents (**1b, c, g**) hamper the reaction. The selective oxidation of **1** by molecular oxygen is only feasible in this reaction with copper ions as catalyst. Nevertheless, for the catalytic reaction the Schiff base **1** must contain three donor atoms, whereas two donor atoms are sufficient for the stoichiometric copper-mediated reaction.^[6] The copper-catalyzed reaction affords heterobi-

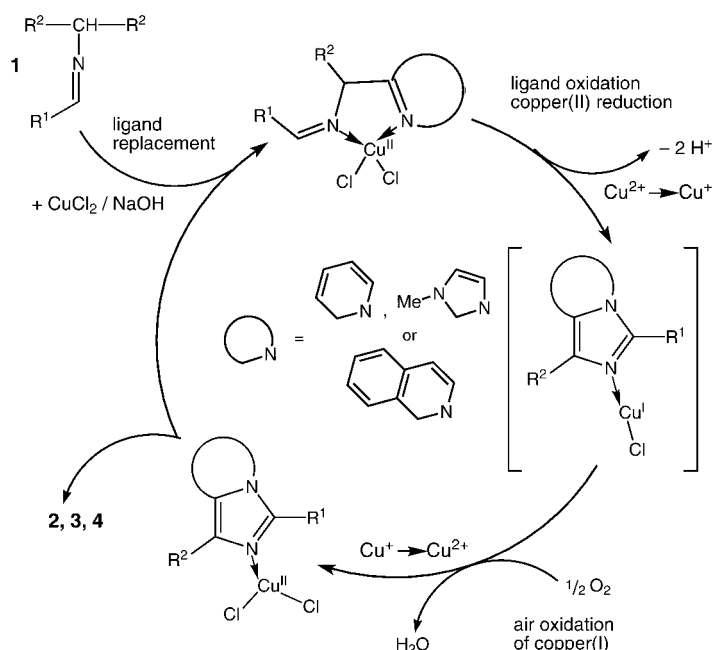


cycles (yields between 35 and 60%), which are either not accessible with the stoichiometric variant or can only be obtained in very low yields.

The X-ray structure analyses of **2a** (Figure 1) and **3** (Figure 2) show the planar arrangement of the imidazo[1,5-*a*]-



Scheme 1. Synthesis of the aldimines **1**.



Scheme 2. Catalytic cycle with Cu^{II} catalyst and O_2 as oxidant (for R^1 , R^2 see Scheme 1).

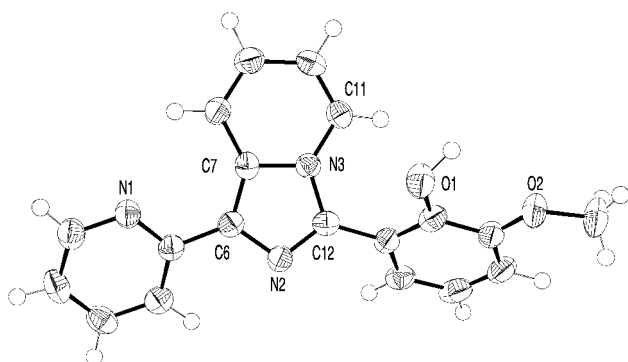


Figure 1. Molecular structure of **2a**. Selected C–N distances [$\text{\AA}$] and C–N–C angles [$^\circ$]: C12–N2 1.330, C6–N2 1.377, C12–N3 1.382, C11–N3 1.386, C7–N3 1.401; C12–N2–C6 107.0, C12–N3–C7 107.3, C11–N3–C7 121.8.

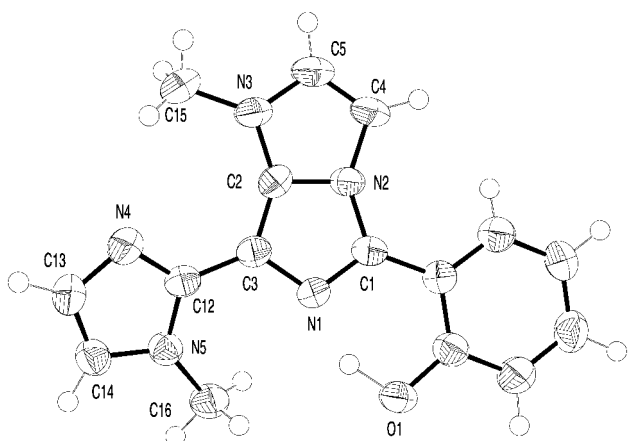


Figure 2. Molecular structure of **3**. Selected C–N distances [$\text{\AA}$] and C–N–C angles [$^\circ$]: C1–N1 1.342, C3–N1 1.386, C1–N2 1.389, C2–N2 1.388, C2–N3 1.373, C5–N3 1.390, C15–N3 1.463, C12–N5 1.378, C16–N5 1.458, C12–N4 1.333, C13–N4 1.384, C14–N5 1.385; C1–N1–C3 109.4, C1–N2–C2 107.9, C2–N3–C5 106.9, C2–N2–C4 108.4, C12–N4–C3 104.8, C12–N5–C14 106.3.

pyridine (**2a**) and the imidazo[1,5-*a*]imidazole (**3**) heterobicycles. The 1-methylimidazol-2-yl unit in **3** is flipped by 20° from the imidazo[1,5-*a*]imidazole backbone. The H atom at O1 in **3** forms a hydrogen bond with the N1 atom (1.53 $\text{\AA}$). In contrast, in **2a** the analogous *ortho*-hydroxy group forms a hydrogen bond with the pyridyl-N1 atom of a second molecule (1.95 $\text{\AA}$).

To investigate the selective influence of the copper catalyst on the reaction, we attempted to oxidize different Schiff bases in the absence of copper ions. No selective oxidation was observed for reactions with other oxidants, such as iron(III) salts, manganese(IV) and lead(IV) acetate, and air oxygen under basic conditions, and no heterobicycles were isolated.

This copper-catalyzed reaction provides a facile route to heterobicycles which previously had only been accessible in low yields by dehydration of amides under severe conditions (imidazo[1,5-*a*]pyridines,^[9] imidazo[1,5-*a*]imidazoles,^[10] and imidazo[5,1-*a*]isoquinolines^[11]). Analogous copper-catalyzed reactions of other Schiff base compounds, as well as the isolated copper(I) and copper(II) intermediates will be reported in due course.

Experimental Section

2a: The Schiff base **1a** (1920 mg, 6 mmol), NaOH (25 mg, 0.6 mmol), and CuCl_2 (80 mg, 0.6 mmol) were heated in methanol (50 mL) under reflux for 7 h, while dry air was bubbled through the solution. After the mixture had been allowed to cool to room temperature, a solution containing $\text{NH}_4\text{CH}_3\text{COO}$ (10 g) and NaCl (10 g) in distilled water (50 mL) was added, and the mixture was heated up to 60°C for 10 min. After the mixture had cooled down to room temperature, the crystallate was dissolved in CHCl_3 . The solution was extracted three times with CHCl_3 , and the combined organic layers were dried with Na_2SO_4 . The CHCl_3 was then removed in vacuo. Column chromatography of the brown oil on silica in acetone afforded **2a** as a major yellow band. After removal of the solvent, **2a** was recrystallized from ethanol. The crystallization was completed by cooling the mother liquor to -20°C . Yield of **2a**: 670 mg (2.1 mmol, 45 %); m.p. 185°C ; ^1H NMR (200 MHz, CDCl_3): δ = 11.58 (s, br., OH), 8.70 (m, 1H), 8.58 (m, 1H), 8.37 (m, 1H), 8.05 (m, 1H), 7.68 (m, 1H), 7.33 (m, 1H), 7.07 (m, 1H), 6.91 (m, 3H), 6.67 (m, 1H), 3.94 ppm (s, 3H); ^{13}C NMR (50.3 MHz, CDCl_3): δ = 154.0, 149.2, 149.0, 146.2, 136.3, 135.5, 129.5, 128.6, 122.6, 122.1, 121.5, 120.7, 119.6, 119.0, 117.5, 114.5, 112.3, 56.2 ppm; EI^+ -MS: m/z (%): 317 (100) [M^+]; C, H, N analysis (%) calcd for **2a**: C 71.91, H 4.76, N 13.24; C 71.71, H 4.89, N 12.89.

2b: Method A: The Schiff base **1b** (1160 mg, 3.5 mmol), NaOH (20 mg, 0.5 mmol) and CuCl_2 (90 mg, 0.5 mmol) were first heated in methanol (40 mL) under reflux for 1 h, while bubbling dry air through the solution. After the reaction mixture was cooled down to room temperature, the precipitated solid was filtered and recrystallized in ethanol/water (2/1). Compound **2b** (720 mg, 2 mmol; 63 %) was obtained as yellow crystals. Method B: A solution of bis(2-pyridyl)methylamine (2 g, 11 mmol) in ethanol (10 mL) was added dropwise to a solution of 4-formylmethoxybenzoic ester (1.8 g, 11 mmol) in absolute ethanol (10 mL). The mixture was refluxed for 1 h under argon. Then CuCl_2 (90 mg, 0.5 mmol) and NaOH (20 mg, 0.5 mmol) were added. The mixture was refluxed for another 1.5 h, while bubbling dry air through the solution. The precipitated yellow solid was filtered and washed with ethanol. After drying in vacuo, **2b** (1.25 g, 3.8 mmol; 35 % relative to the used amine) was obtained as a yellow solid. M.p. 204°C ; ^1H NMR (200 MHz, CDCl_3): δ = 8.70 (m, 1H), 8.60 (m, 1H), 8.16–8.31 (m, 4H), 7.93 (m, 2H), 7.71 (m, 1H), 7.09 (m, 1H), 6.95 (m, 1H), 6.68 (m, 1H), 3.94 ppm (s, 3H); ^{13}C NMR (50.3 MHz, CDCl_3): δ = 166.6, 154.8, 149.0, 136.8, 136.2, 134.4, 131.4, 130.8, 130.2, 129.9, 127.8, 122.1, 121.5, 121.4, 120.6, 120.0, 114.5, 52.2 ppm; EI^+ -MS: m/z (%): 329 (100) [M^+]; elemental analysis calcd (%) for **2b**: C 72.94, H 4.59, N 12.76; found: C 72.93, H 4.63, N 12.61.

2c: The Schiff base **1c** (1000 mg, 4 mmol), NaOH (16 mg, 0.4 mmol), and CuCl₂ (54 mg, 0.4 mmol) were first heated in methanol (60 mL) under reflux for 7 h, while bubbling dry air through the solution. After the mixture had been stirred at room temperature for a further 12 h, the solvent was removed in vacuo. Column chromatography of the residue on silica with hexane/ethyl acetate (1/3) afforded **2c** as a major yellow band (400 mg, 1.6 mmol; 40%). M.p. 92 °C; ¹H NMR (200 MHz, CDCl₃): δ = 8.65 (m, 1H), 8.61 (m, 1H), 8.06–8.21 (m, 2H), 7.69 (m, 1H), 7.05 (m, 1H), 6.83 (m, 1H), 6.55 (m, 1H), 1.59 ppm (s, 9H); ¹³C NMR (50.3 MHz, CDCl₃): δ = 155.0, 148.5, 145.3, 136.6, 130.6, 127.4, 123.2, 121.8, 120.0, 119.9, 112.6, 33.5, 28.2 ppm. EI⁺-MS: *m/z* (%): 251 (90) [*M*⁺], 236 (100) [*M*⁺–CH₃]; elemental analysis (%) calcd for **2c**: C 76.46, H 6.82, N 16.72; found: C 76.13, H 6.47, N 16.54.

2d: The Schiff base **1d** (2500 mg, 11 mmol), NaOH (57 mg, 1.4 mmol), and CuCl₂ (194 mg, 1.4 mmol) were first heated in methanol (100 mL) under reflux for 3 h, while bubbling dry air through the solution. The solvent was then removed in vacuo. Column chromatography of the residue on silica with hexane/CH₂Cl₂/ethyl acetate (6/6/1) afforded **2d** as a major green fluorescent band. Recrystallization of the collected fraction with toluene yielded pale yellow crystals of **2d** (1250 mg, 5.6 mmol; 50%). M.p. 150 °C; ¹H NMR (200 MHz, CDCl₃): δ = 7.92 (d, 1H), 7.46 (m, 1H), 7.35 (m, 1H), 7.08 (m, 2H), 6.81 (m, 2H), 6.63 (m, 1H), 2.57 ppm (s, 3H); ¹³C NMR (50.3 MHz, CDCl₃): δ = 156.2, 134.0, 129.8, 127.2, 126.4, 124.6, 122.2, 119.0, 118.6, 118.2, 117.7, 114.0, 113.8, 12.0 ppm; EI⁺-MS: *m/z* (%): 224 (100) [*M*⁺]; elemental analysis (%) calcd for **2d**: C 74.98, H 5.39, N 12.49; found: C 74.85, H 5.27, N 12.41.

2e: The Schiff base **1e** (2300 mg, 8 mmol), NaOH (40 mg, 1 mmol), and CuCl₂ (130 mg, 1 mmol) were heated in methanol (40 mL) under reflux for 30 min while bubbling dry air through the solution. The color of the reaction mixture changed to brown. After the addition of distilled water (150 mL), EDTA (500 mg), ammonium acetate (500 mg) and NaCl (20 g) to the hot reaction mixture a brown solid precipitated. This precipitate was dissolved in ethyl acetate and the aqueous methanolic solution was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate. The ethyl acetate was removed in vacuo. Column chromatography of the residue on neutral Al₂O₃ with hexane/ethyl acetate (1/1) and removal of the solvents afforded a yellow oil which crystallized in the cold. For the removal of a few impurities the solid was dissolved again in acetic acid (20 mL) and distilled water (50 mL). After addition of NaCl (15 g) and ice (50 g) to the colorless solution a brown precipitate appeared, which was filtered from the dissolved product. NaHCO₃ was added to the filtrate and a yellow solid precipitated which was filtered from the solution. Recrystallization of the solid with ethanol/water (1/1) yielded yellow crystals of **2e** (800 mg, 2.8 mmol; 35%). M.p. 146 °C; ¹H NMR (400 MHz, C₆D₆): δ = 8.02 (d, 2H), 7.55 (m, 1H), 7.36 (m, 1H), 7.29 (m, 2H), 7.12 (m, 1H), 7.00 (m, 1H), 6.59 (m, 1H), 6.40 (m, 1H), 6.12 (m, 1H), 5.72 (m, 1H), 4.77 ppm (s, 2H); ¹³C NMR (100 MHz, C₆D₆): δ = 147.1, 136.8, 136.0, 131.6, 129.9, 128.9, 128.4, 127.1, 126.6, 122.5, 119.5, 119.0, 117.1, 116.8, 114.2, 112.5 ppm; EI⁺-MS: *m/z* (%): 286 (30) [*M*⁺]; elemental analysis (%) calcd for **2e**: C 79.98, H 5.30, N 14.73; found: C 79.53, H 5.13, N 14.34.

3: The Schiff base **1f** (970 mg, 3.3 mmol), NaOH (20 mg, 0.4 mmol), and CuCl₂ (50 mg, 0.4 mmol) were heated in ethanol (30 mL) under reflux for 1 h, while bubbling dry air through the boiling solution. The color of the reaction mixture changed from green to brown. After cooling the mixture to room temperature, the crude product **3** precipitated. The product was recrystallized in a water/DMSO (1/1) mixture to give crystalline **3** (345 mg, 1.1 mmol; 36%). M.p. 204 °C; ¹H NMR (200 MHz, CDCl₃): δ = 12.65 (s, br., OH), 6.84–7.50 (m, 8H), 4.06 (s, 3H), 3.95 ppm (s, 3H); ¹³C NMR (50.3 MHz, CDCl₃): δ = 155.6, 137.4, 122.7, 127.4, 127.1, 126.6, 122.0, 121.1, 118.8, 116.9, 114.6, 104.7, 102.5, 35.1, 34.8 ppm; EI⁺-MS: *m/z* (%): 293 (100) [*M*⁺]; elemental analysis calcd for **3**: C 65.52, H 5.15, N 23.88; found: C 65.31, H 5.01, N 23.72.

4: The Schiff base **1g** (890 mg, 2.8 mmol) and CuCl₂ (40 mg, 0.28 mmol) were heated in methanol (20 mL) under reflux for 30 min, while bubbling dry air through the solution. The color of the reaction mixture changed to brown. After the addition of distilled water (200 mL), EDTA (250 mg) and ammonium acetate (1000 mg) to the hot reaction mixture a yellow-brown solid precipitated. The residue was filtered from the solution and dissolved in ethyl acetate. Column chromatography of the residue on weak basic Al₂O₃ with hexane/ethyl acetate (1/1) afforded **4** as a major blue fluorescent band. Recrystallization of the collected fraction with hexane/

toluene (4/1) (35 mL) yielded pale-yellow crystals of **4** (310 mg, 0.97 mmol; 35%). M.p. 197 °C; ¹H NMR (200 MHz, C₆D₆): δ = 10.07 (d, 1H), 8.73 (m, 1H), 8.48 (m, 1H), 8.39 (m, 1H), 8.03 (m, 2H), 7.44 (m, 2H), 7.03–7.30 (m, 5H), 6.68 ppm (m, 2H); ¹³C NMR (50.3 MHz, C₆D₆): δ = 152.2, 148.5, 138.1, 137.6, 137.2, 137.0, 136.7, 130.8, 129.6, 128.2, 127.4, 127.3, 126.3, 126.2, 125.3, 123.6, 123.5, 122.2, 114.4 ppm; EI⁺-MS: *m/z* (%): 321 (100) [*M*⁺]; elemental analysis (%) calcd for **4**: C 82.22, H 4.70, N 13.08; found: C 81.88, H 4.76, N 12.69.

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Real-Time Photoacoustic Parallel Detection of Products from Catalyst Libraries**

Thorsten Johann, Armin Brenner, Manfred Schwickardi, Oliver Busch, Frank Marlow, Stephan Schunk, and Ferdi Schüth*

Over the last few years, high-throughput experimentation has found increasing acceptance as a powerful methodology to accelerate the discovery of solid catalysts. Although interesting developments in product analysis have been reported,^[1–4] there is an urgent need for fast and truly parallel techniques for analysis. Moreover, versatile automated procedures for catalyst synthesis are not easy to implement. Herein we report developments which address both problems: 1) Detection of a pressure pulse after laser excitation of the target molecules (photoacoustic detection) is used to monitor catalytic activity in a real-time, parallel fashion. 2) Automated libraries of high surface area multinary oxides are synthesized by using activated carbon as an “exotemplate” for the generation of small particles. Using the synthesis approach and the detection method, novel low-temperature CO-oxidation catalysts have been discovered.

The high-throughput search for novel catalytic materials is hampered by two conflicting targets: On the one hand, catalysts should be measured under plug-flow conditions at a defined residence time, which requires reactors such as those described by Hoffmann et al.^[5,6] On the other hand, the parallel techniques for product analysis described so far are difficult to adapt to such reactor systems. The system we have developed to reconcile these conflicting objectives relies on the photoacoustic effect, which has been used for nonparallel gas analysis in the past.^[7] To convert it into a parallel-detection technique we developed the setup which is shown schematically in Figure 1. The exit streams from the different channels of a parallel reactor are directed into an array of tubes (eight in our case), arranged in line with each other. A laser tuned to an absorption frequency of the target molecule is passed through

the free-flowing exhaust plumes of all catalysts. We used a pulsed CO₂ laser (10 Hz or 100 Hz modulated 25 W laser with a pulse length of 35 μ s or 25 μ s), emitting at 943–950 cm^{–1}, because ethene (one of the target products) has a strong absorption band in this range. In addition, CO₂ lasers are cheap, readily available, high-power light sources. However, other lasers can also be used for target molecules with absorption bands in other ranges of the spectrum. A microphone (Brüel & Kjaer condenser microphone) with a fast response time and decay is used to record the pressure pulse generated after energy absorption of the target molecules. The time lag between laser pulse and different pressure pulses can be used to localize the origin of the pulse with a resolution of about 3 cm. Shorter pulses will improve the spatial resolution because they lead to sharper signals which could ideally be slightly longer than the time the pressure pulse needs to propagate a distance equal to the diameter of the gas exhaust. This, however, would also require the use of a microphone with better damping characteristics.

In Figure 1, the voltage signal from the microphone after a laser pulse at $t = 0$ s is also shown. The minima correspond to pressure pulses from subsequent gas outlets, the decrease of intensity with increasing time is caused by the increasing

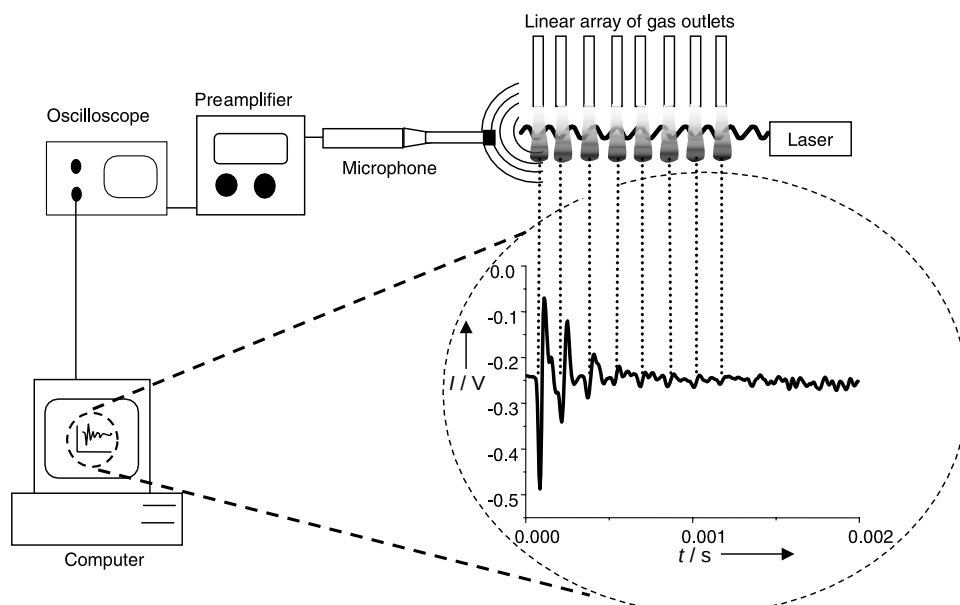


Figure 1. Setup of the photoacoustic free-field measurement. The diagram shows a real signal of voltage versus time, with $t = 0$ being the moment of the laser pulse. 2% ethene flowed through all channels. The minima correspond to the subsequent reagent outlets, additional minima result from residual echos.

distance to the microphone. The signal-to-noise ratio can be improved by summing signals from several laser pulses which, in the present setup, increased the time for a complete set of data to 2.5 s. Automated on-line calibration of the signal uses substrate gas (0% ethene) and product gas, typically 2% ethene. Despite the fact that absorption of laser light could be nonlinear in terms of laser power, a linearity of concentration and measured signal intensity between 0 and 2% was shown in calibration experiments. Deviations from linearity were not detectable within the error margin (about 1% of the maximum for 2.5 s signal averaging). Because of the higher signal, precision of the measurements is better for the

[*] Prof. Dr. F. Schüth, T. Johann, M. Schwickardi, O. Busch, Dr. F. Marlow
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim (Germany)
Fax: (+49)208-306-2995
E-mail: schueth@mpi-muelheim.mpg.de

Dr. A. Brenner, Dr. S. Schunk
hte-AG
Kurpfalzring 104, 69123 Heidelberg (Germany)

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channels close to the microphone, but even for the most distant channels, 0.3 % ethene could be reliably measured. By using several microphones suitably placed, it will be possible to analyze a two-dimensional sound field from an array of gas outlets, which allows a much higher degree of parallelization than described in this initial study.

One can even use the technique for the analysis of molecules with very low extinction coefficients, such as CO_2 . The CO_2 laser relies on transitions between excited vibrational states of the CO_2 molecule. CO_2 has thus a very low extinction coefficient at the emission wavelength of the laser. In this case, analysis in the free-flowing gas described above is not possible, but the signal can be amplified by resonance. The gas from each reactor channel is directed to a metal pipe that acts as a resonance tube, which is equipped with a separate microphone (cheap electret microphone for about 1 €). The laser is modulated on a resonance frequency of the tubes. The microphone signal is detected with a lock-in amplifier and a multiplexer, which switches between the different microphones. A setup with 16 parallel channels has been realized. Analysis speed is essentially determined by the electronics of the system. In the present setup, the single channels can be read in times below 1 s. For a molecule such as CO_2 , a detection limit of 100 ppm was achieved, the detection limit for ethene can be estimated to be in the ppb range with the resonance setup.

There are two other laser-based techniques which have been used to analyze the products of a catalytic reaction, resonance-enhanced multiphoton ionization (REMPI)^[8] and photothermal deflection.^[9] The new development reported here solves two problems associated with these methods. While thermal-deflection spectroscopy is not a parallel but a sequential method, the REMPI setup makes it necessary to expose an electrode array to the product stream, which can lead to severe contamination and disturbance of the electrode array. In addition, more absorption frequencies and combinations of frequencies could be used than in REMPI, which can make this method more selective. Suitable absorption frequencies can be selected based on the known IR spectra of substrates and possible products. The only limitation is the availability of commercial laser sources that emit in the selected range of the electromagnetic spectrum.

Both detection techniques described above, the resonant method and the free-field method, were used to evaluate libraries of high surface-area metal oxides. The automated synthesis of this class of important catalysts has so far not been possible using automated procedures.^[10] We have now developed a synthesis route to solve this problem. There are scattered reports that impregnation of a micro- or mesoporous mold and subsequent removal of the mold can lead to highly porous solids.^[11,12] If activated carbon is impregnated with a highly concentrated metal-salt solution (nitrates have been best in most cases) and then dried and calcined, a highly disperse oxide remains. Random libraries of such mixed oxides were generated by random selection of components from a pool of ten. The desired compositions were then automatically recalculated to volumes of solution for impregnation, and the resulting file of pipetting data transferred to an automated dispenser, where a library of 77 catalysts was

prepared in one go by impregnating the activated carbon. The whole library was then calcined simultaneously and the catalysts transferred to the reactor for testing.

We prepared several such libraries for various catalytic applications. About 150 different compositions were tested in total with the photoacoustic setups described above. For the oxidative dehydrogenation (ODH) of ethane, activity has been detected in some of the compositions, and the results of the photoacoustic parallel detection correspond very well to separate measurements in a conventional reactor with GC analysis (Figure 2). It is noteworthy that, because of the fast analysis, systems could also be identified which had very good performance over the first 20 min of the reaction, but then deactivated rapidly.

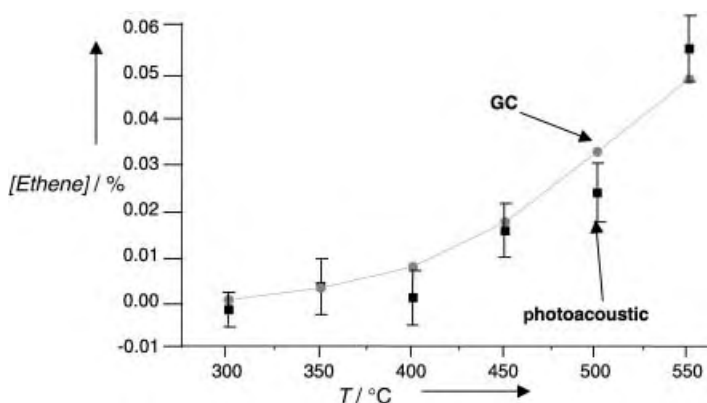


Figure 2. Measurement of ethene concentration in the oxidative dehydrogenation of ethane; comparison between novel free-field photoacoustic setup and conventional GC analysis. The composition of the catalyst was 12 % La, 2 % Ba, 9 % Pb, 7 % Th, 27 % Mn, 24 % Ni, and 19 % Cu as oxides, synthesized by the activated-carbon route described in the text.

In the CO oxidation, novel low-temperature CO-oxidation catalysts that are free of noble metals have been identified. The best catalyst is much better than most noble-metal-based systems, with the exception of the Sn-promoted Pt catalysts. Only Haruta-type gold catalysts^[13] and some other formulations, such as the Co_3O_4 -based systems^[14] and the hopcalite-related (Cu-Mn-O) systems,^[15] show better activity than the materials discovered. Figure 3 shows the conversion versus temperature curves for different catalysts analyzed in parallel during a dynamic heating/cooling experiment. The agreement is excellent, which demonstrates that photoacoustic detection can be used as a quantitative tool under optimized conditions. Figure 4 shows the powder diffraction pattern and the sorption isotherm of the best CO-oxidation catalyst discovered in the screening of the samples. Because the best systems contain Cu and Mn, these materials are probably related to the hopcalite system. The diffraction pattern corresponds to a spinel phase or a mixture of several similar spinel phases, the exact nature of which is not yet known, and amorphous by-products. The sorption isotherm shows a Brunauer–Emmett–Teller (BET) surface area of $60 \text{ m}^2 \text{ g}^{-1}$, both the phase and the sorption behavior is also rather typical for other members of the libraries investigated here.

In summary, we have introduced: 1) a real-time, parallel, and fast detection technique for the analysis of products from

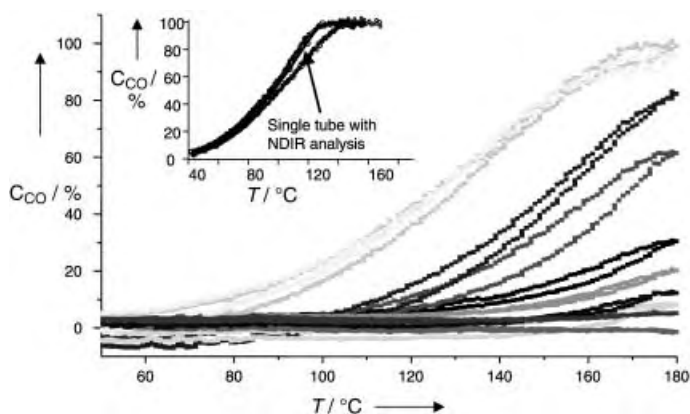


Figure 3. CO-conversion curves measured simultaneously with the resonance setup. Out of the 16 curves only 10 are shown, to increase readability. The inset shows the comparison of the results for the best catalyst ($\text{Fe}_{17}\text{Ni}_{25}\text{Mn}_{27}\text{Cu}_{30}$) measured with the resonance photoacoustic setup and in a conventional reactor with a nondispersive IR system (URAS 3E).

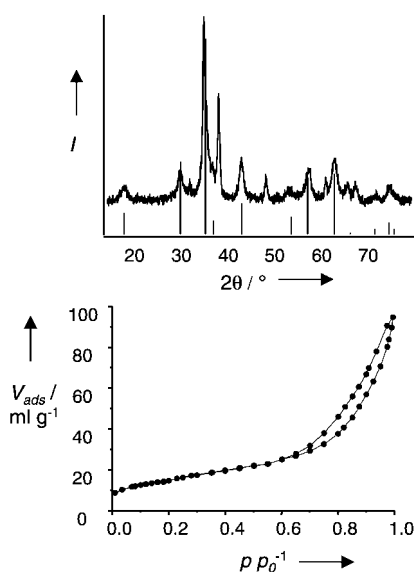


Figure 4. Nitrogen-sorption isotherm (bottom) and X-ray diffraction pattern (top) of the $\text{Fe}_{17}\text{Ni}_{25}\text{Mn}_{27}\text{Cu}_{30}$ catalyst. The material has a surface area of $60\text{ m}^2\text{ g}^{-1}$, the lines in the diffraction pattern correspond to $\text{CuNi}_{0.5}\text{Mn}_{1.5}\text{O}_4$, which suggests that the crystalline part of the catalyst—in addition to the amorphous material present—is a spinel phase.

catalytic reactions, 2) a method to synthesize libraries of complex mixed oxides automatically, and 3) applied the setup to investigate ethane ODH and low-temperature CO oxidation, for which several novel noble-metal-free catalysts were discovered. These components will form the basis for a new technology platform for high-throughput screening in catalysis research.

Experimental Section

Fluka 05120 and Darco KB-B, supplied by Aldrich, were used as activated carbon. Metal compounds were hydrates of nitrate salts supplied by Fluka. All precursor solutions were saturated.

Catalyst impregnation was performed using a commercial pipette system (Gilson XL 232). The carbon was transferred into vials in a 77-well plate by using fixed volumes which were equal to 230 mg (± 10 mg) in weight. We used a total amount of 450 μL of mixed precursor solution which

corresponds to incipient-wetness conditions. The composition of the precursor solution was determined by a random algorithm which first determines whether a precursor is chosen as an ingredient or not, and afterwards which quantity of the chosen precursor contributes to the total composition. The impregnated samples were then calcined on a 77-well plate covered with gauze to prevent oxide particles being expelled during carbon combustion. Samples were dried at 90°C overnight and slowly heated to 500°C within 3 h. After remaining at 500°C for 2 h, which led to full combustion of the carbon, the samples were allowed to cool down.

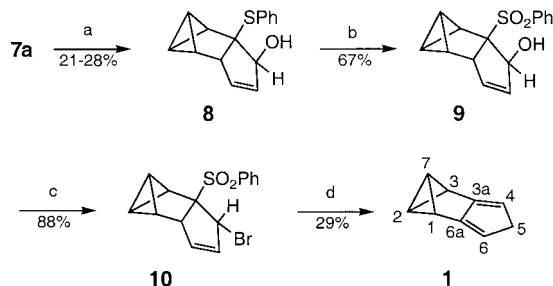
For the free-field measurements, we used a DEOS 25 W radio-frequency-excited CO_2 laser, modulated by a (TTL) signal that was generated by an external pulse generator. The same pulse triggered the Tektronix TDS 380 digital real-time oscilloscope. The generated pressure wave was detected by a condenser microphone (Brüel & Kjaer, Falcon $\frac{1}{4}$ Zoll, type 4938). A conventional Nexus two-channel conditioning amplifier was used to produce the signal for the Oscilloscope. The signals were accumulated (up to 100 per second) to reduce the signal-to-noise ratio. The software, which is based on LabVIEW, functioned as a controlling unit for the reaction parameters and as an evaluating system of the data produced. Every 10 seconds, the pressure curve, averaged over 2.5 s, was transferred to the PC and automatically integrated in the interesting time domains, which are directly correlated to the position of the sound origin and the concentration. For the resonance setup we used the same laser as for the free-field setup. For data collection we used self-built amplifiers and small electret microphones. The amplification was automatically done by a commercial Lock-In amplifier (model 5105 EG&G) with the TTL signal of the laser as a reference. Data collection and process conditions were controlled by LabVIEW. GC experiments were performed on two HP 6940 GCs operated in series.

ODH experiments were carried out under a constant flow of 37.5 mL min^{-1} of 2% ethane in air with 50 mg of catalyst. The temperature was increased in steps of 50°C and maintained for 30 min at each temperature. CO oxidations were carried out in a flow of 12.5 mL min^{-1} of 3% CO in air. Temperature was constantly raised by 1°C min^{-1} .

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of **7** were oxidized to the sulfones, from which the allyl bromides were prepared by employing the Appel reaction. Finally, the bromine atom and the sulfonyl group were removed by reductive elimination. Scheme 3 illustrates this reaction sequence with the intermediate products **8–10**, the isomers of which (two in the case of **8** and **9** and three in the case of **10**) analogously served as precursors of **1**.



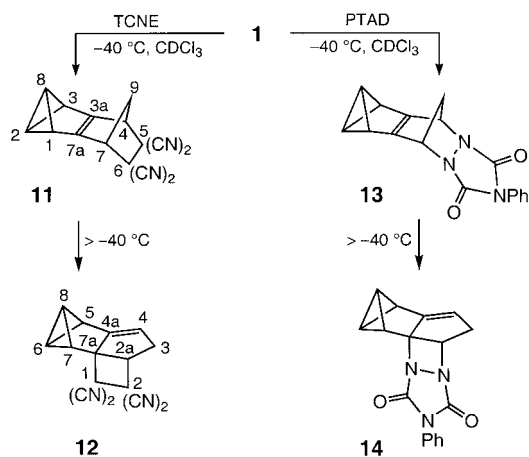
Scheme 3. Synthesis of **1** from **7**. Reagents and conditions: a) diisobutylaluminum hydride, petroleum ether (b.p. 40–65 °C)/dichloromethane 5:1, 0–5 °C; besides **8**, its stereoisomer (34–38 %, from **7a**) and its regioisomer (7–9 %, from **7b**) are formed (yields apply to the total amount of the 10:1 mixture of **7a** and **7b** employed); all isomers have been obtained pure by flash chromatography on SiO₂. b) *m*-Chloroperbenzoic acid, dichloromethane, –20 °C; c) P(NMe₃)₃, CBr₄, NEt₃, THF, –20 °C to +20 °C (30 min) and then 60 °C (20 h); besides **10**, its stereoisomer and a regioisomer were formed in small amounts; d) Na/Hg (3 % Na), THF/MeOH 3:1, –20 °C.

Initially, a tautomer of **1** should result from **10** and its isomers. The observation of only **1** characterizes it as the most stable species. The tautomer having a double bond between the bridgehead positions 3a and 6a should be the second intermediate. Burger et al.^[10] obtained a small amount of this compound and described it as stable at low temperatures. The ¹H NMR spectrum of **1** shows the peculiarity of an interaction through six bonds, which leads to line distances of about 1.8 Hz in the signals of H2, H7, and H5 (Table 1).

The reactions of **1** with dimethyl acetylenedicarboxylate (20 °C), (*E*)-bis(phenylsulfonyl)ethene (20 °C), and 1,2-dihydrobenzene (–40 °C) yielded the aromatized isomers instead of the Diels–Alder adducts. Probably, the benzvalenes were formed initially, but rearranged subsequently, although unsubstituted benzvalene has a half life of 48 h at 30 °C.^[11]

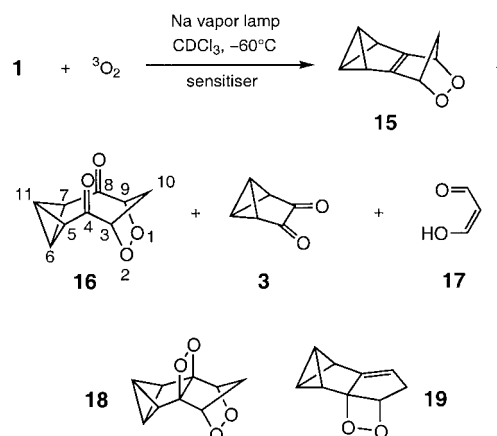
When we treated **1** at –40 °C with tetracyanoethene (TCNE) and 4-phenyl-1,2,4-triazole-3,5(4*H*)-dione (PTAD), the benzvalenes **11** (Table 1) and **13**, respectively, were observed at low temperature, but on warming up transformed to the formal [2+2] cycloadducts **12** (Table 1) and **14** (Scheme 4), probably via zwitterionic intermediates. Compounds analogous to **12** and **14** have been obtained by the reaction of 1,2,3,5-tetrahydro-1,3-methanopentalene with TCNE and PTAD, without the Diels–Alder adducts having been observed.^[12]

The reaction of **1** with an excess of singlet oxygen (¹O₂) in CDCl₃ at –60 °C gave the dioxoninedione **16** (Table 1), the α-diketone **3**, and the *cis*-enol of malondialdehyde (**17**).^[13] By using an internal standard the yields of **16**, **3**, and **17** have been determined to be 14, 16, and 11 %, respectively. Use of a smaller amount of oxygen allowed the observation of the



Scheme 4. Products of the reactions of **1** with TCNE and PTAD.

Diels–Alder adduct **15** (ratio **15**:**16**:**3**:**17**:**1** = 3.1:2.1:1.5:1.1:1.0) (Scheme 5). During the recording of NMR spectra at –40 °C the product ratio did not change over several hours, but **15** and **16** decomposed unspecifically at higher temperatures.



Scheme 5. Products of the reaction of **1** with ¹O₂ and possible intermediates en route to **3**, **16**, and **17** (sensitizer = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin).

We assume that **15** reacts with ¹O₂ to give the 1,2-dioxetane **18**, which, in competing processes, turns into **16** on one hand as well as **3** and **17** on the other. Whilst the transition **18**→**16** corresponds to the standard process of 1,2-dioxetanes,^[14] the formation of **3** and malondialdehyde, brought about by the rupture of four bonds, seems to be without precedent. The most closely related process is the generation of succinaldehyde and ethene on flash vacuum thermolysis of 2,3-oxabicyclo[2.2.2]octane, which involves the cleavage of only three bonds.^[15] Alternatively, the dioxetane **19** could serve as a precursor to **3** and **17**. To that end, it would have to combine with ¹O₂ to afford a bis(dioxetane) or to undergo a [2+2] cycloreversion resulting in an α,β-unsaturated ketone carrying an aldehyde functionality, which would in turn have to yield a further dioxetane on addition of ¹O₂. The cleavage of these dioxetanes would clearly account for the formation of **3** and **17**, however, neither the reaction of 1,3-dienes with ¹O₂ to give bis(dioxetanes) nor the addition of ¹O₂ to α,β-unsatu-

rated ketones is known.^[14] Since **15** does not rearrange to **19** at -40°C , **19** would have to be generated parallel to **15** and to be subject to a subsequent reaction immediately. We believe this to be highly unlikely, since simple dioxetanes are frequently observable or even isolable,^[14] which also applies to the dioxetane accessible from unsubstituted benzvalene.^[16]

Lacking direct structural information, we performed a quantum-chemical calculation (UB3LYP/cc-pVDZ)^[17] of **20**, the parent hydrocarbon to **11**. The geometry of the energy minimum is shown in Figure 1. In particular, the projection in the direction of the double bond illustrates its pyramidalization, which has a value of 21.2° and thus amounts almost to that of a *syn*-sesquinorbornatriene (22.7°)^[2c]

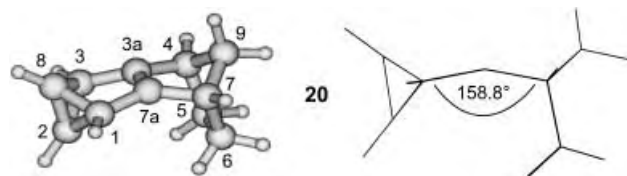
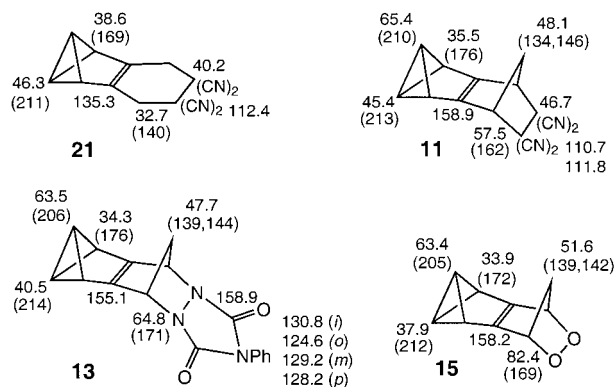


Figure 1. Quantum-chemical calculation of the minimum geometry of 2,3,4,5,6,7-hexahydro-4,7-methano-1,2,3-metheno-1*H*-indene (**20**): perspective view (left) and projection in the direction of the double bond (C3a–7a, right).

As a possible consequence of the pyramidalization, we consider the exceptionally large differences between the chemical shifts of the bicyclobutane bridgehead carbon atoms of **11**, **13**, and **15** (20.0, 23.0, and 25.5 ppm, respectively, Scheme 6). Moreover, the olefinic carbon atoms experience a strong deshielding. The comparison of the data of the ordinary benzvalene **21**^[18] with those of **11** emphasizes the unusual character of the benzvalene subunits of **11**, **13**, and **15**.



Scheme 6. ^{13}C chemical shifts and one-bond C,H coupling constants (in parentheses) of benzvalene derivatives: CDCl_3 , -40°C for **11**, **13**, and **15**; $(\text{CD}_3)_2\text{CO}$, 24°C for **21**.

In conclusion, a challenging synthetic goal has been achieved by the preparation of the title compound **1**. It is a cyclopentadiene derivative, the Diels–Alder adducts of which are highly reactive and hence observable at best at low temperatures. Further, we anticipate interesting properties for the cyclopentadienyl anion of **1**.

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- [18] F. Lanzendörfer, M. Christl, *Angew. Chem.* **1983**, *95*, 896–897; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 871–872; different from the published value (3.0 Hz), the coupling constant between the central and the lateral bicyclo[1.1.0]butane protons of **21** has a value of only 1.5 Hz.

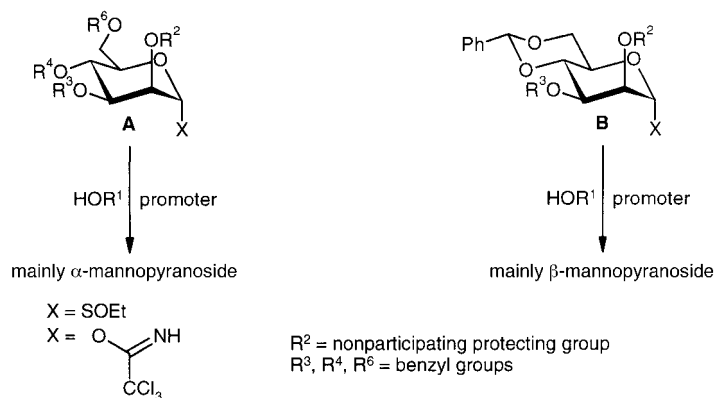
Stereoselective Synthesis of β -D-Mannopyranosides with Reactive Mannopyranosyl Donors Possessing a Neighboring Electron-Withdrawing Group**

Adel A.-H. Abdel-Rahman, Simon Jonke, El Sayed H. El Ashry,* and Richard R. Schmidt*

Dedicated to Professor Wolfgang Pfeleiderer on the occasion of his 75th birthday

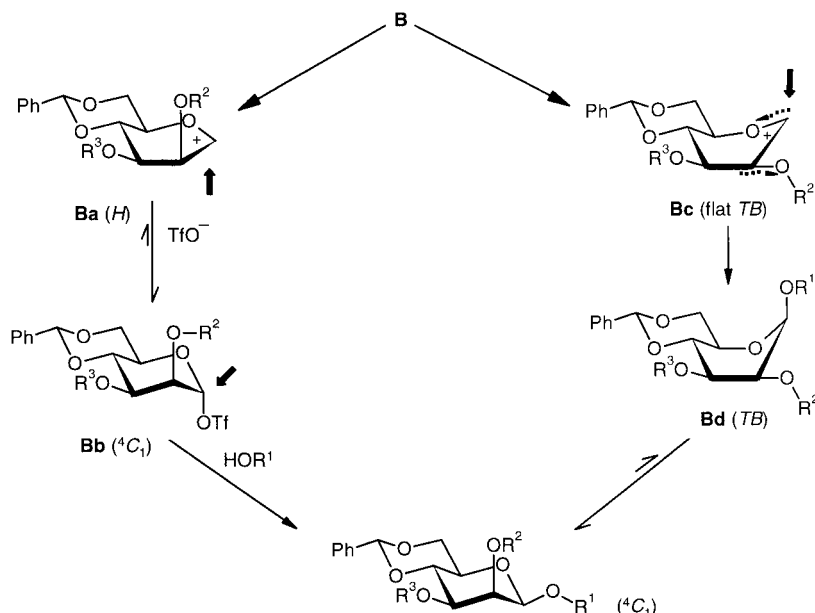
The presence of β -linked mannopyranosides in various natural products,^[1] particularly in the N-glycan core structure of glycoproteins,^[1,2] led to the search for efficient methodologies for producing this difficult target structure. Above all, mannopyranosyl donors **A** (Scheme 1), with nonparticipating protecting groups and different leaving groups X, were investigated for their β selectivity. However, in general, α products were obtained.^[1,3–5] Several specific methods^[6–12] have led to some success in this endeavour. Finally epimerization of β -glucopyranosides to β -mannopyranosides through an S_N2 reaction^[12–16] and intramolecular aglycon delivery^[17–19] appeared to be the method of choice.

Mannopyranosyl donors with diol O-protecting groups, which lead to ring annelation, had already been investigated, but again with limited success.^[20] However, the use of 2,3-di-O-alkyl-4,6-O-benzylidene-protected mannopyranosyl sulfoxides as donors (Scheme 1, **B**) gave preferentially β products with various acceptors at low temperatures.^[21] The same result is more conveniently achieved with trichloroacetimidate leaving groups, because these mannopyranosyl donors are highly reactive and accessible to activation with catalytic amounts of trimethylsilyltrifluoromethanesulfonate (TMSOTf).^[22] The results obtained on varying the reaction parameters in this reaction are not compatible with the reaction mechanism proposed for sulfoxide activation,^[22] in which α -triflate intermediate **Bb**, formed via intermediate **Ba** (with a half-chair conforma-



Scheme 1. Preferred α - and β -mannopyranoside synthesis.

tion), is thought to play a decisive role (Scheme 2).^[21] Rather, the anomeric stereocontrol is caused by a conformational effect enforced by the 4,6-O-benzylidene group on the pyranosyl ring, which thus favors the generation of a flattened



Scheme 2. Mechanistic proposals for preferred β -mannopyranoside formation. TB = Twist-Boat conformation, H = half-chair conformation.

twist-boat conformation **Bc** as the intermediate.^[22] For stereoelectronic and steric reasons, **Bc** will be preferentially attacked from the β side, which gives a twist-boat intermediate **Bd** that equilibrates to the $^4C_1$ conformer. This mechanistic proposal reconciles all results thus far found with different 4,6-O-benzylidene protected mannopyranosyl donors.

Based on these mechanistic considerations, β -mannopyranoside formation should be facilitated by nonparticipating, strongly electron-withdrawing groups R^2 at the 2-O atom (Scheme 2), because generation of the twist-boat intermediate **Bc** would gain from a strong dipole effect, as indicated by the dotted arrows in **Bc**. Earlier investigations with 2-O-mesyl- and 2-O-benzylsulfonyl-mannopyranosyl chlorides and tosylates as donors with some simple acceptors led to formation of the preferential β product,^[23,24] which supports

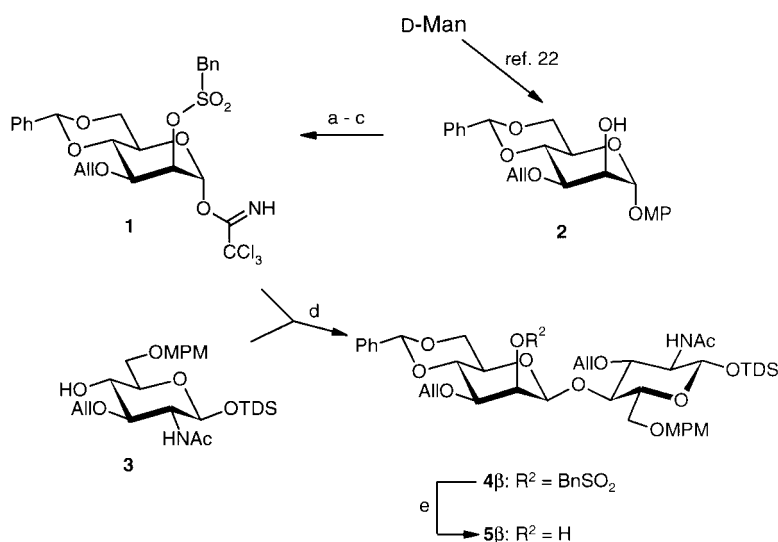
[*] Prof. Dr. R. R. Schmidt, Prof. Dr. A. A.-H. Abdel-Rahman, S. Jonke
Department of Chemistry
University of Konstanz
78457 Konstanz (Germany)
Fax: (+49) 7531-88-3135
E-mail: Richard.Schmidt@uni-konstanz.de
Prof. Dr. E. S. H. El Ashry
Department of Chemistry
Faculty of Science, Alexandria University
Alexandria (Egypt)
Fax: (+20) 3-4271360
E-mail: eelashry@link.net

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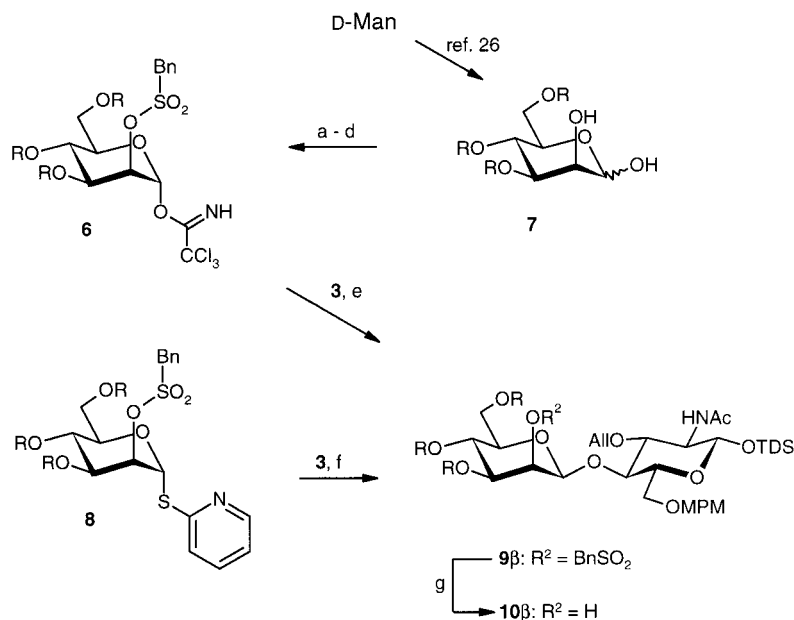
our postulate. However, to demonstrate the potential of this direct approach to β -mannopyranoside synthesis 1) an excellent leaving group at the glycosyl donor, 2) success with an important acceptor, and 3) successful removal of the strong electron-withdrawing 2-*O*-protecting group are required. These preconditions are met by the method outlined herein.

For our study 3-*O*-allyl-2-*O*-benzylsulfonyl-4,6-*O*-benzylidene-protected mannopyranosyl trichloroacetimidate (**1**) was selected as the donor because this is a properly protected building block for the glycopeptide N-glycan synthesis^[16] (Scheme 3). Compound **1** was synthesized from readily available methoxyphenyl (MP) mannopyranoside (**2**).^[22] Treatment with benzylsulfonyl chloride in pyridine followed by removal of the MP group with ceric(III) ammonium nitrate (CAN) in a mixture of acetonitrile/water at 0°C, and then reaction with trichloroacetimidate in the presence of DBU as the base afforded **1** in a high overall yield. Coupling of donor **1** (1.5 equiv) with 4-*O*-unprotected glucosamine derivative **3**^[25] as the acceptor (1 equiv), in dichloromethane at -50°C and in the presence of TMSOTf as the catalyst, under inverse conditions afforded, as hypothesized, mainly the β (1-4)-linked disaccharide **4 β** (80% based on **3**, β : α =8:1); the mixture of anomers could be readily separated by flash column chromatography. The benzylsulfonyl group was removed by treating **4 β** with a solution of sodium amide in DMF at room temperature,^[23f] which afforded 2-*O*-unprotected **5 β** in 91% yield.

Because of the principal importance, 2-*O*-benzylsulfonyl-3,4,6-tri-*O*-benzyl-protected mannopyranosyl trichloroacetimidate (**6**) (Scheme 4) was also investigated in β -mannopyranoside synthesis. The strong dipole effect enforced by the benzylsulfonyl group should favor formation of the twist-boat intermediate of type **Bc** (Scheme 2) even in the absence of the 4,6-*O*-benzylidene ring, and thus lead to β product formation. The required donor **6** was prepared from 3,4,6-tri-*O*-benzyl-D-mannose (**7**)^[26] by regioselective anomeric-O-silylation^[11] with thexyldimethylsilyl (TDS) chloride in the presence of imidazole; the ensuing reaction with benzylsulfonyl chloride in pyridine, removal of the TDS group with tetrabutylammonium fluoride (TBAF) in THF, and then treatment with trichloroacetimidate in the presence of DBU afforded the donor **6** in high overall yield. Coupling **6** with acceptor **3** under the above-described conditions led to even better results than **1**, and mainly afforded β -linked disaccharide **9 β** (82%, **9 β** :**9 α** 9:1). Similar results were obtained with the corresponding mannopyranosyl donor **8**,^[27] presumably, because of the lower reactivity, the β : α -ratio was somewhat decreased (78%, **9 β** :**9 α** 7:1). The 2-*O*-benzylsulfonyl group ($\rightarrow$ **10 β**) was again removed in high yield.^[28]



Scheme 3. Synthesis of **4** from **1**; a) BnSO_2Cl , pyr (91%); b) CAN, MeCN/ H_2O (4:1), 0°C (82%); c) CCl_3CN , 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (94%); d) TMSOTf, CH_2Cl_2 , -50°C (80% β : α =8:1); e) NaNH_2 , DMF, RT (91%). All = allyl; MPM = *para*-methoxybenzyl.



Scheme 4. Synthesis of Man β (1-4)GlcNAc disaccharide from **6** and **8** ($\text{R} = \text{Bn}$); a) TDS-Cl, imidazole, DMF (95%); b) BnSO_2Cl , pyr (92%); c) TBAF, THF (90%); d) CCl_3CN , DBU, CH_2Cl_2 (97%); e) TMSOTf, CH_2Cl_2 (82%; β : α =9:1); f) TMSOTf, CH_2Cl_2 (78%, β : α =7.4:1); g) NaNH_2 , DMF, RT (93%).

The α and β configuration of the disaccharides **4 α , β** , **5 α , β** , **9 α , β** , and **10 α , β** , could be assigned with the $^1J_{\text{IC,1H}}$ coupling constants of the anomeric protons. As expected,^[29] these values are 174.1–175.7 Hz for the α anomers and 162.3–163.6 Hz for the β anomers.

In conclusion, a convenient and highly efficient method for the synthesis of β -mannopyranosides is introduced. The mannopyranosyl donors possess a strongly electron-withdrawing 2-*O*-benzylsulfonyl group and a trichloroacetimidate or pyridylthio group, respectively, as the leaving group at the anomeric center. The deprotection of the 2-*O*-benzylsulfonyl group was readily performed; thus, in addition, an often

advantageous selective access to the 2-hydroxy group of the mannose residue is provided.

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- [25] **3**: TLC (petroleum ether:ethyl acetate, 2:1) $R_f = 0.54$; $[\alpha]_D = -6.5^\circ$ ($c = 1.0$, chloroform); $^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta = 0.02$ (s, 3H; CH_3), 0.09 (s, 3H; CH_3), 0.80, 0.82, 0.84, 0.86 (4s, 12H; 4 CH_3), 1.20–1.34 (m, 1H; CH), 1.98 (s, 3H COCH_3), 3.21 (m, 1H; 2-H), 3.45 (m, 1H; 4-H), 3.56 (m, 1H; 5-H), 3.73–3.81 (m, 4H; 6-H, OCH_3), 4.10–4.21 (m, 3H; 6'-H, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.35–4.40 (m, 3H; 3-H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.28 (d, $J = 7.8$ Hz, 1H; 1-H), 5.48 (s, 1H; CH_2Ar), 5.56–5.63 (m, 2H; NH, $\text{CH}_2\text{CH}=\text{CH}_2$), 7.03 (d, $J = 7.5$ Hz, 2H; Ar-H), 7.34 ppm (d, $J = 7.4$ Hz, 2H; Ar-H); FAB-MS: (positive mode, NBOH/Nal-matrix); m/z : 524 $[\text{MH}^+]$, 546 $[\text{MNa}^+]$.
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- [27] **8**: TLC (petroleum ether:ethyl acetate, 3:1) $R_f = 0.53$; $[\alpha]_D = +111^\circ$ ($c = 0.2$, chloroform); $^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta = 3.70$ (d, $J = 11.0$ Hz, 1H; 6-H), 3.85 (dd, $J = 4.0, 11.2$ Hz, 1H; 6-H), 3.99 (dd, $J_{3,2} = 3.2$ Hz, $J_{3,4} = 9.3$ Hz, 1H; 3-H), 4.15 (t, $J = 9.6$ Hz, 1H; 4-H), 4.16 (m, 1H; 5-H), 4.45 (d, $J = 11.9$ Hz, 1H; CH_2), 4.53 (d, $J = 10.7$ Hz, 1H; CH_2), 4.55 (d, $J = 11.2$ Hz, 1H; CH_2), 4.59 (s, 2H; SO_2CH_2), 4.66 (d, $J = 11.9$ Hz, 1H; CH_2), 4.75 (d, $J = 11.2$ Hz, 1H; CH_2), 4.80 (d, $J = 10.9$ Hz, 1H; CH_2), 5.66 (m, 1H; 2-H), 6.45 (d, $J = 1.8$ Hz, 1H; 1-H), 7.19 (d, $J = 7.0$ Hz, 1H; Ar-H), 7.23 (d, $J = 7.1$ Hz, 1H; Ar-H), 7.25–7.33 (m, 20H; 4 Ph), 7.50 (d, $J = 7.1$ Hz, 1H; Ar-H), 8.50 ppm (d, $J = 6.0$ Hz, 1H; Ar-H); MALDI-MS: m/z : 720 $[\text{MNa}^+]$.
- [28] **10b**: TLC (petroleum ether:ethyl acetate, 5:1) $R_f = 0.34$; $[\alpha]_D = +53.1^\circ$ ($c = 0.1$, chloroform); $^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta = 0.12$ (s, 3H; CH_3), 0.23 (s, 3H; CH_3), 0.85–0.89 (m, 12H; 4 CH_3), 1.64–1.71 (m, 1H; CH), 1.98 (s, 3H; COCH_3), 3.31 (m, 1H; 2_a-H), 3.50 (m, 1H; 4_a-H), 3.56 (m, 1H; 5_a-H), 3.66–3.71 (m, 10H; 2_b-H, 3_b-H, 4_b-H, 2 6_a-H, 2 6_b-H, OCH_3), 4.01–4.19 (m, 4H; 3_a-H, 5_b-H, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.48 (m, 2H; CH_2), 4.52–4.68 (m, 9H; 1_b-H, 3 CH_2 , $\text{CH}_2\text{CH}=\text{CH}_2$), 5.44–5.58 (m, 3H; 1_a-H, NH, $\text{CH}_2\text{CH}=\text{CH}_2$), 7.09 (d, $J = 7.5$ Hz, 2H; Ar-H), 7.16 (d, $J = 7.5$ Hz, 2H; Ar-H), 7.22–7.33 ppm (m, 15H; 3Ph); MALDI-MS: m/z : 979 $[\text{MNa}^+]$.
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ULTRA Loaded Resins Based on the Cross-Linking of Linear Poly(ethylene imine). Improving the Atom Economy of Polymer-Supported Chemistry**

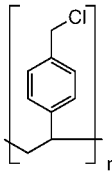
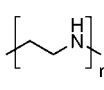
Jörg Rademann* and Michael Barth

Employing insoluble polymer supports for chemical transformations belongs to the most important and far-reaching innovations in organic chemistry during the last decades.^[1] The method had enormous impact as it not only revolutionized the synthesis of peptides, oligonucleotides, heterocycles, and other molecule classes, but also triggered the evolution of combinatorial methods in chemistry and biochemistry.^[2] In recent years, polymer supports have found broad application in solid-supported solution-phase syntheses as well.^[3]

To date the vast majority of solid-supported chemistry is conducted on cross-linked, swellable polymeric gels; most often polystyrene gels are employed.^[4] If increased polarity of the resin is required, polystyrene grafted with poly(ethylene glycol) (PEG) is preferred.^[5] By cross-linking of PEG chains, biocompatible supports are obtained that can be penetrated by small to medium-sized biological macromolecules; these polymers are of great interest for biological assays.^[6]

One major drawback of the current methods of solid-supported chemistry with conventional resins^[8] is the low atom economy^[7] in comparison to solution-phase synthesis; this disadvantage excludes solid-supported methods from many resource- and cost-sensitive applications such as scale-up projects. Polystyrene resins are further restricted in the choice of solvents, thermal and chemical stability, and extensive adsorption of reagents.^[9]

We anticipated that a novel class of resins constructed of low molecular-weight monomers with efficient functionalization sites at each monomer would greatly enhance the resin capacity. Poly(ethylene imines) (PEI)^[10] possess a loading of 23 mmol g⁻¹ amines, thus ULTRA resins based on the cross-linking of PEI could permit solid-phase chemistry with significantly higher atom economy than conventional polymers (Scheme 1). Linear poly(ethylene imine) (**1**) was selected as the polymeric starting material, which allowed control over the degree of cross-linking and the degree of amine

			
M_{monomer} [g mol ⁻¹]	152.5	44	43
loading [mmol g ⁻¹]	6.6	22.7	23.3

Scheme 1. Potential building blocks for ULTRA loaded resins based on poly-(4-chloromethyl styrene), poly(vinyl alcohol) (PVA), and poly(ethylene imine) (PEI).

substitution in the resin product. ULTRA resins were also prepared from tetraethylene pentamine, a well-defined, linear-PEI fraction.

Polyaldehydes, polyacids, and polyvalent alkylating agents were investigated for cross-linking. Polyaldehydes, which furnish the resin structure through a thermodynamically controlled equilibrium reaction, were found to be superior, allowing the preparation of resins with robust methods from inexpensive and easily available precursors. Reducing the condensation product of linear poly(ethylene imine) (**1**) with terephthalic dialdehyde (**2**) afforded the chemically, mechanically, and thermally robust ULTRA resin (**3**; Scheme 2).^[11] A support prepared from a molar ratio of 1.67 dialdehydes per PEI chain was selected for detailed characterization and synthetic studies. Resin micropellets of a defined size range were generated by polymer extrusion in the swollen state, followed by sieving.

Whereas polymeric salt **4** swelled only slightly in organic solvents, in water it extended to the remarkable gel volume of 180 mL g⁻¹,^[12] larger than any of the commercially available resins and suggesting the possible penetration of the resin by large molecules. The free-amine resin **3**, as was the case with the chemically derivatized resins **5–10** and **12–14**, displayed swelling volumes between 3–8 mL g⁻¹ in various solvents—useful for polymer-supported chemistry (Scheme 3). Spectroscopic resin analysis was conducted by FT-ATR-IR, ¹³C suspension NMR, and ¹H magic-angle-spinning (MAS) suspension NMR spectroscopy, which revealed the absence of aldehyde, alcohol, and primary amine functionalities in the resin network of **3**; this indicates complete cross-linking and reduction of the imine groups. The ratio of PEI to the cross-linker (1.55) was derived from the integrated ¹H NMR spectrum and was consistent with the starting mixture; the ratio of secondary to tertiary amines in **3** was calculated from the ratio of PEI to cross-linker to be 8:1.

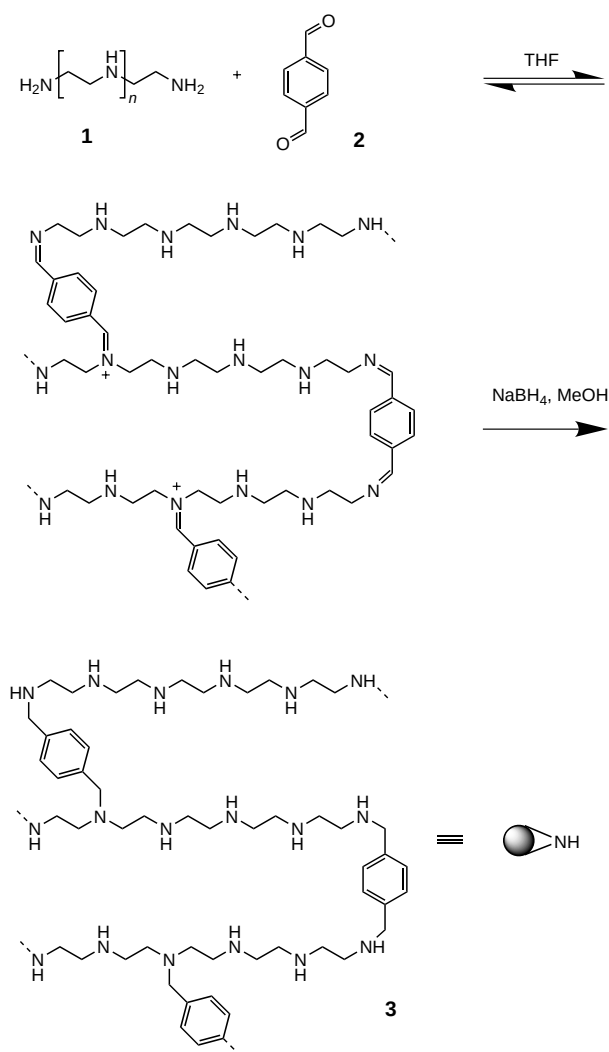
Accessibility of the secondary amines in ULTRA resin **3**—a crucial prerequisite for successful polymer-supported chemistry—was investigated by acylation (**5** and **10**), nitrosylation (**6**), and alkylation reactions (**7–9**; Scheme 3). Efficient reactions were indicated by the complete removal of the band arising from the NH group in the IR spectrum, consistent weight increase of the resins, and by elemental analysis.

[*] Dr. J. Rademann, Dipl.-Chem. M. Barth
Institute for Organic Chemistry
University of Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49) 7071-295-560
E-mail: joerg.rademann@uni-tuebingen.de

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



Scheme 2. Preparation of ULTRA resin **3** from **1** and **2**.

ULTRA resins were employed for the preparation of polymeric reagents as well as for solid-phase synthesis. ULTRA resin **4** can be directly employed as a polymeric base with a loading of 15.2 mmol g^{-1} . Following reductive amination with formaldehyde, resin **7**, containing 13.2 mmol g^{-1} tertiary amines, was obtained. ULTRA resin **8** for ion exchange was prepared by alkylation of **7** with methyl iodide; the maximum loading of the resin with chloride was 8 mmol g^{-1} , which corresponds to a chlorine content of 28%. The acylation catalyst **9** could be constructed from **3** by microwave-assisted synthesis at 220°C ^[17].

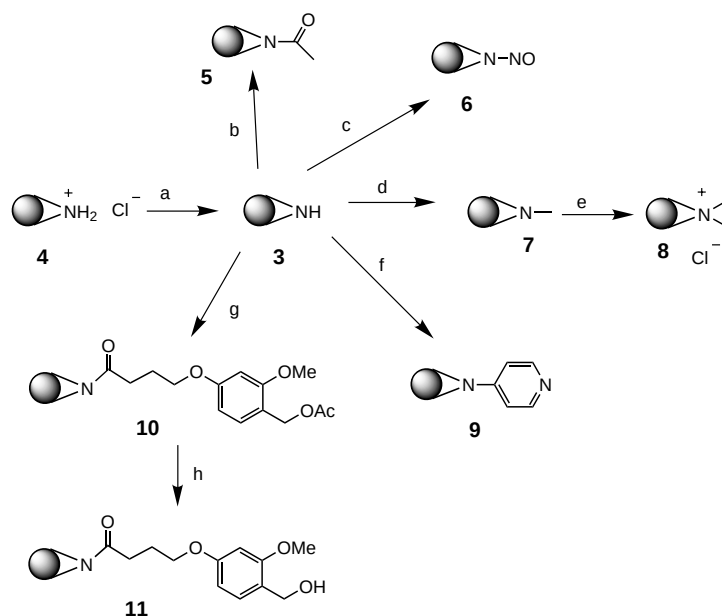
An ULTRA resin for solid-phase synthesis (**10**) was constructed by coupling resin **3** with 4-(4'-acetoxymethyl-3'-methoxy-phenoxy)butyrate. Following complete deacetylation (detected by IR), resin **12**, with a loading^[15] of 2.5 mmol g^{-1} , was employed in the synthesis of heterocycles as well as peptides. Pyrazole carboxylic acid **13** was prepared on **11** using a procedure^[13] established for Wang polystyrene without modification (Scheme 4). After three steps that were monitored by IR, 8.8 mg of product **13** were obtained from 5 mg of the starting ULTRA resin **3**

(80% purity of the crude product, 65% yield following chromatography).

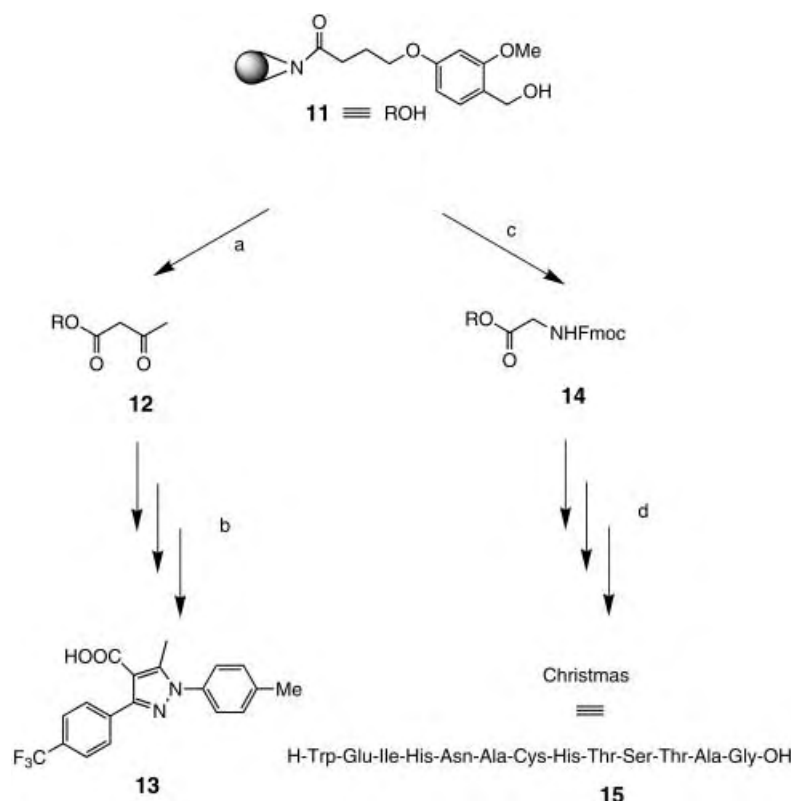
To investigate limitations in product size, several peptides of various lengths were synthesized on ULTRA resin **11**. Peptides with 7, 9, 13, and 19 amino acids were prepared on a synthesis robot employing Fmoc-protected amino acids and carbodiimide–hydroxybenzotriazole activation (0.25 M) without detection of deletion products. To illustrate the remarkable economy of the ULTRA resin, in this example 3.4 mg of the starting resin **4** sufficed for the synthesis of 42 mg resin with fully protected tridecapeptide. The crude product was obtained by trituration with diethyl ether in excellent purity and yield (90% purity in the crude product, 78%, 13.1 mg, following preparative HPLC).^[16]

In summary, ULTRA resins based on the cross-linking of linear PEI have been realized as a novel support concept with high potential for polymer-supported synthesis in solution as well as for solid-phase synthesis. In contrast to any of the currently available supports, which are obtained by radical, anionic, or cationic polymerizations, ULTRA resin **3** is formed under thermodynamic control in an equilibrating reaction system with potentially significant implications for polymer structure and properties.

ULTRA resins were prepared with extremely high loading compared to the standard resins in use today. The secondary amine groups of the resin were very accessible to various efficient derivatizations and even larger product molecules could be assembled successfully in the resin interior. Thus, the resins allow solid-supported chemistry with greatly improved atom economy and could be a significant contribution to the efficient scale-up of polymer-supported syntheses. Extended



Scheme 3. Accessibility of ULTRA resin **3** investigated by chemical derivatization: a) 1. 2 M NaOH, 2. triethylamine, DMF; b) Ac_2O , pyridine; c) NaNO_2 , HOAc, water; d) CH_2O , NaCNBH_3 ; e) 1. MeI, 2. HCl, water; f) 4-chloropyridinium chloride, diisopropylethylamine (DIPEA), DMF, 220°C , 10 min, microwave irradiation; g) 4-(4-acetoxymethyl-3-methoxyphenoxy)butyric acid, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBUTU), DIPEA, DMF (2 ×); h) NaOMe, MeOH.



Scheme 4. Synthesis of pyrazole carboxylic acids and peptides on linker-functionalized ULTRA resin **11**; a) diketene, *N,N*-dimethyl-4-aminopyridine (DMAP);^[12] b) 1. 3 equiv 4-trifluoromethyl benzaldehyde, DIPEA, *N*-methylpyrrolidin-2-one (NMP), 16 h, 2. 3 equiv 4-methylphenylhydrazinium hydrochloride, 3. $\text{CH}_2\text{Cl}_2/\text{HOAc}$, 30 min, 4. TFA/water 95:5. c) Fmoc-Gly-OH, 2-mesitylenesulfonyl-3-nitro-1*H*-1,2,4-triazole (MSNT), *N*-methylimidazole, CH_2Cl_2 , 2 $\times$ 2 h; d) 1. amino acid coupling: protected Fmoc amino acid, *N,N*-diisopropylcarbodiimide (DIC), 1-hydroxybenzotriazole (HOBt), DMF, 2. amine deprotection: 20% piperidine, DMF, 3. TFA, water (5%), triisopropylsilane (2.5%), ethanedithiol (2.5%).

synthetic investigations will scrutinize further the potential of PEI-based ULTRA resins as well as variations of this concept starting from alternative starting primary polymers and cross-linkers.

Experimental Section

Linear poly(ethylene imine) (**1**): Elemental analysis: C 53.1, H 11.9, N 34.5. C/N = 1.54. The degree of polymerization (*n*) was calculated from the C/N ratio ($n = 0.583/(\text{N/C} - 0.583)$) and was 8.74 corresponding to an average molecular mass of $M_n = 393.5 \text{ g mol}^{-1}$ ($M_n = 43.07n + 17.03$). M_n was specified by the supplier as 423 g mol^{-1} .

Preparation of ULTRA resin **3**: **1** (4.17 g, Aldrich, $M_n = 393.5 \text{ g mol}^{-1}$, $n = 8.74$, 10.6 mmol, 103.2 mmol amine groups) was dissolved in THF (5 mL) in a 50 mL round-bottomed flask with magnetic stirring. **2** (2.38 g, 17.7 mmol) was added rapidly in THF (17.5 mL solution). After 30 s the flask had warmed to about 40 °C, after 4 min the stirrer bar ceased rotating because of increasing viscosity, after 6 min it remained stationary. The initially transparent polymer gel became opaque after 10 min. 3 h after initiation of the reaction the polymer was granulated in a mortar and reduced using NaBH_4 (1 g) in MeOH (100 mL) for 1 h. After quenching with water (100 mL), the polymer was filtered, washed (1M HCl, water, THF), and extruded through a metal sieve (400 μm pores) with the addition of MeOH. The resin was washed again (THF, CH_2Cl_2) on a ceramic filter (P3, ca. 40 μm max. pore size) and dried in vacuo over P_2O_5 yielding resin micropellets of a defined size range (4.8 g). The hydrochloride resin **3** was transformed to the free-amine resin **4** by swelling in 2M NaOH,

followed by washing with water, 20% triethylamine in DMF, DMF, THF, and CH_2Cl_2 .

3: ^1H NMR (250 MHz, D_2O , HR-MAS with 4500 Hz rotation): $\delta = 2.7\text{--}3.5$ (m, PEI- CH_2 , relative integration 100), 4.31 (bs, N- CH_2 -aryl, 14.6), 7.4–7.6 ppm (bs, aryl-H, 17.7). FT-ATR-IR: $\tilde{\nu} = 1443, 1590, 2768, 2950, 3371 \text{ cm}^{-1}$. Elemental analysis: C 41.9, H 8.0, N 14.5 (10.4 mmol g^{-1}), Cl 23.3.

4: ^{13}C NMR (62.9 MHz, D_2O , DEPT-135): $\delta = 49.7$ (CH_2), 54.5 (CH_2), 131.4 ppm (CH). FT-ATR-IR: $\tilde{\nu} = 1110, 1164, 1331, 1392, 1554, 2826, 2941, 3291 \text{ cm}^{-1}$. Elemental analysis: C 61.8, H 10.5, N 21.3 (15.2 mmol g^{-1}).

13: ^1H NMR (250 MHz, CDCl_3): $\delta = 2.36$ (s, 3H, PhMe), 2.52 (s, 3H, 5-Me), 7.25 (dd, 4H, 1-Ph), 7.60, 7.78 (2 d, 4H, 3-Ph). Calcd ($\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2$): 360.33 Da, found (ESI-MS, positive mode): 361.0 m/z ; (ESI-MS, negative mode): 359.0 m/z .

15: Calcd ($\text{C}_{60}\text{H}_{87}\text{N}_{19}\text{O}_{20}\text{S}_1$): 1425.61 Da, found (ESI-MS, positive mode): 1426.6 m/z .

Spectra of the ULTRA resins are provided in the Supporting Information.

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- [16] The efficiency of the acylation steps on the ULTRA resins was highlighted by the structure of the main by-product (6%), which was not a deletion product, but **15** + *tert*-butyl, an incompletely deprotected 13mer-peptide.
- [17] Microwave-assisted syntheses were performed on a SmithSynthesizer from Personal Chemistry AB, Uppsala, Sweden.

A Model Nucleoside for Electron Injection into DNA: 5-Pyrenyl-2'-Deoxyribose**

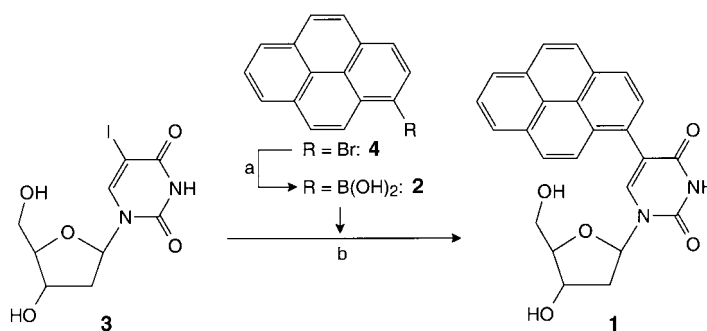
Nicole Amann, Evgeni Pandurski, Torsten Fiebig,* and Hans-Achim Wagenknecht*

Charge-transfer processes through DNA have been studied intensively in the past 15 years.^[1] It is important to emphasize, that in most of these experiments oxidative hole transfer has been observed. On the other hand, reductive electron transfer (ET) is currently used extensively in DNA chip technology^[2] and DNA nanotechnology^[3] without an understanding of the mechanism of this type of charge-transfer. Recently, Carell and co-workers described the repair of a thymine–thymine dimer by a distant flavine derivative, which was incorporated into the DNA as an artificial base.^[4] Despite the fact that spectroscopic measurements with this system have not been published, the cleavage of the thymine–thymine dimer was interpreted as the chemical result of a reductive ET through the DNA base stack. To date, suitable DNA assays for the

time-resolved spectroscopic investigation of reductive ET through DNA are elusive.

We present herein the synthesis and pH-dependent spectroscopic investigation of the ET in the model nucleoside 5-pyrenyl-2'-deoxyuridine (Py-dU, **1**). Pyrene derivatives have been used previously as artificial DNA bases by Kool et al.^[5] We chose a different approach and attached the pyrenyl group covalently to the uracil or thymine nucleobases. Excitation of the pyrene moiety at 340 nm leads to an intramolecular ET, which yields the corresponding uracil radical anion and the pyrenyl radical cation (Py⁺–dU[–]). This charge-transfer assignment has been proven previously by Netzel et al.^[6] Based on the reduction potential for the Py⁺/Py redox couple of 1.52 V (vs. normal hydrogen electrode)^[7] and $E_{00} = 3.25$ eV,^[6] the driving force ΔG of this ET process has a maximum value of –0.5 eV based on the potential of –1.2 V for the dU/dU[–] redox couple.^[8] However, this value of $|\Delta G|$ seems to be too large with respect to a recent femtosecond time-resolved study on the reduction of thymine, which suggests a potential of approximately –1.8 V for the dT/dT[–] redox couple.^[9] Based on steady-state fluorescence spectroscopy and nanosecond fluorescence lifetime measurements, it was proposed that ET from the photoexcited pyrene to the uracil moiety should be more favorable in MeOH than in MeCN because of a proton-coupled ET process.^[6] However, this hypothesis is in disagreement with the proposed pK_a value of 6.9 for the protonated uracil radical anion dU(H)[–] reported by Steenken.^[10] Therefore, the protonated radical dU(H)[–] represents a stronger acid than MeOH and cannot be protonated by this solvent. To elucidate the possibility of a proton-coupled ET in more detail, we chose water at different pH values and measured the steady-state fluorescence and time-resolved transient absorption spectra. An understanding of the protonation dynamics of radical anions of DNA bases is crucial to understand both ET and hole transfer through DNA. Moreover, to investigate the competition between ET to adjacent DNA bases and protonation by surrounding water molecules and/or hydrogen-bonded bases, it is particularly important to evaluate the applicability of **1** as an electron injector into DNA.

The nucleoside **1** was prepared by using the palladium-catalyzed Suzuki–Miyaura type cross coupling^[11] of pyren-1-ylboronic acid (**2**) to 5-iodo-2'-deoxyuridine (**3**) in a good yield of 79% (Scheme 1). Suzuki–Miyaura type couplings



Scheme 1. Synthesis of **1**: a) 1) *n*BuLi (1.1 equiv), Et₂O, 0°C, 30 min; 2) B(OCH₃)₃ (5.0 equiv), –78°C, 6 h, then room temperature, 20 h; 3) H₃O⁺, RT, 3 h, 73%; b) **2** (1.0 equiv), [Pd(PPh₃)₄] (0.1 equiv), NaOH (20 equiv), THF/MeOH/H₂O 2:1:2, reflux, 20 h, 79%.

[*] Dr. T. Fiebig, E. Pandurski
Institut für Physikalische und Theoretische Chemie
Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
Fax: (+49)89-289-13244
E-mail: fiebig@ch.tum.de
Dr. H.-A. Wagenknecht, N. Amann
Institut für Organische Chemie und Biochemie
Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
Fax: (+49)89-289-13210
E-mail: wagenknecht@ch.tum.de

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have been used for the preparation of arylated and alkenylated purines,^[12] but have not yet been used for the direct synthesis of aryl-modified nucleosides. In contrast to the published procedure of a Stille-type coupling of pyren-1-yl-(tributyl)-stannane to a fully protected 5-iodo-2'-deoxyuridine derivative in a glovebox,^[6] our synthetic approach has the advantage that the starting material **1** does not need to be protected. Furthermore, the Suzuki-type coupling works in aqueous solutions, which facilitates the synthetic procedure. Pyren-1-ylboronic acid (**2**) was synthesized by lithiation of 1-bromopyrene (**4**) and subsequent treatment with trimethyl borate and acidic workup.^[13] The structure of the nucleoside **1** was confirmed by mass spectrometry and by 2D NMR spectroscopy (e.g. DQF-COSY and HMQC).

In the nucleoside **1**, the two chromophores are linked covalently by a single C–C bond, thus resulting in strong electronic coupling between them. Such systems are generally characterized by intense, unstructured fluorescence bands with solvent-dependent spectral maxima. Such emissions indicate that efficient charge transfer (CT) takes place.^[14] As a result of this specific mode of interaction between pyrene and the attached chromophore, one can expect the formation of strongly fluorescent intramolecular CT states, which may be considered as intramolecular exciplexes. These exciplex states contain locally excited (LE, $\text{Py}^*\text{-dU}$) and CT ($\text{Py}^+\text{-dU}^-$) contributions. In fact, exciplex emission of **1** has been observed in organic solvents such as THF, MeCN, and MeOH.^[15]

Interestingly, the steady-state fluorescence spectra of **1** in water (ca. pH 8) displays mostly LE character (Figure 1 A, $\lambda_{\text{exc}} = 340$ nm). Furthermore, the observed emission is quenched completely at about pH 4. To evaluate the complete pH dependence, we measured the emission intensity of **1** at different pH values between 2 and 12 (Figure 1 B). The typical sigmoidal curve represents a $\text{p}K_{\text{a}}$ value of approximately 5.5 for the protonated $\text{Py}^+\text{-dU(H)}^+$ biradical. This value lower than the $\text{p}K_{\text{a}}$ value of 6.9 given by Steenken^[10] and possibly reflects the electronic influence of the directly attached pyrene moiety in **1**. The small loss of emission at pH values above 10 is probably a result of the deprotonation of the uracil moiety. Consequently, the redox properties of the model nucleoside are changed already in the ground state.

To characterize the products that are formed upon excitation of **1**, we measured the transient absorption spectrum in water at two different pH values (8 and 4), in both cases 13 ps after excitation (Figure 2). The spectra at both pH values show a strong absorption peak at around 475 nm, which is characteristic of Py^+ .^[16] In addition, a shoulder is observed in the spectrum (at pH 8) at around 505 nm, which provides evidence for Py^* .^[17] This shoulder is absent in the spectrum recorded at pH 4. Additional absorption bands at longer wavelength can be assigned to the radical product states involving the uracil moiety. Depending on the pH value, one can see clear differences in the intensity and spectral position of the bands which strongly suggests that the final products involve different uracil species.

Based on the steady-state fluorescence spectra and the femtosecond time-resolved pump-probe data, we conclude that ultrafast intramolecular ET occurs upon photoexcitation

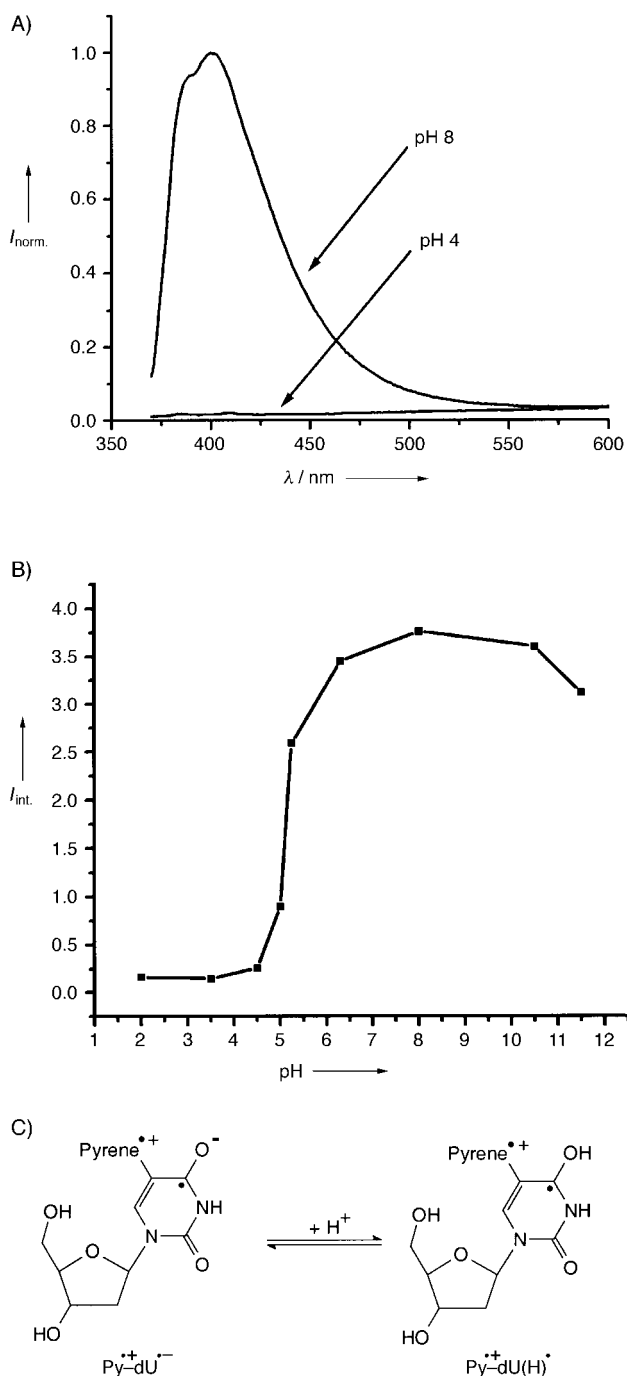


Figure 1. A) Steady-state fluorescence spectra of **1** (40 μM ; $\lambda_{\text{exc}} = 340$ nm) in water at pH 8 and pH 4; B) pH dependence of the fluorescence intensity; C) the emission is quenched completely at pH < 5 as a result of the protonation of the uracil radical anion.

of **1**, independent of the pH value. Moreover, the charge-separated species that is initially formed ($\text{Py}^+\text{-dU}^-$) is not fluorescent and equilibrates with the fluorescent LE form $\text{Py}^*\text{-dU}$ (Scheme 2). The dU^- moiety can only be protonated in the presence of excess protons. This important observation excludes a proton-coupled ET mechanism, which means that protonation is not a prerequisite for ET. However, the transient absorption spectra show significant differences in the spectral range between 500 and 700 nm at pH 4 and pH 8, which suggests that a proton-transfer step occurs after ET.

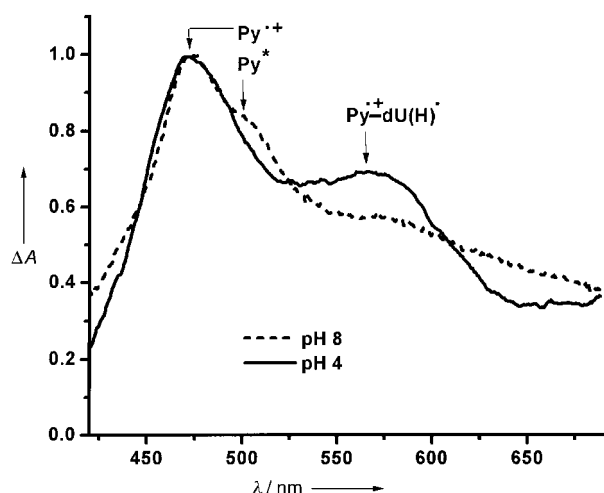
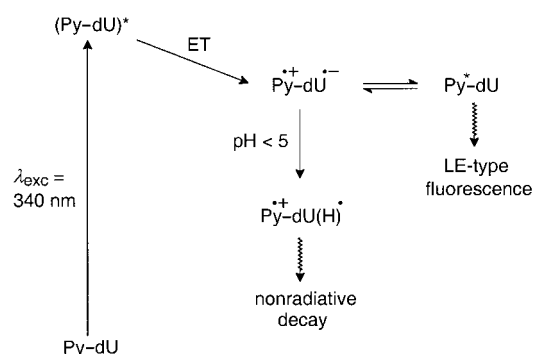


Figure 2. Transient absorption spectra of **1** in water (400 μ M) at pH 8 and pH 4, obtained 13 ps after excitation.



Scheme 2. Summary of the processes that occur in **1**: Excitation of **1** (Py-dU) at 340 nm results in intramolecular ET. The charge-separated species ($\text{Py}^{\bullet+}\text{-dU}^{\bullet-}$) itself is not fluorescent, but equilibrates with the fluorescent $\text{Py}^{\bullet-}\text{-dU}$ form. At pH < 5, the fluorescence is quenched as a result of the protonation of the uracil radical anion which yields $\text{Py}^{\bullet+}\text{-dU(H)}^{\bullet}$.

From the temporal evolution of the spectra (data not shown) we estimate the rate of protonation to be similar to the rate of charge transfer, that is, in the order of 100 fs.

Finally, we observed strong differences in the lifetimes of $\text{Py}^{\bullet+}\text{-dU}^{\bullet-}$ by its transient absorption, depending on the pH value. At pH 8, the ET intermediates show a lifetime in the range of several nanoseconds, whereas at pH 4 the transient absorption has decayed almost completely after 100 ps.

In summary, we have characterized the dynamics and pH dependence of the ET in the model nucleoside **1**. The intramolecular ET is an ultrafast process, $\text{Py}^{\bullet+}\text{-dU}^{\bullet-}$ can already be observed a few picoseconds after excitation in water. The pK_a value of the protonated $\text{Py}^{\bullet+}\text{-dU(H)}^{\bullet}$ biradical has been determined by steady-state fluorescence to be about 5.5. This value shows clearly that neither water in the environment of the nucleoside nor H-bonding donors such as the complementary DNA bases are able to protonate the uracil radical anion $\text{dU}^{\bullet-}$. Furthermore, our results suggest that reductive ET through DNA is not coupled to protonation. At pH values above 7, the lifetime of $\text{Py}^{\bullet+}\text{-dU}^{\bullet-}$ is in the nanosecond range. Assuming only a small change in the free energy of this ET process within DNA duplexes, the nucleo-

side **1** should be a suitable electron injector, as ET to adjacent DNA bases probably occurs on a subnanosecond timescale.

Experimental Section

The synthesis of 5-(1-pyrenyl)-2'-deoxyuridin (**1**) and a brief description of the laser setup is provided in the Supporting Information. Steady-state fluorescence spectra were obtained with a Fluoromax-3 fluorimeter (Jobin Yvon) and were intensity-corrected.

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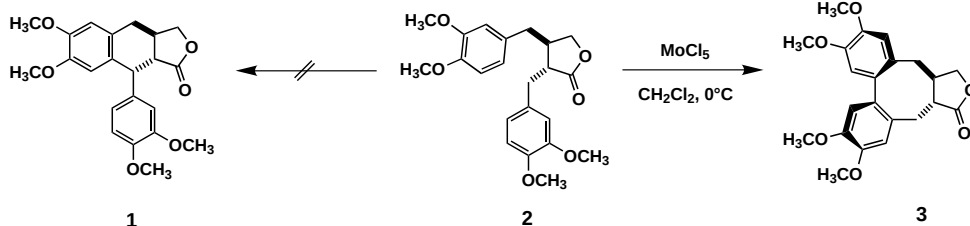
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Highly Selective Formation of Eight-Membered-Ring Systems by Oxidative Cyclization with Molybdenum Pentachloride—An Environmentally Friendly and Inexpensive Access to 2,2'-Cyclolignans**

Beate Kramer, Anne Averhoff, and Siegfried R. Waldvogel*

Dedicated to Professor Hans J. Schäfer on the occasion of his 65th birthday

The tetramethoxybiaryl moiety is a common unit in natural products.^[1] Because of their high biological activities eight-membered-ring lignans (2,2'-cyclolignans), which contain this structural unit, are of particular interest.^[2] The key step in lignan synthesis is often an oxidative biaryl coupling reaction in which the axial chirality is determined by the stereochemical information in the backbone of the precursor. In the oxidative cyclization reaction, most transition-metal reagents and hypervalent-iodine derivatives give mixtures of the desired eight-membered-ring compounds (2,2'-cyclolignans) and of six-membered-ring derivatives (2,7'-cyclolignans).^[3] Of particular interest for the non-phenolic oxidative coupling reaction is the dehydrodimerization of the natural product (–)-dimethylmatairesinol (**2**) to (+)-5-detigloyloxysteganolid (**3**; Scheme 1).

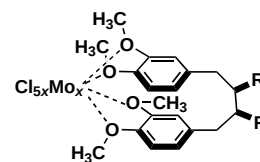


Scheme 1. Undesired six-membered-ring formation ($\rightarrow$ **1**) and desired eight-membered-ring formation ($\rightarrow$ **3**) upon oxidative coupling of (–)-dimethylmatairesinol (**2**).

Excellent selectivities favoring the 2,2'-cyclolignans are obtained with the highly toxic thallium(III) reagents or complex reaction mixtures, which require a combination of solvents and strong Lewis acids.^[4] We report herein an efficient and highly selective formation of 2,2'-cyclolignans which employs molybdenum pentachloride as the sole reagent. Molybdenum pentachloride is a widely available and inexpensive reagent that can be exploited for the oxidative coupling reaction of electron-rich arenes.^[5] The resulting

metal waste is easily removed from the reaction mixture and can be recovered.^[6]

The (–)-dimethylmatairesinol (**2**), which is required for the cyclization, was synthesized according to the method of Pelter et al.^[7] The conversion with molybdenum pentachloride proceeded without problems; even a high concentration of starting material resulted in 50 % yield of the desired 2,2'-cyclolignan.^[8] The six-membered-ring compound was not detected in the reaction mixture. The other components obtained were unreacted starting material **2** and oligomeric products. The present reaction is the first application of molybdenum pentachloride as an oxidant in the total synthesis of natural products. Similar to the thallium-mediated coupling reaction, the high selectivity for the eight-membered lignans and the lack of benzylic coupling might be explained by the formation of a complex that involves the oxophilic Lewis acid (Scheme 2).



Scheme 2. Complexation of the molybdenum center through the methoxy oxygen atoms

In the oxidative coupling reaction, molybdenum pentachloride favors substrates with a 1,2-dialkoxy substitution pattern. Most likely, the reaction is initiated by an electron transfer from a benzene moiety to the molybdenum fragment. A subsequent intramolecular electrophilic cyclization and rearomatization sequence affords the product.^[9] Since the substrate **2** contains many oxygen atoms to coordinate the reagent, we reasoned that two or more clustered molybdenum centers are involved. To gain support for such an intermediate (Scheme 2), we synthesized two further 1,4-bis(3,4-dimethoxyphenyl)butanes **4a** and **4b**^[10] and subjected both to the cyclization

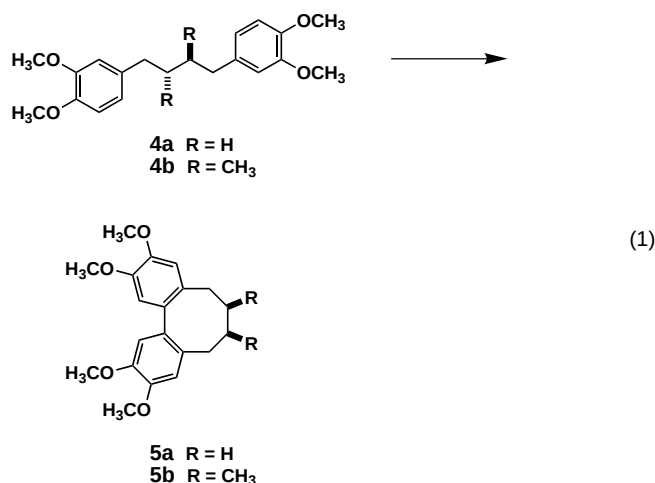
reaction. The key step in the stereoselective construction of **4b** is the nickel-catalyzed Grignard coupling reaction of the *meso*-1,4-diiodo-2,3-dimethylbutane, which is readily made from *meso*-2,3-dimethylsuccinic acid.^[10] The spatial arrangement of both substituents in the butanediyl bridge of the intermediate, the conversion into **5b** should be disfavored [Eq. (1)].

Compound **4a** was already converted at ice-bath temperature and high concentration into **5a** (76 % yield). In contrast, reflux conditions and high dilution were required for the successful synthesis of **5b**.^[11] Besides the desired lignan **5b** (30 % yield), we recovered mainly unreacted starting material. In both conversions the only cyclization products are the 2,2'-cyclolignans **5**.

In conclusion, eight-membered-ring systems, which are of particular interest for the total synthesis of 2,2'-cyclolignans, are exclusively formed when using molybdenum pentachloride as the oxidant. Harsher reaction conditions are required for the synthesis because of unfavorable steric interactions in

[*] Dr. S. R. Waldvogel, B. Kramer, A. Averhoff
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49)251-83-39772
E-mail: waldvog@uni-muenster.de

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the butanediyl moiety. Molybdenum pentachloride is an environment-friendly alternative to the highly toxic thallium(III) reagents. Furthermore, no additional Lewis acids are required. We are currently investigating the application of this powerful reagent to the synthesis of other natural products.

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Rhenium(VII) Oxo Complexes as Extremely Active Catalysts in the Dehydration of Primary Amides and Aldoximes to Nitriles

Kazuaki Ishihara, Yoshiro Furuya, and Hisashi Yamamoto*

The synthetic importance of the dehydration of primary alkyl or aryl amides to their corresponding nitriles has been thoroughly documented in the literature.^[1,2] Many of these reported methods, however, require the use of stoichiometric or excess amounts of highly reactive reagents or harsh conditions in acidic or basic media, or they involve tedious workup procedures. More recently, several methods for dehydration of primary amides under milder conditions have been developed.^[3] In 1990, Watanabe et al.^[3a] found that dichlorotris(triphenylphosphane)ruthenium (1 mol %) catalyzes the dehydration of primary amides in the presence of urea derivatives (1 equiv) in diglyme at 180 °C. In 1996, Mioskowski and co-workers^[3b] developed the paraformaldehyde-catalyzed (490 mol %) water-transfer reaction of primary amides in a formic acid/acetonitrile mixture. In this reaction, acetamide is produced instead of water. In 1999, Bose et al.^[3c,d] reported the first catalytic dehydration of primary amides in the absence of any additives except for catalyst. Unfortunately, this method requires a large amount of highly toxic dibutyltin oxide (25–35 mol %^[3c] or 37 mol %^[3d]) as a catalyst.

In our continued studies on the development of various catalytic dehydration reactions in the absence of any additives except for catalyst, such as direct amide condensation,^[4] direct ester condensation,^[5] and dehydration of alcohols to alkenes,^[6] we were interested in nitrile synthesis by catalytic dehydration reactions. We describe herein rhenium(VII) oxo complexes^[7,8] as extremely active catalysts (1 mol %) for dehydration of not only primary amides but also of aldoximes to the corresponding nitriles.

We first investigated the catalytic activities (10 mol %) of various metal salts, metal alkoxides, metal oxides, and organometallic compounds that promote the model reaction of 4-phenylbutyramide in toluene at azeotropic reflux (120 °C) with removal of water (Dean–Stark apparatus) for 16 hours (Table 1). Commercially available trimethylsilylperhenate^[9] was the most effective catalyst for this reaction (Table 1, entry 1), and a 65–70 wt % aqueous solution of perrhenic acid^[9] and rhenium(VII) oxide^[9] exhibited higher catalytic activities than other metal compounds (Table 1, entries 2 and 4). When the temperature was raised from 120 °C to 125 °C, the perrhenic acid catalyzed conversion into the corresponding nitrile was increased from 38 % to 78 % (Table 1, entry 3), whereas rhenium(VI) and rhenium(IV) oxides were inert (Table 1, entries 12 and 13). As trimethylsilyl-

Table 1. Dehydration of 4-phenylbutyramide catalyzed by metal compounds.

Entry	Catalyst	1/2/3
1	[(Me ₃ SiO)ReO ₃]	15:82:3
2	aqueous [(HO)ReO ₃] ^[a]	60:38:2
3 ^[b]	aqueous [(HO)ReO ₃] ^[a]	19:78:3
4	[(ReO ₃) ₂ O]	62:32:6
5 ^[c]	Zr(OiPr) ₄	77:23:0
6 ^[c]	Hf(OiBu) ₄	82:18:0
7	[WOCl ₃]	81:14:5
8	[MoO ₂ Cl ₂]	81:11:8
9	Ti(OiPr) ₄	89:11:0
10	Bu ₂ SnO	99:1:0
11	[VO(OiPr) ₃]	100:0:0
12	[ReO ₃]	100:0:0
13	[ReO ₂]	100:0:0
14	[RuCl ₂ (<i>p</i> -cymene)] ₂	100:0:0

[a] A 65–70 wt % solution of perrhenic acid (9–10 mol %) in water. [b] 125 °C (bath temperature). [c] 130 °C (bath temperature), 20 h.

lylperhenate and rhenium(VII) oxide are very moisture-sensitive and highly expensive compounds, we chose aqueous perrhenic acid (which is easy to handle and less expensive than trimethylsilylperhenate) as a practical dehydration catalyst. Interestingly, dibutyltin oxide was almost inert under the same conditions (Table 1, entry 10).^[3c,d]

We next investigated the solvent effect on the dehydration reaction of 4-phenylbutyramide catalyzed by aqueous perrhenic acid (9–10 mol %) under azeotropic reflux conditions (Table 2). The yield of the corresponding nitrile was increased in the order toluene < chlorobenzene < *o*-xylene (Table 2, entries 4, 3, and 2). Anisole was also a good solvent, but its polarity slightly lowered the catalytic activity of perrhenic acid (Table 2, entry 1). The dehydration of 4-phenylbutyramide occurs smoothly only at temperatures above 125 °C. The addition of molecular sieves to the reaction mixture disturbed the dehydration.

To explore the generality and scope of the above perrhenic acid catalyzed dehydration reaction, various structurally

Table 2. Solvent effect on the dehydration of 4-phenylbutyramide catalyzed by aqueous perrhenic acid.^[a]

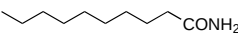
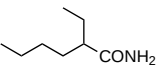
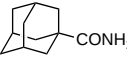
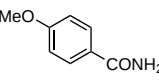
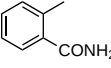
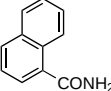
Entry	Solvent	<i>t</i> [°C]	1/2/3
1	anisole	165	11:85:4
2	<i>o</i> -xylene	155	7:91:2
3	PhCl	140	9:89:2
4	toluene	125	62:36:2
5	heptane	110	98:2:0
6	EtCN	110	95:5:0
7	dioxane	110	91:9:0

[a] A 65–70 wt % solution of perrhenic acid (9–10 mol %) in water.

[*] Prof. Dr. H. Yamamoto, Prof. Dr. K. Ishihara, Y. Furuya
Graduate School of Engineering, Nagoya University
SORST, Japan and Science Technology Corporation (JST)
Furo-cho, Chikusa, Nagoya 464-8603 (Japan)
Fax: (+81) 52-789-3222
E-mail: yamamoto@cc.nagoya-u.ac.jp

diverse primary amides were examined (Table 3). The use of perrhenic acid (1 mol %) under azeotropic reflux conditions in mesitylene was adequate for dehydrating not only aliphatic amides but also aromatic amides. The catalyst could be quantitatively recovered from the reaction mixture by distillation of products and solvents or extraction with water. For

Table 3. Dehydration reaction of primary amides catalyzed by aqueous perrhenic acid.^[a]

$\text{R-CONH}_2 \xrightarrow[\text{mesitylene (2 mL), azeotropic reflux (bath temp. 165–170 °C), 1 day}]{\text{aqueous } [(\text{HO})\text{ReO}_3] \text{ (0.9–1 mol\%)}} \text{R-CN}$		
Entry	Primary amide	Yield [%]
1		54 (81 ^[b])
2	PhCH ₂ CH ₂ CH ₂ CONH ₂	91
3		79 ^[c]
4		84
5	Ph-CH=CH-CONH ₂	64
6		91 (25 ^[d])
7 ^[e]		> 99 (1 st run) > 99 (2 nd run) > 99 (3 rd run)
8		93 ^[f]

[a] A 65–70 wt % solution of perrhenic acid (9–10 mol %) in water. [b] [(Me₃SiO)ReO₃] (1 mol %) for 2 days. [c] [(Me₃SiO)ReO₃] (10 mol %), toluene. [d] Bu₂SnO (10 mol %). [e] Perrhenic acid (1 mol %) was reused. [f] Anisole.

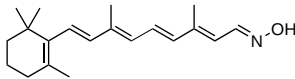
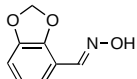
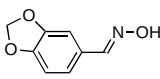
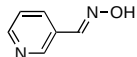
example, the catalyst was reused for the dehydration of *o*-toluamide more than three times with no loss of catalytic activity (Table 3, entry 7).^[10] This result means that the turnover number (TON) is greater than 300. The reaction was successful for sterically congested amides such as 1-adamantanecarboxamide and *o*-toluamide (Table 3, entries 4 and 7). The reaction of 3-ethylhexanamide was carried out in toluene in the presence of trimethylsilylperrhenate (10 mol %) because the boiling point of the corresponding nitrile is close to that of mesitylene (Table 3, entry 3). The use of dibutyltin oxide instead of perrhenic acid under the same conditions gave poor results, even in mesitylene (Table 3, entry 6).^[3c,d] Anisole was effective as a solvent for the reaction of a less soluble amide (1-naphthalenecarboxamide; Table 3, entry 8).

Dehydration of aldoximes with an appropriate dehydrating agent is an alternative method for the synthesis of nitriles.^[11] Very recently, Yang and Chang reported that catalytic dehydration of aldoximes can be performed efficiently with [{RuCl₂(*p*-cymene)}]₂ (3 mol %).^[11a] However, this reaction requires molecular sieves (2 wt equiv) to increase the reaction

rate. According to our comparative experiment indicated in Table 1, entry 14, [{RuCl₂(*p*-cymene)}]₂ was inert for the dehydration of primary amides. Thus, we took an interest in the catalytic activity of perrhenic acid for dehydration of aldoximes to nitriles.

The dehydration reaction was examined with various structurally diverse aldoximes in the presence of aqueous perrhenic acid (1 mol %) under azeotropic reflux conditions in toluene or mesitylene (Table 4). The reaction was complete in less than 1 h for all aliphatic and aromatic substrates, except nicotinaldoxime, and the corresponding nitriles were isolated in good to excellent yields. Sterically congested aldoximes such as cyclohexanecarboxaldoxime (Table 4, entry 2), *o*-methoxybenzaloxime (Table 4, entry 5), α -naphthalene-carboxaldoxime (Table 4, entry 10), and mesitylenecarboxaldoxime (Table 4, entry 11) were more reactive than less hindered aldoximes such as decanaldoxime (Table 4, entry 1), *m*- and *p*-methoxybenzaloximes (Table 4, entries 6 and 7), and nicotinaldoxime (Table 4, entry 12): the former were dehydrated at reflux in toluene, whereas the latter were dehydrated at reflux in mesitylene. *trans*-2-Decenaldoxime and *all-trans*-retinaldoxime^[11a] were readily converted into their corresponding nitriles in high yield with partial inversion of the double bond (Table 4, entries 3 and 4). The present method was useful for acid-sensitive substrates such as 2,3-(methylenedioxy)benzaloxime (Table 4, entry 8) and 3,4-(methylenedioxy)benzaloxime (Table 4, entry 9). Further-

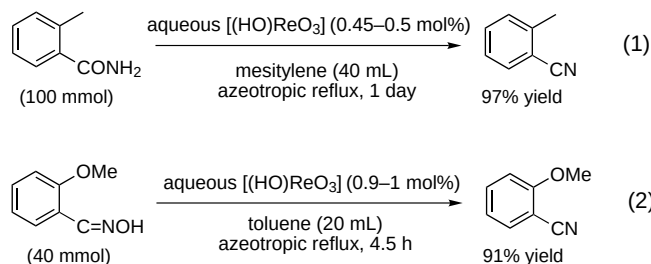
Table 4. Catalytic dehydration of aldoximes to nitriles.

$\text{R-CH=N-OH} \text{ or } \text{R-CH=N-OH} \xrightarrow[\text{toluene (2 mL), azeotropic reflux, 1 h}]{\text{aqueous } [(\text{HO})\text{ReO}_3] \text{ (0.9–1 mol\%)}} \text{R-CN}$			
Entry	Aldoxime ^[a]	<i>syn/anti</i>	Yield [%]
1	<i>n</i> -C ₁₀ H ₂₁ CH=NOH	0:100	> 99 ^[b]
2	<i>cyclo</i> -C ₆ H ₁₁ CH=NOH	63:37	91
3	(2 <i>E</i>)- <i>n</i> -C ₈ H ₁₇ CH=CHCH=NOH	93:7	91
4		100:0	91 ^[d,e]
5	<i>o</i> -(MeO)C ₆ H ₄ CH=NOH	100:0	94
6	<i>m</i> -(MeO)C ₆ H ₄ CH=NOH	100:0	86 ^[b]
7	<i>p</i> -(MeO)C ₆ H ₄ CH=NOH	100:0	97 ^[b]
8		100:0	95 ^[b]
9		100:0	99 ^[b]
10	1-NapCH=NOH	100:0	98
11	2,4,6-Me ₃ C ₆ H ₂ CH=NOH	100:0	> 99
12		100:0	84 ^[b,e,f]

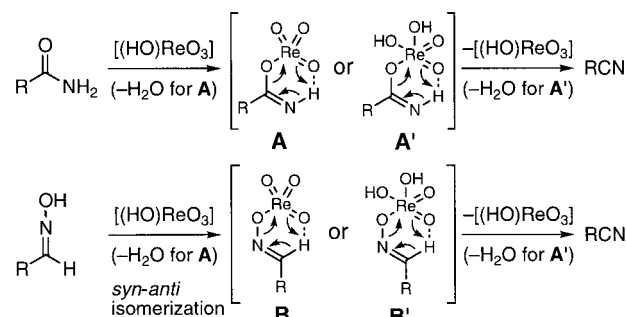
[a] Aldoximes were prepared in good yields by reaction of the corresponding aldehydes with NH₂OH·HCl (in pyridine/EtOH 1:1^[11a]) or in an aqueous solution of Na₂CO₃^[12]. [b] Mesitylene. [c] The *E/Z* ratio of the product was 92:8. [d] *o*-Xylene, 2 h. [e] The isolated product was > 98% *all-trans*. [f] 3 h.

more, perrhenic acid could be used as a dehydration catalyst in the presence of basic nitrogen-containing compounds: nicotinaldioxime was smoothly dehydrated with the catalyst system to give 3-cyanopyridine in 84% yield (Table 4, entry 12).

The applicability of the present protocol to a large-scale process was then investigated. Complete dehydration of *o*-toluamide (100 mmol) and *o*-methoxybenzaloxime (40 mmol) was observed in the presence of aqueous perrhenic acid (< 1 mol %), and the corresponding nitriles were isolated in high yields [Eqs. (1) and (2)].



Based on the reactivities of primary amides and aldoximes in perrhenic acid catalyzed dehydrations, we propose the mechanism shown in Scheme 1. The reaction of the substrates and perrhenic acid leads to six-membered cyclic transition states **A** and **B** (upon dehydration) or to the analogous transition states **A'** and **B'** (without dehydration)^[3c,d]. Dehydration of primary amides and aldoximes to produce nitriles



Scheme 1. Proposed mechanism for the dehydration of primary amides and aldoximes to form nitriles.

should be promoted by selective coordination of rhenium(VII) oxo complexes with their oxygen atoms. On the contrary, the coordination of the catalyst with the nitrogen atom of primary amides should give the corresponding imides. Therefore, the oxophilicity of rhenium(VII) oxo complexes is a significant factor in obtaining nitriles as major products.^[13,14] The high reactivity of sterically congested aldoximes and the low reactivity of less hindered aldoximes can be explained through **B** or **B'**, which is generated from a *syn* isomer of aldoximes. *Syn/anti* isomerization of aldoximes is known to occur under thermal or acidic conditions.^[15] Therefore, the reactivity of aldoximes for dehydration may depend on their *syn/anti* equilibrium under the reaction conditions. It is not

clear why trimethylsilylperrhenate is more active than perrhenic acid and rhenium(VII) oxide. Pure perrhenic acid has not been isolated because it exists preferentially as the dimeric anhydride [O₃ReOReO₃] under anhydrous conditions,^[16] whereas trimethylsilylperrhenate is monomeric. Therefore, monomeric rhenium(VII) oxo species may be more active than dimeric or oligomeric complexes.

In conclusion, we have reported herein several noteworthy features of new catalysts for the dehydration of primary amides and aldoximes. The reaction proceeds under essentially neutral conditions, and the catalyst is recoverable and reusable. This protocol can be readily applied to large-scale processes with high efficiency and selectivity, making it an economical and environmentally benign process for the preparation of nitriles.

Experimental Section

General procedure (Tables 3 and 4):^[10] A solution of primary amides (1 mmol) or aldoximes (1 mmol), perrhenic acid (65–70 wt % solution in water, 1.66 μ L, 0.009–0.010 mmol, 0.9–1.0 mol %), and solvent (2 mL) was heated at azeotropic reflux with the removal of water. After several hours, the mixture was cooled to ambient temperature and saturated aqueous NaHCO₃ (100 μ L) was added. After stirring for 10 min, the mixture was dried over MgSO₄, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel.

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- The catalysts, aqueous [(HO)ReO₃] (colorless), and [(Me₃SiO)ReO₃] (white), were often recovered as a dark solid by partial reduction to lower valent rhenium oxides such as [ReO₃·xH₂O] (black), [ReO₂] (brown), [ReO₃] (red), or [Re₂O₃] (blue). However, the recovered catalyst was still active for the dehydration. Lower valent rhenium oxides could be oxidized to perrhenic acid (colorless) or its anhydride (yellow) by treatment with hydrogen peroxide (35 %) at 50 °C for 12 h and removal of excess hydrogen peroxide and water under vacuum at

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Lewis Acid Promoted, O-Selective, Nucleophilic Addition of Silyl Enol Ethers to N=O bonds**

Norie Momiyama and Hisashi Yamamoto*

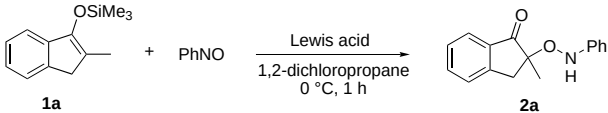
We report herein the first regioselective synthesis of α -aminoxy ketones from silyl enol ethers and nitrosobenzene [Eq. (1)]. The direct introduction of aminoxy or hydroxy-amino groups at the α position of carbonyl compounds has not been part of synthetic practice, in sharp contrast to the very widespread addition of formyl electrophiles at the α position of ketone enolates or their equivalents, that is, aldol synthesis.^[1] In fact, there are only a few reports on the use of nitrosobenzene^[2] for nucleophilic addition with the silyl enol ethers of acetophenone and propiophenone to generate the corresponding α -hydroxyamino derivatives [Eq. (2)].^[3] We were surprised to learn that treatment of silyl enol ethers with nitrosobenzene in the presence of various Lewis acid catalysts

proceeds smoothly to generate previously unknown α -aminoxy ketones in high yields. The present procedure has important implications in the N–O–C-bond construction from these simple starting compounds and can open a new entry to useful building blocks for potentially important, biologically active compounds.^[4]

Our initial design of a nucleophilic addition of silyl enol ethers to nitrosobenzene rested on finding a suitable catalyst that could facilitate N-alkylation with various silyl enol ethers. Trimethylsilyl triflate was chosen as a Lewis acid for this reaction based on its use in Mukaiyama-type aldol reactions.^[5] However, nucleophilic addition catalyzed by trimethylsilyl triflate did not provide the N-adduct (hydroxyamino ketone). An X-ray crystallographic study or chemical transformation with acetyl chloride demonstrated that the N-adduct was not formed; instead the O-adduct (aminoxy ketone) was the product of the reaction [Eq. (1)].^[6] We then focused on Lewis acid catalyzed O-selective nucleophilic addition as a new strategy for constructing N–O–C bonds.

A variety of Lewis acid catalysts were examined and are summarized in Table 1. Alkylsilyl triflates efficiently mediated the O-selective nucleophilic addition of silyl enol ether **1a** to nitrosobenzene (1,2-dichloropropane, 0 °C) to give the O-adduct **2a** in excellent yield (Table 1). The use of triethylsilyl triflate (10 mol %) led to the isolation of **2a** in 94 % yield (Table 1, entry 3); even a lower amount of the catalyst (1 mol %) still provided the product in 74 % yield (Table 1, entry 5). Titanium(IV) chloride, iron(III) chloride, and copper(II) triflate also led to the formation of **2a** in moderate to good yields (Table 1, entries 7, 8, 11).

Table 1. O-Alkylation of **1a** catalyzed by various Lewis acids.



Entry	Lewis acid	Equiv [mol %]	Yield [%] ^[a]
1	none		< 1
2	Me ₃ SiOTf	5	86
3	Et ₃ SiOTf	10	94
4	Et ₃ SiOTf	5	88
5	Et ₃ SiOTf	1	74
6	<i>t</i> BuMe ₂ SiOTf	5	83
7	TiCl ₄	5	71
8	FeCl ₃	5	60
9	Me ₃ SiNTf ₂	5	54
10	[AgOTf]	5	52
11	[Cu(OTf) ₂]	5	58
12	[Sn(OTf) ₂]	5	50

[a] Yield of isolated product.

Since aromatic C-nitroso compounds are known to exist as blue or green monomers and colorless dimers,^[7] chemical models of the catalyst–nitrosobenzene complex predict the two coordination geometries **A** and **B** (Scheme 1). However, as Lewis acids promote the dimerization of the monomer nitrosobenzene,^[8,9] O-alkylation may proceed via intermediacy of the Lewis acid coordinated nitroso dimer complex **A**. This process does not proceed through an aldol pathway in

[*] Prof. H. Yamamoto, N. Momiyama
Graduate School of Engineering, Nagoya University, SORST
Japan Science and Technology Corporation (JST)
Chikusa, Nagoya 464-8603 (Japan)
Fax: (+81)52-789-3222
E-mail: yamamoto@cc.nagoya-u.ac.jp

[**] We thank Prof. Akira Yanagisawa (Department of Chemistry, Faculty of Science, Chiba University) for helpful discussion, Dr. Yujiro Hoshino for stimulating discussion and X-ray crystallographic analysis, and Mr. Kin-ichi Oyama (Chemical Instrument Center of Nagoya University) for measurement of ESI mass spectra.

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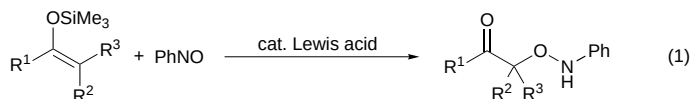
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Peter Göltz, Editor

Lewis Acid Promoted, O-Selective, Nucleophilic Addition of Silyl Enol Ethers to N=O bonds**

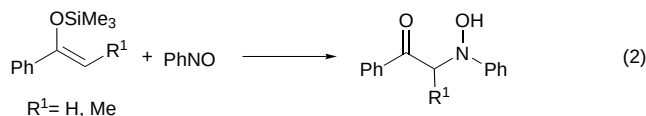
Norie Momiyama and Hisashi Yamamoto*

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been part of synthetic practice, in sharp contrast to the very widespread addition of formyl electrophiles at the α position of ketone enolates or their equivalents, that is, aldol synthesis.^[1] In fact, there are only a few reports on the use of

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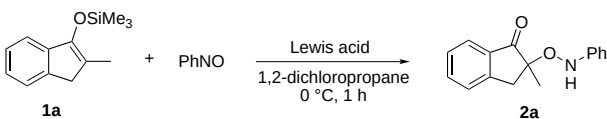


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[a] Yield of isolated product.

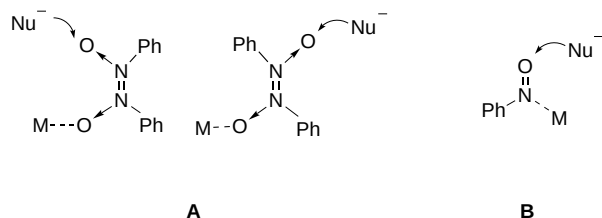
[*] Prof. H. Yamamoto, N. Momiyama
Graduate School of Engineering, Nagoya University, SORST
Japan Science and Technology Corporation (JST)
Chikusa, Nagoya 464-8603 (Japan)
Fax: (+81)52-789-3222
E-mail: yamamoto@cc.nagoya-u.ac.jp

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Since aromatic C-nitroso compounds are known to exist as blue or green monomers and colorless dimers,^[7] chemical models of the catalyst–nitrosobenzene complex predict the two coordination geometries **A** and **B** (Scheme 1). However,



Scheme 1. Proposed active species of nitrosobenzene in the presence of Lewis acid.

as Lewis acids promote the dimerization of the monomer nitrosobenzene,^[8,9] O-alkylation may proceed via intermediacy of the Lewis acid coordinated nitroso dimer complex **A**. This process does not proceed through an aldol pathway in which nitrosobenzene behaves like a carbonyl compound **B** (Scheme 1).

Significant structural variation in the silyl enol ether component is possible without any loss in regioselectivity (Table 2). An aromatic substituent such as phenyl provides good reactivity in this reaction (Table 2, entries 1–3). The reaction of α -disubstituted substrates (Table 2, entries 1–3, 5–6) is more facile than that of monosubstituted (Table 2, entries 4, 8).

In conclusion, we have documented a new strategy for aminoxy ketone synthesis that has enabled the development of the first highly O-selective, Lewis acid catalyzed, nucleophilic addition reaction to N=O bonds. Further studies to address the scope of this reaction and the coordination chemistry of the N=O bond are underway.

Experimental Section

General procedure: an oven-dried Schlenk tube equipped with a magnetic stirrer was charged with nitrosobenzene (1 equiv, 107.1 mg, 1 mmol) under argon. The tube was fitted with a septum cap, 1,2-dichloropropane (3 mL) was added through a syringe, and the solution was then stirred at room temperature for 5 min. After cooling to 0°C, trimethylsilyl enol ether (1 equiv, 1 mmol) was added to the resulting green solution at this temperature. A solution of the Lewis acid (0.05 equiv, 0.05 mmol) in dry 1,2-dichloropropane (2 mL) was added to the mixture at 0°C over a period of 10 min with a syringe pump. The mixture was stirred for 1 h at 0°C to produce a cloudy orange mixture. The reaction mixture was quenched with cooled brine (20 mL), and the aqueous layer was extracted with diethyl ether (3 $\times$ 20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure after filtration. The residual crude product in 1,2-dichloropropane was purified by chromatography, with cooling, on a two-layered column filled with Florisil (upper layer) and silica gel (lower layer) with a mixture of ethyl acetate and hexane as the eluent to give the product.

2a: Nitrosobenzene (1 equiv), triethylsilyl triflate (23 μ L, 0.1 mol) and **1a** (230 μ L, 1 mmol) were treated as described in the General Procedure. Purification by flash column chromatography (eluent by hexane/ethyl acetate 7:1) provided **2a** (238.1 mg, 94 %) as a yellowish oil. TLC R_f = 0.30 (hexane/ethyl acetate 3:1); IR (neat): $\tilde{\nu}$ = 3270, 3050, 2977, 2926, 1715, 1605, 1495, 1470, 1304, 1233, 907 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.78 (d,

Table 2. O-Alkylation of various silyl enol ethers.

$\text{R}^1-\text{C}(\text{OSiMe}_3)=\text{C}(\text{R}^2)-\text{C}(\text{R}^3)-\text{H} + \text{PhNO} \xrightarrow[\text{1,2-dichloropropane, 0}^\circ\text{C, 1 h}]{\text{Et}_3\text{SiOTf (5 mol\%)}} \text{R}^1-\text{C}(=\text{O})-\text{C}(\text{OSiMe}_3)(\text{R}^2)-\text{C}(\text{R}^3)-\text{H}$				
1			2	
Entry	1		Yield [%] ^[a]	
1		1a	94	
2		1b	51	
3		1c	62	
4		1d	44	
5		1e	54	
6		1f	62	
7		1g	46	
8		1h	37	

[a] Yield of isolated product.

1 H, J = 7.7 Hz; ArH), 7.78 (t, 1 H, J = 7.4 Hz; ArH), 7.34–7.40 (m, 2 H; ArH), 7.23 (t, 2 H, J = 8.0 Hz; ArH), 7.13 (s, 1 H; NH), 6.91–6.94 (m, 3 H; ArH), 3.54 (d, 1 H, J = 16.8 Hz; CH₂H_b), 3.13 (d, 1 H, J = 16.8 Hz; CH₂H_a), 1.49 ppm (s, 3 H; CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ = 205.3, 151.6, 148.3, 135.5, 134.4, 128.8 (2C), 127.7, 126.7, 124.4, 122.1, 114.3 (2C), 87.1, 38.0, 21.9 ppm; elemental analysis: calcd for C₁₆H₁₅NO₂: C 75.87, H 5.97, N 5.53; found: C 75.76, H 6.13, N 5.64.

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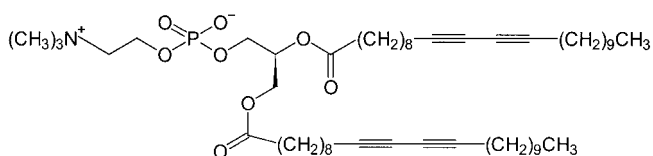
Chiral Templating of Silica–Lipid Lamellar Mesophase with Helical Tubular Architecture**

Annela M. Seddon, Harish M. Patel,
Sandra L. Burkett, and Stephen Mann*

The use of amphiphilic surfactants and polymers in the template-directed synthesis of periodically ordered hybrid mesophases has produced a diverse range of new inorganic-based materials with controlled mesoporosity and function-

ality.^[1] A key challenge for the future lies with the reproducible processing of mesostructured materials, and specifically with the control of higher order properties such as structural hierarchy and macroscopic shape. Although mesostructured nanoparticles,^[2] colloids,^[3] tubes,^[4] fibers,^[5] hollow shells,^[6] gyroids, and helicoids^[7] have been prepared, these rely on the subtle interplay of extrinsic factors associated with the growth mechanism, which are often difficult to control. An alternative strategy is to use molecular structure to direct the expression of form so that increased levels of morphological control can be achieved through the transcription of internal information. In this respect, chiral organic molecules known to be efficient gelators of organic solvents have been used recently to prepare helical tapes of silica by in situ coating of gel filaments.^[8] However, although these molecules are capable of self-assembly and directing the surface deposition of silica, they show no propensity to coassemble with the inorganic phase at the mesostructural level.

Herein we demonstrate that the diacetylenic-containing chiral lipid, 1,2-bis(10,12-tricosadiyonyl)-*sn*-glycero-3-phosphatidylcholine (DC_{8,9}PC, Scheme 1) can be used simultaneously as a structure-directing template, “morphogen” and photoactive monomer to synthesize high aspect ratio helical



Scheme 1. Molecular structure of DC_{8,9}PC. The polar lipid headgroup is zwitterionic over the pH range 3 to 13.^[19]

tubules and ribbons that consist of polymerizable periodic mesostructured silica–lipid walls with a twisted lamellar architecture. Although organic tubules formed from DC_{8,9}PC have been extensively investigated,^[9] and studies on silica^[10] and metallic coatings,^[11] and surface decoration with gold nanoparticles^[12] or polypyrrole threads^[13] have been carried out, there are to the best of our knowledge no reports on the coassembly of periodic hybrid mesostructures using this or other chiral lipids.

Addition of aqueous HBr to a solution of DC_{8,9}PC and tetraethylorthosilicate (TEOS) in ethanol at room temperature at a TEOS:DC_{8,9}PC molar ratio of 8.3:1 resulted in instantaneous formation of a white precipitate. Transmission electron microscopy (TEM) studies revealed that over 90 % of the sample was in the form of open-ended silicified helical tubules and ribbons with diameters, lengths, and wall thickness of 0.5–1.5 μm, > 5 μm, and 50–150 nm, respectively (Figure 1a). The hybrid microstructures consisted of smooth external and internal surfaces, which, along with the general absence of colloidal silica precipitation, suggested that TEOS acid hydrolysis and condensation were specifically associated and coupled with self-assembly of the lipid molecules. This was confirmed by high-resolution TEM images of areas of the helical tubules in which the lipid bilayers were fortuitously oriented approximately parallel to the electron beam. Under such conditions, continuous lattice fringes were observed with

[*] Prof. S. Mann, A. M. Seddon, Dr. H. M. Patel
School of Chemistry
University of Bristol
Bristol BS8 1TS (UK)
Fax: (+44) 117-929-0509
E-mail: s.mann@bristol.ac.uk

Dr. S. L. Burkett
Department of Chemistry
Amherst College
Amherst, MA 01002-5000 (USA)

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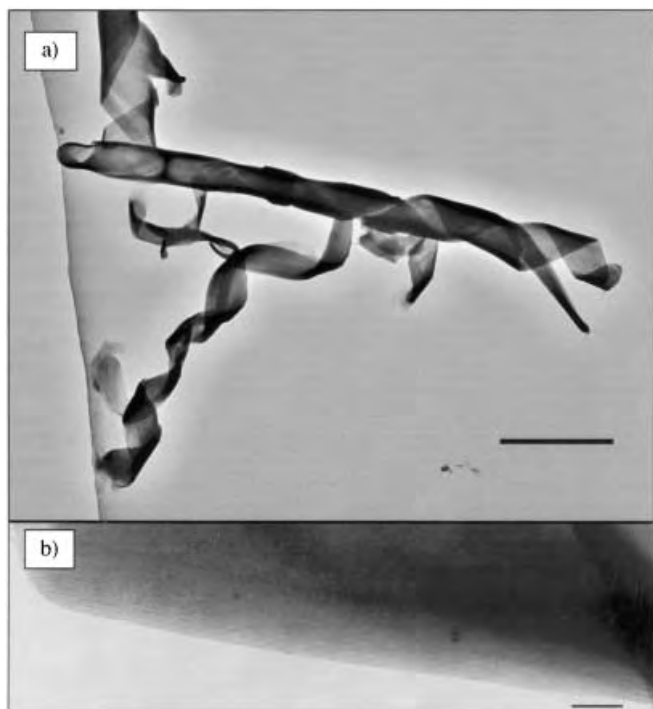


Figure 1. TEM images of a) silica-lipid helical tubules and ribbons, scale bar = 2 μm , b) tubule edge showing lattice fringes corresponding to a lamellar hybrid mesostructure. Scale bar = 50 nm.

spacings of about 4.5 nm (Figure 1 b) that were consistent with a twisted multilamellar hybrid mesophase in which the lipid bilayers were intercalated with thin sheets of amorphous silica. Energy-dispersive X-ray (EDX) analysis showed the presence of Si, P, and Br associated with the mineralized tubules, and thermogravimetric analysis (TGA) indicated that they contained about 70 wt % lipid. Significantly, calcination at 410 °C produced inorganic replicas that consisted of intact tubes and twisted ribbons of amorphous silica.

Powder X-ray diffraction (XRD) patterns showed three broad low-angle peaks with d spacings of 4.0, 1.4, and 0.84 nm, corresponding to the (002), (006), and (0010) reflections of a partially ordered lamellar mesophase with an interlayer spacing of about 8.4 nm (Figure 2 a). A very broad high-angle peak centered at $2\theta = 22^\circ$, attributed to amorphous silica was also observed. In contrast, XRD data from a sample of unmineralized lipid tubules/ribbons (Figure 2 b) showed sharp

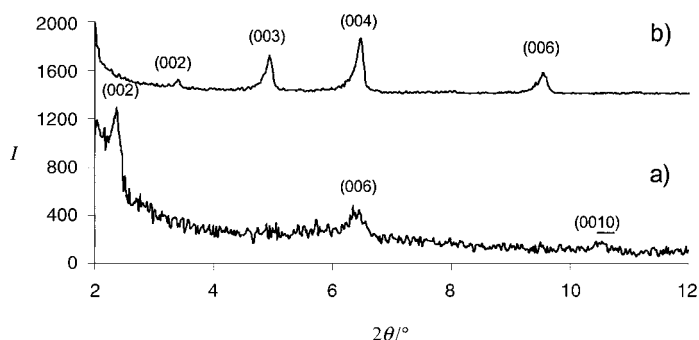


Figure 2. XRD data; a) silica-lipid mesophase, b) unmineralized lipid tubules. I = intensity.

(002), (003), (004), (006), (008), (0010), and (0012) reflections corresponding to a lamellar L_c mesostructure with 5.6 nm interlayer spacing and noninterdigitated crystalline chain packing.^[14] Similar data were obtained for a sample of silica-coated lipid microstructures produced by adding TEOS to dispersions of preformed tubules, except that the diffraction lines were broadened. The results indicate therefore that in situ acid hydrolysis of TEOS during lipid self-assembly results in an expansion of the interlayer spacing by about 3 nm due to intercalation of silica between the DC_{8,9}PC bilayers. Given a wall thickness of 50 to 150 nm, this corresponds to a stack of five to 15 hybrid sheets, which must be sufficiently flexible to undergo twisting in response to the stress field associated with intralayer crystalline packing of the chiral lipid molecules.

FTIR and Raman spectra were consistent with previous observations on unmineralized tubules^[15] and indicated that the crystalline packing of the lipid molecules was not significantly changed by silica intercalation. For example, FTIR spectra showed DC_{8,9}PC bands at 718 (CH_2 rock), 1469 (CH_2 scissors), 2849 (CH_2 str), and 1725 cm^{-1} (C=O str) in both the unmineralized and mineralized samples. The former also showed bands between 1175 and 1345 cm^{-1} corresponding to the P–O stretch but these were masked to some extent in the mineralized tubules/ribbons by additional Si–O–Si framework vibrations at 1050 cm^{-1} (large band) and 1200 cm^{-1} (shoulder). Raman spectra of the silica-lipid lamellar mesophase showed a peak at 2263 cm^{-1} corresponding to the monomer $\text{C}\equiv\text{C}$ stretch of the diacetylene groups.

Dried samples of the white silicified tubules turned blue due to diacetylene polymerization when left for two days in the light under ambient conditions. No changes in the FTIR spectra were observed, but corresponding Raman spectra showed a characteristic shift in the $\text{C}\equiv\text{C}$ stretch from 2263 to 2086 cm^{-1} and the appearance of a new band at 1454 cm^{-1} ,

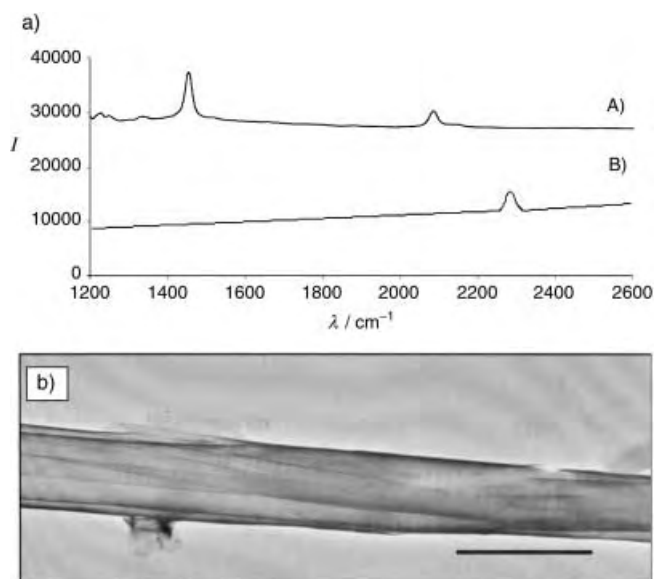


Figure 3. a) Raman spectra of silica-lipid tubules; A) before and B) after diacetylenic polymerization by exposure to light for two days. I = intensity. b) TEM image of polymerized silica-lipid tubule showing absence of helical architecture. Scale bar = 2 μm .

corresponding to the C=C stretch (Figure 3a). This is consistent with the polymerization of the diacetylenic monomer backbone and the formation of conjugated ene-yne linkages^[16] in the self-assembled lipid-silica architecture (Figure 4). Corresponding TEM images showed that the silica-lipid tubules were preserved after polymerization but usually without the helical surface patterning (Figure 3b), indicating that the side edges of the helical seam become fused into a continuous wall structure during polymerization. Diacetylene polymerization in surfactant and lipid bilayers occurs below the chain melting temperature (T_m) and involves a topotactic reaction in which the adjacent monomers are fixed at appropriate distances and angles.^[17] Moreover, chain ordering would be best accommodated along the length of the helical microstructure, rather than around the tubule, because of the lower curvature associated with the direction of elongation, and this could explain why diacetylene polymerization results in fusion of the seam edges in the polymerized hybrid materials.

Finally, addition of ethanol to the polymerized silica-lipid tubules/ribbons resulted in a blue-to-red solvatochromic response that corresponded to a shift in the diffuse reflectance UV/Vis band at 650 nm (blue sample) to two bands at 496 and 536 nm (red material) (Figure 5). The change in color, which is attributed to shortening of the conjugation length of the polydiacetylenic backbone by solvation stresses,^[18] was not reversed when the ethanol was removed by evaporation. However, the blue-to-red response was also observed when samples of the polymerized silica-lipid tubules were heated to above 40 °C, exposed to an X-ray beam, or mechanically

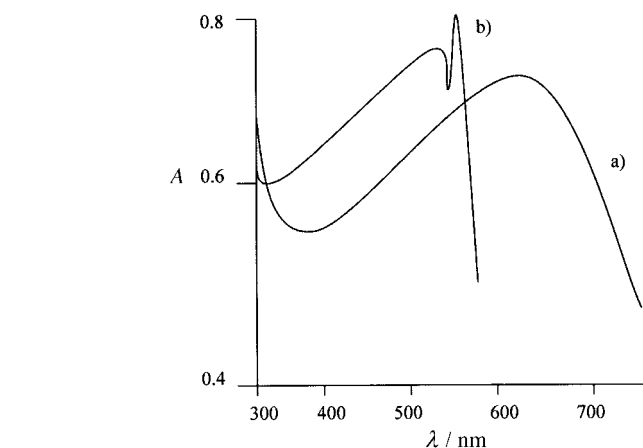


Figure 5. Diffuse reflectance UV/Vis spectra of polymerized silica-lipid tubules; a) before (blue material), and b) after addition of ethanol (red material). A = absorbance.

scratched or sheared, indicating that a range of external stress fields can induce the chromatic response.

In conclusion, in situ synthesis of silica by acid hydrolysis and condensation of TEOS in the presence of DC_{8,9}PC lipid molecules results in the synergistic coassembly of a lamellar hybrid mesostructure containing polymerizable diacetylenic groups, which is subsequently twisted into high aspect ratio tubules and ribbons with helical architecture. The resulting solvatochromic, thermochromic, and mechanochromic responses suggest that the hybrid materials could have a range of uses as colorimetric transduction agents, for example in sensors, thin films, and smart coatings.

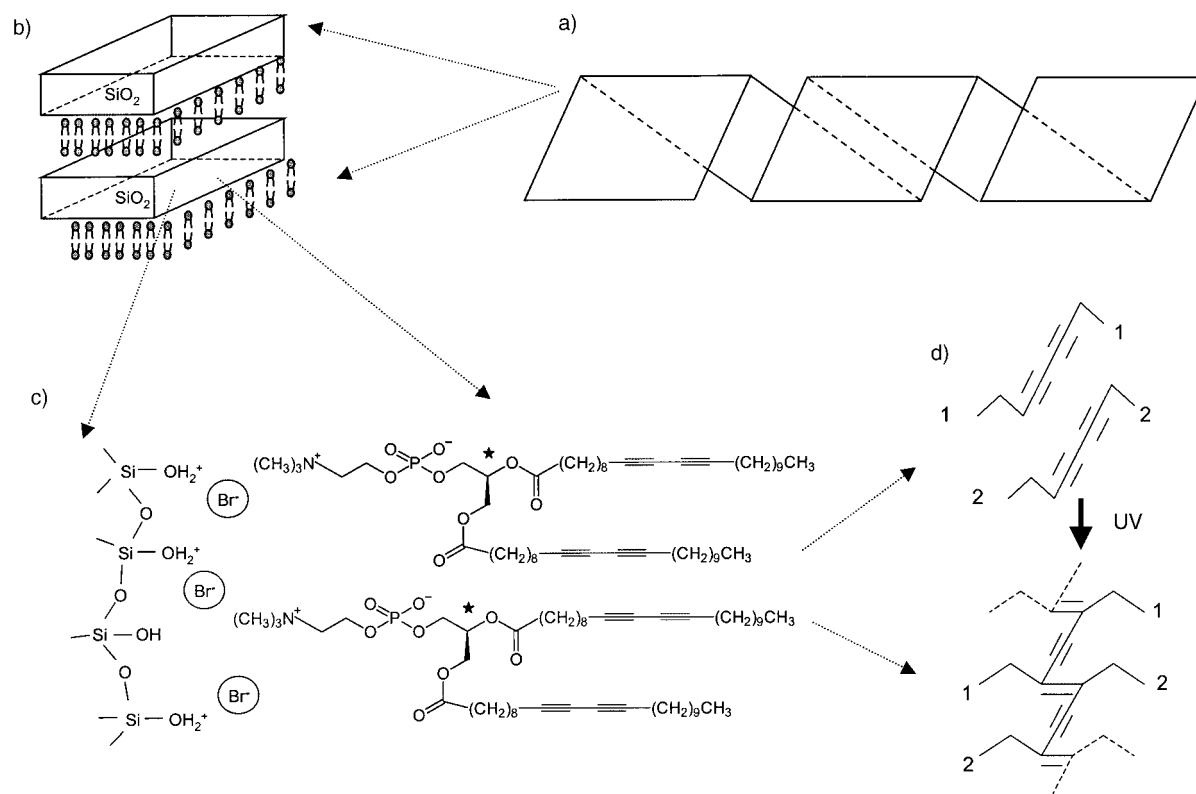


Figure 4. Schematic representation showing silica-lipid lamellar mesostructure and diacetylenic polymerization. a) Helical silica-lipid tubule with twisted multilamellar architecture; b) 3 nm-thick sheets of silica interspaced with lipid bilayers, 5.6 nm in width; c) hypothetical section across the interface showing interactions between the lipid headgroup, Br⁻ counterions and protonated silica surface; d) formation of ene-yne linkages.

Experimental Section

DC₈PC was obtained from Avanti Polar Lipids and used without further purification. TEOS was obtained from Aldrich and used as received. Mineralized lipid tubules were prepared in situ as follows. Typically, DC₈PC (40 mg) was dissolved in ethanol (2 mL) by sonication (lipid concentration, 0.044 mM), and TEOS (82.4 μ L) was added to give a TEOS:lipid molar ratio of 8.3:1. A solution (0.38 g) prepared from H₂O (0.8 g) and 48 wt% aqueous HBr (3.0 g) was added to the lipid/TEOS mixture (final pH 0.5) and a white precipitate formed instantly. The sample was stirred for 5 min, left sealed overnight, and then centrifuged at 5000 rpm for 10 min and the supernatant decanted. Similar preparations were undertaken at TEOS:lipid molar ratios between 4:1 and 1:4. Polydiacetylenic derivatives were prepared by leaving samples of the dried mineralized lipid tubules for two days under ambient conditions in the laboratory. Unmineralized lipid tubules were prepared by addition of H₂O (1 mL) to a solution of DC₈PC (0.0044 mM) in ethanol (1 mL). Lipid microstructures were also coated externally with silica by addition of TEOS (82.4 μ L) to a suspension (20 mg mL⁻¹) of preformed tubules.

Samples were characterized by TEM (JEOL 1200EX), SEM (JEOL JSM 5600 LV), EDXA (Oxford Instruments, ISIS300), and XRD (Siemens D500 diffractometer, Cu_{K α} radiation, λ = 0.15405 nm). Samples were prepared either as a suspension in ethanol in a quartz cuvette or evaporated from ethanol onto a quartz slide for UV/Vis (800–200 nm) and diffuse reflectance UV/Vis spectroscopy (Perkin Elmer Lambda II with Labsphere titania mirrors), respectively. FT-IR spectroscopy (Perkin Elmer Spectrum 1) was carried out using KBr discs. Raman spectra (Renishaw System 2000) were recorded using a 35 mW HeNe laser at an excitation frequency of 632.8 nm, and probe size of about 1 μ m. TGA (Netzsch TG409EP) was carried out at a heating rate of 5 K min⁻¹ from room temperature to 600 °C in air with a flow rate of 90 mL min⁻¹. Calcined samples were prepared at 410 °C for 2 h using a heating rate of 3 K min⁻¹.

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Aryl C–H Activation by Cu^{II} To Form an Organometallic Aryl–Cu^{III} Species: A Novel Twist on Copper Disproportionation**

Xavi Ribas, Deanne A. Jackson, Bruno Donnadieu, José Mahía, Teodor Parella, Raül Xifra, Britt Hedman,* Keith O. Hodgson,* Antoni Llobet,* and T. Daniel P. Stack*

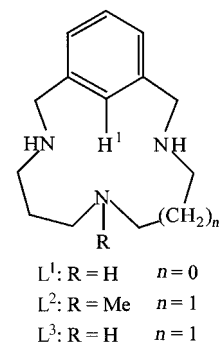
Selective activation of hydrocarbon C–H bonds by metals under mild conditions is an important pursuit in the functionalization of organic substrates.^[1] While such oxidative trans-

- [*] Prof. A. Llobet, Dr. X. Ribas, R. Xifra
 Departament de Química, Universitat de Girona
 Campus de Montilivi, E-17071, Girona (Spain)
 Fax: (+34) 972-41-8150
 E-mail: antoni.llobet@udg.es
- Dr. B. Hedman, Prof. K. O. Hodgson, D. A. Jackson
 Department of Chemistry and
 Stanford Synchrotron Radiation Laboratory
 Stanford University
 Stanford, CA 94305-5080 (USA)
 Fax: (+1) 650-725-0259
 E-mail: hedman@slac.stanford.edu, hodgson@ssrl.slac.stanford.edu
- Prof. T. D. P. Stack
 Department of Chemistry, Stanford University
 Stanford, CA 94305-5080 (USA)
 Fax: (+1) 650-725-0259
 E-mail: stack@stanford.edu
- Dr. J. Mahía
 Servicios Xerais de Apoio Á Investigación
 Universidade da Coruña
 15071 A Coruña (Spain)
- Dr. B. Donnadieu
 Service de Cristallogénie
 Laboratoire de Chimie de Coordination, UPR CNRS 8241
 Route de Narbonne 205, 31077 Toulouse Cedex 4 (France)
- Dr. T. Parella
 Departament de Química, Universitat Autònoma de Barcelona
 Bellaterra, 08193 Barcelona (Spain)

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formations are complicated, the fact that the C–H-activation step often determines the selectivity and the rate of the reaction provides ample motivation for understanding the mechanistic details of this step.^[2] Assuming the intermediacy of an initial weak C–H adduct with the metal, two limiting mechanisms of C–H activation are possible:^[3,4] direct heterolytic C–H-bond cleavage ($M^{n+} + R-H \rightarrow M^{n+}-R + H^+$), which requires an exogenous base and no change in the formal oxidation state of the metal atom, and oxidative addition ($M^{n+} + R-H \rightarrow H-M^{n+2}-R$), which involves a high-valent metal-hydrido complex.^[2,5,6] Activation of C–H bonds by first-row transition metals under mild conditions is generally limited to intramolecular reactions in which the decrease in entropy can potentially compensate for the weaker M–C bonds formed with first-row metals relative to heavier metals.^[3,7]

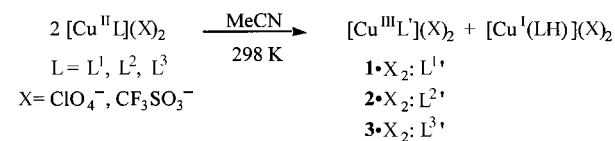
Herein we present three related Cu^{II} coordination complexes that activate an aryl C–H bond of a ligand at room temperature (RT) to form a stable organoaryl– Cu^{III} complex. Spectral and structural characterization of these Cu^{III} species are presented along with mechanistic insight into the activation process.



Scheme 1. Triazamacrocyclic ligands.

The triazamacrocyclic ligands used in this study are presented in Scheme 1.^[9,10] Structurally, these ligands are analogous to the tetraazamacrocyclic ligands synthesized from α, α' -2,6-dibromomethylpyridine rather than α, α' -1,3-dibromomethylbenzene, as the latter ligands readily adopt a square-planar binding conformation. Reaction of equimolar amounts of $Cu^{II}(ClO_4)_2 \cdot 6H_2O$ with L^2 in CH_3CN at RT under anaerobic conditions resulted in a rapid decay

of the initially formed paramagnetic $[Cu^{II}L^2]^{2+}$ complex to equimolar amounts of two diamagnetic products (Scheme 2). One product is consistent with $[Cu^IL^2H]^{2+}$, which could be independently prepared and characterized (^1H NMR,



Scheme 2. Disproportionation reaction.

ESI MS). An anaerobic optical titration of the final reaction mixture with an excess of phenanthroline confirmed an overall conversion of the initial Cu^{II} into Cu^I of about 50%, and this suggests a disproportionation of Cu^{II} . The second diamagnetic product selectively crystallizes in about 50% yield, and is indefinitely stable in protic media (MeOH, H_2O) under aerobic conditions. Analytical data support a 1:1 Cu:ligand complex with two counteranions, $2-(ClO_4)_2$, fully consistent with a robust, low-spin Cu^{III} complex. However, Cu^{III} complexes are generally stabilized in square-planar, anionic coordination environments, a ligation mode not

initially envisioned for L^1 – L^3 . The reactions of L^1 – L^3 with $Cu^{II}(ClO_4)_2$ or $Cu^{II}(CF_3SO_3)_2$ result in analogous crystalline products, $1-(ClO_4)_2$ – $3-(ClO_4)_2$ or $1-(CF_3SO_3)_2$ – $3-(CF_3SO_3)_2$, respectively, in similar overall yields.

Crystallographic characterization of $1-(ClO_4)_2$ and $2-(ClO_4)_2$ ^[11] showed that each copper atom is coordinated by six ligands, although the two perchlorate anions are only weakly associated in axial positions (Cu–O ca. 2.4–2.7 Å). An ORTEP plot of **2** shows the nearly planar coordination environment provided by the macrocyclic ligand (Figure 1).

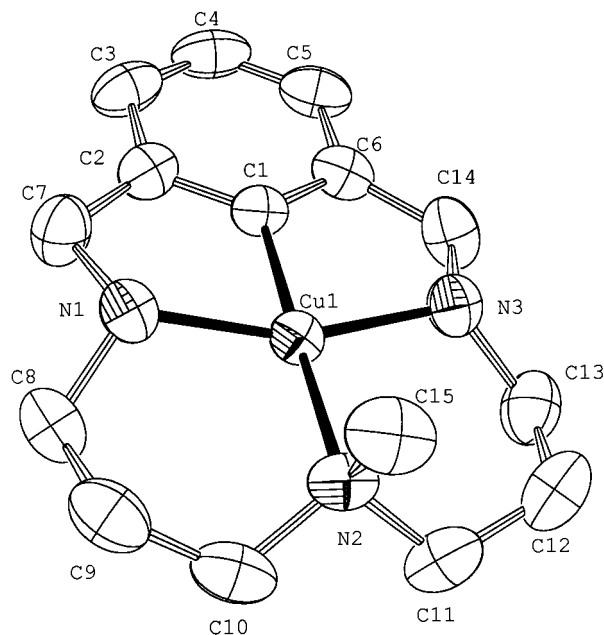


Figure 1. ORTEP plot of **2**– $(ClO_4)_2$ with 50% probability thermal ellipsoids, excluding the two perchlorate anions. Selected bond lengths [Å] and angles [°] of **2**– $(ClO_4)_2$ (corresponding values of **1**– $(ClO_4)_2$ in brackets): Cu1–C1 1.905(3) [1.848(4)], Cu1–N1 1.965(3) [1.899(4)], Cu1–N2 2.031(3) [2.000(8)], Cu1–N3 1.961(3) [1.911(3)]; N1–Cu1–C1 82.9(2) [84.6(2)], C1–Cu1–N3 82.3(2) [84.4(2)], N1–Cu1–N2 96.9(1) [105.6(2)], N2–Cu1–N3 97.4(1) [85.1(2)], C1–Cu1–N2 177.6(1) [163.5(2)], N1–Cu1–N3 160.7(2) [169.0(2)], Cu1–O1 2.442(4) [2.428(6)], Cu1–O8 2.736(4) [2.584(6)].

The equatorial Cu ligation is composed of three nitrogen atoms of the triazamacrocycle and one aryl C donor. Activation of the aryl C–H¹ bond (Scheme 1) creates a C ligand and allows the macrocycle to adopt a square-planar metal-binding conformation akin to the analogous pyridine-derived tetraazamacrocyclic ligand (see above). The Cu–C distances in **1** and **2** are the shortest in the coordination sphere at 1.848 Å and 1.905 Å, respectively. The Cu–N bond lengths systematically vary within each structure; the two benzylic Cu–N distances in **1** and **2** average 1.90 Å and 1.96 Å, respectively, and are shorter than the nonbenzylic Cu–N distances of 1.96 Å and 2.03 Å, respectively. The lack of extremely short Cu–ligand distances and the hexacoordinate ligation, albeit weak in the axial direction, is unusual for low-spin Cu^{III} complexes.^[12] Regarding the C ligand as an anionic donor, designation as Cu^{III} is appropriate with two counteranions.^[13] Furthermore, Cu K-edge X-ray absorption spectra^[14] of solid

samples of **1**-(ClO₄)₂–**3**-(ClO₄)₂ and **1**-(CF₃SO₃)₂ clearly exhibit an intense pre-edge feature at 8981 ± 0.5 eV, characteristic of a 1s → 3d_{x²–y²} transition in a low-spin Cu^{III} center.^[15] The spectra also indicate that this transition is sensitive to the size of the azamacrocycle, but not to the nature of the coordinating counteranions (Figure 2). The higher energy pre-edge transition for **1**-(ClO₄)₂ (8981.2 eV) compared to **2**-(ClO₄)₂ (8980.7 eV) correlates with the more compact

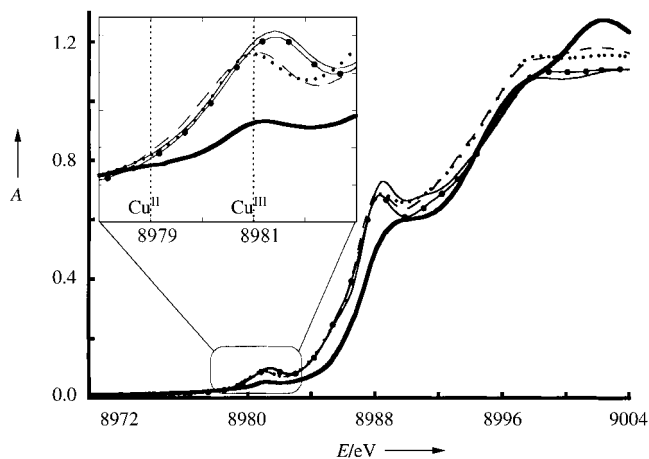


Figure 2. Cu K-edges for Cu^{III} complexes **1**-(CF₃SO₃)₂ (—), **1**-(ClO₄)₂ (•••), **2**-(ClO₄)₂ (---), **3**-(ClO₄)₂ (—••), and [Cu^{III}(H₃Aib₃)]^[14] (—). The amplified inset shows the pre-edge region (1s → 3d_{x²–y²} transition, 8978–8983 eV). A = normalized absorption, E = energy.

equatorial ligation; the average equatorial bond lengths in **1** are about 0.05 Å shorter than in **2**. Comparison of **1** with **2** suggests that the difference in the transition energies results primarily from destabilization of the 3d_{x²–y²} level of **1** relative to **2**. The more unfavorable Cu^{III} → Cu^I reduction potential of **1** compared to either **2** or **3** (> 0.250 V)^[16] further supports this notion. A consistent interpretation of this data is that the more compact ligation afforded by the smaller macrocyclic ligand in **1** better stabilizes a Cu^{III} center.

The size of the macrocycle and derivatization dramatically influence the rate of disproportionation of [Cu^{II}L]²⁺. Optical monitoring of the progress of the reaction (300–800 nm) suggests a complex mechanism for the formation of **1**–**3**. Starting with a 1:1 Cu^{II}:L stoichiometry (L = L¹–L³), the disappearance of each initially formed [Cu^{II}L]²⁺ complex exhibits an induction period followed by an exponential decay suggestive of an autocatalytic reaction. While a slight excess of Cu^{II} completely inhibits the disproportionation reaction, a slight excess of ligand (Cu^{II}:L 1:1.3) accelerates the reaction by elimination of the induction period. Under such conditions, the process is first order in [Cu^{II}] from 0.5 to 2.5 mM, and the observed rate constants for [Cu^{II}L¹]²⁺ and [Cu^{II}L²]²⁺ of 2.1(1) × 10^{–2} and 1.9(1) × 10^{–1} s^{–1}, respectively, clearly show that the complex of the larger, more flexible L² ligand reacts faster.^[17] The rate of disproportionation of [Cu^{II}L³]²⁺ is comparable to that of [Cu^{II}L²]²⁺.

Assuming similar mechanisms for the formation of **1**–**3**, the rate-determining step (RDS) involves C–H¹ bond cleavage; a large primary kinetic isotope effect (KIE) was measured with

selectively monodeuterated L³.^[18] The combined data suggests that the RDS in the disproportionation reaction is a base-assisted, heterolytic C–H bond cleavage to give a [Cu^{II}L']⁺ complex, where L' represents the deprotonated ligand (Scheme 2). The inhibition of the disproportionation reaction by excess Cu^{II} suggests that free ligand can act as the exogenous base. Subsequent fast electron transfer from [Cu^{II}L]⁺ to another [Cu^{II}L]²⁺ complex would result in the observed diamagnetic Cu^{III} and Cu^I products. The ability of an amine such as the free ligand to readily deprotonate an aryl C–H bond in the RDS is potentially explained by an enhanced σ_{CH}–Cu interaction. Such interactions can significantly reduce the pK_a of an aryl C–H group.^[3,19] The macrocyclic constraints of L¹–L³ ligated to Cu^{II} through all three nitrogen atoms requires the aryl C–H¹ bond to be in close, if not intimate, contact with the Cu^{II} center.^[20] Deprotonation and formation of a [Cu^{II}L]⁺ complex would then lead to products.^[19]

While aryl C–H-insertion chemistry and formation of stabilized Cu^{III}–aryl complexes in these simple triazamacrocyclic ligands is intriguing, their subsequent reactivity with hydroxide to yield Cu^{II}–phenoxoazamacrocyclic complexes is perhaps more interesting.^[21] Most remarkable is that the same Cu^{II} phenoxo products result from exposing the Cu^I triazamacrocyclic complexes to dioxygen, and this reaction proceeds through an intermediate observed in the Cu^{III}/hydroxide reaction. This oxidative chemistry is reminiscent of the aromatic hydroxylation performed by tyrosinase, a binuclear copper enzyme.^[22] While the generally accepted enzymatic mechanism does not involve direct aryl C–H activation by a Cu^{II} center, no current data precludes it. Further studies on these complexes are necessary to highlight the mechanistic similarities to or differences from the biological systems.

Experimental Section

The synthesis of **1**-(ClO₄)₂ is representative of all complexes prepared in this study.

Equimolar amounts of L¹ (30 mg, 1.4 × 10^{–4} mol) and Cu^{II}(ClO₄)·6H₂O (51 mg, 1.4 × 10^{–4} mol) were dissolved in CH₃CN (3 mL) under Ar. The resulting yellow solution was stirred for 30 min and filtered through Celite. Slow diffusion of diethyl ether into the filtered solution resulted in the formation of yellow crystals of [Cu^{III}L¹](ClO₄)₂ (**1**-(ClO₄)₂) in 50 % yield of isolated product (32 mg, 7 × 10^{–5} mol) after 24 h. The analogous procedure with Cu^{II}(CF₃SO₃)₂ resulted in nearly identical yields of isolated **1**-(CF₃SO₃)₂. X-ray quality crystals of **1**-(ClO₄)₂ and **2**-(ClO₄)₂ were obtained by recrystallization from CH₃CN/diethyl ether.

1-(ClO₄)₂: ESI-MS (CH₃CN): *m/z* 380 [L-(ClO₄)]⁺; UV/Vis (CH₃CN): λ_{max}(ε) = 273 (6900), 409 nm (280); ¹H NMR (500 MHz, CD₃CN, 25 °C): δ = 7.28 (t, 1H), 7.03 (d, 1H), 7.01 (d, 1H), 6.85 (m, 1H), 5.96 (m, 1H), 4.65 (d, 1H), 4.60 (m, 2H), 4.51 (d, 1H), 3.48 (dt, 1H), 3.37 (td, 1H), 3.24 (dd, 1H), 3.13 (m, 3H), 2.97 (qd, 1H), 2.75 (q, 1H), 2.17 (m, 1H), 1.65 ppm (m, 1H); elemental analysis (%) calcd for C₁₃H₂₀N₃CuCl₂O₈: C 32.5, H 4.2, N 8.7; found: C 32.9, H 4.0, N 8.6.

2-(ClO₄)₂: ESI-MS (CH₃CN): *m/z* 408 [L-(ClO₄)]⁺; UV/Vis (CH₃CN): λ_{max}(ε) = 291 (7500), 440 nm (sh, 250); ¹H NMR (500 MHz, CD₃CN, 25 °C): δ = 7.27 (t, 1H), 6.95 (d, 2H), 6.33 (m, 2H), 4.67 (d, 2H), 4.52 (d, 2H), 3.24 (m, 2H), 3.08 (m, 2H), 3.05 (m, 2H), 2.73 (s, 3H), 2.65 (dt, 2H), 2.15 (m, 2H), 1.95 ppm (m, 2H); elemental analysis (%) calcd for C₁₅H₂₄N₃CuCl₂O₈: C 35.4, H 4.7, N 8.3; found: C 35.7, H 4.4, N 8.4.

3-(ClO₄)₂: ESI-MS (CH₃CN): *m/z* 394 [L-(ClO₄)]⁺; UV/Vis (CH₃CN): λ_{max}(ε) = 280 (8200), 448 nm (sh, 280); ¹H NMR (500 MHz, CD₃CN, 25 °C): δ = 7.27 (t, 1H), 6.95 (d, 2H), 6.12 (m, 2H), 4.61 (dd, 2H), 4.49 (dd, 2H),

3.14 (m, 1H), 3.09 (m, 3H), 2.99 (dq, 2H), 2.63 (dq, 2H), 2.04 (m, 2H), 1.77 (m, 2H); elemental analysis (%) calcd for $C_{14}H_{23}N_3CuCl_2O_8$: C 33.9, H 4.7, N 8.5; found: C 34.1, H 4.6, N 8.4.

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- [17] At 298 K, $[\text{Cu}^{\text{II}}\text{L}^1]_i = 1.25$ mM; $[\text{L}^1]/[\text{Cu}^{\text{II}}]_i = 1.28$; $[\text{Cu}^{\text{II}}\text{L}^2]_i = 1.21$ mM, $[\text{L}^2]/[\text{Cu}^{\text{II}}]_i = 1.28$.
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Migration of a Phosphane Ligand between the Two Metal Centers in Diruthenium Hydrido Complexes**

Yasuhiro Ohki and Hiroharu Suzuki*

In the coordination sphere of a metal cluster complex, the substrate can often interact with multiple metal centers simultaneously. The bridging coordination of hydride or carbon monoxide is a typical example of such interaction, and the multiple coordination of the ligand seems to be closely related to the dynamic behavior and reactivity of the ligand. Indeed, a carbonyl ligand in a cluster complex often undergoes intramolecular migration between the metal centers by way of an intermediary species with the bridging carbonyl.^[1] For a better understanding of the nature of *multi-metallic activation*, it is important to elucidate the interaction between the ligand and the multiple metal centers through the

[*] Prof. H. Suzuki, Y. Ohki⁺
Department of Applied Chemistry
Graduate School of Science and Engineering
Tokyo Institute of Technology and
CREST, Japan Science and Technology Corporation (JST)
O-okayama, Meguro-ku, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-3913
E-mail: hiroharu@n.cc.titech.ac.jp

[⁺] Present address: Department of Chemistry
Graduate School of Science
Nagoya University

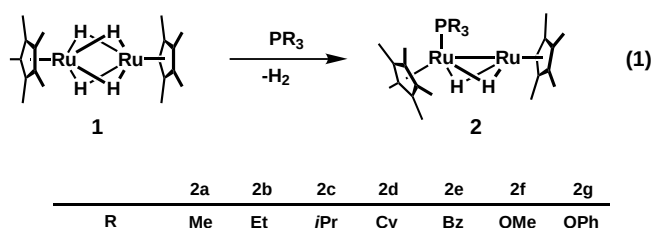
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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

analysis of the molecular structure and the dynamic processes of the cluster complex. Previously, we reported that a bridging phosphido complex $[(\eta^5\text{-C}_5\text{Me}_5\text{Ru})_2(\mu\text{-H})(\mu\text{-PPh}_2)(\mu\text{-}\eta^2\text{:}\eta^2\text{-C}_6\text{H}_6)]$ was formed in the reaction of $[(\eta^5\text{-C}_5\text{Me}_5\text{Ru})_2(\mu\text{-H})_4]$ (**1**)^[2] with triphenylphosphane as a result of P–C(aromatic) bond cleavage induced by synergy of the adjacent metal centers.^[3] We report herein the formation of novel dinuclear dihydrido complexes $[(\eta^5\text{-C}_5\text{Me}_5\text{Ru})_2(\text{PR}_3)(\mu\text{-H})_2]$ (**2**) in the reaction of $[(\eta^5\text{-C}_5\text{Me}_5\text{Ru})_2(\mu\text{-H})_4]$ (**1**) with a phosphorus ligand containing no aryl substituents. We also discuss the intramolecular migration of the phosphorus ligand between the two ruthenium atoms.

The reaction of **1** with an equimolar amount of a series of phosphorus ligands such as phosphanes and phosphites in toluene resulted in the quantitative formation of novel complexes $[(\eta^5\text{-C}_5\text{Me}_5\text{Ru})_2(\text{PR}_3)(\mu\text{-H})_2]$ (**2**) which bear the phosphorus ligand on one of the two ruthenium atoms [Eq. (1)]. Treatment of **2** with additional amounts of the



phosphorus ligand does not yield the corresponding bisphosphane complexes, probably due to the steric hindrance to the incoming phosphorus ligand. Complexes **2a–2g** are highly unsaturated (30e) and sensitive to moisture and air. Selected spectral data of **2** are listed in Table 1. The ratio of integral

intensities among the ^1H NMR signals for C_5Me_5 , PR_3 , and Ru–H of **2a–2g** indicated the formation of the dinuclear ruthenium dihydrido complexes containing a terminal phosphorus ligand. The ^{31}P NMR signals of **2a–2g** were observed in the range of $\delta = -7$ to 180 ppm. For example, the chemical shifts are $\delta = -6.9$, 77.9, 26.9, and 175.3 ppm for **2a**, **2c**, **2e**, and **2f**, respectively. These shifts are consistent with the coordination of the phosphorus ligands in the terminal mode.

The molecular structures of **2a–2g** were determined by X-ray diffraction studies.^[4] The perspective views of the structures are shown in Figure 1, and the selected geometric parameters are listed in Table 1. The ORTEP drawings clearly show the unsymmetrical structure of **2** in each, with PR_3 terminally coordinated to one of the two ruthenium atoms. The Ru–Ru vector is almost perpendicular to the C_5Me_5 ligand coordinated to the Ru2. The Ru1 atom adopts an approximate piano-stool geometry. The Cp–Ru1–P1 angles are around 130° irrespective of the cone angle of the phosphorus ligands.^[5] It is noteworthy that there is a significant correlation among the $\Sigma\chi_i$ values of PR_3 ,^[5] the Ru1–P distances, and the Ru2–Ru1–P1 angle; with the increase of the electron-withdrawing character of the substituents on the phosphorus, the Ru1–P distance becomes shorter and the Ru2–Ru1–P1 angle narrows. Another notable feature of the structures is a short Ru–Ru distance (2.5084(4)–2.5502(7) Å) in agreement with the highly unsaturated (30e) character of **2**. A preliminary result of the DFT (B3LYP) calculation using a Gaussian98 A9 program package indicated that there was a direct bonding interaction between the two ruthenium atoms, which was less than that for a single bond;^[6] however, the metal–metal bond is never a triple bond in accord with the EAN rule. The shortening the Ru–Ru bond is, therefore, probably due to the presence of bridging hydride.

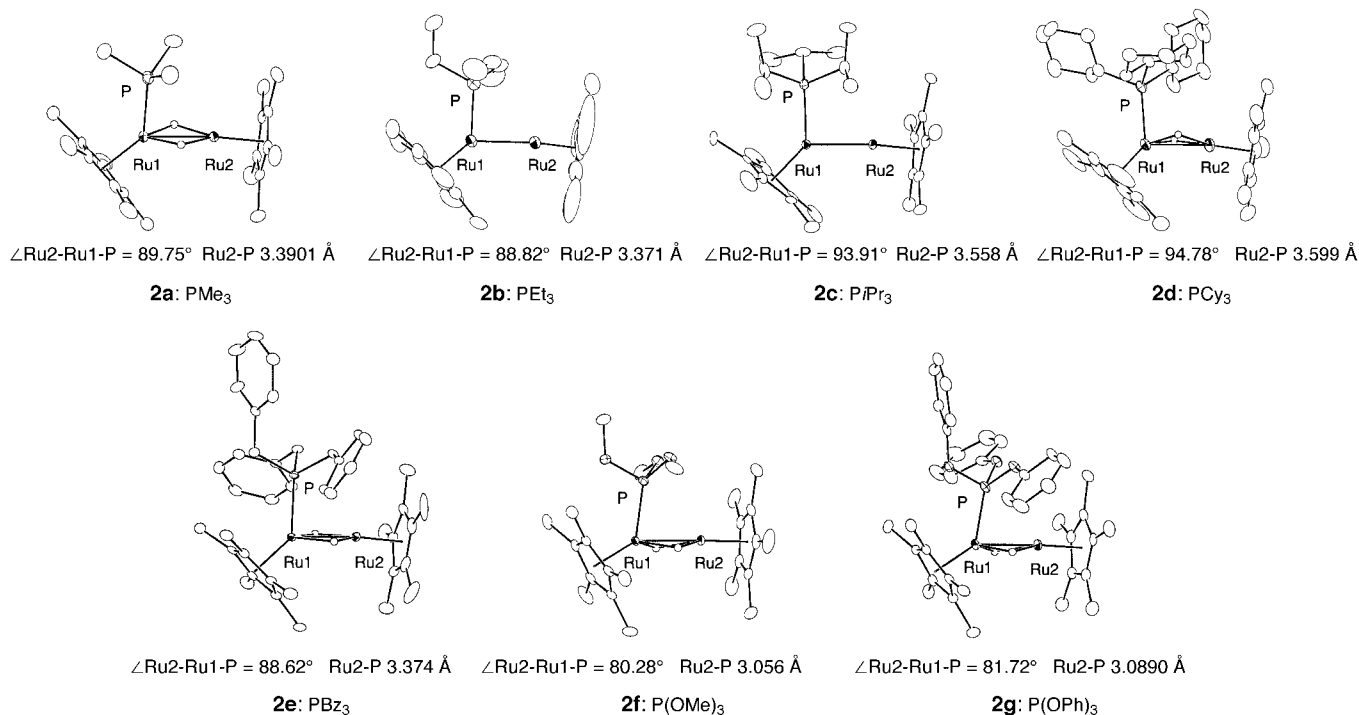
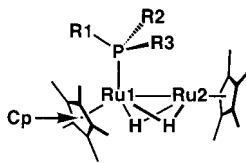


Figure 1. Molecular structures of **2a–2g**, with thermal ellipsoids at 30% probability level.

Table 1. Structural parameters and spectral data for complexes **2**.^[a]

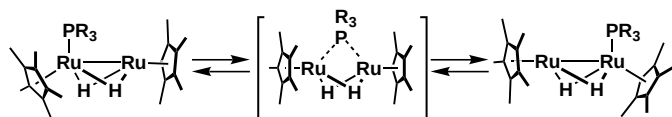


R	Me	Et	<i>i</i> Pr	Cy	no. 1	Bz no. 2	OMe	OPh
Ru1–P distance	2.281(2)	2.285(2)	2.340(2)	2.336(2)	2.292(1)	2.299(1)	2.2175(9)	2.200(1)
P–Ru1–Cp angle	131.1	132.8	134.9	133.7	133.1	133.9	128.7	131.3
Ru2–Ru1–P angle	89.75(5)	88.82(6)	93.91(6)	94.78(4)	88.62(3)	86.16(3)	80.28(3)	81.72(3)
P–R1 distance	1.831(7)	1.845(8)	1.854(10) ^[b]	1.899(7)	1.880(4)	1.864(4)	1.625(2)	1.641(2)
P–R2, P–R3 distances	1.807(7)	1.81(1)	1.857(9) ^[b]	1.874(5)	1.860(4)	1.869(4)	1.616(2)	1.636(3)
	1.812(7)	1.846(9)	1.881(9) ^[b]	1.875(6)	1.847(4)	1.870(4)	1.611(2)	1.638(3)
Ru1–Ru2 distance	2.520(1)	2.5262(9)	2.5361(9)	2.5502(7)	2.5326(4)	2.5356(5)	2.5102(4)	2.5084(4)
$\Sigma\chi_i$ value ^[c]	7.8	5.6	3.1	0.3	10.3	10.3	23.4	29.2
Cone angle for PR3 ^[c]	118	132	160	170	165	165	107	128
¹ H NMR (C ₅ Me ₅ , δ , RT) ^[d]	1.88	1.87	1.71, 1.95	1.80, 2.00	1.75	1.75	1.90	1.77
¹ H NMR (Ru–H, δ , RT) ^[d]	–13.65	–13.89	–14.75	–14.70	–13.44	–13.44	–14.23	–14.14
³¹ P{ ¹ H} NMR (δ , RT) ^[d]	–6.89	36.3	77.9	64.9	26.9	26.9	175.3	147.1
$\Delta H^\ddagger$ migration [kcal mol ^{–1}]	6.8	9.2	12.6	15.7	7.2	7.2	6.2	– ^[e]
$\Delta S^\ddagger$ migration [eu]	–8.0	–5.6	–8.8	–3.5	–16.3	–16.3	–14.0	– ^[e]

[a] Labeling scheme as shown. [b] P–R1 in **2c** does not stretch toward Ru2. [c] These values are cited in reference [5]. [d] In C₆D₆. [e] The activation parameters for **2g** could not be determined because the signals for C₅Me₅ groups are observed to be equivalent in the range from –110 °C to 25 °C.

Although the two cyclopentadienyl ligands in **2** are each in a different steric environment in the solid state, their ¹H NMR signals were observed to be equivalent above room temperature. As the temperature was lowered, the signal for the C₅Me₅ group was remarkably broadened and split into two peaks below about –100 °C. The intramolecular migration of

the line-shape analysis of the variable-temperature ¹H NMR spectra (Figure 2) are also listed in Table 1. The small $\Delta S^\ddagger$ values rule out the possibility of an intermolecular process, and are consistent with the above-mentioned intramolecular process. The values are similar to those found in migration of a



Scheme 1. Fluxional behavior of the diruthenium hydrido complexes.

the phosphorus ligand between the two ruthenium centers likely accounts for this fluxional behavior (Scheme 1). Only a few examples are thus far known for the migration of a terminal phosphane ligand among metal centers,^[7] but the mechanistic details are still uncertain. The possibility of an intermolecular process, namely, liberation of the PR₃ group from one of the ruthenium centers and its recombination with another ruthenium atom, is ruled out because the coordinated PR₃ group in **2** is not exchanged with added phosphanes [Eq. (2)]. Kinetic parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, estimated from

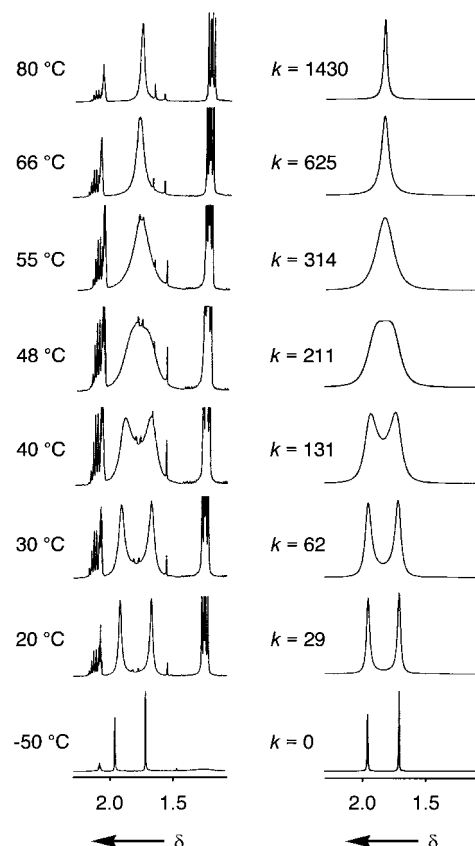
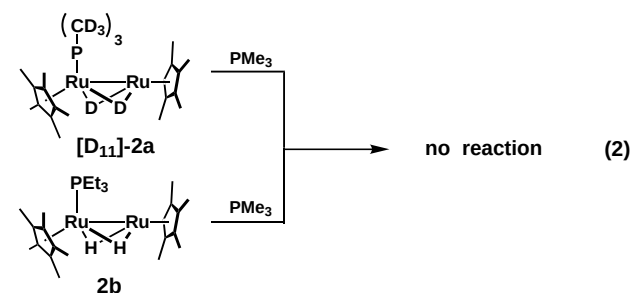


Figure 2. Variable-temperature ¹H NMR spectra of **2c** (left) and calculated spectra (right; C₅Me₅ region).

silyl group on a diruthenium core.^[8] A dinuclear species with a bridging five-coordinate phosphane ligand in between the two ruthenium atoms is plausible for the transition state (Scheme 1). Such a dinuclear μ -PR₃ complex has been reported recently,^[9] and a dipalladium complex bridged by the pentacoordinate phosphane has also been reported.^[10] There is a close correlation between the $\Delta H^\ddagger$ values and the electronic parameters $\Sigma\chi_i$ defined by Tolman.^[5] The more electron-withdrawing the substituent on the phosphane ligand is, the smaller the $\Delta H^\ddagger$ value is. This result suggests that through-space interaction between the phosphorus and Ru2, $\sigma^*(\text{P}-\text{C})-\text{d}(\text{Ru}2)$ and/or $\text{p}(\text{P})-\text{d}(\text{Ru}2)$, possibly leads to the migration of the phosphorus ligand. Although we have not yet deduced which interaction is predominant, a linear relationship between the Ru2-Ru1-P angle and the $\Sigma\chi_i$ value for the phosphorus ligand (Figure 3) is consistent with such a backbonding interaction. The enhancement of the Ru2-P back-

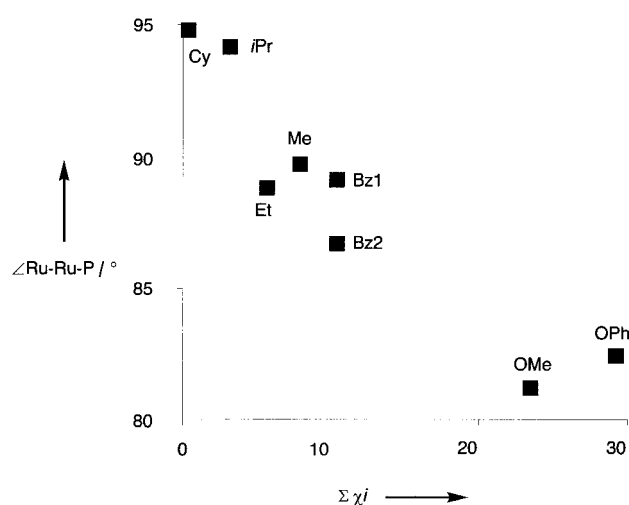


Figure 3. Relationship between Ru2-Ru1-P angles and electronic parameters $\Sigma\chi_i$.

bonding interaction due to introduction of electron-withdrawing substituents on the phosphorus atom likely leads to the decrease of the Ru2-Ru1-P angle. The $\sigma^*(\text{P}-\text{C})-\text{d}(\text{Ru}2)$ backbonding interaction may be rationalized by the coplanarity of the Ru2, Ru1, P, and R in **2a**, **2b**, **2f**, and **2g**, observed in the X-ray structure analyses.

We have synthesized novel diruthenium complexes containing a phosphorus ligand and demonstrated the migration of the phosphorus ligand between the two ruthenium centers. From a thermodynamic and structural standpoint, we propose a through-space backbonding interaction between the ruthenium and phosphorus atoms.

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- [4] The diffraction data were measured on an AFC-7R four-circle diffractometer (**2a**, **2c**, **2f**) or RAXIS-2 imaging plate area detector (**2b**, **2d**, **2e**, **2g**). The structures were solved by the Patterson method (DIRDIF92 PATTY). All non-hydrogen atoms were refined anisotropically, and hydrogen atoms except for Ru-H (refined isotropically) were fixed at the calculated positions. Crystal data for **2a**: monoclinic, $P2_1/n$, $a = 11.439(4)$, $b = 14.208(6)$, $c = 15.527(5)$ Å, $\beta = 90.79(3)^\circ$, $V = 2523(1)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.450$ g cm⁻³; 6316 reflections ($5^\circ \leq 2\theta \leq 55^\circ$), 4048 observed with $F > 3\sigma(F)$, 244 parameters; $R = 0.040$, $R_w = 0.037$. Crystal data for **2b**: monoclinic, $P2_1/c$, $a = 16.63(1)$, $b = 8.446(1)$, $c = 20.57(2)$ Å, $\beta = 95.00(7)^\circ$, $V = 2878(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.368$ g cm⁻³; 6646 reflections ($5^\circ \leq 2\theta \leq 60^\circ$), 4603 observed with $F > 3\sigma(F)$, 263 parameters; $R = 0.057$, $R_w = 0.054$. Crystal data for **2c**: monoclinic, Pn , $a = 11.168(4)$, $b = 11.170(4)$, $c = 11.902(4)$ Å, $\beta = 94.04(3)^\circ$, $V = 1481.0(9)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.424$ g cm⁻³; 3361 reflections ($5^\circ \leq 2\theta \leq 55^\circ$), 2859 observed with $F > 3\sigma(F)$, 290 parameters; $R = 0.038$, $R_w = 0.047$. Crystal data for **2d**: monoclinic, $P2_1/n$, $a = 30.8323(7)$, $b = 11.899(2)$, $c = 11.342(4)$ Å, $\beta = 91.27(2)^\circ$, $V = 4159(1)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.321$ g cm⁻³; 8667 reflections ($5^\circ \leq 2\theta \leq 60^\circ$), 5376 observed with $F > 3\sigma(F)$, 396 parameters; $R = 0.048$, $R_w = 0.060$. Crystal data for **2e**: triclinic, $P\bar{1}$, $a = 18.421(4)$, $b = 20.121(4)$, $c = 10.129(2)$ Å, $\alpha = 90.90(1)$, $\beta = 98.44(1)$, $\gamma = 88.19(2)^\circ$, $V = 3711(1)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.394$ g cm⁻³; 15623 reflections ($5^\circ \leq 2\theta \leq 60^\circ$), 11404 observed with $F > 3\sigma(F)$, 810 parameters; $R = 0.034$, $R_w = 0.033$. Crystal data for **2f**: monoclinic, $P2_1/n$, $a = 19.823(4)$, $b = 15.991(5)$, $c = 8.351(4)$ Å, $\beta = 98.86(3)^\circ$, $V = 2615(1)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.520$ g cm⁻³; 6638 reflections ($5^\circ \leq 2\theta \leq 55^\circ$), 4836 observed with $F > 3\sigma(F)$, 271 parameters; $R = 0.027$, $R_w = 0.025$. Crystal data for **2g**: monoclinic, $P2_1/a$, $a = 17.146(5)$, $b = 17.8115(9)$, $c = 11.599(2)$ Å, $\beta = 96.28(2)^\circ$, $V = 3521.0(10)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.481$ g cm⁻³; 7385 reflections ($5^\circ \leq 2\theta \leq 60^\circ$), 5970 observed with $F > 3\sigma(F)$, 406 parameters; $R = 0.037$, $R_w = 0.027$. CCDC-173306 to CCDC-173312 contains the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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A Combined Effect of Molecular Electrostatic Potential and N7 Accessibility Explains Sequence-Dependent Binding of *cis*-[Pt(NH₃)₂(H₂O)₂]²⁺ to DNA Duplexes**

Véronique Monjardet-Bas, Miguel-Angel Elizondo-Riojas,* Jean-Claude Chottard, and Jiří Kozelka*

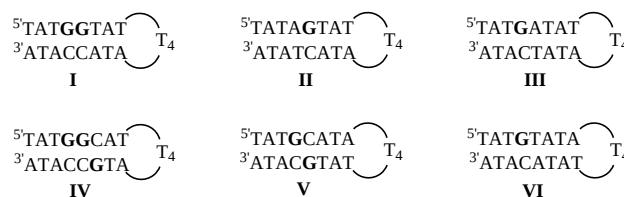
The sequence selectivity that characterizes the DNA binding of the antitumor drug cisplatin (*cis*-[PtCl₂(NH₃)₂]) has been subject to a number of investigations.^[1–8] The drug binds preferentially to guanine residues involved in G_n runs (*n* ≥ 2), where it forms N7–N7 intrastrand GG–Pt chelates as the major adducts. The species actually reacting with DNA are the hydrolyzed forms of cisplatin, namely, *cis*-[PtCl(NH₃)₂(H₂O)]⁺ (**1**) and/or *cis*-[Pt(NH₃)₂(H₂O)₂]²⁺ (**2**).



As the overall selectivity observed for the cisplatin–DNA interaction may arise from a combination of individual binding preferences of the two hydrolyzed species, our goal is to investigate the factors determining the kinetics of DNA binding of each complex. Understanding these factors should, on one hand, give us a clue to the overall sequence selectivity of cisplatin and, on the other hand, reveal the impact of exchanging a single ligand on the kinetics of platination. This latter point is interesting in the more general context of sequence-dependent binding of electrophiles to DNA.

Our strategy has been to examine the reactions of **1** and **2** with hairpin-stabilized duplex oligonucleotides in which one to three guanine residues are placed in different local sequences, while the overall environment is retained. Measuring the rate constants for platination of the individual

guanine residues of these duplexes enabled us to study the influence of the adjacent bases on the platination of a guanine within duplex DNA. For the diaqua species **2**, we have now measured the platination rate constants of all the guanines involved in the duplexes shown in Scheme 1. We demonstrate here that the rate constants determined for the individual



Scheme 1. Schematic representation of the hairpin-stabilized duplex oligonucleotides used in the reactions with **1** and **2**.

guanine residues can be accounted for by a kinetic model consisting of an initial, rapid, and reversible association of **2** on the surface of DNA and a subsequent irreversible ligand substitution step. Our model considers the molecular electrostatic potentials (MEP) and accessible areas (aa) of the van der Waals spheres of the N7 atoms as the principal variables determining the sequence-dependent reaction kinetics. It differs from the accessible surface integrated field (ASIF) model introduced earlier by Lavery and Pullman to interpret sequence-dependent N7-alkylation,^[9,10] which combined the influences of accessibility and electrostatics by calculating the flux of the electrostatic field through the accessible surface. In our model, electrostatics is considered mainly to affect the local concentration of the electrophile on the N7 van der Waals surface, whereas accessibility determines the kinetics of the proper ligand substitution step.

From the rate constants shown in Table 1, we infer that within duplex DNA, the reactivity of a guanine residue G towards **2** decreases in the series TGG > GGT > TGA ≈ AGT > GGC ≈ TGT > TGC. This order is similar to but not identical with the order of the MEP in the vicinity of the N7 atoms of G, as calculated for double-stranded B-DNA triplets:^[11] GGT > TGG > GGC > AGT > TGA ≈ TGT > TGC. This suggests that one component of the observed sequence selectivity of **2** may arise from different local concentrations of **2** on the DNA surface. A reversible association between the cationic complex **2** and the anionic DNA has been shown to precede ligand substitution.^[12] The substitution step is expected to proceed with its own sequence

Table 1. Apparent rate constants measured for the reaction of **2** with the individual guanine residues of the DNA duplexes shown in Scheme 1. The rate constants correspond to the underscored guanine.^[a]

Sequence	Duplex	<i>k</i> _{app} [M ^{−1} s ^{−1}]	Ref.
T <u>G</u> GT	I	18(1)	[7]
T <u>G</u> GT	I	15(1)	[7]
A <u>G</u> T	II	9(1)	[7]
T <u>G</u> A	III	9.6(5)	[19]
T <u>G</u> GC	IV	32(5)	[32]
T <u>G</u> GC	IV	2.0(5)	[32]
T <u>G</u> C	V	0.5(1) ^[b]	[32]
T <u>G</u> T	VI	1.9(5)	[19]

[a] Reaction conditions: 20 °C, 0.1 M NaClO₄, pH 4.5 ± 0.1. [b] Rate constant for each individual guanine residue.

[*] M.-A. Elizondo-Riojas⁺, Dr. J. Kozelka, V. Monjardet-Bas, Prof. J.-C. Chottard
Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques
UMR 8601 CNRS, Université René Descartes
45, rue des Saints-Pères, 75270 Paris (France)
Fax: (+33)1-4286-8387
E-mail: melizond@ccr.dsi.uanl.mx,
kozelka@biomedicale.univ-paris5.fr

[+] On leave from the Centro Universitario Contra el Cancer (CUCC)
Hospital Universitario “Dr. José Eleuterio González”
Universidad Autónoma de Nuevo León
Monterrey, N.L. (México)

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

selectivity, and the ordering of the apparent rate constants is thus likely to correspond to a combination of the selectivities of both steps. The kinetics of the second step will depend on 1) the accessibility of the N7 atom and 2) its intrinsic reactivity, which is related to the stability of the transition state. The energy of the transition state is expected to be a function of the interactions between the platinum ligands and the neighboring DNA residues, and also of the MEP, which will influence the electrostatic component of the Pt–N7 bond being formed. In our work we have tested a hypothesis according to which the major factor determining the sequence dependence of the substitution step is the accessibility of the N7 center. We show in the following that a simple mathematical model combining the electrostatic effect in the association step with the accessibility effect in the substitution step indeed allows one to account for the observed rate constants.

The two-step mechanism that we considered is shown in Scheme 2. Since the reversible association step, driven by diffusion and electrostatic forces, is expected to be very fast,^[13] the apparent rate constant will be equal to the product of the equilibrium constant K and the rate constant k for the ligand substitution step. The local concentration of the cationic platinum complex in the vicinity of a given N7 atom is proportional to K , which is dependent on the local MEP. This dependence is accounted for by an exponential term derived from Boltzmann statistics, that is, $K \propto \exp(-q \text{MEP}(\epsilon_L RT)^{-1})$, where ϵ_L is the local dielectric coefficient, q is the unitless formal charge of the species reacting with DNA, and the MEP

as well as RT are expressed in kcal mol^{-1} . The rate constant k is considered to be proportional to the accessible area aa on the N7 van der Waals surface. Thus, the apparent rate constant is given by Equation (1), where c_1 is a proportionality factor

$$k_{\text{app}} = Kk = c_1 aa \exp(-q \text{MEP}(\epsilon_L RT)^{-1}) \quad (1)$$

with the dimensions of $\text{M}^{-1} \text{s}^{-1} \text{\AA}^{-2}$ which includes the rate constant for the proper chemical step (ligand substitution).

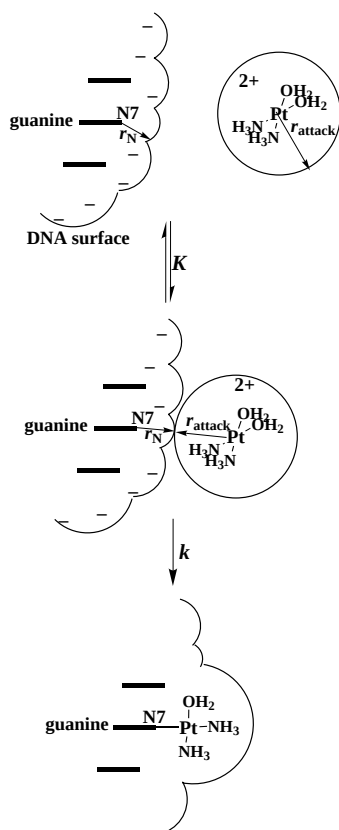
In this model, sequence-dependent effects on c_1 —resulting, for example, from nonbonding interactions in the transition state or from structural variations of the double helix—are not taken into account. Equation (1) can be transformed into Equation (2).

$$\ln(k_{\text{app}} aa^{-1}) = \ln(c_1) - q \text{MEP}(\epsilon_L RT)^{-1} = c'_1 + c'_2 \text{MEP} \quad (2)$$

The constants c'_1 and c'_2 can be obtained by plotting $\ln(k_{\text{app}} aa^{-1})$ against MEP (by using the observed rate constants listed in Table 1 for k_{app} and the calculated values for aa and MEP) and determining the regression line. The aa and MEP values were calculated for each guanine environment by using B-DNA model structures, as outlined in the Experimental Section. In these calculations, the reacting platinum complex was approximated as a sphere of radius r_{attack} (Scheme 2) that is considered to roll over the DNA van der Waals surface.^[9,14] The MEP values associated with each aa were determined for the point on the bisector of the C5–N7–C8 angle having a distance of $(r_{\text{attack}} + r_N)$ from N7 (r_N is the van der Waals radius of the N atom).

Both aa and MEP were calculated for the interval $3.8 \text{\AA} \leq r_{\text{attack}} \leq 5 \text{\AA}$. The lower limit corresponds to the radius of a spherical van der Waals envelope of complex **2** and the upper limit to that of an envelope of complex **2** associated axially with two molecules of water.^[15] Within the interval considered for r_{attack} , the MEP values undergo approximately linear parallel shifts; thus, only those calculated for one selected value of r_{attack} ($4.9 \text{\AA}$) are shown in Figure 1 a. In contrast, the variations of the accessible areas upon increasing r_{attack} are clearly nonlinear (Figure 1 b) and the relative order changes. In order to find out for which r_{attack} Equations (1) and (2) work the best, we have plotted $\ln(k_{\text{app}} aa^{-1})$ against MEP and carried out a linear regression corresponding to Equation (2) for each considered value of r_{attack} . The root-mean-square (rms) deviation between the left- and right-hand sides of Equation (2), determined with the optimized values for c'_1 and c'_2 over the eight rate constants listed in Table 1, was plotted against r_{attack} (see the Supporting Information). The best fit is obtained for $r_{\text{attack}} = 4.88 \text{\AA}$. Deconvolution of the optimized value of $-0.14 \text{ mol kcal}^{-1}$ for c'_2 into $-q(\epsilon_L RT)^{-1}$ ($q = 2$, $R = 0.002 \text{ kcal mol}^{-1} \text{K}^{-1}$, $T = 293 \text{ K}$) yields an ϵ_L value of about 24, which seems reasonable for a short-distance interaction at the DNA surface. The observed k_{app} values are plotted against the calculated values (right-hand side of Equation (1) with $c_1 = 9.57 \text{ M}^{-1} \text{s}^{-1} \text{\AA}^{-2}$ and $\epsilon_L = 24.4$, as optimized for $r_{\text{attack}} = 4.88 \text{\AA}$) in Figure 2. It can be seen that the fit is fairly satisfactory.

Sequence-selective electrophilic attack on guanine N7 centers of DNA has been observed for N7-methylation with



Scheme 2. The two-step mechanism considered in the mathematical model.

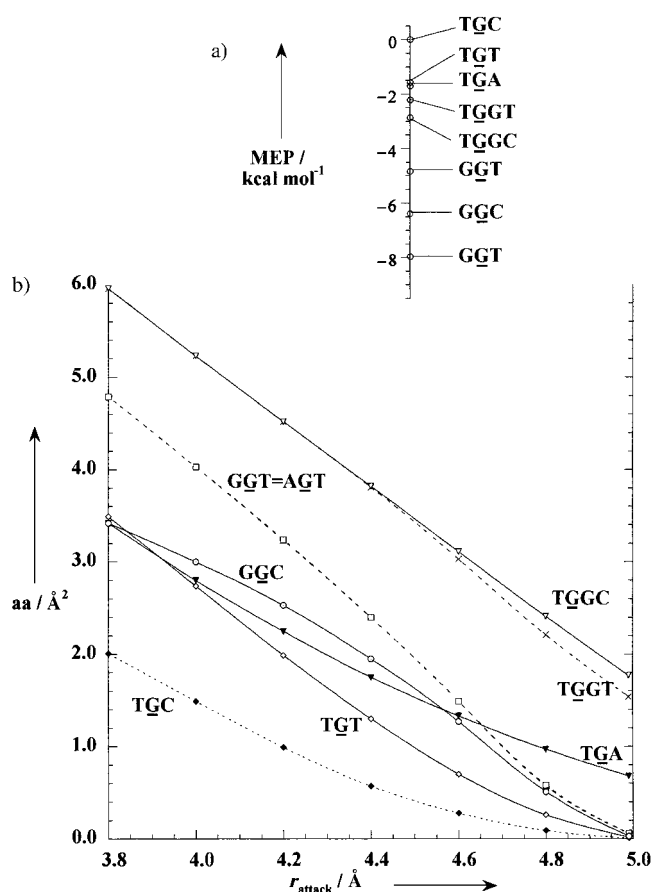


Figure 1. a) The molecular electrostatic potentials calculated for guanine residues in the sequences of the duplexes shown in Scheme 1 at $r_{\text{attack}} = 4.9 \text{ \AA}$ (see the Experimental Section and Scheme 2). The MEP value for TGC was set arbitrarily to zero. b) Accessible areas aa around N7 atoms calculated as a function of r_{attack} for the same sequences.

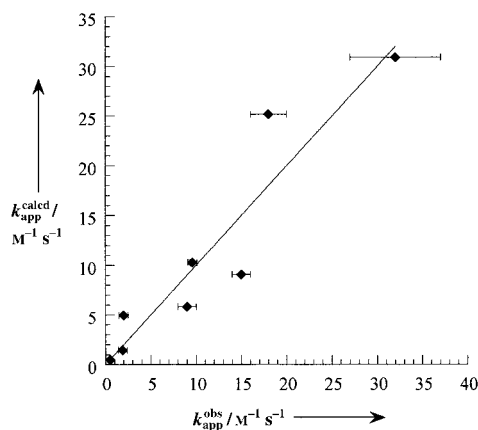


Figure 2. Observed apparent rate constants k_{app} (from Table 1) for the reactions between the individual guanine residues of the DNA duplexes shown in Scheme 1 and complex **2**, plotted against values calculated by using Equation (1), with the optimized constants $c_1 = 9.57 \text{ M}^{-1} \text{ s}^{-1} \text{ \AA}^{-2}$ and $\epsilon_L = 24.4$. The aa and MEP values were calculated with $r_{\text{attack}} = 4.88 \text{ \AA}$.

nitrogen mustards.^[16] For the least bulky nitrogen mustard, mechlorethamine, the relative rates of methylation roughly correlate with the MEP calculated at the N7 lone pair. For methylation of tRNA^{Phe} with dimethylsulfate, Lavery and Pullman found that a reactivity index combining steric and electrostatic factors, called accessible surface integrated field

(ASIF), yields a qualitative correlation with relative methylation rates of individual guanines of tRNA^{Phe}.^[9]

For DNA platination, we^[7,17] and others^[18] have previously suggested that hydrogen bonds between platinum ligands and DNA residues in the transition state could be responsible for the observed sequence selectivity. However, our later attempts to correlate the rate constants listed in Table 1 with the energies calculated for the corresponding pentacoordinate transition states were unsuccessful.^[19] The results presented here suggest that the main factors determining the sequence dependence of DNA platination with **2** are electrostatic potential and accessibility, while effects of noncovalent interactions in the transition state are probably of secondary importance. Hydrogen bonds from platinum ligands certainly do influence the reaction kinetics, as the reactivity of complexes $\text{cis-}[\text{PtL}(\text{NH}_3)_2(\text{H}_2\text{O})]^{n+}$ ($n = 1, 2$) towards a given DNA guanine residue increases with increasing hydrogen bonding capacity of the ligand L.^[7] However, as our present results suggest, and also in agreement with recent model calculations by Hambley,^[20] these interactions may be rather sequence-unspecific. For example, sequence-neutral hydrogen bonds from the platinum ligands to the 5'-phosphodiester group probably favor the approach of the platinum complex to any guanine N7 site, as indicated by the fact that a 5'-phosphate accelerates the platination of guanine nucleotides^[21,22] and dinucleotides.^[23]

The way our kinetic model accounts for electrostatic effects is principally different from Lavery's ASIF approach used to quantify the rate of guanine methylation by CH_3^+ cations generated from dimethylsulfate.^[9] The ASIF model considers the rate constant to be proportional to the flux of the electrostatic field through the accessible surface fragment of the van der Waals sphere around the N7 atom. In this model, the crucial variable is the radial component of the electric field at the center of the attacking sphere rolling over the van der Waals surface. We have calculated the sequence-dependent variations of this component within the interval $3.8 \text{ \AA} \leq r_{\text{attack}} \leq 5 \text{ \AA}$ and found them to be rather small ($\leq 13\%$) and almost independent of r_{attack} (not shown). Thus, multiplication of each accessible surface element with the radial field component modifies the sequence dependence of the accessible area around N7 only slightly. As a result, we found that the correlation of the experimental rate constants (Table 1) with the ASIF values is not better than that with the accessible areas only. At variance with ASIF, our present model considers that the electrostatic forces mainly determine the local concentration of the cationic species at the DNA surface, which depends on the MEP, a scalar entity. The corresponding function, $\exp(-q \text{MEP}(\epsilon_L RT)^{-1})$, undergoes sequence-dependent variations up to a factor of 6. Thus, the influence of electrostatics on the rate constant is significantly more important in our model than in the ASIF model.

As already mentioned, the MEP is expected to affect not only the preassociation equilibrium constant K but also the rate constant k for the substitution step, since a large electron density at the N7 lone pair will strengthen the Pt–N7 bond being formed. Thus, the exponential term in Equation (1) may contain some influence of the MEP on k , even though the refined ϵ_L value of 24 agrees reasonably well

with what would be expected for an outer-sphere preassociation.

Some striking features of the sequence-selective binding of **2** to DNA (Table 1) can now be interpreted on the basis of our kinetic model. First, the very low reactivity of the TGC sequence seems to be a combined effect of the steric bulk exerted by the flanking pyrimidines and of the low negative MEP. Second, the high reactivities of TGG and GGT are apparently also a combined effect of that of high aa and highly negative MEP. Finally, the similar reactivities of TGA and AGT towards **2** appear to originate from a compensation between the higher negative MEP of AGT and a higher accessibility of TGA. Interestingly, this compensation occurs only at $r_{\text{attack}} > 4.65 \text{ \AA}$, since below this value both aa and MEP favor AGT (Figure 1). Size and charge of the attacking species are therefore expected to affect selectivity.

In conclusion, the sequence dependence of guanine N7 platination with complex **2** can be accounted for by a combined effect of the molecular electrostatic potential, considered in our kinetic model to determine the local concentration of **2** at the DNA surface, and the steric bulk of the neighboring bases, quantified as the accessible area of the van der Waals sphere around the N7 atom. The good fit that we obtain between calculated and experimental rate constants suggests that other effects, such as nonbonding interactions in the transition state, are less important. This result is interesting for two reasons. First, it indicates that accessibility is a main factor determining the sequence-dependent binding of platinum complexes to DNA. This is further supported by our preliminary results showing that the same kinetic model holds also for the N7 platination by the monocationic complex **1**. Second, our model delineates a concept of treating the influence of electrostatics and accessibility in a simple mathematical formula which is formally in accord with the two-step mechanism (Scheme 2) generally accepted for ligand exchange reactions on metal complexes.^[24] This concept may be applicable—with eventual extensions, for example, to include the effects of solvation on the MEP^[25,26] or the influence of sequence-dependent variations of DNA structure on both the MEP and aa^[10]—to other metal complex–DNA systems, and possibly to DNA alkylation by organic electrophiles as well.

Experimental Section

The accessible areas (aa) around guanine N7 atoms and the associated molecular electrostatic potential (MEP) were calculated for the duplex parts of the hairpins shown in Scheme 1; canonical Arnott B-DNA structures were constructed by using the NUCGEN module of AMBER,^[27] and the helices were truncated on both sides after the third base pair from the central G–C base pair. (Thus, the calculations were carried out on double-stranded DNA heptamers.) The principle of the determination of aa has been outlined by Lavery and Pullman.^[9,28] Briefly, the reacting complex is approximated by a sphere of a radius r_{attack} which is considered to roll over the van der Waals surface of the molecule. The accessible area is defined as the surface that the center of the sphere describes while the sphere is in contact with the van der Waals sphere of the N7 atom; aa was calculated by using the Korobov method^[29] to generate a regular distribution of points on a sphere of the radius $(r_{\text{N7}} + r_{\text{attack}})$ around the selected N7 atom. (We used a Korobov index of 26, generating 196418 points.) Subsequently, we employed the algorithm by Lavery and Pullman^[9] to check for each point whether it lay within the van der Waals distance

$(r_{\text{X}} + r_{\text{attack}})$ of any atom X. The fraction of points outside all van der Waals contacts multiplied with $4\pi(r_{\text{N}} + r_{\text{attack}})^2$ finally yielded aa. The MEP was calculated for the space point at the C5–N7–C8 bisector at the distance $r_{\text{N}} + r_{\text{attack}}$ from the N7 atom (r_{N} is the van der Waals radius of N), as the sum $332\sum q_i/r_i$ [kcal mol^{−1}] calculated over all atoms, q_i [e] being the charge of atom i and r_i its distance from the space point in Å. For convenience, all MEP values were shifted so as to set the MEP for TGC to zero. (This offset modifies c_1 and c_1' but not c_2' or ϵ_{L} .)

The MEP and aa values plotted in Figure 1 were determined using the van der Waals radii and ESP atomic charges of Lavery and Pullman.^[28] Alternative use of van der Waals radii and/or atomic charges from the AMBER force field^[30] or of van der Waals radii by Bondi^[31] modified the numerical aa and MEP values but did not appreciably affect their sequence dependence.

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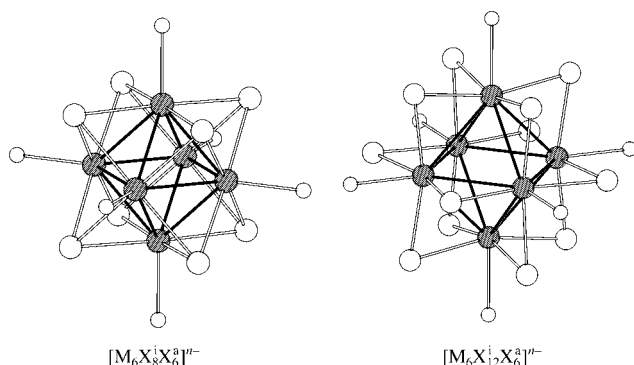
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Two $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ Isomer Anions in Two Nb_6 Cluster Oxyhalides:

$\text{Cs}_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]\cdot 4\text{H}_2\text{O}$ and $(\text{Me}_4\text{N})_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]\cdot 5\text{H}_2\text{O}^{**}$

Nikolai G. Naumov,* Stephane Cordier, and Christiane Perrin

The $(\text{M}_6\text{X}_8)^{n+}$ and $(\text{M}_6\text{X}_{12})^{n+}$ cluster cores (M = transition metal; X = halogen, chalcogen) constitute the basic building blocks of the early transition metal cluster chemistry.^[1–4] These $(\text{M}_6\text{X}_8)^{n+}$ and $(\text{M}_6\text{X}_{12})^{n+}$ entities are characterized by an M_6 octahedral cluster that is face-capped or edge-bridged by μ_3 or μ_2 inner ligands X^i . The clusters are stabilized by six additional ligands X^a in terminal positions to form $[\text{M}_6\text{X}_8^i\text{X}_6^a]^{n-}$ and $[\text{M}_6\text{X}_{12}^i\text{X}_6^a]^{n-}$ units. In mixed-ligand compounds, the fact



that the M_6 cluster is bonded to ligands of different sizes and charges should lead to great distortions and various electronic counts, which in turn affect the properties of the cluster itself.

Up to now, a large number of $(\text{M}_6\text{X}_8)^{n+}$ cluster core isomers have been obtained in chalcogenide chemistry. With few exceptions^[5,6] the crystallographic ligand sites are randomly occupied by halogen and chalcogen atoms; thus, the isomers are orientationally disordered.^[7–9] Furthermore, such complexes exhibit the same valence electron count for the cluster ($\text{VEC} = 24$). In contrast, the Nb_6 and Ta_6 oxyhalides recently obtained, which were built from $(\text{M}_6\text{X}_{12})^{n+}$ cluster cores, provide mixed-ligand cluster phases with an ordered distribution of oxygen and halogen atoms at inner ligand positions. Hitherto, a series of solids containing different isomer cluster

cores such as $(\text{Nb}_6\text{Cl}_{12-m}\text{O}_m)^{n+}$ ($m = 1–4$), $(\text{Nb}_6\text{Cl}_6\text{O}_6)^{n+}$, and $(\text{Ta}_6\text{X}_9\text{O}_3)^{n+}$ ($\text{X} = \text{Cl}, \text{Br}$) have been described.^[10–12] Their structures are based on $[\text{M}_6\text{X}_{12}^i\text{X}_6^a]^{n-}$ units containing a distorted M_6 cluster with various electronic counts ($\text{VEC} = 14–16$). Recently, the first W_6 oxychlorides based on the same type of unit were isolated.^[13] All these compounds are prepared by standard solid-state routes, that is, stoichiometric reactions in sealed quartz tubes at 650–850 °C. They are insoluble in water and common organic solvents.

The aim of the present work was to synthesize oxyhalide cluster isomers and to characterize them in solution and in the solid state in order to determine the influence of the position of oxygen in the cluster core on the structural and physical properties. Further, the clusters could be used as starting materials to design new inorganic polymeric cluster materials of different dimensionality.^[14]

To this purpose we have investigated the interaction of the solid-state niobium cluster oxyhalides $\text{Cs}_2\text{LaNb}_6\text{Cl}_{15}\text{O}_3$ ^[11d] and $\text{ScNb}_6\text{Cl}_{13}\text{O}_3$ ^[11a]—each contains a $(\text{Nb}_6\text{Cl}_9\text{O}_3)^{n+}$ cluster core that differs by the distribution of the three oxygen atoms at the inner positions—with aqueous KCN solution to replace the apical chlorine atom by a CN^- ligand. In this reaction, the $(\text{Nb}_6\text{Cl}_9\text{O}_3)^{n+}$ cluster core was expected to be unchanged, as observed for $(\text{M}_6\text{X}_8)^{n+}$ in transition metal octahedral cluster chemistry.^[15] Accordingly, we have now isolated the soluble salts $\text{Cs}_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]\cdot 4\text{H}_2\text{O}$ (**1**) and $(\text{Me}_4\text{N})_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]\cdot 5\text{H}_2\text{O}$ (**2**) containing $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ isomer anions that have been “excised” from the starting materials.

The niobium clusters $\text{Cs}_2\text{LaNb}_6\text{Cl}_{15}\text{O}_3$ and $\text{ScNb}_6\text{Cl}_{13}\text{O}_3$ react with deoxygenated aqueous solutions of KCN at room temperature. The solids fully dissolve to give green-brown solutions of $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ anions. The insoluble residues do not contain any traces of starting materials. The solutions and crystals of **1** and **2** are quite stable under an inert atmosphere but quickly decompose when exposed to air to give white hydrated niobium oxide(v) $\text{Nb}_2\text{O}_5\cdot x\text{H}_2\text{O}$. This decomposition is accelerated after addition of organic solvents—such as DMF, acetonitrile, methanol, or ethanol—containing traces of dissolved oxygen.

The excision reaction did not change the composition and ligand distribution of the $(\text{Nb}_6\text{Cl}_9\text{O}_3)^{n+}$ cluster cores observed in the parent oxychlorides. The $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ anions in **1** and **2** have a typical M_6X_{18} niobium octahedral cluster arrangement. The three oxygen and nine chlorine atoms are ordered over the 12 μ_2 positions, but their distribution in the two anions is strictly different (Figure 1). While in **1** the $\text{Nb}_6\text{Cl}_9\text{O}_3$ cluster core has an idealized D_3 symmetry, in **2** it has C_2 symmetry. The Nb–Nb, Nb–Cl, and Nb–O distances in **1** and **2** are very close to the corresponding distances in the two starting materials. The mean Nb–O distance is 1.952 Å for **1** and 2.006 Å for **2**, while the mean Nb–Cl distance is 2.493 Å for **1** and 2.492 Å for **2**. The difference between the sizes of the oxygen and chlorine atoms results in a large distortion of the Nb_6 cluster. Indeed, the Nb–Nb distances range from 2.790(2) to 2.9979(15) Å in **1** and from 2.7817(15) to 3.0251(15) Å in **2**. The shortest Nb–Nb distances of 2.790(2) Å for **1** and 2.7817(15) Å for **2** are seen for the oxygen-bridged edges of the octahedrons; these are comparable to the corresponding distances in octahedral niobium oxychlorides and ox-

[*] Dr. N. G. Naumov
Institute of Inorganic Chemistry, SB RAS
Ak. Lavrentiev prosp. 3
Novosibirsk 630090 (Russia)
Fax: (+7) 3832-344-489
E-mail: naumov@che.nsk.su

Dr. S. Cordier, Dr. C. Perrin
Institut de Chimie de Rennes
Laboratoire de Chimie du Solide et Inorganique Moléculaire
UMR 6511 CNRS-Université de Rennes 1
Avenue du Général Leclerc
35042 Rennes cedex (France)

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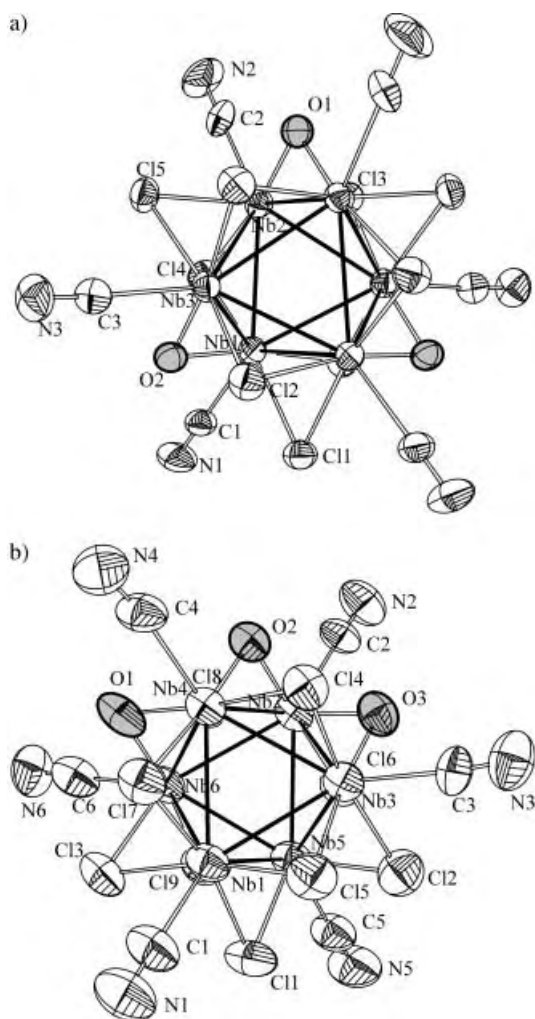


Figure 1. Structure of the $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ anion in a) **1** and b) **2**.

ides.^[11,12,16] The differences in the Nb–Nb distances result in a distortion of the outer ligand environment.^[17]

In **1** all three crystallographically independent niobium atoms lie in a similar environment made up of one μ_2 oxygen atom, three μ_2 chlorine atoms, and one terminal CN^- ligand. On the other hand, in **2** each of the two crystallographically independent $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ anions contain three kinds of Nb atoms which show a different coordination sphere: Nb1, Nb6 (Nb7, Nb12) are surrounded by four Cl atoms, Nb3, Nb4 (Nb9, Nb10) by three Cl and one O atoms, and Nb2, Nb4 (Nb8, Nb11) by two Cl and two O atoms. Additionally each niobium atom is coordinated by a terminal CN^- group.

The mean Nb–C distances of 2.33 Å for **1** and 2.31 Å for **2** are slightly longer than those found in $[\text{Nb}(\text{CN})_8]^{5-}$ (2.282, 2.242 Å),^[18a] $[\text{Nb}(\text{CN})_8]^{4-}$ (2.225 Å),^[18b] and $[\text{Nb}_4\text{OTe}_4(\text{CN})_{12}]^{6-}$ (2.225 Å).^[18c] This point could be explained by the decrease in the formal charge of the Nb atom in the title compounds in terms of the ionic model. For **1** and **2**, the valence electron count per cluster is calculated to be 14, as in the starting compounds. This result evidences that no redox process occurs during the excision reaction.

Previous theoretical studies of the bonding situation in the D_3 and C_2 $[(\text{Nb}_6\text{Cl}_9\text{O}_3)\text{Cl}_6]^{n-}$ cluster isomers have provided

further evidence for the differences in the electronic structures. In particular, different HOMO–LUMO energy gaps were found for the D_3 and C_2 isomers (1.456 and 0.607 eV, respectively).^[19] Different electronic properties are expected for the CN^- -substituted isomers. Indeed, the electronic absorption spectra for the D_3 and C_2 isomers exhibit band maxima that are shifted with respect to one another (Figure 2). The IR spectrum of **1** shows one CN^- stretching vibration of medium intensity at 2111 cm^{-1} , which corresponds to one type of Nb center linked by a CN^- group. For **2**,

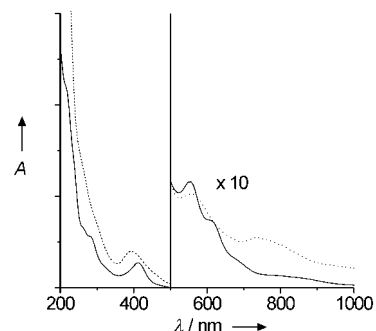


Figure 2. Electronic absorption spectra for **1** (solid line) and **2** (dashed line) resulting from the two different isomers of the $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ anion. The absorption A is given in arbitrary units.

the IR spectra present two vibrations at 2116 and 2132 cm^{-1} with a relative intensity of 2:1, which relates to the presence of niobium atoms with different environments containing μ_2 ligands.^[20]

In conclusion, the interaction of the octahedral niobium clusters $\text{Cs}_2\text{LaNb}_6\text{Cl}_{15}\text{O}_3$ and $\text{ScNb}_6\text{Cl}_{13}\text{O}_3$ with a cyanide solution resulted in excision of the cluster cores and isolation of two $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ isomer anions. The reactions proceed under mild conditions with no exchange of inner ligands. This approach could be expanded to other mixed-ligand octahedral halides and oxyhalides of niobium and tantalum. These anions could serve as a virtual library of anions for the construction of new cluster solids.

Experimental Section

All experiments were carried out under an argon atmosphere and with deoxygenated solutions. For the structure analyses, single crystals were selected directly from the reaction products. The data were collected on a Nonius KappaCCD diffractometer with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å) and corrected for Lorentz polarization and absorption effects. The structures were solved by direct methods and refined against all data using SHELXL-97.^[21]

$\text{Cs}_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6] \cdot 4\text{H}_2\text{O}$ (**1**):^[22] $\text{Cs}_2\text{LaNb}_6\text{Cl}_{15}\text{O}_3$ ^[11d] (200 mg, 0.130 mmol) was added to 50 mL of an aqueous solution of KCN (127 mg, 1.95 mmol) and CsCl (570 mg, 3.39 mmol), and the mixture was stirred for 24 h. The resulting green-brown solution was filtered, and the filtrate was reduced in volume under vacuum at ambient temperature to 5 mL and then added to 50 mL of ethanol. Dark-brown crystals were collected by filtration, washed with ethanol, and dried under argon. Yield: 142 mg (60%). EDAX: Cs:Nb:Cl = 4.9:6.0:8.9; IR: $\tilde{\nu} = 2111$ cm^{-1} (CN^-); UV-Vis: λ (ϵ) = 220 (30000), 245sh (18900), 263 (8980), 286 (7500), 420 (3600), 555 (580), 612 (410), 680sh (195), 800br (85). Crystallographic analysis: The crystal for X-ray structure analysis was grown by slow evaporation of a solution of **1** in a desiccator under Ar. Dark-brown crystals formed within several days together with mixed crystals of KCl/KCN and were collected manually.

$\text{C}_3\text{Cl}_{4.50}\text{Cs}_{2.50}\text{N}_3\text{Nb}_3\text{O}_{3.50}$, $T = 293$ K, orthorhombic, space group $C222_1$; $a = 8.7854(3)$, $b = 23.9393(8)$, $c = 18.0270(8)$ Å; $V = 3791.4(2)$ Å³, $Z = 8$, $\rho_{\text{calc}} = 3.170$ g cm⁻³, $R_1 = 0.0516$, $wR_2 = 0.1016$ for 3143 data (19433 independent), 205 parameters with no restraints. The Cs cations were split over several closely spaced sites. Only positions with high occupancy were refined anisotropically.

$(\text{Me}_4\text{N})_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6] \cdot 5\text{H}_2\text{O}$ (**2**):^[22] $\text{ScNb}_6\text{Cl}_{13}\text{O}_3$ ^[11a] (200 mg, 0.180 mmol) was added to 40 mL of an aqueous solution of KCN (176 mg, 2.70 mmol) and Me_4NCl (592 mg, 5.4 mmol), and the mixture was stirred for 24 h. The volume was reduced under vacuum at ambient temperature to 5 mL and allowed to dry in a desiccator over silica gel under Ar. Dark brown crystals were collected manually from the reaction mixture. Yield: 153 mg (55 %). EDAX: Nb:Cl = 6.0:9.1; IR $\tilde{\nu} = 2116$, 2132 cm⁻¹ (CN⁻); UV-Vis: λ (ϵ) = 220 (28000), 245sh (9700), 300sh (5170), 390 (2800), 560 (540), 730 (275), 760sh (270). Crystallographic analysis: $\text{C}_{52}\text{H}_{120}\text{Cl}_{18}\text{N}_{22}\text{Nb}_{12}\text{O}_{14}$, $T = 293$ K, monoclinic, space group Pc ; $a = 12.27900(10)$, $b = 12.64800(10)$, $c = 37.695(2)$ Å; $\beta = 100.231(9)^\circ$, $V = 5761.1(3)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.747$ g cm⁻³, $R_1 = 0.0645$, $wR_2 = 0.1532$ for 15 169 data (20879 independent), 998 parameters with 27 restraints. The crystal of **2** was a racemic twin (Flack parameter 0.53(7)). A portion of the tetramethylammonium cations have a high displacement factor and their geometry was fixed by restraints. Solvent water molecules were disordered over multiple positions in the structure. $(\text{Et}_4\text{N})_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6] \cdot x\text{H}_2\text{O}$: Addition of an excess of Et_4NCl to a solution of **1** and slow evaporation resulted in crystallization of $(\text{Et}_4\text{N})_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6] \cdot x\text{H}_2\text{O}$. EDAX: K:Nb:Cl = 0.02:6.0:8.9; FAB MS⁺: M/z : 1861.11 $\{(\text{Et}_4\text{N})_6[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]\}^+$. Crystallographic analysis: The structure and bond lengths of the $[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6]^{5-}$ anion in $(\text{Et}_4\text{N})_5[\text{Nb}_6\text{Cl}_9\text{O}_3(\text{CN})_6] \cdot x\text{H}_2\text{O}$ are very similar to that found in **1**. The tetraethylammonium cations and water molecules were strongly disordered, and we were not able to achieve a satisfactory R value. Space group: $I432$, $a = 24.8199(4)$ Å, $V = 15289.7(4)$ Å³, $Z = 8$, $R_1 = 0.124$. Selected bond distances (Å): av Nb–Nb 2.95 (μ_2 -Cl bridge), av Nb–Nb 2.89 (μ_2 -O bridge), Nb–O 2.10(1), av Nb–Cl 2.46, Nb–C 2.30(1), C–N 1.10(1).

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Trifluoroacetophenone Derivatives as Amino Acid Selective Ionophores for the Potentiometric Determination of Phenylalanine**

Shin-ichi Sasaki, Akio Hashizume, Daniel Citterio, Eiji Fujii, and Koji Suzuki*

The development of artificial receptors/ionophores for the selective recognition of biologically important species has attracted much attention because of their possible application to chemical sensors, such as ion-selective electrodes (ISEs) or optical chemosensors (optodes).^[1] So far, many ionophores for cations or anions have been developed and applied to ion sensing.^[2] On the other hand, molecular recognition and determination of amino acids by artificial ionophores is still challenging because of their highly hydrophilic character. Because amino acids are essential for the human body,^[3] several analytical methods for the determination of amino acids have been developed.^[4] However, simpler and more inexpensive devices are required, and a potentiometric sensor seems to be a promising candidate for this purpose. Although there are several examples of ionophores which can bind amino acids in the zwitterionic form through multiple-point binding,^[5] charged species have to be transported into a lipophilic membrane from the water phase to allow the potentiometric detection with carrier-based ISEs. Because amino acids exist in the cationic form in acidic solutions, most studies of ionophore-based ISEs have evaluated the ammonium form. This approach results in a cationic response, in which the more lipophilic amino acid esters are measured instead of the amino acid itself.^[6] It was recently reported that Mn^{III} porphyrin^[7] and lead phthalocyanine^[8] can be used as ionophores for underivatized cysteine- and histidine-selective electrodes, respectively. However, to our knowledge, there is no report on the rational design and synthesis of artificial ionophores for potentiometric determination of underivatized amino acids. Here we report on the characteristics of trifluoroacetophenone derivatives as neutral ionophores for ISEs. It was shown that electrodes based on preorganized tripodal ionophores with trifluoroacetophenone moieties respond to phenylalanine with a monoanionic Nernstian response.

Trifluoroacetophenone is known to form adducts with amines or alcohols,^[9] and almost all ionophores for carbonate

are trifluoroacetophenone derivatives.^[1b,10,11] To bind the amino and the carboxylate groups of an amino acid in the anionic form simultaneously, more than two trifluoroacetophenone moieties are included in one molecule. Thus, the tripodal ionophores **1–3**, with a hexasubstituted benzene ring as a spacer,^[12,13] were designed and synthesized, together with a reference compound **4**. As illustrated in Figure 1b, it is expected that two of the three functional groups participate in binding with the amino and the carboxylate groups of phenylalanine and, additionally, the benzene ring of phenylalanine is suitably accommodated in the hydrophobic cavity formed by three benzene rings of the binding arms and the spacer benzene ring. The characteristics of the ISEs based on these neutral ionophores combined with a cationic additive (tridodecylmethylammonium chloride; TDDMACl) were examined under the conditions reported in reference [11e], in which the condition for carbonate-selective ionophores was optimized. In the first stage, the relationship between ionophore structure and the carbonate selectivity was examined (see Supporting Information). All of the ISEs based on ionophores **1–4** (see Figure 1a) exhibited almost the same response curves to carbonate with a theoretical Nernstian slope (≈ -30 mV/decade). Because the observed carbonate selectivity was in the order of **3** > **4** > **2** > **1**, it was concluded that the binding ability to carbonate is mainly influenced not

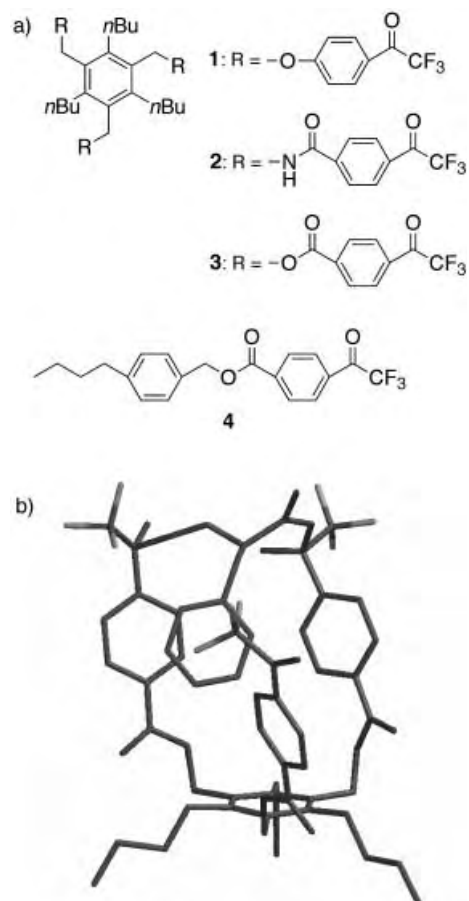


Figure 1. a) Chemical structures of tripodal ionophores **1–3** and reference compound **4**. b) Proposed structure of the complex of ionophore **3** with the anionic form of phenylalanine. The structure was optimized by use of AM1 calculations. Hydrogen atoms are omitted for clarity.

[*] Prof. Dr. K. Suzuki, Dr. S.-i. Sasaki, A. Hashizume, E. Fujii
Department of Applied Chemistry
Keio University
3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522 (Japan)
Fax: (+81) 45-564-5095
E-mail: suzuki@apple.keio.ac.jp

Dr. D. Citterio
Kanagawa Academy of Science and Technology (KAST)
KSP West-614, 3-2-1 Sakato, Kawasaki 213-0012 (Japan)

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by the number of binding sites, but rather by the electronic nature of the connecting unit (ester > amide > ether).^[14] On the other hand, the ISEs based on tripodal ionophores **1–3** exhibited a Nernstian response to the anionic form of phenylalanine (≈ -59 mV/decade) whereas the ISE based on **4** exhibited only a weak response in the relatively high concentration range, as shown in Figure 2.^[15] These results are coincident with the expected molecular design; it is necessary

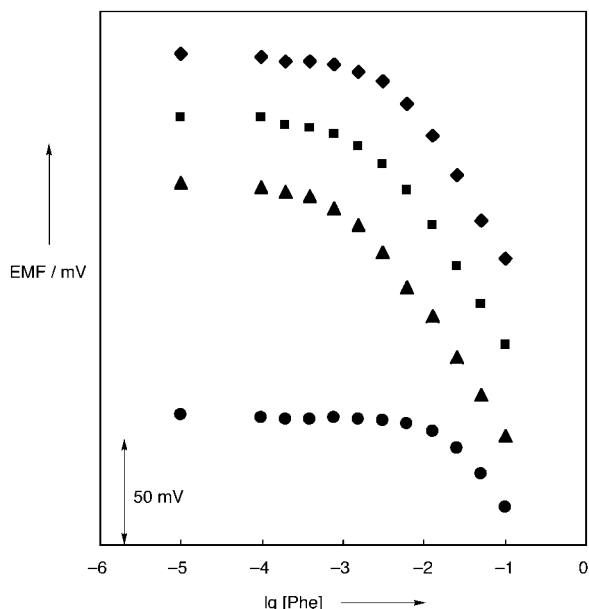


Figure 2. EMF response curves of the electrodes based on ionophores **1** (◆), **2** (■), **3** (▲), and **4** (●) to phenylalanine.

to introduce more than two binding sites in one molecule to interact effectively with the amino acids in the aqueous phase. Moreover, it should be pointed out that the electrode based on TDDMACl without addition of ionophore showed little response towards relatively lipophilic phenylalanine, apparently because of the strong hydration of the amino acid. The gain in selectivity caused by the ionophore was two orders of magnitude, with the electrode responding to the amino acid from 10^{-4} M and 10^{-2} M for the membrane with and without ionophore, respectively. The electrodes based on neutral ionophores without cationic additive did not show any response towards phenylalanine.

The selectivity coefficients of the electrodes for essential amino acids are summarized in Table 1. Although all electrodes showed phenylalanine selectivity among the amino acids examined,^[16] it should be noted that the selectivity of the ISEs based on tripodal ionophores **1–3** is better than that of the ISE based on **4**. Therefore, it is concluded that the observed selectivity is not only caused by the lipophilicity of the phenylalanine itself, but also by the preorganized shape of the tripodal ionophores with a hydrophobic pocket. Among the electrodes based on **1–3**, ISEs based on **3** are superior to the others, probably because of the electron-withdrawing ability of the connecting ester groups, as observed in the carbonate determination. The phenylalanine selectivity towards several representative inorganic anions was also investigated, and the

Table 1. Potentiometric selectivity coefficients ($\log K_{\text{Phe,J}}^{\text{pot}}$) for ISEs based on ionophores **1–4** for essential amino acids.^[a]

Amino acids	1	2	3	4
glycine	−1.1	−1.2	−1.7	−0.4
alanine	−1.2	−1.3	−1.7	−0.4
valine	−1.1	−1.2	−1.3	−0.7
leucine	−0.8	−0.7	−0.9	−0.6
isoleucine	−0.9	−0.7	−0.9	−0.7
serine	−1.3	−1.5	−1.7	−0.6
threonine	−1.2	−1.4	−1.7	−0.6
methionine	−0.8	−0.7	−0.9	−0.6
proline	−1.3	−1.6	−1.8	−0.7
histidine	−1.4	−1.4	−1.8	−0.8
lysine	−1.2	−1.5	−1.9	−0.8
arginine	−1.3	−1.4	−1.7	−0.6
aspartic acid	−1.0	−0.9	−1.4	−0.3
asparagine	−1.4	−1.4	−1.8	−0.7
glutamic acid	−1.2	−0.9	−1.6	−0.5
glutamine	−1.1	−1.0	−1.7	−0.4

[a] The selectivity coefficients were calculated from the response potentials to 0.1 M sample solutions using the separate solution method (SSM).

best result was obtained for the ISE based on **3**. We found that the electrode has good selectivity over carbonate or other anions, though the interference of lipophilic perchlorate is still high ($\log K_{\text{Phe,J}}^{\text{pot}}$: $\text{ClO}_4^- + 0.61$, $\text{CO}_3^{2-} - 0.99$, $\text{I}^- - 0.83$, $\text{Br}^- - 1.64$, $\text{Cl}^- - 1.71$, $\text{HPO}_4^{2-} - 2.34$). Thus, we have demonstrated an example of rationally designed artificial ionophores for ISEs that respond to underivatized phenylalanine with a theoretical Nernstian response.

Experimental Section

Electrode preparation and EMF measurements: PVC matrix-based membranes were prepared from a mixture of ionophore (3 wt %), membrane solvent bis(2-ethylhexyl)sebacate (DOS; 67 wt %), PVC (30 wt %), and tridodecylmethylammonium chloride (TDDMACl; 50 mol %, relative to the ionophore). The components dissolved in THF were poured into a vial which was placed on a hotplate. Slow evaporation of THF at 40 °C gave ion-sensitive membranes of approximately 100 μm thickness. A 6 mm diameter circle was cut from a prepared membrane and placed on the tip of a PVC ion-selective-electrode body assembly (Liquid Electrode Membrane Kit, DKK Co., Ltd., Tokyo, Japan). The prepared electrodes were immersed in 0.1 M aqueous NaCl solution for more than 24 h for preconditioning before use. The external reference electrode was a double-junction-type Ag–AgCl electrode (HS-305DS, Toa Electronics, Ltd., Tokyo, Japan). The electrode potential (emf) measurements were performed at 25 ± 0.5 °C by using the electrochemical cell system, Ag | AgCl | saturated KCl | 0.3 M NH_4NO_3 || sample solution | ISE membrane | 0.1 M NaCl | AgCl | Ag.

All sample solutions were prepared with 0.1 M Tris– H_2SO_4 buffer solution (Tris = tris(hydroxymethyl)aminomethane) at pH 8.6. The pH values of 0.1 M glutamic acid and aspartic acid in 0.1 M Tris solution were 6.10 and 5.83, respectively, and were adjusted to pH 8.6 using NaOH. The selectivity coefficients $K_{\text{I,J}}^{\text{pot}}$ where I stands for the primary ion ($\text{PhCH}_2\text{CH}(\text{NH}_2)\text{COO}^-$ for Table 1 and CO_3^{2-} for Table S1 in the Supporting Information) and J for the interfering ion, were calculated from the response potentials using the separate-solution method (SSM; $[\text{I}] = [\text{J}] = 0.1$ M), according to the recommendations of IUPAC^[17] and JIS.^[18]

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Combinatorial and Rational Strategies To Develop Nonpeptidic $\alpha 4\beta 7$ -Integrin Antagonists from Cyclic Peptides

Dirk Gottschling, Jürgen Boer, Anja Schuster, Bernhard Holzmann, and Horst Kessler*

The development of low-molecular-weight, nonpeptidic, and orally available drugs starting from biologically active peptides or proteins is one of the great challenges in medicinal chemistry. Herein we present an example in which a biologically active tripeptide has been reduced to a dipeptide in which the activity has been retained. New concepts in the treatment of inflammatory diseases have recently emerged.^[1] One promising target to treat inflammatory diseases in the intestine is the inhibition of the $\alpha 4\beta 7$ -integrin/MAdCAM-1 interaction (MAdCAM-1 = mucosal addressin cell-adhesion molecule 1) interaction.^[2] In contrast to other cell adhesion molecules, MAdCAM-1 is expressed only on a few cell types.^[3,4] The interference of the $\alpha 4\beta 7$ -integrin/MAdCAM-1 interaction, which selectively mediates lymphocyte recruitment to the mucosa-associated lymphoid tissues of the intestine, is not expected to affect other parts of the immune system. As a consequence, no systemic side effects should occur during this therapy. The potential value of this therapy has already been shown with antibodies in animal models of colitis.^[5,6] Recently, we and others reported the synthesis of peptidic $\alpha 4\beta 7$ -integrin antagonists that contain the Leu-Asp-Thr (LDT) recognition sequence for $\alpha 4\beta 7$ -integrins.^[7–10] In our previous work we showed that the amide bond between Thr⁴ and Asp⁵ in the cyclic peptide *cyclo*-(Phe¹-Leu²-Asp³-Thr⁴-Asp⁵-D-Pro⁶) was not essential. Furthermore, Thr⁴ could be substituted with Val without loss of biological activity. Therefore, we synthesized a library of cyclic hexapeptides of the general formula *cyclo*-(Phe-Leu-Asp-Xaa-Asp-D-Pro). The biological evaluation of the corresponding compounds with a cell adhesion assay showed that when Xaa = phenylalanine (see **1**) or phenylglycine (see **2**) the biological activity towards inhibiting the $\alpha 4\beta 7$ -integrin/MAdCAM-1 interaction was maintained (Table 1). Based on these results and on the results of Shroff et al.,^[9,10] we developed a library illustrated in Figure 1. Four different building blocks **A**, **B**, **C**, and **D** were used. Starting from isoquinoline-3-carbonyl-Leu-Asp-Thr-OH (**3**)^[10] only one building block was changed each time. The resulting library was consequently not completely combinatorial. The synthesis of these compounds was performed step-by-step in parallel on solid supports, according to the Fmoc-strategy.^[11] The incorporation of fluoroaromatics as

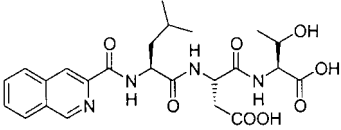
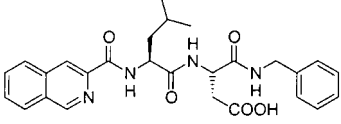
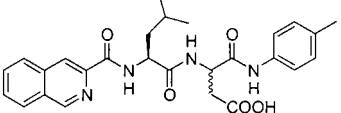
[*] Prof. Dr. H. Kessler, D. Gottschling, Dr. J. Boer
Institut für Organische Chemie und Biochemie
Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
Fax: (+49) 89-289-13210
E-mail: kessler@ch.tum.de

A. Schuster, Prof. Dr. B. Holzmann
Chirurgische Klinik und Poliklinik
Technische Universität München
Ismaningerstrasse 22, 81675 München (Germany)



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Table 1. Specific effects of peptidomimetics (1 mg mL^{-1}) on $\alpha 4\beta 7$ - and $\alpha 4\beta 1$ -integrin-mediated cell adhesion to MAdCAM-1 and VCAM-1.^[a]

Structure	No.	Cell adhesion [%]		
		$\alpha 4\beta 7/\text{MAdCAM-1}$	$\alpha 4\beta 7/\text{VCAM-1}$	$\alpha 4\beta 1/\text{VCAM-1}$
<i>cyclo</i> -(F-L-D-F-D-p)	1	59 ± 29	93 ± 9	81 ± 15
<i>cyclo</i> -(F-L-D-Phg-D-p) ^[b]	2a	38 ± 24	89 ± 2	80 ± 21
	2b	73 ± 20	101 ± 3	98 ± 3
	3 ^[10]	48 ± 29	81 ± 4	NT ^[c]
	4	44 ± 21	67 ± 13	103 ± 1
	5a	53 ± 24	93 ± 18	101 ± 6
	5b	26 ± 7	51 ± 37	98 ± 13

[a] Cell adhesion is presented as a percentage of medium control. The data represents the mean $\pm$ standard deviation of three experiments, repeated three times. [b] Racemization occurred during synthesis. [c] NT = not tested.

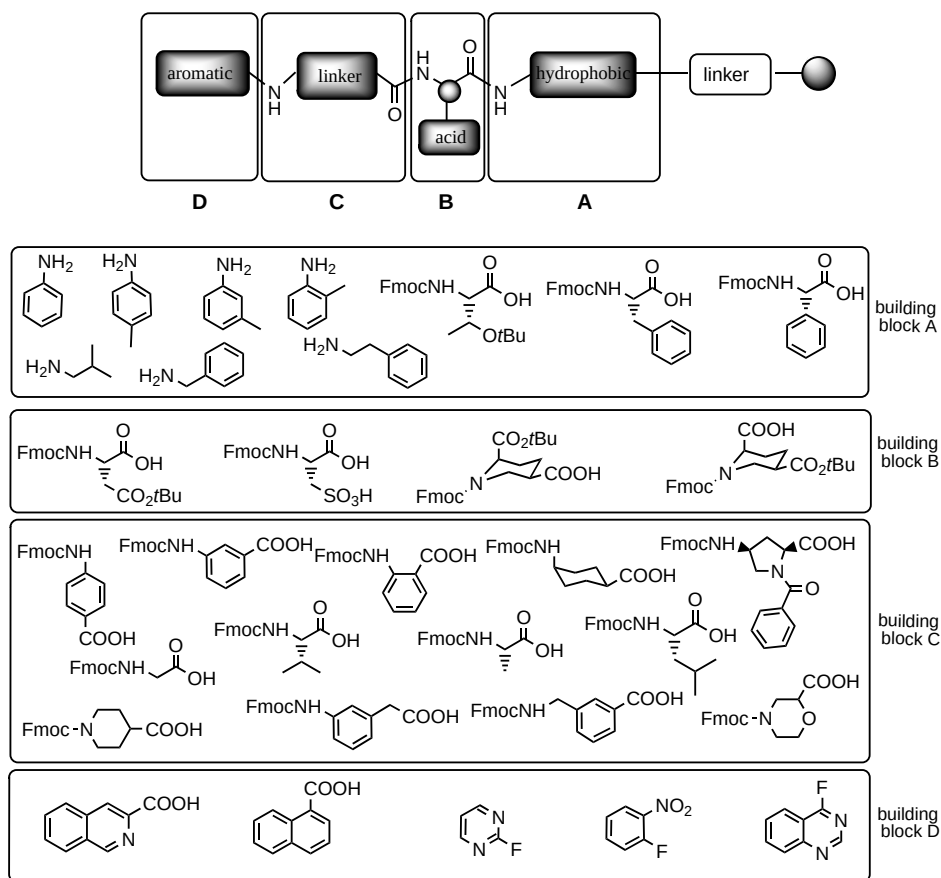


Figure 1. Building blocks used for the synthesis of a LDT-mimetic library.

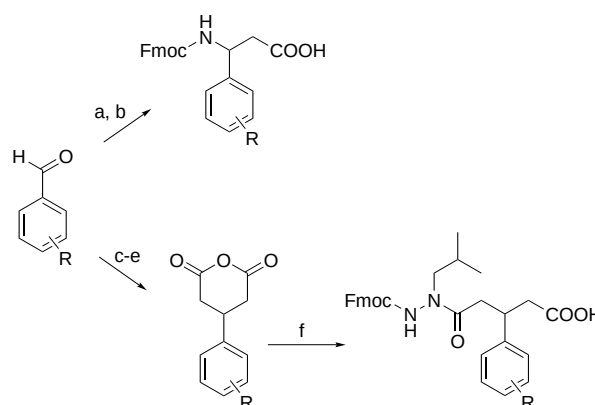
building block **D** was achieved on solid supports by nucleophilic substitution.^[12] The use of aniline derivatives as building block **A** afforded a fragment condensation of isoquinoline-3-carbonyl-Leu-Asp(OtBu)-OH and the corresponding aniline derivative in solution. All compounds were purified by

preparative HPLC and tested separately in a cell-adhesion assay.

For that purpose, the $\alpha 4$ -integrin ligands MAdCAM-1 and VCAM-1 (VCAM-1 = vascular cell-adhesion molecule 1) were immobilized on microtiter plates and the adhesion of the lymphoid cell lines 38C13- $\beta 7$ ($\alpha 4\beta 7^{\text{pos}}$, $\alpha 4\beta 1^{\text{neg}}$) and Jurkat ($\alpha 4\beta 1^{\text{pos}}$, $\alpha 4\beta 7^{\text{neg}}$) was analyzed in the presence or absence of the peptidomimetics at a concentration of 1 mg mL^{-1} . The inhibitory activity of the previously characterized $\alpha 4\beta 7$ -integrin antagonist *cyclo*-(Phe-Leu-Asp-Thr-Asp-D-Pro) was always measured at 1 mg mL^{-1} as a positive control.^[7] The results of the biological evaluation of the library are summarized in Table 1. Only compounds of the general formula isoquinoline-3-carbonyl-Leu-Asp-Xbb-OH with Xbb = benzylamine (see **4**), aniline or *m*-, *o*-, *p*-toluidine (e.g. **5**) were able to inhibit the $\alpha 4\beta 7$ -integrin/MAdCAM-1 interaction. Notably, these compounds were highly selective, because they did not inhibit $\alpha 4\beta 1$ -integrin binding to VCAM-1 and only partially blocked $\alpha 4\beta 7$ -integrin/VCAM-1 interactions. In contrast to cyclic peptide **2a** (Xaa = Phg), the use of Xbb =

Phg resulted in an inactive compound and in the case of Xbb = Phe the corresponding compound precipitated during biological evaluation. As Thr (building block **A**) could be substituted in compound **3** by an aromatic system, we tried to shift the phenyl ring along the peptide backbone. In medicinal

chemistry, it is sometimes possible to replace amide bonds by a phenyl ring, because of their similar structural properties.^[13] We thus replaced the amide bond between Asp and Thr in compound **3** by a phenyl ring. We chose 3-amino-3-arylpropionic acid as a mimic for the Asp-Thr-residue (Scheme 1).^[14] 3-Amino-aryl-propionic acid-derivatives have already been shown to be useful building blocks for $\alpha\beta 3$ -integrin antagonists.^[15] Furthermore we synthesized (1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid as a conformationally constrained 3-amino arylpropionic acid derivative.^[16] We also used phenylglycine and phenylalanine, which differ only in one methylene group from 3-amino arylpropionic acid, as dipeptide mimetics. Scheme 2 summarizes the Asp-Thr-dipeptide mimetics used. The biological evaluation of these compounds is shown in Table 2; only **6**, **7**, and **8** were able to mimic the Asp-Thr dipeptide residue and to inhibit $\alpha 4\beta 7$ -integrin/MAdCAM-1 interactions. As racemic 3-amino arylpropionic acid derivatives were used, both diastereoisomers of each compound were tested separately. Both isomers exhibited quantitative differences in their inhibitory efficacy, and we are thus currently focusing our attention on the



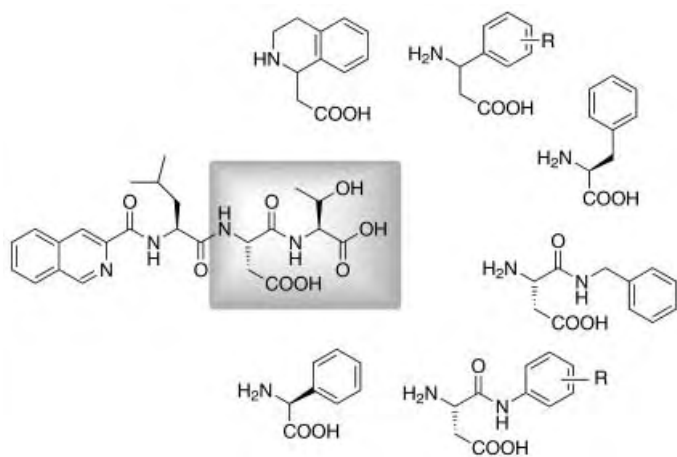
Scheme 1. a) NH_4OAc , malonic acid, EtOH , 80°C ; b) Fmoc-Cl , NaHCO_3 , dioxane, 0°C ; c) ethyl acetoacetate, piperidine, room temperature; d) KOH (20M), 85°C ; e) acetic anhydride, 120°C ; f) N -Fmoc- N' -isopropylhydrazine, THF , 70°C .

determination of their stereochemistry. The substitution pattern of the phenyl ring appeared to have no influence on the biological activity. The 3-amino arylpropionic acid deriv-

Table 2. Specific effects of compounds (1 mg mL^{-1}) that contain a dipeptide mimetic on $\alpha 4\beta 7$ - and $\alpha 4\beta 1$ -integrin-mediated cell adhesion to MAdCAM-1 and VCAM-1.^[a]

Structure	No.	$\alpha 4\beta 7/\text{MAdCAM-1}$	Cell adhesion [%] $\alpha 4\beta 7/\text{VCAM-1}$	$\alpha 4\beta 1/\text{VCAM-1}$
	6a	60 ± 26	79 ± 21	NT
	6b	19 ± 4	27 ± 6	NT
	7a	44 ± 1	66 ± 15	NT
	7b	15 ± 5	12 ± 4	NT
	8a	47 ± 8	65 ± 5	NT
	8b	18 ± 11	35 ± 11	NT
	9 ^[c]	65 ± 14	102 ± 22	107 ± 6
	10 ^[c]	100 ± 11	114 ± 2	111 ± 1
	11a	10 ± 4	41 ± 0	71 ± 14
	11b	11 ± 3	18 ± 6	19 ± 5
	12 ^[c]	64 ± 2	91 ± 27	79 ± 24

[a] Cell adhesion is presented as a percentage of medium control. The data represents the mean $\pm$ standard deviation of three experiments, repeated three times. [b] NT = not tested. [c] Tested as a racemic mixture.



Scheme 2. Different building blocks were used as Asp-Thr dipeptide mimetics. Fmoc = 9-fluorenylmethoxycarbonyl.

atives **6**, **7**, and **8** were slightly less selective than the cyclic compound **2**. The use of (1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid, phenylglycine, or phenylalanine as Asp-Thr mimetics resulted in inactive compounds. To decrease the peptidic character of compound **8**, we used the corresponding azaamino acid azaLeu (**9**) and the peptoid building block Nleu (**10**) instead of Leu (Table 2). However, these modifications led to a significant loss of biological activity. Furthermore, the reduction of the amide bond between Leu and 3-amino-3-(4-methylphenyl)propionic acid in compound **8** resulted in biological active diastereoisomers (**11**). These compounds fulfill "Pfizer's rule of five"^[17] (number of hydrogen donors: 3, number of hydrogen acceptors: 3, M_w : 433.5, $\log P$: 4.19) and

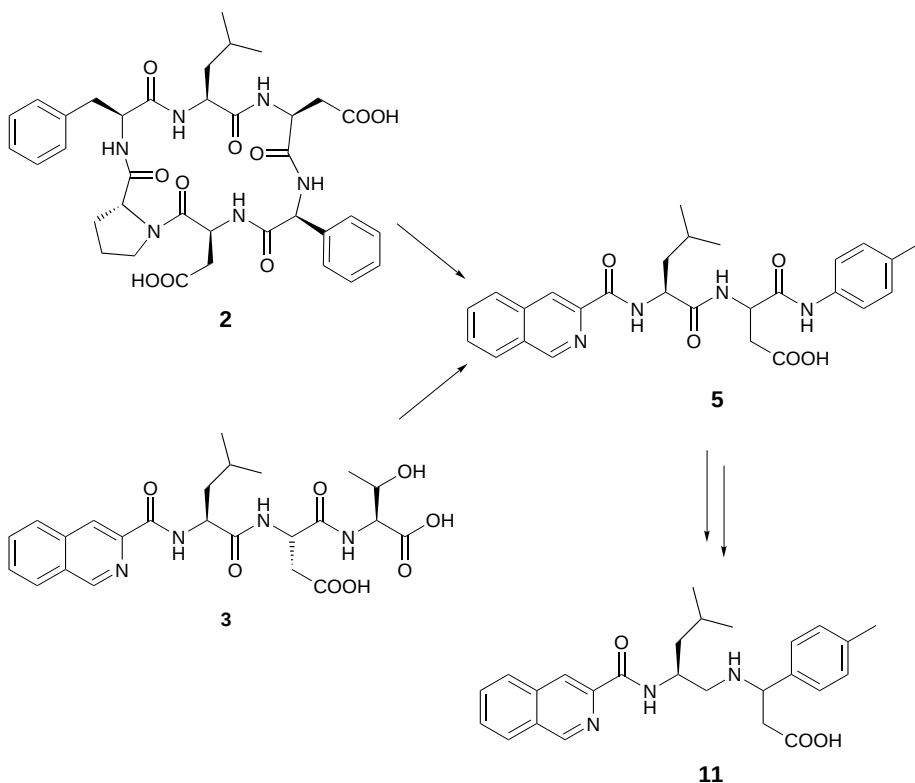
represent a promising starting point for further development. Scheme 3 summarizes the process of developing this compound.

We also used 3-phenylglutamic acid derivatives instead of the 3-amino arylpropionic acid residue (Scheme 1).^[18] Recent work by our group has shown that 3-aryl-5-hydrazino-5-oxopentanoic acids represent a very promising pharmacophoric scaffold for $\alpha\text{v}\beta 3$ -integrin antagonists.^[15] It seems, that compound **12** shows only a very weak inhibitory activity for the $\alpha 4\beta 7$ -integrin/MAdCAM-1 interaction. Nonetheless, it is conceivable that these compounds could be further optimized. In this case, the diacylhydrazine moiety would represent a universal scaffold for integrin antagonists. This would also support the assumption of Zheng and coworkers that $\alpha\text{IIb}\beta 3$ -integrin antagonists could be easily transformed into $\alpha 4$ -integrin antagonists.^[19]

In summary, we have shown that it is possible to develop low-molecular-weight, nonpeptidic $\alpha 4\beta 7$ -integrin antagonists by using rational and combinatorial strategies. In the post-genomic area, inhibition of protein-protein interactions becomes increasingly important as an independent approach to interfere with the function of defined target structures. We have demonstrated that the stepwise procedure: protein-sequence $\rightarrow$ cyclic, constrained peptides $\rightarrow$ peptido-mimetics $\rightarrow$ nonpeptidic leads can be a valuable method to develop new drugs.

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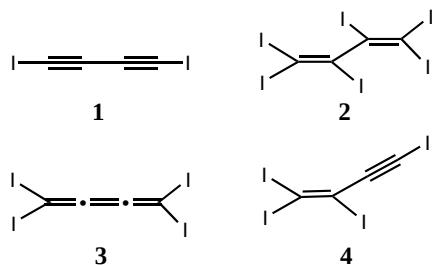
Scheme 3. Stepwise development of nonpeptidic $\alpha 4\beta 7$ -integrin antagonists.

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Tetraiodobutatriene: A New Cumulenenic Carbon Iodide**

Jeffrey A. Webb, Pei-Hua Liu, Olga L. Malkina, and Nancy S. Goroff*

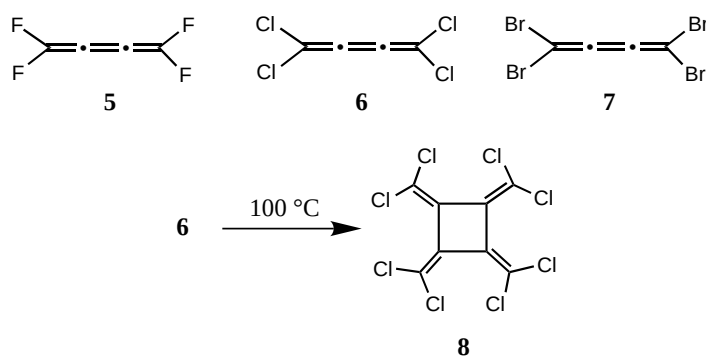
Diiodopolynes such as **1** have attracted our attention as potential precursors to all-carbon molecules and materials. Lespieau and Prévost reported 75 years ago that diiodobutadiyne (**1**) reacts with molecular iodine to form hexaiodobutadiene (**2**).^[1] Others repeated this experiment with similar results, each time obtaining a yellow solid that melted at about 165°. ^[2] We now present evidence that, under appropriate conditions, this same reaction can instead give cumulene **3**, which is stable, isolable, and fully characterized (Scheme 1).



Scheme 1. A family of carbon iodides C_4I_4 .

We recently synthesized two longer diiodopolynes, C_6I_2 and C_8I_2 ,^[3] and began exploring methods for the ordered polymerization of such iodine-capped polyynes. As part of our studies, we collected X-ray data on a crystal from a previously pure sample of **1** which had been sitting on a benchtop for several months. Instead of the expected butadiyne **1**, the sample contained novel butatriene **3**. Evidently, **1** (C_4I_2) can disproportionate over time to yield **3** (C_4I_4), with unknown carbon-rich by-products. However, the majority of crystals in the sample still contained **1** instead of **3**; the decomposition reaction had occurred in low overall yield.

Compound **3** is one of only a handful of halogenated cumulenes that have been characterized. Perfluorobutatriene **5** (Scheme 2) is extremely unstable; it reportedly explodes above its boiling point of -5°C and decomposes even at -80°C .^[4] Perchlorobutatriene **6** is more stable (m.p. $59-60^\circ\text{C}$), but like many cumulenes it dimerizes to form radialene **8** when heated.^[5] Perbromobutatriene **7** has not been reported, and compound **3** is, to the best of our knowledge, the first known iodine-substituted cumulene of any sort.^[6]



Scheme 2. Cumulenes **5** and **6** are known; **7** is not.

We have now found conditions which lead cleanly to **3** in good yield. Iodination of **1** in concentrated solution in hexanes produces a yellow precipitate after only a few minutes.^[7] Filtration separates the solid from the solvent and any remaining I_2 , leaving a yellow powder (m.p. $142-143^\circ\text{C}$). As discussed below, mass spectrometry, IR and NMR spectroscopy, and X-ray diffraction studies all confirm that this material is cumulene **3**.

Without careful handling, however, compound **3** rapidly decomposes in solution to give **2**. The decomposition reaction occurs in pure solutions of **3**, suggesting a disproportionation mechanism, much like the observed decomposition of **1**. The simplest disproportionation of **3**, to give equal parts of **1** and **2**, would be endothermic by 9.1 kcal mol^{-1} , according to density-functional (B3LYP/LanL2DZ) calculations.^[8] Furthermore, we found no evidence for the formation of **1** during the decomposition reaction. Thus far, we have been unable to identify the by-product(s) of this reaction.

The decomposition of **3** can be monitored by thin-layer chromatography (TLC; AlO_3 /hexanes).^[9] When **3** is dissolved in a variety of solvents (e.g., THF, CS_2), the diyne disappears over several minutes, while a new TLC spot appears simultaneously, corresponding to **2**. In some solvents (acetone, benzene, CCl_4), TLC indicates that **3** is stable unless exposed

[*] Prof. Dr. N. S. Goroff, J. A. Webb, Dr. P.-H. Liu
 Department of Chemistry, State University of New York
 Stony Brook, NY 11794-3400 (USA)
 Fax: (+1) 631-632-8356
 E-mail: nancy.goroff@sunysb.edu
 Dr. O. L. Malkina
 Institute of Inorganic Chemistry and Computing Center
 Slovak Academy of Sciences
 Bratislava (Slovakia)

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to light. In pyridine, compound **3** appears to form a stable solvent–solute complex and does not decompose.

The instability of **3** in many solvents makes spectroscopic characterization difficult. GC/MS experiments on the crude yellow precipitate indicate that it contains only one compound, with molecular formula C_4I_4 , consistent with either cumulene **3** or enyne **4**. Density-functional (B3LYP/LanL2DZ) calculations place compound **4** higher in energy than **3** by 4.5 kcal mol^{−1}, but the B3LYP functional is known to overestimate the stability of cumulenes relative to acetylenic isomers.^[10] Previous literature reports contain examples of both 1,4- and 1,2-addition to diynes, and often mixtures of the two.^[11,12]

¹³C NMR spectroscopy should distinguish between **3** and **4** easily, but initial NMR spectroscopic experiments were difficult to interpret. Figure 1a shows the ¹³C NMR spectrum of starting diyne **1**, whereas Figures 1b–d show the NMR spectra of the yellow precipitate dissolved in various solvents.

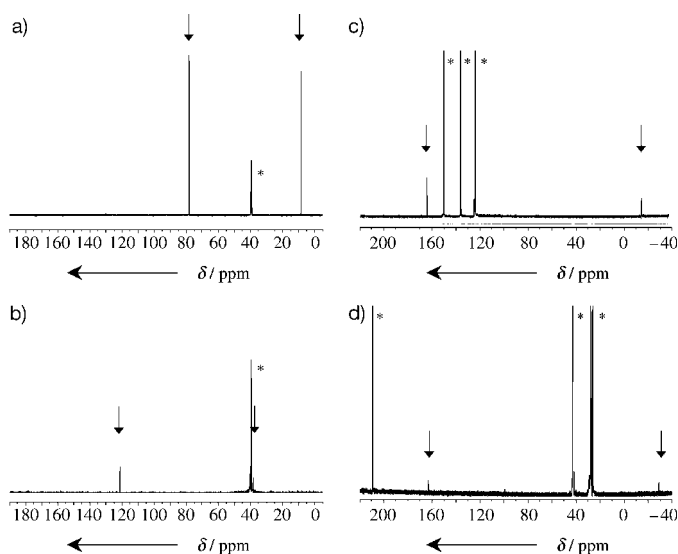


Figure 1. ¹³C NMR spectra; ↓ denotes sample signal, * denotes solvent or deuterium lock. a) **1** in [D₆]DMSO; b) **3**, decomposed, in [D₆]DMSO; c) **3** in [D₅]pyridine; d) **3** in cyclohexanone with internal [D₁₂]cyclohexane lock.

The spectrum in Figure 1b was obtained first, with dimethyl sulfoxide (DMSO) as solvent. Initially, based on symmetry, we assigned the two peaks in this spectrum at δ = 37.7 and 121.2 ppm to compound **3**.

To confirm the assignment, we calculated the ¹³C NMR spectrum of **3**, including the spin-orbit coupling effect of the iodine atoms.^[13–15] These calculations predict chemical shifts for C1 and C2 at δ = −48.9 and 163.2 ppm, respectively, far from the observed spectrum in DMSO. This difference provided our first evidence for the decomposition of **3** in solution.

Figures 1c and d show the NMR spectra of freshly prepared samples of the yellow precipitate, dissolved in pyridine and in cyclohexanone, respectively. Each spectrum includes two peaks: δ = 163.5 and −14.9 ppm in pyridine and δ = 162.9 and −27.5 ppm in cyclohexanone. We assign both these spectra to compound **3**, despite the difference between the lower-frequency shifts and the calculated value of δ =

−48.9 ppm. The discrepancy most likely results, at least in part, from a Lewis acid–base interaction between **3** and the solvent.^[3,16] The ≈12-ppm difference in the low-frequency peak in the spectra when in pyridine or in weakly basic cyclohexanone supports this hypothesis.

The NMR spectroscopic data contain no evidence of enyne **4**. Furthermore, vibrational spectroscopy confirms the structure of **3**. The extremely simple experimental IR spectrum matches calculations well: 668 and 1678 cm^{−1} (calculated) compared to 603 and 1616 cm^{−1} (experimental). We have been unable to obtain Raman or UV spectra of **3** because of its swift decomposition upon irradiation in solution.

As final proof of the structure, we obtained X-ray diffraction data on a new crystal grown from the yellow powder. These data confirm that the yellow solid is tetraiodobutatriene (**3**), just like the initial material from decomposition of **1**. The two samples, prepared in very different ways, have indistinguishable crystal structures. The crystal packing is shown in Figure 2a. Figure 2b shows a crystal structure of **2**, prepared directly from **1** and then cocrystallized with 1,7-phenanthroline.^[17]

As a solid, cumulene **3** is more stable than diyne **1**. Upon heating, compound **1** decomposes at 90 °C, but **3** melts at 142–

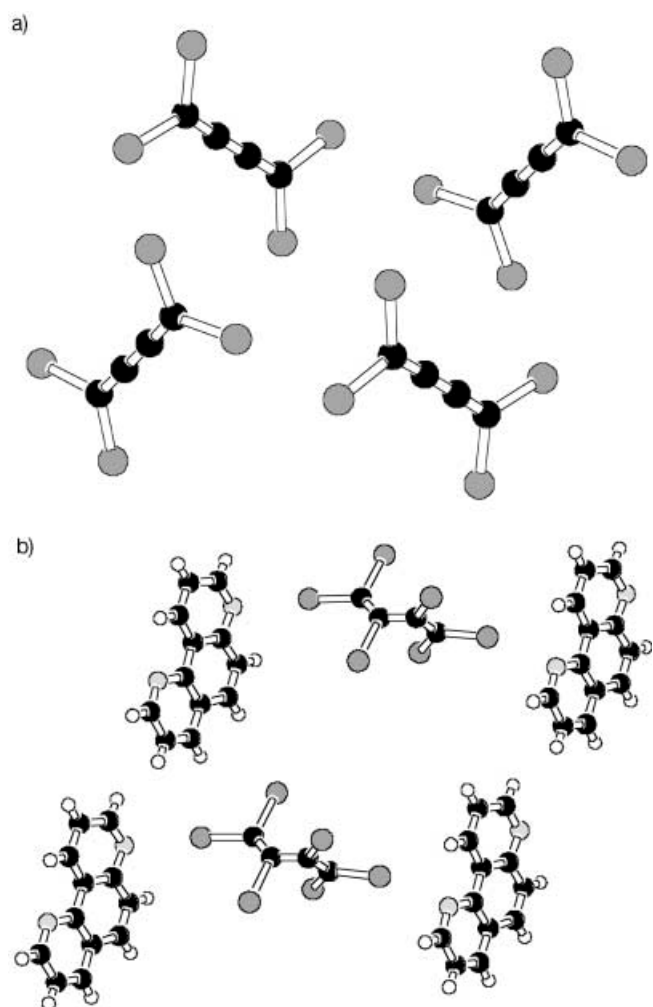


Figure 2. a) X-ray crystal structure of **3**; b) X-ray structure of 1:1 cocrystal of **2** and 1,7-phenanthroline.

143°C. We have produced **3** in gram quantities without difficulty and can keep solid samples in the freezer indefinitely. Nonetheless, compound **3** decomposes much more readily in solution than **1**.

The weakness of carbon–iodine bonds makes compound **3** a promising precursor to all-carbon and carbon-rich molecules and materials. Compound **3** also offers another Lewis acid for the crystal engineer's toolbox. Carbon iodides have previously found use as components in designed materials by acting as Lewis acid templates. For example, diiodoacetylene and other carbon iodides can determine the spacing of ions in multi-component conducting solids.^[18] The stability of **3** in pyridine solution indicates that it can survive Lewis acid–base interactions without decomposition, making it a suitable candidate for such multicomponent systems.

Cumulene **3** is surprisingly easy to prepare and to isolate in a pure form, is surprisingly stable in the solid state, and disproportionates surprisingly readily in solution. It is one more example of the unusual chemistry of carbon and iodine.

Experimental Section

3: I₂ (340 mg, 1.32 mmol) was added to a solution of **1** (400 mg, 1.32 mmol) in hexanes (5 mL). Aluminum foil was used to wrap the reaction vessel. The reaction mixture was stirred vigorously at room temperature for 15 min, forming a yellow precipitate. The yellow powder was filtered and washed with hexanes to yield crude product (604 mg, 82%). The crude products from three iterations were combined and recrystallized from cyclohexanone/hexanes to yield pure **3** as fine yellow needles (1.47 g, 67% total). M.p. 143–144°C; MS (EI): *m/z* (%): 556 (24) [*M*⁺ (C₄I₄)], 429 (45) [*M*⁺–I], 302 (100) [*M*⁺–2(I)], 175 (28) [*M*⁺–3(I)], 127 (27) [*I*⁺].

2: Iodine (2.52 g, 9.93 mmol) was added to a solution of **1** (1.0 g, 3.3 mmol) in methanol (30 mL). After stirring at room temperature for 2 h, the precipitate was filtered and washed with hexanes to yield **2** as a yellow powder. The material left in solution was not recovered, and no yield was determined. M.p. 165–166°C; MS (EI)^[19]: *m/z* (%): 682 (22) [*M*⁺–I], 556 (34) [*M*⁺–2(I)], 429 (34) [*M*⁺–3(I)], 302 (100) [*M*⁺–4(I)], 175 (38) [*M*⁺–5(I)], 127 (50) [*I*⁺]. To prepare cocrystals of **2** and 1,7-phenanthroline, compound **2** (0.14 g, 0.25 mmol) was dissolved in acetone (3 mL). A solution of 1,7-phenanthroline (0.045 g, 0.25 mmol) in methanol (2 mL) was added dropwise to this solution with stirring. The solution, in a small vial, was cooled to –10°C, forming small crystals.

X-ray structure analysis: X-ray intensity data were measured on a Bruker AXS diffractometer. The structures were solved by direct methods and refined by using full-matrix least-squares methods (SHELXL97).^[20] Empirical absorption corrections were applied. Compound **3** crystallizes in space group *P*₂₁/*n*, with *a* = 4.4362(4) Å, *b* = 17.1459(14) Å, *c* = 12.5217(10) Å, β = 96.716(2)°, *V* = 945.90(14) Å³, *Z* = 2, ρ_{calcd} = 4.877 g cm^{–3}, *T* = 293(2) K, 4223 reflections measured, 1352 crystallographically independent (*R*_{int} = 0.068), and 1154 reflections with *I* > 2σ(*I*), *MoK*_α = 0.71073 Å, 2θ_{max} = 53°, *R*(*F*_{obs}) = 0.034, *wR*(*F*²)_{all} = 0.113. Compound **2** forms cocrystals with [1,7]-phenanthroline in the space group *P**1*, with *a* = 7.4475(17) Å, *b* = 10.609(2) Å, *c* = 14.845(3) Å, α = 103.128(4)°, β = 103.840(4)°, γ = 91.510(4)°, *V* = 1105.0(4) Å³, *Z* = 2, ρ_{calcd} = 2.974 g cm^{–3}, *T* = 293(2) K, 6417 reflections measured, 4390 crystallographically independent (*R*_{int} = 0.174), and 3591 reflections with *I* > 2σ(*I*), *MoK*_α = 0.71073 Å, 2θ_{max} = 53°, *R*(*F*_{obs}) = 0.120, *wR*(*F*²)_{all} = 0.379. Unit cells and ORTEP representations are available as supplementary material. CCDC-181226 and –181227 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Atom-Transfer Tandem Radical Cyclization Reactions Promoted by Lewis Acids**

Dan Yang,* Shen Gu, Yi-Long Yan, Hong-Wu Zhao, and Nian-Yong Zhu

Tandem radical cyclization reactions are powerful methods for the synthesis of a wide range of highly functionalized polycyclic natural products as multiple stereocenters can be constructed in one step under mild conditions.^[1,2] However, no enantioselective tandem radical cyclization reactions have been reported.^[3] Herein we describe a Lewis acid catalyzed atom-transfer tandem radical cyclization method for the formation of various bicyclic and tricyclic ring skeletons. Furthermore, the first enantioselective tandem radical cyclization was achieved by using chiral Lewis acids as catalysts.

We recently reported an enantioselective atom-transfer radical monocyclusation catalyzed by a chiral Lewis acid to prepare cyclic 2,3-disubstituted ketones.^[4] Yb(OTf)₃ (OTf = trifluoromethanesulfonate) and Mg(ClO₄)₂ were found to be the best Lewis acids in these monocyclusation reactions. Therefore, the two Lewis acids were further used to promote tandem cyclization of α -bromo β -keto esters **1a–f** with Et₃B/O₂ as the radical initiator (Table 1). Substrates **1a** and **1b** with

two C=C bonds in the same carbon chain exclusively underwent 6-*endo* and then 5-*exo* cyclization for **1a** and 6-*exo* cyclization for **1b** in the presence of a Lewis acid to give the fused ring products 6,5-*cis*-**2a** and 6,6-*trans*-**2b**, respectively (Table 1, entries 1–4). In each case, four stereocenters of the cyclization products **2a/2b** were set up in one step. Furthermore, as little as 0.3 equivalents of Yb(OTf)₃ was sufficient to catalyze the cyclization of **1a** to give **2a** in 69% yield (Table 1, entry 2), and a decrease in the amount of Mg(ClO₄)₂ (to 0.5 equiv) did not decrease the yield of **2b** in the cyclization of **1b** (Table 1, entry 4). For substrates **1c–e**,^[5] which have an allyl substituent in the α -position, 6-*endo* (6-*exo* for substrate **1d**) followed by 5-*exo* cyclization gave the corresponding bicyclic products **2c–e** in moderate yields in the presence of a stoichiometric amount of Mg(ClO₄)₂ (Table 1, entries 5–7). Furthermore, triple cyclization of **1f** gave product **2f** as one of 16 possible stereoisomers in 26% yield (Table 1, entry 8). When Yb(OTf)₃ was used as the Lewis acid catalyst, no more than 16% yield can be obtained in the cyclization of substrates **1b–f**. For all the substrates investigated, no atom-transfer radical cyclization was observed in the absence of Lewis acids. These results demonstrate that the Lewis acids not only promote tandem radical cyclization reactions, but also control the stereoselectivities of the cyclization products.^[6] The major side products of those tandem cyclization reactions were the corresponding reductive debromination products (< 12% yield), monocyclusation products (< 30% yield), and even a bicyclusation product (for **1f** only; 12% yield).^[7] Especially for substrate **1b**, the 1,3-diaxial interaction of two methyl groups made the second ring cyclization unfavorable, and as a result the radical chain process was partially terminated in the monocyclusation stage with the isolation of a monocyclusation product in up to 30% yield.

Then we investigated the enantioselective tandem cyclization of **1a** and **1b** by using Mg(ClO₄)₂ and bisoxazoline ligand **L1** as a chiral catalyst (Table 2). Poor *ee* values were observed in the cyclization of **1a** (Table 2, entry 1). Although the addition of activated 4-Å molecular sieves^[4,8] improved the *ee* value, it decreased the yield dramatically (Table 2, entry 2). High *ee* values (82–84%) were observed in the cyclization of **1b** at higher temperature, despite lower yields (Table 2, entries 3 and 4). With Yb(OTf)₃ as the catalyst,^[9] the effects of chiral ligands,^[10] additives,^[11] and solvents on the enantioselective tandem cyclization of **1a** were evaluated. As shown in Table 3, the **L3**/Yb complex gave the best results (60% yield and 66% *ee*; Table 3, entry 4). Dichloromethane was found to be a better solvent than toluene in this tandem cyclization system (Table 3, entry 4 vs. 6). The addition of Et₂O or water had negative effects on these reactions (Table 3, entries 2 and 3). Surprisingly, the addition of molecular sieves led to reversed enantiofacial selectivity of the cyclization^[11e] (Table 3, entry 5).

The stereochemistry of tandem radical cyclization reactions in the presence of the chiral complex [Yb(Ph-pybox)(OTf)₃] (pybox = 2,6-bis(2-oxazolin-2-yl)pyridine) can be explained using the transition-state model shown in Scheme 1. Similar to the chiral complex [Sc(Ph-pybox)(ethyl glyoxylate)(OTf)]²⁺ proposed by Evans et al.,^[12] the ytterbium center adopts a square-pyramidal geometry with the ester carbonyl group

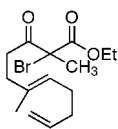
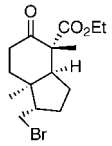
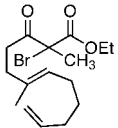
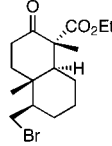
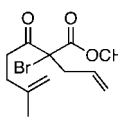
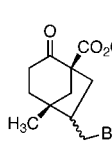
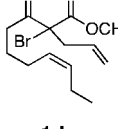
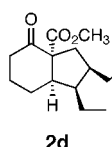
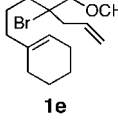
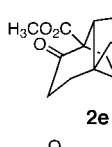
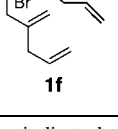
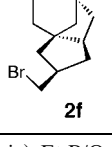
[*] Prof. D. Yang, S. Gu, Y.-L. Yan, H.-W. Zhao, N.-Y. Zhu
Department of Chemistry, The University of Hong Kong
Pokfulam Road, Hong Kong (P. R. China)
Fax: (+852) 2859-2159
E-mail: yangdan@hku.hk

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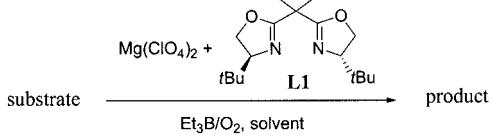
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Table 1. Lewis acid promoted free-radical tandem cyclization reactions.^[a]

Entry	Substrate	Lewis acid	Solvent	<i>t</i> [h]	Product	Yield [%] ^[b]
1		Yb(OTf) ₃	Et ₂ O	2		85
2 ^[c]	1a	Yb(OTf) ₃	Et ₂ O	2	2a	69
3 ^[d]		Mg(ClO ₄) ₂	toluene	2		20
4 ^[d,e]	1b	Mg(ClO ₄) ₂	toluene	4	2b	20
5		Mg(ClO ₄) ₂	CH ₂ Cl ₂	2		51 (α/β 1:1.8) ^[f]
6		Mg(ClO ₄) ₂	CH ₂ Cl ₂	2.5		47
7		Mg(ClO ₄) ₂	CH ₂ Cl ₂	2		40 (α/β 1.2:1) ^[f]
8		Mg(ClO ₄) ₂	CH ₂ Cl ₂	2		26
	1f				2f	

[a] Unless otherwise indicated, all reactions were carried out at −78 °C with the indicated Lewis acid (1.0 equiv), Et₃B/O₂ (5.0 equiv) in the indicated solvent (0.025 M). [b] Yield of isolated product. [c] Yb(OTf)₃ (0.3 equiv). [d] The reaction was carried out at −40 °C. [e] Mg(ClO₄)₂ (0.5 equiv). [f] Ratio of epimers.

Table 2. Chiral Lewis acid promoted enantioselective atom-transfer radical tandem cyclization reactions.^[a]

						
Entry	Substrate	<i>T</i> [°C]	Solvent	Product	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	1a	−78	CH ₂ Cl ₂	2a	41	13 ^[d]
2 ^[e]	1a	−78	CH ₂ Cl ₂	2a	24	33 ^[d]
3	1b	−40	toluene	2b	23	82 ^[f]
4	1b	−20	toluene	2b	16	84 ^[f]

[a] Unless otherwise indicated, all reactions were carried out with substrate (0.2 mmol) in the indicated solvent (0.025 M), Mg(ClO₄)₂ (1.0 equiv), and (*S,S*)-**L1** (1.1 equiv). [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC analysis with a Chiralcel OD or AD column. [d] The absolute configuration of product **2a** was determined to be (2*R*,3*S*,4*S*,5*S*) by X-ray analysis. [e] Activated molecular sieves (4 Å, powder, 500 mg/mmol substrate) were added. [f] The absolute configuration of product **2b** was not determined.

bound in the equatorial position and the ketone carbonyl group in the apical position. To avoid steric interactions between the alkyl chain of the substrate and the phenyl groups

of ligand **L3**, the *Re*-face cyclization is favored over the *Si*-face cyclization (not shown). In the 6-*endo* cyclization, a chairlike transition state is preferred, which gives a tertiary radical

Table 3. Enantioselective tandem cyclization of **1a** mediated by chiral Yb(OTf)₃ complexes.^[a]

L2: R = *i*Pr
L4: R = *t*Bu

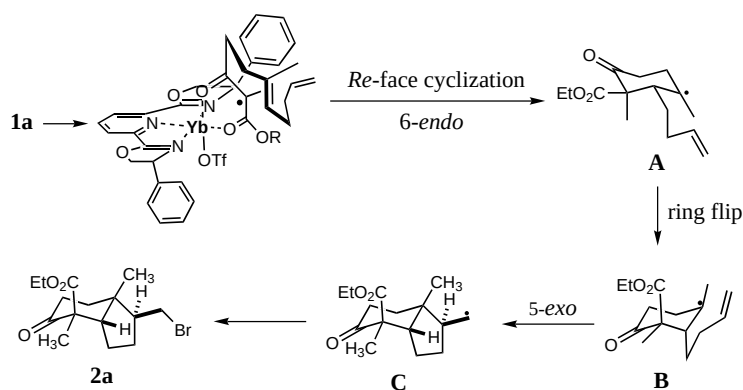
L3

L5

L6

Entry	Ligand	Solvent	Additive	<i>t</i> [h]	Yield [%] ^[b] (3a)	Yield [%] ^[b] (2a)	<i>ee</i> [%] ^[c] (2a)
1	L2	CH ₂ Cl ₂	–	13	11	28	–37
2 ^[d]	L2	CH ₂ Cl ₂	H ₂ O	24	– ^[e]	– ^[e]	– ^[e]
3 ^[f]	L2	CH ₂ Cl ₂	Et ₂ O	24	14	26	–13
4	L3	CH ₂ Cl ₂	–	15	23	60	66 ^[g]
5 ^[h]	L3	CH ₂ Cl ₂	4-Å MS	13	68	11	–56
6	L3	toluene	–	12	30	37	50
7	L4	CH ₂ Cl ₂	–	21	66	18	< 1
8	L5	CH ₂ Cl ₂	–	12	51	13	< 1
9	L6	toluene	–	10	64	17	–43

[a] Unless otherwise indicated, all reactions were carried out at –78 °C in the indicated solvent at 0.025 M concentration with Yb(OTf)₃, the indicated ligand (1.1 equiv), and Et₃B/O₂ (5 equiv). [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column. [d] H₂O (1.0 equiv) was added. [e] The major product was the corresponding debromination compound **3a** (TLC analysis), but no attempt was made to isolate the products. [f] Et₂O (1.0 equiv) was added. [g] The absolute configuration of the major enantiomer was determined to be 2*R*,3*S*,4*S*,5*S* by X-ray crystallographic analysis. [h] Activated molecular sieves (MS; 4 Å, powder, 500 mg/mmol substrate) were added.



Scheme 1. Proposed transition-state model for the {Yb(Ph-pybox)} complex promoted radical cyclization reaction of **1a**.

intermediate **A** with an equatorial homoallylic group. After a ring flip from **A** to **B**, 5-*exo* cyclization affords a 6,5-*cis* ring-fused primary radical **C**, which abstracts the bromine atom from **1a** to yield (2*R*,3*S*,4*S*,5*S*)-**2a**.

In summary, we have developed an efficient and stereoselective Lewis acid catalyzed atom-transfer radical tandem cyclization method for the construction of polycyclic ring skeletons under mild and neutral conditions. Furthermore, the first enantioselective version of those atom-transfer tandem cyclization reactions was developed with the *ee* values up to 84%. This method should have great potential for the enantioselective synthesis of complex natural products with significant biological activities.

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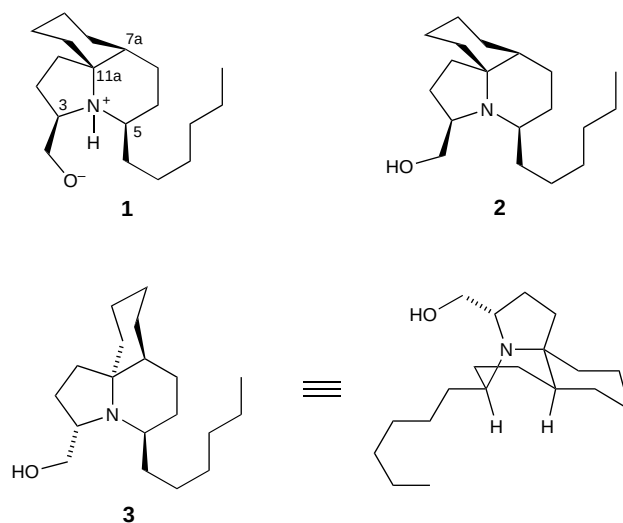
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Total Synthesis of the Natural Enantiomer of (–)-Lepadiformine and Determination of Its Absolute Stereochemistry**

Hideki Abe, Sakae Aoyagi, and Chihiro Kibayashi*

Lepadiformine was isolated by Biard et al. in 1994 from the marine tunicates *Clavelina lepadiformis* collected in Tunisia^[1] and from *Clavelina moluccensis* found along the Djibouti coast.^[2] It has been shown to exhibit moderate cytotoxic activity against various tumor cell lines in vitro.^[1] Moreover, a recent study indicated that lepadiformine is very active in the cardiovascular system in vivo and in vitro and suggested that it

has antiarrhythmic properties.^[2] On the basis of extensive NMR spectroscopic experiments, its structure and relative stereochemistry were reported as the zwitterion **1** (Scheme 1) with a novel azatricyclic skeleton.^[1] Although its specific rotation value in a chloroform solution was reported to be zero, it was believed that lepadiformine is not racemic. However, the absolute configuration has remained hitherto unknown. The unique structural features and biological significance of this novel marine alkaloid have made it an important target for synthesis. Weinreb and co-workers^[3] reported the synthesis of the structure **1** proposed for lepadiformine and found that the synthetic material exists as a nonzwitterionic form **2** and that neither the free amine nor its hydrochloride salt corresponds to the natural product. Moreover, Pearson et al.^[4] synthesized the other three C3/C5 diastereomers of **2** and found that they different from lepadiformine (Scheme 1). Following these synthetic efforts, we recently published the total synthesis of compound **3** in the racemic form, based on an intramolecular acylnitroso Diels–Alder-based approach and found by spectral comparison that the corresponding hydrochloride salt was identical to the reported natural product.^[5] We thus concluded that the originally assigned structure of lepadiformine was actually that of the hydrochloride salt and that its relative stereochemistry should be revised to be that of **3** (Scheme 1).



Scheme 1. The originally proposed structure of lepadiformine was that of **1**. The revised structure is that of **3**.

After establishment of the relative stereochemistry, two syntheses of racemic lepadiformine were reported by the groups of Weinreb^[6] and Funk^[7] based on a spirocyclization of an allylsilane N-acyliminium ion and on an amidoacrolein-derived Diels–Alder reaction, respectively. However, because the natural product is not crystalline and its derivatives could not be prepared, efforts to obtain an X-ray structure of natural lepadiformine for the determination of the absolute configuration have so far been unsuccessful.^[1,8] This prompted us to undertake the enantioselective synthesis of lepadiformine and to determine the absolute configuration of the natural product.

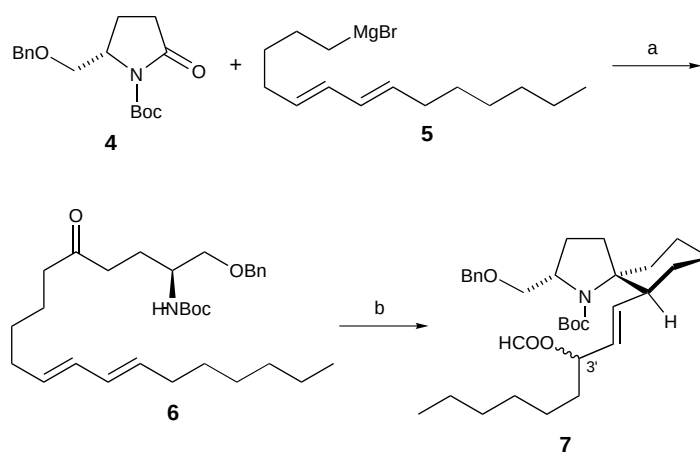
[*] Prof. Dr. C. Kibayashi, H. Abe, S. Aoyagi
School of Pharmacy, Tokyo University of Pharmacy & Life Science
1432-1 Horinouchi, Hachioji, Tokyo, 192-0392 (Japan)
Fax: (+81)426-76-4475
E-mail: kibayasi@ps.toyaku.ac.jp

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A crucial element in our approach to the target compound was the *N*-acyliminium-ion-initiated olefin azacyclization^[9] to elaborate the azaspirocyclic core of lepadiformine (**3**). Such cyclizations, which lead to spirocyclic compounds, were initially developed by Speckamp and co-workers^[10] and Evans et al.^[11] Recently, this reaction was applied successfully by Weinreb and co-workers^[6] in the total synthesis of ($\pm$)-**3**. Herein we describe the first total synthesis of (–)-lepadiformine (**3**) by using a new variant of the *N*-acyliminium-ion-initiated intramolecular spirocyclization in which a conjugated diene was exploited as a π nucleophile and has been proven to be quite effective for the highly stereoselective and extremely short approach to **3**. Furthermore, the synthesis of **3** allowed the absolute configuration of natural lepadiformine to be established as 3*S*,5*R*,7*aS*,11*aS* (Scheme 1).

Our synthesis commenced with the known (*S*)-*N*-Boc-2-pyrrolidinone **4**,^[12] which upon treatment with the (5*E*,7*E*)-tetradeca-5,7-dienyl Grignard reagent **5** underwent selective attack at the endocyclic (ring) carbonyl group^[13] to yield ketone **6** (Scheme 2). When a solution of **6** in toluene/THF (95:5) was treated with formic acid at 0 °C for 2 h and neutralized with NH₄OH, in situ generation of the *N*-acyliminium ion followed by spirocyclization proceeded with synchronous formation of the new C–O bond at C3' to furnish the 1-azaspirocyclic formate ester **7** in 88 % yield. Notably, the spirocyclization of the *N*-acyliminium ion generated from **6**, which bears a conjugated diene, proceeded quite smoothly and was completed in a short time, in marked contrast to the case with the reported spirocyclization of *N*-acyliminium ions that bear nonconjugated olefins which require long reaction times.^[10,11]

The 6-*exo-trig* ring closure^[14] gave **7** with complete regio-control, as predicted by considering the initially formed carbocation, which is stabilized through resonance with the olefin π bond in the alkene side chain. In this manner, the nucleophilic attack of the olefin moiety occurred exclusively at the sterically less hindered β face (opposite to the 5-benzyloxymethyl group) of the 1-pyrroline ring, with exclusive introduction of the desired 6*S* chirality. The concomitant

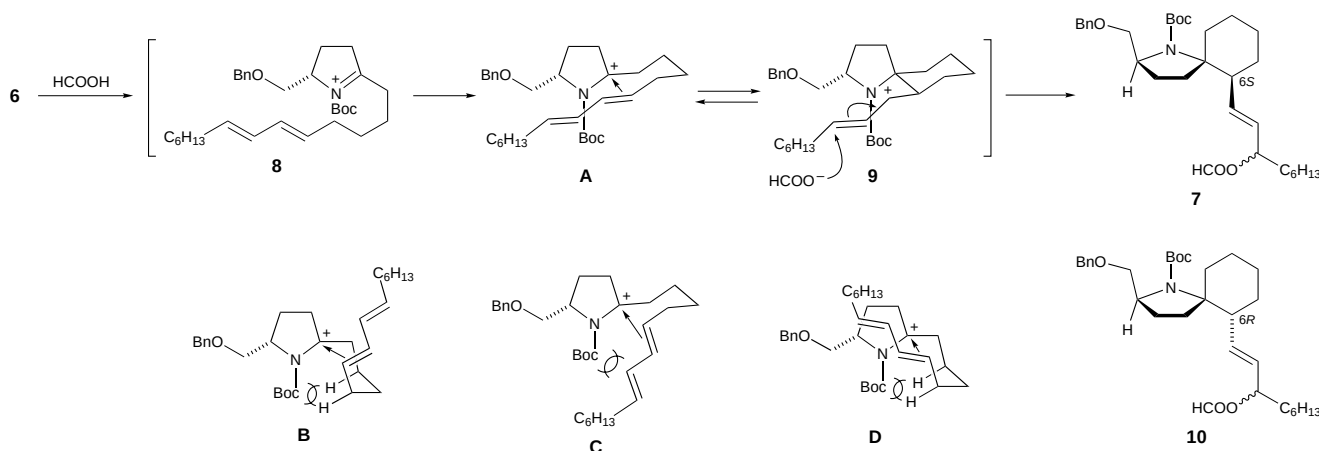


Scheme 2. Reagents and conditions: a) THF, 0 °C, 79 %; b) HCOOH, toluene/THF (95:5), 0 °C, 2 h, 88 %.

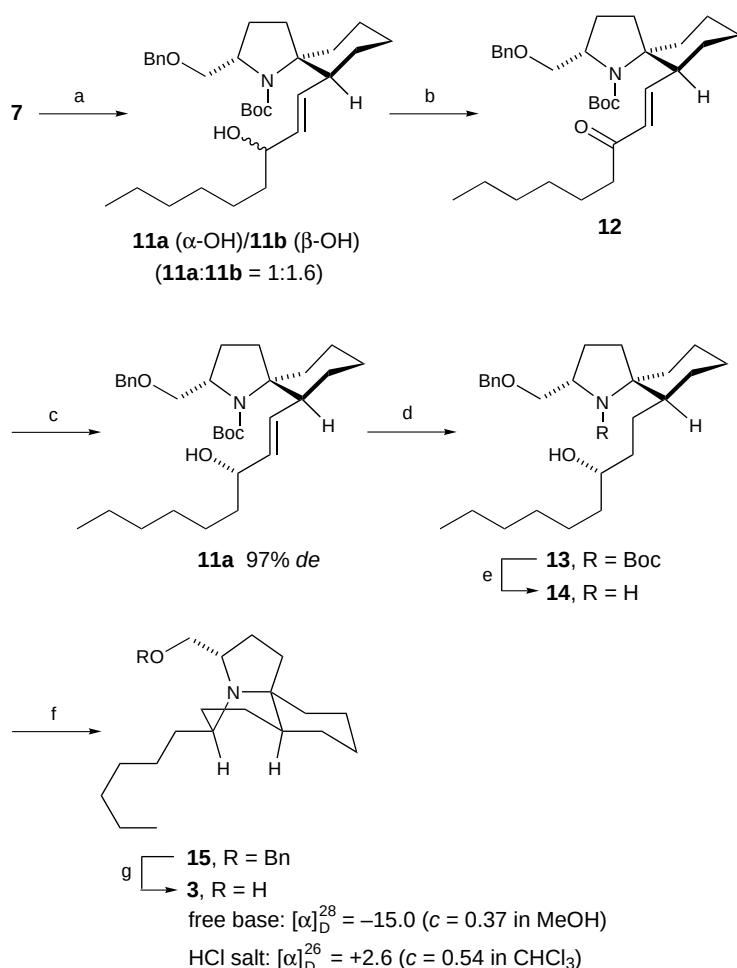
formate substitution at C3' occurred with low diastereoselectivity (1.6:1 favoring the 3' β -formate) as determined by HPLC analysis (see below).

Exclusive preferential formation of (6*S*)-**7** can be understood by comparison of the stabilities of the configurations of the six-membered chairlike π complexes **A–D**, which arise from the in situ generation of the *N*-acyliminium ion **8** as shown in Scheme 3. In the transition states **C** and **D**, which lead to (6*R*)-**10**, the *N*-Boc group displays unfavorable nonbonding interactions with the axially oriented diene moiety and the 1,3-diaxial hydrogen atoms of the newly formed cyclohexane ring, respectively. The latter steric interaction between the *N*-Boc group and the 1,3-diaxial hydrogen atoms is also present in the transition state **B**, which leads to (6*S*)-**7**. Neither of these interactions are present in the transition state **A** and therefore, of the four possible chairlike transition states **A–D**, **A** is the least disfavored and leads to the observed (6*S*)-**7**.

The formate ester **7**, which is epimeric at C3', underwent basic hydrolysis to give the allylic alcohols **11a/11b**, whose diastereomeric ratio was determined to be 1:1.6 by HPLC.^[15] This diastereomeric mixture was oxidized with MnO₂ to give



Scheme 3. The selective formation of **7** from **6** occurs via transition state **A**. Transition states **B–D** are disfavored.



Scheme 4. Reagents and conditions: a) K_2CO_3 , MeOH/ H_2O , 98%; b) MnO_2 , CH_2Cl_2 , 91%; c) (*S*)-BINAL-H, THF, -78°C , 92%; d) H_2 , PtO_2 , EtOAc, 86%; e) TFA, CH_2Cl_2 , 91%; f) CBr_4 , PPh_3 , Et_3N , CH_2Cl_2 , 82%; g) H_2 , $\text{Pd}(\text{OH})_2$, MeOH, 87%; **3** (free base): $[\alpha]_D^{28} = -15.0$ ($c = 0.37$ in MeOH), **3-HCl**: $[\alpha]_D^{26} = +2.6$ ($c = 0.54$ in CHCl_3). (*S*)-BINAL-H = 2,2'-binaphthoxyaluminum hydride, TFA = trifluoroacetic acid.

the α,β -conjugated ketone **12** (Scheme 4). Reduction of **12** to the corresponding alcohol with $\text{BH}_3\cdot\text{THF}$ (THF, 0°C) was almost nonstereoselective (**11a/11b** 1.15:1). (*S*)-BINAL-H diastereoselective reduction^[16] provided the alcohol (3'*S*)-**11a** in 92% yield with 97% *de*. Catalytic hydrogenation of **11a** over palladium on carbon (10%) in methanol was carried out in the presence of diethylamine (1 equiv) to prevent hydrolysis of the benzyl ether^[17] and afforded **13** in 64% yield. Alternatively, the use of PtO_2 catalyst and ethyl acetate as solvent without diethylamine remarkably improved the yield of **13** to 86%. After removal of the Boc protecting group with trifluoroacetic acid, the resulting amino alcohol **14** was treated with CBr_4 and PPh_3 to form the tricyclic amine **15** in 82% yield, with complete inversion of the configuration at C3'. Hydrogenolytic removal of the benzyl protecting group afforded lepadiformine (**3**) whose spectral properties were identical in all respects with those of an authentic sample of racemic lepadiformine ($\pm$)-**3** previously prepared by us.^[5b] The optical rotation of synthetic alkaloid **3** was measured: $[\alpha]_D^{28} = -15.0$ ($c = 0.37$ in MeOH) for the free base (oil) and $[\alpha]_D^{26} = +2.6$ ($c = 0.54$ in CHCl_3) for the hydrochloride salt

(colorless gum). However, it was not possible to determine the absolute stereochemistry of natural lepadiformine by comparison of the optical rotations, since, as described above, the natural product (actually the hydrochloride salt) had been reported to have no optical rotation in chloroform.

The absolute stereochemistry was assigned successfully by comparison of synthetic and natural lepadiformine on a chiral HPLC column. In the chiral HPLC analysis, the authentic sample of racemic lepadiformine ($\pm$)-**3**^[5b] gave peaks at different retention times [(+)-**3**, 45 min; (–)-**3**, 48 min] (Figure 1). Comparison of retention times and co-injection revealed that the synthetic (–)-enantiomer corresponds to the natural product, thus allowing the absolute stereochemistry of natural lepadiformine to be assigned as 3*S*,5*R*,7*aS*,11*aS*.

In summary, we have reported the first total synthesis of the natural enantiomer of lepadiformine (**3**) by employing an intramolecular conjugated diene cyclization of an *N*-acyliminium ion. The 1-azaspiro formate ester **7** is obtained in a single step from the simple keto amide **6**, which bears the conjugated diene. The total synthesis is highly stereoselective and is completed in nine steps with an overall yield of 31.4% starting from the (*S*)-*N*-Boc-2-pyrrolidinone **4** and provides a highly efficient and extremely short route to **3**. Furthermore, the present synthesis allowed us to establish the 3*S*,5*R*,7*aS*,11*aS* absolute configuration of natural lepadiformine.

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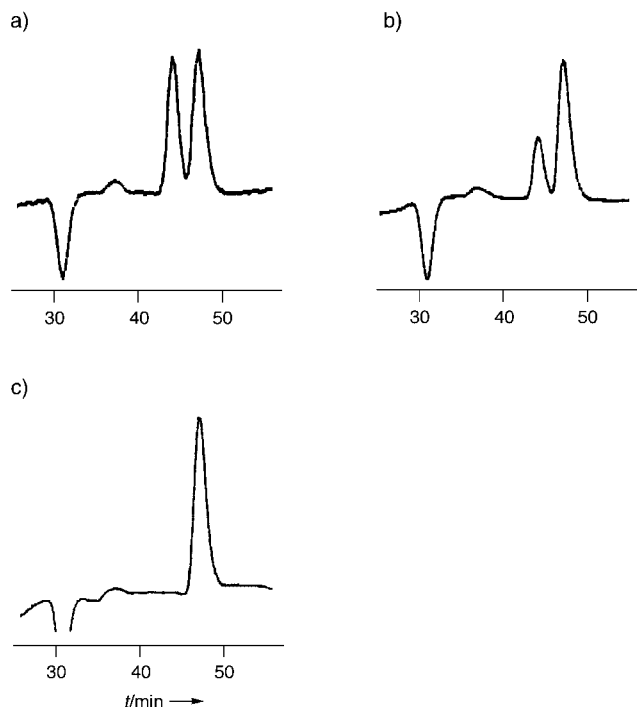


Figure 1. HPLC chromatogram of lepadiformine on a Daicel Chiralpak OD: a) racemate; b) mixture of racemate and natural; c) mixture of synthetic (–)-enantiomer and natural. Conditions: mobile phase, hexane/2-propanol/ Et_3NH (500:10:1); flow rate: 0.1 mL min^{-1} ; detection: RI (refractive index).

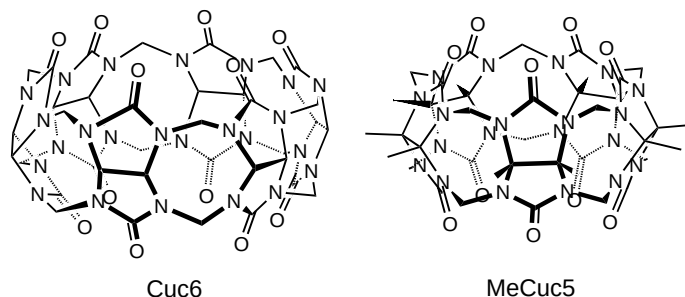
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“Molecular” Molecular Sieves: Lid-Free Decamethylcucurbit[5]uril Absorbs and Desorbs Gases Selectively**

Yuji Miyahara,* Kazuaki Abe, and Takahiko Inazu

Several types of inorganic crystalline materials and organic polymers function as molecular sieves, the most common of which are numerous types of zeolites.^[1] While some organic host molecules encapsulate small molecules in solution,^[2] practical applications have never been attempted because of their inaccessibility. Here we report that the title compound, which can be readily synthesized from simple starting materials, shows potential for use as molecular sieves in the solid state by utilizing its molecular cavity.

In 1981 Mock and co-workers reported^[3] that the compound which Behrend prepared from glycoluril and formalin in 1905^[4] has a beautiful barrel-like macrocyclic structure composed of six glycoluril units; they named it cucurbituril (Cuc6). Since then extensive studies have been conducted on this unique host compound.^[5]



In 1982, in his PhD thesis on cucurbituril, Shih also described a compound, assumed to have a pentameric structure, which was obtained by heating dimethylglycoluril under reflux with formalin in dilute HCl.^[6] Shih and Mock did not study the compound further because of its inactivity as a host molecule.^[3b] In 1992, Stoddart and co-workers confirmed its basic structure by X-ray structure analysis of a crystal grown in dilute HNO₃ and named it decamethylcucurbit[5]uril (MeCuc5).^[7] At the time when the paper by Stoddart and co-workers appeared we had already found that the product obtained under the reaction conditions contained two NH₄Cl

[*] Dr. Y. Miyahara, K. Abe, Prof. Emer. Dr. T. Inazu
Department of Chemistry, Faculty of Sciences
Kyushu University
6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581 (Japan)
Fax: (+81) 92-642-2607
E-mail: miyahscc@mbox.nc.kyushu-u.ac.jp

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

units resulting from decomposition of dimethylglycoluril,^[8] but we were unable to disclose our results because of its curious properties as described below. Since then, several groups have published papers on properties of MeCuc5 without knowing the true composition of the product.^[9–11] We have now unequivocally confirmed the structure of the product as the bis-NH₄Cl salt adduct by X-ray structural analysis on a crystal grown under a He atmosphere (Figure 1).^[12,14]

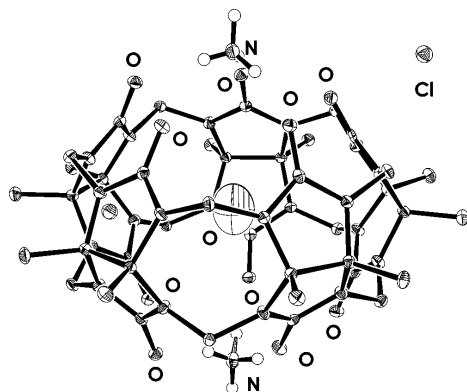
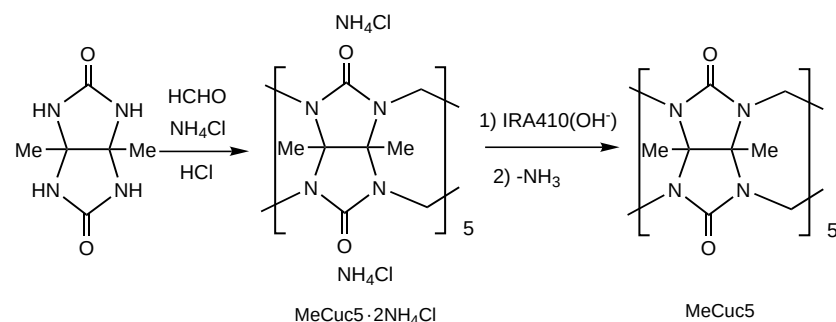


Figure 1. Crystal structure of MeCuc5·2NH₄Cl·4H₂O. The O atom of the cavity water molecule has an occupancy of 0.47. One of the external water molecules (not shown) has an occupancy of 0.28; with these values the structure converged to give $R_1 = 0.044$.

Once the product was confirmed to be the bis-NH₄Cl adduct, the yield could be raised from 14%^[7] to 36% by addition of excess NH₄Cl to the reaction mixture (Scheme 1). The higher yield is caused by the low solubility of the NH₄Cl adduct in concentrated HCl solution, because little difference was noticed either when NH₄Cl was added before or after the reaction.

The NH₄Cl was removed quantitatively by converting it into the corresponding hydroxide using Amberlite IRA 410 ion-exchange resin, OH[−] form, and then heating in vacuo to expel NH₃ (Scheme 1).

While complexes of MeCuc5 with NH₄⁺ or metal cations demonstrate gas encapsulation in solution,^[11] they were inactive in the solid state. Once the lids (the NH₄⁺ ions or metal cations) are removed, however, MeCuc5 behaves as a molecular sieve in the solid state.



Scheme 1. Synthesis of MeCuc5 from dimethylglycoluril.

The crystals of MeCuc5, large transparent plates formed from an aqueous solution, lost the water of crystallization slowly at room temperature and rapidly on heating at 80 °C to give a white powder (m.p. > 370 °C). The powder rapidly gained in weight on cooling in air and gave copious air bubbles on dissolving in water. We determined the absorption capacities of the powder for a variety of gases. After circulating a gas through a powder of MeCuc5 to cause gas absorption, the volume of the gas released on heating (110 °C) was measured by means of a gas burette. At the same time, the composition and identity of the released gas was analyzed by GC–MS.

Gases of small kinetic diameters such as He, Ne, and H₂ (260, 289, and 275 pm, respectively),^[1] which can move freely in and out of the portals (320 pm in diameter), were not released in appreciable amounts on heating. On the other hand, Kr, Xe, and CH₄, with larger diameters (360, 396, and 380 pm, respectively)^[1] were not absorbed significantly. The gases of intermediate sizes (N₂, O₂, Ar, N₂O, NO, CO, and CO₂) were absorbed and released repeatedly. The most efficient absorption–release process was observed with N₂O, with the capacity of MeCuc5 for this gas as high as 40 mL g^{−1}, followed by CO₂ (26 mL g^{−1}). The capacities for the others fall in the range of 11–16 mL g^{−1}. The absorption of acetylene is so strong that the capacity for this gas could not be measured.

These gases are encapsulated in the molecular cavity and not in the lattice space as in zeolites (see Figure 2). In contrast to the absorption behavior in the solid state, MeCuc5 in aqueous solution absorbed the whole range of gases studied. A gas was bubbled into the solution by use of a syringe pump and the progress of inclusion of the gas into the molecular cavity was monitored by the intensities of newly appearing NMR signals for the CH₂ protons and for the C=O, CH₂, and even the remote CH₃ carbon atoms. Of special interest are: 1) when paramagnetic O₂ was included, the NMR signals, in particular that of the CO carbon atoms, became very broad, 2) in the case of CH₄, new signals for the included CH₄ appeared at $\delta = -0.87$ ppm (¹H NMR spectrum) and at -4.81 ppm (¹³C NMR spectrum), 3) although CO₂-saturated D₂O showed a barely discernible signal at $\delta = 127.41$ ppm in the ¹³C NMR spectrum, CO₂ in the cavity gave rise to a readily recognizable signal at 127.12 ppm, and 4) acetylene, insoluble in water, gave rise to new signals at $\delta = 1.02$ ppm (¹H NMR spectrum) and at $\delta = 73.64$ ppm (¹³C NMR spectrum; usually 1.80 and 71.9 ppm, respectively^[13]).

Most of the gases were encapsulated by bubbling them through a solution of MeCuc5 at room temperature; crystals were deposited when the MeCuc5 was saturated with gas (4×10^{-3} mol L^{−1}). However, large gases (CH₄, Kr, and Xe) required heating at 80 °C to cause them to be included. Because concomitant release of the included gas occurs at higher temperatures, the optimal conditions were difficult to find. In monitoring the extent of encapsulation by comparing the intensities of the signals caused by the carbonyl C atoms in the ¹³C NMR spectrum, we

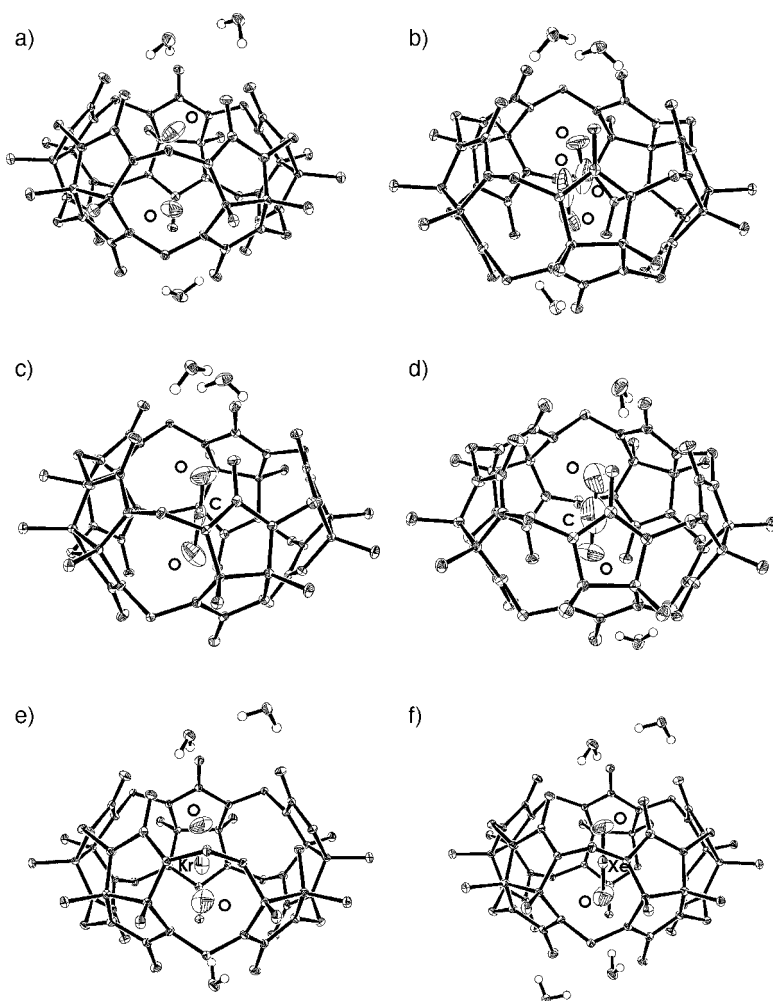


Figure 2. Crystal structures of gas-inclusion complexes of MeCuc5. The external water molecules (six in total, in all cases) are not shown except for those which are hydrogen bonded to carbonyl groups and not as the lids (occupancies of atoms in the cavity, convergence index): a) He complex (He not treated, $O = 0.83$, $R_1 = 0.047$), b) O_2 complex ($O = 0.34$ and $O_{\text{central}} = 0.12$, $R_1 = 0.044$, c) CO_2 complex ($C = O = 0.76$, $R_1 = 0.040$), d) CH_4 complex ($C = 0.49$, $O = 0.64$, $R_1 = 0.049$), e) Kr complex ($Kr = 0.42$, $O = 0.47$, $R_1 = 0.045$), f) Xe complex ($Xe = 0.52$, $O = 0.34$, $R_1 = 0.033$).

observed fluctuation of the signal positions of the gas-included species beyond instrumental error.

A clue to understanding this puzzling behavior in the ^{13}C NMR spectra came from X-ray crystal structure determination (Figure 2).^[14] Although the diffraction data were collected at $-180^\circ C$ on crystals freshly formed in gas-saturated solutions, the occupancies of the gases were considerably less than unity in all cases. There are also some water molecules inside the cavity, near the $C=O$ carbon atoms. The cavity is large enough to accommodate both a Xe atom and water molecules. The fluctuation of signal positions in the ^{13}C NMR spectra appears to indicate that the amount of water included depends upon the bubbling conditions.

As expected, gas absorption in the solid state was also strongly influenced by the residual included water molecules. While the water molecules in the lattice and those at the portals are readily removed by heating in air, those in the cavity stay even after prolonged heating in vacuo. For a large,

weakly interacting gas, removal of the residual water is a rather high hurdle to clear. For example, when Ar was absorbed into a MeCuc5 powder conditioned to the maximum capacity for N_2 (16 mL g^{-1}), only 4 mL g^{-1} was initially absorbed. After several absorption-desorption cycles, however, the capacity reached 15 mL g^{-1} . On the other hand, strongly interacting gases such as N_2O readily expelled the internal water. Then, after a rapid release of the gas on heating, a gradual decrease in volume of the gas was observed by absorption of the water vapor in the gas into the water in the gas burette.

Therefore, while the MeCuc5 powder shows selective gas inclusion, even Xe atoms and CH_4 molecules can be encapsulated in aqueous solution. In view of the presence of water molecules or metal ions as lids, as well as the cavity water molecules, this is remarkable. Because enlargement of the portals by heating is unlikely, when the rigidity of the cage is considered, the gas molecules may be pushed into the cavity by colliding water molecules.

Preliminary studies on MeCuc5 demonstrate its potential in practical applications. For example, a rather high level of CO_2 in air (5%) was decreased to 0.01% (0.035% in fresh air) in 1 h by circulating the air through a powder of MeCuc5. While MeCuc5 has a lower capacity and activity than 5 Å molecular sieves (MS), its lower regeneration temperature ($110^\circ C$ as compared to $350^\circ C$) and low affinity for water (prior drying necessary for 5 Å MS) may be of great advantage in controlling the amounts of CO_2 in air. MeCuc5 may also be used to decrease the amount of NO_x in air, because it has a high absorption capacity for N_2O and NO , and can be quantitatively regenerated by recrystallization.

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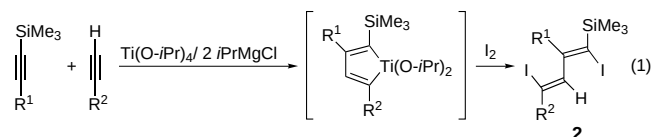
Efficient and General Synthetic Approach to Pentasubstituted Conjugated Dienes Using Site-Selective Coupling of Cuprates with 1,4-Diiodo-1,3-alkadienes as the Key Reaction**

Ryota Nakajima, Christophe Delas, Yuuki Takayama, and Fumie Sato*

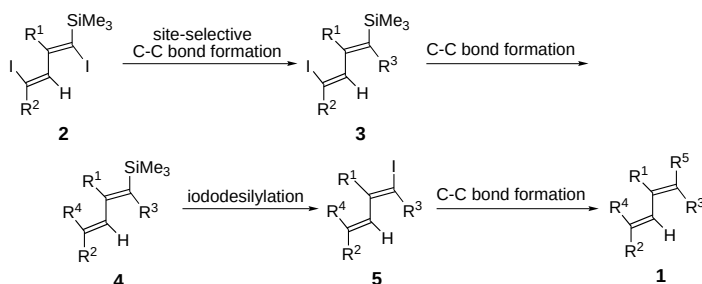
Selective preparation of polysubstituted conjugated dienes is an important transformation, because such dienes are useful intermediates and/or important structural constituents in natural product chemistry and materials science. When the regio- and stereoselective alignment of the substituents on the diene skeleton are considered, their synthesis is not necessarily an easy process, and the synthetic difficulty becomes more

and more marked with an increase in the number of substituents. We report herein a general method for preparing 1,1,2,4,4-pentasubstituted 1,3-butadienes **1**.

Recently, we developed a highly efficient method for synthesizing titanacyclopentadienes by regioselective coupling of 1-trimethylsilyl-1-alkynes and terminal acetylenes, mediated by a divalent titanium reagent Ti(O-*i*Pr)₄/2*i*PrMgCl.^[1,2] Treatment of the titanacyclopentadienes thus generated in situ with iodine furnishes 1,4-diiodo-1,3-alkadienes **2** in high yields [Eq. (1)].^[1,3]



With an efficient and practical entry to **2** in hand, we planned the preparation of **1** from **2**, according to the reaction pathway shown in Scheme 1. If the reaction proceeded as we expected, quite a number of dienes **1** with a variety of substituents could be prepared. For the success of our synthetic plan, the following two transformations hold the key, as other transformations were expected to occur readily by using established reactions. One transformation is the conversion of **2** into the monoiodides **3** by the site-selective



Scheme 1. Synthetic plan of 1,1,2,4,4-pentasubstituted 1,3-butadienes **1** from 1,4-diiodo-1,3-alkadienes **2**.

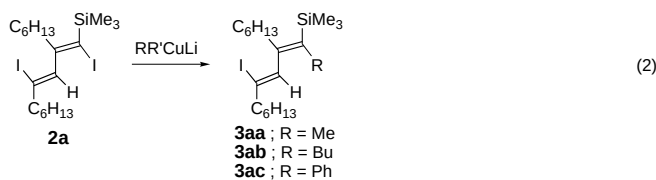
carbon–carbon bond formation at one of the two vinyliodo moieties in **2**. The other transformation is the stereoselective conversion of **4** into **5** because, although there are many precedents for converting vinylsilanes into isomerically pure vinyl iodides, there are few reports for the conversion of dienyisilanes into dienyl iodides.

For the transformation of **2** into **3**, we anticipated that the reaction with organocuprates might occur selectively at the α -silyl vinyliodide moiety, because it was reported that the presence of a silyl group in the α position of vinyl bromides causes acceleration of their coupling reaction with organocuprates.^[4] The reaction of **2a**, prepared from 1-trimethylsilyl-1-octyne and 1-octyne, with three equivalents of Me₂CuLi in diethyl ether at –50 °C for 3 h provided monomethylated product **3aa** exclusively in 90% yield, as shown in Equation (2) (for R' see Table 1).

It is noteworthy that no possible monomethylated and/or dimethylated product was produced in more than 1% yield,

[*] Prof. Dr. F. Sato, R. Nakajima, Dr. C. Delas, Dr. Y. Takayama
Department of Biomolecular Engineering
Tokyo Institute of Technology
4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501 (Japan)
Fax: (+81)45-924-5826
E-mail: fsato@bio.titech.ac.jp

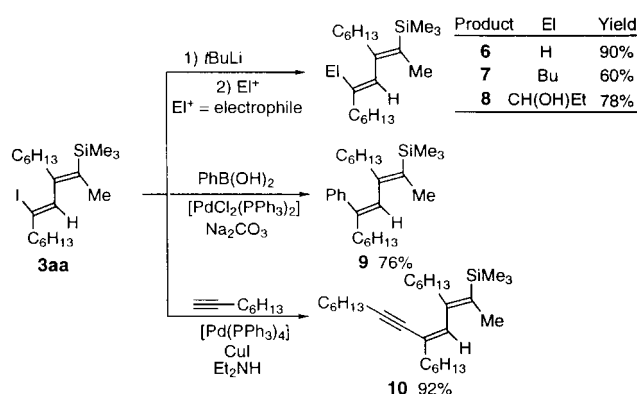
[**] C.D. would like to thank the Japan Society for the Promotion of Science (JSPS) for financial support.



even if three equivalents of the cuprate were used. The reaction of **2a** with Bu_2CuLi , which provided the expected monobutylated product **3ab**, did not proceed with satisfactory selectivity and yield; however, use of Bu(PhS)CuLi as the cuprate furnished **3ab** exclusively in 72 % yield. The reaction of **2a** with Ph_2CuLi also provided monophenylated product **3ac** in 59 % yield (^1H NMR spectroscopic analysis) but, in this case, other unseparable products, presumably including a regioisomer and a diphenylated compound, were coproduced; the selectivity was not improved by use of Ph(PhS)CuLi or Ph(CN)CuLi . These results, as well as the results of the reaction of other 1,4-diiodo-1,3-alkadienes **2b–e** with organocuprates,^[5] are shown in Table 1. Although the site selectivity of the reaction is somewhat dependent on the olefinic substituents R^1 and R^2 in **2**, excellent to high selectivity was attained in every case. Thus, we now have a highly efficient approach to a variety of dienes **3**, including functionalized ones such as those in entries 4–6.

With the success of the regioselective preparation of **3** from **2**, we carried out a carbon–carbon bond-forming reaction at the vinyl iodide moiety of **3**. As shown in Scheme 2, lithiation of **3aa** with $t\text{BuLi}$ followed by reaction with electrophiles such as H_2O , BuI , or EtCHO afforded the corresponding reaction products **6**, **7**, and **8**. Suzuki–Miyaura coupling^[6] of **3aa** with PhB(OH)_2 , and Sonogashira coupling^[7] with 1-octyne proceeded smoothly to afford the expected products **9** and **10**, respectively.

Having succeeded in synthesizing a variety of dienes of the type **4** (Scheme 1), we converted them into 1,1,2,4,4-penta-substituted 1,3-butadienes **1** via the iodide **5**. However, the



Scheme 2. C–C bond-forming coupling reactions of vinyl iodide **3aa**.

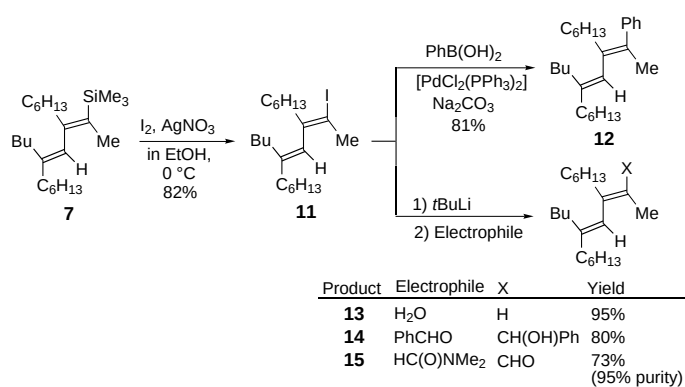
conversion of **4** into **5** did not proceed smoothly under the standard reaction conditions for converting a vinylsilyl moiety into a vinyl iodide. Thus, treatment of **7** with I_2 or $\text{ICl}^{[8]}$ afforded a complicated reaction mixture, and the yield of the expected product of the type **5** was less than 10 % (^1H NMR analysis). We then carried out the reaction using I_2/AgNO_3 ,^[9] and, to our satisfaction, the reaction proceeded readily with retention to afford the expected compound **11** in 82 % yield.^[10] The iodide **11** thus produced was finally converted into 1,1,2,4,4-pentasubstituted 1,3-butadienes **12**, **13**, **14**, and **15** using conventional reactions (Scheme 3).

In conclusion, a series of reactions (see Scheme 1) proceeded highly efficiently, thus opening up the first general method for synthesizing 1,1,2,4,4-pentasubstituted 1,3-butadienes with a variety of substitution patterns, which starts with readily available silylacetylenes and 1-alkynes. As the deiodination of **3** and/or **5** can be readily carried out by treatment with $t\text{BuLi}$ and then with H_2O , this method can also allow preparation of a variety of tri- and tetrasubstituted conjugated dienes. The present method is highly practical as all the reagents used for the transformations are inexpensive and

Table 1. Results of the reaction of 1,4-diiodo-1,3-alkadienes **2** with organocuprates.

Entry	Compound 2 ^[a,b]	Cuprate (3 equiv)	Conditions	Compound 3 ^[c] Selectivity ^[d]	Yield [%] ^[e]
1	2a R ¹ C ₆ H ₁₃ R ² C ₆ H ₁₃	(67 %) Me ₂ CuLi	–50 °C, 3 h	3aa Me 99:1	90
2	2a	Bu(PhS)CuLi	–78 °C, 1 h → 0 °C, 18 h	3ab Bu 99:1	72
3	2a	Ph ₂ CuLi	0 °C, 18 h	3ac Ph 87:13	68 ^[f]
4	2b C ₆ H ₁₃ C ₂ H ₄ OBn	(74 %) Me ₂ CuLi	–50 °C, 3 h	3ba Me 92:8	87 ^[f]
5	2c CH(OEt) ₂ C ₂ H ₄ OBn	(78 %) Bu(PhS)CuLi	–78 °C, 1 h → 0 °C, 8 h	3cb Bu –[g]	69
6	2d CO ₂ tBu C ₆ H ₁₃	(84 %) Bu(PhS)CuLi	–78 °C, 2 h	3db Bu –[g]	84
		–50 °C, 4 h			
7	2e	(63 %) Me ₂ CuLi			98:2 ^[h] 84

[a] The isolated yield of **2** after the reaction in Equation (1) is shown in parentheses. [b] The iodolysis was carried out by adding excess I_2 directly to the reaction mixture at -50°C ; addition of a THF solution of I_2 lowered the yield. [c] The stereochemistry was verified by NOESY or NOE experiments. [d] The ratio of **3**: other products was determined by ^1H NMR spectroscopic analysis of the crude product unless otherwise noted. [e] Yield of **3** after column chromatography. [f] Total yield; **3** and other product(s) could not be separated by column chromatography. [g] Not determined. [h] GC measurement.



Scheme 3. Transformation of **7** to the vinyl iodide **11** and the following coupling reaction.

easily available in quantity, and the reaction operation is easy.

Experimental Section

Typical procedure for the site-selective C–C bond formation of **2** with organocuprates (preparation of **3aa**, Table 1, entry 1): To a stirred solution of CuI (1.99 g, 10.4 mmol) in Et₂O (10 mL) was added a 1.04 M solution of MeLi in ether (20.0 mL, 20.8 mmol) at 0 °C, under argon, to give a homogeneous solution. The solution was cooled to –50 °C, then **2a** (1.90 g, 3.48 mmol) was added to the solution. After stirring at –50 °C for 3 h, the reaction mixture was quenched by the addition of aqueous NH₄Cl and the organic products were extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give a crude oil. Chromatography on silica gel (hexane) afforded compound **3aa** (1.35 g, 90%). ¹H NMR (300 MHz, CDCl₃): δ = 0.16 (s, 9H), 0.85–0.90 (m, 6H), 1.25–1.60 (m, 16H), 1.65 (s, 3H), 2.18 (t, *J* = 8.0 Hz, 2H), 2.51 (t, *J* = 7.1 Hz, 2H), 6.19 ppm (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 0.41, 14.18, 14.21, 19.67, 22.73, 22.76, 27.94, 28.84, 29.45, 29.85, 31.63, 31.91, 36.61, 45.06, 110.59, 131.35, 136.40, 149.32 ppm.

Typical procedure for conversion of **4** into **5** (synthesis of **11**; Scheme 3): To a stirred solution of **7** (0.126 g, 0.345 mmol) in absolute ethanol (6 mL) was added AgNO₃ (0.088 g, 0.518 mmol) at 0 °C. The mixture was stirred for 10 min to ensure complete dissolution. Iodine (0.114 g, 0.449 mmol) was added in one portion and stirred at 0 °C for 20 min. The reaction mixture was diluted with diethyl ether, filtering through a celite pad. The filtrate was washed with sodium thiosulfate solution, dried over Na₂SO₄, and concentrated in vacuo to give a crude oil. Chromatography on silica gel (hexane) afforded compound **11** (0.118 g, 82%). ¹H NMR (300 MHz, CDCl₃): δ = 0.86–0.91 (m, 9H), 1.21–1.42 (m, 20H), 1.89 (t, *J* = 7.4 Hz, 2H), 2.05 (t, *J* = 7.1 Hz, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 5.47 ppm (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 14.16, 14.20, 14.23, 22.74, 22.76, 23.13, 27.94, 28.04, 29.20, 29.27, 29.61, 30.75, 31.67, 31.82, 31.86, 35.47, 43.36, 96.24, 121.60, 142.69, 143.15 ppm.

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Reaction of “[Mn^{II}(CH₂tBu)₂]” with Bidentate Diimine Ligands: From Simple Base Adducts to C–C Activation of the Ligand**

Virginie Riollot, Christophe Copéret,* Jean-Marie Basset, Laurence Rousset, Denis Bouchu, Laurent Grosvalet, and Monique Perrin

Base adducts of dialkyl Mn^{II} complexes are typically monomeric tetrahedral high-spin systems;^[1] our synthetic target is to extend these adducts to bidentate diimine ligands. Gambarotta and co-workers^[2] recently reported an approach to Mn^{II} analogues of Brookhart–Gibson complexes^[3] and compared their performance in olefin polymerization with those of Fe^{II} and Ni^{II} catalysts. In this approach, they showed that the reaction of [MnCl₂L₂] complexes with organolithium reagents gave the corresponding Mn^I and Mn⁰ alkyl complexes, that is, the lithium reagents alkylate and reduce the Mn^{II} dichloro complex. These results have led us to disclose our investigation on the reaction of a bisneopentyl Mn^{II} complex with bidentate Schiff base ligands that were designed to generate complexes with structure **1** (Scheme 1). The major difference in our approach is the reaction of diimine ligands

[*] Dr. C. Copéret, V. Riollot, Dr. J.-M. Basset
Laboratoire de Chimie Organométallique de Surface
UMR-9986 CNRS-ESCE Lyon
43 bd du 11 Novembre 1918, 69616 Villeurbanne Cedex (France)
Fax: (+33)472-431-795
E-mail: coperet@cpe.fr
L. Rousset, Dr. D. Bouchu
Centre de Spectrométrie de Masse
Université Claude Bernard Lyon I
43 bd du 11 Novembre 1918, 69622 Villeurbanne Cedex (France)
L. Grosvalet, Prof. Dr. M. Perrin
Laboratoire de Cristallographie UMR-5078
Université Claude Bernard Lyon I
43 bd du 11 Novembre 1918, 69622 Villeurbanne Cedex (France)

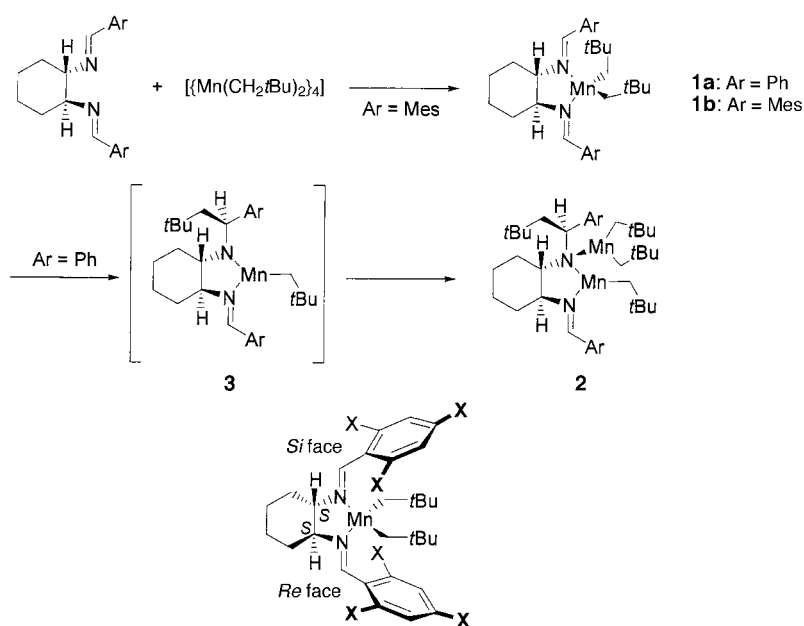
[**] We are indebted to the CNRS and ESCPE Lyon for financial support. V.R. is grateful to the Région Rhône-Alpes for a predoctoral fellowship. We also thank Prof. R. A. Andersen (U. C. Berkeley), Prof. Dr. Koelher (TUM), Dr. R. Gauvin (LCOMS), and Dr. C. Boisson (LCPP) for helpful discussions.



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with manganese(II) dialkyl complexes, which proceeds without reduction. Depending on the structure of the ligand it is possible to isolate either the desired base adduct or compounds in which the imine functional group is alkylated.

A brown solution of $[\text{Mn}(\text{CH}_2\text{tBu})_2]$ (1 equiv) in toluene was added to a colorless solution of *trans*-*N,N*-bis(benzylidene)-1,2-cyclohexanediamine in toluene, and the solution turned dark-purple. After 12 h, removal of toluene and addition of pentane led to precipitation of unconsumed ligand (excess ligand: vide infra). After complete removal of the ligand and concentration to dryness, a concentrated solution of the solid in toluene was cooled to -30°C to give single crystals as brown rectangular parallelepipeds (20%). However, X-ray analysis revealed the presence of **2** (Figure 1) with a structure that was dramatically different from that of the expected **1a**.^[4] Complex **2** is dinuclear, and the Mn–Mn distance of 2.822 Å implies that there is no metal–metal bond. Mn(1) is bound to one neopentyl ligand as well as to an imino and an amido ligand, whereas Mn(2) is bonded to the electron lone pair of the nitrogen atom of this amido group, but retains the two neopentyl ligands. Complex **2** is probably obtained via the expected **1a** (Scheme 1), which then undergoes migration of the neopentyl ligand onto the imine group^[5] to generate a mononeopentyl Mn^{II} complex with one imine and one amido ligand, which further reacts with the putative “ $[\text{Mn}(\text{CH}_2\text{tBu})_2]$ ” to give **2**. Thus, two equivalents of “ $[\text{Mn}(\text{CH}_2\text{tBu})_2]$ ” are required for each equivalent of ligand. This suggested reaction pathway is, however, difficult to substantiate, since starting material and product(s) contain high-spin Mn^{II} . Moreover, **2** was isolated as a single stereoisomer. The stereochemistry at the carbon center corresponds to the attack of the neopentyl fragment



Scheme 1. Generation of **2** via **1**, through migration of a neopentyl group and further reaction with the putative “ $[\text{Mn}(\text{CH}_2\text{tBu})_2]$ ”.

from the *Si* face of the imine moiety, that is, the face with the methine hydrogen atom rather than the C–C framework of the cyclohexane ring.

Reaction of a more highly substituted bisbenzylidene ligand ($\text{Ar} = \text{mesityl (Mes)}$) with “ $[\text{Mn}(\text{CH}_2\text{tBu})_2]$ ” gave the desired base adduct **1b** in 36% yield of isolated product. X-ray analysis shows that the geometry of the complex is a distorted tetrahedron with a wide C–Mn–C bond angle of 146.4° (Figure 2).^[4] The methyl substituents of the aromatic ring probably shield the imino group (see Scheme 1 and Figure 2) and thus prevent the migration of the neopentyl ligand to the imino group.

To understand the scope of this chemistry further, we also investigated the reaction of the Brookhart imino ligand with

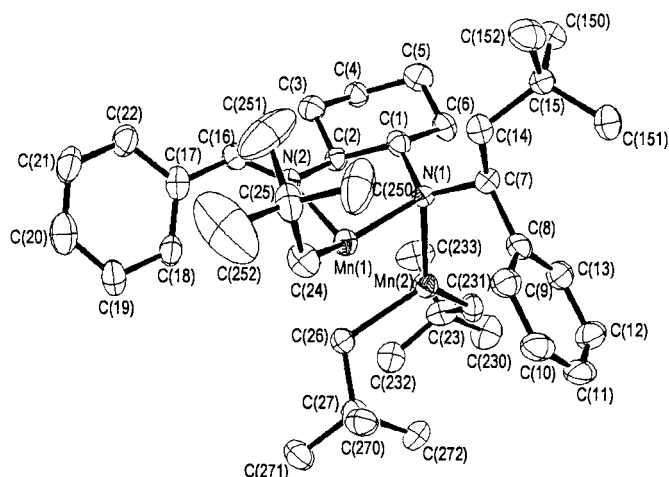


Figure 1. Thermal-ellipsoid plot of **2**. Selected bond lengths [Å] and angles [$^\circ$]: Mn(1)–C(24) 2.121(5), Mn(1)–C(26) 2.419(5), Mn(1)–N(1) 2.132(4), Mn(1)–N(2) 2.242(4), Mn(2)–C(26) 2.223(5), Mn(2)–C(231) 2.122(5), Mn(2)–N(1) 2.129(4); N(1)–Mn(1)–N(2) 79.35(2), N(1)–Mn(1)–C(24) 142.63(2), N(2)–Mn(1)–C(24) 118.48(2), N(1)–Mn(2)–C(26) 104.05(2), N(1)–Mn(2)–C(231) 129.99(2), C(26)–Mn(2)–C(231) 123.8(2).

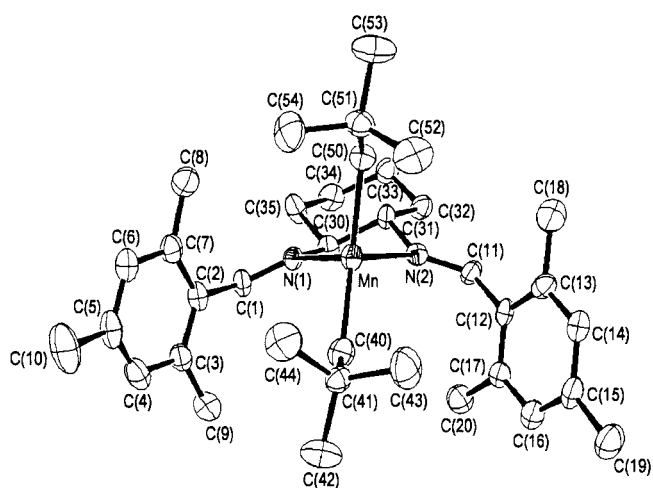


Figure 2. Thermal-ellipsoid plot of **1b**. Selected bond lengths [Å] and angles [$^\circ$]: Mn–C(40) 2.141(6), Mn–C(50) 2.165(6), Mn–N(1) 2.344(4), Mn–N(2) 2.279(4); C(40)–Mn–C(50) $146.4(2)$, C(40)–Mn–N(1) $102.1(2)$, C(40)–Mn–N(2) $110.3(2)$, C(50)–Mn–N(1) $105.62(2)$, C(50)–Mn–N(2) $95.71(2)$, N(1)–Mn–N(2) $73.12(2)$.

"[Mn(CH₂tBu)₂]⁺". In this case the reaction yield is higher (51 % of single crystals), but structural analysis again showed major reorganization of the putative base adduct by carbon–carbon migration within the ligand (Figure 3).^[4] The reaction probably involves adduct formation followed by the events outlined in Scheme 2. Migration of one neopentyl ligand in **4**

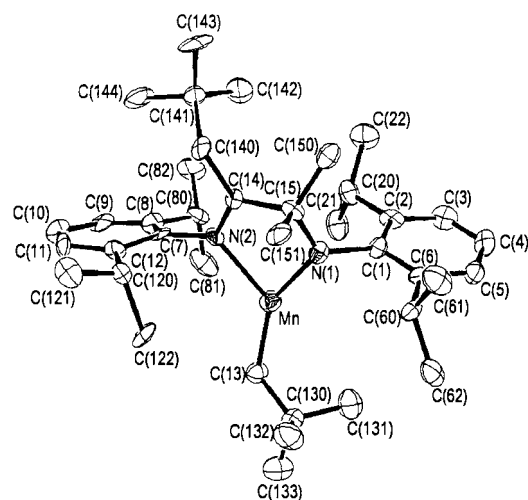
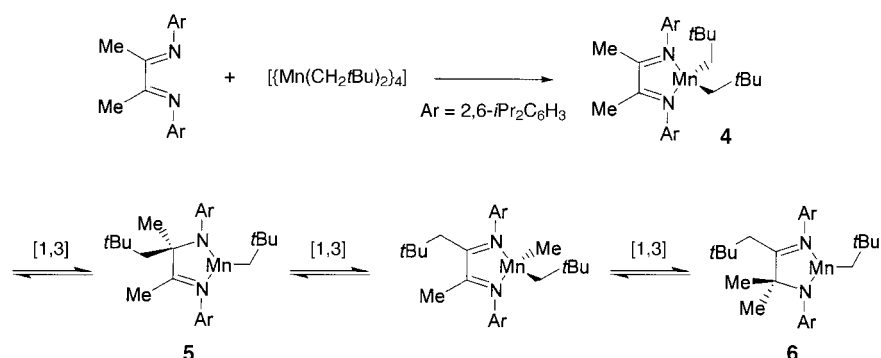


Figure 3. Thermal ellipsoid plot of **6**. Selected bond lengths [Å] and angles [°]: Mn–C(13) 2.105(3), Mn–N(1) 1.960(2), Mn–N(2) 2.185(3); C(13)–Mn–N(1) 150.86(12), C(13)–Mn–N(2) 129.68(11), N(1)–Mn–N(2) 79.11(10).



Scheme 2. Proposed mechanism for the migration reaction.

onto the imino group to give **5** is apparently followed by a 1,2-migration to the vicinal imino group. This rearrangement could also be a two-step process involving successive reversible 1,3-migration of the Me group from the C atom to the Mn atom and then to the other C atom to give an apparent overall 1,2-migration. Complex **6** has an Mn^{II} center in a trigonal environment with an imino, an amido, and a neopentyl ligand, like in **2**, but does not undergo further reaction with "[Mn(CH₂tBu)₂]⁺", probably because the 2,6-diisopropylphenyl substituent prevents access to the lone pair of the amido ligand.

In conclusion, we have shown that diimine Mn^{II} dialkyl complexes are accessible without reduction of the Mn center, which demonstrates the importance to access perhydrocarbyl metal complexes with the appropriate oxidation state. We have also demonstrated the necessity to protect the imino group with bulky substituents to avoid their reaction with

metal–carbon bonds. Most interestingly, we have uncovered pathways in which the C=N bonds undergo alkylation to amido groups. These reactions might be important deactivation pathways in some olefin polymerization reactions.^[6]

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- [6] No ethylene polymerization activities were found in either case using MAO or B(C₆F₅)₃ as co-catalysts.

Facile Oxidation of Alcohols to Carbonyl Compounds Using a Tris(2-methylphenyl)-bismuth Dichloride–DBU Binary System**

Yoshihiro Matano* and Hazumi Nomura

Various methods for the oxidation of alcohols to carbonyl compounds, one of the most important organic transformations, are available.^[1] Although individually having some synthetic advantages, most conventional methods suffer from one or more experimental drawbacks, such as severe or delicate reaction conditions, complicated reaction procedures, and the need to use toxic, unstable, or potentially explosive reagents. Therefore, the search for a mild but efficient oxidation method with easy handling, nontoxicity, and reasonably stable oxidants is still the subject of numerous studies on organic synthesis.^[2]

Pentavalent organobismuth compounds are attractive oxidants because of their inherent oxidizing ability derived from the facile Bi^V/Bi^{III} redox process^[3] and due to the low toxicity of bismuth.^[4] In 1934 Challenger and Richards reported that ethanol, *n*-propanol, and 2-propanol were oxidized by triphenylbismuth dihydroxide to acetaldehyde, propionaldehyde, and acetone, respectively.^[5] Several decades later Barton et al. and Dodonov et al. independently developed a new oxidation method using polyphenylbismuth(v) reagents such as (Ph₃BiCl)₂O, Ph₃BiCO₃, and Ph₃Bi(OAc)₂,^[6,7] in which a variety of alcohols are oxidized to the corresponding carbonyl compounds under neutral or basic conditions. However, their method often requires a long reaction time and/or a high reaction temperature to attain good results,^[8] and so there is still room for practical improvement in the Bi^V-based oxidation systems.

Recently, we found that dimeric tris(2-methoxyphenyl)bismuthane oxide (**1**)^[9] oxidizes alcohols to carbonyl compounds more rapidly (within 10 min) and under milder conditions (at room temperature) than the known organobismuth(v) reagents^[6,7,10] or polymeric tris(4-methylphenyl)bismuthane oxide.^[11] Although the bismuthane oxide **1** itself is thermally unstable and does not have the prerequisites for a practically usable oxidant, this finding suggested to us that the aryl ligands on the Bi^V center play an important role in alcohol oxidation. Thus, we set out to develop a one-pot oxidation system by the direct use of triarylbi-muth dichlorides bearing

suitable substituents, since this class of compounds are thermally stable and easy to handle.

Here we report a new, practical oxidation method using a binary system made up of tris(2-methylphenyl)bismuth dichloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which converts primary alcohols to aldehydes and secondary alcohols to ketones with high efficiency and chemoselectivity under mild conditions. In this system, the *ortho*-tolyl groups on the Bi^V center give rise to a remarkable oxidizing ability, one which is difficult to attain with the *para*- and non-substituted phenyl groups. An additional improvement upon previous systems is that the carbonyl products can be easily isolated by simple work-up procedures.

To determine the effect of the substituent, we first compared oxidizing abilities among five triarylbi-muth dichlorides **2a–e** in a reaction with *p*-bromobenzyl alcohol (**3**) (Table 1). In the presence of 2.2 equiv of *t*BuOK and 6.1 equiv

Table 1. Oxidation of alcohol **3** using Ar₃BiCl₂ (**2**) and a base.

Compd 2	Ar	Conversion of 3 [%] ^[a]	
		<i>t</i> BuOK system	DBU system
2a	<i>o</i> -MeC ₆ H ₄	> 99 (62) ^[b] (15) ^[c]	98 (> 99) ^[d]
2b	<i>o</i> -MeOC ₆ H ₄	94 (55) ^[b] (17) ^[c]	78
2c	<i>p</i> -MeC ₆ H ₄	38	19
2d	<i>p</i> -MeOC ₆ H ₄	28	5
2e	Ph	52	43

[a] Determined by ¹H NMR spectroscopy. Compound **3** was converted quantitatively into **4**. [b] Only 1.2 equiv of *t*BuOK was used. [c] Water was not added. [d] Toluene was used as the solvent.

of water, the *ortho*-substituted derivatives **2a** and **2b** oxidized **3** to *p*-bromobenzaldehyde (**4**) much more rapidly than the *para*- and nonsubstituted derivatives **2c–e**. When the reaction was performed in the absence of water or in the presence of only 1.2 equiv of *t*BuOK, the conversion of **3** into **4** was dramatically depressed. During these oxidations, equimolar amounts of arene (ArH) and Bi^{III} compounds of the types [Ar₃Bi] and [Ar₂BiOAr]^[12] were formed as by-products. These outcomes indicated that the triarylbi-muth(v)-oxo or -hydroxo species is the active oxidant generated in situ. Actually, the independently prepared **1** showed almost the same efficiency as the **2b**/*t*BuOK/H₂O system.

We next examined the one-pot oxidation using DBU instead of *t*BuOK (Table 1). The best result was again obtained with the *ortho*-tolyl derivative **2a**, which quantitatively converted **3** into **4** in the presence of one equivalent of DBU. In this system, the reaction proceeded efficiently without water, and the Bi^{III} by-product was a crystalline complex, [*o*-Tol₂BiCl₂][DBUH⁺] (**5**), which was characterized by spectroscopy as well as by X-ray crystallography.^[13]

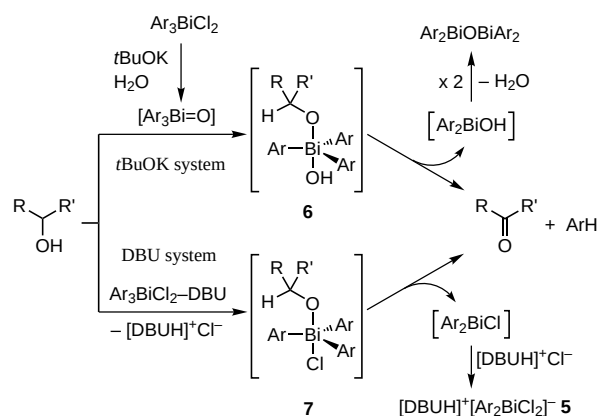
[*] Prof. Y. Matano*, H. Nomura
Department of Chemistry, Graduate School of Science
Kyoto University
Sakyo-ku, Kyoto 606-8502 (Japan)

[+] Present address: Department of Molecular Engineering
Graduate School of Engineering
Kyoto University
Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81)75-751-7279
E-mail: matano@mee3.moleng.kyoto-u.ac.jp

[**] This work was partially supported by a Grant-in-Aid (12640516) from the Ministry of Education, Science, Sports and Culture of Japan and a Toray Award in Synthetic Organic Chemistry, Japan. We thank Prof. Keiji Maruoka (Kyoto University) for his encouragement. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Owing to its ionic character, complex **5** is insoluble in nonpolar solvents. Thus, when the reaction was carried out in benzene or toluene, **5** was deposited from the reaction medium and could be removed by filtration. This brought a practical advantage over the *t*BuOK system in that the carbonyl product could be purified by passing it through a short silica gel bed with a small amount of eluent (hexane/EtOAc).^[14]

It has been confirmed that, in both systems, the steric environment around the Bi^V center plays an important role in the alcohol oxidation. Plausible reaction mechanisms of these oxidations are depicted in Scheme 1. Apparently, the α -hydrogen atom of the alcohol is abstracted by the aryl group via alkoxybismuth(v) intermediates **6** and **7**.^[15] The kinetic isotope effects observed in the oxidation of *p*-BrC₆H₄CH(D)OH by **2a** ($k_H/k_D = 3.3$ for *t*BuOK/H₂O/CDCl₃ and 3.4 for DBU/toluene at 25 °C, estimated by ¹H NMR spectroscopy) suggested that the rate-determining steps involved α -hydrogen abstraction from **6** and **7**. Presumably, the *ortho*-substituted aryl groups accelerated these Bi^V/Bi^{III} redox processes for steric reasons.



Scheme 1. Plausible reaction mechanisms for the oxidation of alcohols by the *t*BuOK and DBU systems.

With the availability of a mild and efficient oxidation system, **2a**/DBU, we examined the oxidation of various primary and secondary alcohols in toluene at room temperature (Table 2). The *para*- and *ortho*-substituted benzyl

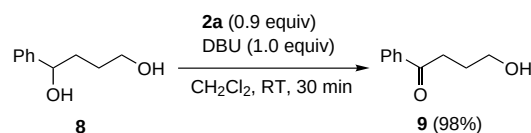
Table 2. Oxidation of alcohols using the **2a**/DBU system in toluene.

$\text{R}-\text{CH}(\text{OH})-\text{R}' \xrightarrow[\text{toluene, RT}]{\text{2a (1.1 equiv), DBU (1.1 equiv)}} \text{R}-\text{C}(=\text{O})-\text{R}'$							
Entry	Alcohol	<i>t</i> [h]	Yield [%] ^[a]	Entry	Alcohol	<i>t</i> [h]	Yield [%] ^[a]
1		0.5	94	11		2.0	94
2		0.5	95	12		2.0	90 ^[c]
3		0.5	99	13		0.5	— ^[d]
4		0.5	98	14		0.5	99
5		0.5	98	15		0.5	89
6		0.5	> 99	16		32	98 ^[e]
7		0.5	95	17		0.5	> 99
8		0.5	> 99	18		1.0	93
9		0.5	94	19		2.0	93
10		0.5	> 99 ^[b]	20		2.0	> 99

[a] Yield of isolated carbonyl compound unless otherwise noted. [b] Neral and geranial compounds were obtained in a 98:2 ratio. [c] 2-(*o*-Tolyl)-5-phenylpentanal was obtained in 5% yield. [d] A complex mixture was formed and the alcohol was recovered in moderate yield. [e] Yield determined by NMR spectroscopy. The reaction was carried out in C₆D₆.

alcohols were oxidized to the corresponding substituted benzaldehydes in excellent yields (entries 1–7). Thiomethyl, triethylsiloxy, amino, and amido groups remained intact under the present reaction conditions. Allylic and nonconjugated aliphatic alcohols were also oxidized in high yields to α,β -unsaturated aldehydes and nonconjugated aliphatic aldehydes, respectively (entries 8–12). Complete stereochemical retention was observed for geraniol (entry 9), whereas a slight isomerization was observed for nerol (entry 10). In these reactions, the aldehydes produced were not oxidized further to carboxylic acids, thus indicating the potential utility of the **2a**/DBU system as a selective oxidant. A limitation was observed in the oxidation with 2-phenylethanol, which could not be efficiently converted into phenylacetaldehyde (entry 13). In this reaction, a complex mixture was formed with only moderate recovery of the starting alcohol. It seems that the acidic α -proton of the initially formed phenylacetaldehyde is readily abstracted by DBU, causing undesired reactions.^[16] Secondary alcohols were oxidized to the corresponding ketones in high yields (entries 14–20). It is worth noting that 2,2,2-trifluoro-1-phenylethanol could be cleanly oxidized to α,α,α -trifluoroacetophenone, though a longer reaction time was necessary (entry 16).^[17] When **2c** (Ar = *p*-Tol) was used in place of **2a**, the trifluoromethyl ketone was not formed under all the same conditions.

To estimate the relative reactivity of allylic, benzylic, and nonconjugated alcohols toward the **2a**/DBU system, both intermolecular and intramolecular competitive oxidations were examined. As summarized in Table 3, the **2a**/DBU system oxidized cinnamyl and benzylic alcohols preferentially



Scheme 2. The intramolecular competitive oxidation of alcohol **8** by the **2a**/DBU system.

promises facile conversion of alcohols into carbonyl compounds with high efficiency and selectivity under mild conditions. The remarkable oxidizing ability of this new system is derived from the steric effect of the *ortho*-tolyl groups attached to the Bi^V center. The present system also has a practical advantage over the previously reported Bi^V-based oxidation systems in that the carbonyl products can be easily isolated by simple filtration following treatment on a short column. Further studies on the use of this method in other organic transformations are currently in progress.

Experimental Section

Oxidation of alcohol: DBU (46 mg, 0.30 mmol) was added to a stirred suspension of tris(2-methylphenyl)bismuth dichloride (**2a**;^[19] 166 mg, 0.30 mmol) and alcohol (0.27 mmol) in toluene (3 mL) at room temperature, and the resulting mixture was monitored by TLC at several intervals. After the alcohol was consumed, the precipitated complex **5** was filtered off through a thin celite bed. The filtrate was concentrated under reduced pressure to leave an oily residue, which contained the desired carbonyl product in a high state of purity (> 90%). The residue was then passed through a short silica gel column (710 mm² × 18–45 mm of Wako-gel C-200, about 50 mL of hexane/EtOAc (5/1) as eluent) to afford the carbonyl compound in the yields listed in Table 2. Complex **5** was recovered quantitatively and could be converted into tris(2-methylphenyl)bismuthane by treatment with 2.5 equiv of *o*-TolMgBr in THF.

5: M.p. 181–184 °C (decomp); ¹H NMR (400 MHz, CDCl₃, TMS): δ = 1.63–1.74 (m, 6H), 1.92 (tt, *J* = 5.9, 5.9 Hz, 2H), 2.58 (s, 6H), 2.76–2.79 (m, 2H), 3.19 (t, *J* = 5.9 Hz, 2H), 3.39 (t, *J* = 5.9 Hz, 2H), 3.43–3.45 (m, 2H), 7.31 (dd, *J* = 7.6, 7.3 Hz, 2H), 7.44 (dd, *J* = 7.6, 7.3 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 8.49 (d, *J* = 7.6 Hz, 2H), 10.84 ppm (brs, 1H); IR (KBr): $\tilde{\nu}$ = 3217, 3126, 3038, 2980, 2937, 2856, 1651, 1589, 1470, 1448, 1383, 1323, 1292, 1271, 1207, 1159, 1109, 984, 845, 756, 743, 706, 606, 536, 436, 430 cm^{−1}; elemental analysis (%) calcd for C₂₃H₃₁BiCl₂N₂: C 44.89, H 5.08, N 4.55; found: C 44.85, H 4.99, N 4.51.

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Table 3. Competitive oxidation of alcohols by **2a** and Dess–Martin periodinane.^[a]

RR'CHOH + EtOH	2a /DBU or Dess–Martin CDCl ₃ , RT, 15 min	RR'C=O + MeCHO
RR'CHOH	Ratio of RR'C=O to MeCHO ^[b]	
	2a /DBU	Dess–Martin
Ph-CH=CH-CH ₂ -OH	98:2	91:9
Ph-CH ₂ -OH	96:4	90:10
Ph-CH(OH)-CH ₃	95:5	75:25

[a] Three equivalents each of RR'CHOH and ethanol were used. [b] Determined by ¹H NMR spectroscopy.

in the presence of ethyl alcohol, and their selectivities were found to be much higher than those attained by Dess–Martin periodinane.^[18] The high chemoselectivity of benzylic versus nonconjugated aliphatic alcohols was also observed in the reaction of 1-phenyl-1,4-butanediol (**8**): When treated with 0.9 equiv of **2a**/DBU, **8** was converted exclusively into 4-hydroxy-1-phenylbutan-1-one (**9**) in 98% yield based on **2a** (Scheme 2). These results clearly demonstrate the synthetic utility of the **2a**/DBU system as a chemoselective oxidant.

In summary, we have established a new practical oxidation method using the (*o*-Tol)₃BiCl₂/DBU binary system, which

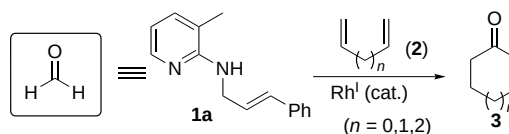
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Synthesis of Cycloalkanones from Dienes and Allylamines through C–H and C–C Bond Activation Catalyzed by a Rhodium(II) Complex**

Dae-Yon Lee, In-Jung Kim, and Chul-Ho Jun*

Among numerous examples of transition-metal-mediated cyclization to obtain medium-sized ring compounds,^[1] intramolecular hydroacylation provides the most promising way to prepare cyclopentanones from 4-pentenal through the C–H-bond activation of an aldehyde.^[2,3] However, its application has been limited to the synthesis of five-membered rings with a few exceptions,^[3] because the competing decarbonylation of the acyl metal hydride intermediate prevails during the formation of the larger ring. In the course of our studies into chelation-assisted C–H- and C–C-bond activation,^[4] allylic amine **1a**, which bears a coordination site, was devised and used as a masked form of formaldehyde in the hydroacylation of 1-alkenes to synthesize dialkyl ketones.^[4d] We envisaged a cyclization of dienes **2**^[5–7] with **1a** to furnish cycloalkanones **3** with various sizes, since decarbonylation cannot occur in the reaction of **1a** (Scheme 1). Herein we present a facile synthesis of various cycloalkanones from the reaction of allylic amines with dienes through chelation-assisted C–H- and C–C-bond activation.



Scheme 1. Formation of cycloalkanone **3** from the reaction of allylamine **1a** and diene **2**.

The reactions of **1a** with various dienes (**2**) are summarized in Table 1. For example, when **1a** was allowed to react with 1,4-pentadiene (**2a**) in the presence of $[(\text{C}_8\text{H}_{14})_2\text{RhCl}]_2$ (**4**, 5 mol %) and PCy_3 (**5**, 15 mol %) at 150 °C for 2 h, cyclohexanone (**3a**) and 2-methylcyclopentanone (**3b**) were obtained in 87 % and 13 % yield, respectively, after hydrolysis (Table 1, entry 1). Furthermore, the reaction with 1,5-hexadiene (**2b**) provided cycloheptanone (**3c**), 2-methylcyclohexanone (**3d**), and 2-ethylcyclopentanone (**3e**) in a ratio of 38:40:22 (Table 1, entry 2).^[8]

The mechanism for this reaction is depicted in Scheme 2. Aldimine **6a** is generated by Rh-catalyzed isomerization of **1a**. Subsequent intermolecular hydroiminoacylation^[9] of **2b**

[*] Prof. Dr. C.-H. Jun, D.-Y. Lee, I.-J. Kim
Department of Chemistry, Yonsei University
Seoul 120-749 (Korea)
Fax: (+82)2-364-7050
E-mail: junch@yonsei.ac.kr

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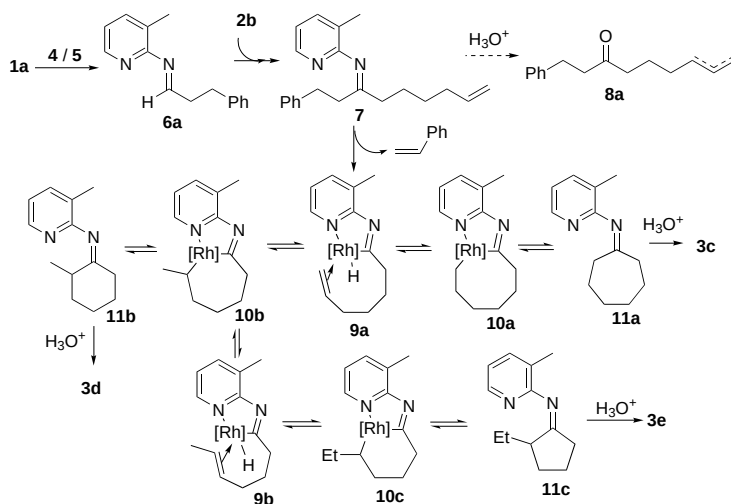
Table 1. The cyclization of dienes **2** with **1a**^[a]

Entry	Dienes 2	<i>t</i> [h]	Cycloalkanones 3 ^[b]	Yield
1 ^[c]	2a	2	3a 3b	(100%, 87:13)
2 ^[c,d]	2b	2	3c 3d 3e	(82%, 38:40:22)
3 ^[e]	2c	0.5	3f	(56%)
4 ^[f]	2d	2	3g	86% (100%)
5	2e	4	3h	84% (100%)
6	2f	5	3i	77% (100%)
7 ^[c]	2g	3	3j	67% (100%)
8 ^[g]	2h	18	3b	(77%)

[a] **1a** (0.25 mmol), **2** (0.75 mmol), **4** (0.0063 mmol), **5** (0.039 mmol) in toluene (100 mg) at 170°C. The products were identified after hydrolysis. [b] Yields of isolated cycloalkanones (GC yields are given in parentheses). [c] The reaction temperature was 150°C. [d] A mixture of alkenyl ketones **8a** (9%) and **8b** (9%), which were identified as 1-phenyl-3-nonanone and dihexyl ketone, respectively, were also observed (GC) after hydrogenation. [e] A mixture of alkenyl ketones **8c** (23%) and **8d** (21%) was also obtained. [f] The ratio of meso-**2d** (±-**2d** (ca. 45:55) was retained in **3g** (determined by ¹H NMR spectroscopy). [g] A mixture of alkenyl ketones, identified as a hydrogenated form, 1-phenyl-3-octanone, was obtained (33% yield by GC).

with **6a** gives ketimine **7**, which is hydrolyzed to give acyclic ketone **8a**.^[4d] Further C–C-bond activation of **7**, and subsequent β-hydrogen elimination leads to iminoacylrhodium(III) hydride **9a**, and styrene is liberated.^[4c,d] The intramolecular hydrometalation of **9a** affords ketimines **11a–c**, which furnish corresponding cycloalkanones **3c–e** after hydrolysis. Among the products, ketimine **11a** is derived from anti-Markovnikov hydrometalation of **9a** via metallacyclic intermediate **10a**, whereas **11b** is formed from Markovnikov reaction of **9a** via **10b**. Further skeletal isomerization of **10b** leads to the formation of **11c** via **9b** and **10c**.

Monitoring the change in the ratio of cycloalkanones in the reaction of **1a** with **2b** revealed that the seven-membered ring



Scheme 2. Postulated mechanism for the cyclization of **2b** with **1a**.

3c was the sole product after 5 min (Figure 1). The ratio of **3c** decreased while those of **3d** and **3e** increased as the reaction progressed.^[10] This type of skeletal rearrangement by C–C-

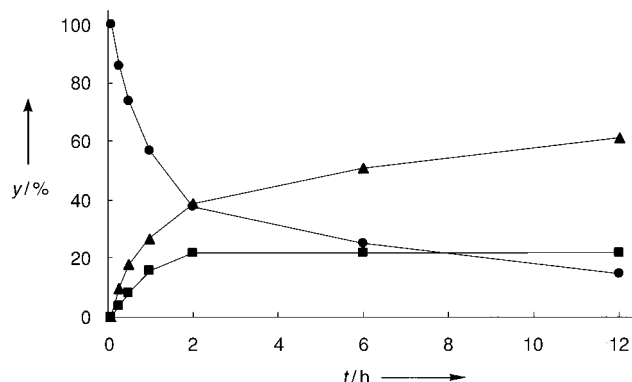
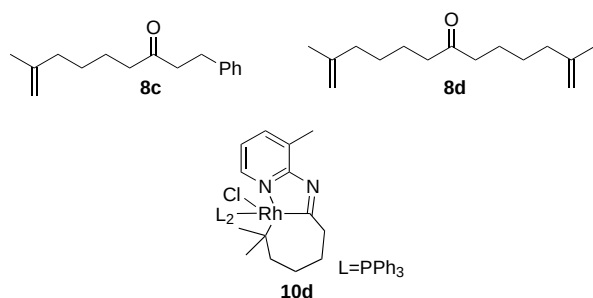


Figure 1. Plot of the ratio of cycloalkanones vs time plot for the reaction of **1a** and **2b** at 150°C. y = Ratio of cycloalkanones determined by GC: ● = **3c**, ▲ = **3d**, ■ = **3e**.

bond activation, which leads to the spontaneous ring contraction of the seven-membered ring to the more stable six- and five-membered rings, has been already studied.^[4f,11] However, the initial formation of a seven-membered ring implies that anti-Markovnikov hydrometalation (Scheme 2, **9a** to **10a**) is favored over Markovnikov hydrometalation (Scheme 2, **9a** to **10b**), maybe as a result of the steric congestion of the (iminoacyl)rhodium system.^[4a]

The exclusive formation of a seven-membered ring was observed with substituted dienes. For instance, the reaction of 2-methyl-1,5-hexadiene (**2c**) with **1a** gave 3-methylcycloheptanone (**3f**) as the sole cyclization product in 56% yield, along with alkenyl ketones **8c** and **8d**, which shows that the initial hydroiminoacylation takes place at the less substituted olefin, that is, C5=C6 in **2c** (Table 1, entry 3). The subsequent cyclization occurs at C1=C2 in **2c** to form **3f**, but further ring contraction did not proceed, because the formation of the resulting metallacycle intermediate **10d** is disfavored as a result of steric congaestion.

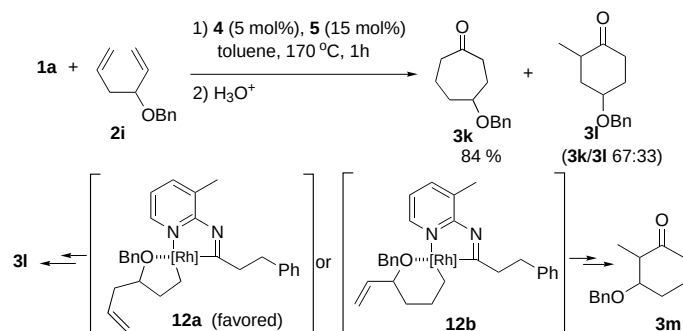


Other 1,5- or 1,4-dienes that bear substituents at C2 or C3 also exclusively yielded seven- or six-membered rings, respectively, without forming ring-contraction products (Table 1, entries 4–7). Notably, even the 1,3-diene piperylene (**2h**) also underwent cyclization to give **3b** in good yield (Table 1, entry 8). So far, the hydroacylation of conjugated dienes has been known to afford β,γ -unsaturated ketone via π -allyl intermediates.^[12]

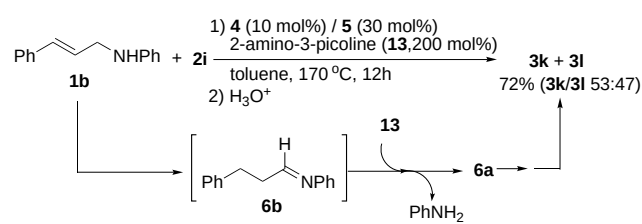
Another interesting substrate is 3-benzyloxy-1,5-hexadiene (**2i**), which reacted with **1a** to give cycloalkanones **3k** and **3l** (67:33; Scheme 3). The formation of **3l** instead of **3m** as a ring-contraction product illustrates that initial hydroiminoacylation occurs exclusively at C1=C2 in **2i** to give intermediate **12a**, which is favored over **12b** as a result of the directing effect of the benzyloxy group, thus forming the stable five-membered metallacycle in **12a**.^[13]

Allylic amines that have no coordination site could also be applied to this reaction. For example, *N*-cinnamylamine (**1b**) reacted with **2i** in the presence of 2-amino-3-picoline (**13**) to give **3k** and **3l** in 72% yield after hydrolysis (Scheme 4). This reaction proceeds through the isomerization of **1b** and subsequent transimination^[4e,14] of the resulting aldimine **6b** to form **6a**.

In summary, the synthesis of various cycloalkanones by the reaction of allylic amines with dienes was achieved through chelation-assisted C–H- and C–C-bond activation. The use of



Scheme 3. Reaction of **2i** with **1a** in the presence of **4** and **5**.



Scheme 4. Reaction of **1b** and **2i** through transimination.

1a as a masked form of formaldehyde allows the formation of six- and seven-membered cycloalkanones, which has rarely been possible by intramolecular hydroacylation as a result of competing decarbonylation. Furthermore, the reaction with substituted 1,4- or 1,5-dienes exclusively gave cyclohexanones or cycloheptanones, respectively. Even allylic amines that have no coordination site can also be applied to this reaction by utilizing a transimination protocol.

Experimental Section

Reaction of 1b and 2i: A screw-capped pressure vial (1 mL) was charged with **1b** (39.2 mg, 0.190 mmol), **2i** (44.9 mg, 0.239 mmol), **13** (43.2 mg, 0.400 mmol), [(C₈H₁₄)₂RhCl]₂ (**4**; 7.3 mg, 0.012 mmol), tricyclohexylphosphane (**5**; 10.8 mg, 0.0599 mmol), and the reaction mixture was dissolved in toluene (100 mg). It was stirred in a preheated oil bath (170 °C) for 12 h. Upon completion, the reaction mixture was hydrolyzed (1 N HCl) and purified by column chromatography (SiO₂, *n*-hexane/ethyl acetate 5:2) to afford a mixture of **3k** and **3l** in 84% yield (24.8 mg). The ratio of **3k/3l** was determined by GC analysis as 53:47.

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An Analogue of Cymantrene [$(\eta^5\text{-C}_5\text{H}_5)\text{Mn}(\text{CO})_3$] That Contains a Dimetalladithiacyclopentadienyl ring**

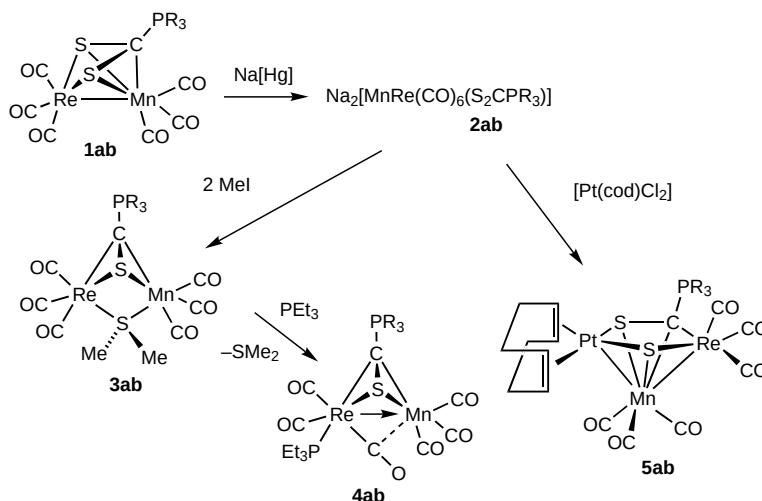
Daniel Miguel,* Dolores Morales,
V́ctor Riera, and Santiago Garća-Granda

The discovery of metal complexes with aromatic rings as π -donors initiated a new age of organo-transition-metal chemistry.^[1] Many complexes of this type, which bear heteroatom-substituted rings, are now known^[2] and in the last decades metal-complexed metallaarenes^[3] and metallaheteroatomarenes^[4] have been prepared.

Metal π complexes of dimetallacycles have been reported by Chisholm et al.^[5] and by Rothwell and co-workers.^[6] The latter can be considered as metallaarenes, whereas the former show a severe distortion from planarity, which has been taken as indicative of non-aromatic character. This seems to be the current frontier in the transition from purely carbon-based rings to heteroatom- or metal-substituted rings as π ligands. We report herein the first example of a transition-metal π complex of a ring that contains two heteroatoms and two different transition metals.

We previously found that the reaction of dianions $[\text{MnRe}(\text{CO})_6(\mu\text{-S}_2\text{CPR}_3)]^{2-}$ (**2a–b**) with excess of NH_4PF_6 leads to C–S cleavage and double protonation.^[7] Analogously, reaction of **2a–b** with excess MeI gave complexes **3a–b** (Scheme 1). Spectroscopic data support the structure depicted in Scheme 1, resulting from double methylation at the sulfur atom. Reaction of **3a–b** with PEt_3 afforded more stable derivatives **4a–b**. An X-ray determination of the structure of **4a** (Figure 1)^[8] showed that the SMe_2 group had been substituted by Et_3P , and the presence of the thiocarbonylphosphorane ligand SCPtPr_3 .^[9]

We speculated that C–S-bond breaking occurs in the reactions of **2a–b** with H^+ and Me^+ because electrons are required to create the new bond to H or Me groups, and that using a high-electron-count metal fragment as electrophile instead could result in bond formation without concomitant bond breaking. We found that **2a–b** react with $[\text{PtCl}_2(\text{cod})]$



Scheme 1. Preparation of **4** and **5**. **a**: R = *i*Pr, **b**: R = Cy.

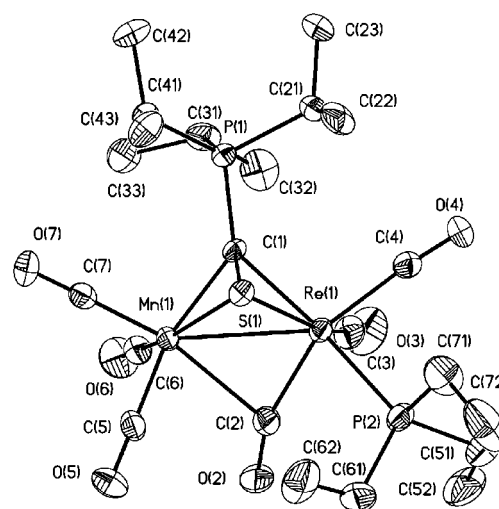


Figure 1. Molecular structure of **4a**: selected bond lengths [Å] and angles [°]: Re(1)–Mn(1) 2.7824(13), Re(1)–S(1) 2.4456(17), Re(1)–C(1) 2.138(6), Mn(1)–S(1) 2.310(2), Mn(1)–C(1) 2.009(7), Re(1)–C(2) 1.986(8), S(1)–C(1) 1.798(7), Mn(1)–C(2) 2.430(9), C(4)–Re(1)–C(2) 156.5(3), C(1)–Re(1)–P(2) 145.45(19), C(3)–Re(1)–S(1) 153.9(3), C(5)–Mn(1)–C(1) 155.1(3), C(6)–Mn(1)–S(1) 155.2(3).

(cod = cycloocta-1,5-diene) to yield the trimetallic derivatives **5a–b**. A molecule of **5a** (Figure 2)^[10] contains an angular Pt–Mn–Re framework with Pt–Mn (2.956(1) Å) and Re–Mn (2.822(1) Å) distances consistent with metal–metal bonds.^[11] Contrary to our expectation, C–S-bond breaking took place to give SCPtR_3 and S ligands, both of which act as bridges between the three metal centers.

The Pt–S(2)–C(1)–Re–S(1) ring is planar; the highest deviation occurs with Re(1), which is 0.115(3) Å out of plane. The Mn atom is bonded to all five atoms in the ring in a fairly symmetrical disposition. The plane formed by the carbon atoms of the three carbonyl groups bonded to Mn is virtually parallel to the Pt–S–C–Re–S ring (angle between planes 6.31°). All these geometrical features suggest that the structure of **5a** can be viewed as a dithiadimetallal analogue of cymantrene $[\text{Mn}(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_3]$.^[12] This can be rationalized by considering that all the fragments involved in the five-membered ring

[*] Dr. D. Miguel
Departamento de Química Inorgánica, Facultad de Ciencias
Universidad de Valladolid
47005 Valladolid (Spain)
Fax: (+34)983-423-232
E-mail: dmsj@qi.uva.es

Dr. D. Morales, Prof. V. Riera
Departamento de Química Orgánica e Inorgánica
Facultad de Química, Universidad de Oviedo
33071 Oviedo (Spain)
Dr. S. García-Granda
Departamento de Química Física y Analítica
Facultad de Química, Universidad de Oviedo
33071 Oviedo (Spain)

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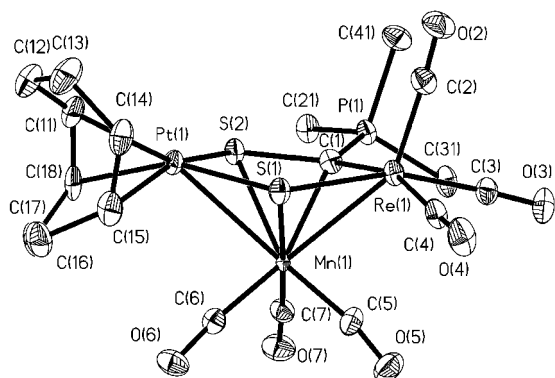


Figure 2. Molecular structure of **5a**: selected bond lengths [Å] and angles [°]: Pt(1)–S(2) 2.272(2), Pt(1)–S(1) 2.290(2), Pt(1)–Mn(1) 2.9563(13), Re(1)–C(1) 2.115(9), Re(1)–S(1) 2.428(2), Re(1)–Mn(1) 2.8216(13), Mn(1)–C(1) 2.220(10), Mn(1)–S(2) 2.426(3), Mn(1)–S(1) 2.479(3), S(2)–C(1) 1.803(10), S(2)–Pt(1)–S(1) 88.89(9), Pt(1)–S(1)–Re(1) 120.74(10), C(1)–Re(1)–S(1) 84.9(3), S(2)–C(1)–Re(1) 128.0(5), C(1)–S(2)–Pt(1) 115.4(3), Re(1)–Mn(1)–Pt(1) 90.42(4).

are isolobal with neutral or charged CH fragments.^[13] The ring itself is thus isolobal with Cp, and the five metal atoms are able to donate a total of five electrons to the {Mn(CO)₃} fragment (13 electrons) to fulfil the 18-electron rule.

Complexes **5a–b** represent the highest degree of heavy-atom substitution (two transition-metal atoms and two sulfur atoms) in a metal π -complexed ring, and the first example of a dimetallacyclopentadiene with two different metal atoms.

Theoretical studies addressing the issue of aromaticity in **5a–b**, as well as attempts to liberate the {Mn(CO)₃} fragment will be pursued.

Experimental Section

3a: CH₃I (39 μ L, 0.6 mmol) was added to a cooled (–78 °C) solution of dianion **2a** (0.3 mmol)^[7] in THF, and the stirred mixture was allowed to warm to room temperature for about 2 h. The color changed from yellow-brown to orange, and IR monitoring showed the formation of **3a**. IR (THF): $\tilde{\nu}(\text{CO}) = 2000$ (s), 1961 (vs), 1899 (s), 1876 (m), 1864 (m), 1829 cm^{–1} (w); ³¹P{¹H} NMR (CD₂Cl₂): $\delta = 47.8$ ppm; ¹H NMR (CD₂Cl₂): $\delta = 3.05$ (m, 3H; CH of *i*Pr, CH₂ of cod), 1.87 to 1.15 [m, 18H; CH₃ of *i*Pr].

4a: PEt₃ (40.7 μ L, 0.3 mmol) was added to a solution of **3a** (0.3 mmol) in THF (prepared as described above), and the mixture was stirred at 40 °C for 1 h. The solvent was evaporated in vacuo, and the solid residue was dissolved in CH₂Cl₂/hexane (1:1) and filtered through alumina (activation degree III). Slow concentration of the filtrate gave **4a** (0.18 g, 82%) as orange microcrystals with the correct C,H analysis. IR (THF): $\tilde{\nu}(\text{CO}) = 2002$ (s), 1964 (s), 1899 (s), 1893 (sh), 1882 (m), 1651 cm^{–1} (w); ³¹P{¹H} NMR (CD₂Cl₂): $\delta = 48.4$ (s; SCPtPr₃), –0.3 ppm (s, PEt₃); ¹H NMR (CD₂Cl₂): $\delta = 2.9$ (m, 3H; CH of *i*Pr), 1.94 (m, 6H; CH₂ of Et), 1.52 (m, 18H; CH₃ of *i*Pr), 1.05 ppm (m, 9H; CH₃ of Et).

5a: [Pt(cod)Cl₂] (0.118 g, 0.3 mmol) was added to a cooled (–78 °C) solution of dianion **2a** (0.3 mmol)^[7] in THF, and the stirred mixture was allowed to warm to room temperature while stirring for about 2 h. Workup as described for **4a** gave **5a** as orange microcrystals (0.15 g, 53%) with correct C,H analysis. IR (THF): $\tilde{\nu}(\text{CO}) = 2002$ (s), 1971 (vs), 1902 (s), 1885 (sh), 1864 cm^{–1} (m); ³¹P{¹H} NMR (CD₂Cl₂): $\delta = 58.2$ ppm (s, ³J(P,Pt) = 224.2); ¹H NMR (CD₂Cl₂): $\delta = 5.55$ –5.22 (m, 4H; CH of cod), 2.97–2.14 (m, 11H; CH of *i*Pr, CH₂ of cod), 1.87 to 1.15 ppm (m, 18H; CH₃ of *i*Pr).

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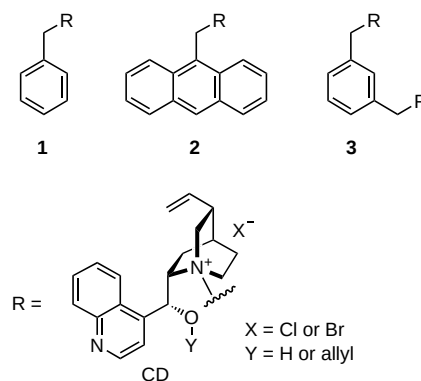
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Highly Enantioselective and Practical Cinchona-Derived Phase-Transfer Catalysts for the Synthesis of α -Amino Acids**

Hyeung-geun Park,* Byeong-Seon Jeong, Mi-Sook Yoo, Jeong-Hee Lee, Mi-kyoung Park, Yeon-Ju Lee, Mi-Jeong Kim, and Sang-sup Jew*

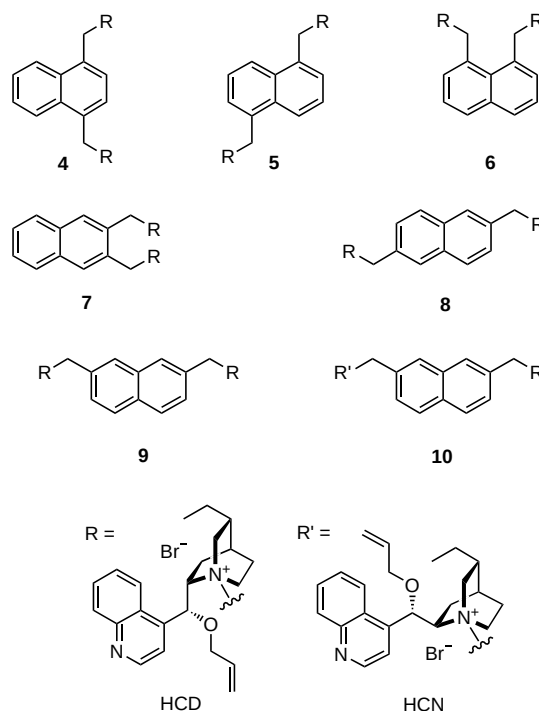
Phase-transfer catalysis (PTC) is one of the most useful methods for practical synthesis, because of its operational simplicity and mild reaction conditions, which enable this method to be applied to industrial processes.^[1] Recently, PTC has been applied extensively to asymmetric synthesis by using chiral quaternary ammonium salts.^[2] Chiral phase-transfer catalysts derived from the cinchona alkaloids have been developed and successfully applied to various useful organic reactions.^[1d,e,3] Since the first cinchona alkaloid-type phase-transfer catalysts **1** were introduced by O'Donnell et al.,^[4] more efficient catalysts **2** have been developed independently by Lygo et al.^[5] and Corey et al.^[6] by the introduction of the *N*-9-anthracenylmethyl group instead of the *N*-benzyl group in **1** (Scheme 1).

Based on the fact that the introduction of a bulky subunit at N1 of cinchona alkaloids leads to an enhancement of the stereoselectivity, we recently reported the efficient catalysts **3** by the formation of the *meta*-dimer, using benzene as a ligand (Scheme 1).^[7] The enhancement of the stereoselectivity is a result of the screening effect between each cinchona unit (CD), which can make the substrate approach from only one direction. As part of our program to develop practical catalysts that can be used in industrial processes, we further investigated more optimal dimeric catalysts by modifying the ligand, that is, the benzene group in **3**. We report herein the



Scheme 1.

preparation of new symmetrical dimeric cinchona-alkaloid-derived catalysts (Scheme 2), which have a naphthalene moiety as a ligand, and their application to the catalytic enantioselective phase-transfer alkylation of glycine derivative **11** (see Tables 1 and 2).



Scheme 2.

New dimeric quaternary ammonium salts **4–10** were prepared in two steps from (–)-hydrocinchonidine (for **4–9**) or (+)-hydrocinchonine (for **10**) and the corresponding bis(bromomethyl)naphthalenes, which can be easily prepared by the allylic bromination of the dimethylnaphthalenes. (–)-Hydrocinchonine or (+)-hydrocinchonine and the bis(bromomethyl)naphthalenes were stirred at 100 °C in EtOH/DMF/ CHCl_3 (5:6:2) for 6 h, followed by O9-allylation with allyl bromide and aqueous KOH (50%), to give the corresponding dimeric quaternary ammonium salts **4–10** in 90–95% overall yields. The enantioselective efficiency of the naphthalene-based dimeric catalysts was evaluated by the enantioselective phase-transfer alkylation of **11**: the catalysts

[*] Prof. H.-g. Park, Prof. S.-s. Jew, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim
College of Pharmacy, Seoul National University
San 56-1, Shinlim-Dong, Gwanak-Gu, Seoul 151-742 (Korea)
Fax: (+82)2-872-9129
E-mail: hgpk@plaza.snu.ac.kr, ssjew@plaza.snu.ac.kr

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

Table 1. Enantioselective phase-transfer-catalyzed benzylation of **11** catalyzed by **4–10**.^[a]

Entry	Catalyst	mol %	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c] (Config.) ^[d]
1	4	5	0	2	92	91 (<i>S</i>)
2	5	5	0	3	90	86 (<i>S</i>)
3	6	5	0	10	82	44 (<i>S</i>)
4	7	5	0	10	88	36 (<i>S</i>)
5	8	5	0	3	90	79 (<i>S</i>)
6	9	5	0	0.5	95	97 (<i>S</i>)
7	9	5	20	0.05	95	92 (<i>S</i>)
8	9	5	−20	6	93	98 (<i>S</i>)
9	9	5	−40	20	90	99 (<i>S</i>)
10	10	5	−40	20	88	96 (<i>R</i>)
11	9	1	0	10	95	97 (<i>S</i>)

[a] The reaction was carried out with benzyl bromide (5.0 equiv) and aqueous KOH (50 %, 13.0 equiv) in toluene/chloroform (7:3) under the given conditions. [b] Yields of isolated products. [c] The enantiopurity was determined by HPLC analysis of the benzylated imine **12g** by using a chiral column (DAICEL Chiralcel OD) with hexanes/2-propanol (500:2.5) as solvent; in this case it was established by analysis of the racemate, of which the enantiomers were fully resolved. [d] The absolute configuration was determined by comparison of the HPLC retention time with that of an authentic sample, which was synthesized independently by reported procedures.^[4–7]

(1–5 mol %) were mixed with ester **11**, benzyl bromide, and aqueous KOH (50 %) in toluene/chloroform (7:3) at −40 to 20 °C for 0.05–20 h.

As shown in Table 1, the 2,7-dimeric catalyst **9** showed the highest enantioselectivity (*S*, 97 % *ee*, 0 °C, 5 mol %) of the six (−)-hydrocinchonidine catalysts (**4–9**), whereas **6** and **7** gave poor selectivities (44 % *ee* and 36 % *ee*, respectively). The low selectivity might arise from the unfavorable conformation as a result of the severe steric repulsion between the two HCD units in **6** and **7**, which is in agreement with our previous study.^[7a] Generally, a lower temperature results in higher enantioselectivities in the case of **9** (Table 1, entries 6–9). Notably, **9** can conserve its high catalytic efficiency in terms of both reactivity and enantioselectivity, even when present in a smaller quantity (1 mol %; Table 1, entry 10). Interestingly, the molecular structure of **9** markedly resembles that of **3**, except for the distance between the two cinchona alkaloid units. The naphthalene ligand of **9** is about 2.4 Å longer than the benzene ligand of **3**. The reason for the high enantioselectivity of **9** is not clear, but it is thought that the 2,7-naphthalene ligand confers a spatial benefit to form a more favorable conformation by decreasing the steric hindrance between the two HCD subunits relative to that in the 1,3-benzene ligand in **3**. The optimal ligand was adapted to prepare the dimeric (+)-hydrocinchonine catalyst **10** for the synthesis of the *R* isomer of **12**. As we expected, **10** also showed very high enantioselectivity (*R*, 96 % *ee*, −40 °C). Table 2 summarizes the results obtained for the alkylation of **11** with various alkyl halides in the presence of catalyst **9** (1 mol %) at 0 °C. The very high enantioselectivities (94–99 % *ee*) indicate that the catalyst **9** is a very efficient and

Table 2. Catalytic enantioselective phase-transfer alkylation of **11** with various alkyl halides in the presence of **9** (1 mol %).^[a]

Entry	RX	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c] (Config.) ^[d]
a	(CH ₃ O) ₂ SO ₂	12	70	94 (<i>S</i>)
b	CH ₃ CH ₂ I	12	83	97 (<i>S</i>)
c	CH ₃ (CH ₂) ₄ CH ₂ I	12	80	> 99 (<i>S</i>)
d		6	95	97 (<i>S</i>)
e		10	95	96 (<i>S</i>)
f		6	90	98 (<i>S</i>)
g		10	95	97 (<i>S</i>)
h		10	95	98 (<i>S</i>)
i		8	90	96 (<i>S</i>)
j		10	90	98 (<i>S</i>)
k		4	95	98 (<i>S</i>)
l		12	90	96 (<i>S</i>)
m		2	95	99 (<i>S</i>)

[a] The reaction was carried out with RX (5.0 equiv) and aqueous KOH (50 %, 13.0 equiv) in the presence of **9** (1 mol %) in toluene/chloroform (7:3) at 0 °C. [b] Yields of isolated product. [c] Determined by chiral HPLC (see Supporting Information). [d] The absolute configuration was determined by comparison of the HPLC retention time with that of an authentic sample, which was independently synthesized by the reported procedure.^[4–7]

practical phase-transfer catalyst for the enantioselective synthesis of natural and nonnatural α -amino acids.

In conclusion, we have developed a new class of naphthalene-based dimeric cinchona alkaloids as very efficient and practical phase-transfer catalysts (**4–10**). Among them, the 2,7-naphthalene-based dimeric catalysts **9** and **10** show excellent enantioselectivity in the alkylation of **11** to give (*S*)-**12** and (*R*)-**12**, respectively. The mild reaction conditions and the high catalytic efficiency could make **9** and **10** practical catalysts in the industrial synthetic process for natural and nonnatural chiral α -amino acids. Applications to various other types of phase-transfer catalytic reactions with **9** and **10** are currently being studied.

Experimental Section

For the detailed synthesis of **9** and its precursors, see Supporting Information.

General procedure (alkylation): Benzyl bromide (0.1 mL, 0.85 mmol) was added to a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**11**; 50 mg, 0.17 mmol) and the chiral catalyst **9** (1.7 mg, 0.0017 mmol) in toluene/chloroform (7:3, 0.75 mL). The reaction mixture was then cooled (0°C), aqueous KOH (50%, 0.25 mL) was added, and the reaction mixture was stirred at 0°C until the starting material had been consumed (10 h). The suspension was diluted with diethyl ether (20 mL), washed with water (2 × 5 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc 50:1) afforded the desired product **12g** (62 mg, 95% yield) as a colorless oil. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD, hexane/2-propanol (500:2.5), flow rate 1.0 mL min⁻¹, 23°C, λ 254 nm, retention times: *R* (minor) 12.2 min, *S* (major) 22.5 min, 97% *ee*). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the reported procedure.^[4–7]

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Facile Syntheses of Copper(I) Alkynyl Clusters Stabilized by Hexafluoroacetylacetonate (hfac) Ligands: The Structure of [Cu₂₆(hfac)₁₁(1-pentynyl)₁₅]**

Timothy C. Higgs,* Phillip J. Bailey, Simon Parsons, and Peter A. Tasker*

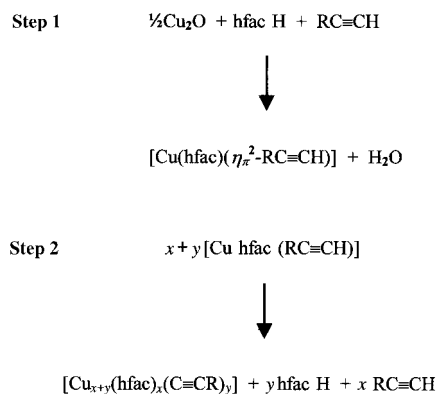
Whilst the copper(I) alkynyl complexes have been widely studied, for their potential as synthetic reagents,^[1] their photophysical (luminescent) properties,^[2–18] and the extraordinary variety of binding modes exhibited by alkynyl ligands,^[14,18–24] only a few homometallic and homovalent Cu^I clusters with low nuclearities of 2,3,4, or 6 have been structurally characterized.^[1,3–15,18–27] One of the problems in preparing and isolating high-nuclearity copper(I) complexes containing terminal alkynyl ligands is the propensity of such systems to aggregate indiscriminately to yield highly insoluble polymers or oligomers. One approach to overcoming this problem is to employ suitable “capping ligands” to protect the periphery of the cluster. If such ligands were available they could, in principle, be used to control the size and shape of clusters by varying the relative concentrations of capping and interstitial (alkynyl) ligands. To date, this synthetic strategy has been employed using predominantly neutral ligands, mostly phosphane-based (for example, PPh₃ and Ph₂PCH₂PPh₂),^[2,3,5–10,12–15,18–22,24] and in a few cases mono-anionic ligands (for example, 2-Me₂NCH₂C₆H₄S[–]).^[1,25]

Herein, we report a very convenient method for the synthesis of homovalent Cu^I clusters of the type [Cu_{x+y}(hfac)_x(RC≡C)_y] (hfac = hexafluoroacetylacetonate) and the structural characterization of the largest Cu^I cluster obtained to date, [Cu₂₆(hfac)₁₁(1-pentynyl)₁₅]. When hfacH is added dropwise to a suspension of Cu₂O and anhydrous MgSO₄ in excess alkyne (RC≡CH, R = *n*-C₃H₇, *n*-C₄H₉, *n*-C₅H₁₁, *n*-C₆H₁₃) an exothermic reaction is observed. After addition of *n*-hexane, filtration and washing, a lime-green solution is obtained which is presumed to contain mononuclear [Cu(hfac)(η²-RC≡CH)] or similar species containing more than one neutral 1-alkyne ligand (Scheme 1).

Evaporation and subsequent heating (65°C) in vacuo gives viscous red or orange oils or, more frequently, crystalline solids containing discrete organometallic complexes of the type [Cu_{x+y}(hfac)_x(RC≡C)_y], with yields in the range 20–50%. In certain cases, partial aerial oxidation of such systems has generated new [Cu_{x+y}(hfac)_x(RC≡C)_y]-type clusters with higher nuclearities. Thus, when 1-pentyne was used as the reagent, [Cu₁₈(hfac)₁₀(pentynyl)₈] (orange solid) was isolated which, in

[*] Dr. T. C. Higgs, Prof. P. A. Tasker, Dr. P. J. Bailey, Dr. S. Parsons
The Department of Chemistry
The King's Buildings, The University of Edinburgh
West Mains Road, Edinburgh, Lothian, Scotland, EH9 3JJ (UK)
Fax: (+44) 131-650-6452
E-mail: pat01@holyrood.ed.ac.uk, pat05@holyrood.ed.ac.uk

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Scheme 1.

turn, was oxidatively converted into $[\text{Cu}_{26}(\text{hfac})_{11}(1\text{-pentynyl})_{15}]$ (red solid), of which crystals of X-ray crystallographic quality were grown from an *n*-hexane solution.^[28]

A discrete cluster molecule $[\text{Cu}_{26}(\text{hfac})_{11}(1\text{-pentynyl})_{15}]$ defines the asymmetric unit. The disc-shaped cluster is neutral, with all 26 ligands present as monoanions; 25 copper atoms are located within four concentric annuli, as shown in Figure 1. The cross-section of the disc (Figure 2) reveals two layers of Cu atoms which are spaced by a linear two-coordinate $\text{Cu}(\eta^1\text{-C}\equiv\text{CR})_2$ unit containing Cu(1) (see also Figure 1). Each of the $(\eta^1\text{-C}\equiv\text{CR})$ alkynyl ligands of this central unit coordinates in a $\mu_3\text{-(}\eta^1\text{)}_3$ fashion through long bonds (2.181(5)–2.366(4) Å) to three of the Cu atoms in the second ring. The triangles defined by these Cu atoms in the upper and lower layers, Cu(2), Cu(4), Cu(6) and Cu(3), Cu(5), Cu(7), respectively, are nearly eclipsed when viewed along the $\text{RC}\equiv\text{C-Cu(1)-C}\equiv\text{C}$ axis (Figure 1), thus forming a distorted trigonal prismatic arrangement.

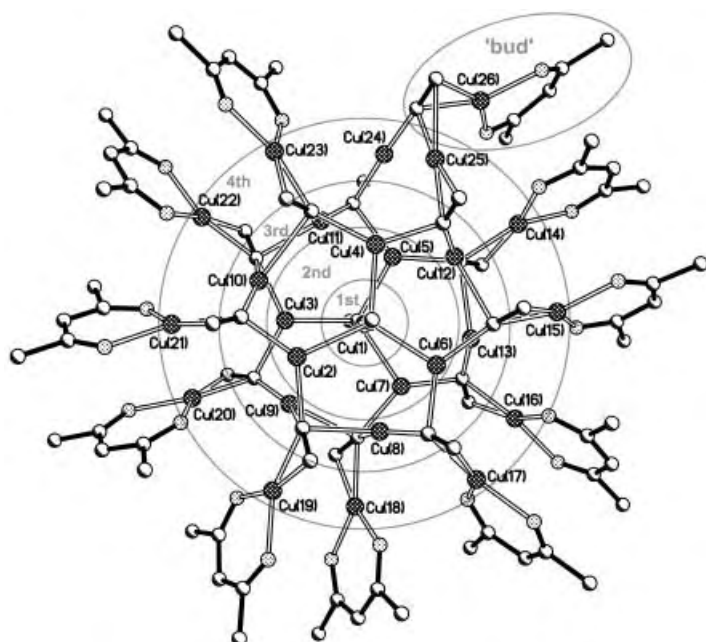


Figure 1. Representation of the disc-shaped cluster $[\text{Cu}_{26}(\text{hfac})_{11}(1\text{-pentynyl})_{15}]$ showing the radial distribution of the Cu atoms in four concentric annuli and in a "bud" on the rim of the disc. Possible Cu...Cu interactions, H and F atoms, and the C_3H_7 groups of the 1-pentynyl ligands are omitted for clarity.

The six Cu atoms in the second annulus in Figure 1 all have trigonal planar geometry. In addition to the η^1_π bond to the central $\text{Cu}(\text{RC}\equiv\text{C})_2$ unit, each of these atoms is linked to alkynyl ligands in the third annulus of the cluster through η^1_σ and η^1_π bonds. The third annulus also contains six Cu atoms, Cu(8–13). These are linked to the inner alkynyl ligands predominately through η^1_σ bonds.

The fourth annulus contains 12 Cu atoms linked through η^2_π bonds to inner pentynyl ligands. Ten of these Cu atoms are capped by hfac ligands which radiate outwards to define the edge of the disc (see Figure 2). The two other Cu atoms, Cu(24) and Cu(25), are linked to Cu(26). The latter center has

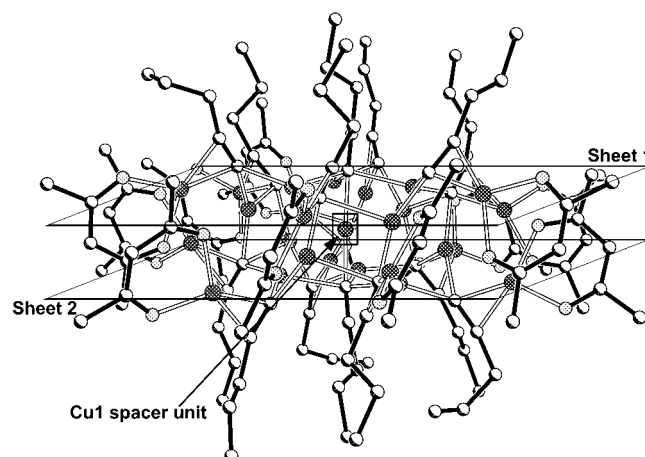


Figure 2. Lateral view of the $[\text{Cu}_{26}(\text{hfac})_{11}(1\text{-pentynyl})_{15}]$ molecule. For the purposes of clarity all possible Cu...Cu interactions, H, and F atoms are omitted, and the disorder within one of the C_3H_7 groups is simplified.

a unique environment, in which it forms a "bud" on the exterior of the cluster that breaks down the otherwise symmetrical radial distribution of Cu–hfac units on the rim of the disc.

The distribution of the pentynyl and hfac ligands is strikingly anisotropic. All of the pentynyl groups are involved in bridging between Cu atoms in the various annuli or the bud, and are thus distributed across the faces of the disc, with their associated propyl groups lying approximately parallel to the axis perpendicular to the plane of the disc. In contrast, the "terminal" anionic hfac ligands are associated exclusively with the rim of the disc (see above).

The linear $\text{Cu}(\eta^1\text{-C}\equiv\text{CR})_2$ arrangement at the central Cu(1) atom is also observed for Cu(24), which provides a link to the bud. These are the first crystallographically characterized examples of this mode of complexation. Another unusual copper coordination environment is displayed by Cu(25), which forms two linearly disposed η^2_π bonds to alkynyl ligands. Such an arrangement has also been observed in the mixed Cu^I/Pt^{II} cluster, $[\text{Pt}_2\text{Cu}_4(\text{C}\equiv\text{CPh})_8]_2$ ^[29] and the mixed-metal Cu^I/Re^I alkynyl complex, $[[\eta^2\text{-Re}(\text{CO})_3(\text{bpy})(\text{C}\equiv\text{CPh})]_2\text{-Cu}][\text{PF}_6]_2$.^[30] The prevalence of low coordination numbers for these copper ions raises the question of the nature and strength of $\text{Cu}^I\cdots\text{Cu}^I$ ($d^{10}\text{--}d^{10}$) closed-shell interactions in the cluster.^[31–34] Numerous pairs of Cu atoms are in proximity; 28 Cu...Cu contacts are shorter than the sum of the van der

Waals radii for two Cu^I atoms (2.8 Å).^[35] The 12 closest contacts (2.520(1)–2.601(1) Å) exist between Cu atoms in the second annulus approaching two Cu atoms in the third annulus.^[36] Weak Cu^I...Cu^I interactions have been used to rationalize the excited states of several luminescent Cu^I–alkynyl complexes.^[3,31] Recent theoretical studies^[33] have indicated that Cu^I(d¹⁰–d¹⁰) attractive interactions can have energies of up to 4 kcalmol^{–1}, which is comparable to the strength of hydrogen bonds. Therefore, these closed shell interactions in the [Cu₂₆(hfac)₁₁(1-pentynyl)₁₅] cluster make only a minor contribution to defining its primary structure.^[37] The hfac-capped Cu atoms all have near-planar O₂C₂ donor-sets with hfac chelate ring dimensions similar to those in other Cu^I complexes.^[38,39]

The simplicity of the preparation of these clusters and the range of nuclearities obtained is remarkable. Work is in hand to establish the nature of the intermediate arising from the reaction of Cu₂O and hfacH in excess 1-alkyne. Control experiments indicate that Cu₂O does not react directly with aliphatic 1-alkynes in the presence of MgSO₄, probably as a result of their low acidity (1-hexyne, pK_a = 25),^[40] whereas more acidic 1-alkynes such as 1-phenylethyne (pK_a = 18.5)^[41] react quickly to form bright-yellow voluminous solids, which are presumed to contain [(Cu(μ_x-η_{σ/π}^y-C≡CPh))_n].

If, as postulated in Scheme 1, the intermediate contains only neutral 1-alkynes, it can be envisaged that cluster formation involves deprotonation of 1-alkyne ligands to form Cu-bridged units, with the protons transferring to hfac moieties, which are then readily removed from the system in vacuo as the volatile hfacH (b.p. 70–71 °C). This reaction has similarities to those reported by Vicente and Chicote^[42] where protic acids were treated with metal complexes containing acetylacetonate (acac) ligands (M(acac) + BH → MB + (acac)H). The cluster size increases as the ratio of alkynyl to hfac in the complex increases. Oxidation provides another mechanism for increasing the alkynyl to hfac ratio by the loss of {Cu(hfac)₂} units from the periphery of the cluster. Under these circumstances the nature of the cluster isolated will depend on a subtle balance of the relative volatilities and pK_a values of the 1-alkyne and hfacH.

Experimental Section

All chemicals were purchased from Aldrich. *n*-Hexane was distilled over sodium/benzophenone/tetraglyme (trace) under nitrogen. All reactions and manipulations were carried out under nitrogen (dried 4-Å molecular sieves, deoxygenated with BTS-catalyst) by using standard Schlenk-line techniques. 1-Pentyne and hfacH were degassed by three freeze–vacuum–thaw cycles.

[Cu₁₈(hfac)₁₀(1-pentynyl)₈]: Cu₂O (2.53 g, 17.66 mmol) and anhydrous MgSO₄ (2.0 g, 16.6 mmol) were added to 1-pentyne (7.0 mL), to yield a red suspension into which hfacH (2.50 mL, 17.66 mmol) was then added dropwise. The reaction mixture, which refluxed under the heat of reaction during addition of hfacH, was then stirred at room temperature for 66 h. *n*-Hexane (10 mL) was then added to mobilize the reaction mixture, a viscous orange suspension, before it was cannula-filtered and the residual solid washed three times with *n*-hexane (10 mL aliquots). The combined filtrate and washings, which were pale-green in color, were evaporated to dryness in vacuo yielding an orange-brown oil. This was then dried at 65 °C (water bath) in vacuo for a further 30 min. During this time the oil thickened, turned opaque, and ultimately solidified. This solid was suspended in *n*-

hexane (20 mL), a process that required ultrasonic agitation, to give a green solution containing a microcrystalline orange solid. The solution was removed by cannula filtration leaving behind a bright-orange solid, which was washed twice with *n*-hexane (5 mL aliquots) and dried in vacuo. Yield 2.87 g (43.3 %). IR (KBr disk): $\tilde{\nu}$ = 3499, 2964, 1672, 1642, 1554, 1528, 1513, 1463, 1255, 1209, 1146, 1100, 795, 743, 662, 580, 526 cm^{–1}; elemental analysis calcd for C₉₀H₆₀Cu₁₈F₆₀O₂₀: C 28.82, H 1.77; found: C 28.93, H 1.83%.

[Cu₂₆(hfac)₁₁(1-pentynyl)₁₅]: Crystals of [Cu₁₈(hfac)₁₀(1-pentynyl)₈] were obtained by dissolving the orange solid, described above (2.50 g, 0.667 mmol), in the minimum volume of refluxing Et₂O. The resultant orange solution was allowed to cool to room temperature and was exposed to the air for several minutes (max. 5 min). The solution was then placed back under a nitrogen atmosphere and then cooled to 4 °C for several days, during which time a mixture of deep-red and green block crystals deposited from the solution. The mother liquor was removed with a cannula and the crystals washed with *n*-hexane (3 mL) and dried in vacuo. The crystals were then recrystallized twice from a minimum volume of refluxing *n*-hexane to yield solely deep-red block crystals, which were collected, washed with *n*-hexane, and dried in vacuo. Yield 0.26 g (15.8 %). IR (KBr disk): $\tilde{\nu}$ = 2966, 2927, 2879, 1892, 1641, 1555, 1529, 1468, 1343, 1257, 1207, 1147, 1099, 796, 743, 671, 587, 528 cm^{–1}; elemental analysis calcd for C₁₃₀H₁₁₆Cu₂₆F₆₆O₂₂: C 31.62, H 2.35; found: C 31.50, H 2.27%.

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- [28] a) Crystal structure analysis for $[\text{Cu}_{26}(\text{hfac})_{11}(1\text{-pentynyl})_{15}]$: Crystals were grown by slow cooling of a supersaturated solution of the complex in hot *n*-hexane and were analyzed with a Bruker smart APEX CCD area detector equipped with an Oxford Cryosystems LT device operating at 150 K. $\text{C}_{133}\text{H}_{115}\text{Cu}_{26}\text{F}_{66}\text{O}_{22}$, $\lambda = 0.71073 \text{ \AA}$, crystal size = $0.44 \times 0.38 \times 0.29 \text{ mm}$, cell determination: range $4^\circ < 2\theta < 58^\circ$, no. reflections: 4764, monoclinic, space group *Cc* (checked with MISSYM^[28b-d]), $Z = 4$, $a = 26.009(3)$, $b = 21.114(2)$, $c = 31.078(4) \text{ \AA}$, $\beta = 94.214(2)^\circ$, $V = 17021(3) \text{ \AA}^3$, $\rho_{\text{calcd}} = 1.943 \text{ g cm}^{-3}$, $\mu = 3.300 \text{ mm}^{-1}$. 75941 reflections were collected in the range $1.31^\circ < \theta < 28.94^\circ$, of which 38578 were unique and 33027 had $F_o > 4\sigma(F_o)$. A multiscan absorption correction was applied using Sadabs^[28e] ($T_{\text{max}} = 0.862$; $T_{\text{min}} = 0.679$). The structure was solved by direct methods (SHELXS-97),^[28f] and refined by block-matrix least-squares against F^2 (SHELXL97),^[28f] All non-hydrogen atoms were modeled with anisotropic displacement parameters, except for one half-occupancy hexane solvate molecule, and H atoms were included in ideal positions. Numerous CF_3 groups were disordered, a combination of similarity and ADP equalization restraints were used to model this. The conventional R_1 factor ($F_o > 4\sigma(F_o)$) was 0.0409 and wR_2 was 0.0913. ($w = 1/[\sigma^2(F_o^2) + (0.0490 P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$). Largest max/min residual electron density: $+1.094/-0.917 \text{ e \AA}^{-3}$; b) Y. LePage, *J. Appl. Crystallogr.* **1999**, 20, 264; c) A. L. Spek, *J. Appl. Cryst.* **1987**, 21, 578; d) L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, 32, 837; e) G. M. Sheldrick, SADABS, Program for Empirical Correction of Area Detector Data, University of Göttingen, Göttingen (Germany), **1998**; f) G. M. Sheldrick, SHELXL97, Program for the refinement of crystal structures, University of Göttingen, Göttingen (Germany), **1997**. CCDC-186669 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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Synthesis and Evaluation of Transition-State Analogue Inhibitors of α -1,3-Fucosyltransferase**

Michael L. Mitchell, Feng Tian, Lac V. Lee, and Chi-Huey Wong*

Glycosidases and glycosyltransferases involved in the biosynthesis of glycoconjugates associated with intercellular recognition, metastasis, and immune response represent viable therapeutic targets.^[1-7] Of particular interest are the fucosyltransferases (FucTs), which play a key role in the biosynthesis of many important fucose-containing oligosaccharides such as sialyl Lewis x (sLe^x), a determinant in numerous cell-cell interactions, for example, in inflammation^[8,9] and tumor metastasis.^[10,11] The terminal step in the biosynthetic pathway of these fucose-containing saccharides is the transfer of L-fucose from guanosine diphosphate β -L-fucose (GDP-Fuc) to the corresponding glycoconjugate acceptors,^[12,13] which is catalyzed by α -1,3-fucosyltransferase (α -1,3-FucT).^[14,15] Since inhibitors of fucosyltransferase may disrupt the biosynthesis of these saccharides, they have potential medicinal applications as anti-inflammatory or antitumor agents.

In the proposed transition state of α -1,3-FucT V₁^[16] the pyrophosphate chelates a divalent manganese and the fucose ring adopts a flattened half-chair conformation with substantial oxocarbenium ion character (Scheme 1). Recognition of these salient features of the transition state guided our design of potential inhibitors **1–3** for fucosyltransferase.

In the present study, analogues of fucose, which incorporate the geometry or charge of the fucose moiety in the transition state, were linked to GDP, thereby retaining the contribution of GDP to binding. The cyclohexene ring of **1** was designed to mimic the flattened half-chair conformation of the fucose moiety. In addition, the carbocyclic ring is chemically more stable than its pyranose counterpart and may be more stable in vivo.

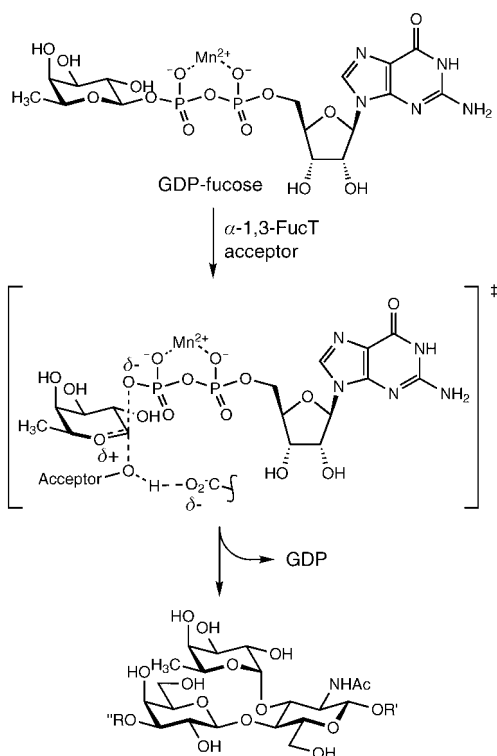
Triazoles also resemble the flattened conformation of the fucose moiety in the transition state.^[17] Previous work based on fucose-derived triazoles lacking the negative charge normally present in the GDP-fucose substrate only weakly inhibited fucosyltransferase.^[18] Therefore, a triazole was attached to GDP providing **2**, which allowed us to exploit the electrostatic interactions of the pyrophosphate and residues in the active site.

[*] Prof. C.-H. Wong, Dr. M. L. Mitchell, Dr. F. Tian, Dr. L. V. Lee
Department of Chemistry and the Skaggs Institute
for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2409
E-mail: wong@scripps.edu

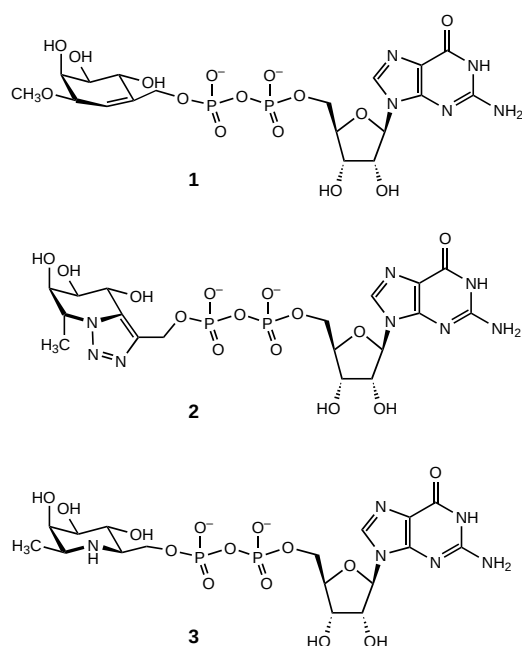
[**] This work was supported by the NIH and the Skaggs Institute. M.L.M. acknowledges fellowships from UNCF-Merck Science Initiative and Skaggs Predoctoral Fellows Program.



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



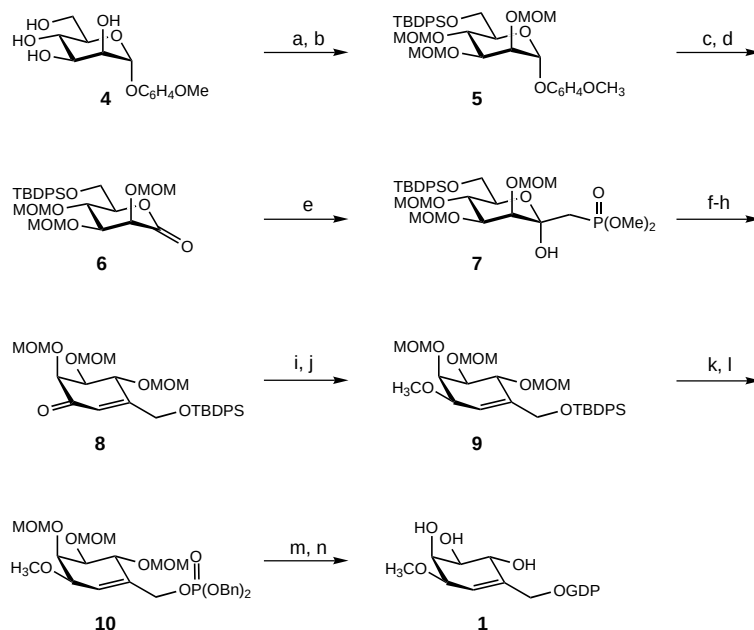
Scheme 1. Proposed transition state of α -1,3-FucT V.^[16]



While the cyclohexene and triazole motifs mimic the conformation of the fucose moiety in the transition state, iminocyclitols mimic the partial positive charge developed in the transition state. Iminocyclitols are good inhibitors of glycosidases,^[19,20] but are only modest inhibitors of glycosyltransferases.^[21,22] Covalently linking the negatively charged GDP to the six-membered iminocyclitol may provide a more potent inhibitor (**3**). Reported here is the synthesis and evaluation of

compounds **1–3**, which are designed to mimic the transition state of the GDP–fucose moiety of fucosyltransferase-catalyzed reactions.

Since three contiguous secondary alcohols of D-mannose and L-fucose share the same configuration, D-mannose was chosen as the starting material for the construction of **1**. Synthesis began with differential protection of the hydroxy groups of α -4-methoxyphenyl D-mannopyranoside (**4**)^[23] (Scheme 2). The C6 primary alcohol was protected as a *tert*-butyldiphenylsilyl (TBDPS) ether and the remaining secondary alcohols were masked as methoxymethyl (MOM) ethers to give mannopyranoside **5**. Treatment with ceric ammonium nitrate (CAN)^[24,25] revealed the anomeric hydroxy group, and subsequent Albright–Goldman oxidation^[26] afforded lactone **6**. Nucleophilic addition of lithium dimethyl methylphosphonate to the carbonyl group of **6** then provided tertiary alcohol **7**. Reductive ring opening with sodium borohydride to generate a diol, subsequent Swern oxidation,^[27] and intramolecular Horner–Emmons olefination^[28] yielded the enone **8**. Stereoselective 1,2-reduction of **8** by Luche reduction^[29] gave exclusively the pseudo-equatorial alcohol that was converted to a methyl ether with sodium hydride and iodomethane to furnish **9**. The *tert*-butyldimethylsilyl ether was removed with tetrabutylammonium fluoride (TBAF) to give the corresponding alcohol that was phosphorylated by using dibenzyl diisopropylphosphoramidite and subsequently oxidized with 3-chloroperoxybenzoic acid (*m*CPBA) to give **10**.^[30] Global deprotection with trifluoroacetic acid and thiophenol^[31] gave the intermediate phosphate, which was coupled to GMP using GMP-morpholidate and 1*H*-tetra-



Scheme 2. Reagents and conditions: a) TBDPSCl, DMAP, pyridine, 86 %; b) MOMCl, DIPEA, DMAP, CH₂Cl₂, 88 %; c) CAN, CH₃CN/H₂O; d) DMSO, Ac₂O, 77 %; e) CH₃P(O)(OCH₃)₂, *n*BuLi, THF, 82 %; f) NaBH₄, THF; g) DMSO, TFAA, CH₂Cl₂, –78 °C; h) NaH, diglyme, 65 °C, 70 % for three steps; i) NaBH₄, CeCl₃, MeOH, 95 %; j) NaH, MeI, THF, 100 %; k) TBAF, THF, 92 %; l) (*i*Pr)₂N–P(OBn)₂, 1*H*-tetrazole, CH₂Cl₂; *m*CPBA, 77 %; m) 95 % aq. TFA, thiophenol, 86 %; n) GMP-morpholidate, 1*H*-tetrazole, pyridine, 25 %. DMAP = 4-dimethylamino-pyridine, DIPEA = diisopropylethylamine, TFAA = trifluoroacetic anhydride.

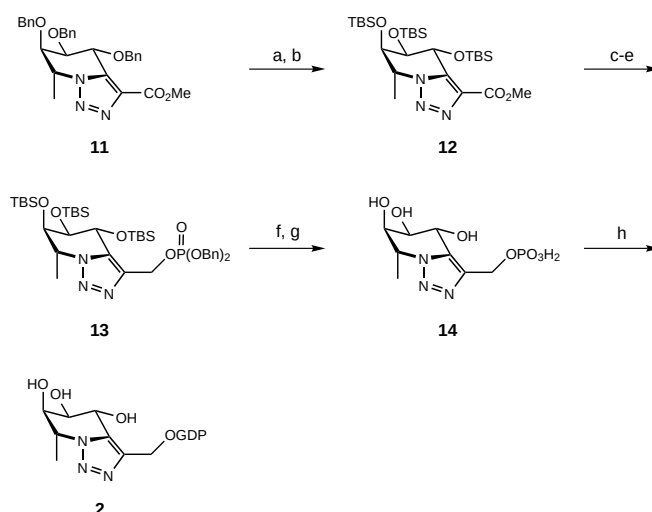
zole^[32] to provide target **1**. These named reactions were also used by Marquez and Lim^[33a] and Vasella and co-workers^[33b] for the synthesis of other carbocycles.

Beginning from the known triazole **11**,^[18] catalytic hydrogenolysis generated the hydroxy groups, which were then protected as *tert*-butyldimethylsilyl ethers to give **12** (Scheme 3). Reduction of the carboxylic ester with lithium aluminum hydride (LAH), followed by phosphorylation of the resulting hydroxy group with dibenzyl diisopropylphosphoramidite and subsequent oxidation with *m*CPBA furnished intermediate **13**.^[30] Treatment with TBAF, followed by catalytic hydrogenolysis gave phosphate **14**, which underwent 1*H*-tetrazole-catalyzed coupling with GMP-morpholidate to give target **2**.

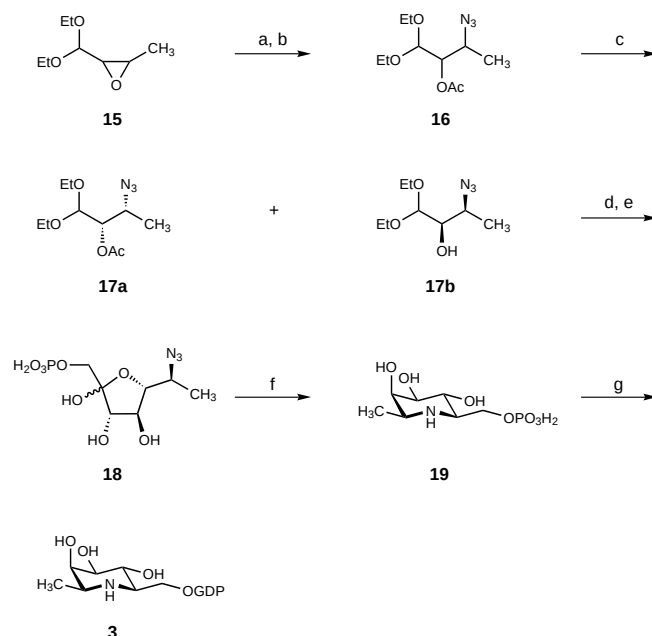
Scheme 4 illustrates the chemoenzymatic synthesis of **3**. Regiospecific epoxide opening of **15**^[34] with sodium azide, followed by acetylation provided acetate **16**. Resolution of the diastereomers was accomplished with *Pseudomonas* lipase (PSL)^[35] to give products **17a** and **17b**, which were separable by chromatography. Treatment of **17b** with 0.1*N* HCl unmasked the aldehyde, which underwent an FDP aldolase-catalyzed aldol reaction^[34] with dihydroxyacetone phosphate (DHAP)^[36] to give phosphate **18**. The azido-sugar **18** was then hydrogenated in the presence of platinum oxide under a hydrogen atmosphere to give the iminocyclitol phosphate **19**. Whereas reductive amination using palladium catalysts reductively cleaved the phosphate group as a side reaction, no corresponding side product was observed with platinum oxide. Coupling with GMP-morpholidate and 1*H*-tetrazole^[32] then provided the desired iminocyclitol **3**.

The transition-state analogues were evaluated by using a fluorescence-based assay that couples the production of GDP to the consumption of NADH with pyruvate kinase (Sigma) and lactate dehydrogenase (Sigma).^[16] Compounds **1–3** exhibited good competitive inhibition of both FucT V and VI, with *K_i* values between 6 and 13 μ M (Table 1), although no general trend of inhibition was clearly discernable. Also included in Table 1 are published inhibition data for FucT inhibitors known in the literature. The fluorinated GDP-fucose analogues (e.g. **20**) are the most potent inhibitors of FucTs known to date.^[37] GDP-fucose analogue **23** is a good competitive inhibitor,^[38] but inhibition activity for C-fucopyranosyl analogue **22**^[39] could not be found. Transition-state analogues such as the five-membered GDP-iminocyclitol **21**^[40] show competitive inhibition against FucT V, whereas the cyclohexene **24** has an affinity constant similar to that of GDP-fucose (8–34 μ M).^[38] No significant inhibition of **1–3** was observed with other commercially available glycosyltransferases such as sialyltransferases.

In summary, aspects of the transition state of GDP-fucose in fucosyltransferase-catalyzed reactions were investigated through the use of transition-state analogues. The importance of charge and conformation appear to be roughly equivalent as evident by the similar inhibition constants of transition-state analogues **1–3**. The procedures described for the synthesis of **1–3** are relatively straightforward and efficient. Of particular interest in the reductive amination of the aldolase product azido-sugar phosphate **18** provides iminocyclitol phosphate **19** for subsequent coupling to give iminocyclitol



Scheme 3. Reagents and conditions: a) H_2 , Pd/C, MeOH/AcOH, 85%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 93%; c) LAH, THF, 97%; d) $(iPr)_2N-P(OBn)_2$, 1*H*-tetrazole, CH_2Cl_2 ; e) *m*CPBA, CH_2Cl_2 , 94% for two steps; f) TBAF, THF; g) H_2 , Pd/C, EtOH, 88% for two steps; h) GMP-morpholidate, 1*H*-tetrazole, pyridine, 39%.



Scheme 4. Reagents and conditions: a) NaN_3 , NH_4Cl , EtOH/ H_2O , reflux, 44%; b) Ac_2O , pyridine, 95%; c) PSL 800, pH 7.0 phosphate buffer, 51% conversion; d) 0.1*N* HCl, 50 °C; e) DHAP, FDP-aldolase, pH 6.7, 70% for two steps; f) H_2 , PtO_2 , MeOH/ H_2O , 60%; g) GMP-morpholidate, 1*H*-tetrazole, pyridine, 40%.

Table 1. The inhibition constants were determined for FucT V and VI at 2 Km LacNAc (70 and 10 mM, respectively), pH 7.4, and 10 mM $MnCl_2$. FucT V and VI were from CalBiochem. NA = data not available.

	FucT V [μ M]	FucT VI [μ M]	Ref.	FucT V [μ M]	FucT VI [μ M]	Ref.
1	8	6	–	21	45	NA [40]
2	8	13	–	22	NA	NA [39]
3	13	11	–	23	< GDP ^[a]	[38]
20	4	10	[37a]	24	~ GDP-Fuc ^[b]	[38]

[a] Inhibitory activity described as better than that of GDP (*K_i* for GDP = 29 mM). [b] Inhibitory activity described as comparable to that of GDP-fucose (*K_m* for GDP-Fuc = 8–34 mM).

nucleotide **3**. This new chemoenzymatic strategy should find use in the synthesis of other iminocyclitol nucleotides. We believe that compounds **1–3** should be useful as general inhibitors of fucosyltransferases.

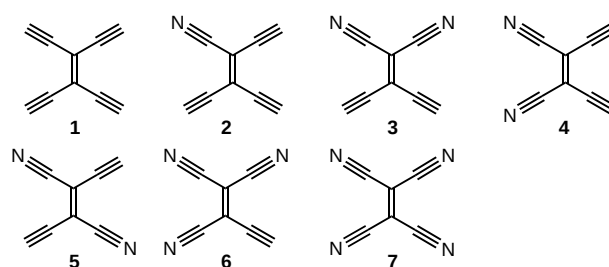
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Cyanoethynylethenes: A Class of Powerful Electron Acceptors for Molecular Scaffolding**

Nicolle N. P. Moonen, Corinne Boudon, Jean-Paul Gisselbrecht, Paul Seiler, Maurice Gross, and François Diederich*

Tetraethynylethene (**1**, TEE, Scheme 1) was introduced in 1991 as a useful building block for the synthesis of one- and two-dimensional π -conjugated scaffolds, such as poly(triacetylene) oligomers, expanded radialenes, and dehydroannulenes.^[1] Incorporation of donor and acceptor substituents resulted in interesting electronic^[1e,2] and nonlinear optical properties.^[1e,3] Furthermore, the strain-free planarity allows reversible, photochemical *cis-trans* isomerization of *cis*- and *trans*-arylated TEEs without competition from undesirable thermal isomerization.^[4]



Scheme 1. Progression from tetraethynylethene (TEE, **1**) to tetracyanoethene (TCNE, **7**).

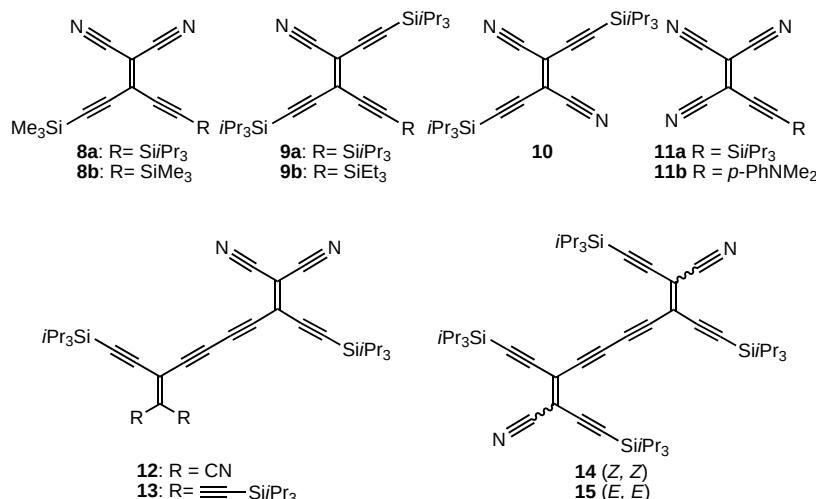
Cyanoethynylethenes (**2–6**, CEEs) are an interesting class of hybrid derivatives combining the scaffolding power of TEE with the electronic properties of tetracyanoethene (**7**, TCNE), which is one of the strongest organic electron acceptors known, and has been widely used in the formation of charge-transfer complexes.^[5] So far, only derivatives of **3**, with SiMe₃ (**8b**, Scheme 2) or phenyl substituents,^[6] and arylated derivatives of **6**^[7] have been reported. Hopf and Kreutzer demonstrated that there was an enhanced reactivity of the triple bonds in derivatives of **3** and **6** towards Diels–Alder reactions^[6] and in the [2+2] cycloaddition to tetrathiafulvalene, with subsequent ring opening.^[8] A similar reaction was also observed by Hirsch and co-workers at the terminal acetylene moiety of α,ω -dicyanopolynes.^[9]

We have now extended the family of CEEs and report herein the synthesis of **9–11a** (Scheme 2), silylated derivatives

[*] Prof. Dr. F. Diederich, N. N. P. Moonen, P. Seiler
Laboratorium für Organische Chemie
ETH-Hönggerberg, HCI, 8093 Zürich (Switzerland)
Fax: (+41)1-632-1109
E-mail: diederich@org.chem.ethz.ch

Dr. C. Boudon, Dr. J.-P. Gisselbrecht, Prof. Dr. M. Gross
Laboratoire d'Electrochimie et de Chimie Physique du Corps Solide
UMR 7512, C.N.R.S.
Université Louis Pasteur
4, rue Blaise Pascal, 67000 Strasbourg (France)

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Scheme 2. New cyanoethynylethenes (CEEs) and extended cyanoethynylethenes for molecular scaffolding.

of the missing parent members **2**, **5**, and **6**. In addition, the first extended CEEs **12–15** are reported and the electron-accepting properties of both classes of chromophores are investigated by cyclic voltammetry (CV). Furthermore, a donor-acceptor-substituted CEE (**11b**) with promising advanced materials properties will be described.

In the series of CEEs (Scheme 3), the geminal dinitrile **8a** was obtained from ketone **16a** by a Knoevenagel reaction according to the procedure used by Hopf and Kreutzer to prepare **8b**.^{[6][10]} Monocyanoethynylethene **9a** (Scheme 2)

was also obtained in 97% yield by a Knoevenagel reaction of ketone **16c** ($R = \text{SiPr}_3$) with $i\text{Pr}_3\text{SiC}\equiv\text{C}-\text{CH}_2-\text{CN}$ and $i\text{Pr}_2\text{EtN}$. Remarkably, while this conversion required stirring for 8 h at 50 °C, the corresponding reaction of the sterically less-encumbered **16b** ($R = \text{SiEt}_3$) to give **9b** (47%) was completed within 1 min at 20 °C.^[11]

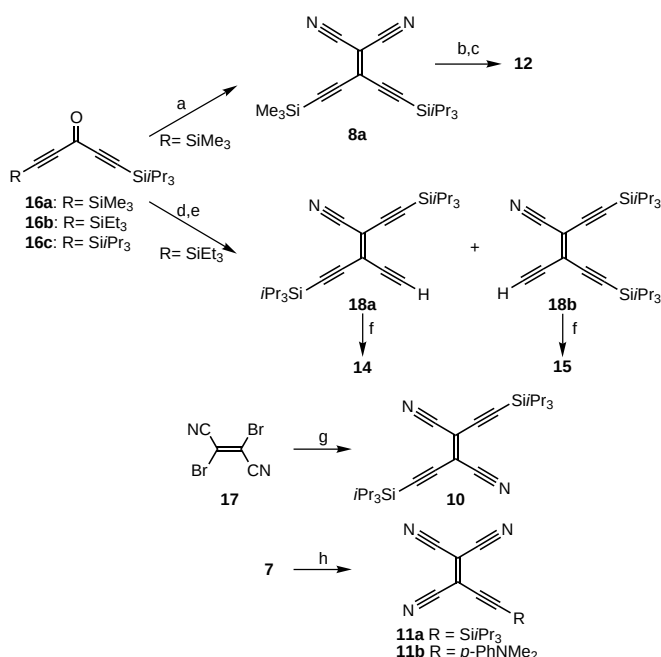
Sonogashira cross-coupling^[12] of dibromide **17** with $i\text{Pr}_3\text{SiC}\equiv\text{CH}$ gave *trans*-dicyanoethynylethene **10** in 30% yield. Replacing $i\text{Pr}_2\text{NH}$ with $i\text{Pr}_2\text{EtN}$ as the base in this reaction resulted in a lower yield (19%) whereas the use of Et_3N only gave undefined side products. Tricyanoethynylethenes **11a** and **b** were prepared according to the method of Dulog et al.^[7b] by nucleophilic substitution of TCNE with the corresponding copper(I) acetylide.

In the series of extended CEEs, tetranitrile **12** was obtained starting from **8a** (Scheme 3). An attempt to remove the Me_3Si group of **8a** under standard conditions (K_2CO_3 , MeOH/THF) only led to decomposition. Gratifyingly, mono-deprotection could be accomplished by simply stirring **8a** in the solvent mixture in the absence of K_2CO_3 . Copper(I)-mediated oxidative acetylenic couplings are usually carried out in the presence of nitrogen-containing ligands.^[13] Use of these ligands, however, caused a severe problem in the coupling of mono-deprotected **8a**. Even 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) caused instantaneous decomposition of the starting material. The delicate, highly electrophilic cyanoethynylated chromophores readily undergo nucleophilic additions with amines and probably also participate in electron-transfer processes. Finally, it appeared that the activating (pK -lowering) effect of the two cyano groups was large enough to enable oxidative coupling in the absence of any ligand, thus affording **12**.

For the preparation of **14** and **15**, **9b** was mono-deprotected to give *Z*-configured **18a** and the less stable *E* isomer **18b**. Oxidative Hay coupling of **18a** and **18b** subsequently led to the extended CEEs **14** (*Z,Z*-configured) and **15** (*E,E*-configured), respectively. Unambiguous proof for the configurational assignments of **14** and **15** (and of **18a** and **b**) was obtained from the X-ray crystal structure of **14** (Figure 1),^[14] which clearly showed the *Z* configuration of both CEE moieties. The structure reveals planarity in the carbon-nitrogen core, with the largest out-of-plane deviation being approximately 0.05 Å.

All CEE derivatives are air-stable, but their sensitivity towards nucleophiles increases with their acceptor potential. Thus, the strong acceptors **11a** and **12** decompose rapidly in the presence of any nucleophile. CEE derivatives **8–11a** are nearly colorless oils, whereas the extended systems **12–15** are bright-yellow solids or oils.

The electron-accepting properties of the CEE derivatives were investigated by cyclic voltammetry in CH_2Cl_2 (+0.1 M Bu_4NPF_6) as previously described (Table 1).^[2b] All species gave a reversible one-electron reduction as well as a second



Scheme 3. Reagents and conditions: a) $\text{CH}_2(\text{CN})_2$, Al_2O_3 (act. II–III), CH_2Cl_2 , 40 °C, 85%; b) THF/MeOH 1:5, 20 °C; c) $\text{Cu}(\text{OAc})_2$, CH_2Cl_2 , 20 °C, 22% (two steps); d) $i\text{Pr}_3\text{SiC}\equiv\text{CCH}_2\text{CN}$, $i\text{Pr}_2\text{EtN}$, EtOH , 20 °C, 47% (**9b**), 27% (**18a**), 15% (**18b**); e) K_2CO_3 , THF/MeOH 1:1, 20 °C, 46% (**18a**), 29% (**18b**); f) CuCl , TMEDA , CH_2Cl_2 , 20 °C, 91% (**14**), 85% (**15**); g) $[\text{PdCl}_2(\text{PPh}_3)_2]$, $i\text{Pr}_3\text{SiC}\equiv\text{CH}$, $i\text{Pr}_2\text{NH}$, CuI , 20 °C, 30%; h) $i\text{Pr}_3\text{SiC}\equiv\text{CLi}$, CuBr , THF , 50 °C, 33% (**11a**) or $\text{HC}\equiv\text{CPhNMe}_2$, CuOAc , THF , 50 °C, 29% (**11b**). $\text{TMEDA} = N,N,N',N'$ -tetramethylethylenediamine.

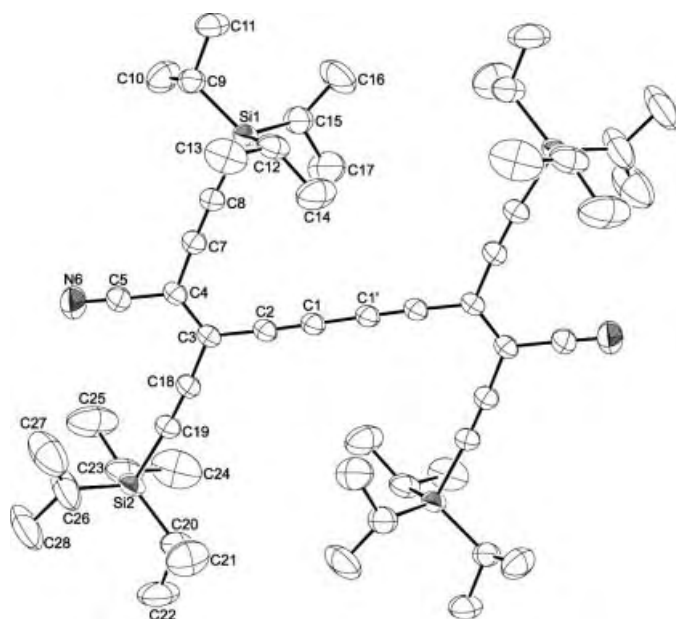


Figure 1. ORTEP representation of **14** with vibrational ellipsoids shown at the 30% probability level. H atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [°]: C5–N6 1.142(4), C4–C5 1.430(5), C3–C4 1.364(4), C2–C3 1.413(4), C1–C2 1.200(4), C1–C1' 1.369(7); N6–C5–C4 178.9(4), C3–C4–C5 119.2(3), C4–C3–C2 119.7(3), C1–C2–C3 177.6(3), C2–C1–C1' 179.5(4).

Table 1. Cyclic voltammetry data in CH₂Cl₂ (+ 0.1 M Bu₄NPF₆).^[a]

19	20	19	20
E^o [V] ^[b]	E_p [V] ^[c]	E^o [V] ^[b]	E_p [V] ^[c]
19 ^[d]	–1.96	20 ^[d]	–1.52
9a	–1.58		–1.89
	–2.34		–2.90
10	–1.25	14	–1.07
	–2.05		–1.37
8a	–1.15	15	–1.06
	–1.95		–1.36
11a	–0.72	13	–0.90
	–1.69		–1.44
7	–0.32	12	–0.57
	–1.35		–0.84
11b	+0.79		–2.24
	–0.86		

[a] Potentials versus the ferrocene/ferrocenium couple. Working electrode: glassy carbon electrode; counter electrode: Pt; reference electrode: Ag/AgCl. [b] $E^o = (E_{pc} + E_{pa})/2$, where E_{pc} and E_{pa} are the cathodic and anodic peak potentials. [c] E_p = Irreversible peak potential at $v = 0.1$ V s^{–1}. [d] Solvent: THF.^[2a]

reduction, which was irreversible for **8–11a** and reversible for **12–15**.

All CEE derivatives are much stronger electron acceptors than the corresponding TEE derivatives such as **19** and **20**. On the basis of the first reduction potentials of the monomeric CEEs **8–11a**, the increase in electron-acceptor strength upon

substituting one RC≡C- group by a N≡C- group is, on average, 380 mV, whereas replacing one NC–C–CN group with RC≡C–C–C≡CR increases the average electron-acceptor strength by 830 mV.^[15] A linear correlation ($R = 0.994$) was obtained between the calculated electron affinities (B3LYP, 3-21G)^[16] and the first reduction potentials for CEEs **8–11a**, TCNE (**7**), and TEE (**19**). The extended CEE **12** is an exceptionally good electron acceptor, which approaches the strength of TCNE (**7**). A clear increase in acceptor strength with extension of π -electron conjugation was observed (**8a** versus **13**), however the effects of adding a cyanide group and extension of conjugation could not yet be quantified.

The deep-blue solid CEE **11b**, which has an *N,N*-dimethylanilino substituent, is a donor-acceptor derivative with potentially interesting nonlinear optical properties. The UV/Vis spectrum exhibits an intense intramolecular charge-transfer band at 591 nm (λ_{max} , $\epsilon = 43\,800$ M^{–1} cm^{–1}, Figure 2), a bathochromic shift of 60 nm (0.24 eV) relative to the corresponding band in 4-(tricyanovinyl)-*N,N*-dimethylaniline ($\lambda_{max} = 530$ nm, $\epsilon = \text{ca. } 40\,000$ M^{–1} cm^{–1}).^[17] Most importantly,

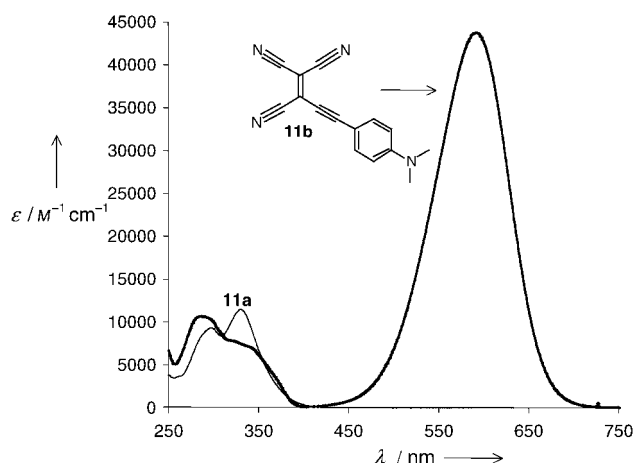


Figure 2. UV/Vis spectrum (CHCl₃) of **11b** with $\lambda_{max} = 591$ nm ($\epsilon = 43\,800$ M^{–1} cm^{–1}) and **11a** ($\lambda_{max} = 330$ nm, $\epsilon = 11\,500$ M^{–1} cm^{–1}).

11b can be sublimed without decomposition (100 °C, 0.1 mbar), which indicates the potential for ultra-thin film preparation by vapor deposition techniques, which has not been possible with donor-acceptor-substituted TEEs. Investigations of **11b** for optoelectronic applications are under way. In addition, the powerful new CEE acceptors have now been introduced through acetylenic scaffolding into larger molecular systems for modulation of the properties.

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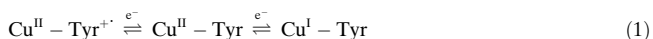
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A Structural and Functional Model of Galactose Oxidase: Control of the One-Electron Oxidized Active Form through Two Differentiated Phenolic Arms in a Tripodal Ligand

Fabrice Thomas,* Gisèle Gellon, Isabelle Gautier-Luneau, Eric Saint-Aman, and Jean-Louis Pierre

Galactose oxidase (GOase) is a type II copper protein (68 kDa) that catalyzes the oxidation of primary alcohols to aldehydes with the concomitant reduction of molecular oxygen.^[1] Its crystal structure^[2] reveals a unique mononuclear copper site with two nitrogen (from histidine imidazole groups) and two oxygen (from one axial and one equatorial tyrosine group) donor atoms, plus an exogenous water or acetate molecule in a distorted square-pyramidal coordination. The enzyme exists in three well-defined oxidation levels: the EPR-silent active form (cupric ion antiferromagnetically coupled to the equatorial tyrosyl radical), an intermediate form, and the reduced copper(I) form [Eq. (1)].



The axial tyrosine group is involved in protonation-deprotonation processes during the catalytic cycle (Scheme 1 b).

Among the structural models of the active site of GOase described,^[3] only a few contain two phenolic arms and involve the $[\text{N}_2\text{O}_2]$ copper coordination sphere of the enzyme.^[4] Some of the functional models of GOase involve salen-type ligands and exhibit interesting catalytic activity only with activated alcohols as substrates.^[5] The best results have been obtained by Wieghardt et al. with a very nice set of complexes in which the redox chemistry during the catalytic cycle is ligand-based.^[6–7] Another interesting model developed by Wieghardt and co-workers involves true GOase chemistry but is not, strictly speaking, a structural model.^[8]

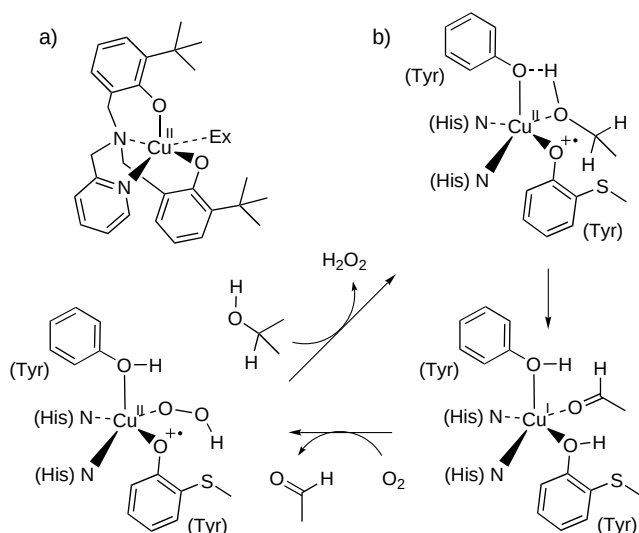
We have previously described a model, unfortunately not functional, involving an axial phenoxyl radical associated with a Cu^{II} center possessing a $[\text{N}_2\text{O}_2]$ coordination sphere. It was built from a tripodal ligand (Scheme 1 a).^[9] With a model close to ours, the phenoxyl radical species was obtained spontaneously by disproportionation.^[10]

We present here a structural and functional model of galactose oxidase. Our strategy was based on the differentiation of the two phenolic arms in the tripodal ligand

[*] Dr. F. Thomas, G. Gellon, Dr. I. Gautier-Luneau, Prof. Dr. J.-L. Pierre
Laboratoire de Chimie Biomimétique
LEDSS, UMR CNRS 5616
Université J. Fourier
BP 53, 38041 Grenoble cedex 9 (France)
Fax: (+33) 4-76-51-48-36
E-mail: fabrice.thomas@ujf-grenoble.fr
Prof. Dr. E. Saint-Aman
LEOPR, UMR CNRS 5630
Université J. Fourier
BP 53, 38041 Grenoble Cedex 9 (France)



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Scheme 1. a) Our previous model (Ex represents an exogenous ligand) and b) the simplified reaction mechanism of GOase.

LH₂^[11] to allow the geometric control of the one-electron oxidized active form. One of *tert*-butyl phenolic arms bears an electron-withdrawing nitro group and the other an electron-donating methoxy group.

[Cu^{II}(LH)(OAc)] is obtained upon mixing LH₂ and copper(II) acetate in the absence of base, while the dimeric complex [Cu₂^{II}(L)₂] is obtained in presence of two equivalents of base and copper(II) perchlorate. [Cu₂^{II}(L)₂] is converted into [Cu^{II}(LH)(OAc)] upon addition of N(Et)₃HCH₃CO₂ ($K_D = 10^4 \text{ M}^{-1}$).

The X-ray structure analysis of [Cu^{II}(LH)(OAc)] (Figure 1) reveals a mononuclear complex in which the copper(II) ion resides within a square-pyramidal geometry.^[12] The crystal structure unambiguously provides evidence of the geometric control of the two different phenolic arms. The electron-donating effect of -OCH₃ relative to -NO₂ makes deprotonation of the hydroxy

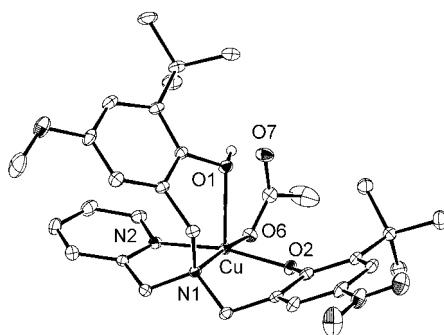


Figure 1. Structure of [Cu^{II}(LH)(OAc)] (ORTEP view; ellipsoids drawn at the 30% probability level). Selected bond lengths [Å] and angles [°]: Cu-O1 2.399(2), Cu-O2 1.912(2), Cu-O6 1.955(2), Cu-N1 2.024(3), Cu-N2 1.990(3); O1-Cu-O2 98.30(8), O1-Cu-O6 99.59(8), O1-Cu-N1 88.03(9), O1-Cu-N2 92.39(9), O2-Cu-O6 87.49(9), O2-Cu-N1 94.4(1), O2-Cu-N2 169.0(1), O6-Cu-N1 171.8(1), O6-Cu-N2 93.1(1), N1-Cu-N2 83.6(1).

group harder: The weak Cu^{II}...OH(Ar) bond occupies the more labile position, that is axial. After dissolution of the crystalline material into a CH₃CN/CH₂Cl₂ (1:1) solution, the EPR spectrum reveals only one species: no isomerization into a complex involving axial nitrophenol moieties occurs. The g_{zz}/A_{zz} ratio is characteristic for a copper center within a square-planar geometry with an axial coordinated phenol group. The electronic spectrum shows an absorption at 500 nm ($\epsilon = 760 \text{ M}^{-1} \text{ cm}^{-1}$), which is attributed to the nitrophenolate-to-copper charge transfer, while the band at 392 nm is assigned to the π - π^* transition of this nitrophenolate moiety. [Cu^{II}(LH)(OAc)] was not deprotonated upon addition of N(Et)₃ in excess, probably due to intramolecular hydrogen bonding (O1-H1...O7).

The one-electron oxidized forms of [Cu^{II}(LH)(OAc)] and [Zn^{II}(LH)(OAc)] (diamagnetic complex prepared for comparative studies) were generated electrochemically. The cyclic voltammogram of [Cu^{II}(LH)(OAc)] (Figure 2, insert) as well as [Zn^{II}(LH)(OAc)] exhibits in the anodic region a fully reversible one-electron (as judged by coulometric titration) redox couple at +0.075 V versus Fc/Fc⁺.

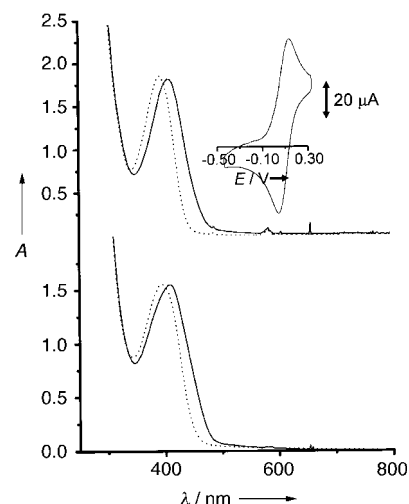


Figure 2. UV/Vis absorption spectra in CH₂Cl₂/CH₃CN (1:1) + tetrabutylammonium perchlorate (TBAP; 0.1M) of [Cu^{II}(LH)(OAc)] (top, (···)), [Zn^{II}(LH)(OAc)] (bottom, (···)) and the electrochemically generated radicals [Cu^{II}(LH)(OAc)]⁺ (top, (—)), [Zn^{II}(LH)(OAc)]⁺ (bottom, (—)); [Cu^{II}(LH)(OAc)] = 90 μM , [Zn^{II}(LH)(OAc)] = 100 μM . Insert: CV curve of [Cu^{II}(LH)(OAc)], 1 mM in CH₂Cl₂/CH₃CN (1:1) + TBAP (0.1M); scan rate: 0.1 V s⁻¹; E/V versus Fc/Fc⁺.

Exhaustive electrolysis at +0.15 V was performed directly in the UV/Vis spectrophotometer. At one exchanged electron, the absorption at 392 nm shifts to 410 nm for both [Cu^{II}(LH)(OAc)] and [Zn^{II}(LH)(OAc)] (Figure 2, $\epsilon = 19 \times 10^3$ and $17 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$, respectively). Similar results obtained with the two complexes attest that oxidation is ligand-based. The UV/Vis features of the oxidized species are close to those previously described for phenoxyl radicals.^[13] On the other hand, while [Zn^{II}(LH)(OAc)]⁺ is EPR-active,^[14] [Cu^{II}(LH)(OAc)]⁺ is EPR-silent (Figure 3): This indicates a significant overlap between the $d_{x^2-y^2}$ magnetic orbital of Cu^{II} and the half-occupied π orbital of the phenoxyl radical leading to an ($S = 0$) ground state.

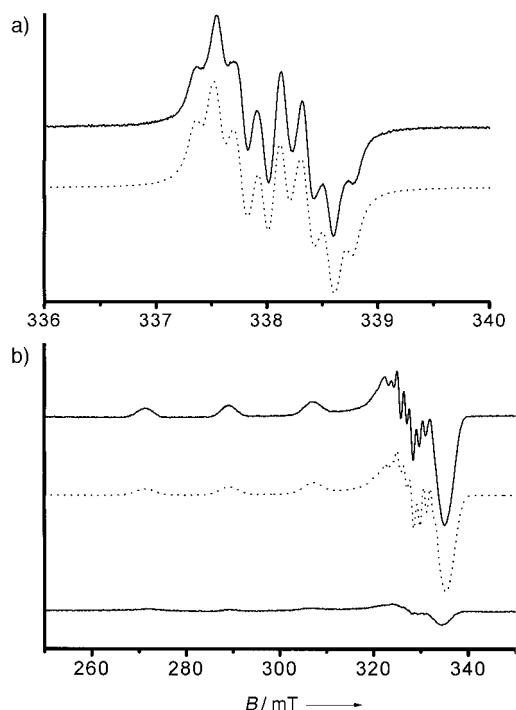


Figure 3. X-band EPR spectra of: a) the electrochemically generated $[\text{Zn}^{\text{II}}(\text{LH})(\text{OAc})]^+$ in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (1:1) + TBAP 0.1 M (experimental (—), simulation (···)). $[\text{Zn}^{\text{II}}(\text{LH})(\text{OAc})]^+ = 3 \text{ mM}$, $T = 22^\circ\text{C}$, frequency: 9.4901 GHz, 2 mW; modulation: 0.0987 mT, 100 KHz. b) $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]$ (experimental (—), simulation (···)) and $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+$ (bottom): $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (1:1) + TBAP (0.1 M); $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+ = [\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})] = 3 \text{ mM}$, $T = 100 \text{ K}$, frequency: 9.4112 GHz, 20 mW; modulation: 0.1756 mT, 100 KHz.

Even though the axial phenol is substituted by an electron-donating group, its remaining protonation makes its substitution insufficient to lower its redox potential below the redox potential of the deprotonated nitrophenolate. Moreover, the fully reversible redox process observed on the electrolysis time scale suggests that no chemical reaction, for example protonation–deprotonation, is associated with the electron transfer as expected for the oxidation of a protonated phenol.^[15] The radical is thus located on the equatorial nitrophenolate group.

Oxidation of benzyl alcohol by $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]$ and O_2 (in the presence of catalytic amounts of KOH) was monitored by GC. After two days 220 turnovers were achieved. A lag time during the first few hours indicates that $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]$ is not the active species; the active species is more likely the radical $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+$, generated by aerobic oxidation. Use of PhCD_2OH instead of PhCH_2OH increased the lag time (only 50 turnovers/2 days). This isotopic effect indicates that the rate-limiting step during oxidation of alcohol is the C–H bond breakage as for GOase.

Use of the electrochemically generated $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+$ leads to oxidation of benzyl alcohol at a higher rate (220 turnovers in 2 h, 300 turnovers in one day). Using unactivated primary alcohols, 40 turnovers in one day were obtained for oxidation of the sterically hindered neopentyl alcohol, and 80 turnovers in one day for the oxidation of ethanol (aldehydes were titrated by a method previously developed by Wieghardt and co-workers).^[7] Secondary alcohols (cyclohexanol or 2-

hexanol) are not oxidized: no trace of ketone could be detected by GC after one week of reaction. The model thus reproduces the chemoselectivity of the enzyme. H_2O_2 was not detected after catalysis due to its fast disproportionation in basic medium (2 mM KOH or $\text{N}(\text{Et})_3$). However, mixing together LH_2 and CuCl in a glove box (formation of a Cu^{I} complex) leads, upon exposure to air, to the formation of one equivalent of H_2O_2 (detected by a method developed by Wieghardt and co-workers).^[7]

$[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+$ is moderately stable at 25°C in THF ($k_{\text{dec}} = 0.0175 \text{ s}^{-1}$).^[16] Addition of an excess of benzyl alcohol under an anaerobic atmosphere increased k_{dec} , while quantitative formation (relative to the catalyst) of benzaldehyde was evidenced by GC. Monoexponential decay was fitted to obtain the observed pseudo-first-order constants $k_{\text{dec}}^{[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]}$. The plot of $k_{\text{dec}}^{[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]} - k_{\text{dec}}$ versus benzyl alcohol concentration shows a linear dependence (second-order rate constant $k_{\text{Cu}} = 0.0271(5) \text{ M}^{-1} \text{ s}^{-1}$) indicating that one benzyl alcohol is oxidized by one $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+$ complex^[17] and thus the catalyst formally stores two oxidative equivalents, that is the phenoxyl/phenolate and the $\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ couples.

In summary, the complex presented here may be considered as both a structural and functional model of GOase. It involves a similar $[\text{N}_2\text{O}_2]$ coordination sphere around the Cu^{II} center. The one-electron oxidized form (Cu^{II} –phenoxyl radical) reproduces the magnetic control observed in the active form of the enzyme. It is also a good model for the chemistry and chemoselectivity of GOase, that is the oxidation of primary alcohols into aldehyde, with formation of H_2O_2 . Finally, the complex $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]^+$ could be considered as a new possible intermediate in the catalytic pathway of GOase: the axial phenol is protonated and the equatorial phenoxyl antiferromagnetically coupled to the cupric center.

Experimental Section

$[(\text{Cu}^{\text{II}})_2(\text{L})_2]$: LH_2 (173 mg) was treated with two equivalents of $\text{N}(\text{Et})_3$ in CH_3CN (10 mL) prior to addition of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (118 mg). After 3 h a dark brown precipitate formed, which was filtered and washed with diethyl ether. Elemental analysis calcd (%) for $\text{C}_{64}\text{H}_{87}\text{N}_7\text{Cu}_2\text{O}_{13} \cdot 1/2 \text{CH}_3\text{CN} \cdot 3/2 \text{H}_2\text{O}$: C 59.76, H 6.33, N 7.68, Cu 10.72; found: C 59.75, H 6.31, N 7.49, Cu 9.88; FAB + MS: m/z : 1139 ($[(\text{Cu}^{\text{II}})_2(\text{L})_2]$). Single crystals of $[\text{Cu}^{\text{II}}(\text{L})_2] \cdot 2 \text{CH}_3\text{CN}$ and $[\text{Cu}^{\text{II}}(\text{L})_2]$ were obtained by recrystallization from $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (1:1) or $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ (1:1). UV/Vis (CH_2Cl_2): λ_{max} (ϵ) = 296 (11.4×10^3), 391 (28.1×10^3), 500 sh nm ($5.1 \times 10^3 \text{ L mol}^{-1} \text{ cm}^{-1}$).

$[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]$: LH_2 (100 mg) and $\text{Cu}(\text{OAc})_2$ (40 mg) were dissolved in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (1:1). After one night CH_2Cl_2 was evaporated under vacuum. The solution was allowed to stand for three days at -20°C . Green microcrystals of $[\text{Cu}^{\text{II}}(\text{LH})(\text{OAc})]$ were collected by filtration. Elemental analysis calcd (%) for $\text{C}_{31}\text{H}_{30}\text{N}_3\text{CuO}_7 \cdot 1 \text{CH}_2\text{Cl}_2 \cdot 1/2 \text{CH}_3\text{CN}$: C 53.95, H 5.83, N 6.67, Cu 8.65; found: C 54.97, H 5.83, N 6.63, Cu 8.75; EPR (9.41 GHz, 100 K, $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$): g_{xx} : 2.042; g_{yy} : 2.059; g_{zz} : 2.256; A_{xx} : 1 mT; A_{yy} : 2.5 mT; A_{zz} : 17.8 mT; A_{N} : 1.3 mT; FAB + MS: m/z : 569 ($[\text{Cu}^{\text{II}}(\text{LH})]$); UV/Vis ($\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$): λ_{max} (ϵ) = 298 (10.3×10^3), 393 (20.0×10^3), 500 sh (0.76×10^3), 600 sh nm ($0.51 \times 10^3 \text{ L mol}^{-1} \text{ cm}^{-1}$).

$[\text{Zn}^{\text{II}}(\text{LH})(\text{OAc})]$: $\text{Zn}(\text{OAc})_2$ (40 mg) was added to an ethanolic solution (5 mL) of LH_2 (100 mg); the mixture was stirred for 3 h and then filtered, extracted by CH_2Cl_2 , washed, and dried over Na_2SO_4 . $[\text{Zn}^{\text{II}}(\text{LH})(\text{OAc})]$ was obtained as a yellow powder. Elemental analysis calcd (%) for $\text{C}_{31}\text{H}_{30}\text{N}_3\text{ZnO}_7 \cdot 1 \text{H}_2\text{O}$: C 57.36, H 6.37, N 6.47, Zn 10.07; found: C 57.38, H 6.34, N 6.41, Zn 9.70; ^1H NMR (300 MHz, CDCl_3 , 25°C , TMS): $\delta = 1.34$,

1.42 (s, 18H; 2*t*Bu), 2.17 (s, 3H; CH₃ acetate), 3.74, 3.82, 3.87, 3.89 (s, 9H; 3CH₂, 1OCH₃), 6.52, 6.81, 7.15, 7.92 (d, 4H; CH phenol), 8.15, 8.69 (d, 2H; CH pyridine), 7.33, 7.75 ppm (t, 2H; CH pyridine). FAB + MS: *m/z*: 569 ([Zn^{II}(LH)]); UV/Vis (CH₃CN:CH₂Cl₂): λ_{max} (ε) = 316 (5.2 × 10³), 392 nm (16.7 × 10³ L mol⁻¹ cm⁻¹).

Caution: Perchlorates are potentially explosive and should be handled with special care.

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Experimental Detection of the Pentaazacyclopentadienide (Pentazolate) Anion, *cyclo-N₅⁻***

Ashwani Vij,* James G. Pavlovich,
William W. Wilson, Vandana Vij, and
Karl O. Christe*

*Dedicated to Professor George Olah
on the occasion of his 75th birthday*

Nitrogen and oxygen are unique among the chemical elements. In contrast to the other elements, their homonuclear single-bond energies are significantly less than one third of their triple- or one half of their double-bond energies. Consequently, homonuclear polynitrogen and polyoxygen species are thermodynamically highly unstable and the number of known compounds is very limited. Owing to the highly endothermic heats of formation, their syntheses and handling present great challenges. It is, therefore, no surprise that for oxygen only one metastable allotrope, that is, ozone, is known and for nitrogen none are known that can be isolated in bulk, while most other elements can exist in the form of many stable allotropes.

Polynitrogen compounds have been studied extensively for the last two decades. In view of the great experimental difficulties, most of the efforts have been limited to theoretical studies.^[1–9] The first major breakthrough in the synthesis area was achieved in 1999 with the synthesis of the N_5^+ ion in the form of a marginally stable AsF_6^- salt.^[10] Subsequently, the thermally more stable $N_5^+SbF_6^-$ was synthesized, and the crystal structure of $N_5^+Sb_2F_{11}^-$ was determined.^[11]

Based on Born–Haber cycle considerations, the stability of an ionic salt is governed by three factors: the lattice energy, the electron affinity of the cation, and the first ionization potential of the anion. Furthermore, each ion must possess a sufficiently high activation energy barrier toward decomposition. For the successful combination of N_5^+ with a poly-

nitrogen anion in the form of a stable salt, an anion with a high first ionization potential is required. Theoretical calculations from our and other^[1,5,8,12–18] research groups predict that the unknown pentazolate anion (see Figure 1) has a first ionization potential and activation energy barrier toward decomposition that might be high enough for the formation of stable $N_5^+N_5^-$. As a result, the synthesis of the N_5^- ion is hotly pursued in numerous laboratories.

Although the existence and stability of substituted pentazole ring compounds have been demonstrated successfully more than 40 years ago by Huisgen and Ugi^[19–22] and substituted pentazoles have been well characterized,^[23–28] all attempts to prepare either the parent HN_5 molecule^[29,30] or its anion, N_5^- , have so far been unsuccessful. Herein, we report the first experimental detection of this important anion.

In our pursuit of the N_5^- ion, the following strategy was employed: a) the use of Ugi–Huisgen-type, substituted phenylpentazoles as starting materials; b) the transfer of maximum negative charge to the pentazole ring by the use of highly electron-donating substituents on the phenyl ring in *para*-position to the pentazolyl substituent to increase the aromaticity and stability of the pentazole ring, while at the same time weakening the connecting C–N bond; c) the selective cleavage of the C–N bond, while keeping the N–N bonds of the pentazole ring intact; and d) the use of an analytical method that is ideally suited for the generation and detection of anions. Similar approaches have been described, but attempts to cleave the C–N bond by ozonolysis were unsuccessful.^[22,31] The reasons, outlined above, prompted us to choose *para*-hydroxy-^[31] and *para*-dimethylamino-substituted phenylpentazoles^[21] as starting materials and negative-ion electrospray ionization mass spectrometry (ESI-MS)^[32–34] as the analytical tool.

The arylpentazoles and the corresponding diazonium salt precursors were prepared and characterized by multinuclear NMR spectroscopy.^[24–28] For the cleavage experiments, these pentazoles were dissolved in strongly polar solvents, such as CH_3CN or a mixture of CH_3OH and CH_2Cl_2 , and infused into the spectrometer's ion source at $10 \mu L min^{-1}$ with a syringe pump.^[35] In tandem mass spectrometry (MS-MS) experiments, the desired negative-ion peaks are mass-selected and subjected to product ion mass analysis following collision-induced dissociation (CID) at variable collision voltages using N_2 or Ar as the collision gas.

The most interesting results were obtained with *para*-hydroxyphenylpentazole in CH_3CN . An intense [parent–H][–] base peak was observed at m/z 162 and mass-selected for subsequent MS-MS studies (Figure 2). It was found advantageous to add a base, such as pyridine, to the CH_3CN solutions to increase significantly the concentration of this *para*-pentazolylphenolate anion. Using a low collision voltage of -10 V, the m/z 162 ion $[OC_6H_4N_5]^-$ underwent stepwise N_2 , N_2 , and CO loss (see Scheme 1), giving rise to intense peaks with m/z values of 134 $[OC_6H_4N_3]^-$, 106 $[OC_6H_4N]^-$, and 78 $[C_5H_4N]^-$, respectively. The loss of the first N_2 molecule is due

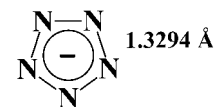


Figure 1. Minimum energy structure of the planar D_{5h} pentazolate anion from ref. [1], calculated at the CCSD(T)/aug-cc-pVTZ level of theory.

[*] Dr. A. Vij, Dr. K. O. Christe, Dr. W. W. Wilson, V. Vij
ERC, Inc. and Propulsion Sciences and Advanced Concepts Division
Air Force Research Laboratory (AFRL/PRSP)
Edwards Air Force Base, CA 93524 (USA)
Fax: (+1) 661-275-5471
E-mail: ashwani.vij@edwards.af.mil
karl.christe@edwards.af.mil

and
Loker Hydrocarbon Research Institute
University of Southern California
Los Angeles, CA 90089-1661 (USA)

Dr. J. G. Pavlovich
Department of Chemistry
University of California, Santa Barbara, CA 93106 (USA)

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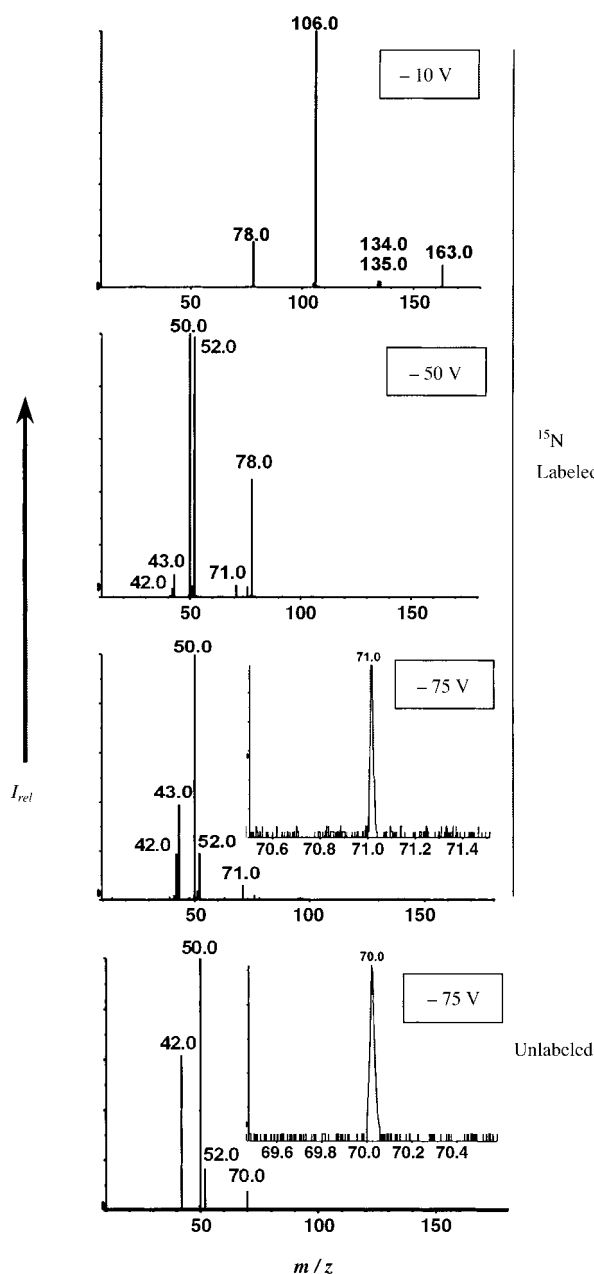
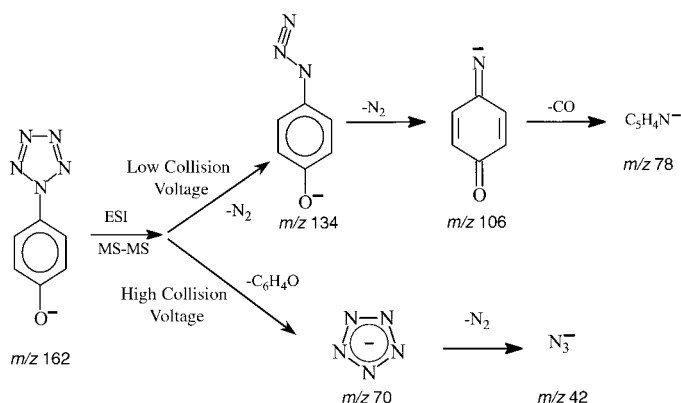


Figure 2. Negative ion, full-range CID mass spectra of the mass selected, ^{15}N labeled (m/z 163) and unlabeled (m/z 162) peaks due to $[\text{OC}_6\text{H}_4\text{N}_3]^-$ recorded at collision voltages of –75, –50, and –10 V. All spectra are multichannel spectra and the typical mass resolution and noise level are shown for the m/z 70 and 71 peaks in the inserts.

to the opening of the pentazole ring and produces the 4-azidophenolate ion. The second N_2 loss occurs from the azido group and generates the deprotonated quinone-imide, $[\text{N}=\text{C}_6\text{H}_4=\text{O}]^-$. This ion then undergoes CO extrusion giving a $[\text{C}_5\text{H}_4\text{N}]^-$ ion. Secondary fragmentation of the m/z 134 ion at a collision voltage of –30 V gave rise to intense peaks at m/z 78 $[\text{C}_5\text{H}_4\text{N}]^-$, 52 $[\text{C}_3\text{H}_2\text{N}]^-$, and 50 $[\text{C}_3\text{N}]^-$. The product ion spectra of the m/z 106 and 78 ions at collision voltages of –75 V gave only a very intense m/z peak at 50 $[\text{C}_3\text{N}]^-$.

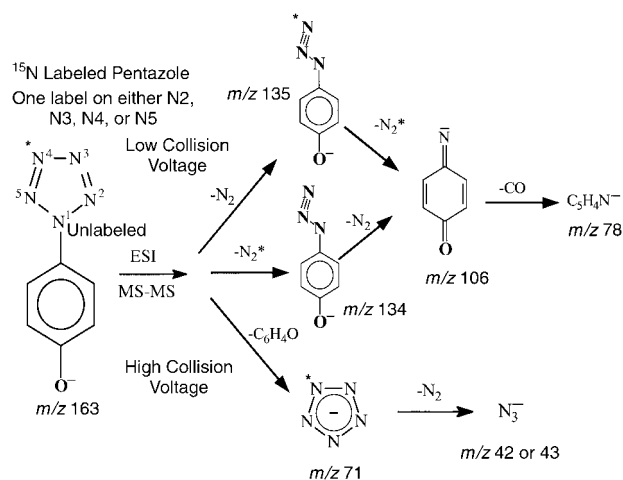
Using high collision voltages of about –75 V for the CID of the m/z 162 ion, however, gave a very different fragmentation pattern. The only peaks observed were m/z 70, 52, 50, and 42. The m/z 70 peak can only be due to N_5^- , and the m/z 52 and 50



Scheme 1. ESI-MS-MS fragmentation of the mass-selected unlabeled 4-pentazolyphenolate anion at low and high collision voltages.

peaks are due to $[\text{C}_3\text{H}_2\text{N}]^-$ and $[\text{C}_3\text{N}]^-$, respectively, and, as shown above, result from the fragmentation of the $[\text{C}_5\text{H}_4\text{N}]^-$ ion. The m/z 42 peak is attributed to the azide anion, N_3^- . Since the 4-azidophenolate ion does not eliminate N_3^- but only N_2 (see above results for the MS-MS of the m/z 134 peak), the N_3^- ion can only come from the decomposition of an N_5^- ion. These results clearly demonstrate that at high collision voltages the pentazolate anion is formed. The fragmentation of the m/z 70 ion to N_3^- by loss of dinitrogen is in accord with the theoretically predicted decomposition pathway of N_5^- ^[8] and further supports its identification as N_5^- .

Additional evidence for the formation of the pentazolate anion was obtained by studies using ^{15}N labeled 4-hydroxyphenylpentazole. In these experiments, the 4-hydroxyphenyldiazonium salt was reacted with azide that was ^{15}N labeled in one terminal position. This resulted in a pentazole ring containing one ^{15}N label either in the N2, N3, N4, or N5 positions. Its ESI-MS spectrum (see Figure 2 and Scheme 2) at high collision voltages gave the m/z 71 peak expected for a singly labeled pentazolate anion. Furthermore, the observation of both an m/z 135 peak and an m/z 134 peak for the ^{15}N -labeled and unlabeled $[\text{OC}_6\text{H}_4\text{N}_3]^-$ ions, respectively, and of single m/z 106 and 78 peaks provides proof that the first two steps of the low collision voltage decomposition must involve



Scheme 2. ESI-MS-MS fragmentation observed for the mass-selected ^{15}N singly labeled 4-pentazolyphenolate anion at low and high collision voltages.

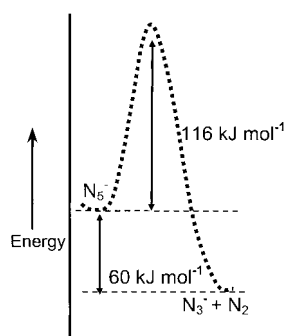


Figure 3. Activation energy barrier and decomposition enthalpy of the pentazolate anion calculated at the CCSD(T)/aug-cc-pVTZ level of theory.^[8]

pentazole ring and the vibrational instability of open-chain N_5^- ^[8] establish beyond doubt that the observed N_5^- species must be the long-sought pentazolate anion.

In summary, our results constitute the first experimental detection of the pentazolate anion and demonstrate that in suitably substituted phenylpentazoles the C–N bond can be cleaved while leaving the pentazole ring intact. Since the substituted phenylpentazoles are easily accessible, this approach holds great promise for the bulk synthesis of N_5^- salts, and experiments in this direction are in progress in our laboratories. The pentazolate anion is the polynitrogen counterpart to the cyclopentadienide anion. It, therefore, has great potential as a pentahapto ligand for transition metals^[13,36] and could lay the foundation for a field of purely inorganic metallocene-type chemistry. Our results on N_5^+ ^[10,11] and N_5^- , together with the recent observations of the N_4 molecule as a metastable species with a lifetime exceeding one microsecond,^[37] the observation of a new but ill-characterized polynitrogen species from a discharge generated nitrogen plasma,^[38] and exciting progress in high nitrogen compounds,^[28,39] indicate a bright future for experimental polynitrogen chemistry.

Experimental Section

Caution! Although no explosions were encountered in the course of this work, pentazoles can spontaneously lose nitrogen and should be handled by using appropriate safety precautions (small scale, face shield, leather gloves, protective clothing, and blast shields) until reliable safety data for these compounds become available.

The NMR spectra were recorded at 400.13 MHz (^1H), 100.62 MHz (^{13}C), 29.91 MHz (^{14}N), and 40.56 MHz (^{15}N) on a Bruker Avance 400 NMR spectrometer using solutions in a standard glass precision 5 mm tube at $-10 \pm 1^\circ\text{C}$. The pentazoles are more stable in 1:1 mixtures of CD_2Cl_2 and CD_3CN than in other solvent mixtures that contain some CD_3OD . The following external references were used: ^1H , TMS (0 ppm), ^{13}C (CD_2Cl_2) 54.00 ppm or (CD_3CN) 1.39 ppm referenced to $(\text{CH}_3)_4\text{Si}$ (0 ppm); $^{14/15}\text{N}$, 1:1 mixture of 50% ^{15}N labeled CD_3NO_2 and CH_3NO_2 (0 ppm).

The following arylpentazoles were prepared from the corresponding aryldiazonium salts and sodium azide in water at ice/salt-bath temperatures: *para*- $\text{R}-\text{C}_6\text{H}_4\text{-cyclo-}\text{N}_5$ ($\text{R} = \text{OH}$, O^- (for the counterions see below), OCH_3 , OC_6H_5 , $\text{N}(\text{CH}_3)_2$, $\text{O}-\text{C}_6\text{H}_4\text{-cyclo-}\text{N}_5$). For the preparation of ^{15}N -labeled pentazoles, singly labeled $\text{Na}^+[\text{N}_5^-]$ was used. In a typical preparation, 4-hydroxyaniline hydrochloride (2.4 mmol) was dissolved in water ($\approx 15\text{ mL}$) in a 50 mL beaker, cooled in an ice-salt bath, and slightly acidified with 1N aqueous HCl. A cold solution of sodium nitrite (2.6 mmol) in water ($\sim 10\text{ mL}$) was slowly added with vigorous stirring,

resulting in the instant formation of 4-hydroxyphenyldiazonium chloride. A cold aqueous solution of sodium azide (2.5 mmol) was slowly added with stirring, resulting in spontaneous effervescence and the formation of a brownish solid. This solid was filtered off at 0°C , washed with ice-cold water and then with cold methanol (-25°C) twice, and finally dried in vacuo. 4-Hydroxyphenylpentazole was obtained in 20–35% yield, contaminated with $\approx 10\%$ of 4-hydroxyphenylazide, and characterized by multinuclear NMR studies. For the preparation of the cesium or tetramethylammonium (TMA) salts, equivalent amounts of $\text{N}(\text{CH}_3)_4\text{OH}$ or CsOCH_3 in methanol, respectively, were added to the 4-hydroxyphenylpentazole solutions at -40°C and these solutions were then allowed to warm slowly to -10°C . Alternatively, the 4-pentazolyphenolate anion could be generated by adding pyridine to a solution of 4-hydroxyphenylpentazole in CH_3CN at -25°C .

For the following ^1H NMR spectra, H_a and H_b correspond to the hydrogen atoms at the *ortho* and *meta* positions, respectively, relative to the pentazole-bearing carbon atom (C_{ipso}), and for the ^{13}C NMR spectra, the carbon in the *para* position, bearing the electron-releasing group, that is $-\text{OH}$ or $-\text{O}^-$, is labeled as (C_p). In the case of the $^{14/15}\text{N}$ NMR spectra, N1 is the nitrogen atom in the pentazole ring that is bonded to the aryl group, N2/N5 are bonded directly to N1, and N3 and N4 are bonded to N2 and N5, respectively. In the corresponding azides, N1 refers to the nitrogen atom attached to the phenyl group and N3 is the terminal nitrogen atom. The ^{15}N -labeled azides were obtained by the thermal decomposition of the corresponding pentazoles at 25°C , resulting in the 2 and 3 positions being labeled. Evolved N_2 gas can be observed at $\delta = -72\text{ ppm}$ (literature value $\delta = -73\text{ ppm}$ ^[25]). Spectral data, obtained for the compounds in either a 1:1 mixture of CD_2Cl_2 and CD_3CN or a mixture of other solvents are:

4-Hydroxyphenylpentazole: ^1H : $\delta = 7.02$ (H_b , AB, 2H, $^3J_{\text{H,H}} = 9.2\text{ Hz}$), 7.95 ppm (H_a , AB, 2H, $^3J_{\text{H,H}} = 9.2\text{ Hz}$); ^{13}C : $\delta = 126.4$ (s, C_i), 123.2 (s, C_o), 117.0 (s, C_m), 161.2 ppm (s, C_p); ^{14}N : $\delta = -81.6\text{ ppm}$ (br, N1); ^{15}N : $\delta = 4.2$ (s, N2/N5), -27.6 ppm (s, N3/N4). Literature values^[31]: ^1H : $\delta = 7.04$ (d, H_b , $J = 6.4\text{ Hz}$), 8.01 ppm (d, 2H, $J = 6.5\text{ Hz}$). The previously reported coupling constant of about 6.4 Hz appears to be incorrect.

4-Hydroxyphenylazide: ^1H : $\delta = 6.75$ (H_b , AB, 2H, $^3J_{\text{H,H}} = 8.8\text{ Hz}$), 6.83 ppm (H_a , AB, 2H, $^3J_{\text{H,H}} = 8.8\text{ Hz}$); ^{13}C : $\delta = 131.5$ (s, C_i), 120.4 (s, C_o), 116.9 (s, C_m), 155.3 ppm (s, C_p); ^{15}N : $\delta = -136.6$ (s, N2), -149.1 ppm (s, N3); ^{15}N : $\delta = -141.2$ (s, N2), -152.5 ppm (s, N3). Literature values^[40]: ^1H : $\delta = 6.83$ (H_b , d, 2H, $J = 9\text{ Hz}$), 6.92 ppm (H_a , d, 2H, $J = 9\text{ Hz}$).

Cesium/TMA 4-pentazolyphenolate: ^1H : $\delta = 6.66$ (H_b , AB, 2H, $^3J_{\text{H,H}} = 7.2\text{ Hz}$), 6.74 ppm (H_a , AB, 2H, $^3J_{\text{H,H}} = 7.2\text{ Hz}$); ^{13}C : $\delta = 122.8$ (s, C_i), 120.7 (s, C_o), 119.9 (s, C_m), 172.1 ppm (s, C_p); ^{14}N : $\delta = -81.1\text{ ppm}$ (br, N1); ^{15}N : $\delta = 1.9$ (s, N2/N5), -29.7 ppm (s, N3/N4).

Cesium/TMA 4-azidophenolate: ^1H : $\delta = 6.61$ (H_b , AB, 2H, $^3J_{\text{H,H}} = 6.8\text{ Hz}$), 7.95 ppm (H_a , AB, 2H, $^3J_{\text{H,H}} = 6.8\text{ Hz}$); ^{13}C : $\delta = 125.1$ (s, C_i), 120.2 (s, C_o), 120.1 (s, C_m), 165.4 ppm (s, C_p); ^{15}N : $\delta = -135.7$ (s, N2), -150.9 ppm (s, N3). Literature values^[31]: CD_3OD (CD_2Cl_2): ^1H : $\delta = 6.59$ (6.47) (d, 2H, $J = 9.0$ (8.8) Hz), 6.69 ppm (6.65) (d, 2H, $J = 9.0$ (8.8) Hz); ^{15}N (CD_2Cl_2): $\delta = -131.7$ (s, N1), -148.4 ppm (s, N1). In the literature data,^[31] no assignments to the individual nitrogen atoms were given, and due to the nuclear Overhauser effect, the ^{15}N signals cannot be integrated.

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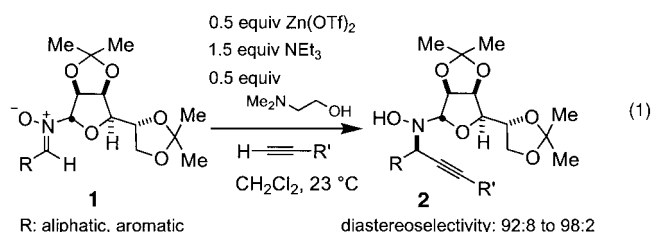
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First Synthesis of Optically Pure Propargylic *N*-Hydroxylamines by Direct, Highly Diastereoselective Addition of Terminal Alkynes to Nitrones**

Roger Fässler, Doug E. Frantz, Jürg Oetiker, and Erick M. Carreira*

Dedicated to Professor Andrea Vasella

Optically active propargylic alcohols serve as versatile building blocks for asymmetric synthesis.^[1] The corresponding propargylic amines or *N*-hydroxylamines could also serve in a similar capacity were it not for the fact that general, useful methods that provide access to such compounds are not available.^[2] The latter are not only synthetic equivalents of the former, but also are amenable to further elaborations, such as cyclization to afford isoxazolines.^[3] Herein, we document the first general method for the preparation of optically active propargylic *N*-hydroxylamines [Eq. (1), Tf = trifluorometh-



anesulfonyl]. The method prescribes the use of nitrones which are conveniently prepared through condensation of the corresponding aldehydes and a mannose-derived glycosidic *N*-hydroxylamine.^[4] Reaction of the nitrones with a broad range of terminal acetylenes in the presence of Zn^{II} ions, 2-dimethylaminoethanol, and NEt_3 gives adducts in high diastereoselectivity and yield. Following its addition, the auxiliary is easily removed by treatment of the products with *N*-hydroxylamine hydrochloride; a process which allows for re-isolation and reuse of the auxiliary. The method we document should find use in medicinal chemistry to provide access to a new class of useful building blocks for the asymmetric synthesis of pharmacologically important compounds.

There are scant, scattered reports that document diastereoselective additions to chiral nitrones. These typically involve additions of Grignard or organolithium compounds

[*] Prof. Dr. E. M. Carreira, R. Fässler, J. Oetiker
Laboratorium für Organische Chemie
ETH Hönggerberg
Wolfgang-Pauli-Strasse 10, 8093 Zürich (Switzerland)
Fax: (+41) 1-632-1328
E-mail: carreira@org.chem.ethz.ch
Dr. D. E. Frantz
Merck & Co., Inc, WYN-3
466 Devon Park Drive
Wayne, PA 19087 (USA)

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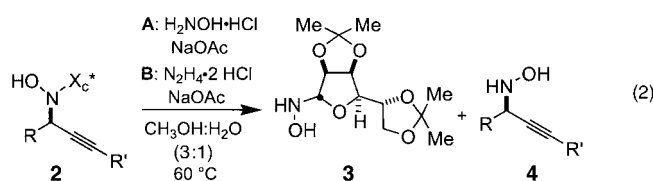


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to chiral starting materials, and are limited in scope.^[4b,5-8] Moreover, because they are generally single-substrate studies, the generality of these additions as a means to provide broad access to chiral *N*-hydroxylamines is unclear.

We recently reported a method for the catalytic in situ generation of Zn^{II} -alkynilides and their addition to achiral nitrones.^[9] Accordingly, we were interested in extending the methodology to include an asymmetric version. Preliminary screening of auxiliaries for use in diastereoselective nitronone additions led us to single out carbohydrate-based structures, such as **3**, derived from mannose, acetone, and *N*-hydroxylamine.

The use of *N*-glycoside-derived nitrones and in particular those prepared from mannose were deemed attractive on account of: 1) the preparation of the glycosidic *N*-hydroxylamines from inexpensive starting materials has been shown to be straightforward (two steps, 85 %); 2) addition reactions of phosphinates to such nitrones have been shown to furnish a limited number of aminophosphinic acids in high diastereoselectivity;^[5a,b] and 3) after the addition reaction, the auxiliary **3** is easily removed and recycled [Eq. (2), X_C^* = chiral auxiliary].^[5c]



The requisite nitrones for study (**1**) were conveniently prepared by treating a solution of glycosyl *N*-hydroxylamine **3** and aldehyde in CH_2Cl_2 with a desiccant such as Na_2SO_4 or MgSO_4 . As shown in Table 1, the additions can be carried out on a wide variety of branched, unbranched, aromatic, and C-substituted nitrones as well as with an equally broad range of terminal alkynes. Thus, treatment of a solution of a terminal alkyne and a nitrone **1** with 0.5 equivalents of $\text{Zn}(\text{OTf})_2$, 0.5 equivalents of 2-dimethylaminoethanol, and 1.5 equivalents of NEt_3 in CH_2Cl_2 (0.33 M) at 23 °C affords adducts **2** in up to 99 % yield and excellent diastereomeric ratios ranging from 92:8 to 98:2.^[10,11] In the course of optimization studies, we observed that the use of 2-dimethylaminoethanol was beneficial, because not only did its use lead to enhanced reaction rates (fivefold), it also furnished homogenous solutions throughout the course of the reaction.

A convenient aspect of the process is the fact that removal of the auxiliary is effected upon heating a $\text{MeOH}:\text{H}_2\text{O}$ (3:1) solution of adducts **2** with 1.6 equivalents of $\text{H}_2\text{NOH}\cdot\text{HCl}$ and 1.5 equivalents of NaOAc at 50–60 °C (Table 2, method A).^[5c] In certain cases (entries 1 and 6) more forcing conditions were necessary to effect removal of the auxiliary, wherein $\text{N}_2\text{H}_4\cdot 2\text{HCl}$ was substituted for $\text{H}_2\text{NOH}\cdot\text{HCl}$ (Table 2, method B). Optically active propargylic *N*-hydroxylamines **4** can be isolated in useful yields by using either method.

In summary, we report a novel, general, practical method for the highly stereoselective synthesis of optically active secondary propargylic *N*-hydroxylamines. A key salient feature of this process is the fact that a wide range of terminal

Table 1. Diastereoselective additions of in situ generated Zn^{II} -alkynilides to nitrones **1**.^[a]

Entry	R	R'	Yield [%]	<i>dr</i> ^[b]
1	Me	Ph	88	95:5
2		$\text{Ph}(\text{CH}_2)_2$	45	96:4 ^[c]
3			99	95:5 ^[d]
4		Me_3Si	75	92:8
5		<i>n</i> - C_4H_9	80	97:3 ^[e]
6	<i>i</i> Pr	Ph	89	92:8
7		$\text{Ph}(\text{CH}_2)_2$	87	97:3
8			98	96:4 ^[d]
9			94	96:4
10	<i>c</i> - C_6H_{11}	Ph	91	94:6
11		$\text{Ph}(\text{CH}_2)_2$	91	95:5
12			94	93:7 ^[d]
13		<i>n</i> - C_4H_9	82	98:2
14	<i>c</i> - C_3H_5	Ph	92	94:6
15		$\text{Ph}(\text{CH}_2)_2$	73	96:4
16			54	96:4
17	<i>t</i> Bu	Ph	91	97:3
18	Ph	Ph	82	95:5 ^[f,g]
19		Me_3Si	88	95:5 ^[g]
20			83	95:5 ^[d,g]
21		Ph	79	95:5

[a] Addition reactions were conducted as described in the text. For additional details, see the Supporting Information. [b] The diastereomeric ratio of the adducts was assayed by ^1H NMR spectroscopy. [c] The corresponding isoxazoline, generated by cyclization of the adduct, was isolated as the main product in 48 % yield. [d] 2-Methyl-3-butene-2-ol was utilized as the solvent, and gave much higher yields than the standard reaction protocols (entry 16). [e] Besides the product (80 %), 12 % of the corresponding isoxazoline was isolated. [f] In the course of the reaction, the adduct entirely cyclized to the corresponding isoxazoline which was then isolated. [g] The reaction was conducted using $\text{Zn}(\text{OTf})_2$ (1.1 equiv), NEt_3 (1.5 equiv), and 2-dimethylaminoethanol (1.1 equiv).

Table 2. Cleavage of the auxiliary and generation of **4**.^[a]

Entry	R	R'	<i>t</i> [h]	Method	Yield [%]
1	Me	Ph	4.5	B	99
2		Me_3Si	3	A	86
3	<i>i</i> Pr	Ph	1.5	A	96
4			4.5	A	95
5	Ph	Me_3Si	2	A	85
6	Ph		3.5	B	73 ^[b]
7	Me		1	A	54 ^[b]

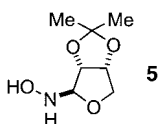
[a] For reaction conditions, see text. [b] The moderate yield in entries 6 and 7 is caused by the high polarity and low stability of the product. The work-up and isolation procedures are currently being optimized.

acetylenes and nitrones participate in additions under conditions where the nucleophilic alkynilides are generated in situ by utilizing substoichiometric amounts of $\text{Zn}(\text{OTf})_2$; as such, the terminal alkynes were used directly without

requiring a separate deprotonation or activation step. Given the fact that acetylenes are readily and conveniently converted into numerous other functional groups, the method provides access to a large range of *N*-hydroxylamines in optically active form for the first time. Such compounds are of increasing importance in medicinal chemistry, where the corresponding hydroxamic acids, for example, have been shown to possess potent broad-spectrum activities against matrix metalloproteases and tumor necrosis factor α (TNF- α) converting enzymes.^[12]

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- [10] Nitrones bearing the erythronolactone-derived auxiliary **5** furnished the addition products with opposite absolute configurations in comparable yield and stereoselectivity.



- [11] The absolute configuration of the products was determined by conversion of the propargylic *N*-hydroxylamine adducts (entries 1, 6, and 19, Table 1) into the corresponding *N*-(2-naphthoyl)alanine, -valine, and -phenylglycine derivatives, which were compared against authentic standards.

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A Stoichiometric Aromatic C–H Borylation Catalyzed by Iridium(III)/2,2'-Bipyridine Complexes at Room Temperature



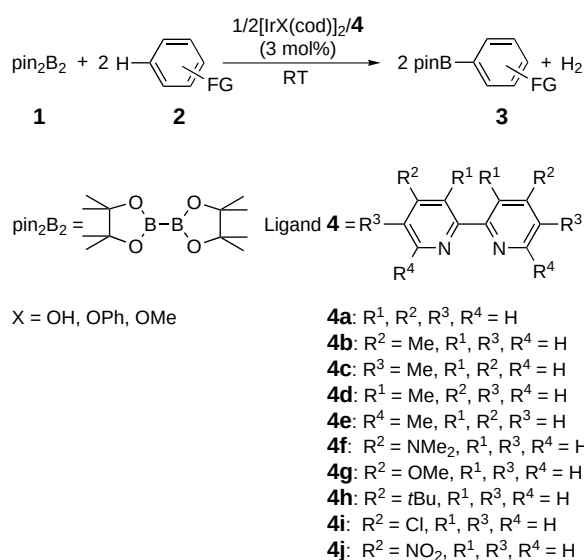
Tatsuo Ishiyama,* Jun Takagi, John F. Hartwig, and Norio Miyaura*

Increasing attention has been devoted to the direct functionalization of unreactive hydrocarbons by metal-catalyzed reactions because of their wide availability and low cost.^[1] A recently developed protocol for hydrocarbon functionalization provides a convenient and direct method for the synthesis of arylboron compounds by the C–H borylation of arenes by bis(pinacolato)diboron (pin_2B_2 , $\text{pin} = \text{Me}_2\text{C}_2\text{O}_2$) or pinacolborane (pinBH) catalyzed by $[\text{Cp}^*\text{Ir}(\text{PMe}_3)(\text{H})(\text{Bpin})]$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$),^[2] $[\text{Cp}^*\text{Re}(\text{CO})_3]$,^[3] $[\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)]$,^[4] $[\text{RhCl}(\text{P}(\text{t}Pr)_3)_2(\text{N}_2)]$,^[5] $[(\text{Cp}^*\text{-RhCl}_2)_2]$,^[5] $[(\eta^5\text{-C}_9\text{H}_7)\text{Ir}(\text{cod})]/\text{dppe}$ or dmpe ($\text{cod} = 1,5\text{-cyclooctadiene}$; $\text{dppe} = 1,2\text{-bis}(\text{diphenylphosphanyl})\text{ethane}$; $\text{dmpe} = 1,2\text{-bis}(\text{dimethylphosphanyl})\text{ethane}$),^[6] and $1/2[\text{IrCl}(\text{cod})]_2/2,2'\text{-bipyridine}$.^[7] Among them, iridium(III) complexes generated from $[\{\text{IrCl}(\text{cod})\}_2]$ and 2,2'-bipyridine (bpy) exhibited exceptionally high catalyst activity and turnover numbers in neat arene substrate at 80 °C.^[7] Moreover, the combination of $[\text{IrCl}(\text{coe})_2]_2$ ($\text{coe} = \text{cyclooctene}$) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) catalyzed the same reaction at room temperature.^[7] We report here the development of catalysts that allow for the first time the direct borylation of arenes or heteroarenes at room temperature in an inert solvent with a stoichiometric ratio of pin_2B_2 ^[8] (**1**) to arene (**2**) to produce the corresponding arylboronates (**3**) in high yields (Scheme 1).

During subsequent studies of the aromatic C–H borylation, we found that the effect of varying the anionic ligands (X) on iridium(III) precursors could provide a greater effect on catalyst

[*] Prof. T. Ishiyama, Prof. N. Miyaura, J. Takagi
Division of Molecular Chemistry
Graduate School of Engineering
Hokkaido University
Sapporo, 060-8628 (Japan)
Fax: (+81) 11-706-6562
E-mail: ishiyama@org-mc.eng.hokudai.ac.jp
miyaura@org-mc.eng.hokudai.ac.jp

Prof. J. F. Hartwig
Department of Chemistry
Yale University
P.O. Box 208107, New Haven, CT 06520-8107 (USA)



Scheme 1. Aromatic C–H borylation.

activity than varying the alkene ligands. To exploit this observation, we sought improved catalysts by studying the effect that variations on the (alkoxo)iridium(I) precursors (0.03 mmol of Ir) and substituents on the 2,2'-bipyridine ligands (**4**) (0.03 mmol) would have on the C–H borylation of neat benzene (60 mmol) by pin₂B₂ (**1**; 1.0 mmol) at room temperature (Table 1).

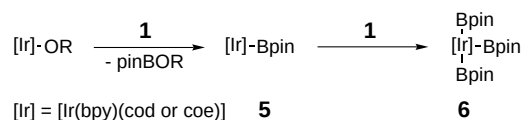
Although halide and cationic complexes containing a bpy ligand (**4a**) did not catalyze the reaction (Table 1, entries 1 and 2), air-stable iridium complexes possessing OH, OPh, or OMe ligands catalyzed the borylation within 4 h (Table 1, entries 3–5, respectively). Reactions conducted by preparing [Ir(OMe)(cod)]₂ from [IrCl(cod)]₂ and NaOMe in situ gave a comparable result (Table 1, entry 6). The less-basic

Table 1. Effect of ligands on the borylation of benzene by pin₂B₂ **1** at room temperature.^[a]

Entry	Ir ^I precursor	Ligand	Time [h]	Conversion ^[b] [%]	Yield ^[c] [%]
1	[IrCl(cod)] ₂	4a	24	0	0
2	[Ir(cod) ₂]BF ₄	4a	24	3	0
3	[Ir(OH)(cod)] ₂	4a	4	100	88
4	[Ir(OPh)(cod)] ₂	4a	4	100	84
5	[Ir(OMe)(cod)] ₂	4a	4	100	90
6	[IrCl(cod)] ₂ /4NaOMe	4a	4	100	73
7	[Ir(OAc)(cod)] ₂	4a	24	19	1
8	[Ir(OMe)(cod)] ₂	4b	4	100	89
9	[Ir(OMe)(cod)] ₂	4c	2	100	82
10	[Ir(OMe)(cod)] ₂	4d	8	100	60
11	[Ir(OMe)(cod)] ₂	4e	24	27	0
12	[Ir(OMe)(cod)] ₂	4f	2	100	89
13	[Ir(OMe)(cod)] ₂	4g	4	100	90
14	[Ir(OMe)(cod)] ₂	4h	4	100	83
15	[Ir(OMe)(cod)] ₂	4i	24	16	0
16	[Ir(OMe)(cod)] ₂	4j	24	46	0

[a] A mixture of pin₂B₂ (**1**; 1.0 mmol), benzene (60 mmol), an Ir^I precursor (0.03 mmol of Ir), and a ligand **4** (0.03 mmol) was stirred at 25 °C for the time given. [b] Conversions of pin₂B₂ (**1**). [c] GC yields based on boron atom in **1**.

OAc complex did not catalyze the reaction (Table 1, entry 7). The high catalyst efficiency of the (hydroxo)- or (alkoxo)iridium complexes can be attributed to the more facile formation of (boryl)iridium complexes. Tris(boryl)iridium(III) complexes (**6**) have been independently isolated by Marder et al.,^[9] Smith et al.,^[6] and Hartwig et al.^[7] as possible intermediates in the borylation of arenes. Presumably, mono-(boryl)iridium(I) complexes (**5**), which would be generated by oxidative addition of **1** to (alkoxo)iridium(I) complexes and **1**, undergo oxidative addition of **1** to yield **6** (Scheme 2).

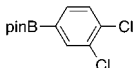
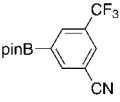
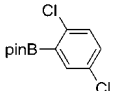
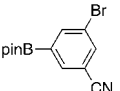
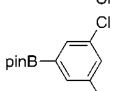
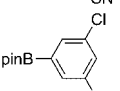
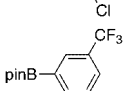
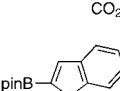
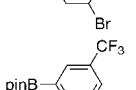
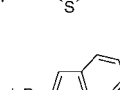
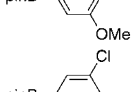
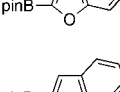


Scheme 2. Tris(boryl)iridium intermediate.

The steric and electronic effects of substituents in 2,2'-bipyridine ligand **4** are shown in (Table 1, entries 8–16).^[10] No large difference between the efficiency of catalysts bearing 4,4'- and 5,5'-dimethyl-2,2'-bipyridine (**4b** and **4c**) was observed at room temperature (Table 1, entries 8 and 9). In contrast, the catalyst bearing the 3,3'-dimethyl derivative (**4d**) was less active and gave a moderate yield (Table 1, entry 10). This result revealed the importance of a parallel arrangement of two pyridine rings. Complexes of the 6,6'-dimethyl derivative (**4e**) did not promote the reaction at all due to steric congestion around the iridium center (Table 1, entry 11). Further investigation of the electronic effect of 4,4'-disubstituted 2,2'-bipyridines revealed the superiority of electron-rich derivatives containing NMe₂, OMe, or *t*Bu groups (**4f**, **4g**, or **4h**) (Table 1, entries 12–14). Complexes of the electron-poor ligands with Cl or NO₂ groups (**4i** or **4j**) showed no catalyst activity at room temperature (Table 1, entries 15 and 16). Complexes of the NMe₂, OMe, and *t*Bu derivatives and of bpy itself exhibited catalyst activities at room temperature that were comparable to each other.

Although the borylation has been carried out in the presence of a large excess of substrate to pin₂B₂ (**1**) to avoid multiple borylation of arenes **2**, reaction of a stoichiometric amount of substrate in an inert solvent would be desirable for solid or expensive substrates. Among the solvents and catalysts screened, a combination of hexane and 1/2[Ir(OMe)(cod)]₂/dtbpy (**4h**) was found to be most effective for reactions of such stoichiometric ratios of **1** and **2** at room temperature that form arylboronates **3** (Table 2). The reactions were fast in nonpolar solvents, such as hexane, but the reactions were slow in more coordinating solvents and showed an order of reactivity of hexane > DME > DMF.^[11] The superiority of the dtbpy complex can be ascribed to its greater solubility in hexane. This protocol is suitable for the C–H borylation of disubstituted arenes that have one site for borylation and that can not undergo polyborylation. It is also suitable for the C–H borylation of benzo-fused

Table 2. Synthesis of arylboronates **3** (Scheme 1).^[a]

Entry	3	Time [h]	Yield ^[b] [%]	Entry	3	Time [h]	Yield ^[b] [%]
1		8	82	7		2	84
2		24	53	8		2	83
3		2	84	9		8	80
4		4	91	10		2	81
5		8	81	11		4	83
6		4	82	12		0.5	88

[a] A mixture of pin₂B₂ (**1**; 1.0 mmol), an arene **2** (2.0 mmol), [Ir(OMe)(cod)]₂ (0.015 mmol), and dtbpy (0.03 mmol) was stirred in hexane (6 mL) at 25 °C for the period shown in the Table. [b] GC yields based on boron atom in pin₂B₂ (**1**).

heteroarenes that have one site that is much more reactive than others.

Previous studies demonstrated that the borylation occurs at C–H bonds located *para* or *meta* to a substituent and does not occur at sterically hindered C–H bonds *ortho* to a substituent. In addition, there is a weak electronic effect that directs reaction at the more electron-poor carbon.^[7] Thus, the reaction occurs regiospecifically with disubstituted arenes **2**. 1,2-, 1,4-, and 1,3-Dichlorobenzenes all gave a single product **3** (Table 2, entries 1–3). The reaction at the *o*-carbon atom of the 1,4 isomer was slow due to steric hindrance of the substituent. The borylation of 1,3-disubstituted **2** selectively occurred only at the common *meta* position; therefore, isomerically pure **3** were obtained in excellent yields even with two distinct substituents on **2** (Table 2, entries 4–9). The reaction was suitable for **2** possessing a wide variety of functional groups, such as Cl, Br, I, CF₃, OMe, CO₂Me, and CN. The borylation of benzo[*b*]thiophene, benzo[*b*]furan, or indole in hexane occurred selectively at the 2-position because the C–H bond at the 2-position in these substrates is activated by the heteroatom (Table 2, entries 10–12).^[12]

In summary, iridium complexes comprised of [Ir(OMe)(cod)]₂ and 4,4'-di-*tert*-butyl-2,2'-bipyridine are highly active catalysts for the aromatic C–H borylation by bis(pinacolato)-diboron. This high activity allowed for the first room temperature borylation of arenes with a stoichiometric amount of arene to produce the corresponding arylboronates in high yields. With this advance, the aromatic C–H borylation provides a practical tool for preparing arylboronates. The catalytic C–H borylation of other hydrocarbons is being actively investigated.

Experimental Section

A representative procedure for **3**: A flask containing [Ir(OMe)(cod)]₂ (0.015 mmol), dtbpy (0.03 mmol), and pin₂B₂ (**1**; 1.0 mmol) was flushed with nitrogen, and then charged with hexane (6 mL) and 1,2-dichlorobenzene (2.0 mmol). The mixture was then stirred at 25 °C for 8 h. The product was isolated by Kugelrohr distillation to give an analytically pure sample: ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 1.34 (s, 12H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.60 (dd, *J* = 1.3 and 7.9 Hz, 1H), 7.87 ppm (d, *J* = 1.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25 °C, TMS): δ = 24.82, 84.32, 129.99, 132.24, 133.73, 135.48, 136.54 ppm; ¹¹B NMR (128 MHz, CDCl₃, 25 °C, BF₃·OEt₂): δ = 30.61 ppm; HRMS calcd for C₁₂H₁₅BCl₂O₂: 272.0542; found: 272.0515.

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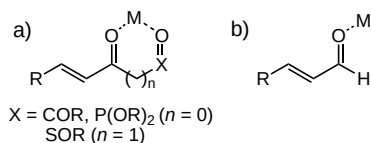
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Highly Enantioselective Inverse-Electron-Demand Hetero-Diels–Alder Reactions of α,β -Unsaturated Aldehydes**

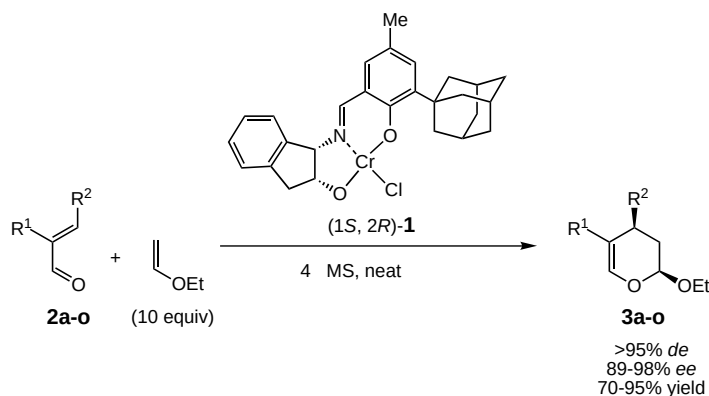
Karl Gademann, David E. Chavez, and Eric N. Jacobsen*

Dihydro- and tetrahydropyran derivatives are prevalent structural subunits in a variety of biologically important compounds, including carbohydrates, pheromones, iridoids, and polyether antibiotics. The inverse-electron-demand hetero-Diels–Alder (HDA) reaction of oxabutadienes with electron-rich olefins is a synthetically attractive route to such heterocycles, allowing the direct formation of dihydropyran derivatives with up to three stereogenic centers in one convergent step from simple achiral precursors.^[1] Although there are numerous diastereoselective variants of the inverse-electron-demand HDA reaction known,^[2] very few examples of catalytic, enantioselective versions have been identified to date.^[3] The scope of reported methods is limited to oxabutadiene derivatives bearing electron-withdrawing groups such as sulfone groups,^[3a] phosphonate groups,^[3b] or ester groups.^[3c] These ancillary groups serve both to activate the oxadiene electronically and to anchor the substrate to the catalyst by two-point binding (Scheme 1a). Chelation in this manner appears to be essential for attaining good reactivity and stereoselectivity.



Scheme 1. a) Two-point binding of oxabutadiene derivatives to a Lewis acid (M = Lewis acid); b) one-point binding of an α,β -unsaturated aldehyde to a Lewis acid.

Development of asymmetric inverse-demand HDA reactions involving simple α,β -unsaturated aldehyde substrates would expand the utility of this methodology significantly (Scheme 2).^[4] This task presents a clear challenge, however, which requires effective activation and enantiofacial discrimination of the carbonyl solely through one-point binding to catalyst (Scheme 1b), while simultaneously avoiding unproductive decomposition of the sensitive oxadiene and electron-



Scheme 2. Hetero-Diels–Alder reactions catalyzed by **1**; MS = molecular sieves, *de* = diastereomeric excess.

rich dienophile partners. Herein we describe the first example of a successful solution to this problem, in the highly enantioselective (Schiff base) Cr^{III} -catalyzed HDA reactions of alkyl vinyl ethers with α,β -unsaturated aldehydes.

The tridentate (Schiff base)chromium complex (**1**, see Scheme 2) has been identified as a highly diastereoselective and enantioselective catalyst in hetero-Diels–Alder (HDA) reactions between aldehydes and mono-oxygenated 1,3-diene derivatives.^[5] The crucial feature of this catalyst system lies in its ability to effect activation of simple aldehydes toward pericyclic reactions with only mildly nucleophilic partners, with concomitant high enantioselectivity.^[6] With an eye toward determining whether such properties might be extended to reactions of conjugated aldehydes, we evaluated the reaction of crotonaldehyde and ethyl vinyl ether as a model system for the inverse-demand HDA. The uncatalyzed HDA reaction takes place only at elevated temperatures and pressures, yielding the corresponding dihydropyran **3a** in good yields but poor *endo/exo* selectivity.^[7] We were encouraged to find that the same reaction proceeded in the presence of 4 Å molecular sieves with 5 mol % **1**^[8] in *tert*-butyl methyl ether (TBME) or CH_2Cl_2 solution at RT to provide **3a** with excellent diastereoselectivity (*endo/exo* > 96:4),^[9] and promising enantioselectivity (72–78% *ee*; *ee* = enantiomeric excess). Unfortunately, aldehyde conversions of only approximately 20% were achieved using 1:1 molar ratios of the reactants at 1 M concentration. A dramatic improvement was observed in reactions carried out under solvent-free conditions and excess ethyl vinyl ether^[10] (94% *ee* and 75% isolated yield, Table 1, **2a**). Indeed, introduction of solvents (CH_2Cl_2 , toluene, acetone, and *tert*-butyl methyl ether) generally resulted in significantly lower enantioselectivity in the cycloaddition (40–80% *ee*). Ethyl vinyl ether was shown to be the optimal dienophile partner. The selectivity and reactivity decreased as the steric bulk of the alkyl group was increased ($\text{Et} > n\text{Pr} > n\text{Bu} \approx i\text{Bu}$), to the point that *tert*-butyl vinyl ether was found to be unreactive.

With these reaction parameters defined, a variety of aldehydes were examined in the inverse-electron-demand HDA reaction with ethyl vinyl ether (Table 1). A wide range of α,β -unsaturated aldehydes bearing aliphatic β substituents (**2a–e**) underwent cycloaddition with high enantioselectivity

[*] Prof. Dr. E. N. Jacobsen, Dr. K. Gademann, D. E. Chavez
 Department of Chemistry and Chemical Biology
 Harvard University
 Cambridge, MA 02138 (USA)
 Fax: (+1) 617-496-1880
 E-mail: jacobson@chemistry.harvard.edu

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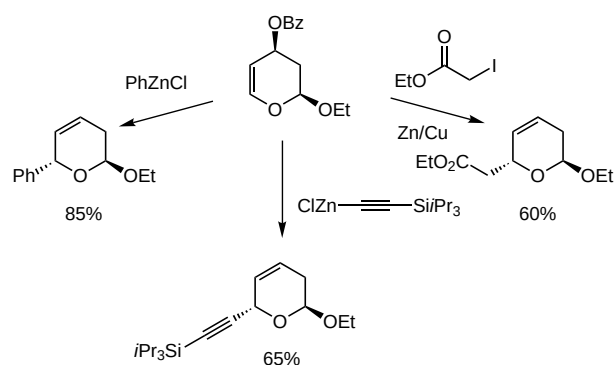
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Table 1. Asymmetric inverse-electron-demand hetero-Diels–Alder reactions of α,β -unsaturated aldehydes with ethyl vinyl ether, catalyzed by **1**.^[a]

Aldehyde	R ¹	R ²	Catalyst loading [mol %] ^[b]	Reaction time [h]	Yield [%] ^[c]	ee [%] ^[d]
2a	H	Me	5	24	75	94
2b	H	Et	5	48	75	94
2c	H	<i>i</i> Pr	10	48	72	94
2d	H	<i>n</i> Pr	5	48	73	94
2e	H	<i>n</i> Bu	5	48	70	95
2f	H	Ph	10	48	75	98
2g	H	4-MeO-C ₆ H ₄	10	96	40	98
2h	H	4-NO ₂ -C ₆ H ₄	10	72	90	98
2i	H	2-NO ₂ -C ₆ H ₄	10	120	80	98
2j	H	CH ₂ OBn	5	24	90	95
2k	H	CH ₂ OTBS	5	24	95	92
2l	H	CO ₂ Et	5	24	90	95
2m	H	OBz	5	48	80	89
2n	Br	Ph	5	48	75	98
2o	Me	Me	7	96	75	92

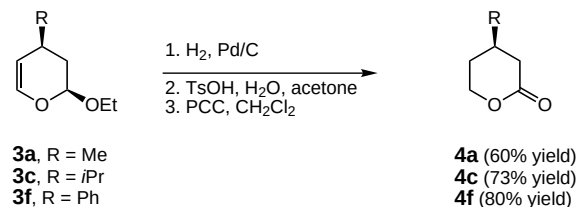
[a] Reactions were performed with aldehyde (1 mmol) and ethyl vinyl ether (10 equiv), in the presence of finely powdered 4 Å molecular sieves (150 mg). [b] Catalyst loadings refer to the amount of chromium employed, assuming the molecular structure depicted in Scheme 2. [c] Product isolation was accomplished by dilution of the reaction mixture with pentane, filtration, and distillation or column chromatography. Yields given are after isolation. [d] Enantioselectivities were determined either by HPLC or GC analysis, using commercially available chiral stationary phases. For details see the Supporting Information.

(94–95% *ee*, 70–75% yield). Whereas use of 5 mol % catalyst was adequate in most cases, the sterically more demanding 4-methyl-2-pentenal (**2c**) required 10 mol % of **1** to attain complete conversion within 48 h. Cinnamaldehyde derivatives (**2f–i**) underwent reactions with ethyl vinyl ether with very high enantioselectivity, and excellent diastereoselectivity. Substrates bearing functionality within R² (e.g. **2j–l**) were among the very best in all respects, displaying good reactivity and consistently high enantioselectivity and yields (92–95% *ee*, 90–95% yield). The successful application of 3-benzoylacrolein (**2m**) in the HDA reaction provides ready access to the 4-benzoyl-substituted dihydropyran derivative, a versatile intermediate poised for an assortment of useful substitution reactions (Scheme 3).^[11] Finally, the promising scope of this method is illustrated further by the demonstrated tolerance for substituents at the 2-position of the aldehyde. Both 2-bromocinnamaldehyde (**2n**) and 2-methyl-2-butenal (**2o**) provided cycloadducts with high enantioselectivity.



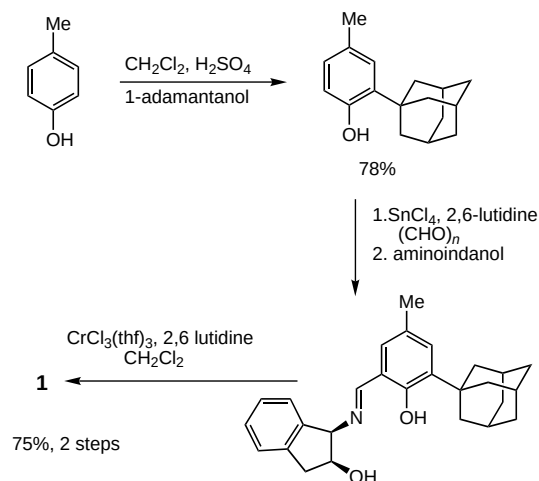
Scheme 3. Substitution reactions of the dihydropyran derivative **3m**, Bz = benzyl.

The absolute configuration of the products was established by conversion into the known 4-substituted pyranones (Scheme 4).^[12] Thus, reduction of the dihydropyrans **3a**, **3c**, and **3f** with H₂ in the presence of Pd on charcoal, followed by hydrolysis (TsOH, H₂O, acetone; Ts = tosyl) and pyridinium chlorochromate (PCC) oxidation of the resulting lactol afforded the corresponding lactones (**4**). This straightforward procedure provides a relatively concise and high-yielding (60–80% overall) route to synthetically useful 4-substituted pyranone derivatives in an enantioenriched form.^[13]



Scheme 4. Preparation of β -substituted pyranones from dihydropyrans **3a**, **3c**, and **3f**.

In an effort to render the HDA methodology as useful and accessible as possible, we have devised a new and significantly improved synthesis of catalyst **1** (Scheme 5).^[14] As compared



Scheme 5. Practical synthesis of catalyst (1*R*,1*S*)-**1**.

to the procedure disclosed previously,^[5] the new route avoids the use of sensitive and expensive Cr^{II} salts and can be carried out conveniently on the bench. More significant, it provides material of higher quality with respect to its chemical properties. In particular, compound **1** obtained from the new procedure requires no aging with molecular sieves to attain optimal performance, and confers 5–10% higher enantioselectivity than does catalyst prepared by the original procedure.^[15]

Insight into the basis for stereoinduction in these cycloaddition reactions will rely on a detailed understanding of the mechanism of catalysis. In this context, inspection of the crystal structure of **1** may provide a valuable starting point (Figure 1).^[16] In the solid state, catalyst **1** exists as a dimeric

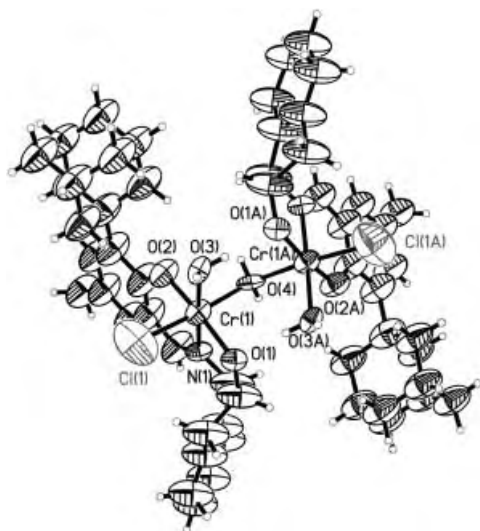


Figure 1. X-ray crystal structure of catalyst **1**; ellipsoids drawn at the 50 % probability level.

structure, bridged through a single water molecule and bearing one terminal water ligand on each chromium center. On the basis of preliminary solution molecular-weight and kinetic studies,^[17] it appears that this dimeric structure is maintained in the catalytic cycle. Dissociation of a terminal water molecule to open a coordination site for complexation of the aldehyde substrate is expected to be energetically difficult, and may serve to explain the crucial role of molecular sieves in these reactions.^[18]

In summary, the scope of (Schiff base)Cr^{III}-catalyzed cycloaddition reactions has been expanded to inverse-demand HDA reactions of simple α,β -unsaturated aldehydes. The broad range of aldehydes utilized effectively by catalyst **1** allows access to a series of synthetically useful dihydropyran derivatives in a highly enantioenriched form. Future studies will be directed toward further extending the scope of this promising methodology in the context of more elaborate intermediates and natural product targets.

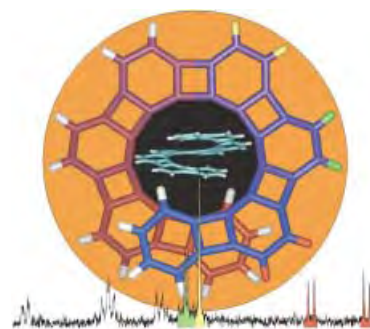
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- [17] R. T. Ruck, E. N. Jacobsen, unpublished results.
- [18] No cycloaddition is observed in the absence of dessicant. For a discussion on a related system, see ref [6].

COVER PICTURE

The cover picture shows the molecular structure of the helically extended angular [8]phenylene. An unprecedented cobalt-catalyzed triple cyclization of an appropriate nonayne was successful in assembling the largest crystallographically characterized helical phenylene (heliphen). Its properties are intriguing; the heliphen is unusually configurationally labile and has a strongly attenuated bathochromic increment in the UV spectrum, shielding of the terminal rings as a result of spatial overlap, and alternating ring-current intensities along the angular frame. The X-ray crystallographic data detail the helical and σ - π distortive features. Most surprisingly, the remarkable flexibility of the heliphen provided an unusually low barrier ($\Delta G^\ddagger$ (-4.5°C) = $13.4 \pm 0.4 \text{ kcal mol}^{-1}$) for enantiomerization. The ^1H NMR spectrum was consistent with the alternation of cyclohexatrienoid and aromatic character; the terminal rings are the most diatropic and the penultimate ones the least. Further details about this chiral polycyclic benzenoid hydrocarbon are described by K. P. C. Vollhardt, et al. on p 3227 ff.

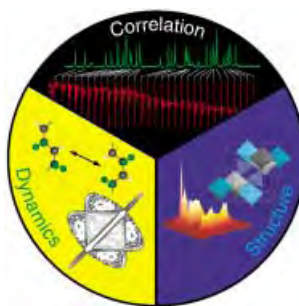


REVIEWS

Contents

Broad, uninterpretable bands in solid-state NMR spectra are a thing of the past. Modern implementations of methods such as magic-angle spinning, cross polarization, hetero- and homonuclear decoupling and recoupling, etc., allow one to obtain multidimensional correlation spectra with a resolution as good as that of liquid-state NMR spectra. In addition, anisotropy parameters characteristic of solids are accessible.

Angew. Chem. **2002**, *114*, 3224–3259



D. D. Laws, H.-M. L. Bitter,
A. Jerschow* 3096–3129

Solid-State NMR Spectroscopic Methods
in Chemistry

Keywords: multipulse techniques • NMR spectroscopy • solid-state structures • spin-spin coupling • structure elucidation

Get your teeth into this! Calcium phosphates such as polycrystalline fluoroapatite (top picture) are common minerals which can also be formed in living organisms. This process (biomineralization) is not yet fully understood. A thorough understanding of the structure, formation, and resolution of biominerals should lead to improved treatment of, for example, bone diseases by use of endoprostheses (bottom picture). The significance of biological tissues containing calcium phosphates is reviewed from a chemical point of view, and explained with examples.

Angew. Chem. **2002**, *114*, 3260–3277



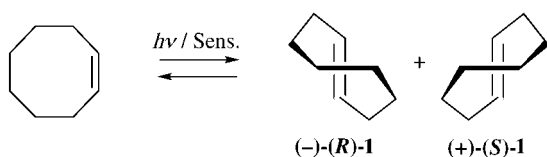
S. V. Dorozhkin, M. Epple* 3130–3146

Biological and Medical Significance of Calcium Phosphates

Keywords: bioinorganic chemistry • biomaterials • biomimetic synthesis • biomineralization • materials science

MINIREVIEW

Researching the origins of chirality leads to a strong interest in selective and atom-economic syntheses of enantiomerically pure target molecules from non-chiral starting materials. New developments in the field of asymmetric photochemistry (as an example see the photochemical *cis*–*trans* isomerization in which the chiral cyclooctene **1** is formed; Sens = sensitizer) and photochirogenesis are described with special emphasis on absolute asymmetric synthesis.



Angew. Chem. **2002**, *114*, 3279–3286

A. G. Griesbeck,*

U. J. Meierhenrich* 3147–3154

Asymmetric Photochemistry and Photochirogenesis

Keywords: asymmetric synthesis • chirality • photochemistry • photochirogenesis

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.org>

Metallabenzenes and Valence Isomers: Synthesis and Characterization of a Platinabenzene

V. Jacob, T. J. R. Weakley, M. M. Haley* ◆

The Total Synthesis of Diazonamide A

K. C. Nicolaou,* M. Bella, D. Y.-K. Chen, X. Huang, T. Ling, S. A. Snyder ◆

Syntheses and Crystal Structures of the New Ag-S Clusters [Ag₇₀S₁₆(SPh)₃₄(PhCO₂)₄(triphos)₄] and [Ag₁₈₈S₉₄(PnPr₃)₃₀]

X.-J. Wang, T. Langetepe, C. Persau, B.-S. Kang, D. Fenske*

Protonated Benzene: IR Spectrum and Structure of C₆H₇⁺

N. Solcà, O. Dopfer*

Single-Step Assembly of a C₂-Symmetrical Palladium(IV) Spirocyclic Complex

Y. Yamamoto,* T. Ohno, K. Itoh

Changeable Pore Sizes Allowing Effective and Specific Recognition by a Molybdenum-Oxide Based “Nanosponge”: En Route to Sphere-Surface and Nanoporous-Cluster Chemistry

A. Müller,* E. Krickemeyer, H. Bögge, M. Schmidtman, S. Roy, A. Berkle

A great researcher, communicator, and human being: Not only was Max Perutz (see picture) a very gifted chemist who shared the Nobel prize for chemistry with John Kendrew in 1962 for their pioneering work on the elucidation of the structures of hemoglobin and myoglobin, he was also the chairman of the extremely successful Laboratory of Molecular Biology. Above all, he was magnanimous and extraordinarily generous, according everyone the same level of respect.



Angew. Chem. **2002**, *114*, 3287–3298

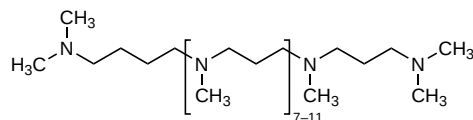
J. M. Thomas* 3155–3166

The Scientific and Humane Legacy of Max Perutz (1914–2002)

Keywords: history of science • Nobel Prize • obituary • Perutz, Max

HIGHLIGHT

Directed precipitation of silicic acid during the formation of diatom cell walls is promoted by polyamines (see picture) and peptides. These species-specific organic matrices, which direct the biomineralization process to amorphous SiO₂, are accessible only after dissolution of the silica cell wall with hydrogen fluoride.



Angew. Chem. **2002**, *114*, 3299–3301

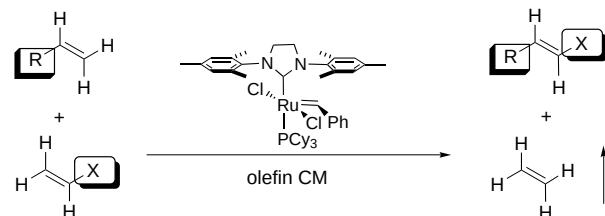
G. Pohnert* 3167–3169

Biomineralization in Diatoms Mediated through Peptide- and Polyamine-Assisted Condensation of Silica

Keywords: biomineralization • biosynthesis • diatoms • enzymes • silicates

COMMUNICATIONS

Stereoselective and chemoselective olefin cross metathesis can be viewed as a highly selective and efficient set of reactions that provide the same products as would selective C–H activation and allylic oxidation (see scheme for an example). More active catalyst systems will provide an efficient process to functionalized products from readily available olefins. Cy = cyclohexyl.



Angew. Chem. **2002**, *114*, 3303–3306

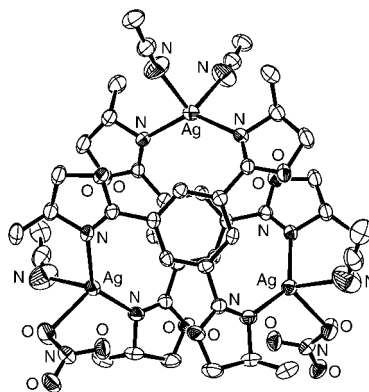
A. K. Chatterjee,
R. H. Grubbs* 3171–3174

Formal Vinyl C–H Activation and Allylic Oxidation by Olefin Metathesis

Keywords: alkenes • C–H activation • cross-coupling • metathesis



Self-recognition of ligand chirality leads to the completely stereospecific self-assembly of a propeller-shaped supramolecular capsule induced by a rigid chiral tris(oxazoline) acting as a tris-monodentate ligand and Ag^I metal ions having a tetrahedral coordination geometry (the structure of one helical complex is shown).



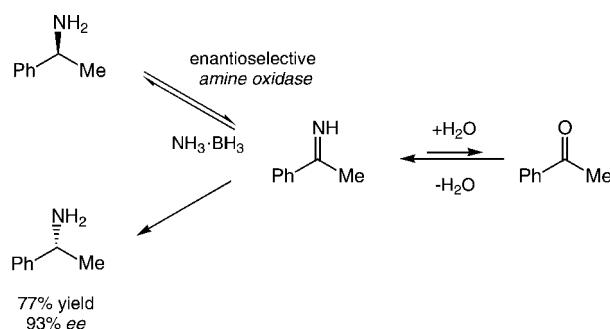
Angew. Chem. **2002**, *114*, 3306–3309

H.-J. Kim, D. Moon, M. S. Lah,
J.-I. Hong* 3174–3177

An Enantiomerically Pure Propeller-Shaped Supramolecular Capsule Based on the Stereospecific Self-Assembly of Two Chiral Tris(oxazoline) Ligands around Three Ag^I Ions

Keywords: chirality • self-assembly • silver • supramolecular chemistry

Both the catalytic activity and enantioselectivity of the amine oxidase used in the deracemization of D,L- α -methylbenzylamine (see scheme) have been enhanced by in vitro evolution methods to give α -methylbenzylamine in 77% yield and 93% *ee*.



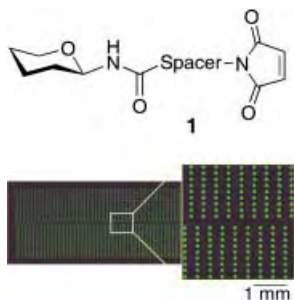
Angew. Chem. **2002**, *114*, 3309–3312

M. Alexeeva, A. Enright, M. J. Dawson,
M. Mahmoudian,
N. J. Turner* 3177–3180

Deracemization of α -Methylbenzylamine
Using an Enzyme Obtained by In Vitro
Evolution

Keywords: amino acids •
deracemization • enzyme catalysis •
reduction

A new tool for the high-throughput study of carbohydrate–protein interactions: Maleimide-linked carbohydrates (e.g. **1**) were immobilized on thiol-derivatized glass slides, and the microspots were probed with fluorescein-labeled lectins (see picture). The binding of lectins to the carbohydrates on the slide depends on the concentration of the immobilized carbohydrates and on the length of the tethers.



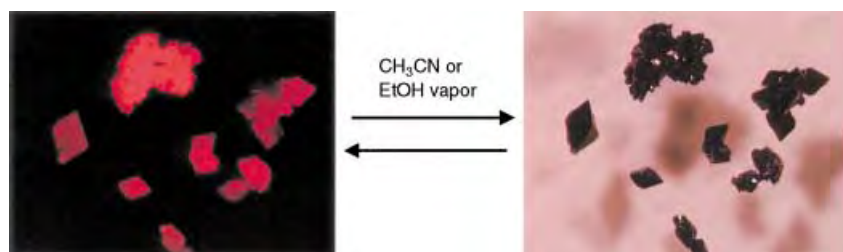
Angew. Chem. **2002**, *114*, 3312–3314

S. Park, I. Shin* 3180–3182

Fabrication of Carbohydrate Chips for
Studying Protein–Carbohydrate
Interactions

Keywords: carbohydrate chips •
fluorescence • glycoconjugates • high-
throughput screening • proteins

Remarkable vapochromic effects are observed in a dinuclear platinum(II) complex, where changes in luminescence are facilitated in the presence of solvated organic molecules, such as acetonitrile and ethanol (see scheme).



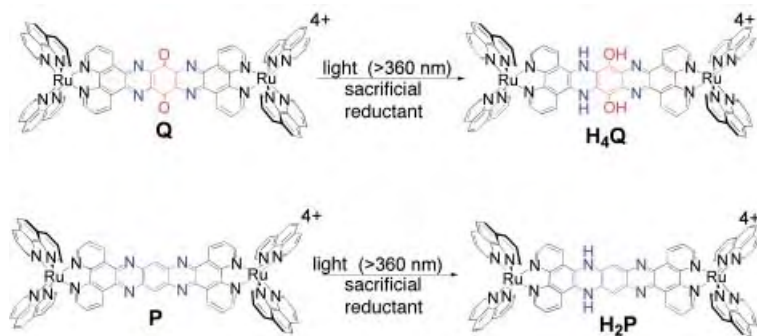
Angew. Chem. **2002**, *114*, 3315–3317

M. Kato,* A. Omura, A. Toshikawa,
S. Kishi, Y. Sugimoto 3183–3185

Vapor-Induced Luminescence Switching
in Crystals of the *Syn* Isomer of a
Dinuclear (Bipyridine)platinum(II)
Complex Bridged with Pyridine-2-
Thiolate Ions

Keywords: luminescence • platinum •
sensors • structure elucidation •
vapochromism

Reversible storage of up to two or four electrons is possible in complexes **P** and **Q**, respectively, upon irradiation with visible light in the presence of triethylamine. This ability could lead to photocatalysts capable of concerted multielectron reduction of important substrates.



Angew. Chem. **2002**, *114*, 3317–3319

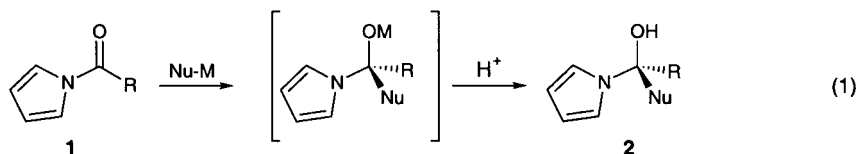
R. Konduri, H. Ye, F. M. MacDonnell,*
S. Serroni, S. Campagna,
K. Rajeshwar 3185–3187

Ruthenium Photocatalysts Capable of
Reversibly Storing up to Four Electrons in
a Single Acceptor Ligand: A Step Closer
to Artificial Photosynthesis

Keywords: bridging ligands •
multielectron storage • photochemistry •
ruthenium • spectroelectrochemistry



Sufficiently stable intermediates formed in the reaction of *N*-acylpyrroles (**1**) with hydride and Grignard reagents can undergo further synthetic transformations and chromatographic purification to enable the generation of pyrrolecarbinols **2** in 76–95 % yields [Eq. (1)].



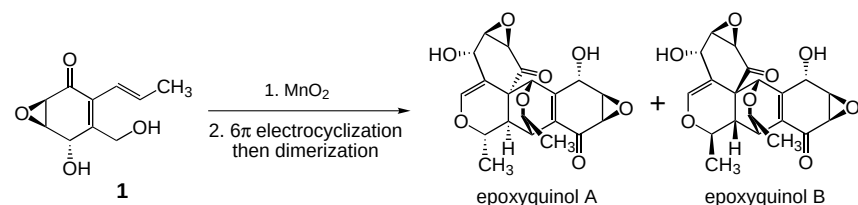
Angew. Chem. **2002**, *114*, 3320–3323

D. A. Evans,* G. Borg,
K. A. Scheidt 3188–3191

Remarkably Stable Tetrahedral
Intermediates: Carbinols from
Nucleophilic Additions to *N*-Acylpyrroles

Keywords: carbinols • nitrogen
heterocycles • nucleophilic addition •
reaction intermediates • reaction
mechanisms

A highly stereoselective HfCl₄-mediated Diels–Alder reaction of furan and the chiral acrylate ester of Corey's auxiliary to subsequently give **1**, and the realization of the postulated biosynthetic pathway for the construction of epoxyquinols A and B, namely, oxidative 6 π electrocyclicization, followed by Diels–Alder reaction of the unprotected monomer are the key steps in the asymmetric total synthesis of (+)-epoxyquinols A and B.



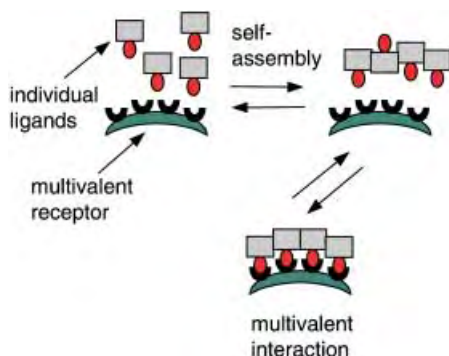
Angew. Chem. **2002**, *114*, 3324–3326

M. Shoji, J. Yamaguchi, H. Kakeya,
H. Osada, Y. Hayashi* 3192–3194

Total Synthesis of (+)-Epoxyquinols A
and B

Keywords: asymmetric synthesis •
Diels–Alder reaction • dimerization •
epoxyquinol • total synthesis

Size is important: Noncovalent nanoparticles are formed by the self-assembly of glycodendrimers containing both a ligand and a self-assembling moiety. Particle size reaches an optimum at the second and third generation, larger dendritic species show less efficient self-assembly. It is the nanoparticles, not the individual molecules, that governs their potency as polyvalent receptor blockers (see scheme), both in vitro and in vivo.



Angew. Chem. **2002**, *114*, 3327–3330

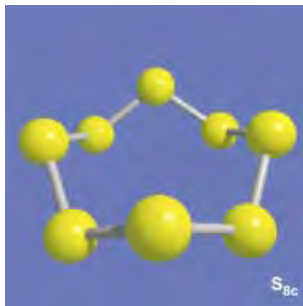
G. Thoma,* A. G. Katopodis,
N. Voelcker, R. O. Duthaler,
M. B. Streiff 3195–3198

Novel Glycodendrimers Self-Assemble to
Nanoparticles which Function as
Polyvalent Ligands In Vitro and In Vivo

Keywords: aggregation • carbohydrates •
dendrimers • polyvalence •
supramolecular chemistry



A challenging problem is the structure determination of liquid sulfur. By using a quantum thermodynamical model the authors found that liquid sulfur below the λ -transition temperature is predominantly built upon cyclic structures S_{8c} (see structure) accompanied by trace amounts of other ring structures such as S_{7c}, S_{6c}, S_{9c}, S_{10c}, and S_{12c}.



Angew. Chem. **2002**, *114*, 3331–3335

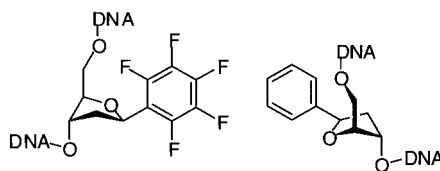
R. Ludwig,* J. Behler, B. Klink,
F. Weinhold 3199–3202

Molecular Composition of Liquid Sulfur

Keywords: ab initio calculations • density
functional calculations • liquids • sulfur •
structure elucidation

The inverse quadrupolar moments

of the phenyl and pentafluorophenyl residues in the non-hydrogen-bonded, artificial base pair shown here promotes strong intramolecular stacking interactions in oligonucleotide duplexes. The greater the number of natural base pairs that are replaced by this novel pair, the higher the thermodynamic stability of the resulting oligonucleotide duplex if they are arranged in an alternating fashion.



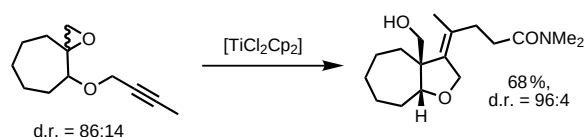
Angew. Chem. **2002**, *114*, 3335–3338

G. Mathis, J. Hunziker* 3203–3205

Towards A DNA-Like Duplex without Hydrogen-Bonded Base Pairs

Keywords: DNA recognition • DNA structures • nucleobases • oligonucleotides • pi interactions

Intramolecular C–C bond formation based on a titanocene-catalyzed epoxide ring opening selectively leads to tri- and tetrasubstituted olefins (see scheme). This represents an excellent method for the otherwise difficult synthesis of such compounds.



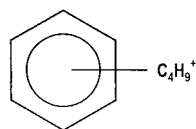
Angew. Chem. **2002**, *114*, 3341–3343

A. Gansäuer,* M. Pierobon, H. Blum 3206–3208

Stereoselective Synthesis of Tri- and Tetrasubstituted Olefins by Tandem Cyclization Addition Reactions Featuring Vinyl Radicals

Keywords: alkenes • diastereoselectivity • domino reactions • radical reactions • titanium

Constantly in motion: The attack of the *tert*-butyl cation on benzene gives a π complex whose stability is similar to that of the σ complex. The frequently employed notation for real or proposed π complexes (see picture) has now to be interpreted as indicating the mobility of the cation along the ring periphery: the position of the cation above the delocalized π -electron belt cannot be established.



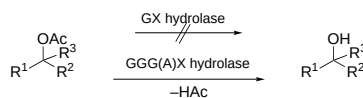
Angew. Chem. **2002**, *114*, 3343–3346

D. Heidrich* 3208–3210

Do Isopropyl and *tert*-Butyl Cations Form π Complexes with Benzene?

Keywords: ab initio calculations • arenes • aromatic substitution • carbocations • electrophilic substitution

A single amino acid pattern (GGG(A)X motif) in hydrolases controls their activity towards tertiary alcohols. Consequently, a range of active lipases and esterases which catalyze the efficient conversion of acetates of different tertiary alcohols (see scheme) and thereby facilitate access to this class of building blocks for organic synthesis, flavors, and fragrances was identified by sequence comparison. Hydrolases bearing an alternative GX motif were inactive.



Angew. Chem. **2002**, *114*, 3338–3341

E. Henke, J. Pleiss, U. T. Bornscheuer* 3211–3213

Activity of Lipases and Esterases towards Tertiary Alcohols: Insights into Structure–Function Relationships

Keywords: biotransformation • enzyme catalysis • esterases • lipases • molecular modeling • tertiary alcohols

Teaching an old ion new tricks: Zintl ions can be used as building blocks to construct complex structures with interesting electronic properties. The reaction of Ge_9 ions with elementary mercury leads to the unusual polymer $^1[\text{HgGe}_9]^{2-}$ (see picture) which is structurally characterized in the form of its $\text{K}[2.2.2]\text{cryptand}$ salt.



Angew. Chem. **2002**, *114*, 3352–3355

A. Nienhaus, R. Hauptmann, T. F. Fässler* 3213–3215

$^1[\text{HgGe}_9]^{2-}$ —A Polymer with Zintl Ions as Building Blocks Covalently Linked by Heteroatoms

Keywords: cluster compounds • germanium • mercury • polymers • Zintl anions



Single-molecule sequencing comes into sight: exonuclease III of *E. coli* has been shown to perform the processive sequential hydrolysis of double-stranded DNA with one strand being completely rhodamine-labeled at each pyrimidine base. The performance of the exceptional enzyme was studied by steady-state kinetic analysis based on quantitative fragment-length determination.

Angew. Chem. **2002**, *114*, 3350–3352

S. Brakmann,*

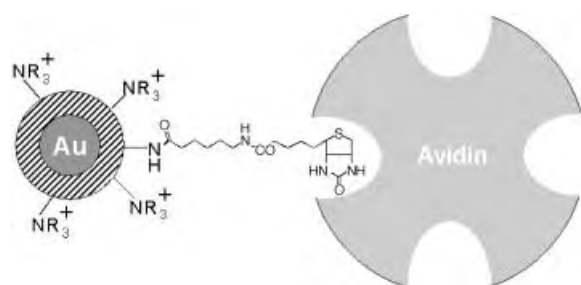
S. Löbermann 3215–3217

A Further Step towards Single-Molecule Sequencing: *Escherichia coli* Exonuclease III Degrades DNA that is Fluorescently Labeled at Each Base Pair

Keywords: exonuclease • fluorescence • nucleotides • phosphoric ester hydrolysis • sequence determination



An ambitious goal in the area of nanobiosciences is to combine the functionality and stability of nanostructured inorganic solids with the structural variety and the self-organizing abilities of biochemical molecules. How the ligand shell of nanoparticles needs to be built up to achieve a stable and specific conjugation with biological molecules and to coordinate the chemical properties of nanoparticles and biomolecules is exemplified for gold nanoparticles conjugated with avidin (see picture).



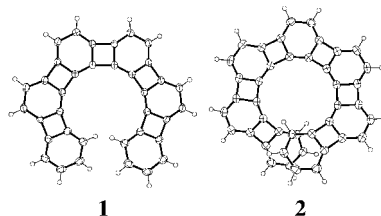
Angew. Chem. **2002**, *114*, 3346–3350

A. Schroedter, H. Weller* .. 3218–3221

Ligand Design and Bioconjugation of Colloidal Gold Nanoparticles

Keywords: colloids • conjugation • nanostructures • sol–gel processes • supramolecular chemistry

Two plus two plus two times two: A double cobalt-catalyzed cycloisomerization was used to convert appropriate hexaynes into hydrocarbons **1** and **2**. Their X-ray structures reveal pronounced helical topologies, but their barriers to enantiomerization are low compared to those of the helicenes.



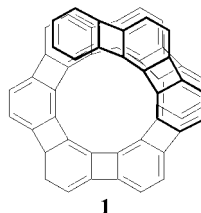
Angew. Chem. **2002**, *114*, 3357–3361

S. Han, A. D. Bond, R. L. Disch, D. Holmes, J. M. Schulman, S. J. Teat, K. P. C. Vollhardt,*
G. D. Whitener 3223–3227

Total Syntheses and Structures of Angular [6]- and [7]Phenylene: The First Helical Phenylenes (Heliphenes)

Keywords: antiaromaticity • cyclotrimerization • helical structures • phenylenes • small ring systems

Six of the final cyclobutadiene rings in angular [8]phenylene and [9]phenylene (**1**) are closed in an unprecedented cobalt-catalyzed triple cyclization of appropriate nonaynes. These strained products are the largest known phenylenes and display unusual configurational lability. Their synthesis has enabled a first estimate of the properties of the hypothetical polyheliphenes.



Angew. Chem. **2002**, *114*, 3361–3364

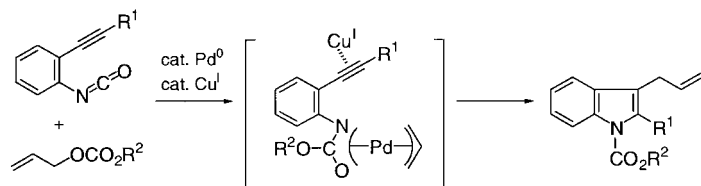
S. Han, D. R. Anderson, A. D. Bond, H. V. Chu, R. L. Disch, D. Holmes, J. M. Schulman, S. J. Teat, K. P. C. Vollhardt,*
G. D. Whitener 3227–3230

Total Syntheses of Angular [7]-, [8]-, and [9]Phenylene by Triple Cobalt-Catalyzed Cycloisomerization: Remarkably Flexible Heliphenes

Keywords: antiaromaticity • cyclotrimerization • helical structures • phenylenes • small ring systems



Carboamination of alkynes is catalyzed by a Pd^0 – Cu^I bimetallic species. The Pd^0 species act as a precursor for a π -allylpalladium intermediate while the Cu^I centers behave as a Lewis acid for $\text{C}\equiv\text{C}$ bonds. This catalyst allows the synthesis of indoles from isocyanates and allyl carbonates (see scheme).



Angew. Chem. **2002**, *114*, 3364–3367

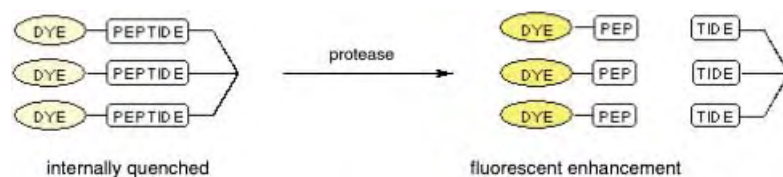
S. Kamijo, Y. Yamamoto* ... 3230–3233

A New Pd^0 – Cu^I Bimetallic Catalyst for the Synthesis of Indoles from Isocyanates and Allyl Carbonates

Keywords: carboamination • copper • homogeneous catalysis • indoles • palladium



A way to reduce the synthetic work associated with FRET-based techniques for protease analysis and characterization is shown here. Protease-mediated cleavage of fluorescent peptides attached to dendrimers results in large increases in fluorescence (see scheme).



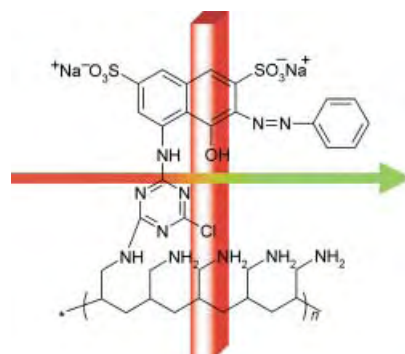
Angew. Chem. **2002**, *114*, 3367–3370

J. M. Ellard, T. Zollitsch, W. J. Cummins, A. L. Hamilton, M. Bradley* 3233–3236

Fluorescence Enhancement through Enzymatic Cleavage of Internally Quenched Dendritic Peptides: A Sensitive Assay for the AspN Endoproteinase

Keywords: dendrimers • fluorescence • lyases • peptides • solid-phase synthesis

A combination of electrostatic interactions and covalent bonding is used to form films with low-molecular-weight chromophores by a layer-by-layer deposition process. Using a common, commercially available red dye, this deposition process results in noncentrosymmetric films (see scheme) that exhibit second-harmonic generation (red $\rightarrow$ green), with $\chi^{(2)}$ values as large as 11.3×10^{-9} esu, that is, six times that of quartz.



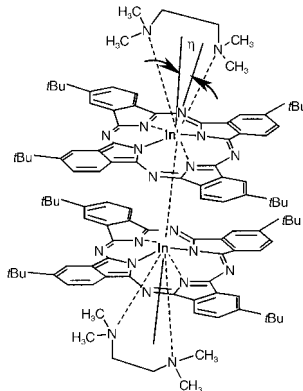
Angew. Chem. **2002**, *114*, 3370–3372

K. E. Van Cott,* M. Guzy, P. Neyman, C. Brands, J. R. Heflin, H. W. Gibson, R. M. Davis 3236–3238

Layer-By-Layer Deposition and Ordering of Low-Molecular-Weight Dye Molecules for Second-Order Nonlinear Optics

Keywords: chromophores • nonlinear optics • self-assembly • thin films

Enhanced nonlinear optical response is observed in a soluble dimeric indium–phthalocyanine (Pc) complex stabilized as a Lewis base adduct. The Pc moieties are tilted 14.5° from an axis connecting the In centers, which are out of plane with respect to the Pc macrocycles (see diagram). The In–In separation was calculated to be $3.24 \text{ \AA}$ by using extended X-ray absorption fine structure (EXAFS) spectroscopy.



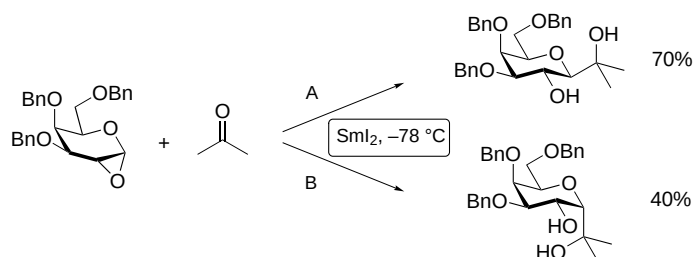
Angew. Chem. **2002**, *114*, 3373–3376

Y. Chen, M. Barthel, M. Seiler, L. R. Subramanian, H. Bertagnolli, M. Hanack* 3239–3242

An Axially Bridged Indium Phthalocyanine Dimer with an In–In Bond

Keywords: dimerization • EXAFS spectroscopy • indium • nonlinear optics • phthalocyanines

Sugar mimics: 1,2-anhydro sugars can be cross-coupled with aldehydes and ketones under very mild conditions and using a wide range of protecting groups to give C-glycosides in good yield in a radical reaction mediated by SmI_2 (see scheme; A = no proton source, B = in the presence of water).



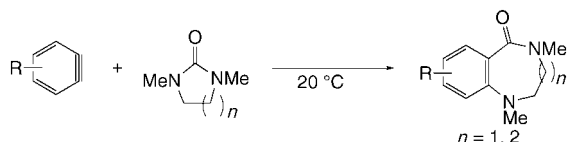
Angew. Chem. **2002**, *114*, 3376–3380

J. L. Chiara,* E. Sesnilo 3242–3246

Samarium Diiodide-Mediated Reductive Coupling of Epoxides and Carbonyl Compounds: A Stereocontrolled Synthesis of C-Glycosides from 1,2-Anhydro Sugars

Keywords: C-glycosides • electron transfer • radical reactions • samarium

Seven- and eight-membered heterocycles are formed straightforwardly, in modest to high yields in this novel addition reaction of ureas to arynes (see scheme; R = alkoxy, alkyl, aryl). The reaction of a *meta*-substituted aryne affords the product with perfect regioselectivity, whereas a *para*-substituted aryne gives a mixture of regioisomers.



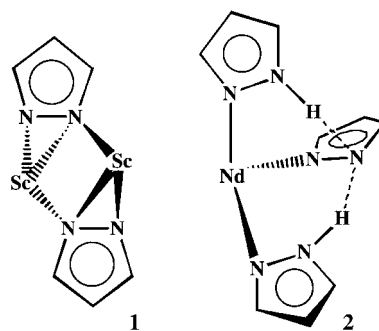
Angew. Chem. **2002**, *114*, 3381–3383

H. Yoshida, E. Shirakawa,* Y. Honda, T. Hiyama* 3247–3249

Addition of Ureas to Arynes: Straightforward Synthesis of Benzodiazepine and Benzodiazocine Derivatives

Keywords: arynes • nitrogen heterocycles • regioselectivity • ureas

New pyrazolate ligation modes continue to be uncovered: $[\text{Sc}_2(\text{Ph}_2\text{pz})_6]$ (**1**; Ph_2pz = 3,5-diphenylpyrazolate) displays the new $\mu\text{-}\eta^2\text{:}\eta^1$ binding mode and $[\text{Nd}(\eta^2\text{-Me}_2\text{pz})_2(\eta^1\text{-Me}_2\text{pz})(\text{Me}_2\text{pzH})_2\text{py})]$ (**2**; Me_2pz = 3,5-dimethylpyrazolate; py = pyridine) displays the first example of unidentate $\eta^1(\text{N})$ coordination of a pyrazolate to a lanthanide ion.



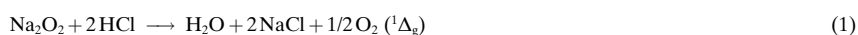
Angew. Chem. **2002**, *114*, 3383–3385

G. B. Deacon,* C. M. Forsyth, A. Gitlits, R. Harika, P. C. Junk, B. W. Skelton, A. H. White 3249–3251

Pyrazolate Coordination Continues To Amaze—The New $\mu\text{-}\eta^2\text{:}\eta^1$ Binding Mode and the First Case of Unidentate Coordination to a Rare Earth Metal

Keywords: lanthanides • N ligands • neodymium • scandium

$^1\Delta\text{-O}_2$ can now be made safely and efficiently from gas–solid reactions between alkali-metal peroxides and hydrogen halides [Eq. (1)]. This method avoids the liquid-phase quenching and instability problems associated with the hydrogen peroxide/chlorine system.



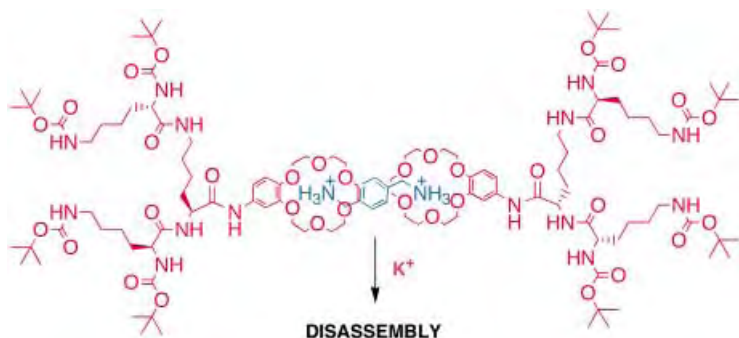
Angew. Chem. **2002**, *114*, 3386–3388

A. J. Alfano, K. O. Christe* 3252–3254

Singlet Delta Oxygen Production from a Gas–Solid Reaction

Keywords: hydrogen halides • oxygen • peroxides • quenching • singlet delta oxygen

Supramolecular dendrimers have been assembled in solution by using the interactions between dendritic branches functionalized with [18]crown-6 and a bis-ammonium cation as a template (see scheme). Disassembly is triggered by the addition of K^+ ions, which enables controlled release of the encapsulated template.



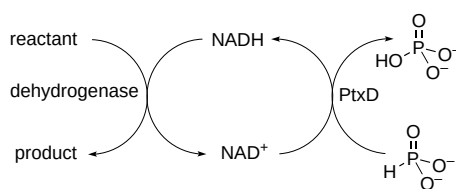
Angew. Chem. **2002**, *114*, 3388–3391

G. M. Dykes, D. K. Smith,*
G. J. Seeley 3254–3257

Controlled Release of a Dendritically Encapsulated Template Molecule

Keywords: crown compounds • dendrimers • NMR spectroscopy • self-assembly • supramolecular chemistry

The highly thermodynamically favorable oxidation of phosphite to phosphate by phosphite dehydrogenase (PtxD) makes the enzyme useful for cofactor regeneration (see figure). Deuterium exchange in D_2O provides labeled phosphite for the preparation of deuterated products.



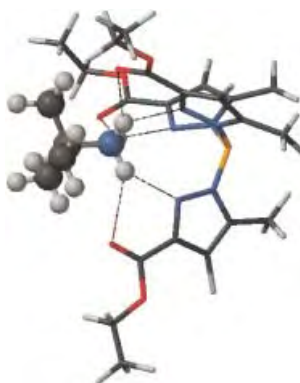
Angew. Chem. **2002**, *114*, 3391–3393

J. M. Vrtis, A. K. White, W. W. Metcalf,
W. A. van der Donk * 3257–3259

Phosphite Dehydrogenase: A Versatile Cofactor-Regeneration Enzyme

Keywords: cofactors • enzyme catalysis • isotopic labeling • nucleotides

The ubiquitous tris(pyrazolyl)borate family of ligands can recognize more than metal cations! Host–guest complexes between elaborated tris-(pyrazolyl)borate ligands and protonated amines (see picture) and cationic octahedral metal complexes are described. The latter is an example of an alternative bio-inspired paradigm, in which the guest is preorganized to promote recognition, rather than the host.



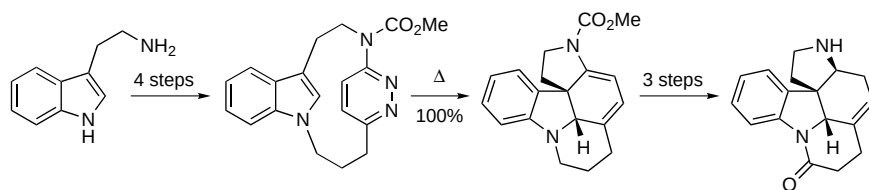
Angew. Chem. **2002**, *114*, 3393–3395

B. S. Hammes, X. Luo, M. W. Carrano,
C. J. Carrano * 3259–3261

Guest Preorganization: An Alternative “Bioinspired” Paradigm in Host–Guest Chemistry

Keywords: cooperative effects • host–guest systems • preorganization • supramolecular chemistry • pyrazolylborates

(±)-Strychnine in 12 easy steps! This concise synthesis involves the construction of a [3.3]cyclophane and its transannular inverse-electron-demand Diels–Alder reaction to afford a pentacycle quantitatively (see scheme), which is rapidly converted into Rawal’s key ABCEG intermediate; thus (±)-strychnine can be synthesized from tryptamine in only 12 steps.



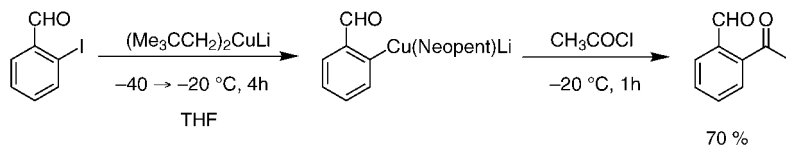
Angew. Chem. **2002**, *114*, 3395–3396

G. J. Bodwell,* J. Li 3261–3262

A Concise Formal Total Synthesis of (±)-Strychnine by Using a Transannular Inverse-Electron-Demand Diels–Alder Reaction of a [3](1,3)Indolo[3](3,6)pyridazinophane

Keywords: cycloaddition • cyclophanes • heterocycles • natural products • pericyclic reaction

 **Even aldehyde and ketone functions are tolerated** in mixed organocuprates prepared by copper–halogen exchange using $(\text{Me}_3\text{CCH}_2)_2\text{CuLi}$ (Neopent₂CuLi) or $(\text{PhMe}_2\text{CCH}_2)_2\text{CuLi}$ (Neophyl₂CuLi). The steric hindrance of the neopentyl and neophyl groups is essential to ensure the chemoselectivity of the reaction (see scheme), and therefore allows a general preparation of polyfunctionalized organocuprates.



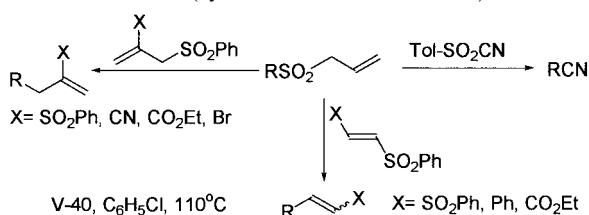
Angew. Chem. **2002**, *114*, 3397–3399

C. Piazza, P. Knochel* 3263–3265

Sterically Hindered Lithium
Dialkylcuprates for the Generation of
Highly Functionalized Mixed Cuprates
through a Halogen–Copper Exchange

Keywords: chemoselectivity • cuprates •
halides • metalation • nucleophilic
addition

 **Primary alkyl radicals** are generated highly efficiently and reliably from alkyl allyl sulfone precursors. The latter are effective in tin-free radical C–C-bond formations, including cyanation, vinylation, and allylation (see scheme; V-40 = 1,1'-azobis(cyclohexane-1-carbonitrile)).



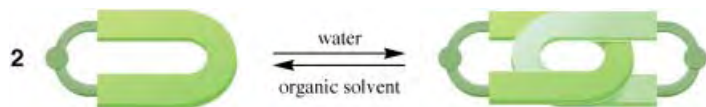
Angew. Chem. **2002**, *114*, 3399–3401

S. Kim,* C. J. Lim 3265–3267

Tin-Free Radical-Mediated C–C-Bond
Formations with Alkyl Allyl Sulfones as
Radical Precursors

Keywords: allylation • C–C coupling •
radical reactions • sulfones

 **Switching on chirality:** Reversible catenation allows switching between achiral, planar, Pd^{II}-linked rings containing a pentakis(*m*-phenylene) unit and a chiral, double-helical conformation of the catenane (see picture). Molecular chirality is induced in the catenane by an ancillary chiral unit on the metal.



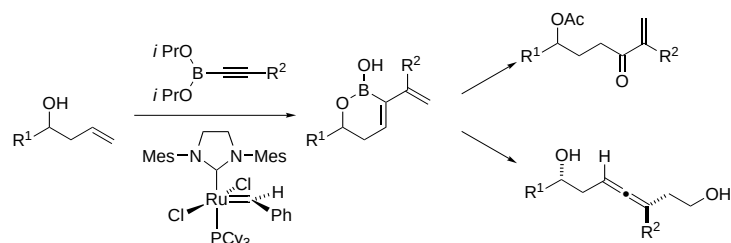
Angew. Chem. **2002**, *114*, 3403–3406

A. Hori, A. Akasaka, K. Biradha,
S. Sakamoto, K. Yamaguchi,
M. Fujita* 3269–3272

Chirality Induction through the
Reversible Catenation of Coordination
Rings

Keywords: catenanes • chirality • helical
structures • palladium • self-assembly

 **Branched networks of reactions** create variety in this synthesis of trisubstituted allenes and functionalized enones from readily available homoallylic alcohols in just two steps, by using a new alkynylboronic ester annulation (see scheme; Mes = 2,4,6-trimethylphenyl, Cy = cyclohexyl).



Angew. Chem. **2002**, *114*, 3406–3410

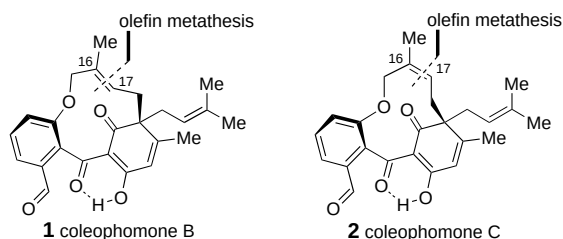
G. C. Micalizio,
S. L. Schreiber* 3272–3276

An Alkynylboronic Ester Annulation:
Development of Synthetic Methods for
Application to Diversity-Oriented
Organic Synthesis

Keywords: allenes • annulation • boronic
acids • metathesis • synthetic methods



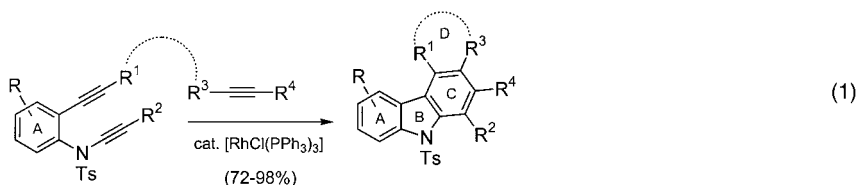
Pushing the frontiers of olefin metathesis: As the coleophomones B (**1**) and C (**2**) differ only in the configuration of the $\Delta^{16,17}$ double bond, ring-closing metathesis was chosen as the method for their construction following an initially convergent route that diverges at a late stage.



Angew. Chem. **2002**, *114*, 3410–3415



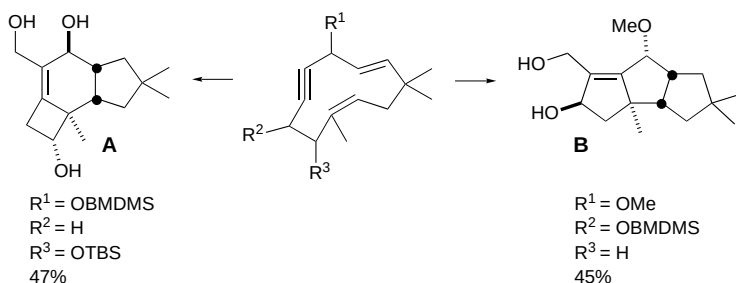
An A $\rightarrow$ ABC or A $\rightarrow$ ABCD ring-formation strategy proves extremely efficient for generating substituted carbazoles ([Eq. (1)]; Ts = tosyl). Inter- and intramolecular alkyne cyclotrimerizations mediated by Wilkinson's catalyst provide substituted carbazoles of relevance for natural product and drug-related synthesis. The diynes required for these reactions are obtained in a few steps by a combination of Sonogashira and N-ethynylation reactions.



Angew. Chem. **2002**, *114*, 3415–3418



A completely selective entry to the triquinane family is described from a highly strained cycloundecadienyne framework, simply by choosing the correct propargylic position for the radical trigger (see scheme; A: natural protoilludane, B: linear triquinane, BMDMS = (bromomethyl)dimethylsilyl, TBS = *tert*-butyldimethylsilyl).



Angew. Chem. **2002**, *114*, 3418–3421



Supporting information on the WWW
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Alkyne Cyclotrimerizations

Keywords: alkynes • cyclotrimerization •
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A.-L. Dhiman, C. Aïssa,
M. Malacria* 3284–3287

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Synthesis of Linear Triquinane

Keywords: cyclization • polycycles •
radicals • strained molecules • synthetic
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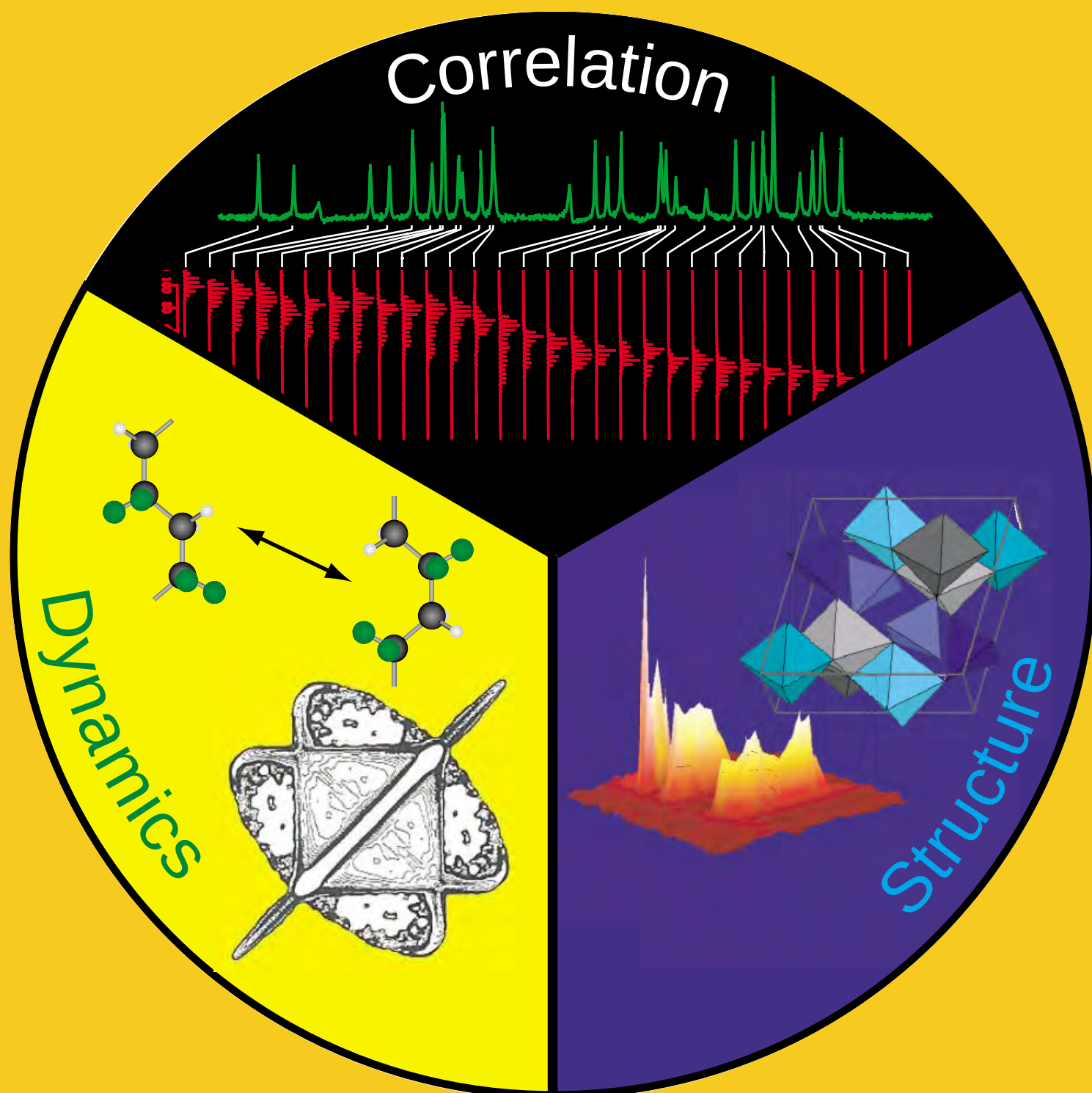
CORRIGENDA

In the Communication by A. Gagnon and S. J. Danishefsky in Issue 9, **2002**, pp. 1581–1584, the wrong reagent was accidentally given in Scheme 2. In f), “3-iodoprop-1-ene” should be replaced by “allyltributyltin”.

In the Communication by S. Spange et al. in Issue 10, **2002**, pp. 1729–1732, two thematically relevant works on sol–gel techniques were not cited. These were: a) U. Deschler, P. Kleinschmit, P. Panster, *Angew. Chem.* **1986**, 98, 237–253; *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 236–252; b) B. Lebeau, J. Maquet, C. Sanchez, E. Toussacre, R. Hierle, J. Zyss, *J. Mater. Chem.* **1994**, 4, 1855–1860.

In the Communication by U. Mazurek, D. Schröder, and H. Schwarz in Issue 14, **2002**, pp. 2538–2541 two molecular formulae were inadvertently cut short on the right-hand side of Figure 2. The correct formulae are as follows: $\text{CrC}_6\text{F}_6\text{O}_{10}\text{H}_{11}^+$ and $\text{CrC}_3\text{F}_2\text{O}_6\text{H}_6^+$ (in place of the incorrectly shown formulae $\text{CrC}_6\text{F}_6\text{O}_{10}\text{H}_1$ und $\text{CrC}_3\text{F}_2\text{O}$). The editorial team apologizes for this oversight.

Solid-State NMR Spectroscopy



Solid-State NMR Spectroscopic Methods in Chemistry

David D. Laws, Hans-Marcus L. Bitter, and Alexej Jerschow*

Over the last decades, NMR spectroscopy has grown into an indispensable tool for chemical analysis, structure determination, and the study of dynamics in organic, inorganic, and biological systems. It is commonly used for a wide range of applications from the characterization of synthetic products to the study of molecular structures of systems such as catalysts, polymers, and proteins. Although most NMR experiments are performed on liquid-state samples, solid-state NMR is rap-

idly emerging as a powerful method for the study of solid samples and materials. This Review outlines some of the developments of solid-state NMR spectroscopy, including techniques such as cross-polarization, magic-angle spinning, multiple-pulse sequences, homo- and heteronuclear decoupling and recoupling techniques, multiple-quantum spectroscopy, and dynamic angle spinning, as well as their applications to structure determination. Modern solid-state NMR spectroscopic techni-

ques not only produce spectra with a resolution close to that of liquid-state spectra, but also capitalize on anisotropic interactions, which are often unavailable for liquid samples. With this background, the future of solid-state NMR spectroscopy in chemistry appears to be promising, indeed.

Keywords: multipulse techniques • NMR spectroscopy • solid-state structures • spin-spin coupling • structure elucidation

1. Introduction

Since the pioneering demonstration of cross-polarization ^{13}C NMR spectra of solid adamantane and benzene,^[1] solid-state NMR spectroscopy has advanced rapidly and is being used to study the structure and dynamics of a variety of solid systems ranging from catalysts and glasses to polymers and proteins. Much of the success of solid-state NMR spectroscopy is due to the evolution of a variety of techniques for studying internuclear distances, anisotropy, torsion angles, atomic orientations, spin diffusion, molecular dynamics, and exchange processes, while maintaining the analytical high resolution and sensitivity that constitute the hallmarks of practically useful NMR experiments in chemistry.

Our goal in this Review is to demonstrate the utility of solid-state NMR spectroscopy for the study of molecular structure and dynamics in solids, and its application as a tool for routine chemical analysis of solid materials. We discuss the interactions between nuclear spins and magnetic fields that give rise to the traditionally broad solid-state NMR signals, as

well as the common and less-common methods designed to eliminate this broadening. We review the concepts behind techniques that are routinely used to exploit internuclear interactions (e.g. methods of internuclear distance determination and correlation experiments in solids). We also discuss solid-state NMR spectroscopy of quadrupolar nuclei such as ^2H , ^{23}Na , and ^{27}Al and outline how they can be used to probe orientation, dynamics, and structure. Numerous excellent review articles have appeared in the past few years showing how the tools of solid-state NMR spectroscopy can be applied to solving specific problems.^[2–31] For the benefit of providing the reader with a more or less complete overview of current solid-state NMR spectroscopic techniques, we refer to those publications and other references given in the text for a presentation of specific applications or specific methods. A detailed mathematical description of solid-state NMR is left out purposely, but, where appropriate, we provide references to books and articles that explain in greater detail the topics presented herein.

2. Solid-state NMR of Low-Abundance Spin $\frac{1}{2}$ Nuclei

The most common NMR experiments performed for solid-state samples are those involving the observation of spin $\frac{1}{2}$ nuclei with low gyromagnetic ratios, for example, ^{13}C , ^{15}N , and ^{29}Si . Thus, we begin with an introduction to the spin interactions that play a role in solid-state NMR spectra of

[*] Prof. Dr. A. Jerschow,^[+] Dr. D. D. Laws, Dr. H.-M. L. Bitter
Materials Sciences Division, Lawrence Berkeley National Laboratory and
Department of Chemistry, University of California at Berkeley
Berkeley, CA 94720 (USA)
E-mail: Alexej.Jerschow@nyu.edu

[+] Present address: Chemistry Department, New York University
New York, NY 10003 (USA)
fax: (+1)212-260-7905

spin $\frac{1}{2}$ nuclei and discuss common spectroscopic methods that manipulate and even eliminate the effects that these interactions have on solid-state NMR spectra.

If one were to dissolve a sample of 1- ^{13}C -labeled (10 %) glycine in water and apply a single $\pi/2$ pulse at the appropriate NMR frequency for ^{13}C nuclei, the familiar ^{13}C spectrum shown in Figure 1 would result. Two well-resolved signals

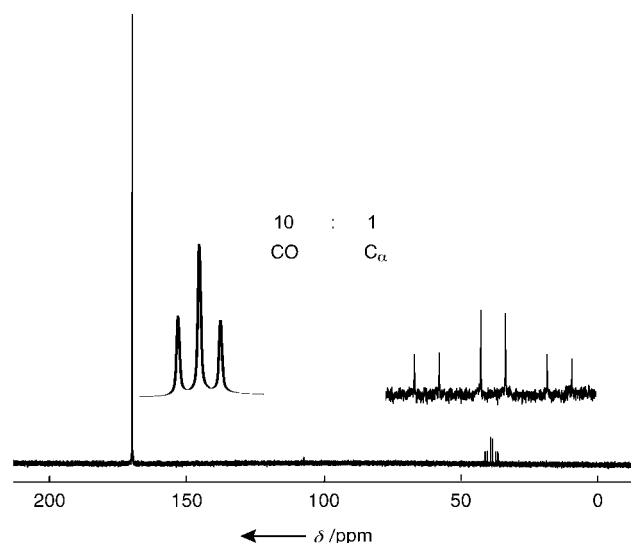


Figure 1. Liquid-state ^{13}C NMR spectrum (75 MHz) of 1- ^{13}C labeled (10 %) glycine dissolved in H_2O (0.2 mL) to a concentration of ~ 10 mM.

appear in the spectrum, corresponding to the ^{13}C -labeled carbonyl carbon atoms and the natural abundance ($\sim 1\%$ for ^{13}C) α carbon atom in the glycine sample. The familiar 1:2:1 splitting pattern of the carbonyl carbon resonance provides information about its J coupling to the two α protons. The splitting of the isotopically dilute α -carbon resonance are a result of J couplings to both the α -protons and the carbonyl carbon atom. In contrast, Figure 2 shows the result of a comparable experiment performed on the same compound in the solid state. The signals for the carbonyl ^{13}C , which were very sharp in the liquid-state spectrum, are now replaced by an extremely broad (≈ 200 ppm) and generally uninterpretable peak. The broadening of the signal for α -carbon atom renders it barely perceptible. These broad solid-state signals are primarily the result of interactions that are present (but rarely observed) in liquid-state NMR spectra. The three primary interactions are the heteronuclear and homonuclear dipolar couplings, and the chemical-shift anisotropy. In the ensuing sections, we examine

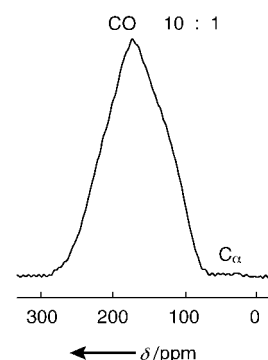


Figure 2. Solid-state ^{13}C NMR spectrum (125 MHz) of 1- ^{13}C labeled (10 %) glycine powder (90 mg).

David Douglas Laws received his B.S. in chemistry in 1995 from the University of Illinois, Urbana-Champaign where he worked with Professor Eric Oldfield on the calculation of NMR chemical shifts in proteins. He then moved to the University of California, Berkeley, where he received his Ph.D. in chemistry working with Professor Alex Pines on developing techniques to study solid-state proteins by NMR spectroscopy. David now resides with his wife Elizabeth in New Jersey, where he teaches chemistry and coaches swimming at The Lawrenceville School.



D. Laws



H.-M. Bitter



A. Jerschow

Hans-Marcus Bitter obtained his B.S. degree from Princeton University in 1995 and received his Ph.D. in 2000 from the University of California at Berkeley under the supervision of Professor Alexander Pines. Currently, he works as an informatics scientist at Biospect, a South San Francisco biotech company. He resides in San Francisco with his wife Catherine.

Alexej Jerschow received his Ph.D. from the University of Linz (Austria) under the supervision of Professor Norbert Müller for work on the analysis of polymers with multidimensional NMR spectroscopy. He was then a postdoctoral fellow with Professor Geoffrey Bodenhausen and supervisor of the NMR facility of West Switzerland at the University of Lausanne. His research involved the development of novel liquid-state NMR methodology, and the study of complex flow with magnetic resonance imaging methods. As an Erwin Schrödinger fellow with Professor Alexander Pines at the University of California, Berkeley, he developed new solid-state high-resolution NMR techniques for quadrupolar nuclei. He lives with his family in New York and is currently an Assistant Professor of Physical Chemistry at New York University.

the origins of each of these interactions and discuss how their effects on solid-state NMR spectra can be coherently manipulated so as to produce spectra with a resolution closer to that of liquid-state spectra. However, these mechanisms often contain a wealth of structural data and we will also review techniques that aid in obtaining this information.

2.1. Heteronuclear Dipolar Coupling

We begin our analysis of the solid-state ^{13}C NMR spectrum of glycine with an examination of the heteronuclear dipolar coupling. The heteronuclear dipolar coupling arises from an interaction between the nuclear magnetic moments of two different nuclear spins. (By convention, nuclear spins are labeled as I for “abundant” spins, for example, that of the proton, and S for “rare” spins such as that of ^{13}C or ^{15}N nuclei.) In an external magnetic field, the Zeeman interaction describes the energy of the spin I based on its orientation, either parallel (“spin-up”) or antiparallel (“spin-down”), with respect to the external field [Eq. (1)], where γ = gyromagnetic ratio, B_0 = external magnetic field, and m_I = nuclear spin quantum number (which is either $+\frac{1}{2}$ or $-\frac{1}{2}$ for a spin $\frac{1}{2}$ nucleus).

$$E_{\text{Zeeman}} = -\hbar\gamma B_0 m_I \quad (1)$$

Similarly, spin S will align itself either parallel or antiparallel to B_0 . Since each spin represents a nuclear magnetic moment that produces a small magnetic field, the S spin will “feel” the magnetic field produced by the I spin and vice versa when the two spins are within reasonable proximity of each other ($< 10 \text{ \AA}$). This magnetic field produced by the I spin will either add to or subtract from the external field felt by the S spin, depending on the orientation of the I spin, thereby increasing or decreasing the effective local magnetic field at the site of spin S and thus changing its resonance frequency. The degree to which spin I affects the magnetic field felt by spin S is characterized by the strength of the heteronuclear dipolar coupling, which is represented by the Hamiltonian in Equation (2).

$$H_{IS} = -d(3\cos^2\theta - 1)I_z S_z \quad (2)$$

The parameter d is the dipolar coupling constant [Eq. (3)].

$$d = \left(\frac{\mu_0}{4\pi}\right) \frac{\hbar\gamma_I\gamma_S}{r_{IS}^3} \quad (3)$$

In this case, r_{IS} = internuclear distance, μ_0 = permeability of free space ($= 4\pi \times 10^{-7} \text{ N A}^{-2}$), γ_I and γ_S = gyromagnetic ratios of the I and S spins, respectively, and I_z and S_z = z components of the nuclear spin angular momentum operators I and S , respectively. The angle θ describes the orientation of the internuclear vector with respect to the orientation of the external magnetic field (Figure 3 shows this for a case in which $I = ^1\text{H}$ and $S = ^{13}\text{C}$). Because the magnitude of the coupling between two nuclear spins depends on the internuclear

distance, the dipolar coupling is a *through-space* interaction. In contrast, J coupling requires the presence of chemical bonds. It is transferred through the electrons engaged in these bonds and thus is confined to nuclei within a molecule. Through-space dipolar coupling, however, also occurs between nuclei in *different* molecules. The two coupling mechanisms are therefore complementary in information content.

Three properties of the heteronuclear dipolar coupling Hamiltonian stand out: 1) The magnitude of the coupling is proportional to the product of the gyromagnetic ratios. This appears intuitively reasonable because the magnetic moment of a nucleus is proportional to γ , and nuclei with greater magnetic moments produce stronger magnetic fields, which in turn increases the dipolar coupling interaction. 2) The dipolar coupling is inversely proportional to the cube of the internuclear distance, so the interaction falls off rapidly as the nuclei are moved farther apart. 3) The dipolar coupling is dependent on the orientation, which is evident from the $(3\cos^2\theta - 1)$ term in the dipolar Hamiltonian. This means that for two nuclei of spins I and S which are separated by a fixed distance, the magnitude of the dipolar interaction will be greater for certain orientations of the $I-S$ internuclear vector than for others. It is the orientational dependence of the dipolar coupling that limits its role in liquid-state NMR spectroscopy. The reorientation time of a molecule in solution is much faster than the time the dipolar coupling would need to evolve, thus causing the $(3\cos^2\theta - 1)$ term of the heteronuclear dipolar coupling Hamiltonian to average to zero. In a static solid sample comprised of randomly oriented crystallites, however, the internuclear vector remains invariant over time, and the resonance frequency produced by each crystallite depends on its orientation with respect to the external field. In a polycrystalline powder sample in which the crystallites are oriented in all possible directions, the presence of a heteronuclear dipolar coupling produces a spectrum such as that shown in Figure 4 (if no other orientation-dependent interactions are present). The two complementary patterns, termed the “Pake doublet”,^[32] arise from energy differences determined by H_{IS} , depending on the parallel or antiparallel alignment of the I spin with respect to the S spin (the $I_z S_z$ term gives positive and negative energies, respectively). The intensity of the pattern at a particular frequency reflects the abundance of the crystallites that resonate at that frequency. In a powdered solid, the singular peaks of the Pake pattern correspond to crystallites for which the $I-S$ internuclear vector lies perpendicular to the magnetic field. The two low edges of the Pake pattern correspond to the relatively few crystallites whose $I-S$ internuclear vectors point toward the poles (parallel to the external field). Notably, there is also an orientation of the $I-S$ vector relative to B_0 at which the

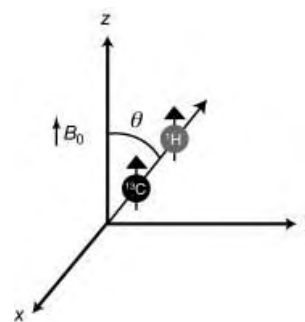


Figure 3. θ is the angle between the $^1\text{H}-^{13}\text{C}$ bond vector and the direction of the external magnetic field B_0 .

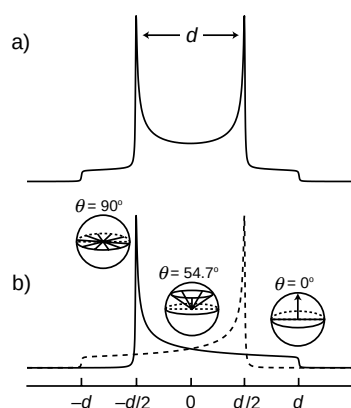


Figure 4. a) Dipolar Pake pattern ("Pake doublet") for two coupled spins in a powder sample; the two signals correspond to a positive (parallel spins) and a negative (antiparallel spins) value of the $I_z S_z$ component. b) The points with maximum intensity corresponds to $\theta = 90^\circ$ —a perpendicular orientation to B_0 is adopted by a majority of the crystals. The smallest number of crystals have the internuclear vector parallel to B_0 ($\theta = 0^\circ$). At the magic angle of $\theta = 54.7^\circ$, the dipolar coupling is zero. The spacing between the points of maximum intensity in a) is equal to the dipolar coupling constant d (d/h if expressed in Hz).

resonance frequency of the crystallites is not altered by the heteronuclear dipolar coupling. This is the case at the "magic angle" of $\theta = 54.74^\circ$ ($(3 \cos^2 \theta - 1) = 0$).

The spectrum in Figure 2 does not resemble a Pake pattern for three reasons: 1) each carbon atom couples to more than one proton; 2) the protons couple with each other; and 3) other anisotropic interactions cause additional broadening of the resonances, as discussed below.

2.2. Heteronuclear Dipolar Decoupling

The heteronuclear coupling that is responsible for much of the broadening in the glycine spectrum in Figure 2 involves the coupling of ^1H nuclear spins to the detected ^{13}C nuclear spins, as the ^1H – ^{13}C dipolar coupling is typically the dominant interaction experienced by the ^{13}C spin. A typical coupling constant for a bonded ^1H – ^{13}C pair (at a distance of about 1 Å) is approximately 30 kHz. However, close inspection of the Hamiltonian in Equation (2) suggests two possible means of eliminating the interaction to give narrower lines. One approach is to take advantage of the fact that the dipolar coupling is zero when the internuclear vector is oriented at the magic angle with respect to the magnetic field. This approach is implemented in a technique known as magic-angle spinning (see Section 2.4). The second method that can be used to eliminate the effect of the ^1H nuclei on the ^{13}C spectrum is to manipulate the proton spins in such a way that their effect on the ^{13}C nucleus, when averaged over time, is equal to zero. This is the solid-state dipolar version of spin decoupling, which is used in solution NMR spectroscopy. As can be seen from the signals for the two transitions shown in Figure 4, a proton whose spin is parallel to the external field ("spin-up") produces a shift in the resonance frequency of a ^{13}C nucleus that is opposite to the shift produced by a proton whose spin is antiparallel to the external field ("spin-down"). By constantly

applying radio-frequency (RF) pulses that rotate the proton nuclear spins between their "spin-up" and "spin-down" states, the average orientation of the ^1H magnetic moments tends to zero, and the dipolar coupling is essentially averaged away (this also applies to the J coupling). This continuous-wave (CW) spin decoupling^[33, 34] is widely used to eliminate heteronuclear couplings in solid-state NMR spectroscopy. As can be seen in Figure 5, under CW irradiation at the ^1H Larmor frequency, the ^{13}C peak is definitely less broad than that in Figure 2. The resulting spectrum is dominated by the chemical-shift anisotropy (see Section 2.3). Notably, ^1H decoupling has a much more dramatic effect on the signal for the α carbon atom (which is now visible in the spectrum) than it does on the signal for the carbonyl carbon atom (Figure 5). This is a result of the distance dependence of the dipolar coupling: with two α protons a distance of ~ 1 Å away, the α carbon atom experiences a much stronger ^1H – ^{13}C coupling than the unprotonated carbonyl carbon atom. In liquid-state NMR spectroscopy, CW decoupling is used much less often as it has been superseded by a number of different multiple-pulse techniques.^[35, 36] These techniques are usually not as effective in solid-state NMR spectroscopy for reasons that we will discuss below.

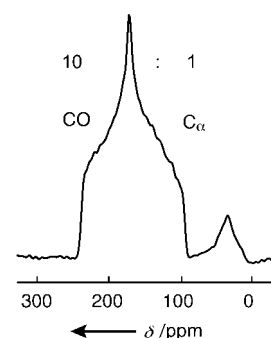


Figure 5. CW ^1H decoupled solid-state ^{13}C NMR spectrum (125 MHz) of a ^{13}C -labeled (10%) glycine powder.

2.3. Chemical-Shift Anisotropy

The origin of the chemical shift can be understood by examining the effect of B_0 on the electrons around a nucleus. When an external magnetic field is applied to an atom, not only are the nuclear spins perturbed, but the surrounding electrons are also affected since they, too, have magnetic moments. The external field induces circulating currents of electrons that in turn produce small magnetic fields (typically $\sim 1 \times 10^6$ times smaller than B_0), which either add to or subtract from the external field felt by the nucleus. Therefore, the effective magnetic field experienced by the nucleus is altered, as is its resonance frequency.

The orientation dependence or *anisotropy* of the chemical shift can be quite dramatic. For a non- sp^3 -hybridized ^{13}C atom, the chemical shift anisotropy (CSA) can be as large as 120–140 ppm (e.g., see Figure 5). Much larger anisotropies (up to 1000s ppm) can be found for some heavier nuclei. The CSA results from the fact that the atoms in molecules rarely possess spherically symmetric electron distributions; instead, the electron density can be thought of as an ellipsoid, typically elongated along bonds or nonbonding p -orbitals. The degree to which the electron density affects the resonance frequency of a nucleus depends on the orientation of the electron cloud (and hence the orientation of the molecule) with respect to B_0 . For example, the resonance frequency of a carbonyl

carbon atom can differ by more than 120 ppm, depending on the orientation of the C=O moiety with respect to the external field, as can be seen in Figure 6. The largest chemical shift (i.e. deshielding effect) in the resonance frequency of the ^{13}C nucleus occurs when the narrowest part of the electron cloud

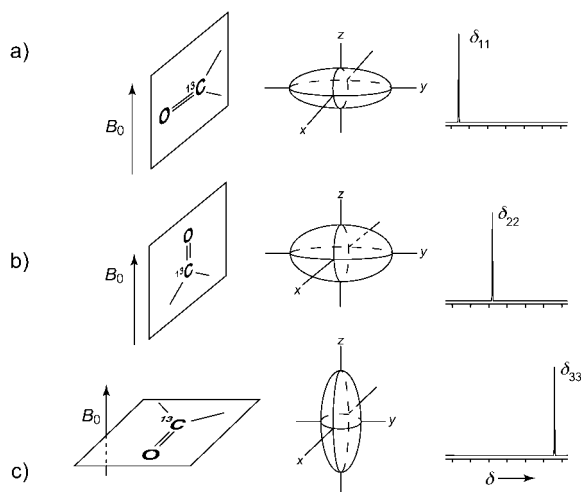


Figure 6. Schematic representation of the principle values of the CSA: δ_{11} (a), δ_{22} (b), and δ_{33} (c). The position of each resonance depends on the orientation of the magnetic field relative to the principal axes of the chemical shift tensor. (Reproduced from ref. [43], with permission.)

is oriented along the B_0 axis (Figure 6a), whereas the smallest shift occurs when the widest part of the electron cloud is oriented along B_0 (Figure 6c). These two chemical shifts, referred to as δ_{11} and δ_{33} , respectively, are two of the three “principal values” of the CSA. The third value δ_{22} is the shift produced by the molecular orientation perpendicular to the axes of δ_{11} and δ_{33} (Figure 6b). These three principal values and the information of the orientation of the ellipsoid (usually specified by the three Euler angles^[37]) provide all the information necessary to describe the CSA of a nuclear spin.^[38, 39]

In powder samples, in which the vast number of randomly oriented crystallites ensures that all of the possible molecular orientations are sampled, a “powder pattern” such as the one shown in Figure 5 emerges. The left and right edges of the C=O signal correspond to the chemical shifts δ_{11} and δ_{33} , respectively, and the position of the maximum intensity of the pattern corresponds to δ_{22} (for the common convention of $\delta_{11} \geq \delta_{22} \geq \delta_{33}$). The broad CSA signal is the result of an interaction between the detected spins and the external field, and so there is no simple way to remove this interaction by RF pulses (as we did with the heteronuclear dipolar coupling) without affecting the free precession of the spins required for signal detection. However, liquid-state NMR spectroscopy provides a clue as to how the effects of the CSA can be eliminated. In liquids, molecules randomly and rapidly sample the full range of orientations, so that even a strongly asymmetric electron distribution will appear spherical when viewed on the NMR timescale. One can divide the chemical-shift Hamiltonian H_{CS} into an isotropic term and an anisotropic term. For the special case in which $\delta_{11} = \delta_{22}$ (so that the ellipsoids in Figure 6 would be axially symmetric like a cigar),

the chemical shift Hamiltonian can be written as shown in Equation (4):

$$H_{\text{cs}} = \gamma B_0 I_z [\delta_{\text{iso}} + \frac{1}{2} \delta_{\text{CSA}} (3 \cos^2 \theta - 1)] \quad (4)$$

δ_{iso} = (isotropic) chemical shielding factor (typically in the order of $10^{-6} \hat{=}$ ppm) [Eq. (5)].

$$\delta_{\text{iso}} = \frac{1}{3} (\delta_{11} + \delta_{22} + \delta_{33}) \quad (5)$$

The angle θ relates the orientation of the unique axis of the ellipsoid with respect to B_0 , and δ_{CSA} dictates the magnitude of the CSA [Eq. (6)]

$$\delta_{\text{CSA}} = \delta_{33} - \delta_{\text{iso}} \quad (6)$$

In a rapidly tumbling molecule, all possible orientations of the ellipsoid are sampled, causing the orientation-dependent term to average to zero and leaving only the isotropic component of the chemical shift, $\delta_{\text{iso}} \gamma B_0 I_z$, which is observed in liquid-state NMR spectra. Imposing a random, liquid-like motion on a solid-state sample is, however, mechanically impractical since it would require motion around multiple axes at speeds that are currently unattainable. By spinning the sample around a unique well-chosen axis (see following Section 2.4), one can also eliminate the anisotropic term of the chemical-shift Hamiltonian.

2.4. Magic-Angle Spinning

We pointed out in Section 2.2 that when the vector between two nuclei makes an angle $\theta = 54.74^\circ$ (the magic angle) with the static magnetic field, the value of the $(3 \cos^2 \theta - 1)$ term in the heteronuclear dipolar coupling Hamiltonian is zero. The same is true for the axially symmetric CSA, for which an analogous angular dependence is found (in this case, θ is the angle that the long axis of the CSA ellipsoid makes with the static field). This could be accomplished by using a single crystal in which the CSA ellipsoid is oriented so that $\theta = 54.74^\circ$. Single crystals are, however, hard to obtain for many samples, and the orientation of the unique CSA axis with respect to the crystallite frame is not known.

Alternatively, by rapidly spinning a polycrystalline powder sample, one can make the average CSA look like an ellipsoid whose long axis is aligned with the spinning axis. This is also true when the CSA is not axially symmetric. The effect of this average CSA on the spectrum is eliminated if the spinning axis is inclined at 54.74° with respect to the static magnetic field. This technique is known as magic-angle spinning (MAS).^[40, 41]

Another qualitative description of the theory that underlies the averaging of the CSA under spinning has been reported.^[38, 39, 42] For a static powder sample, the value of the CSA is fixed for a given crystallite orientation. When the sample is spun, the CSA values of all crystallites become time-dependent, since the orientation of the crystallites change. Figure 7 shows that an axis inclined at an angle of 54.74° represents the direction of the space diagonal of a cube. The x, y, and z

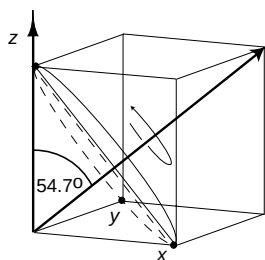


Figure 7. The magic angle (54.7°) is the angle that the space diagonal of a cube makes with the z axis. This is also the direction of the nodal plane in a d_{zz} orbital. Rapid spinning of the sample about this axis removes the dipolar interactions.

coordinate axes appear symmetric when looking down the space diagonal. Over a single rotation period, each crystallite therefore experiences the average of the effective chemical shift $\delta_{\text{iso}} = (\delta_{xx} + \delta_{yy} + \delta_{zz})/3 = (\delta_{11} + \delta_{22} + \delta_{33})/3$, the isotropic chemical shift. MAS can therefore be regarded as a dynamic implementation of cubic symmetry,^[43] which cancels the anisotropic term.

Figure 8a–d show a series of ^{13}C MAS spectra for uniformly ^{13}C -labeled (10%) glycine at different spinning speeds. As the spinning speed decreases, numerous peaks begin to appear at frequency distances of integer multiples of the spinning speed. These peaks, known as spinning sidebands, result from the incomplete averaging of the revolving CSA ellipsoid at slow spinning speeds.^[40, 41] These additional signals always appear in-phase for a perfect

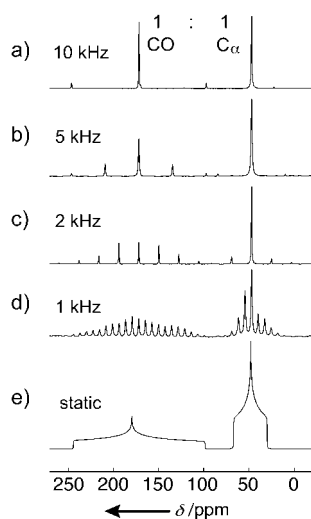


Figure 8. Solid-state ^{13}C NMR spectra (125 MHz) of a uniformly ^{13}C -labeled (10%) glycine powder sample; the spectra were acquired under CW ^1H decoupling and MAS at the given spinning speeds. As the spinning speed decreases the envelope of the spinning sidebands begins to resemble the simulated static NMR spectrum e).

powder, but may be anti-phase when a preferential orientation of the crystallites exists in the sample.^[44] Although these sidebands are often a nuisance (they can be minimized by spinning at a frequency greater than the width of the CSA pattern), in some instances their presence provides additional information about a sample (see Section 4.4). Figure 8e represents a powder spectrum reconstructed from the CSA parameters obtained by fitting the sideband intensities in Figure 8a–d.^[45] This spectrum looks very similar to the experimental spectrum shown in Figure 5, taking into account the difference in the abundance of the ^{13}C labeled α carbon atom.

2.5. Homonuclear Dipolar Coupling

The heteronuclear dipolar coupling is the result of an interaction between the magnetic fields produced by different neighboring nuclear spins (for example ^1H and ^{13}C). The same form of coupling exists between like spins, such as two ^{13}C nuclei. However, whereas two unlike nuclear spins (heteronuclei) have very different resonance frequencies (for example, when ^1H spins resonate at 500 MHz, ^{13}C spins resonate at 125 MHz), two like spins are able to undergo an energy-conserving “flip-flop” transition in which one spin flips up while the other spin flips down (Figure 9). To account for the

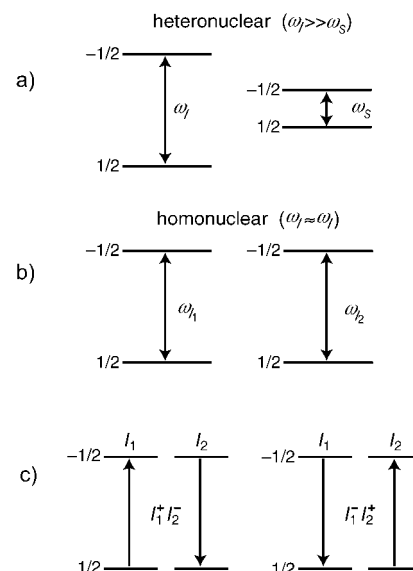


Figure 9. a) At different transition frequencies of two spins ω_I and ω_S , no energy-conserving transition can occur; b) when $\omega_I = \omega_S$, c) the spins can exchange magnetization through an energy-conserving “flip-flop” interaction.

“flip-flop” interaction, an additional term, normally ineffective in the heteronuclear case, is added back in to give the homonuclear dipolar Hamiltonian [Eq. (7)]

$$H_{II} = -d/2(3\cos^2\theta - 1)(3I_{1z}I_{2z} - (\mathbf{I}_1 \cdot \mathbf{I}_2)) \quad (7)$$

Analogously to Equation (3), $d = (\mu_0/4\pi)(\hbar\gamma_I^2/r_{IS}^3)$. The origin of the term $\mathbf{I}_1 \cdot \mathbf{I}_2 (= I_{1x}I_{2x} + I_{1y}I_{2y} + I_{1z}I_{2z})$ can be better understood by rewriting Equation (7) as Equation (9) in terms of raising and lowering operators [Eq. (8)]

$$I^+ = I_x + iI_y; I^- = I_x - iI_y \quad (8)$$

$$H_{IS} = -d/2(3\cos^2\theta - 1)(2I_{1z}I_{2z} - 1/2(I_1^+ I_2^- + I_1^- I_2^+)) \quad (9)$$

The raising operator I^+ increases the angular momentum of a spin by $\hbar$, which amounts to flipping a spin from the “down” orientation to the “up” orientation (Figure 9). Conversely, the lowering operator I^- lowers the angular momentum of a spin by $\hbar$, causing an “up” spin to flip “down”. Together, the $I_1^+ I_2^-$ and $I_1^- I_2^+$ provide for an energy-conserving exchange of spin angular momentum between any two coupled spins whose resonance frequencies overlap. When two like spins have very

different chemical shifts so that there is no overlap between their resonance frequencies, there can be no energy-conserving transition; in the latter case, the homonuclear dipolar Hamiltonian reverts to the form of the heteronuclear dipolar Hamiltonian shown in Equation (2).

For low- γ nuclei such as ^{13}C and ^{15}N , the homonuclear dipolar coupling can often be removed by MAS, as even for directly bonded ^{13}C nuclei, the dipolar coupling constant d does not exceed 5 kHz. However, there still can be “recoupling” effects with certain ratios of spinning speed to chemical-shift difference of the two nuclei (see Section 4). The homonuclear dipolar interaction has perhaps the largest impact on ^1H solid-state NMR spectroscopy, as the strength of the homonuclear dipolar coupling between two proton spins can routinely approach 100 kHz because of their large gyromagnetic ratio. The problem of strong ^1H – ^1H dipolar coupling is exacerbated by the high abundance of protons in most organic systems, which results in a network of strongly coupled spins that are very difficult to decouple from each other. As a result, solid-state ^1H NMR spectra typically consist of a single broad peak, with a line width in the order of 50 kHz. Figure 10a shows a static ^1H NMR spectrum of solid glycine, in which the many protons lead to a spectrum that cannot be interpreted. Although MAS does help to reduce the line width (Figure 10b), it is still too broad to be of general use, even at the very high (>30 kHz) MAS speeds now obtainable. Homonuclear decoupling by using RF-pulse sequences are discussed in Section 3.2.

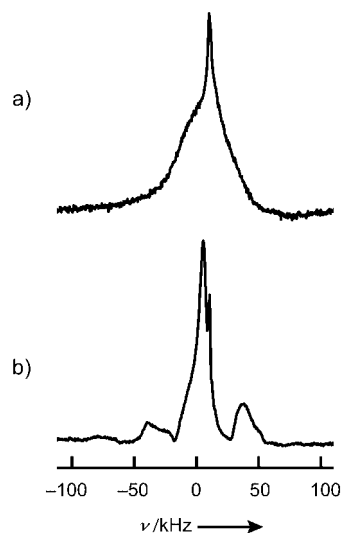


Figure 10. Solid-state ^1H NMR spectrum (500 MHz) of glycine powder: a) without spinning, b) with spinning (10 kHz, at the magic angle).

2.6. Cross Polarization

Thus far we have concentrated on the differences between liquid- and solid-state Hamiltonians and spectra, and how these differences can be overcome by utilizing techniques such as spin decoupling and MAS. To complete this section, we turn our attention to an additional difference between liquid- and solid-state NMR experiments. Even in liquid-state experiments that measure ^{13}C or ^{15}N chemical shifts or

J couplings, the magnetization is often initially transferred from neighboring protons and then transferred back to the protons for detection to exploit the higher sensitivity. In addition, as relaxation is usually more rapid for protons, one can minimize acquisition times.^[46] As a result of the difficulties involved in obtaining high-resolution solid-state ^1H NMR spectra, the majority of solid-state NMR experiments detect the magnetization of other nuclei such as ^{13}C , ^{31}P , and ^{15}N . The drawbacks of directly detecting low- γ nuclei such as ^{13}C and ^{15}N are low isotopic abundances, low spin polarization, and low signal intensity. These drawbacks can be circumvented by a solid-state NMR technique that combines both the high polarization and short relaxation time that is typical of ^1H NMR spectroscopy with high resolution (e.g. of ^{13}C and ^{15}N nuclei)—this would be the conceptual analogue of the INEPT and DEPT experiments.^[47]

To enhance the signals from rare nuclei such as ^{13}C and ^{15}N , many solid-state NMR experiments today routinely involve the transfer of polarization from abundant nuclei (usually ^1H nuclei) by using a technique called cross polarization (CP).^[1, 38, 39] The process of CP occurs through the tendency of the magnetization to flow from highly polarized nuclei to nuclei with lower polarizations when the two are brought into contact, similar to heat flow from a hot object to a cold object when the two are in thermal contact. For homonuclear spins, the magnetization can be exchanged through mutual energy-conserving spin flips (Figure 9b–c). For heteronuclear pairs such as ^1H and ^{13}C , these spin flips are not energy-conserving at high magnetic fields (see Figure 9a). Therefore, the exchange of magnetization must be driven externally by the application of RF fields.

Among the techniques for establishing a dipolar contact between two different spin systems I and S , a particularly effective approach is that of Hartmann and Hahn.^[48]

The Hartmann–Hahn method requires the simultaneous application of two continuous RF fields, one at the resonance frequency of the I spin and one at the resonance frequency of the S spin. The effect of any RF field is to rotate the magnetization about the axis of the applied field. The rotation or nutation rate depends on the frequency and amplitude of the RF field. An RF field that oscillates at the I -spin frequency, for example, 500 MHz, would have essentially no effect on S spins with a frequency of 125 MHz and vice versa. By applying two RF fields, one tuned to the I spins the other to the S spins, both the I and S spins can be rotated independently around a particular axis at rates determined by the amplitudes of the two applied fields. When the nutation frequencies of the I and S spins are equal, an energy-conserving dipolar contact between the two spin systems is created. The differences in energy are supplied by the RF fields. It is through this dipolar contact that the polarization is transferred between the I and S spins. One way to describe how this connection is established is by using a reference frame rotating at both the I and the S spin nutation frequencies. In the doubly rotating frame, the spacing between the spin-up and spin-down energy levels is equal for the I and S spins (Figure 11a).

The experimental implementation of this concept to obtain high-resolution NMR spectra of rare or dilute S spins is shown

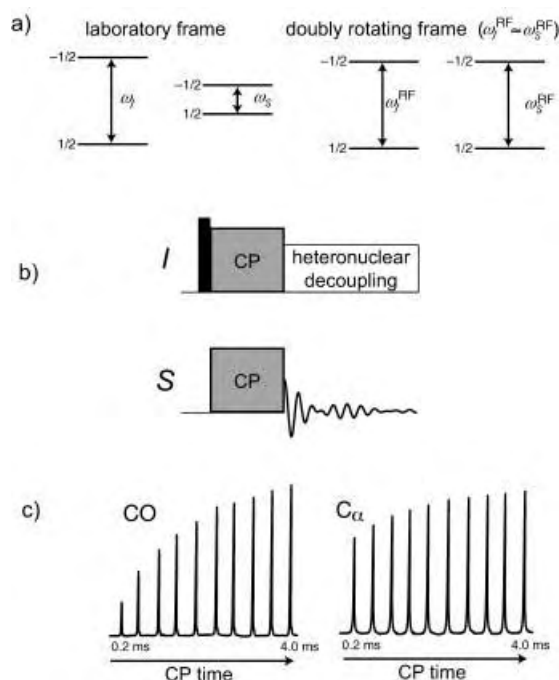


Figure 11. Hartmann–Hahn CP: a) The energy differences between the transitions of the I and the S spins can be made equal in a doubly rotating frame when the nutation frequencies on both spins are equal. b) Pulse sequence for CP of ^{13}C (S) nuclei by protons (I) with detection of the ^{13}C magnetization. c) Solid-state ^{13}C NMR spectra (125 MHz) of uniformly ^{13}C -labeled (10 %) glycine powder acquired by using the pulse sequence in b) as a function of the CP time. Because of the directly bonded H_α protons, the $^{13}\text{C}_\alpha$ nuclei are polarized more rapidly than the unprotonated carbonyl carbon nuclei.

in Figure 11 b. First, the proton magnetization is brought into the xy plane by a $\pi/2$ pulse. RF fields are then applied to the I and S spins for a period τ_{CP} , causing the magnetization to be exchanged between the I spins and the S spins in their respective rotating frame. Finally, the S spins are detected while the I spins are decoupled. This sequence forms the basis of proton-enhanced NMR spectroscopy^[1, 49] which, through the combination of CP and MAS,^[50, 51] opened the way to routine high-sensitivity, high-resolution, solid-state ^{13}C NMR spectroscopy. The increase in the S -spin magnetization during the CP mixing period τ_{CP} depends on the strength of the I – S dipolar coupling (Figure 11 c). The polarization buildup in the unprotonated carbonyl carbon atom requires a longer CP time than for the α carbon atom, which is quickly polarized by its bonded protons (Figure 11 c). Typical mixing times range from 100 μs to 10 ms. The polarization buildup curve starts to decay beyond a certain mixing time as a result of relaxation and magnetization-transport phenomena. A direct link between integrated signal intensities and stoichiometric abundances is no longer available owing to the many parameters involved, which is also true for liquid-state proton-enhanced or inverse spectroscopy.

The maximum enhancement for a CP contact period under the Hartmann–Hahn conditions $\gamma_I\omega_I = \gamma_S\omega_S$ is γ_I/γ_S (γ_I and γ_S = gyromagnetic ratios of spins I and S , respectively; ω_I and ω_S = nutation rates imposed by the RF fields).^[39] Modifications of the basic CP sequence can give sensitivity improvements beyond this theoretical enhancement through multiple

CP contact sequences.^[1] In most NMR experiments, the acquisition or sampling rate is dictated by the relaxation time (T_1) of the detected nuclei. Under CP conditions, the sampling rate depends on the relaxation time of the nuclei from which the magnetization is transferred. As the protons in the solid state typically relax more rapidly than most other spin $1/2$ nuclei, many more scans can be acquired in a given amount of time in such an experiment than in a simple single-pulse experiment that detects the rare ^{13}C nucleus directly. This point is illustrated in Figure 12, which shows a solid-state ^{13}C spectrum of (non- ^{13}C -enriched) alanyl histidine, both with and

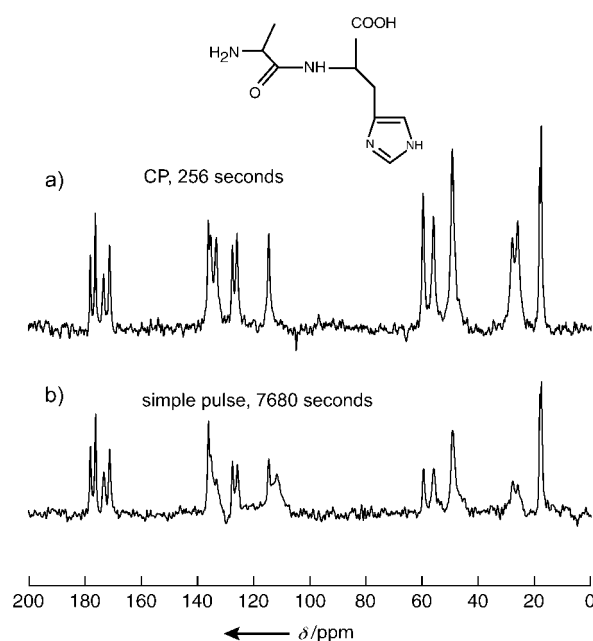


Figure 12. Solid-state ^{13}C NMR spectra (125 MHz) of unlabeled alanyl histidine powder: a) with CP by protons, and b) in a standard single-pulse experiment. Both spectra were recorded under MAS at a speed of 12 kHz and with CW ^1H decoupling. The recycle delay for the spectrum in a) was 2 s. The recycle delay for the spectrum in b) was 60 s, owing to the long ^{13}C relaxation time (~ 18 s for this sample).

without CP from the protons. The signal intensities in the two experiments are not directly proportional for reasons mentioned above. Whereas the overall signal-to-noise ratios of the two spectra in Figure 12 a, b are comparable (~ 1.7 :1 for the rightmost peak) the acquisition time of the non-CP spectrum was 45 times longer than for the CP spectrum, owing to the long relaxation time T_1 (~ 18 s) of the carbon nuclei.

The elegant techniques outlined in this section are powerful and often sufficient tools for many applications in basic chemical analysis and characterization of solid samples. As shown in Figure 12 a, a combination of high-power CW decoupling, cross-polarization, and high-speed MAS, can rapidly yield one-dimensional solid-state spectra of compounds containing spin $1/2$ nuclei of low natural abundance such as ^{13}C , ^{15}N , and ^{29}Si , with sufficient spectral sensitivity and resolution. However, as in liquid-state NMR, more advanced multipulse and multidimensional techniques can be utilized to perform a more detailed analysis of the structure and dynamics of a sample. In the following three sections, we provide an overview of such techniques, with primary emphasis on those methods that are easily implemented.

3. Multidimensional NMR and Multipulse Decoupling

The majority of solid-state NMR experiments performed on organic or biological systems involve the detection of low-abundance nuclei such as ^{15}N and ^{13}C . One reason for this is the fact that the homonuclear dipolar coupling can often be neglected because the probability of having two NMR-active nuclei next to each other is very low. In addition, the low gyromagnetic ratios of these nuclei make the strengths of the homonuclear couplings very small, even when the nuclei are directly bonded. MAS at moderate speeds (a few kHz) can eliminate their effects altogether. In contrast, as the homonuclear dipolar coupling between neighboring protons can be strong (in the order of ~ 100 kHz). Furthermore, because protons have an abundance of almost 100%, MAS does little to narrow the signal, as was shown in Section 2. Reasonably high resolution is achieved in solid-state ^1H NMR spectroscopy through active pulse decoupling of the ^1H spins during signal detection (to be precise: not during the actual sampling of a data point of the signal, but between different data points in the acquisition).^[52–54] These experiments are often very demanding on hardware. A simpler and often more reliable way of acquiring high-resolution spectra of protons is to detect the magnetization *indirectly* by using multidimensional NMR spectroscopy. We first review the general acquisition of multidimensional spectra and then we describe methods of multipulse decoupling sequences that can be used in the indirect dimension of these experiments to minimize the effects of the homonuclear coupling between abundant nuclei.

3.1. 2D NMR Spectroscopy: The WISE Experiment

Although 2D NMR spectroscopy has many different applications,^[54–56] the basic form of all these experiments is essentially the same (Figure 13a). First, the magnetization is prepared in a state appropriate to whatever properties are to be detected in the indirect dimension. For instance, to detect a standard spectrum of the chemical shifts in the indirect dimension, the preparation phase could involve a $\pi/2$ pulse or possibly a CP sequence. Next, the magnetization is allowed to evolve for a time t_1 under a specific NMR Hamiltonian. For instance, if one wishes the I spins in an I – S spin system to evolve only under H_{II} and H_{CS} , then the S spins should be decoupled to remove H_{IS} (a π pulse in the S -spin channel at $t = 1/2 t_1$ suffices for static samples). To evolve only under H_{II} , a π -pulse or a train of π -pulses can be applied during t_1 to create echoes that refocus H_{CS} .

Following the evolution period t_1 , an optional mixing pulse (or a sequence of pulses) is used to prepare the magnetization for the final detection period t_2 . As with the initial preparation period, the nature of the mixing period depends largely on the spectrum desired. In heteronuclear experiments, it is often necessary to transfer the magnetization from one set of spins to another. For instance, in an experiment correlating ^1H and ^{13}C chemical shifts, the mixing period might involve CP from

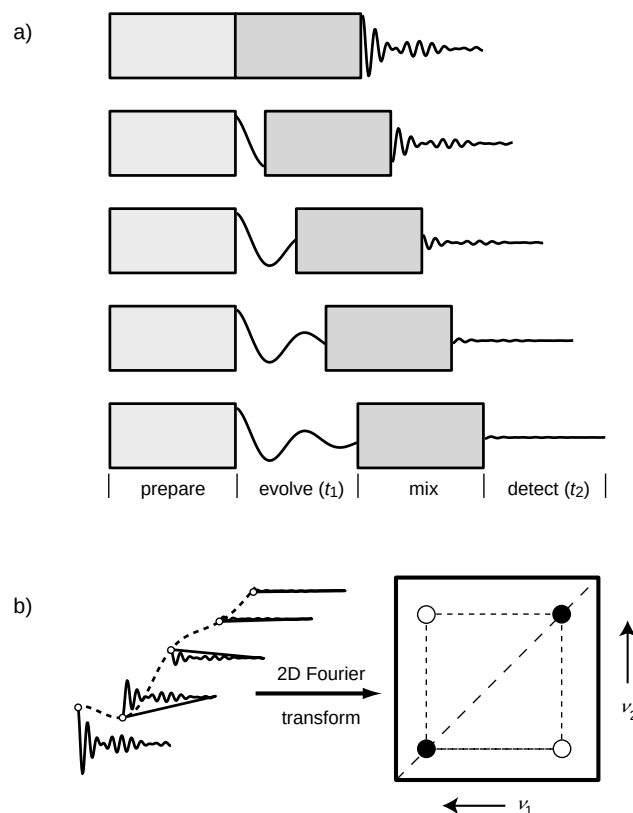


Figure 13. a) Pulse sequence for 2D NMR experiments: The second dimension is obtained by repeating the 1D experiment with sequential time periods t_1 to stroboscopically detect the evolution of the prepared state. b) 2D Fourier transform: First a Fourier transform is performed on each directly detected t_2 signal, followed by a Fourier transform in the t_1 dimension. Since the evolution of the magnetization during t_1 modulates the directly detected t_2 signal, a double Fourier transform produces a spectrum in which the indirectly detected spectrum is correlated with the directly detected spectrum. (Reproduced from ref. [43], with permission.)

the ^1H spins to the ^{13}C spins. Once the mixing period is complete, the resulting magnetization is detected as usual in the direct dimension t_2 .

A 2D free-induction decay is acquired by assembling several 1D free-induction decays acquired at increasing times t_1 . The different 1D spectra are modulated in t_1 based on the Hamiltonians chosen during this time period. By performing a Fourier transform in both dimensions t_1 and t_2 , a 2D spectrum is produced which correlates the interactions detected in the indirect dimension t_1 with the interactions detected in the direct dimension t_2 (Figure 13b).^[55]

A simple example of a useful 2D solid-state NMR experiment is the Wideline SEparation (WISE) experiment (Figure 14a).^[57, 58] The ^1H magnetization is initially rotated into the xy plane by a $\pi/2$ pulse. During t_1 , the magnetization then evolves under the ^1H chemical shifts, the homonuclear dipolar couplings, and the heteronuclear couplings to ^{13}C nuclei ($H_{CS} + H_{II} + H_{IS}$), after which it is transferred through CP to neighboring ^{13}C nuclei for detection in t_2 . A 2D WISE spectrum correlates broad ^1H resonances with the relatively narrow resonances of the neighboring ^{13}C nuclei under MAS (Figure 14b). In this manner, a normally unresolvable 1D ^1H NMR spectrum is separated into the contributions of

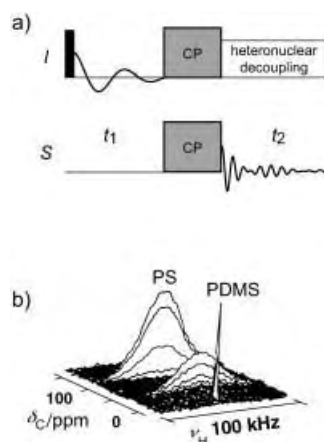


Figure 14. The WISE experiment: a) Pulse sequence for the correlation of ^1H and ^{13}C resonances with WISE. b) 2D ^1H – ^{13}C WISE NMR spectrum of a polystyrene-*b*-polydimethylsiloxane (PS-*b*-PDMS) block copolymer (1:1). The broad ^1H signals correspond to rigid protons, whereas the narrow ^1H signals correspond to mobile protons, in which the homonuclear dipolar coupling is partially averaged out. (Adapted from ref. [57], with permission.)

various ^1H sites in proximity to spectroscopically resolved ^{13}C sites. Usually a short CP period assures that mainly nearby (or bonded) nuclear spins are correlated. The spectrum in Figure 14b is taken from a block copolymer of polystyrene and polydimethylsiloxane (1:1). The resonance line widths of the ^1H sites in the polymer blend provide information about local molecular mobility of the different polymer components. The greater the mobility of a ^1H nucleus, the narrower its ^1H NMR signal. Recently, this method has been used to characterize nanostructured inorganic–organic composites.^[59, 60]

Although WISE does allow the separation and study of broad ^1H resonances based on their coupling to nearby ^{13}C nuclei, the experiment does not achieve the original goal set forth in this section: to remove the ^1H homonuclear coupling and to obtain a resolved ^1H NMR spectrum of the chemical shifts. In Section 3.2 we show that by using appropriate *homonuclear* decoupling sequences during t_1 , the effects of the ^1H – ^1H dipolar coupling can indeed be strongly reduced, while the chemical shift evolution is preserved. The application of these RF pulse sequences during t_1 is notably less demanding than in experiments in which pulses and detection periods are interleaved.^[52–54]

3.2. Homonuclear Dipolar Decoupling

In the previous sections, we discussed *heteronuclear* dipolar decoupling, in which the dipolar coupling between two sets of spins I and S is removed by a strong RF field applied to the I spins while the S spins evolve. The success of CW decoupling is a result of the form of H_{IS} , which is proportional to $I_z S_z$. By constantly rotating the I spins around one axis with a continuous RF field, the sign of the energy determined by $I_z S_z$ oscillates between positive and negative, producing a time-averaged value of zero. On the other hand, the *homonuclear* dipolar coupling is proportional to $3I_{1z}I_{2z} - (\mathbf{I}_1 \cdot \mathbf{I}_2)$. As, by

definition, the magnetization of the two nuclei cannot be manipulated independently, a CW irradiation of the I spins around one axis will have no effect on the sign of the energies. In a more elaborate approach, one can show that if the direction of the local field exerted by the spins on each other is toggled between *all three* axes, the effect of the coupling vanishes. This has been implemented early on in a multipulse sequence by Waugh et al. (WAHUHA or WHH-4).^[61] Although this sequence is not used much any more, it still serves as a good illustrative example of how such techniques work, and how new ones can be designed.

3.2.1. WAHUHA

To understand this and similar sequences, it is helpful to consider a rotation of the reference frame rather than rotations of the spins. Although the rotations of, for example, z magnetization into x magnetization could be considered, the magnetization could also be kept constant and the reference frame rotated in the opposite direction. In this way H_{II} becomes H_{xx} , H_{yy} , or H_{zz} , depending on how the reference frame is rotated by the RF pulses (Figure 15a). H_{xx} , H_{yy} , and H_{zz} are described in Equations (10)–(12)

$$H_{xx} = -d/2(3\cos^2\theta - 1)(3I_{1x}I_{2x} - (\mathbf{I}_1 \cdot \mathbf{I}_2)) \quad (10)$$

$$H_{yy} = -d/2(3\cos^2\theta - 1)(3I_{1y}I_{2y} - (\mathbf{I}_1 \cdot \mathbf{I}_2)) \quad (11)$$

$$H_{zz} = -d/2(3\cos^2\theta - 1)(3I_{1z}I_{2z} - (\mathbf{I}_1 \cdot \mathbf{I}_2)) \quad (12)$$

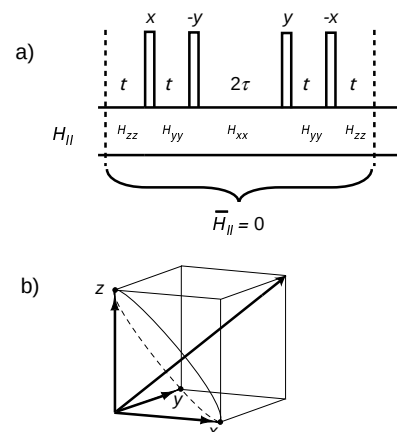


Figure 15. a) Pulse sequence for one cycle of the four-pulse WAHUHA decoupling sequence, in which the magnetization is aligned sequentially along the x , y , and z axes. b) The Lee–Goldburg sequence is the continuous analogue, in which the spins undergo rotation about an axis inclined at the magic angle in spin space (analogous to mechanical magic angle spinning in real space).

Since the scalar product of the two angular momentum operators $\mathbf{I}_1 \cdot \mathbf{I}_2$ can be defined as in Equation (13), the sum $H_{xx} + H_{yy} + H_{zz} = 0$.

$$\mathbf{I}_1 \cdot \mathbf{I}_2 = I_{1x}I_{2x} + I_{1y}I_{2y} + I_{1z}I_{2z} \quad (13)$$

Therefore, any pulse sequence that shifts the reference frame along the x , y , and z axes (and with it the “direction” of

the local dipolar fields) for equal periods of time should successfully eliminate the homonuclear dipolar coupling. On the other hand, the chemical shift in the usual laboratory frame is proportional to I_z alone. When the reference frame is rotated sequentially along all three axes (during three consecutive time periods) the chemical shift will be proportional to $(I_x + I_y + I_z)/3$. The overall average chemical shift evolution is then scaled by a factor of $1/\sqrt{3}$ relative to the evolution without the decoupling sequence.^[61] Thus, the WAHUHA sequence accomplishes our goal of eliminating the ^1H – ^1H homonuclear dipolar coupling while still allowing the magnetization to evolve under H_{CS} .

We could also consider allowing the reference frame to continuously change from the x to the y and the z direction. This has been implemented in an early windowless sequence called Lee–Goldburg decoupling.^[62] The magnetization (or the reference frame) is rotated about an effective magnetic field in the rotating frame that can be created by applying an off-resonance RF irradiation. If the RF strength ω_{RF} is adjusted so that $\omega_{\text{RF}} = \sqrt{2}\Delta\omega$ ($\Delta\omega$ = frequency offset), an effective RF field is produced in the rotating frame and is inclined at the magic angle with respect to z . The magnetization (or the reference frame) follows a conical path, crossing the z , y , and x axes at equal angles (Figure 15b). In MAS, the spatial averaging analogue of the above techniques, one would have exactly the same effect if sufficiently rapid sample reorientation were possible. There is one exception, though: the chemical shift is not scaled in MAS.

3.2.2. Decoupling Supercycles

Although the WAHUHA sequence is theoretically very effective in removing the homonuclear dipolar interaction, complications are often encountered in practice. Pulse imperfections and chemical-shift-offset effects can interfere with ^1H homonuclear decoupling when using WAHUHA. These problems can be circumvented to a large extent by the use of decoupling supercycles, which are repetitive implementations of simple sequences such as WAHUHA, with specific phase shifts of the RF pulses.^[63, 64] For example, the supercycle MREV-8^[65, 66] is a composite sequence of two WAHUHA pulse trains, with a 180° phase shift in two of the last four pulses (Figure 16a). This sequence has been shown to be much more robust against various pulse imperfections and frequency-offset effects.^[38] In addition to MREV-8, there exist more complex decoupling supercycles, including BR-24,^[67] BLEW-12,^[68] CORY-24,^[69] TREV-8,^[70] and MSHOT.^[71]

Often, symmetrization principles are used to improve the performance of different sequences. In the continuous Lee–Goldburg decoupling sequence mentioned above, the symmetrization is implemented by switching the offset between $+\Delta\omega$ and $-\Delta\omega$ and simultaneously changing the phase of the RF irradiation by 180° (Figure 16b). Errors in the averaging trajectories are removed by this procedure (Figure 16c). This method is called the frequency-switched Lee–Goldburg (FS-LG) sequence and has been extremely useful in many applications.^[72–79]

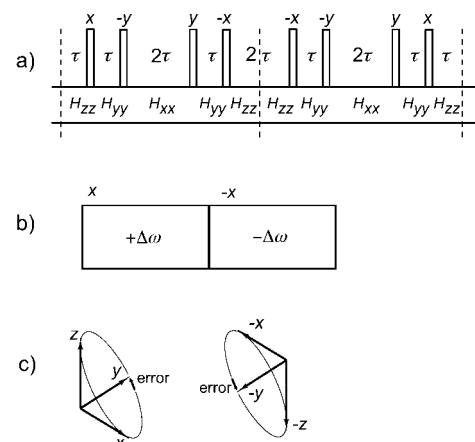


Figure 16. a) Pulse sequence for one cycle of the MREV-8 decoupling sequence; b) FS-LG decoupling; c) compensation for errors in the magnetization trajectories with the FS-LG sequence.

A complication that must be considered when using a homonuclear decoupling sequence under MAS conditions is the possible interference between sample spinning and multipulse decoupling. This affects the time-averaging of H_{II} in different ways, in particular when the spinning speed is very high.^[75] Since this interference often degrades the effectiveness of multipulse decoupling sequences, it is advantageous to optimize the multipulse sequence for MAS. First, the pulse cycles should be rotor-synchronized; that is, an integer number of pulse trains should be applied per rotor cycle. Second, as many pulse cycles should be applied per rotor period as possible. However, these guidelines make the implementation of long sequences (especially the 24-pulse BR-24 sequence) very difficult under fast MAS, in which the rotor cycle can be as short as $30\ \mu\text{s}$. A powerful alternative involves FS-LG.^[72, 73] The full cycle time is typically of the order of 10 – $20\ \mu\text{s}$, which is still significantly shorter than the rotor period at routine speeds (10 – $20\ \text{kHz}$). In practice, FS-LG has proven to be a very effective decoupling sequence at different spinning speeds. Lee–Goldburg irradiation can also be used instead of a continuous-wave field during CP. This leads to homonuclear decoupling during the heteronuclear magnetization transfer, which makes the transfer more selective to directly bonded atoms. This has been exploited to measure the distance between heteronuclei.^[80, 81]

Promising new homonuclear decoupling schemes are being developed that are based on a new class of symmetry rules, allowing for a minimization of the RF–rotation interference.^[82]

3.2.3. Multiple-Quantum Spectroscopy

Although it is possible to remove the effects of the homonuclear dipolar interaction by multipulse sequences, it is also possible to tailor the interaction Hamiltonian to a specific form. The appropriate multipulse sequence can be applied to create an effective double-quantum dipolar Hamiltonian [Eq. (14)].^[83]

$$H_{\text{dq}} = -d/2(3\cos^2\theta - 1)(I_{1+}I_{2+} + I_{1-}I_{2-})$$

In the presence of many coupled spins, this Hamiltonian creates high multiple-quantum coherences, which are limited only by the size of the spin system. One can therefore use this method for spin counting and for determining cluster sizes and the dimensions of coupling networks in solids and in liquid crystals.^[84–86] Since multiple-quantum coherences cannot be detected directly, 2D NMR spectroscopy is required to observe the evolution of multiple-quantum coherences in the indirect dimension t_1 . Selective excitation of certain multiple-quantum coherences has been achieved by using appropriate supercycles.^[87] For molecules oriented by the magnetic field or other means, these methods have led to the simplification of spectra,^[88] which aided in resonance assignment and structure determination. Recently, the alignment of β strands in amyloid fibrils has been investigated by using multiple-quantum NMR spectroscopy.^[89]

3.3. Heteronuclear Correlation

We complete our discussion of homonuclear dipolar decoupling by describing the solid-state heteronuclear correlation (HETCOR) experiment.^[90, 91] Similar to heteronuclear single-quantum (HSQC) and multiple-quantum (HMQC) correlation experiments in liquid-state NMR spectroscopy,^[46] the HETCOR experiment in solids correlates ^1H chemical shifts with the chemical shifts of another nucleus, such as ^{13}C or ^{15}N . One possible HETCOR sequence for ^1H – ^{13}C correlations is shown in Figure 17. As in the WISE sequence, the ^1H magnetization is first excited by a $\pi/2$ pulse.

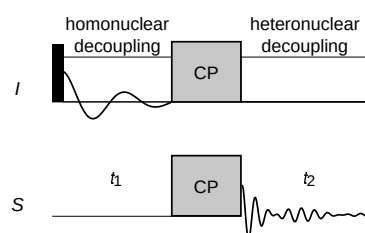


Figure 17. Principle of the HETCOR experiment: The pulse sequence is identical to that of the WISE experiment, except for the incorporation of homonuclear dipolar decoupling in the indirect dimension. Heteronuclear decoupling of the S spins can also be incorporated into the indirect dimension.

During the t_1 period, the protons are decoupled from each other by using one of the decoupling techniques mentioned in Section 3.2. An optional CW-decoupling field can be applied to the ^{13}C nuclei so that H_{IS} is also removed and the protons evolve only under their chemical-shift Hamiltonian H_{CS} . Following the t_1 period, the magnetization is transferred to the ^{13}C nuclei by CP, and is then detected during t_2 . Figure 18 shows a ^1H – ^{13}C HETCOR spectrum of a ^{13}C -labeled chlorophyll a aggregate obtained by using FS-LG homonu-

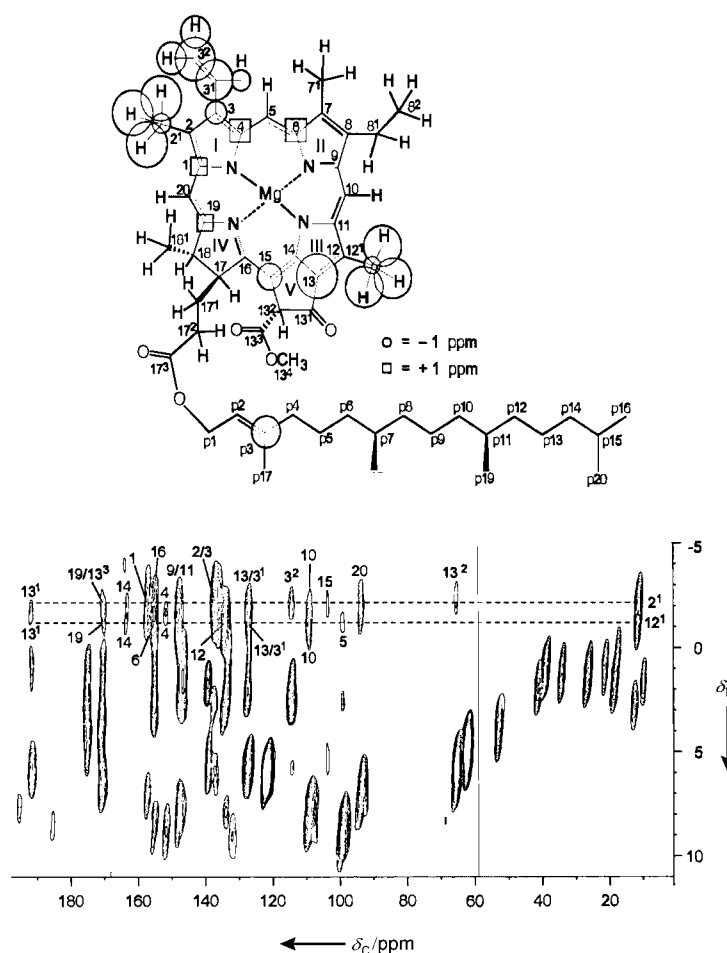


Figure 18. ^1H – ^{13}C HETCOR spectrum of uniformly ^{13}C -enriched chlorophyll a aggregates in water obtained at a field strength of 14.1 T and with a spinning speed of 13 kHz. A pulse sequence similar to that shown in Figure 17 was used. The high resolution in the proton dimension is a result of the FS-LG decoupling during the t_1 period. δ_C and δ_H are the chemical shifts of the carbon atoms and the protons, respectively. (Reproduced from ref. [92], with permission.)

clear dipolar decoupling during t_1 .^[92] Although the ^1H resonances are still somewhat broad (~ 1 – 2 ppm), they are sufficiently narrow to observe and measure the variety of ^1H chemical shifts in the sample.

Unlike HSQC or HMQC in liquids, which both utilize through-bond J couplings to transfer polarization, HETCOR relies on dipolar interactions and thus correlates spatially close bonded and nonbonded nuclei. As was shown in Figure 11 c, strongly coupled spins transfer polarization more rapidly than weakly coupled spins. The distance of magnetization transport during CP can therefore be controlled to some extent by varying the CP mixing time. For long CP mixing times, the magnetization will be transported farther away, even to carbon atoms that are not directly bonded. By comparing HETCOR spectra taken at different mixing times, it is possible to gain insight into the local structure and atomic distribution in the sample.

Closely related to the HETCOR experiment is the separated local field experiment, which allows one to correlate the heteronuclear I – S dipolar coupling constants to the frequency of the chemical shift of the S spin in single crystals or oriented molecules (similar to J spectroscopy in liquids).^[93–95]

In this experiment, a π pulse acting on both the I and the S spins at $t = \frac{1}{2}t_1$ refocuses the chemical shift as well as the CSA, while the homonuclear coupling is removed by one of the homonuclear decoupling sequences. Therefore, only the heteronuclear I – S coupling will be in effect during t_1 . A variant of this technique, called PISEMA (polarization inversion spin exchange at magic angle), has successfully been used to determine the secondary structures of solid proteins.^[96–98] The concerted variations in the ^{13}C and ^{15}N chemical shifts and the ^1H – ^{13}C and ^1H – ^{15}N dipolar couplings cause the signals that arise from different residues to lie along circular paths, the form of which is characteristic of the secondary structure.

3.4. Multipulse Heteronuclear Dipolar Decoupling

Before leaving the discussion of multipulse NMR spectroscopy, we return once again to the topic of heteronuclear dipolar decoupling. We have limited our discussion of heteronuclear decoupling to CW irradiation. However, the beauty and efficiency of multipulse decoupling in the homonuclear case raises the question as to whether an efficient multipulse sequence can be employed for heteronuclear decoupling. In liquids, a wealth of multipulse sequences are available, including MLEV-16, WALTZ-16, and GARP.^[35, 99–101] In the solid state, however, because of the magnitude of the coupling constants and interference effects between heteronuclear and homonuclear couplings (see Section 2.2), these sequences can be inferior to CW decoupling. In addition, sign changes of the dipolar coupling constants under MAS result in a partial cancellation of the effects of these multipulse sequences.^[43] The heteronuclear decoupling technique called two-pulse phase modulation (TPPM)^[102] was shown to produce results superior to simple CW decoupling, particularly under MAS. As shown in Figure 19 the TPPM sequence breaks the CW irradiation into

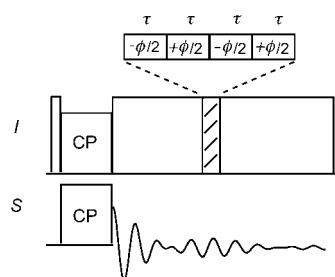


Figure 19. TPPM decoupling sequence: RF irradiation is applied continuously, with an alternating phase shift of $+\phi/2$ and $-\phi/2$, for every time period τ . The values of ϕ and τ are optimized before the experiment to achieve maximum decoupling efficiency.

a series of discrete time periods τ (in the order of 3–20 μs) during which the phase of the irradiation alternates between $+\phi/2$ and $-\phi/2$. Typically, the values of ϕ and τ must be optimized for a particular sample in order to produce the smallest possible line widths. Figure 20 shows the spectra of ^{13}C -labeled calcium formate acquired under proton TPPM

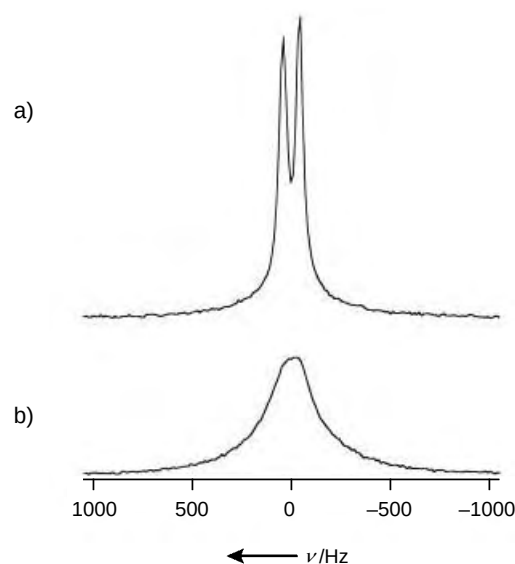


Figure 20. ^{13}C CP MAS NMR spectrum of calcium formate: a) with TPPM decoupling, and b) with CW decoupling. In both cases, the spinning speed was 10.7 kHz. The splitting observed in a) is a result of the chemical shift difference of 80 Hz between the two crystallographically different ^{13}C sites in calcium formate. (Reproduced from ref. [102], with permission.)

decoupling (Figure 20a) and under CW decoupling (Figure 20b). A typical ϕ value is about 50° , and τ is often adjusted to give a flip angle of approximately 150° . With the improved resolution that results from TPPM decoupling, the difference in chemical shifts (80 Hz) between the two crystallographically non-equivalent ^{13}C sites in calcium formate is resolved, which is not possible with standard CW decoupling under the same conditions. Although a rigorous study of why this procedure improves heteronuclear decoupling is still missing, it is believed that the favorable properties of the TPPM sequence are related to a facilitation of flip-flop transitions among the abundant proton nuclei, which assist the heteronuclear decoupling in a process called “self-decoupling”.^[103–106] The less stringent requirements for the decoupling power of the TPPM sequence are particularly apparent with high-speed MAS. As can be seen in the ^{13}C NMR spectrum of (non- ^{13}C -enriched) cyclosporin A (Figure 21), line widths of 10 to 50 Hz can be obtained and the vast majority of the resonances in the spectrum are resolved. Although alternative decoupling methods have been proposed,^[107, 108] TPPM is still the most widely used sequence.

In this section, we showed that it is possible, through a combination of multipulse homonuclear decoupling and 2D NMR spectroscopy, to obtain high-resolution solid-state ^1H NMR spectra. Phase modulation of heteronuclear decoupling sequences can produce CP MAS spectra of rare spins with a resolution close to that of liquid-state spectra. The concept of using a series of pulses to manipulate a Hamiltonian has applications far beyond hetero- and homonuclear decoupling. As will be seen in Section 4, multipulse sequences and 2D NMR spectroscopy can be used to derive information from interactions (e.g. CSA or dipolar coupling) that are normally removed under MAS.

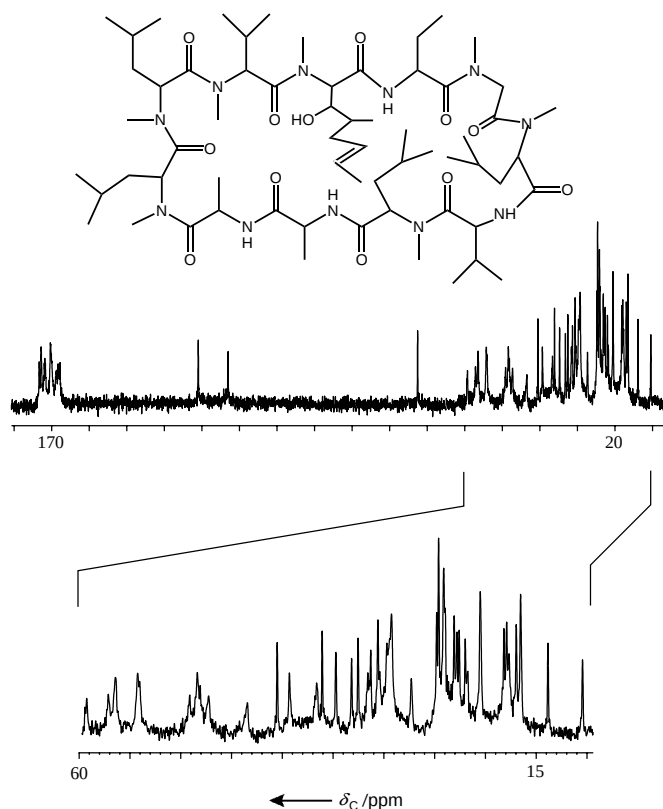


Figure 21. ^{13}C CP MAS NMR spectrum (125 MHz) of cyclosporin A (see structure). The spectrum was measured with a spinning frequency of 33.3 kHz using TPPM decoupling ($\phi = 20^\circ$). With the combination of high spinning speeds and TPPM decoupling, the ^{13}C line widths are 10–50 Hz. (Courtesy of A. Lesage and L. Emsley).

4. Reintroducing Lost Hamiltonians

Section 2 of this review addressed the question of how to remove some of the undesirable effects of interactions that are found in solid-state NMR spectroscopy, for example, dipolar coupling and CSA, by utilizing techniques such as MAS and high-power spin decoupling. The resulting spectrum has a resolution close to that of a liquid-state NMR spectrum (e.g., see Figures 12a and 21). However, the signals produced by dipolar coupling and CSA provide information about the environment of the nuclei, and this information is lost by removing these interactions through spinning and decoupling. In the following section, we discuss techniques that selectively reintroduce dipolar couplings and CSA under MAS to measure distances or establish correlations based on proximity. Although a vast number of methods can be used to reintroduce the dipolar coupling and the CSA, we discuss in detail only a limited number of techniques that serve both as representative examples and as basic building blocks for more complicated experiments.

4.1. Distance Measurements in Solids

An integral part of structure determination in molecular systems is the measurement of distances between atoms. In

liquid-state NMR spectroscopy, this is usually accomplished through the measurement of cross-relaxation rates by nuclear Overhauser effect spectroscopy (NOESY).^[46, 109] These relaxation mechanisms can usually be neglected in solids, as the magnetization can be transferred more directly through the coherent action of heteronuclear and homonuclear dipolar couplings. As shown in Equation (2), the strength of the dipolar coupling between two nuclei is proportional to the inverse cube of the internuclear distance, which is the key to obtaining structural information. However, with the exception of couplings that involve protons (e.g., ^1H – ^1H or ^1H – ^{13}C), the effects of homonuclear and heteronuclear dipolar coupling are often removed under MAS, since the spinning speed can routinely be made greater than the magnitude of the coupling constant. Thus, to measure dipolar couplings while retaining the high resolution afforded by MAS, the couplings must be selectively reintroduced.

4.1.1. Heteronuclear Recoupling: REDOR

The heteronuclear dipolar Hamiltonian introduced in Equation (2) contains the orientation-dependent term $(3\cos^2\theta - 1)$, and the spin-component-dependent term $I_z S_z$. In Section 3 we discussed how one can manipulate the spin component by CW and TPPM decoupling, or the spatial component by MAS. Both methods lead to the removal of the effects of this interaction. In the case of CW decoupling, it is easy to turn this interaction on and off by controlling the RF field. Recoupling a dipolar interaction that is removed by MAS is more complicated, as it is not practical to rapidly turn the spinning on and off.^[110] By properly manipulating the spin component of the dipolar Hamiltonian in synchrony with the sample rotation, however, it is possible to partially undo the effect of MAS on the heteronuclear dipolar coupling.

For a single crystal that moves along a conical path under MAS, the value of the effective heteronuclear dipolar coupling interaction determined by H_{IS} changes both in intensity and sign (Figure 22a). Over a single rotation period,

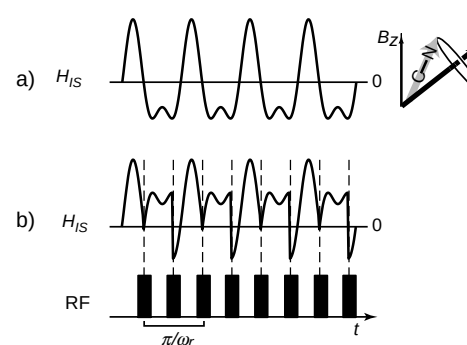


Figure 22. Time-dependent behavior of the heteronuclear dipolar coupling: a) The time-dependent evolution of H_{IS} with MAS; as the integral of the dipolar coupling over a single rotor cycle is zero, the dipolar coupling is effectively removed if the spinning speed is sufficiently high. Right: an internuclear vector between a carbon nucleus and a nitrogen nucleus traverses a conical path. b) The time-dependent evolution of H_{IS} with MAS with two π pulses on the S spin per rotor cycle. Each π pulse reverses the sign of the dipolar coupling Hamiltonian, thus creating a time evolution which no longer averages to zero. (Reproduced from ref. [43], with permission.)

the integrated magnitude of H_{IS} is zero, so the dipolar coupling is effectively removed under MAS. However, by applying RF pulses at proper intervals, it is possible to interfere with the trajectory of H_{IS} so that the value of H_{IS} is not zero over one rotation period. By applying π pulses, the S spin magnetization is flipped ($S_z \rightarrow -S_z$) and the sign of H_{IS} changes. Once again we point out that it is *not* the Hamiltonian that is directly manipulated but the spins. The equivalent picture of rotating the reference frame instead of the spins leads to the description of an effective Hamiltonian that changes sign. Indeed, by applying two π pulses per rotation period (Figure 22b), the evolution of H_{IS} can be altered in such a way that approximately 70% of the heteronuclear dipolar coupling is recoupled (i.e. the integrated magnitude of H_{IS} is 70% of its static value).

This two- π -pulse technique, known as rotational echo double resonance (REDOR),^[111] is a powerful tool for determining dipolar couplings between two different nuclear species such as ^{13}C and ^{15}N . The pulse sequence for REDOR is shown in Figure 23. The ^{13}C nuclei are subjected to a $\pi/2$ pulse

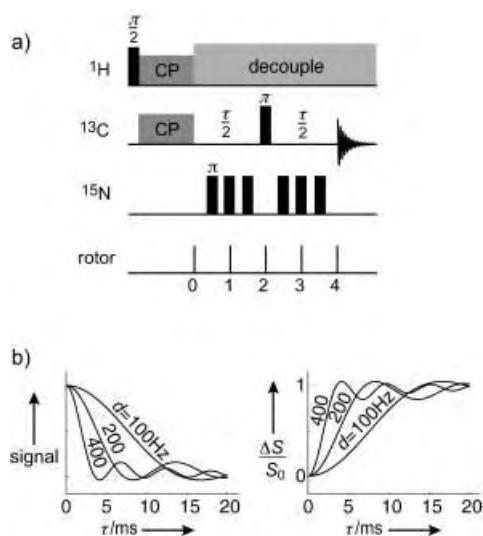


Figure 23. a) The REDOR pulse sequence: CP of the ^{13}C nuclei is followed by a period τ in which the ^{13}C magnetization is dephased by the application of a series of rotor-synchronized pulses on the ^{15}N magnetization, which recouple the ^{13}C – ^{15}N dipolar coupling; the signal decays faster for larger coupling constants. b) Usually, the dephasing curves in the lower right hand corner are used, which show the amount of dephasing relative to the initial signal intensity ($\Delta S/S_0$). Apart from a scaling factor, these curves are mirror images of the actual dephasing curves on the left.

or are polarized through CP from the protons. During τ_m , two ^{15}N π pulses are applied per rotation period, so that the ^{13}C – ^{15}N dipolar coupling is reintroduced. When a π pulse is applied at $t = 1/2\tau_m$ in the ^{13}C channel instead of the ^{15}N channel, recoupling of heteronuclear coupling that involves a third nuclear species is avoided. The experiment is repeated in the absence of the ^{15}N pulses and the two spectra are compared. Under the influence of the (recoupled) ^{13}C – ^{15}N dipolar coupling, the ^{13}C magnetization decays as a result of an averaging effect of the powder sample. By measuring the decay of the magnetization with increasing τ_m , and dividing the intensities by the signals of the “natural” decay measured

without recoupling, a REDOR decay curve such as that shown in Figure 23b can be created. Figure 24 shows an experimental dephasing curve acquired for ^{13}C , ^{15}N -labeled (10%) glycine. From the fitted line, a ^{13}C – ^{15}N dipolar

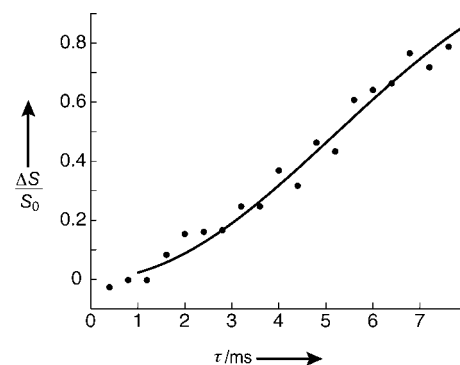


Figure 24. Dephasing curve: ^{13}C magnetization in ^{13}C - and ^{15}N -labeled glycine as a function of the length of the dephasing time τ . $\Delta S/S_0$ (the REDOR difference) is the normalized difference between the ^{13}C signal intensities with and without the ^{15}N pulses. By fitting the decay of the ^{13}C magnetization, the ^{13}C – ^{15}N dipolar coupling was determined to be 195 Hz.

coupling constant of 195 Hz was obtained. From Equation (3), the ^{15}N – ^{13}C internuclear distance was found to be 2.47 Å. As the strength of the heteronuclear dipolar coupling approaches ~ 25 Hz, it becomes very difficult to determine distances by using REDOR. This corresponds to a ^{15}N – ^{13}C distance of ~ 5 Å and a ^{13}C – ^{31}P distance of ~ 7.5 Å. These distances exceed those typically studied in liquid-state NMR spectroscopy^[46, 109] and they can provide useful constraints in structural studies of solids.

When the dephasing curve is a sum of the individual curves of several isolated spin pairs, a dipolar coupling constant spectrum can be obtained by using a so-called REDOR-transform.^[112] Complications may arise when more than two spins are coupled. For this case, special techniques have been proposed for obtaining individual the coupling constants.^[113, 114] A careful study of the viability of distance measurements in multiple-spin systems of unknown structures by REDOR-type recoupling techniques has been conducted by Fyfe and co-workers.^[115, 116] F–Si distances in zeolites have been measured in this way.^[117]

Frequency-selective heteronuclear recoupling can be achieved by using selective pulses on one of the channels, and has been employed, for example, to measure ^{13}C – ^{15}N distances in uniformly labeled proteins.^[118, 119] REDOR is not the only method to recouple heteronuclear dipolar interactions: other techniques are based on windowless frequency-, phase-, and amplitude-modulated sequences,^[120, 121] and, strictly speaking, CP is a type of heteronuclear recoupling sequence.

4.1.2. Homonuclear Recoupling: DRAMA and RR

Homonuclear dipolar recoupling can be accomplished in much the same way as heteronuclear dipolar recoupling—manipulation of the spin component of the dipolar Hamiltonian influences the motional averaging produced by the spinning rotor. The main difference between heteronuclear

and homonuclear dipolar recoupling lies in the difficulty of individually addressing different homonuclear spins. In REDOR, one can repeatedly alternate the sign of H_{IS} by applying pulses to either the I or the S spin. In a homonuclear spin system I_1I_2 the two spins have very similar resonance frequencies, so any π pulse intended to change the sign of I_{1z} , will also result in changing the sign of I_{2z} . Thus, the application of a π pulse has little effect on the overall evolution frequencies determined by H_{II} .

One alternative to using π pulses is to use $\pi/2$ pulses, which change the orientation of the quantization axis of the dipolar coupling. In Figure 22a, we showed that over a single rotation period, the spatial evolution of the dipolar Hamiltonian is such that its average value is zero. However, by toggling between one or more of the Hamiltonians in Equations (10)–(12) during the rotation period by the application of $\pi/2$ pulses, the averaging produced by MAS can be interrupted. One such technique is DRAMA (dipolar recovery at the magic angle).^[122] During this sequence, two $\pi/2$ pulses per rotation period toggle the reference frame from the z axis to the y axis and back again (Figure 25a). Under ideal conditions, the reference frame is directed along the z axis for half of the rotation period ($\tau = \tau_r/2$) and along the y axis for the other half. DRAMA recouples up to 45 % of the homonuclear dipolar coupling. Because the two-pulse sequence also recouples the CSA under MAS, a better implementation of DRAMA also includes π pulses to refocus the CSA (Figure 25b).

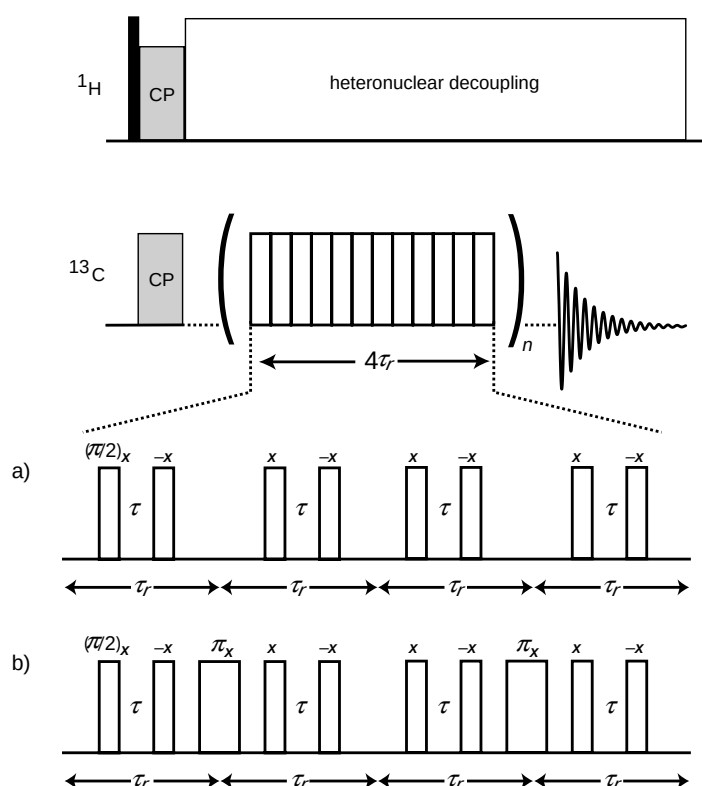


Figure 25. a) Pulse sequence for one cycle of the DRAMA homonuclear dipolar recoupling sequence consisting of $\pi/2$ pulses only. b) The partial recoupling of the CSA that occurs under the sequence in a) can be removed applying a π pulse at the end of each rotor cycle. τ_r = Rotor period.

Distance determination with DRAMA is carried out in generally the same way as with REDOR experiments. During the mixing period τ_m , the magnetization of the recoupled nuclei decays as a result of the dephasing effects of the homonuclear dipolar coupling. For example, Figure 26 shows solid-state NMR spectra of [carbonyl- ^{13}C]polycarbonate obtained by using the pulse sequence in Figure 25b both with

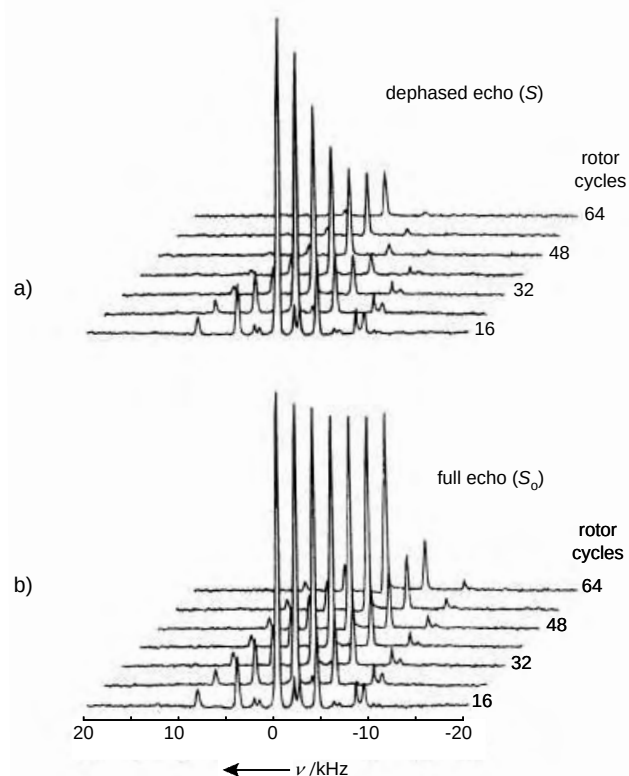


Figure 26. Solid-state ^{13}C NMR spectra of [carbonyl- ^{13}C]polycarbonate, obtained by using the DRAMA sequence in Figure 25b. a) Decay of the ^{13}C carbonyl resonance as a function of the mixing time τ_m . As τ_m increases, the ^{13}C magnetization decays as a result of the reintroduction of homonuclear dipolar coupling between the chains. b) Experiment run without the DRAMA $\pi/2$ pulses. The observed decay is a result of the natural relaxation of the magnetization. The spinning speed was 4167 Hz, which corresponds to 64 rotor cycles with a 15.4-ms mixing time. (Reproduced from ref. [123], with permission.)

(Figure 26a) and without (Figure 26b) the recoupling pulses. As the mixing time increases, the intensities of all of the ^{13}C resonances decrease because of recoupled ^{13}C – ^{13}C dipolar coupling (Figure 26a). This decay is substantially more pronounced than the natural decay of the magnetization when the DRAMA recoupling pulses are removed (Figure 26b). By measuring the decay of the ^{13}C magnetization as a function of τ_m , it is possible to determine the ^{13}C – ^{13}C dipolar coupling constants and the corresponding internuclear distances. For the polycarbonate sample, the ^{13}C – ^{13}C internuclear distances were used to help determine a model for polycarbonate chain packing in the solid state.^[123]

Another example of a commonly used method for recoupling homonuclear dipolar couplings under MAS is rotational resonance or RR.^[124] Unlike DRAMA, rotational resonance

does not require the application of pulses to interrupt the effect of the spinning rotor—in fact, rotational resonance utilizes the spinning rotor to recouple two spins. As shown in Section 2.5, the homonuclear dipolar coupling contains the “flip-flop” interaction terms, $I_1^+ I_2^- + I_1^- I_2^+$. When the chemical shifts of two nuclei differ by a frequency that is larger than the dipolar coupling constant, the flip-flop term is suppressed as it is no longer possible for the spins to undergo an energy-conserving transfer of spin angular momentum. However, when the frequency of the MAS rotor ω_r is set such that it is equal to an integer multiple of the difference in isotropic chemical shifts $\Delta\omega_{\text{iso}}$ of the two nuclear spins [Eq. (15)] then the homonuclear dipolar coupling is effectively recoupled.

$$\Delta\omega_{\text{iso}} = n\omega_r \quad (15)$$

Although the origin of this process is complex, it can generally be understood by considering the rotor to be an additional source of energy for the system to bridge the energy gap between the nuclear spin transitions. Only when the rotor spins at one of the rotational resonance conditions dictated by Equation (15) are the nuclei recoupled. Figure 27 shows a ^{13}C CPMAS spectrum of glycine taken at 12.0 and at 16.6 kHz, which corresponds to off and on rotational resonance conditions ($n=1$) in this case. The splitting in Figure 27c at the rotational resonance condition is a result of the interaction between the nuclei, and is indicative of the coupling strength.

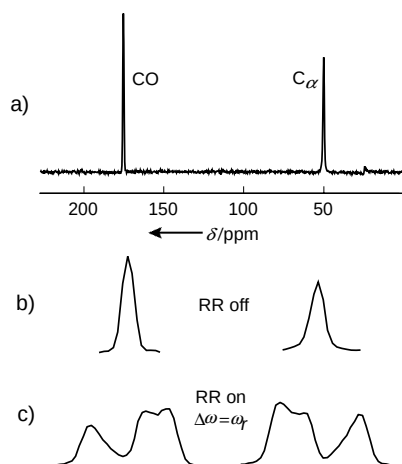


Figure 27. a) CP MAS NMR spectra (125 MHz) of uniformly ^{13}C -labeled (10%) glycine powder. The expansions show the two signals at rotor spinning speeds of 12 kHz (b; RR off) and of 16.6 kHz (c; RR on), which corresponds to the $n=1$ rotational resonance condition [Eq. (15)]. The signals are distorted as a result of the recoupling of H_{II} . (Courtesy of R. H. Havlin).

Distance measurements using RR are accomplished in a somewhat different manner than the recoupling techniques discussed so far. Figure 28a shows a general pulse sequence for measuring ^{13}C – ^{13}C homonuclear dipolar couplings by RR. The first step in RR is to set the spectrometer frequency to the resonance frequency of one of the two nuclei to be recoupled, and set the spinning speed so that it complies with the RR condition of Equation (15). Following the initial CP step, the

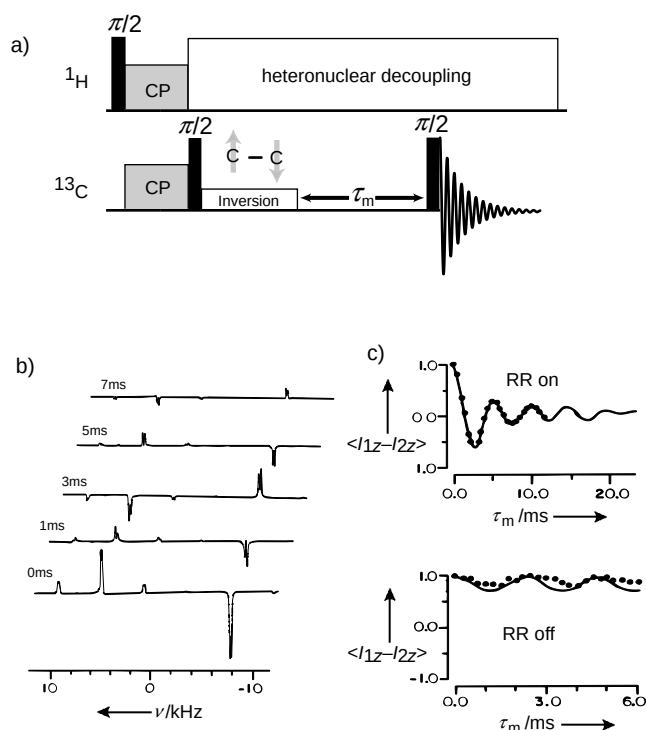


Figure 28. The RR experiment: a) Following ^1H CP, the ^{13}C magnetization is stored along the z axis and one of the resonances is inverted. The magnetization then decays for a period τ_m , before it is returned to the xy plane for detection. b) RR NMR spectra of doubly- ^{13}C -labeled Zn acetate. As the mixing time τ_m increases, the ^{13}C nuclei have more time to exchange magnetization, to oscillate, and to decay back to equilibrium. c) The difference in the magnetization between the two peaks oscillates under RR conditions, but stays fairly constant just 100 Hz off the RR condition. (Adapted from ref. [124], with permission.)

^{13}C magnetization is returned to the z axis, at which point the magnetization of the on-resonance ^{13}C nuclei is inverted by using a long, low-power pulse. In the absence of any dipolar recoupling, the inverted ^{13}C nuclei slowly relax back to their equilibrium state. However, when the ^{13}C – ^{13}C nuclei are recoupled by meeting the RR condition of Equation (15), they undergo energy-conserving flip-flop transitions, that is, the inverted spins flip up and the uninverted spins flop down. Often an oscillatory behavior of the magnetization is observed until the equilibrium is reached at which point the magnetization is equally distributed between the two spins. In Figure 28b a series of ^{13}C RR spectra of a doubly ^{13}C -labeled Zn acetate is shown, acquired at different mixing times τ_m . By observing the oscillatory decay in the intensity of both peaks, it is possible to measure the magnitude of the dipolar coupling between the two ^{13}C sites and thereby determine the internuclear distance.

Especially in weakly enriched or unlabeled compounds with low natural abundance of the NMR-active isotopes (e.g. ^{13}C) it is difficult to observe the decaying signal that arises from a spin pair, as the bulk of the signal comes from isolated spins. To filter out these signals, a difference-spectroscopy technique can be employed.^[125] Only the non-spin-pair magnetization survives long mixing times, and its spectrum can be subtracted from those acquired with shorter mixing times. An alternative and often cleaner approach is to employ

double-quantum filters to specifically select the signals from the spin pairs.^[126, 127]

In addition to DRAMA and RR, a plethora of homonuclear recoupling sequences have been developed with acronyms such as HORROR,^[128] DRAWS,^[129] MELODRAMA,^[130] BABA,^[131] RFDR,^[132] and C7.^[133] Each of these sequences has certain strengths and weaknesses. The quality criteria for these sequences very much depend on the task at hand. They include broadband behavior, selectivity, robustness with respect to pulse errors, CSA dependence, sensitivity, scaling of the recoupled interaction, angular dependence of the recoupling in a powder, and the ability to filter spin pairs cleanly. A detailed evaluation of different homonuclear recoupling techniques is given by Baldus et al.,^[134] Dusold and Sebald,^[135] as well as by Bennett, Griffin and Vega.^[136] In this section, we have focused mainly on DRAMA and RR, merely because these were the first homonuclear recoupling techniques, and serve as instructive and illustrative examples (in much the same way as WAHUHA does for homonuclear decoupling). In practice, however, the most commonly used techniques seem to be RFDR,^[132] C7,^[133] and their variants. Continuous developments are underway in this field, and the advantages of a particular sequence over another is often difficult to rationalize theoretically. Recently, these sequences were classified according to certain symmetry principles, which helps to evaluate them and to choose the appropriate one for a particular application.^[137] The value of these classification schemes cannot be underestimated, as they provide for the first time a uniform treatment of homo- and heteronuclear spin decoupling and recoupling under spinning conditions, ranging from simple CW decoupling and CP to more complicated experiments that involve RR as well as frequency-switched and phase-modulated sequences.^[138]

4.2. Correlation Spectroscopy in the Solid State

We have discussed techniques that allow the reintroduction of the dipolar coupling for both homonuclear and heteronuclear systems and we have outlined how these techniques can be used to determine internuclear distances. In addition, the reintroduction of the dipolar coupling provides a magnetization exchange mechanism between spatially close nuclei that can be used for correlating their resonance frequencies in the same way as in liquid-state NMR techniques such as COSY, NOESY, or HMQC.^[46, 55]

4.2.1. Heteronuclear Correlation Spectroscopy

The concept of heteronuclear correlation in solid-state NMR spectroscopy was introduced

in Section 3 with a discussion of the ^1H – ^{13}C HETCOR experiment. The relative simplicity of the HETCOR experiment is largely a consequence of the ability to transfer the polarization between nuclei using CP. When transferring the polarization between low- γ nuclei such as ^{13}C and ^{15}N , CP may become difficult to optimize as the ^{13}C – ^{15}N dipolar coupling is effectively removed under MAS, even when the Hartmann–Hahn condition is specifically adjusted for rapid spinning.^[139, 140] An alternative and often more robust means of producing heteronuclear dipolar correlation spectra is to utilize a REDOR-like recoupling (see Section 4.1) to exchange the magnetization between the ^{13}C and ^{15}N spins.^[141]

Figure 29a shows a possible pulse sequence that produces a ^{13}C – ^{15}N correlation spectrum in the solid state. The ^{13}C nuclei are first polarized through CP from the protons, after which a REDOR sequence is used to recouple the ^{13}C and ^{15}N nuclei. Following the REDOR sequence, the ^{15}N spins are allowed to evolve for a period t_1 (the indirect dimension), before a second REDOR sequence is used to return the magnetization to the ^{13}C spins for detection. Figures 29b, c show 2D ^{13}C – ^{15}N correlation spectra of a solid sample of formyl-Met-Leu-Phe obtained with such a sequence (Figure 29a) by using different REDOR mixing times.^[141] With short mixing times, the magnetization is transported over shorter distances, and the correlations are limited to neighboring atoms such as N–C' and N–C $_{\alpha}$ (Figure 29b). However, when the spins are

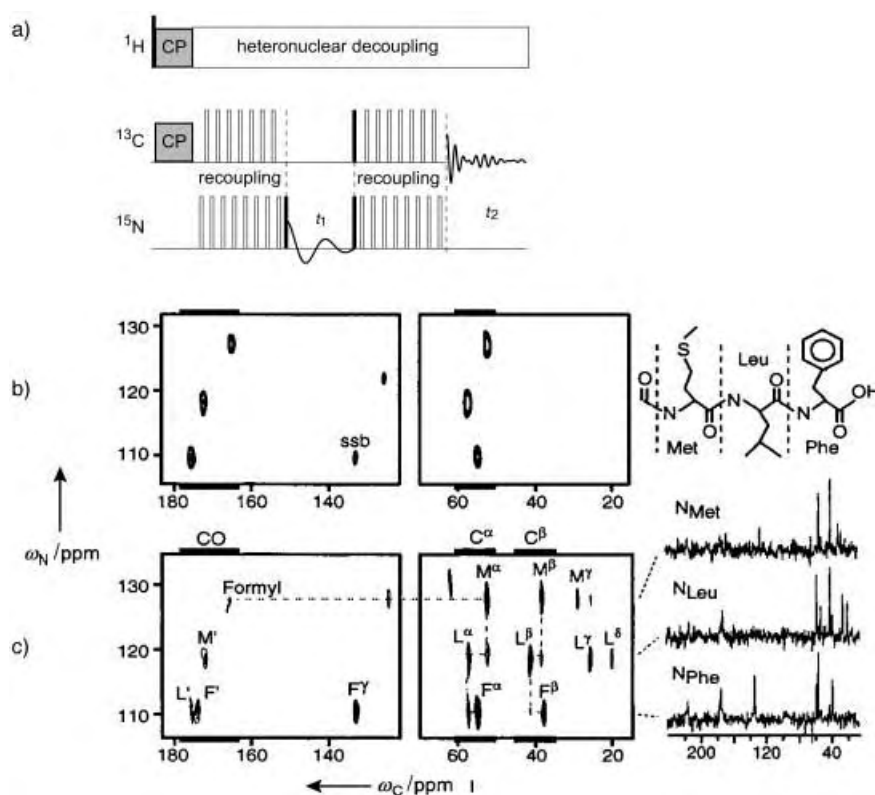


Figure 29. a) Heteronuclear correlation of ^{13}C and ^{15}N nuclei by dipolar recoupling. The modified REDOR pulse sequence incorporates pulses on the ^{13}C nuclei in addition to the standard pulses on the ^{15}N nuclei. b) 2D ^{13}C – ^{15}N correlation spectrum of the tripeptide Formyl-Met-Leu-Phe obtained by using the pulse sequence in a). As a result of the short mixing time of 614.4 μs , the ^{13}C magnetization does not spread much further than one bond, giving rise only to N–C' and N–C $_{\alpha}$ correlations. c) With a mixing time of 2.46 ms, the magnetization is transported further, thus permitting the observation of N–C $_{\beta}$ and N–C $_{\gamma}$ correlations. (Adapted from ref. [141], with permission.)

recoupled for longer periods (Figure 29c), the magnetization has more time to diffuse through the sample, thus leading to chemical shift correlations between more distant atoms (e.g. $N-C_\beta$ and $N-C_\gamma$). This REDOR-type technique has recently been shown to be very efficient in the heteronuclear magnetization transfer between ^1H and ^{13}C , and between ^1H and ^{15}N .^[142, 143] In the latter case, even the reverse transfer from ^{15}N to ^1H has resulted in an improvement in sensitivity (analogous to inverse detection in liquid-state NMR spectroscopy).^[46]

As indicated above, carefully optimized CP is another way of performing heteronuclear correlation experiments between low- γ nuclei and has been particularly effective with large magnetic fields. Remarkable $^{15}N-^{13}C$ correlation spectra have been collected to assign the resonances of uniformly labeled proteins and peptides in the solid state.^[144–146]

4.2.2. Homonuclear Correlation Spectroscopy

Homonuclear 2D correlation spectra can be obtained in solids in a manner very similar to that used for heteronuclear correlations. Figure 30 outlines a general experimental procedure for a $^{13}C-^{13}C$ homonuclear dipolar coupling correla-

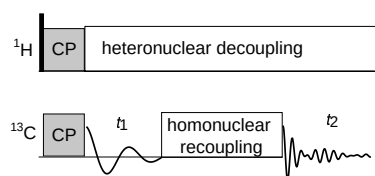


Figure 30. Typical pulse sequence for homonuclear correlation spectroscopy with dipolar recoupling. Once the ^{13}C magnetization has evolved in the indirect dimension, a homonuclear recoupling sequence is used to exchange magnetization between neighboring ^{13}C nuclear spins. The ^{13}C magnetization is then detected in the direct dimension.

tion experiment in the solid state. The sequence begins again with CP of the ^{13}C nuclei from the protons. The ^{13}C magnetization evolves during t_1 , followed by a homonuclear recoupling sequence of the type introduced in Section 4.1 to recouple homonuclear dipolar coupling, thus allowing the transfer of magnetization between neighboring ^{13}C atoms. Finally, the ^{13}C magnetization is detected in the direct dimension t_2 . Figure 31 shows a $^{13}C-^{13}C$ chemical shift correlation spectrum of uniformly- ^{13}C -labeled erythromycin A obtained by using the sequence shown in Figure 30. In the experiment, the CMR7 method was used for ^{13}C homonuclear recoupling;^[147] the method employs windowless rotor-synchronized π and 2π pulses. Resonance assignments become possible in uniformly and partially labeled proteins by using homonuclear correlation experiments of very high quality.^[148–152] As in the heteronuclear correlation spectra of Figure 29b, c, the number of cross peaks in a homonuclear correlation spectrum can be controlled to some extent by the duration of the recoupling period. As the recoupling time increases, the magnetization diffuses further through the sample, thus leading to chemical shift correlations between an increasing number of spins. Many more variants of these experiments exist, including 3D correlation, double-quantum filtration, and double-quantum/single-quantum correlation

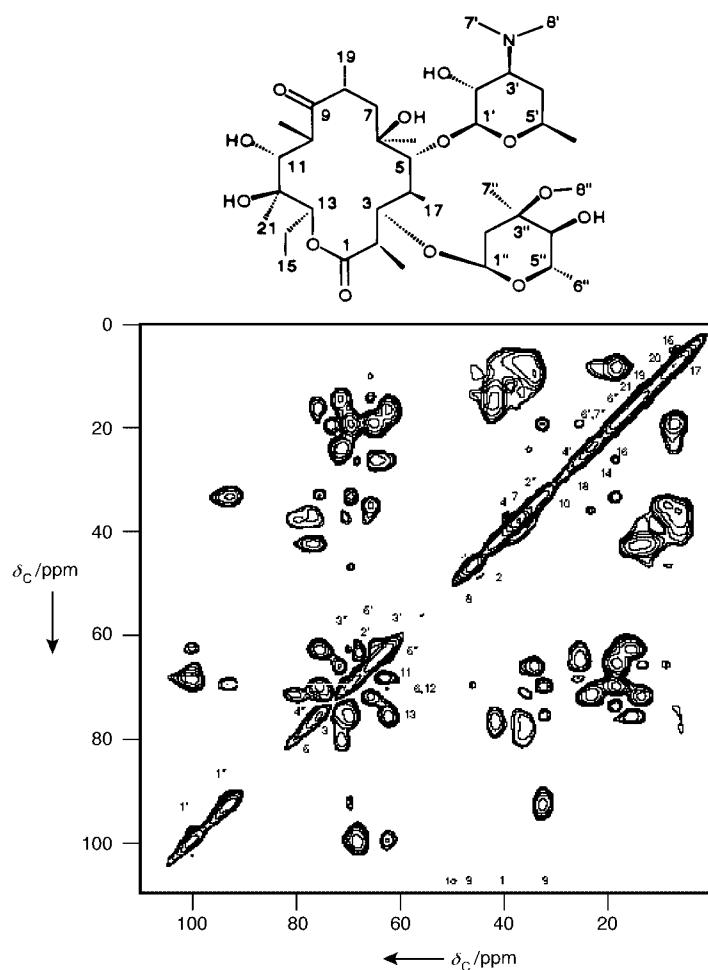


Figure 31. 2D $^{13}C-^{13}C$ correlation spectrum of uniformly ^{13}C -enriched erythromycin A. The spectrum was measured at a field of 9.4 T with a spinning speed of 8 kHz. A CMR-7 sequence was used to recouple the $^{13}C-^{13}C$ homonuclear dipolar coupling and create the $^{13}C-^{13}C$ correlations shown in the spectrum. (Reproduced from ref. [147], with permission.)

experiments.^[145, 153–155] This latter experiment has even been applied to protons for the investigation of the packing and dynamics of triphenylene and hexabenzocoronene derivatives.^[156]

A pure recoupled double-quantum Hamiltonian can be used for spin-counting experiments under MAS (analogous to multiple-quantum spectroscopy in the static case discussed in Section 3.2.3).^[157] In a related example, the time evolution of recoupled double-quantum coherences has been used to probe the torsion angles between different bonds.^[158–160]

4.3. Recoupling away from the Magic Angle

Before leaving the topic of dipolar recoupling, we discuss a method to recouple H_{II} or H_{IS} effectively. As previously mentioned, it is not mechanically feasible to stop and restart the spinning sufficiently rapidly to reinstate the dipolar coupling under MAS. However, there is an alternative solution: as the dipolar coupling is fully removed only at the magic angle, if the axis of the spinning rotor is rotated at another angle (e.g., 0° , parallel to the external magnetic field)

the dipolar coupling emerges. The sample can then be returned to the magic angle for detection. This technique is known as switched-angle spinning or SAS.^[161] Figure 32 shows a SAS spectrum of doubly ^{13}C -labeled zinc acetate in which

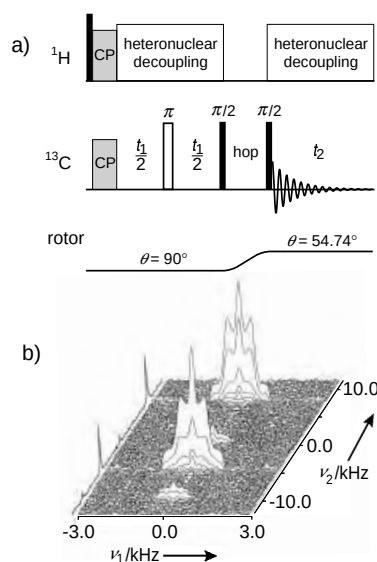


Figure 32. a) Pulse sequence for SAS. The experiment begins with the rotor oriented 90° relative to the external magnetic field. After the magnetization is excited by a CP sequence, the ^{13}C – ^{13}C homonuclear dipolar coupling is detected in t_1 using a π pulse to refocus the CSA. A $\pi/2$ pulse stores the magnetization along the z axis while the rotor axis is reoriented at the magic angle, at which point a second $\pi/2$ pulse returns the magnetization to the xy plane for detection in t_2 . b) 2D SAS NMR spectrum of uniformly 1,2- ^{13}C labeled (10%) zinc acetate. The ^{13}C – ^{13}C homonuclear dipolar coupling (displayed along the ν_1 axis) is attenuated by a factor of two because of the orientation of the rotor during t_1 . ν_2 is the (isotropic) chemical shift dimension. (Reproduced from ref. [161], with permission.)

the ^{13}C – ^{13}C homonuclear dipolar couplings are recoupled. If the rotor is oriented along B_0 during t_1 , the recoupling efficiency is 100%. Mechanical difficulties with sudden changes in angle as well as difficulties in detecting the magnetization in this orientation make the perpendicular alignment of the rotor axis more practical. However, the efficiency in this case is only 50%. Spinning at different angles can also be used to reintroduce the CSA, and to perform isotropic/anisotropic correlation spectroscopy with quadrupolar nuclei. Although this approach requires the use of specialized probes and is mechanically very demanding, from a conceptual point of view these techniques offer significantly more degrees of freedom than spinning around a single axis.^[162] This fact is the driving force behind many new hardware and application developments in this field.

4.4. Reintroduction of the Chemical-Shift Anisotropy

Figure 5 showed a ^{13}C static carbon spectrum of glycine obtained with heteronuclear spin decoupling. The spectrum has two broad lines that correspond to the CSA of the α - and carbonyl carbon atoms. The two signals are the direct result of the electronic structure around the nuclei, and thus contain a

wealth of localized information about the structure, dynamics, and orientation of the nucleus with respect to its surrounding atoms. For example, the CSA for the α carbon atom of most amino acids in proteins and peptides depends on the secondary structure (α -helix versus β -sheet),^[163, 164] as shown in Figure 33 for valine.

Although the measurement of CSA signals from static solid-state NMR spectra is possible in singly and some doubly labeled samples, it is generally not feasible in multispin systems, which result in overlapping CSA powder patterns. Furthermore, static spectra typically require extensive signal averaging to obtain the signal intensity and resolution required to determine the CSA signal. In the following section we describe techniques that combine the high resolution of a MAS experiment with the anisotropic information content available from a static sample, and therefore represent powerful demonstrations of the potential of solid-state NMR spectroscopy.

4.4.1. Spinning-Sideband Analysis

Figure 8 showed a series of MAS spectra taken at different spinning speeds. With a decrease in the spinning speed, an increasing number of spinning sidebands appear in the spectrum as a result of incomplete motional averaging of the CSA by the rotation. As the spinning speed approaches zero, the envelope of the spinning sidebands takes on the shape of the static powder pattern shown in Figure 8e. Indeed, the intensities of the spinning sidebands contain information about the CSA, and through an appropriate analysis one can determine the three CSA parameters, δ_{11} , δ_{22} , and δ_{33} . The Herzfeld–Berger^[45] method uses a series of precalculated surfaces to determine δ_{11} , δ_{22} , and δ_{33} from the integrated intensities of a number of spinning sidebands. The method is conceptually straightforward and not technically demanding, requiring only the acquisition of a 1D MAS spectrum. By taking spectra at different spinning speeds and averaging the values of δ_{11} , δ_{22} , and δ_{33} determined from the Herzfeld–Berger surfaces, the accuracy of the method can be further enhanced. Figure 34 shows a spectrum of ^{15}N -labeled adenosine monophosphate (AMP) acquired at a MAS speed of 1105 Hz. The spinning speed for the spectrum in Figure 34 was chosen specifically to minimize sideband overlap, thus allowing the determination of the CSAs of all five ^{15}N AMP sites by using the Herzfeld–Berger method.

Under circumstances in which the spectra are too crowded with sidebands to resolve the CSAs by this method, it is advantageous to use 2D NMR spectroscopy to spread the overlapping CSA patterns across a second dimension. A powerful technique for this is PASS (phase-adjusted spinning sidebands), which allows one to separate spinning-sideband

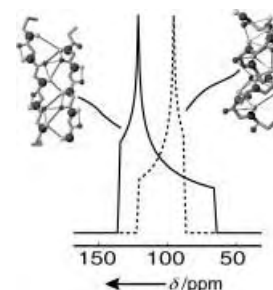


Figure 33. Simulated static spectra of the α -carbon atom of a L-valine residue in a peptide or protein. The shape of the α -carbon CSA depends strongly on whether the residue is located within an α -helix (---) or a β -sheet (—).

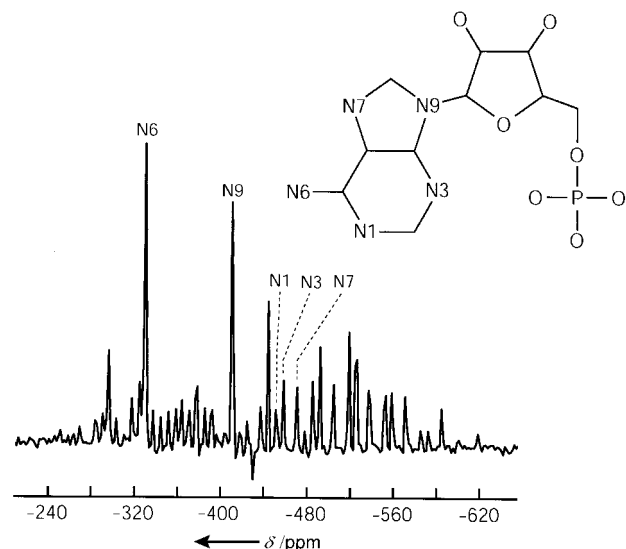


Figure 34. Slow-spinning CP MAS NMR spectrum of uniformly ^{15}N labeled adenosine monophosphate (AMP) obtained at a spinning speed of 1105 Hz. Because the sidebands are spaced at integer multiples of the spinning speed, the identity of each sideband can be ascertained based on its distance from any one of the five isotropic peaks (which are found by spinning at high speed). By fitting all of the sideband intensities (or integrals), the principal values of the CSA for each ^{15}N site were determined.

manifolds in a second dimension.^[165, 166] A series of pulse sequences have been developed which allow one to manipulate sideband manifolds for various purposes, including the removal of spinning sidebands^[167] and 3D experiments.^[168] The many variants of these techniques are described in an excellent review article.^[169] In the ODESSA experiment (one-dimensional exchange spectroscopy by sideband alternation), the magnetization associated with different spinning sidebands is polarized in alternate directions during the preparation period. Dynamic processes that redistribute the magnetization can be characterized by analyzing the sidebands from spectra acquired at different times after the preparation period. Exchange processes between chemically equivalent and non-equivalent nuclei have been determined in this way.^[170, 171] Even regular 1D MAS in combination with a sideband analysis has been used to obtain evidence of otherwise invisible processes, such as bond rearrangements.^[172]

4.4.2. Anisotropic-Isotropic Chemical Shift Correlation

Although slow-spinning MAS is an excellent way to determine the chemical shift anisotropy of a nucleus in the solid state, the method does not *really* reintroduce the CSA. Instead, this method takes advantage of the incomplete averaging of the CSA that occurs when the rotation frequency is smaller than the width of the CSA. It would be useful to observe a “static-like” powder pattern under fast MAS in a manner analogous to that used for dipolar recoupling. This would allow one to observe broad anisotropic peaks in one dimension and isotropic peaks in the directly detected dimension in a 2D NMR experiment.

The evolution of the CSA under MAS is very similar to that of the heteronuclear dipolar coupling. Therefore, a technique similar to REDOR, which applies two π pulses per rotor period effectively reintroduces the CSA under MAS. Although a two-pulse technique does work,^[173] the resulting powder patterns tend to be distorted. An improved method by Tycko et al.^[174] utilizes four π pulses per rotor period to reintroduce the CSA with very little distortion of the signal (Figure 35). By incorporating the 4- π -pulse sequence into the

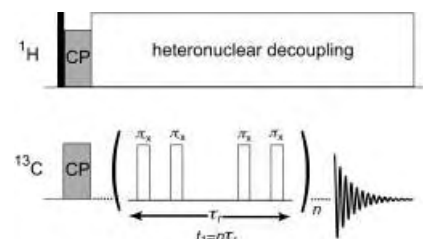


Figure 35. Pulse sequence for recoupling the CSA. τ_r = Rotor period.

indirect detection period of a 2D NMR experiment, it is possible to produce a spectrum that correlates the broad CSA signal in one dimension with the isotropic MAS spectrum in the other dimension. Figure 36 shows a series of CSA patterns from six of the seven ^{13}C sites in methyl- α -D-glucopyranoside. The spectrum was obtained by using the 4- π -pulse technique to reintroduce the CSA under MAS conditions. Below each experimentally obtained spectrum, a simulated best-fit CSA signal is shown.

In addition to the 4- π -pulse method, a variety of other techniques that do not involve traditional pulsed recoupling have been developed to correlate the anisotropic and isotropic components of the chemical shift. Among these techniques are magic-angle hopping (MAH),^[175] magic-angle turning (MAT),^[176, 177] and variable-angle correlation spectroscopy (VACSYS).^[178, 179] The MAT experiment uses $\pi/2$ pulses to interrupt the chemical shift evolution during t_1 at 0, 120, and 270° of the MAS rotor position. The MAH pulse sequence is very similar, but uses rapid hops of the crystal axis around the magic-angle axis to align the former first with the x , then with the y , then with the z axis. After the magnetization has evolved in all three arrangements, the space appears isotropic (as is the case under MAS conditions), the CSA is removed, and a purely isotropic spectroscopic dimension is obtained.

The spinning speeds employed in MAT are usually low (<1 kHz), and therefore the directly detected dimension

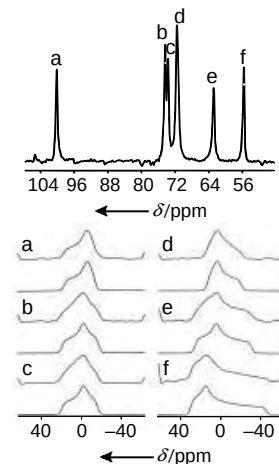


Figure 36. Isotropic ^{13}C NMR spectrum and CSA signals for six carbon atoms (a–f) in methyl- α -D-glucopyranoside obtained by using the 4- π -pulse technique. Best-fit simulations are shown below each experimentally obtained signal. (Reproduced from ref. [174], with permission.)

contains a wealth of spinning sidebands that form the anisotropic dimension. The recently improved MAT technique called FIREMAT achieves higher sensitivity; and an isotropic/anisotropic correlation spectrum is shown for erythromycin A in Figure 37.^[180]

Figure 38 shows a 2D isotropic/anisotropic correlation spectrum of L-tyrosine · HCl produced with the VACSYS method. In this experiment, the demands on hardware are lower than for the SAS experiment mentioned previously, as the spinning angle is only gradually changed between different 1D experiments (within seconds), rather than during the experiment (within a few milliseconds). Nevertheless, the same comment as at the end of Section 4.4 applies: although MAH, MAT, and VACSYS all have definite advantages over slow-spinning MAS or the 4- π -pulse sequence, they are technologically more difficult to implement, and require specialized hardware. Since these methods are potentially more versatile, further developments in hardware can be expected.

4.5. *J* Coupling

As a final note in this section, we briefly introduce a Hamiltonian that has not yet played a role in this Review, the *J*-coupling Hamiltonian. In some instances, the signals in solid-state NMR spectra can be made sufficiently narrow by MAS so that *J* coupling can be exploited for correlation spectroscopy (e.g. COSY and INADEQUATE) in much the same way as in liquid-state NMR spectroscopy.^[117, 181–183] The *J* coupling exhibits no spatial orientation dependence, and is therefore not averaged out under MAS (we neglect here the anisotropic *J*-coupling contribution, which has a form similar to the dipolar coupling and is therefore removed by MAS).^[184] In general, however, very strong dipolar coupling from abundant nuclei make the MAS approach impractical to reveal *J* coupling. Recent technological breakthroughs such as high-speed MAS and high-power proton homo- and heteronuclear decoupling has made it possible to observe and utilize *J* coupling in polycrystalline samples. Figure 39 shows an INADEQUATE spectrum^[185] of a solid sample of L-tyrosine · HCl acquired under MAS with high-power homonuclear proton decoupling. This experiment has also been carried out on disordered solids.^[186] High-power proton homodecoupling sequences have been described which use heteronuclear *J* couplings in solids, anal-

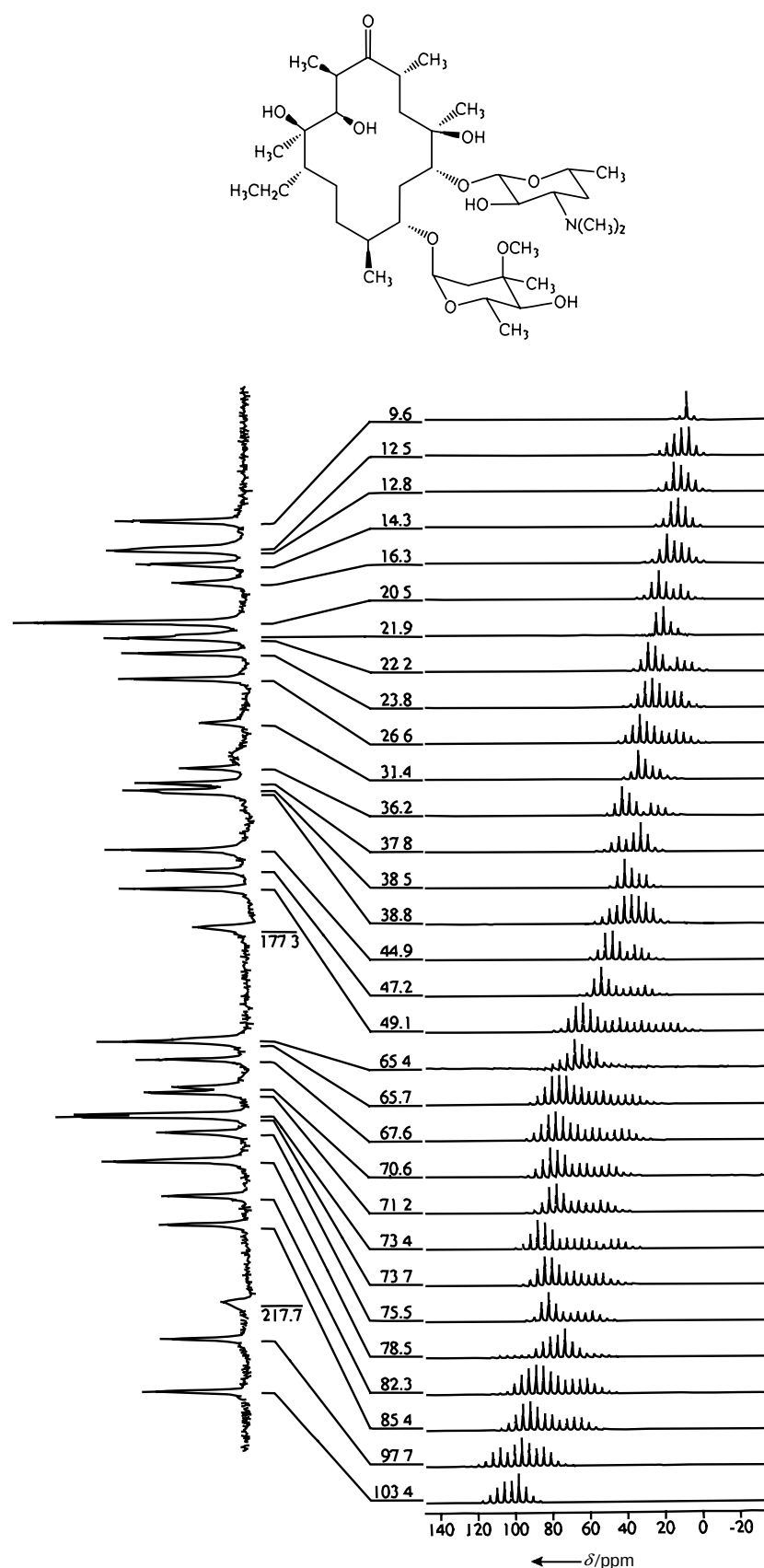


Figure 37. Isotropic chemical shift–CSA correlation spectrum of erythromycin A measured with the FIREMAT technique.^[180] The slow MAS speed of 390 Hz produces a spinning-sideband pattern that closely resembles a CSA powder signal in the directly observed dimension. A multipulse sequence in the indirect dimension in combination with a special processing method produces isotropic lines.

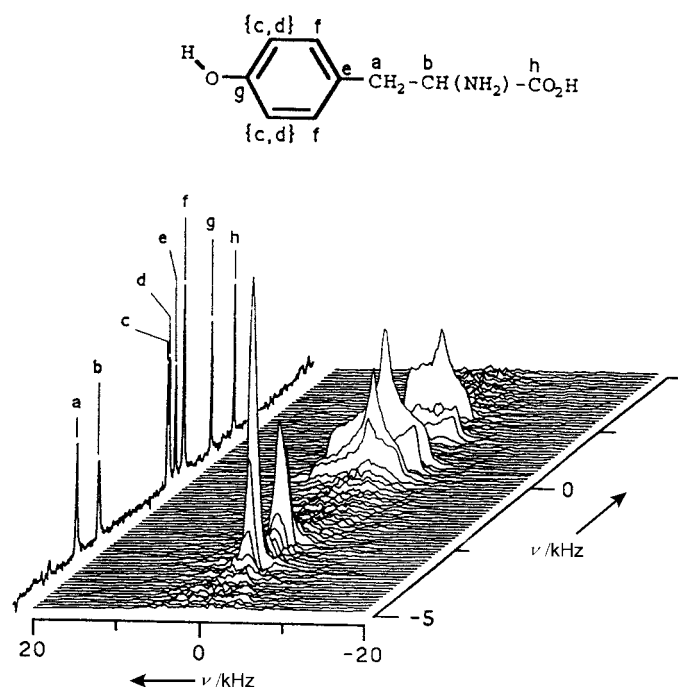


Figure 38. 2D NMR correlation spectrum of the isotropic/anisotropic chemical shifts of L-tyrosine measured with VACSy. The isotropic projection is shown with the assignment of the peaks. (Reproduced from ref. [178], with permission.)

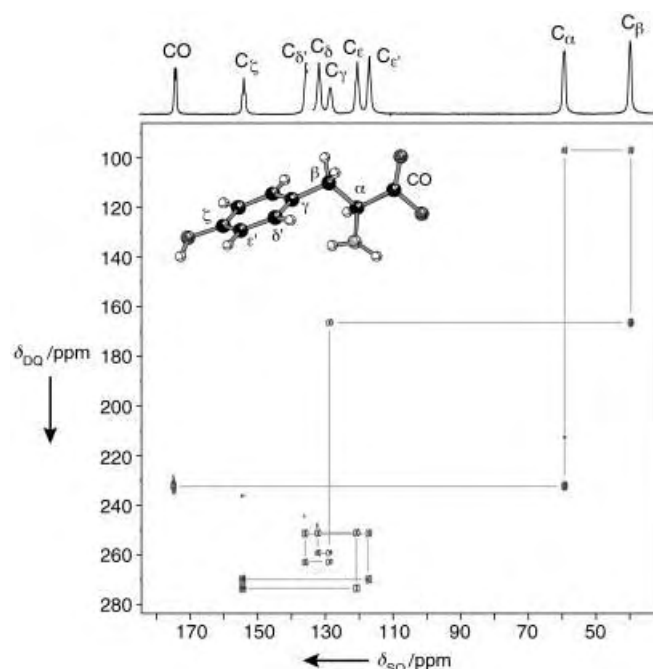


Figure 39. Solid-state 2D INADEQUATE NMR spectrum (125 MHz) of fully ^{13}C -labeled L-tyrosine $\cdot$ HCl. δ_{SQ} and δ_{DQ} are the single-quantum and the double-quantum frequencies, respectively, expressed in ppm. δ_{DQ} is the sum of the chemical shifts of the two correlated carbon atoms. The spinning speed was 22 kHz, and the ^1H decoupling field strength was 120 kHz. (Reproduced from ref. [43], with permission.)

ogous to the liquid-state HMQC experiment.^[79, 187] In a different experiment, a specifically designed pulse sequence was used during the mixing period of the sequence of Figure 30 to eliminate all interactions except for the isotropic

J -coupling interaction. In this way, 2D through-bond homonuclear correlation spectra have been obtained.^[188–190] These techniques provide a convenient additional and complementary assignment tool, as they only indicate intramolecular through-bond coupling, as opposed to assignment strategies based on dipolar-coupling approaches.

In Sections 2 and 3, we discussed the interactions in solid-state NMR spectroscopy that prevent the acquisition of high-resolution NMR spectra as well as ways to counteract the effects of these interactions. Although dipolar coupling, CSA, and quadrupolar coupling (see Section 5) result in poorer resolution in the spectra, they contain useful structural information that is often difficult to obtain from liquid-state NMR spectroscopy. The techniques presented in this section provide a means to combine the advantages of high-resolution NMR spectroscopy with the ability to extract structural information contained in anisotropic interactions such as CSA and dipolar coupling.

5. Quadrupolar Nuclei

So far, our discussion of solid-state NMR spectroscopy has been restricted to spin $\frac{1}{2}$ nuclei such as ^1H , ^{13}C , ^{15}N , ^{31}P , and ^{29}Si . We now extend our survey of solid-state NMR spectroscopy to include the majority of isotopes found in the periodic table, that is, those with spin $I > \frac{1}{2}$. Although these quadrupolar nuclei possess the same set of basic interactions that were introduced in Section 2 (e.g. the CSA, dipolar coupling, etc.), there are two principal differences between spin $\frac{1}{2}$ nuclei and those with spin $I > \frac{1}{2}$: 1) For quadrupolar nuclei, the allowed values of the nuclear spin quantum number m_I are no longer simply $+\frac{1}{2}$ and $-\frac{1}{2}$. For a spin 1 nucleus (e.g. ^2H and ^{14}N), the allowed values for m_I are -1 , 0 , and $+1$; thus, in the presence of an external magnetic field, spin 1 nuclei have three energy levels and two transitions. Likewise, a spin $\frac{3}{2}$ nucleus (e.g. ^{23}Na and ^{87}Rb) has four spin states with $m_I = -\frac{3}{2}$, $-\frac{1}{2}$, $\frac{1}{2}$, and $\frac{3}{2}$. In general, there are $2I + 1$ spin states and $2I$ directly detectable transitions. 2) Quadrupolar nuclei possess a nonspherical charge distribution that can couple to electric-field gradients present in most solid-state materials.^[191] This quadrupolar coupling has an enormous effect on the observed NMR spectrum (as seen below).

5.1. Spin 1 Nuclei

Although spin 1 nuclei are much more rare than half-integer quadrupolar nuclei, the literature on spin 1 nuclei is extensive, mainly because of the usefulness of deuterium (^2H) in NMR spectroscopy.^[22, 192–194] Based on its small electron cloud and relatively low gyromagnetic ratio ($\sim \frac{1}{6}$ that of ^1H), and consequently a small chemical shift range of ~ 3 – 4 ppm and relatively weak dipolar couplings, one might expect static ^2H NMR line widths to be narrow. Thus, it may be somewhat surprising to learn that static ^2H NMR line widths routinely exceed 100 kHz, as shown in the spectrum of CDI_3 in Figure 40. Quadrupolar interactions are at the origin of this very broad line.

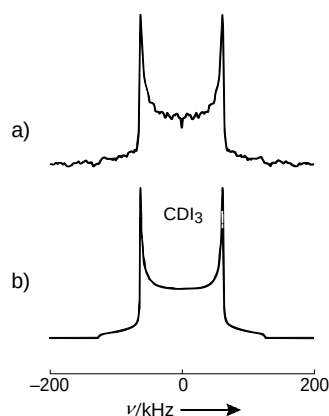


Figure 40. Static ^2H NMR spectrum of CDI_3 : a) experimentally obtained spectrum; b) simulated spectrum based on the quadrupolar coupling constant derived from the spectrum in a); The quadrupolar coupling frequency, ν_Q was determined to be 167.5 kHz, and the anisotropy η to be 0. (Adapted from ref. [257], with permission.)

To understand the ^2H quadrupolar signal displayed in Figure 40, it is helpful to examine the effect of the quadrupolar coupling on the ^2H Zeeman energy levels. In Figure 41 a, we show the energy levels of a spin 1 nucleus in an

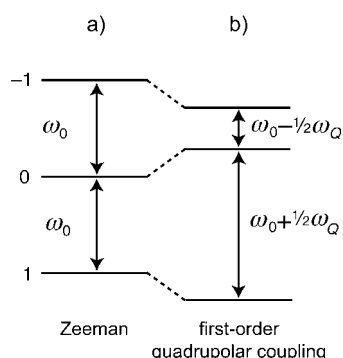


Figure 41. Energy-level diagram for spin 1 nuclei subject to a) the Zeeman interaction and b) to both the Zeeman and the first-order quadrupolar interactions. The splitting shown in b) is a result of the first-order quadrupolar coupling at one particular crystal orientation.

external magnetic field with no quadrupolar coupling present. Both the $-1 \rightarrow 0$ and $0 \rightarrow +1$ transitions have the same resonance frequency as the energy differences between the spin states are identical. Figure 41 b shows the same three energy levels under the influence of the first-order quadrupolar Hamiltonian $H_Q^{(1)}$ (the term “first order” is explained later). Whereas the $m_I = -1$ and the $m_I = +1$ spin states decrease in energy upon the addition of $H_Q^{(1)}$, the $m_I = 0$ spin state increases in energy. As a result, the $-1 \rightarrow 0$ and the $0 \rightarrow +1$ transitions differ in energy, and therefore resonate at two different frequencies. The difference between the frequencies is proportional to the first-order quadrupolar coupling constant ω_Q [Eq. (16)].

$$\omega_Q = \frac{3eqeQ}{2I(2I-1)\hbar} \quad (16)$$

In Equation (16), e is the electron charge, eq is the z component of the electric field gradient felt at the nucleus,

and Q is the nuclear electric quadrupole moment. The constant Q is a nuclear property (like γ) that describes the strength with which a quadrupolar nucleus couples to an electric-field gradient at the nucleus. For example, deuterium has a relatively small nuclear electric quadrupole moment ($Q = 3 \times 10^{-31} \text{ m}^2$), and typically quadrupolar coupling constants are on the order of 100–300 kHz.^[192] On the other hand, $Q = 2 \times 10^{-30} \text{ m}^2$ for ^{14}N (spin 1), and typical quadrupolar coupling constants are ~ 10 times higher (1–5 MHz). The origin of the nuclear electric quadrupole moment (an asymmetric charge distribution) is simply the fact that a nucleus of uniform shape does not necessarily have a symmetric charge distribution, depending on the number of protons and neutrons. Under the influence of the electrostatic interaction, the nucleus arranges itself within an asymmetric electron cloud, which in turn influences the NMR-active energy transitions.

As is also seen in Figure 41 b, the effect of the first-order quadrupolar coupling is to produce a quadrupolar splitting whose magnitude is dictated by ω_Q . However, in Figure 40, we see not only a splitting, but rather a signal that strongly resembles the dipolar Pake pattern shown in Figure 4. This is because the splitting caused by the first-order quadrupolar coupling depends on the orientation of the molecule with respect to the magnetic field (in the same way as the CSA and, in the case of cylindrical symmetry, the dipolar coupling; for ^2H , this is very often a good approximation because of the axially symmetrical C–H bonds). Therefore, just as the width of the Pake pattern of Figure 4 was an exact measure of the dipolar coupling constant d , the width of the ^2H Pake pattern is a measure of the quadrupolar coupling constant ω_Q .

Since the orientational dependence of the first-order quadrupolar coupling is the same as for the CSA it comes as no surprise that this coupling can (in principle) be eliminated by MAS. This is exactly the case in Figure 42 a, which shows a static ^2H NMR spectrum of a mixture of deuterated hexamethylbenzene and deuterated ferrocene; the spectrum consists of two overlapping Pake patterns, which correspond to the two deuterium environments. MAS (Figure 42 b) results in the quadrupolar line width being reduced to a series of spinning sidebands; upon closer inspection of the residual isotropic signals, it is possible to discern the isotropic chemical shifts of the two ^2H sites. For completeness, we mention that the first high-resolution ^2H NMR spectrum of a solid was obtained by exciting the double-quantum transition between the $m_I = -1$ and $+1$ states and measuring it indirectly.^[195] As seen in Figure 41 b the energy splitting between these two states is not affected by the first-order quadrupolar coupling, and is therefore independent of the orientation of the principal axes of the quadrupolar interaction. Incidentally, this transition was also successfully exploited for “double-quantum decoupling” of ^2H from ^1H nuclei. This method was used to acquire early high-resolution ^1H NMR spectra of partly deuterated solids.^[196]

Although MAS can be quite effective in reducing the deuterium quadrupolar line width, ^2H NMR is often performed on static samples. The reasons for this choice are threefold: 1) In contrast to the vast amount of time necessary to acquire a static spectrum of a spin $1/2$ nucleus, a static

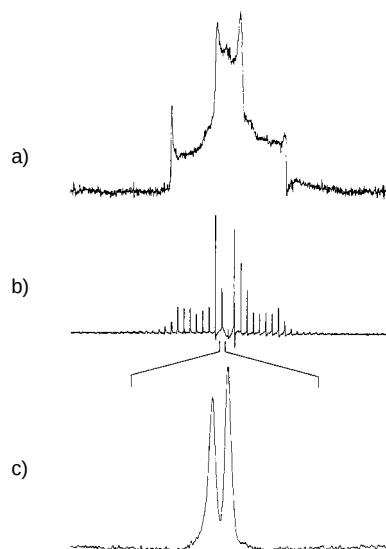


Figure 42. ^2H NMR spectra of a solid mixture of deuterated ferrocene and deuterated hexamethylbenzene, under: a) static conditions, b) magic-angle spinning. c) Expansion of the center band of b), which shows two resonances corresponding to the two deuterium sites. (Adapted from ref. [258], with permission.)

quadrupolar spectrum can be obtained more rapidly because the quadrupolar coupling greatly facilitates the relaxation of quadrupolar nuclei, thus reducing the time required for the magnetization to relax back to thermal equilibrium. 2) The ^2H quadrupolar coupling is a sensitive measure of internal molecular motion.^[193, 197] As the quadrupolar coupling depends on the molecular orientation with respect to the magnetic field, a reorientation of the molecule reduces the width and shape of a static ^2H resonance line. Figure 43 shows a series of ^2H NMR spectra of deuterated DMPC in a lipid bilayer. By adding different species to the bilayer (such as cholesterol or cytochrome c oxidase) it is possible to alter the mobility of the deuterated hydrophobic lipid tails. The narrow quadrupolar signals in Figure 43 b–d indicate that the added compounds increase the mobility of the lipid tails, whereas the addition of cholesterol to the bilayer (Figure 43 e) decreases the lipid mobility. 3) Static ^2H NMR spectroscopy is also a powerful tool for studying molecular orientation and order.^[192, 198, 199] Solid-state ^2H NMR spectroscopy has also been shown to be an excellent probe for paramagnetic reaction centers in proteins.^[200, 201]

Figure 44 a shows the sequence for a 2D exchange experiment. The spins are allowed to evolve with their characteristic resonance frequencies during t_1 . Another $\pi/2$ pulse stores the magnetization along the z direction. During the mixing time τ_m , the nuclei may reorient or chemically exchange, and after the final $\pi/2$ pulse the spins evolve with either the same or—if exchange occurred—a different resonance frequency. In the absence of exchange, a 2D spectrum acquired in this way will display the quadrupolar Pake pattern along its diagonal (similar to that shown in Figure 40). If reorientation occurred during τ_m , the resonance frequency of a particular spin changes to some new location in the Pake pattern, and off-diagonal peaks start to appear (Figure 44 b). In this example,

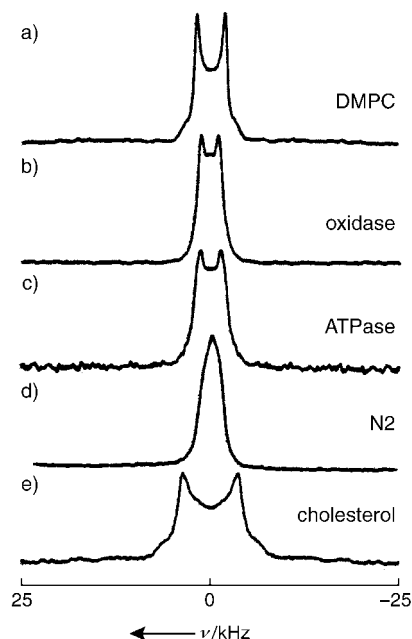


Figure 43. ^2H NMR spectra of $[\text{D}_3]\text{DMPC}$ in the presence of various additives: a) excess water (30°C); b) cytochrome c oxidase (67 wt %); c) sarcoplasmic reticulum adenosinetriphosphatase (67 wt %); d) beef brain myelin proteolipid apoprotein (N2; 67 wt %); e) cholesterol (33 wt %). $[\text{D}_3]\text{DMPC}$ = 1-myristoyl-2(14,14,14-trideutero)myristoyl-*sn*-glycero-3-phosphocholine. (Adapted from ref. [197], with permission.)

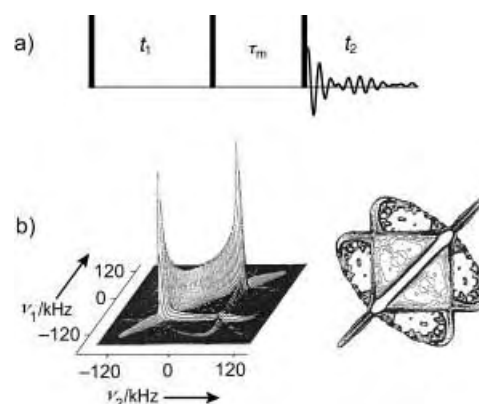


Figure 44. a) Pulse sequence for 2D exchange experiments, equally applicable to spin $1/2$ and spin 1 nuclei. b) Left: 2D exchange spectrum of α -poly(vinylidene fluoride) at 370 K ($\tau_m = 200$ ms); right: contour plot of the spectrum. (Adapted from ref. [202], with permission.)

reorientation angle distributions were determined for the C– ^2H moieties in α -poly(vinylidene fluoride).^[202]

Spin $1/2$ nuclei have also been extensively studied by 2D exchange experiments: exchange and reorientation processes as well as local order have been investigated by correlating CSA and dipolar powder patterns with pulse sequences of the basic type shown in Figure 44 a.^[54, 203, 204] Further modifications of these techniques include improved exchange experiments for spinning samples^[205] and variable spinning-angle exchange experiments.^[206]

Thus far, our discussion has been limited to ^2H NMR spectroscopy. The value of ω_Q for the deuterium nucleus is much smaller than that of other quadrupolar nuclei, and for this reason we have not alluded to the existence of a second,

more complex quadrupolar term—the second-order quadrupolar coupling. In every ^2H spectrum that was shown above, the second-order quadrupolar coupling was present, but relatively small in size. When the quadrupolar coupling is very large, as it is for ^{14}N , the second-order quadrupolar coupling can have a significant effect on the observed signal. Figure 45 shows the effect of the second-order quadrupolar coupling on the energy levels of spin 1 and spin $\frac{3}{2}$ nuclei, which causes an additional asymmetric line broadening. As we will show in Section 5.2, even when the first-order quadrupolar coupling is completely removed, the second-order quadrupolar Hamiltonian can still be large enough to make the spectrum uninterpretable.

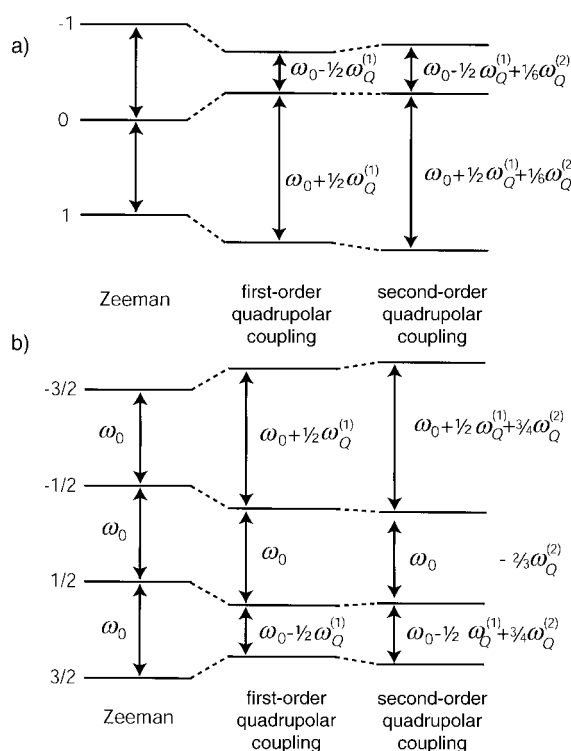


Figure 45. Effect of the Zeeman splitting and first- and second-order quadrupolar coupling on the energy levels of a) spin 1 and b) spin $\frac{3}{2}$ nuclei.

5.2. Nuclei with Spin $I > 1$

With the exception of ^{10}B ($I=3$), ^{50}V ($I=6$), and ^{177}Lu ($I=7$), all nuclei with spin $I > 1$ are half-integer quadrupolar nuclei. Nuclei with half-integer spins behave quite differently from nuclei with integer spins. The reason for this difference is made clear by examining the effect that the quadrupolar Hamiltonian has on the energy levels of a half-integer quadrupolar nucleus. Figure 45b shows the energy levels for a spin $\frac{3}{2}$ nucleus a) without any quadrupolar coupling, b) under the influence of the first order quadrupolar coupling, and c) including the second-order quadrupolar coupling. The first-order quadrupolar Hamiltonian shifts the $m_I = -\frac{1}{2}$ and the $m_I = \frac{1}{2}$ energy levels by the same amount in the same direction. Thus, the resonance frequency of the $-\frac{1}{2} \rightarrow +\frac{1}{2}$ transition, known as the central transition, is unchanged by

the first-order quadrupolar Hamiltonian. In contrast, the resonance frequencies of the $-\frac{3}{2} \rightarrow -\frac{1}{2}$ and $+\frac{1}{2} \rightarrow +\frac{3}{2}$ transitions, known as the satellite transitions, are each shifted by an amount proportional to $\omega_Q^{(1)}$, the first-order quadrupolar coupling constant. The net result of $H_Q^{(1)}$ on a half-integer quadrupolar nucleus is to shift and broaden (in a powdered solid) the resonances that result from the satellite transitions substantially. Therefore, in a standard solid-state NMR experiment performed at the frequency of the central transition, the satellite transitions are seldom observed.^[207] Yet, because the central transition is still broadened by the *second-order* quadrupolar coupling, the resulting line width can be quite large, as seen in the solid-state ^{23}Na NMR spectrum of sodium oxalate in Figure 46b. In some cases, the second-order signal is impossible to detect by traditional methods.^[208]

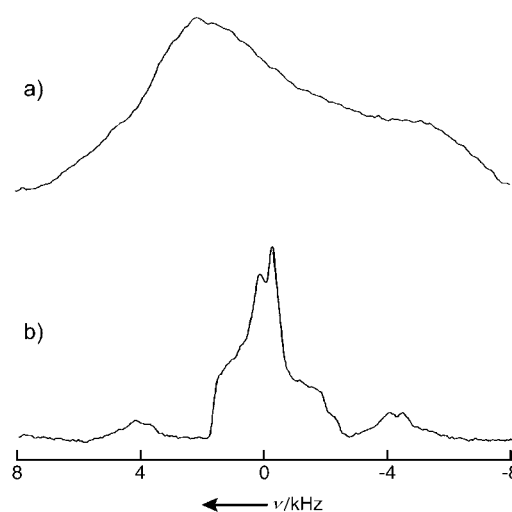


Figure 46. Solid-state ^{23}Na NMR spectrum (105 MHz) of sodium oxalate acquired a) without any sample spinning, and b) with spinning at 4 kHz at the magic angle. (Adapted from ref. [213], with permission.)

A full mathematical description of the second-order quadrupolar Hamiltonian $H_Q^{(2)}$ can be found in the literature.^[207, 209, 210] Here, we just point out two important features of $H_Q^{(2)}$ that are relevant to the study of half-integer quadrupolar nuclei by solid-state NMR spectroscopy. First, $H_Q^{(2)}$ has associated with it a coupling constant $\omega_Q^{(2)}$ [Eq. (17), ω_0 = Larmor frequency].

$$\omega_Q^{(2)} = \frac{(\omega_Q^{(1)})^2}{2\omega_0} \quad (17)$$

From Equation (17) it becomes clear why the effects of the second-order quadrupolar coupling are rarely observed in ^2H NMR spectroscopy. Even if $\omega_Q^{(1)}$ is as large as 300 kHz, the magnitude of $\omega_Q^{(2)}$ in a 2.3-T magnetic field is only ~ 3 kHz. Equation (17) also provides a major motivation for studying quadrupolar nuclei at high fields: the size of $\omega_Q^{(2)}$ can always be decreased by increasing B_0 .

Another important feature of the second-order quadrupolar Hamiltonian $H_Q^{(2)}$ is its orientation dependence, which is more complicated than that of the first-order Hamiltonians $H_Q^{(1)}$ addressed thus far. There are three orientational terms associated with $H_Q^{(2)}$; these terms correspond mathematically

to the zeroth- [Eq. (18)], second- [Eq. (19)], and fourth-order [Eq. (20)] Legendre polynomials:^[162, 211]

$$P_0(\cos\theta) = 1 \quad (18)$$

$$P_2(\cos\theta) = -\frac{1}{2}(3\cos^2\theta - 1) \quad (19)$$

$$P_4(\cos\theta) = \frac{1}{8}(35\cos^4\theta - 30\cos^2\theta + 3) \quad (20)$$

Although these equations are appropriate only for axially symmetric quadrupolar couplings, the following qualitative discussion is equally applicable to the general case. The zeroth-order term is a scalar, and just like the isotropic component of the chemical shift, is not dependent on θ . Indeed, one of the effects of the second-order quadrupolar coupling is to produce an isotropic quadrupolar shift that cannot be removed. This shift is also observed in liquids in which molecular reorientation is not too rapid.^[212] The second-order term of $H_Q^{(2)}$ is dependent on $(3\cos^2\theta - 1)$ and can therefore be removed by MAS. Figure 46 shows ^{23}Na NMR spectra of solid polycrystalline sodium oxalate; the spectra were obtained with (Figure 46b) and without MAS (Figure 46a). Although there is some narrowing, the effect is not nearly as dramatic as that of spin $\frac{1}{2}$ nuclei. The primary reason that the line broadening does not disappear with rotation at the magic angle is that the terms $P_2(\cos\theta)$ and $P_4(\cos\theta)$ equal zero at different values of θ (Figure 47). Therefore, to remove the second-order quadrupolar coupling and produce a narrow line, a technique other than MAS must be employed. For many years, research in high-resolution solid-state NMR spectroscopy was focused on this challenge.

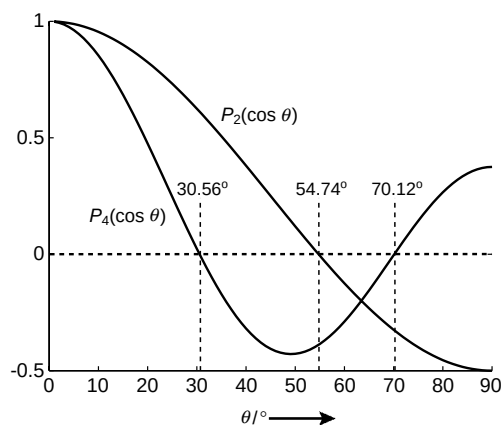


Figure 47. Plot of the second- and fourth-order Legendre polynomials $P_2(\cos\theta)$ and $P_4(\cos\theta)$, respectively, as a function of θ . $P_2(\cos\theta) = 0$ at the magic angle of 54.74° ; $P_4(\cos\theta) = 0$ at angles of 30.56° and 70.12° .

5.2.2. Double Rotation

A number of techniques have been developed to counter the effects of the second-order quadrupolar Hamiltonian in order to produce sharp NMR spectra of quadrupolar nuclei. The first technique that we discuss is conceptually simple but challenging to implement experimentally: to eliminate the CSA in a powdered sample, it is common practice to spin the sample at an angle of 54.74° relative to the magnetic field to average the $P_2(\cos\theta)$ spatial term of the CSA Hamiltonian to

zero. Similarly, double rotation (DOR)^[213–215] eliminates the second-order quadrupolar coupling by spinning at the angles of 54.74° and 30.56° *simultaneously* to remove the $P_2(\cos\theta)$ and $P_4(\cos\theta)$ spatial terms of $H_Q^{(2)}$. This is accomplished by using the “rotor in a rotor” design shown in Figure 48, which

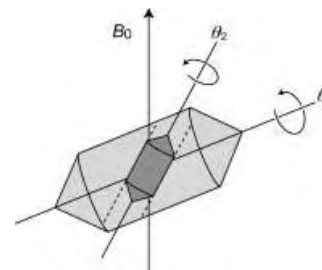


Figure 48. “Rotor-in-a-rotor” design for an NMR probe for DOR experiments. The outer rotor spins about an axis oriented at the magic angle, while the inner rotor spins about an axis oriented at 30.56° with respect to the outer axis.

allows the simultaneous rotation of the sample about two different axes. Under DOR conditions, all the second-order quadrupolar coupling is removed, except for its isotropic component, thus leaving a sharp isotropic peak flanked by a series of sidebands spaced at integer multiples of the outer rotor frequency. Figure 49 shows ^{23}Na DOR NMR spectra

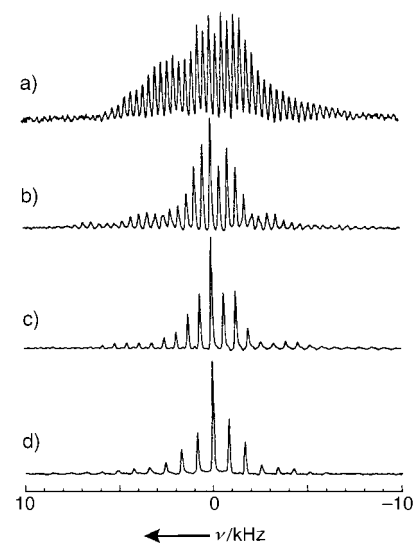


Figure 49. ^{23}Na DOR NMR spectra (105 MHz) of sodium oxalate acquired at outer-rotor spinning speeds of a) 320 Hz, b) 440 Hz, c) 640 Hz, and d) 850 Hz. (Adapted from ref. [259], with permission.)

of sodium oxalate obtained at various outer rotor speeds. When compared to the ^{23}Na NMR spectra of sodium oxalate in Figures 46a, b, the high resolution that is made possible through DOR is quite dramatic, and these experiments were the first to open the door to truly high-resolution NMR spectroscopy of quadrupolar nuclei in the solid state.^[216, 217] In a method similar to the sideband analysis introduced by Herzfeld and Berger (see Section 4.4.1) one can obtain information about the strength of the quadrupolar coupling and asymmetry parameters from the sidebands.^[218]

5.2.3. Dynamic-Angle Spinning

Dynamic-angle spinning (DAS) is an alternative technique for removing the second-order quadrupolar coupling.^[219, 220] Like DOR, DAS seeks to remove the second-order quadrupolar coupling by spinning the sample at multiple angles. However, DAS spins *sequentially* at two different angles rather than simultaneously.

As an example, let us assume that a powdered sample of a sodium salt is spun about an axis inclined at an angle of 37.38° with respect to the static magnetic field. As the central transition magnetization of the ^{23}Na nuclei evolves following a $\pi/2$ pulse, the nuclei in different crystal orientations precess at different frequencies, depending on the value of $H_Q^{(2)}$. As a result, one can expect quadrupolar signals similar to those shown in Figure 50a. When the same sample is spun at an

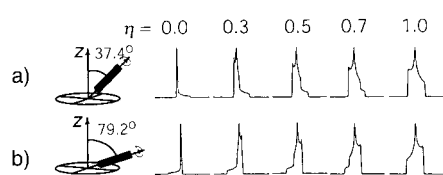


Figure 50. Simulated second-order quadrupolar powder patterns for the central transition of a spin $I = 3/2$ nucleus spinning at an angle of 37.38° (a) and 79.19° (b). η is the anisotropy of the quadrupolar coupling. (Adapted from ref. [218], with permission.)

angle of 79.19° , the second-order quadrupolar signals look like those shown in Figure 50b. It is interesting to see that these two sets of simulated spectra are exact mirror images of each other. This means that $H_Q^{(2)}$ for a crystal spinning at 37.38° has the opposite sign of that for a crystal spinning at 79.19° . Therefore, whatever the contribution of the quadrupolar coupling to the resonance frequencies, its effect can be removed by sequentially spinning the sample at these two angles. In fact, there are an infinite number of so-called DAS angle pairs.^[162, 219, 221] It is no coincidence that the angles 37.38° and 79.19° correspond to the symmetry of an icosahedron (dodecahedron). Just as MAS corresponds to the dynamic implementation of cubic symmetry (see Section 2), DAS is the dynamic realization of icosahedral symmetry.^[162, 222]

Figure 51 a, b shows two possible pulse sequences for the implementation of DAS experiments. For magnetization to evolve at two different angles, one must use a NMR probe that allows the spinning rotor axis to change orientation. As it is impractical to move a spinning rotor while actively acquiring a signal, DAS is incorporated into a two-dimensional experiment in which the second-order quadrupolar coupling is removed in the indirect dimension t_1 but not in the direct dimension t_2 . First, the magnetization is excited with a $\pi/2$ pulse and is allowed to evolve while spinning at 37.38° for a period of time $t_{1a} = 1/2 t_1$. The magnetization is then rotated back along the z axis (so that the evolution is interrupted) and the rotor axis is reoriented at an angle of 79.19° . The magnetization is then returned to the x,y plane by means of another $\pi/2$ pulse. The magnetization then evolves over a period of time t_{1b} . At the end of the t_1 period, the magnetization is detected in the direct dimension t_2 . By incrementing the

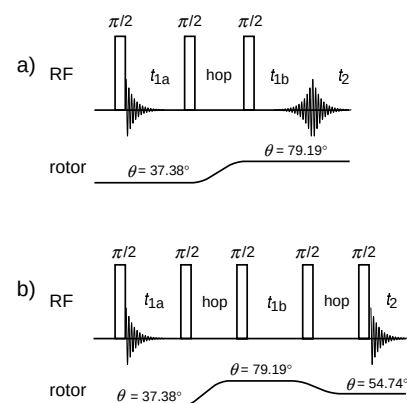


Figure 51. Pulse sequences for 2D DAS NMR experiments. a) Conventional sequence to obtain an isotropic/anisotropic correlation with powder patterns in the direct dimension characteristic of the second spinning angle. b) Sequence with a second hop to allow detection at the magic angle. With the chosen angles, t_{1a} has to be equal to t_{1b} , as the residual powder spectra at both spinning angles are the exact mirror images of each other as shown in Figure 50.

evolution time of the indirect dimension, it is possible to produce a two-dimensional spectrum that correlates the narrow isotropic lines with the broad second-order quadrupolar signal. Figure 52 shows a 2D ^{87}Rb DAS NMR spectrum

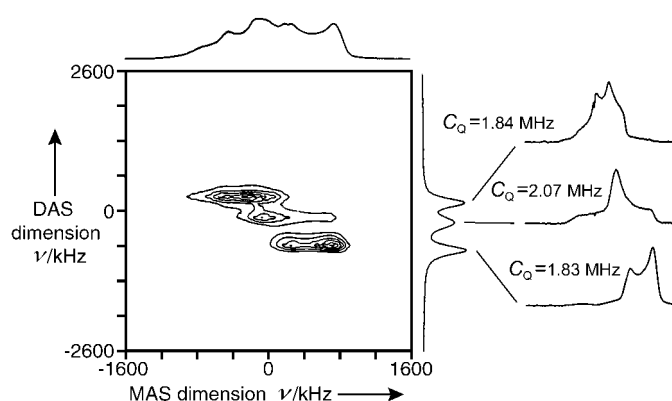


Figure 52. A 2D DAS NMR spectrum of the central transitions of ^{87}Rb in RbNO_3 . The spectrum was obtained by using the pulse sequence in Figure 51b. By taking slices in the isotropic (indirect) dimension at the different isotropic frequencies, powder patterns can be obtained which are characteristic of the different sites and from which the quadrupolar coupling constants and asymmetry parameters can be determined. The quadrupolar coupling is often given as the so-called quadrupolar coupling constant parameter $C_Q = e^2 q Q / h$ (in MHz). (Figure courtesy of P. J. Grandinetti.)

of RbNO_3 , which has three non-equivalent rubidium sites. Although the Rb resonances overlap heavily in the projection of the anisotropic dimension, they are resolved in the isotropic dimension. By fitting the second-order quadrupolar signals obtained by taking slices at the positions of the three isotropic peaks, it is possible to determine the magnitude and anisotropy of the quadrupolar coupling at each site. In recent years, the structural analysis of glasses has relied much on the application of this technique (for examples, see refs. [223, 224]).

5.2.4. Multiple-Quantum MAS

Both DAS and DOR are very good techniques for removing the effects of the second-order quadrupolar coupling in half-integer-spin quadrupolar nuclei. A technically simpler approach, known as multiple-quantum MAS (MQMAS)^[225, 226] capitalizes ingeniously on multiple-quantum coherence and coherence transfer with a standard MAS probe to remove $H_Q^{(2)}$.

Although the mathematical description of MQMAS is beyond the scope of this review, we can provide a conceptual description of the experiment. As shown in the energy-level diagram in Figure 45 b for spin $\frac{3}{2}$ nuclei, the frequency of the central transition was decreased by an amount proportional to $\omega_Q^{(2)}$, whereas the frequency of the triple-quantum transition $-\frac{3}{2} \rightarrow \frac{3}{2}$ was increased by an amount proportional to $\omega_Q^{(2)}$. The first-order quadrupolar coupling is removed for central transitions, and the term for the second-order interaction is removed by MAS, as mentioned above. If one were first to excite the triple-quantum transition, let the magnetization evolve for a period t_{1a} , and then transfer the magnetization into the central (single-quantum) transition and evolve for a period t_{1b} , at the end of the two periods the effects of the second-order quadrupolar coupling could be removed by adjusting the ratio t_{1a}/t_{1b} appropriately, as the resonance-frequency shifts induced by the second-order quadrupolar coupling are proportional to each other for both transitions. This method is analogous to the cancellation of $H_Q^{(2)}$ by the evolution of the magnetization at two different angles in DAS techniques, except that in MQMAS the rotor angle remains fixed and the magnetization evolves under two different coherences.

The similarity between MQMAS and DAS can be further illustrated by examining the MQMAS pulse sequence in Figure 53. First, the triple-quantum transition is excited by using an appropriate RF irradiation pulse. The magnetization then evolves for a period t_{1a} , after which it is transferred to the single-quantum $-\frac{1}{2} \rightarrow \frac{1}{2}$ transition by means of a second pulse. The magnetization then evolves for a period t_{1b} , after which it is detected during t_2 . Similar to the case of the DAS technique, a 2D spectrum is obtained by varying the time $t_1 = t_{1a} + t_{1b}$ of the indirect dimension (but keeping the t_{1a}/t_{1b} ratio constant). Figure 54 shows an ^{27}Al MQMAS NMR spectrum of kyanite (Al_2SiO_5). With the high resolution obtained in the isotropic dimension (ω_1), it is possible to resolve three aluminum sites in the sample. By fitting the second-order quadrupolar signals obtained from slices through the three isotropic peaks, the quadrupolar couplings and anisotropy parameters of all aluminum sites are determined. From this information, it is possible to obtain the magnitude and asymmetry parameters of the electric-field gradients present at each site. A variety of extensions and enhancements of the basic sequence of Figure 53 have been proposed recently, some of which achieve either higher sensitivity, a more convenient quantitative characterization, or a higher resolution of the signals.^[227–232] The MQMAS technique has proved to be very successful for the structure elucidation of minerals,^[233, 234] glasses,^[235–238] cement pastes,^[239] zeolites and molecular sieves,^[240–242] and biological solids.^[31, 243–247]

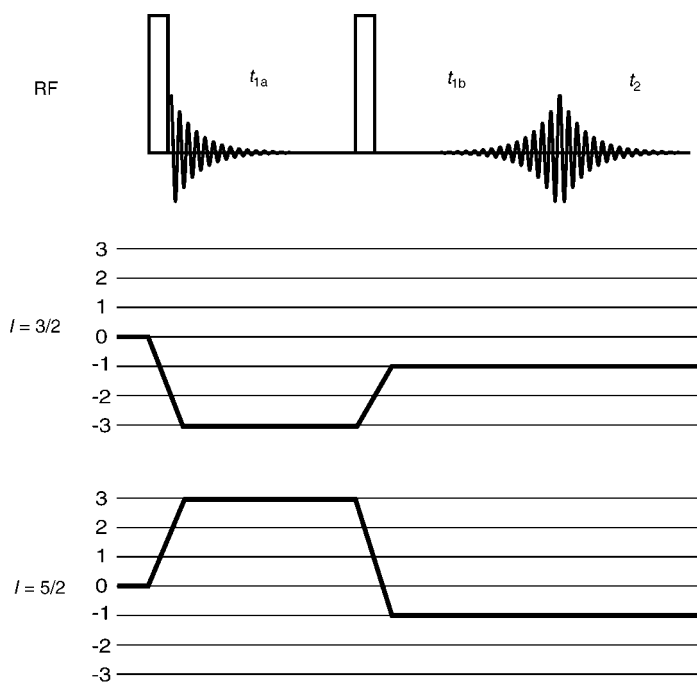


Figure 53. MQMAS pulse sequence and coherence pathway. In the time interval $t_{1a} + t_{1b}$, the second-order quadrupolar coupling is averaged to zero, leaving a scaled isotropic spectrum in the indirect dimension. For spin $3/2$ nuclei, the $0 \rightarrow -3 \rightarrow -1$ coherence pathway is selected. For spin $5/2$ nuclei, the $0 \rightarrow -3 \rightarrow -1$ coherence pathway is selected. (Figure courtesy of S. H. Wang.)

When compared to other solid-state NMR interactions, the quadrupolar coupling appears to be more complex. Nevertheless, we hope that this section has provided some insight into the behavior and spectroscopy of quadrupolar nuclei. For nuclei with small quadrupolar couplings (e.g. ^2H), information on dynamics and orientation is both simple to acquire and relatively easy to interpret. High-resolution spectra of nuclei such as ^{23}Na , ^{43}Mn , or ^{27}Al require more complex experiments such as DAS or MQMAS. The latter techniques have significantly contributed to the recent boom in the study of quadrupolar nuclei for everyday research in chemistry and materials science.^[21] Only recently hetero- and homonuclear correlation experiments based on cross-polarization and recoupling have been developed for quadrupolar nuclei in the solid state.^[248–252] In combination with recent sensitivity-boosting techniques,^[253–256] and satellite-transition correlation experiments,^[262–264] this field holds great promise for facilitating novel methods of spectral assignment and structure elucidation.

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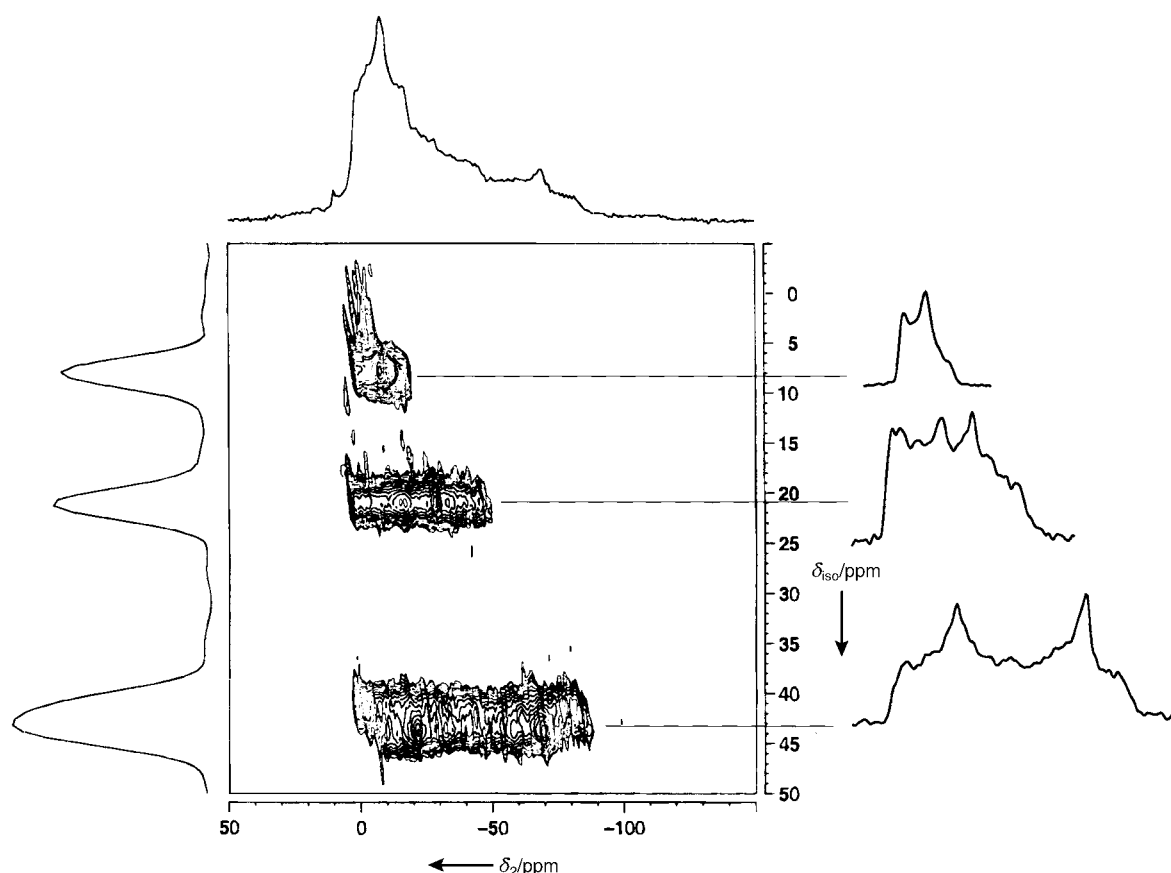


Figure 54. ^{27}Al MQ MAS NMR spectrum (104.217 MHz) of kyanite (Al_2SiO_5) at a MAS spinning speed of 22978 Hz. This spectrum was taken with a variant of the basic pulse sequence shown in Figure 53 with an additional z filter.^[260] 1D spectra for each of the sites were obtained by taking slices through the peaks in the isotropic (δ_{iso}) dimension. (Adapted from ref. [261], with permission.)

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Fertilizers

Hydroxyapatite



Brushite



DCPD

Bone

Implants



Teeth

β -TCP

Tricalcium phosphate

Biological and Medical Significance of Calcium Phosphates

Sergey V. Dorozhkin and Matthias Epple*

Dedicated to Professor Sir John Meurig Thomas on the occasion of his 70th birthday

The inorganic part of hard tissues (bones and teeth) of mammals consists of calcium phosphate, mainly of apatitic structure. Similarly, most undesired calcifications (i.e. those appearing as a result of various diseases) of mammals also contain calcium phosphate. For example, atherosclerosis results in blood-vessel blockage caused by a solid composite of cholesterol with calcium phosphate. Dental caries result in a replacement of less soluble and hard apatite by more soluble and softer calcium hydrogenphosphates. Osteoporosis is a demineralization of bone. Therefore, from a chemical point of view, processes of normal (bone and

teeth formation and growth) and pathological (atherosclerosis and dental calculus) calcifications are just an in vivo crystallization of calcium phosphate. Similarly, dental caries and osteoporosis can be considered to be in vivo dissolution of calcium phosphates. On the other hand, because of the chemical similarity with biological calcified tissues, all calcium phosphates are remarkably biocompatible. This property is widely used in medicine for biomaterials that are either entirely made of or coated with calcium phosphate. For example, self-setting bone cements made of calcium phosphates are helpful in bone repair and titanium

substitutes covered with a surface layer of calcium phosphates are used for hip-joint endoprostheses and tooth substitutes, to facilitate the growth of bone and thereby raise the mechanical stability. Calcium phosphates have a great biological and medical significance and in this review we give an overview of the current knowledge in this subject.

Keywords: bioinorganic chemistry • biomaterials • biomimetic synthesis • biomineralization • materials science

1. Introduction

Calcium phosphates are the most important inorganic constituents of biological hard tissues. In the form of carbonated hydroxyapatite (HA), they are present in bone, teeth, and tendons to give these organs stability, hardness, and function. Calcium phosphate crystals are also found in “dead” nature as mineral deposits of considerable size, having grown over many years under sometimes extreme conditions of pressure and temperature. In contrast, biologically formed calcium phosphates are often nanocrystals that are precipitated under mild conditions (ambient pressure, near room temperature).

The biological formation of minerals by living organisms is commonly called “biomineralization”.^[1–9] Today more than 60 minerals are known that are used by organisms, for

example, for protection (shell), as tools (teeth), as gravity sensors (octocornia or statoliths), or as a skeleton. In terms of absolute quantity, calcium phosphates are minor compared to calcium carbonate (CaCO_3) and silicon dioxide (as silicic acid $\text{SiO}_2 \cdot n\text{H}_2\text{O}$), which both occur in huge amounts in marine single-cell organisms. Another very important class of biominerals are iron oxides that occur, for example, in snail teeth or magnetotactic bacteria.^[1] The presence of calcium phosphates in vertebrates (such as humans) makes them particularly important in biomedicine, as many diseases result from irregularities in the skeletal system (i.e. in bone) or the dental system (in teeth). It must also be stressed that, although the presence of calcium phosphate in these hard tissues is crucial for survival, there are occasions on which calcium phosphate minerals crystallize in an irregular way in undesired regions. These phenomena are called pathological crystallization or ectopic mineralization, of which atherosclerosis, stone formation, or dental calculus are prominent examples.

Herein, we give an overview of the occurrence, formation, and significance of calcium phosphate minerals in living organisms, with a special emphasis on current biomedical questions.

[*] Prof. Dr. M. Epple, Dr. S. V. Dorozhkin
Solid-State Chemistry, Faculty of Chemistry
University of Bochum
Universitätsstrasse 150, 44780 Bochum (Germany)
Fax: (+49) 234-321-4558
E-mail: matthias.epple@ruhr-uni-bochum.de

2. Geological and Biological Occurrence

Calcium and phosphorus are widely distributed elements on our planet. The surface layer of the Earth contains about 3.4 wt % of calcium and 0.10 wt % of phosphorus.^[10] Combinations of oxides of these two elements with or without incorporation of water give different calcium phosphates. Unless doped with a colored transition-metal ion (often the case in nature), all calcium phosphates are white solids. Most calcium phosphates are only sparingly soluble in water, and some can be considered to be insoluble, but all dissolve in acids. Ortho- (PO_4^{3-}), pyro- ($\text{P}_2\text{O}_7^{4-}$), and poly- ($(\text{PO}_3)_n^{n-}$) phosphates can be structurally distinguished. Although calcium pyrophosphates occur in some pathological calcifications, only calcium orthophosphates will be considered here. They are the major component of all human calcified tissues, and natural calcium orthophosphates are the source for phosphorus-containing fertilizers.^[11–14]

Geologically, natural calcium orthophosphates are found in different regions to fluoroapatite deposits, $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$, or phosphorites. Most geological environments contain calcium phosphates, usually as accessory minerals (<5 %). In some sedimentary rocks (phosphorites) and rarely in igneous segregations (fluoroapatite), the concentration is high enough to permit an economic use. The largest world deposits of natural phosphate rock are located in Morocco, Russia, Kazakhstan, and the USA (Florida, Tennessee).^[11–14] Most natural calcium phosphates occur as small polycrystals. Larger crystals usually have the crystal structure of apatites (hexagonal system, space group $P6_3/m$, or monoclinic system, space group $P2_1/b$). None of these crystals are pure compounds; they are always admixtures of other elements. For

example, calcium ions may be partially replaced by Sr, Ba, Mg, K, Na, Fe; phosphate ions may be replaced by AsO_4^{3-} , CO_3^{2-} , and VO_4^{3-} ; hydroxide, chloride, bromide, carbonate, and oxide ions may substitute fluoride ions in the crystal lattice. Moreover, some ions in the crystal structure may be missing, which leaves crystallographic defects. This leads to the formation of nonstoichiometric compounds. Figure 1 shows polycrystalline and single-crystalline calcium phosphate minerals.

The major industrial application of calcium phosphate minerals is in the production of agricultural fertilizers. Natural calcium phosphates that are used for fertilizer production can be of geological or of biological origin for example, guano

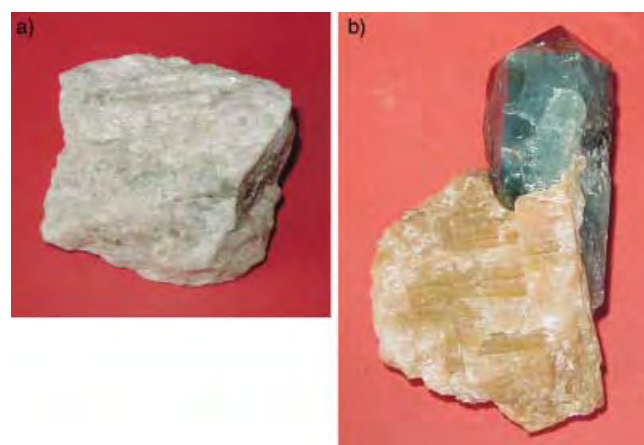


Figure 1. Polycrystalline (a) and single-crystalline (b) fluorapatite (chemical formula: $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$) of geological origin. The single crystal has a grey–green color caused by incorporated transition metals.

Matthias Eppe studied chemistry at the Technical University of Braunschweig and obtained his Ph.D. in 1992 (Prof. H. K. Cammenga). In 1993, he held a postdoctoral position at the University of Washington (Seattle, Prof. J. C. Berg). From 1994 to 1997 he worked on his Habilitation in the group of Prof. Reller at the University of Hamburg, interrupted by research stays at the Royal Institution in London with Prof. J. M. Thomas. In 1998, he received the Heinz-Maier-Leibnitz prize and a Heisenberg stipend from the DFG. Since 2000, he has been Professor of Inorganic Chemistry at the University of Bochum. His research interests include the reactivity of solids, molecular crystals, synchrotron radiation, biomaterials, and biomineralization. He has authored more than 90 publications in these fields. He is also a member of the advisory board for synchrotron radiation at the German Electron Synchrotron Facility (DESY, Hamburg) and a member of the board of the Ruhr Competence Center of Medical Technology.



M. Eppe



S. V. Dorozhkin

Dr. Sergey V. Dorozhkin studied chemistry and chemical engineering at the Moscow Institute of Chemical Technology, Moscow, USSR. Later he joined the Research Institute of Fertilizers (Moscow, USSR) where he worked on the dissolution mechanism of natural fluoroapatite. He received his Ph.D. degree under the supervision of Prof. Igor V. Melikhov (Chemistry Department of the M. V. Lomonosov Moscow State University, Russia) in 1992. Since that he has worked as a post-doctoral researcher on calcium phosphates and biomaterials at the Universities of Strasburg and Nantes (both France), as well as at the University of Aveiro (Portugal). From 2000 to 2002 he was a post-doctoral researcher on biomineralization at the Department of Solid-State Chemistry of the University of Bochum (Germany).

(mineralized excrements of birds, accumulated over thousands of years, e.g. in the South Sea at Nauru, Banaba, and Makatea). On the 21 km² island of Nauru, about 2 million tons of fertilizers are mined every year, which is leading to severe ecological problems. The total capacity of industrial plants in the world exceeds 25 million tons of phosphate fertilizers per year (as P₂O₅).^[12]

In biological systems, calcium orthophosphates occur as the principal inorganic constituent of normal (bones, teeth, fish enameloid, and some species of shells) and pathological (dental and urinary calculus and stones, atherosclerotic lesions) calcifications.^[15–18] Structurally, they occur mainly in the form of poorly crystallized nonstoichiometric sodium-, magnesium-, and carbonate-containing HA (often called “biological apatite” or dahllite). The main constituents of human bones are calcium orthophosphates (≈50–60 wt %), collagen (≈30–40 wt %), and water (≈10 wt %). In microscopic studies of the interface between implanted calcium phosphate biomaterials and the host bone, poorly crystallized nonstoichiometric carbonated apatite similar to that of bone apatite was found.^[19–21] Detailed information on the chemical composition of the most important human normal calcified tissues is given in Table 1. Figure 2 shows a picture of a calcined bone, that is, only the calcium phosphate skeleton, after burning off all organic components.

As a variety of stoichiometric calcium phosphates is known, abbreviations have traditionally been introduced to distinguish between the different compounds. Important parameters are the molar Ca/P ratio and the solubility. Table 2 presents the known calcium phosphate phases. For the chemically pure compounds, the Ca/P ratio can be between 0.5–2.0. In general, the lower this ratio, the more acidic and soluble in water the calcium phosphate is (see ref. [22] for the apparent solubility of these phases as a function of pH value and calcium concentration). A brief description of all calcium orthophosphates is given below. Table 3 contains their crystallographic data.

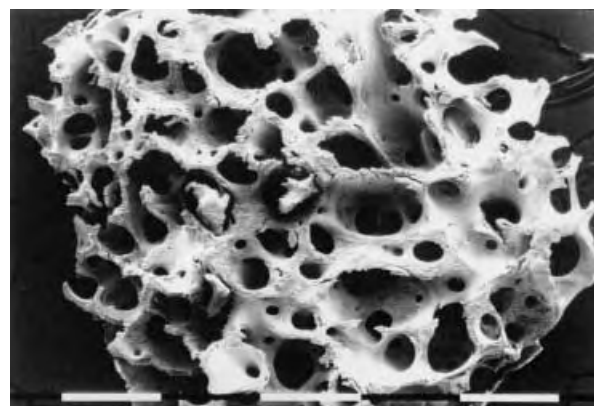


Figure 2. Calcined porous bone (*spongiosa*) showing the high porosity and the interconnecting network of pores (magnification: 20.4 ×).

MCPM (monocalcium phosphate monohydrate, Ca(H₂PO₄)₂·H₂O) is the most acidic and water-soluble calcium phosphate compound. It precipitates from highly acidic solutions that are normally used in the industrial production of phosphorus-containing fertilizer (“triple superphosphate”).^[12] At temperatures above 100 °C, it transforms into MCPA (monocalcium phosphate anhydrate, Ca(H₂PO₄)₂). Because of its comparatively high acidity and solubility, MCPM is never found in biological calcifications. However, MCPM is used in some calcium phosphate cements in medicine.^[23–27] Other applications are as antacids, acidulents, and mineral supplements for baking powders, foods, and beverages.^[28]

MCPA is the anhydrous form of MCPM. It crystallizes under similar conditions as MCPM but at temperatures above 100 °C (e.g. from highly concentrated mother liquors in fertilizer production). Like MCPM, MCPA never appears in calcified tissues, and there is no current application in medicine; it is mainly used as a fertilizer.^[12, 28]

DCPD (dicalcium phosphate dihydrate, CaHPO₄·2H₂O; the mineral brushite) can be easily crystallized from aqueous

Table 1. Comparative composition and structural parameters of inorganic phases of adult-human calcified tissues.^{[a][15, 21]}

Composition	Enamel	Dentin	Bone	Hydroxyapatite (HA)
calcium [wt %] ^[b]	36.5	35.1	34.8	39.6
phosphorus (as P) [wt %] ^[b]	17.7	16.9	15.2	18.5
Ca/P (molar ratio) ^[b]	1.63	1.61	1.71	1.67
sodium [wt %] ^[b]	0.5	0.6	0.9	–
magnesium [wt %] ^[b]	0.44	1.23	0.72	–
potassium [wt %] ^[b]	0.08	0.05	0.03	–
carbonate (as CO ₃ ^{2–}) [wt %] ^[c]	3.5	5.6	7.4	–
fluoride [wt %] ^[b]	0.01	0.06	0.03	–
chloride [wt %] ^[b]	0.30	0.01	0.13	–
pyrophosphate (as P ₂ O ₇ ^{4–}) [wt %] ^[c]	0.022	0.10	0.07	–
total inorganic [wt %] ^[c]	97	70	65	100
total organic [wt %] ^[c]	1.5	20	25	–
water [wt %] ^[c]	1.5	10	10	–
a axis [Å] ^[d]	9.441	9.421	9.41	9.430
c axis [Å] ^[d]	6.880	6.887	6.89	6.891
crystallinity index, (HA = 100)	70–75	33–37	33–37	100
typical crystal sizes [nm] ^[1, 105, 107]	100 × 50 × 50 μm	35 × 25 × 4	50 × 25 × 4	200–600
ignition products (800 °C)	β-TCP + HA	β-TCP + HA	HA + CaO	HA
elasticity modulus (GPa) ^[261]	80	15	0.34–13.8	10
compressive strength (MPa)	10	100	150	100

[a] Because of the considerable variation found in biological samples, typical values are given in these cases. [b] Ashed samples. [c] Unashed samples. [d] Lattice parameters: ± 0.003 Å.

Table 2. Properties of the biologically relevant calcium orthophosphates.^{[a][103, 104]}

Ca/P ratio	Compound	Formula	Solubility at 25 °C, $-\log(K_{sp})$	Solubility at 37 °C, $-\log(K_{sp})$	pH stability range in aqueous solution at 25 °C
0.5	monocalcium phosphate monohydrate (MCPM)	$\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$	1.14	no data	0.0–2.0
0.5	monocalcium phosphate anhydrate (MCPA)	$\text{Ca}(\text{H}_2\text{PO}_4)_2$	1.14	no data	[d]
1.0	dicalcium phosphate dihydrate (DCPD, “brushite”)	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	6.59	6.63	2.0–6.0
1.0	dicalcium phosphate anhydrate (DCPA, “monetite”)	CaHPO_4	6.90	7.02	[d]
1.33	octacalcium phosphate (OCP)	$\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$	96.6	95.9	5.5–7.0
1.5	α -tricalcium phosphate (α -TCP)	$\alpha\text{-Ca}_3(\text{PO}_4)_2$	25.5	25.5	[b]
1.5	β -tricalcium phosphate (β -TCP)	$\beta\text{-Ca}_3(\text{PO}_4)_2$	28.9	29.5	[b]
1.2–2.2	amorphous calcium phosphate (ACP)	$\text{Ca}_x(\text{PO}_4)_y \cdot n\text{H}_2\text{O}$	[c]	[c]	[c]
1.5–1.67	calcium-deficient hydroxyapatite (CDHA)	$\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$ ($0 < x < 1$)	≈ 85.1	≈ 85.1	6.5–9.5
1.67	hydroxyapatite (HA)	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	116.8	117.2	9.5–12
2.0	tetracalcium phosphate (TTCP)	$\text{Ca}_4(\text{PO}_4)_2\text{O}$	38–44	37–42	[b]

[a] The solubility is given as the logarithm of the ion product of the given formulae (excluding hydrate water) with concentrations in mol L⁻¹. [b] These compounds cannot be precipitated from aqueous solutions. [c] Cannot be measured precisely. However, the following values were reported: 25.7 ± 0.1 (pH 7.40), 29.9 ± 0.1 (pH 6.00), 32.7 ± 0.1 (pH 5.28).^[78] [d] Stable at temperatures above 100 °C. [e] Always metastable. The composition of a precipitate depends on the solution pH value and composition.

Table 3. Crystallographic data of calcium phosphates.^[72, 73]

Compound	Space group	Unit cell parameters ^[a]	Z ^[b]	Density [g cm ⁻³]
MCPM	triclinic $P\bar{1}$	$a = 5.6261(5)$, $b = 11.889(2)$, $c = 6.4731(8)$ $\alpha = 98.633(6)$, $\beta = 118.262(6)$, $\gamma = 83.344(6)$	2	2.23
MCPA	triclinic $P\bar{1}$	$a = 7.5577(5)$, $b = 8.2531(6)$, $c = 5.5504(3)$ $\alpha = 109.87(1)$, $\beta = 93.68(1)$, $\gamma = 109.15(1)$	2	2.58
DCPD	monoclinic Ia	$a = 5.812(2)$, $b = 15.180(3)$, $c = 6.239(2)$ $\beta = 116.42(3)$	4	2.32
DCPA	triclinic $P\bar{1}$	$a = 6.910(1)$, $b = 6.627(2)$, $c = 6.998(2)$ $\alpha = 96.34(2)$, $\beta = 103.82(2)$, $\gamma = 88.33(2)$	4	2.89
OCP	triclinic $P\bar{1}$	$a = 19.692(4)$, $b = 9.523(2)$, $c = 6.835(2)$ $\alpha = 90.15(2)$, $\beta = 92.54(2)$, $\gamma = 108.65(1)$	1	2.61
α -TCP	monoclinic $P2_1/a$	$a = 12.887(2)$, $b = 27.280(4)$, $c = 15.219(2)$ $\beta = 126.20(1)$	24	2.86
β -TCP	rhombohedral $R3cH$	$a = b = 10.439(1)$, $c = 37.375(6)$ $\gamma = 120$	21 ^[c]	3.07
HA	monoclinic $P2_1/b$	$a = 9.84214(8)$, $b = 2a$, $c = 6.8814(7)$ $\gamma = 120$ (monoclinic)	4	3.16
	or hexagonal $P6_3/m$	$a = b = 9.4302(5)$, $c = 6.8911(2)$ $\gamma = 120$ (hexagonal)	2	
TTCP	monoclinic $P2_1$	$a = 7.023(1)$, $b = 11.986(4)$, $c = 9.473(2)$ $\beta = 90.90(1)$	4	3.05

[a] a , b , c are given in Å and α , β , γ in °. [b] Number of formula units per unit cell. [c] Per hexagonal unit cell.

solutions. DCPD transforms into dicalcium phosphate anhydrate at temperatures above 80 °C. DCPD is of biological importance because it is often found in pathological calcifications (dental calculi, crystalluria, chondrocalcinosis,^[15–17] and urinary stones^[18]). DCPD has been proposed as an intermediate in both bone mineralization and dissolution of enamel in acids (dental caries).^[15–18] In surgery, DCPD is used in calcium phosphate cements^[27, 29–34] and, in dentistry, in toothpaste together with fluoride-containing compounds (e.g. NaF) for protection against caries.^[35–38] Other applications are in fertilizers,^[12] glass production, calcium supplements in foods, and mineral supplements in cereals.^[28]

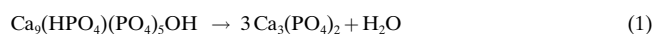
DCPA (dicalcium phosphate anhydrate, CaHPO_4 ; the mineral monetite) is the anhydrous form of DCPD. DCPA, like DCPD, can be crystallized from aqueous solutions but at 100 °C. Unlike DCPD, DCPA occurs in neither normal nor pathological calcifications. It is used in calcium phosphate cements,^[33, 39–44] and other applications are as polishing agents,

sources of calcium and phosphate in nutritional supplements, tableting aids, and toothpaste components.^[28]

OCP (octacalcium phosphate, $\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$) is often found as an intermediate phase during the precipitation of the thermodynamically more stable calcium phosphates (e.g. HA, calcium-deficient HA (CDHA)) from aqueous solutions. OCP consists of apatitic layers (with atomic arrangements of calcium and phosphate ions similar to those of HA) separated by hydrated layers (water molecules). OCP is of great biological importance because it is one of the stable components of human dental and urinary calculi.^[45–47] It plays an important role in the in vivo formation of apatitic biominerals. A “central OCP inclusion” (also known as “central dark line”) is seen by transmission electron microscopy in many biological apatites and in some synthetically precipitated HA (see below for a detailed discussion).^[48–51] Although OCP has not been observed in vascular calcifications, it has been strongly suggested as the precursor phase to

biological apatites found in natural and prosthetic heart valves.^[52, 53]

β -TCP (β -tricalcium phosphate) is the “true calcium orthophosphate” of the stoichiometric composition $\text{Ca}_3(\text{PO}_4)_2$. It cannot be precipitated from solution, but may only be prepared by calcination, e.g. of CDHA (see below), at temperatures above 800 °C [Eq. (1)]:



At temperatures above 1125 °C, it transforms into the high-temperature phase α -TCP. Being the stable phase at room temperature, β -TCP is less soluble in water than α -TCP (Table 2). Pure β -TCP never occurs in biological calcifications. Only the magnesium-containing form called “whitlockite” (chemical formula: β -(Ca,Mg) $_3(\text{PO}_4)_2$) is found in dental calculi and urinary stones,^[15–18, 54] dental caries, salivary stones, arthritic cartilage, as well as in some soft-tissue deposits.^[15–18] In biomedicine, β -TCP is used in calcium phosphate bone cements.^[23, 24, 55–58] In combination with HA, β -TCP is used as a “biphasic calcium phosphate” (“BCP”)^[59–65] as a bone-substitution ceramic. Other applications include fertilizers,^[12] polishing and dental powders, porcelains, pottery, enamel, and animal food supplements.^[28]

α -TCP (α -tricalcium phosphate, α - $\text{Ca}_3(\text{PO}_4)_2$) is a metastable phase at room temperature, prepared from β -TCP at above 1125 °C. α -TCP is more reactive in aqueous systems than β -TCP and can be hydrolyzed to a mixture of other calcium phosphates. It never occurs in biological calcifications and has a limited application in medicine in calcium phosphate cements.^[26, 31, 33, 34, 41–44, 66] α -TCP is also used as a fertilizer.^[28]

ACP (amorphous calcium phosphate) is often encountered as a transient phase during the formation of calcium phosphates in aqueous systems. Usually, ACP is the first phase that is precipitated from a supersaturated solution prepared by rapid mixing of solutions containing of calcium cations and phosphate anions.^[67–71] The chemical composition of ACP strongly depends on the solution pH value and the concentrations of calcium and phosphate ions in the mother liquor. For example, ACP phases with Ca/P ratios in the range of 1.18:1 (precipitated at solution pH 6.6) to 1.53:1 (precipitated at solution pH 11.7)^[72, 73] and even up to 2.5:1^[15–17] have been described.

The structure of ACP is still uncertain. IR spectra of ACP show broad, featureless phosphate absorption bands. The compounds are amorphous, according to X-ray diffraction experiments. Electron microscopy of ACP usually reveals spherical particles with typical diameters of 20–200 nm. However, it is likely that ACP has an apatitic short-range structure, but with a crystal size so small that it appears amorphous in X-ray diffraction experiments (no coherent X-ray scattering). This is supported by X-ray absorption spectroscopic data (EXAFS; extended X-ray absorption fine structure) on biogenic and synthetic samples.^[74–77] On the other hand, it was proposed that the basic structural unit of ACP is a 9.5 Å diameter, roughly spherical cluster of ions with the composition $\text{Ca}_9(\text{PO}_4)_6$.^[72, 73] These clusters were found experimentally as seed nuclei during the crystallization of

HA, and a model was developed to describe the crystallization of HA as a stepwise assembly of these units.^[78] Biologically, ACP (often containing magnesium, carbonate, and pyrophosphate) is found in soft-tissue pathological calcifications (e.g. heart-valve calcifications of uremic patients).^[15–18] In medicine, ACP is sometimes used in calcium phosphate cements.^[31–33] Bioactive composites of ACP with polymers have properties suitable for use in dentistry^[79–82] and surgery.^[83–86]

CDHA (calcium-deficient hydroxyapatite) can be easily prepared by the simultaneous addition of calcium- and phosphate-containing solutions into boiling water, followed by boiling the suspension for several hours. During this time, initially precipitated OCP or ACP (this depends on the solution pH value) are transformed into CDHA. On heating above 700 °C, dry CDHA with Ca/P = 1.5:1 will convert into β -TCP and that with 1.5:1 < Ca/P < 1.67:1 will convert into a mixture of HA and β -TCP (the above-mentioned biphasic calcium phosphate, BCP).^[59–65]

Because of its nonstoichiometric character, CDHA always contains other ions. The extent depends on the counterions of the chemicals used for preparation (e.g. Na^+ , Cl^-). There have been no direct determinations of the structures of CDHA and the unit cell parameters are uncertain. As a first approximation, CDHA may be considered as HA with some ions missing.^[87] According to the chemical formula of CDHA (Table 2), there are vacant calcium ion sites (mainly Ca2 sites,^[88, 89] see HA below) and hydroxide ion sites in the crystal structure of this compound. However, little is known about the vacancies of phosphate ions: in CDHA, part of the phosphate ions is either protonated or substituted by other ions (e.g. carbonate).

Unsubstituted CDHA (i.e. containing calcium, phosphate, hydrogenphosphate, and hydroxide ions only) does not exist in biological systems; it occurs only with ionic substitutions: Na^+ , K^+ , Mg^{2+} , Sr^{2+} for Ca^{2+} ; carbonate for phosphate; fluoride, chloride, and carbonate for hydroxide, and some water, form the so-called “biological apatite” or dahllite—the main inorganic component of animal and human normal and pathological calcifications.^[15, 16] Therefore, CDHA is a very promising compound for the manufacture of artificial bone substitutes.

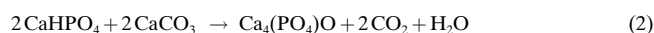
HA (hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) is the most stable and least soluble of all calcium orthophosphates (Table 2). Pure HA crystallizes in the monoclinic space group $P2_1/b$. However, at temperatures above 250 °C, there is a monoclinic to hexagonal phase transition in HA^[72, 73] (space group $P6_3/m$).^[90, 91] Some impurities, like partial substitution of hydroxide by fluoride or chloride ions, stabilize the hexagonal structure of HA at ambient temperature. For this reason, the very rare single crystals of natural HA always exhibit a hexagonal space group.

HA can be prepared in aqueous solutions by mixing exactly stoichiometric quantities of calcium- and phosphate-containing solutions at pH > 9, followed by boiling for several days under a CO_2 -free atmosphere, filtration, and drying. Microcrystalline samples of HA can also be prepared by solid-state reactions of other calcium phosphates (e.g. MCPM, DCPA, DCPD, OCP) with CaO, $\text{Ca}(\text{OH})_2$, or CaCO_3 at temperatures

above 1200 °C, in an atmosphere of equal volumes of water and nitrogen. Single crystals of HA can be prepared by hydrothermal synthesis.^[72, 73] A water-free synthesis can be performed in ethanol from $\text{Ca}(\text{OEt})_2$ and H_3PO_4 .^[92, 93]

Pure HA never occurs in biological systems. However, because of the chemical similarities to bone and teeth mineral (Table 1), HA is widely used as a coating for orthopedic (e.g. hip-joint prosthesis) and dental implants (reviewed in refs. [94, 95]), and a calcium phosphate cement with HA has also been developed.^[29] Because of the great similarity to bone mineral, HA is also used in liquid chromatography of proteins and other biological compounds.^[96–101]

TTCP (tetracalcium phosphate $\text{Ca}_4(\text{PO}_4)_2\text{O}$) is the most basic calcium orthophosphate. However, its solubility in water is higher than that of HA (Table 2). TTCP cannot be precipitated from aqueous solutions, and thus can only be prepared by a solid-state reaction above 1300 °C, for example, by heating homogenized, equimolar quantities of DCPA and CaCO_3 in dry air, or in a stream of dry nitrogen [Eq. (2)].^[72, 73]



TTCP is not very stable in aqueous solutions; it slowly hydrolyses to HA and calcium hydroxide.^[72, 73] Consequently, TTCP is never found in biological calcifications. In medicine, TTCP is widely used for the preparation of various self-setting calcium phosphate cements.^[27, 29–31, 39, 41, 102–104]

3. Biomineralization and Biological Hard Tissues

Biological mineralization (biomineralization) is the process of in vivo formation of inorganic minerals. As shown in Table 1 and discussed above, in the human body all normal and most pathological calcifications consist of calcium phosphates. Other minerals such as calcium carbonate (found in mollusk shells, algae, fish, ascidians, and plants), calcium oxalate (present in plants), CaSO_4 (jellyfish), SrSO_4 (single-celled sea organisms of the genus *acantharia*), and BaSO_4 (algae), silicon dioxide (marine algae and plants), and iron oxide (in bacteria, limpets, chitons, or mollusk teeth) are also found in biological systems,^[1, 4, 5] but that is another story. Only the chemical and structural peculiarities of calcified tissues consisting of calcium phosphates will be discussed here.

According to Weiner and Wagner, “the term bone refers to a family of materials, all of which are built up of mineralized collagen fibrils”.^[105, 106] This family of materials also includes dentin (the material that constitutes the interior of a tooth), cementum (the thin layer between the root of a tooth and the jaw), and mineralized tendons.^[105, 107] Let us start with the “real” bones.

3.1. Bone

Bone is the major calcification present in a human body.^[1] It serves as structural (mechanical) support for the body

and as the major reservoir of calcium and phosphate ions necessary for a wide variety of metabolic functions. From the chemical point of view, bone is a composite material (Table 1) of calcium phosphate and collagen. The physiological fluids present in bone act as plasticizers. Porosity is an important property of bone, as it allows the body fluids and cells to access the various regions of the osseous tissue while also influencing the mechanical anisotropy.^[1, 5, 15–17, 19–21, 105, 108–112]

Usually bone is composed of a relatively dense outer layer (*Corticalis*; the cortical or compact bone) surrounding a less dense, porous tissue (*Spongiosa*; cancellous bone), which is filled with a gel-like tissue known as bone marrow (Figure 3). Bone is a highly complex material that exhibits a strongly hierarchical structure on different length scales (see refs. [1, 5, 105, 108–112] for detailed discussions).



Figure 3. A noncalcined cancellous bone (femoral head) showing the transition from a more compact outer layer (*corticalis*) to a more porous interior (*spongiosa*).

Microscopically, the constituent building blocks of bone are mineralized collagen fibrils of 80–100 nm thickness and a length of a few to tens of microns (Figure 4). These fibrils are composites of biological apatite (i.e. CDHA with ionic substitutions) and molecules of type I collagen. The crystals of biological apatite in bone are always plateletlike (elongated along the crystallographic *c* axis) and very thin; 2–4 nm (in other words, just a few unit cells thick!—see Table 1). The crystals insert themselves in a parallel fashion into the collagen fibrils, while the latter are formed by self-assembly of collagen triple helices.^[105] Recently, this lowest level of hierarchical organization of bone has been successfully simulated by HA precipitation on amphiphilic peptide nanofibers.^[113] However, the interface between collagen and crystals of biological apatite is still poorly understood. It is not known why the crystals of biological apatite are platelet-shaped.^[1, 5, 105, 108–112]

In general, a sequence of temporal events can be recognized during bone formation. The first stage involves the synthesis and extracellular assembly of the collagen I matrix framework of fibrils, followed by its mineralization. The

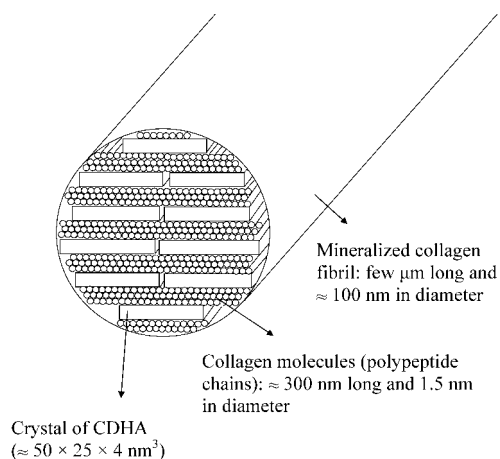


Figure 4. Schematic drawing of the mineralized collagen fibrils that are the basic constituents of bone. Platelet-shaped nanocrystals of CDHA are incorporated in a parallel way between collagen molecules, with the crystallographic *c* axis parallel to the fiber axis.

crystals of biological apatite grow with a specific crystalline orientation—the *c* axes of the crystals are roughly parallel to the long axes of the collagen fibrils within which they are deposited.^[5, 105, 107] The same is true for dentin and enamel,^[114, 115] as well as for more primitive living organisms. For example, in the shell of the mollusk *Lingula unguis* which consists of CDHA, the crystal *c* axes are oriented parallel to the β -chitin fibrils.^[116] Therefore, the orientation of CDHA crystals parallel to the long axes of an organic framework could be a general feature of the calcium phosphate biomineralization process.

Unlike other mineralized tissues, bone continuously undergoes a so-called “remodeling” process as it is resorbed by specialized cells called osteoclasts and formed by another type of cells called osteoblasts in a delicate equilibrium. Osteoporosis is the condition in which bone resorption dominates, and in osteopetrosis, the reverse process is dominant. That is why mature bone consists of a very complex assembly of bone “patches”, each of which has a slightly different structure and a different age.^[1, 5, 105, 107–112]

There is no general agreement on the chemical mechanism of bone formation. It is clear that the inorganic part of bone consists of biological apatite, that is, CDHA in which some ions have been replaced but (surprisingly!) without detectable amounts of hydroxide ions.^[117–119] However, various in vitro experiments on the precipitation of CDHA and HA revealed that none of these compounds directly precipitates from supersaturated aqueous solutions containing calcium and phosphate ions: some intermediate phases (so-called “precursors”) are always involved.^[15–17, 48–53, 67–71] Three compounds (DCPD, ACP, and OCP) are possible precursors to CDHA and HA precipitation in vitro. Therefore, the same compounds are suggested as the precursors to in vivo bone formation. Evidently, the precursor phase of bone is of a transient nature, which complicates its detection, especially in vivo. In 1966, Brown et al. suggested that OCP is the original precipitate on which biological apatite nucleates in the following step.^[120] This idea was extended in

their further investigations.^[121–124] By use of high-resolution transmission electron microscopy, this hypothesis was supported: computer-simulated lattice images of the “central dark line” in mineralized tissues revealed that it consisted of OCP.^[48–50]

Simultaneously with Brown, the research group led by Posner proposed that ACP is the initially precipitated phase of bone formation in vivo.^[125–127] This conclusion was drawn from the following facts:

- When calcium orthophosphates are prepared by rapid precipitation from aqueous solutions containing calcium cations and phosphate anions at pH > 8.5 in vitro, the initial solid phase that appears is amorphous.
- Mature bone mineral is a mixture of ACP and poorly crystallized CDHA.
- Early bone mineral has a lower crystallinity than mature bone,^[125–133] which suggests that after being formed the crystals of bone mineral undergo some transformations during maturation.

For obvious reasons, there is only indirect evidence for the in vivo crystal growth of bone mineral. Studies of animal bones of different ages showed that the X-ray diffraction peaks become sharper with increasing age, that is, the crystallinity and/or the domain size increase. This change occurs anisotropically, that is, it is more pronounced in the crystallographic *a* axis [(310) reflections] than the *c* axis [(002) reflections].^[134, 135] In addition to this, other changes, such as an increase of calcium content and a decrease of HPO_4^{2-} occur in bone mineral with age.^[136, 137] Both crystal size and carbonate content increase during aging in rats and cows.^[137] From a chemical point of view, these changes indicate a slow transformation of a poorly crystallized CDHA into a better crystallized HA.

There is a current debate on the question of whether bone formation is an active or a passive process. As an “active process”, one describes the assembly of calcium phosphate nanocrystals within a spatially confined compartment of an osteoblast, that is, within a matrix vesicle. These structures have been found by transmission electron microscopy for bone and tooth formation.^[138–140] The term “passive process” comes from the observation that blood serum is supersaturated with respect to calcium phosphate precipitation,^[141] therefore mineralization should occur spontaneously at a suitable nucleus (i.e. on a collagen fibril). The collagen fibrils have a specific structure with a periodicity of 67 nm and 35–40 nm gaps or holes between the ends of the collagen molecules, where bone mineral is incorporated in the mineralized fibril. A nucleation within these holes would lead to discrete crystals with a size related to the nucleating cavity in the collagen fibril. It was proposed that the temporary absence of specific inhibitors leads to precipitation and thereby regulates this physicochemical bone formation.^[142–144] The question of whether cells do actively form and deposit bone mineral or whether a systemic regulation of inhibitors controls bone formation is still open.^[145] The truth probably lies somewhere in between, that is, calcium phosphate nanocrystals are formed within cells from a supersaturated medium and excreted near the collagen fibers where they are finally deposited.

3.2. Teeth

Teeth are the second major normal calcification present in mammals.^[1] The structure of teeth is even more complicated than that of bone (Figure 5). For example, unlike bone, teeth consist of at least two different biominerals: enamel (outside) and dentin (interior). As shown in Table 1, dentin and bone have many similarities, and in most aspects they can be regarded as being essentially the same material.^[1, 72, 73, 105, 107–112, 136] Therefore, most statements made above for bone are also valid for dentin.

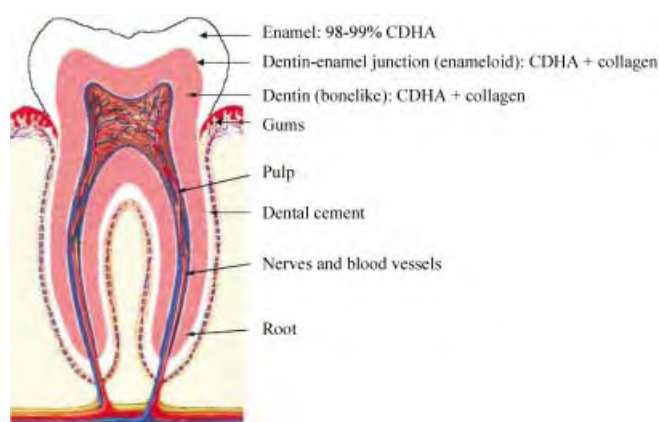


Figure 5. Schematic picture of a tooth and its local chemical composition.

Tooth enamel contains crystals of biological apatite that are much larger than those of bone and dentin (Table 1). In addition, its organic phase does not contain collagen. At the interface between enamel and dentin, there is an “enameloid” phase; a hard tissue that contains enamel-like crystals of biological apatite and collagen fibrils.^[1]

Enamel and enameloid consist of biological apatite crystals that are remarkably different from the other mineralized tissues in humans and vertebrates. In enamel, needlelike crystal rods are tens of microns long (up to 100 μm) but sometimes only 50 nm wide,^[146–150] which is much larger than the mineral crystals of dentin and bone (Table 1), but nevertheless consist of carbonated CDHA.^[151–153] On the surface, there is also some fluoride content in place of hydroxide ions^[154] although the overall content of fluoride ions in enamel is small (about 0.01 wt %;^[16] see also Table 1). Note that fluoroapatite is not found in enamel.^[1]

The enamel crystals are generally organized into parallel arrays under strict biological control. This structure can be deduced from the observation that, at every stage, the parallel arrays are well-ordered and that the crystal rods all have a remarkably uniform cross section (Figure 6).^[146–148] The first detectable crystals in enamel formation are flat, thin ribbons,^[146–148] that were reported to be OCP,^[109, 155–157] β -(Ca,Mg)₃(PO₄)₂,^[156] or DCPD.^[117, 119] During maturation of the enamel, the mineral content increases from initially 45 wt % to 98–99 wt %,^[117] accompanied by widening and thickening of the crystal rods.^[117, 119, 158, 159] Simultaneously, the



Figure 6. Scanning electron micrograph of the forming enamel on a continuously growing rat incisor, which shows ordered rods of calcium phosphates. Scale bar: 10 μm (taken from ref. [1] with permission).

Ca/P ratio increases^[158, 159] and the carbonate content decreases,^[160–162] which finally results in the most highly mineralized and hardest skeletal tissue.

Enamel crystals show the (100) face at the sides and presumably the (001) face at the ends,^[163, 164] as usual for HA. A “central dark line” is observed by TEM in the centers of enamel crystals (also observed in bone and dentin), which consists of OCP.^[48–51] As described above for bone, X-ray diffraction shows that the crystals of “younger” dentin are less ordered than those of more mature dentin.^[136] Therefore, maturation of dentin is a slow transformation of a poorly crystallized CDHA into a better crystallized HA.

The development of individual enamel and dentin crystals was studied by high-resolution transmission electron microscopy.^[165–167] Both processes appear to be roughly comparable and were described in a four-step process. The first two steps include the initial nucleation and formation of nanometer-sized particles of CDHA. They are followed by formation of ribbonlike crystals, which until recently was considered to be the first step of biological crystal formation in the tooth.^[165–167] These complicated processes, starting with the heterogeneous nucleation of inorganic calcium phosphate on an organic extracellular matrix, are controlled in both tissues by the organic matrix and are under cellular control (odontoblasts and ameloblasts).^[168] To complicate the process even further, regular and discrete domains of various charges or charge densities on the surface of CDHA crystals derived from the maturation stage of enamel development were recently discovered by a combination of atomic and chemical force microscopy.^[169] Organic molecules (e.g. amelogenin)^[169] at physiological solution pH values appear to bind on the charged surface domains of CDHA.

On the other hand, dentin and enamel share a common starting location: the dentin–enamel junction.^[170–172] The steps of enamel crystal growth at the junction are a matter of current debate. Some authors claim that the enamel crystals grow epitaxially on the pre-existing dentin crystals, because of a high continuity between enamel and dentin crystals.^[173–175] Others have shown that enamel crystals are formed at a given distance from the dentin surface^[155–157, 176] and could either

reach dentin crystals by a subsequent growth^[177] or remain distant.^[176, 178] Thus, both structure and formation of the teeth appear to be more complicated than those of the bone.

A physicochemical mineralization occurs every day on our teeth. Enamel is only formed during dentinogenesis in the jaw, that is, it will never be repaired by cellular action. If it is etched, for example, by acidic food or beverages, CDHA is dissolved. Fortunately, the saliva in the mouth is supersaturated with respect to CDHA deposition (as is the blood serum), and after a while, the surface layer is restored again. This process does not involve any biological action and therefore can be classified as “passive mineralization” (see also the discussion above on bone formation). Replacement of some hydroxide ions with fluoride ions (which leads to fluorohydroxyapatite) lowers the solubility and therefore improves the acid resistance.^[154]

3.3. Cartilage

Cartilage is usually (but not exclusively) part of the endoskeleton of animals^[1, 179] and exists both in mineralized and unmineralized forms. Only vertebrates develop mineralized cartilage, in some cases in the central portions of the vertebra and close to the surface of jaws. Except for pathological cases, the mineralization of cartilage occurs in two situations in the body: First, during bone formation in the endochondral plate (in almost all vertebrates) and second, as final mineralized product (only in sharks and certain other fishes^[180]).^[1]

Mineralized cartilage consists of the unmineralized cartilage plus crystals of CDHA, as well as considerable amounts of amino acids, phosphoserine, and other biological compounds. The molecular organization of macromolecules of cartilage and CDHA crystals is still not fully understood. Mineralized cartilage and bone coexist in close proximity in the endochondral plate during bone formation. They have similar macromolecular constituents, and both contain CDHA.^[1] However, the shape of the CDHA crystals in mineralized cartilage, in general, resembles that in enamel: the crystals were found to be needlelike (CDHA crystals of bone are platelike),^[1, 105, 108–112] but much shorter (25–75 nm^[181] or 50–160 nm^[182]) than those of enamel (up to 100 μm ^[146–150]). The average thickness of the CDHA crystals in mineralized cartilage was reported as 5–7.5 nm^[181] and 1.8 nm.^[182]

The process of cartilage mineralization has been well-described elsewhere.^[183–185] Before the crystal formation, the organic matrix (consisting of proteoglycans, type II collagen and water)^[1] first takes up calcium and then phosphate.^[185] The first crystals of CDHA, those formed in cartilage, were needlelike and located inside cellular matrix vesicles.^[183, 184] After growth within the vesicles, the crystals extend out of these containers into the surrounding organic matrix. They aggregate into clusters of randomly oriented crystals. In a second step, these clusters further aggregate to form the mature mineralized-cartilage structure with a random arrangement of crystals.^[181] Physicochemical investigations of the crystals revealed their very poor crystallinity and the

presence of significant amounts of nonapatitic calcium phosphates. The concentration of such nonapatitic phosphates was found to increase during the early stages of cartilage mineralization but then decreased as the mineral content steadily rose, until full mineralization was achieved.^[186] Therefore, the CDHA crystals in the vesicles act as centers of cartilage mineralization. However, a detailed understanding of the mechanisms of crystal nucleation and growth in these vesicles is not yet available.^[1]

3.4. Shells

Rarely, calcium phosphates are encountered in mollusk shells (that in most cases consist of calcium carbonate).^[187, 188] When biomineralization was “invented” by nature about 570 million years ago, there were both mollusks with calcium carbonate and calcium phosphate shells. Over time, the ones with calcium phosphate shells mostly disappeared (so-called “problematica”), and today the overwhelming majority of mollusk has shells of calcium carbonate.^[1] Figure 7 shows fossilized shells of the species *Lingula* that consist of calcium phosphate (apatite).^[116]



Figure 7. Fossilized shells of the brachiopod *Lingula* from the Lower Triassic, consisting of calcium phosphate (taken from <http://inyo.topcities.com/ef/lingula.html> with permission).

4. Pathological Crystallization of Calcium Phosphates

Unwanted deposition of calcium phosphates in the body can lead to severe diseases. Calcium phosphate depositions are responsible, among other things, for urinary stones,^[15, 189, 190] atherosclerosis,^[141, 191–193] dental calculus,^[45, 46] calcification of artificial heart valves,^[194–198] and calcified menisci (“chondrocalcinosis”).^[199, 200] Figure 8 shows an example of atherosclerotic depositions of calcium phosphate (together with cholesterol) that was isolated from arteries.^[193, 201] Blockage of arteries by such deposits is the major cause of death in developed countries.

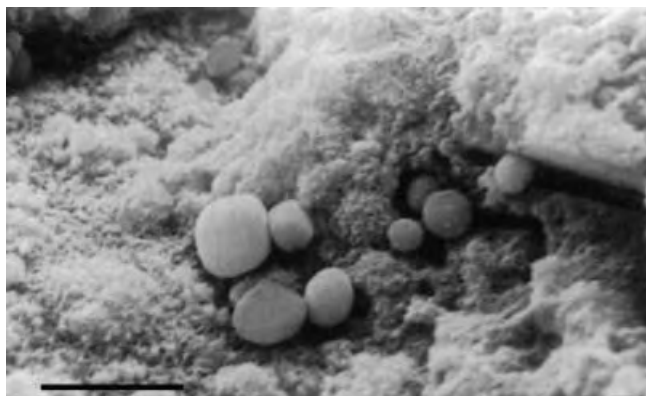


Figure 8. Spherical calcium phosphate particles isolated from an atherosclerotic lesion. Scale bar: 4 μm (taken from ref. [193] with permission).

As many body fluids (blood, saliva) are supersaturated with respect to HA precipitation,^[141] we may conclude that calcification is thermodynamically feasible but kinetically hindered in most parts of the body. Therefore, suitable inhibitory mechanisms must be at work to prevent an unwanted mineralization in the body. The mechanisms of this inhibition are a topic of current research in molecular medicine, as it can be concluded that disruptions of this inhibition are probably the cause of pathological calcifications. In addition, the fine-tuned equilibrium of bone resorption and formation may be based on such processes. For instance, in mice in which the genes that are responsible for the production of the specific blood proteins (fetuine,^[142, 144] matrix Gla protein^[143, 202]) were knocked out, uncontrolled calcification in the arteries occurs. Obviously, these proteins serve as inhibitors of calcium phosphate precipitation by suitable complexation of the dissolved ions or by effectively preventing formed nuclei from further growth by preferential adsorption.^[203–205]

On the other hand, some mechanisms have been identified that enhance crystallization.^[141] Currently discussed, especially for the case of atherosclerosis, are:

- the heterogeneous nucleation of calcium phosphates on the membranes of dead cells that contain phospholipids (phosphate groups act as nucleators),^[192, 195]
- nucleation by antibodies that are specific for cholesterol,^[205, 206] and
- cellular action of osteoblast-like cells (so-called pericytes) within arteries that form bonelike tissue.^[207]

For the case of atherosclerosis, obviously a number of effects are responsible for the pathological calcification; these range from purely physicochemical effects (supersaturation)^[141] over biologically induced nucleation to the biologically controlled deposition of calcium phosphates by specialized cells.^[141]

Similar effects exist during the calcification of artificial heart valves. The replacement of heart valves by implants of either biological (porcine heart valves) or synthetic origin is now a common procedure in cardiosurgery (about 150 000 are implanted every year worldwide).^[196] However, the implanted devices tend to calcify after implantation (in some cases even after a few months), that is, they become stiff because of

deposition of calcium phosphate. The origin of this behavior is not yet clear but, at least with heart valves of biological origin, a nucleation by membranes of dead cells (phospholipids) appears likely.^[194–198]

5. Calcium Phosphates as Biomaterials

The treatment of injuries or diseases often requires surgical action. For the past 50 years, biomaterials have increasingly been applied to improve surgical procedures or to restore lost body functions. Bone fractures are usually treated with metallic wires, nails, screws, and plates, joints are replaced by artificial endoprostheses (hip or knee), and lost teeth are replaced by metallic implants in the jaw, to name a few examples. As soon as foreign materials come into internal contact with the body, the question of biocompatibility becomes paramount, as any adverse effect (namely toxicity, allergy, inflammation, corrosion, and mechanical failure) must be strictly avoided. The search for optimally designed biomaterials is still ongoing as a joint effort of physicians, engineers, chemists, and physicists.^[15, 194, 208–213]

Calcium phosphates generally have an excellent biocompatibility, that is, they are well-accepted by the body and integrate well, for example, into bone upon implantation. This is because of their almost ubiquitous presence in the body in either the dissolved or solid form. Consequently, they have found important applications as biomaterials, particularly for hard-tissue regeneration.^[21, 47, 66, 214–221]

In the bulk form, calcium phosphates are used as artificial bone-substitution material for surgical treatment of bone defects by orthopedic surgeons and maxillofacial surgeons.^[15, 16, 219, 222] A bone defect that is caused, for example, by tumor extraction, complicated fracture, or inflammation must be filled with a suitable material to permit growth of new bone into this defect. Otherwise, ingrowth of fibrous tissue would prevent bone formation within the defect. Because the ideal substitute (the “golden standard”), a patient’s own spongy bone from the *Iliac crest* (hip) is usually not available in sufficient quantities, and as materials of biological origin are critically discussed because of possible infections or immune reactions, the need for a fully synthetic material is evident. Today, many different calcium phosphate ceramics are on the market for the treatment of bone defects (see, for example, refs. [15, 16, 219, 222] for overviews).

Chemically, synthetic bone-substitution materials are usually based on HA, β -TCP, or BCP (i.e. a composite of HA and β -TCP).^[15, 16, 219, 222, 223] The requirements for an ideal substitute are usually:

- a porosity with a pore diameter of some 100 μm size (to permit ingrowth of bone cells; see Figures 2 and 3),
- a biodegradation rate comparable to the formation of bone tissue (i.e. between a few months and about two years), and
- a sufficient mechanical stability.^[15, 16, 219, 222]

HA is more stable than α - and β -TCP under physiological conditions, as it has a lower solubility and slower resorption kinetics.^[15, 16, 219, 222] Implants of calcined HA of high crystallinity are present in a defect even years after implantation in a virtually unchanged form, therefore β -

TCP^[218] or BCP^[21, 61, 63, 64] ceramics are favored today. An ideal material should be degraded inside the defect simultaneously with the formation of a new bone, that is, the full restoration of the defect with biological material is desired. Figure 9 shows three examples of calcium phosphate-based bone-substitution materials of different origins. Implant porosity is a very important property to allow cell invasion and bone ingrowth.

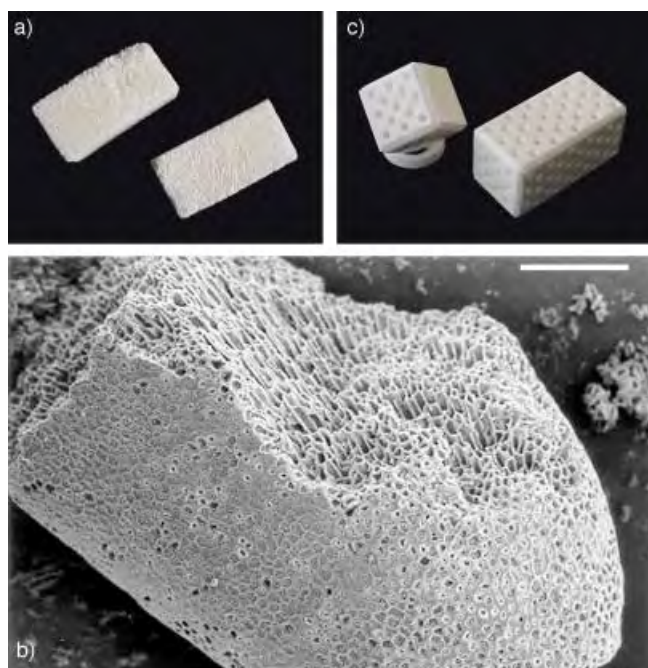
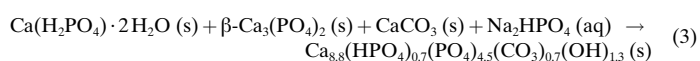


Figure 9. Examples of porous calcium phosphate-based bone-substitution materials: a) Cerabone (hydroxyapatite) from spongy calcined bovine bone (about $3 \times 1 \times 1 \text{ cm}^3$); b) Aligpore (hydroxyapatite) from hydrothermal processing of calcium carbonate-containing algae with ammonium phosphate. Scale bar: 100 μm ; c) Cerasorb (synthetic phase-pure β -TCP) with CNC (computer numerical control)-drilled holes (about $1 \times 1 \times 2 \text{ cm}^3$).

A new concept in the treatment of bone defects was introduced with bone cements based on calcium phosphates, which harden inside the defect. Although different formulations are on the market (see the discussion of the different calcium phosphates above), they usually consist of solid calcium phosphates that are mixed with a solution to induce the precipitation of a CDHA-like phase [Eq. (3), not stoichiometrically balanced].^[66, 102–104, 211, 212]



The advantage of this procedure is that the cement adapts better to the defect geometry than ceramic materials that are implanted as solids. The structure and composition of the hardened calcium phosphate is close to that of bone mineral; therefore, a facilitated resorption is observed.^[66]

Calcium phosphate coatings on metals are often applied in medicine. Metallic implants are encountered in endoprostheses (total hip-joint replacements) and artificial tooth sockets. The requirement for mechanical stability necessitates the use

of a metallic body for such devices. As metals usually do not undergo bone bonding, that is, they do not form a mechanically stable bond between implant and bone tissue, ways have been sought to improve the mechanical contact at the interface.^[194, 208, 224] One possibility is to coat the metal with calcium phosphate ceramics; these increase the roughness of the bone surface and thereby facilitate bone bonding, and may therefore serve as a “glue” between the metal and bone (Figure 10).



Figure 10. Calcium phosphates in hip endoprostheses: a ceramic ball joint (Al_2O_3), a calcium-phosphate coated endoprosthesis (“cementless endoprosthesis”) and an uncoated endoprosthesis that must be fixed in place with PMMA bone cement.

Two methods of bone coating are currently applied: Application of molten calcium phosphate by high-temperature plasma spraying and precipitation from a supersaturated calcium phosphate solution. The first approach^[94, 95, 216, 224] is very rough from a chemical point of view. Solid calcium phosphate is injected into a plasma flame and directed towards an implant that is appropriately rotated to achieve a uniform coating. This extremely fast quenching leads to the formation of a mixture of calcium phosphates on the implant surface. Metal and calcium phosphate are strongly joined after this procedure.^[94, 95, 216, 224]

The second approach involves dipping metallic implants into supersaturated calcium phosphate solutions. This method was strongly promoted by the work of Kokubo and co-workers and van Blitterswijk and co-workers, who showed that after appropriate surface etching, a stable interface evolves between metal and ceramic.^[225–230] The method also permits coating of internal surfaces (difficult with plasma spraying) and the incorporation of biologically active substances, for example, proteins or antibiotics into the coating.^[231] A special case is surface coating with a biomimetic defect apatite by dipping into simulated body fluid (SBF), a solution that contains the inorganic ions of human blood plasma in almost natural concentrations.^[225–228, 232–235] Figure 10 shows both a calcium phosphate-coated and an uncoated hip endoprosthesis. The latter has to be fixed in the femur bone by a suitable bone cement based on poly(me-

thylmethacrylate) (PMMA). Note that this polymer is not biodegradable and remains in the operation site.^[224, 236]

The same principles are valid for tooth implant systems that are fixed into the jawbone, onto which artificial teeth are attached. In general, the mechanical contact between implant and bone is crucial, as considerable forces have to be withstood. Coating of such dental implants with calcium phosphates (usually by plasma spraying) leads to better and faster bone attachment. Figure 11 shows such a plasma-spray-coated tooth implant in low and high magnification. Finally, Figure 12 shows the surface of a nickel-titanium shape-memory alloy (NiTi, “Nitinol”) that was coated with calcium phosphate from solution to improve its biocompatibility.^[237]

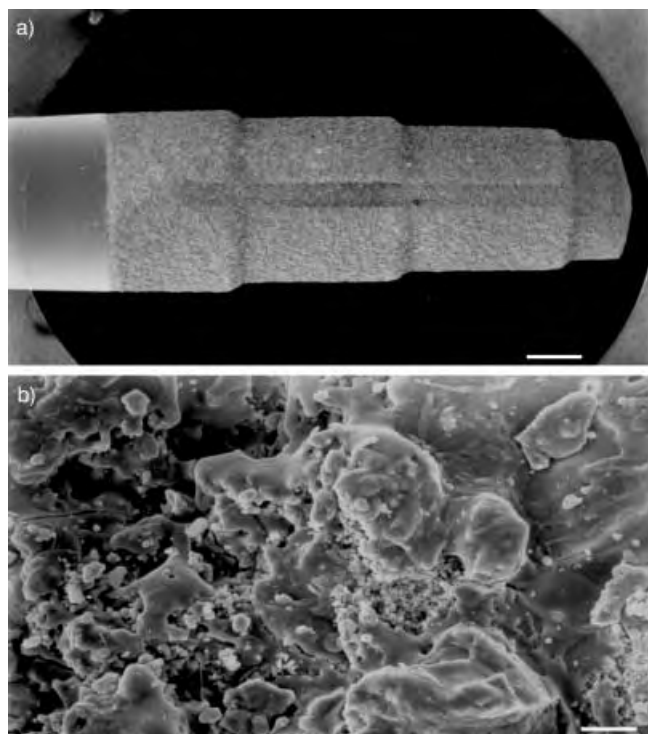


Figure 11. Dental implants (by Friadent) coated with calcium phosphate by a plasma-spray process. a: $\times 10$, b: $\times 1000$. Note the irregular, rough structure of the deposited calcium phosphate at the higher magnification. Scale bars 1 mm and 10 μm , respectively.



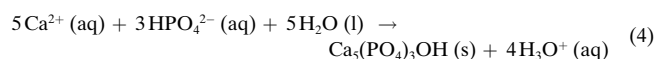
Figure 12. The surface of a nickel–titanium shape-memory alloy (“Nitinol”) that was coated with a calcium phosphate layer by dipping into an supersaturated calcium phosphate solution. The front part shows the etched metal surface from which the calcium phosphate layer has been mechanically removed. Scale bar: 2 μm .

6. Biomimetic Crystallization of Calcium Phosphates

Nature’s ability to assemble inorganic compounds into the biological structures (shells, spicules, teeth, bone, skeletons) is still not reproducible by synthetic procedures. Because of its potential benefits for materials science, research groups around the world are increasingly addressing the question of biomineralization. When considering calcium phosphates, the demand of clinical medicine to design biocompatible implants and to treat diseases related to crystallization phenomena adds a strong practical impetus to understanding these processes. The fundamentals of biomineralization have been reviewed extensively.^[1, 3–7, 238–241] We will limit ourselves to considerations of biologically inspired crystallization of calcium phosphates and present a few examples that demonstrate the current possibilities.

An approach to the preparation of biomimetic bone-substitution materials was made by Pompe et al., who crystallized HA on collagen to obtain a bonelike composite.^[242] Although the ultrastructure of bone could not be realized, such collagen–HA tapes are currently under investigation for clinical use. Note that the final step to make bone out of artificial implants is up to the body’s own remodeling function. Ozin et al. precipitated HA in the presence of surfactants, to obtain a biomimetic lamellar product.^[243] Stupp et al. have prepared so-called “organoapatites” with a bone-like crystallinity by precipitation of calcium phosphate in the presence of organic polyelectrolytes.^[214, 217, 244, 245] Kokubo and co-workers and van Blitterswijk and co-workers were successful in coating different substrates with a bonelike apatite layer (see refs. [229, 234] and those given above on coated metal prostheses). We have recently prepared bulk samples of bonelike apatite and composites of it with biodegradable polymers.^[84–86, 246]

Nancollas and co-workers invented the “Constant-Composition Technique” to monitor and control the external conditions (mainly solution pH value and concentrations of participating ions) during a crystallization experiment.^[22, 247] Generally, during precipitation of calcium phosphates from a neutral solution, the pH value decreases because of the release of protons that were formerly bound to hydrogen phosphate or dihydrogen phosphate [Eq. (4)].



One of the main differences between chemical and biological crystallization is the rate of precipitation. Usually in chemistry, precipitation occurs fast whereas in biology the crystals need days, weeks, or months to grow. A suitable simulation of this process, especially in the presence of (bio)organic additives, must therefore slow down the crystallization. This can be achieved by separating the two components with a suitable membrane or medium that acts as a diffusion barrier (a double-diffusion technique). If this medium itself contains some biomimetic functional groups, it can have a templating influence on the growing crystals. Work along this line has been carried out by Iijima et al.

(collagen matrix from bovine achilles tendon,^[248] and membranes in the presence of bovine^[249] and murine^[250] amelogenins), Kniep and co-workers (matrix of denaturated collagen),^[154, 251, 252] Epple and co-workers (matrix of microporous polyglycolide),^[253–256] Falini et al. (matrix of collagen),^[257] and Stupp and co-workers (carbon-coated TEM grid).^[113] Work on the crystallization from SBF under static and dynamic conditions to yield bonelike apatite was also reported recently by Vallet-Regi and co-workers^[258, 259] and by Epple and co-workers.^[256, 260]

Interactions between collagen and growing fluoroapatite crystals are responsible for a fractal growth of fluoroapatite into dumbbell shapes that finally close to give spheres.^[154, 251, 252] Figure 13 shows this special morphology.



Figure 13. A biomimetically grown aggregate of fluoroapatite that was crystallized in a gelatin matrix. The crystal shape can be explained and simulated by a fractal growth mechanism. Scale bar: 10 μm (taken from ref. [252] with permission).

By combining the constant-composition technique with the double-diffusion setup, we were able to identify different crystal morphologies of fluoroapatite as functions of overall concentration (i.e. supersaturation), pH value, and fluoride ion concentration.^[254, 255] Figure 14 shows a uniform crystal population that was prepared by this method.

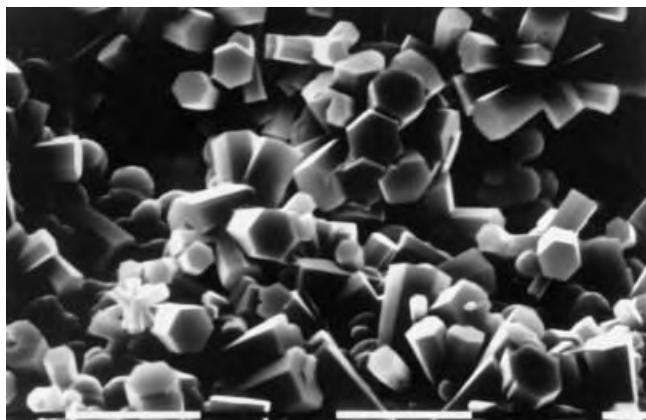


Figure 14. Hexagonal fluoroapatite crystals that were grown by a double-diffusion technique under controlled conditions (pH 7.4, 37 °C, constant ion concentrations, 7 days). Note the well-shaped crystals and their uniform size and morphology. Scale bar: 10 μm .

7. Summary and Outlook

Although it may appear surprising to the nonspecialist, there are still many open questions within the area of calcium phosphate chemistry. The basic questions concerning crystallography, thermodynamics, and phase relationships have been answered. Nevertheless, when it comes to the biological formation of calcium phosphates, issues including rate of crystallization, control of morphology, incorporation of foreign ions, and interaction with biomolecules remain hot topics that are not well understood even today. A better understanding of structure, formation, and dissolution of such biominerals will lead to improved biomaterials that can substitute bone and teeth. This knowledge will also help to counter widespread pathological calcifications such as atherosclerosis, stone formation, or dental calculus. Further progress of unforeseeable impact will come from modern genetics, where gene structures are currently related to hard-tissue formation.

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Asymmetric Photochemistry and Photochirogenesis**

Axel G. Griesbeck* and Uwe J. Meierhenrich*

One of the most interesting phenomena on Earth is the chirality of biomolecules, the origin of which remains unknown. A challenge arising from this phenomenon is the selective, atom-economic synthesis of enantiomerically pure target molecules from nonchiral starting materials. Herein, new developments in the field of asymmetric photochemistry and photochirogenesis are described with special emphasis on absolute asymmetric synthesis. In this context, the elucidation of the ultimate cause of homochirality phenomena on earth and the possible correlation with physicochemical parameters are also presented.

1. Introduction

The majority of the basic biologically relevant molecules on Earth have a defined chirality or handedness, that is, the absolute configuration of these substances is specifically entwined with a biological species and with its molecular function.^[1] Living organisms use, for example, carbohydrates, amino acids, or nucleic acids that are asymmetric and exist preferentially as either right- or left-handed enantiomers. In many cases, molecules with the incorrect absolute configuration can not even be digested, such as L-sugars or D-amino acids, and are thus useless for human beings. Also many man-made drugs exist as mixtures of mirror-image chiral isomers and in many cases only one of these isomers is pharmaceutically active. In a lucky situation, the opposing enantiomer is inactive and can be eliminated unmodified, however, some-

times severe toxic effects are observed with the biologically “wrong” enantiomer.

Two major scientific challenges are linked to these phenomena:

- the synthesis of enantiomerically pure target molecules by selective and atom-economic strategies from nonchiral starting materials with special emphasis on the use of photochemical processes and the development of absolute asymmetric synthesis (AAS)^[2] in this context, and
- the elucidation of the ultimate cause of homochirality phenomena on Earth and the possible correlation with physicochemical parameters.

In recent years, noteworthy progress has been made on both lines of research in the area of organic photochemistry. New processes have been developed either in isotropic or anisotropic media which help to improve the diastereo- and enantioselectivity of the respective transformations. These improvements involve the use of chiral sensitizers, chiral hosts in the photochemistry of host–guest complexes, the *memory of chirality* effect, the use of zeolites and crystals as confined environments for diastereo- and enantioselective transformations, and, last but not least, the use of circularly polarized light for absolute asymmetric synthesis of amino acids by photoderacemization. Two important classes of transformations that are not covered in this review are diastereoselective photochemical reactions that apply chiral auxiliaries, and solid-state photolysis of organic substrates which spontaneously crystallize in chiral space groups. Especially in the field of absolute asymmetric photochemistry, considerable advances have been reported recently. We outline new concepts in this area and describe their applicability to the generation of considerable enantiomeric enhancements in racemic mixtures of organic molecules.

2. Asymmetric Photochemistry in Isotropic Media

2.1. Supramolecular Directivity in Solution

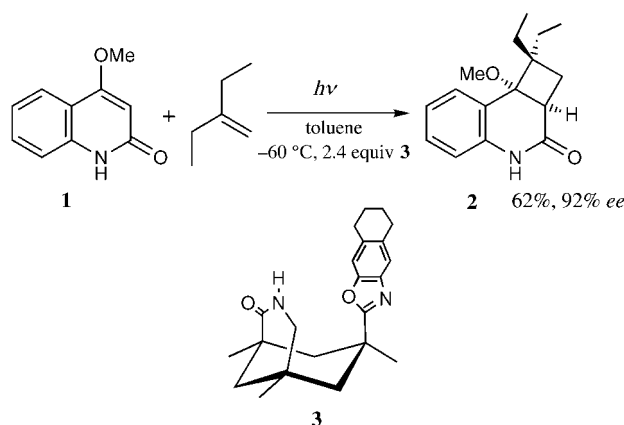
To obtain optimal supramolecular directivity in solution photochemistry, noncovalent binding interactions have to be designed which not only lead to strong host–guest stabilization but also to a sufficient differentiation between enantiotopic groups or faces in the photoactive substrate. The chiral host can be used in catalytic amounts if the photochemical

[*] Prof. Dr. A. G. Griesbeck
Institut für Organische Chemie
Universität Köln
Greinstrasse 4, 50939 Köln (Germany)
Fax: (+49) 221-470-5057
E-mail: griesbeck@uni-koeln.de

Dr. U. J. Meierhenrich
Department of Physical Chemistry
Bremen University
Leobener Strasse, 28359 Bremen (Germany)
Fax: (+49) 421-218-7382
E-mail: mhenrich@uni-bremen.de

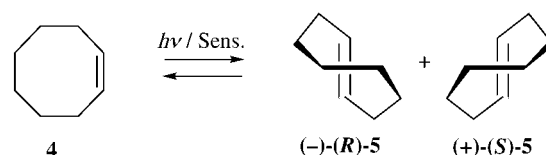
[**] The term photochirogenesis describes the light-induced formation of chiral nonracemic molecules from achiral substrates.

reactivity of the guest is strongly enhanced in the host–guest complex. Stoichiometric amounts of the chiral host are necessary whenever the photochemical behavior is not altered but the binding constants are high. A textbook example for this concept has been developed by Bach et al.^[3] A rigid amide function was used as the binding site; this strongly interacts with other amide groups, for example, those of photoreactive lactams. The molecular architecture was derived from Kemps acid and enantiopure guests were generated through a sequence of modification steps and chiral resolution. The key idea of this approach is the utilization of the complementary amide–amide hydrogen bonding motif which stabilizes the guest molecule in the chiral environment of the host structure and thereby strongly shields one of its enantiotopic faces. One of several examples described by the Bach group is the photocycloaddition of monosubstituted alkenes to the quinolone **1**.^[3a] Remarkably high *ee* values (enantiomeric excess values) were detected (up to 98 %) at low reaction temperatures in the presence of the host molecule **3** (Scheme 1). Also terminal disubstituted alkenes could be applied and gave high *ee* values. Norrish–Yang reactions and [4+4] photocycloadditions could be modified in a similar fashion.^[3b,c]



Scheme 1. Enantioselective [2+2] photocycloaddition of enone **1** with alkene **2** under host–guest conditions.^[3a]

Cyclodextrins have also been intensively investigated as supramolecular hosts.^[4] It is possible to accommodate molecules inside these doughnut-shaped entities and use the chiral cavity as the chiral inductor. To transfer efficiently the excitation energy to the guest molecule, sensitizing groups are covalently attached to the host. Supramolecular enantio-differentiating photoisomerization of (*Z*)-cyclooctene (**4**) to its chiral *E* isomer (**5**) by inclusion and sensitization with modified α -, β -, and γ -cyclodextrin derivatives bearing diverse chromophores (benzoates, phthalates, and tethered benzamides) was investigated in aqueous methanol solutions at varying temperatures (Scheme 2).^[4d] The photostationary *E*/*Z* states reached ratios of 0.4–0.8:1 which were higher than the value of approximately 0.25:1 reported for sensitization by conventional alkyl benzoates in hydrocarbon solvents. β -Cyclodextrin derivatives afforded the highest *ee* values of up to 24 %, depending on the solvent composition.



Scheme 2. *E/Z* photoisomerization of cyclooctene; Sens. = sensitizer.

The modification of cyclodextrins with a sensitizing group successfully enhanced the product selectivity through the excited-state supramolecular interaction within the cavity. Surprisingly, the product *ee* values obtained with these hosts were not a simple function of either temperature or solvent, but correlated with the percentage of occupied host (host occupancy). This correlation shows that the entropy factor plays an insignificant role in this supramolecular photochiro-genesis system, which is in sharp contrast to the decisive role of entropy in the conventional (nonsupramolecular) counterpart performed in homogeneous solutions, where an inversion of product chirality by temperature variation occurs.^[5] The role of entropy for photochemical reactions and the pronounced effects on the temperature dependence of photoisomerization^[6] and photocycloaddition^[7] reactions have recently been clearly demonstrated.

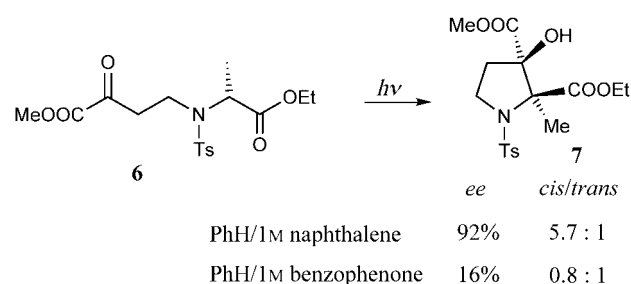
2.2. Sensitized Enantioselective Photochemistry

As already mentioned above, an intensively studied photochemical process which has gained importance as a model reaction for enantioselective transformations is the photolysis of (*Z*)-cyclooctene. This archetype of a photochemical *cis*–*trans* isomerization results in the formation of the chiral (*E*)-cyclooctene. This reaction has been investigated in depth by Y. Inoue and co-workers, and the subtle interplay of enthalpy and entropy factors which governs the enantioselectivity of this reaction has been clearly elucidated by the analysis of sensitizer structure and sensitizer energetics, temperature, pressure, and solvent effects.^[8] Recently, self-sensitizing, diastereodifferentiating systems such as benzoyl-substituted cyclooctenes were applied to study intra- versus intermolecular sensitization processes and selectivities.^[9]

2.3. Memory of Chirality

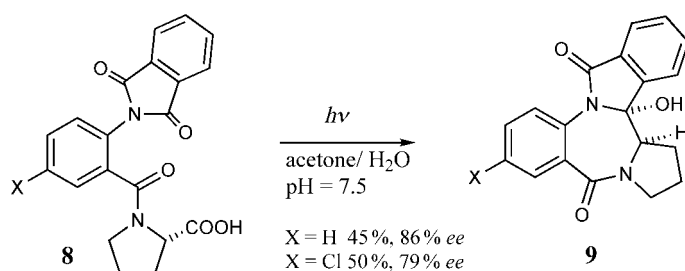
The phenomenon of chirality memory, which was originally developed for carbanion chemistry,^[10] was recently also discovered in photocyclization reactions involving singlet as well as triplet biradical species. As one of the first examples, Giese et al. described an efficient pyrrolidine synthesis from the alanine derivative **6**. Under triplet sensitization conditions with benzophenone, the products were formed with low *cis*/*trans* diastereoselectivity (“simple” stereoselectivity) and with a low degree of enantioselectivity. In contrast, the singlet photocyclization proceeded with remarkable high chirality memory and also high simple (*cis* selective) diastereoselectivity to give the pyrrolidine **7** with an *ee* value of 92 %.^[11] Naphthalene was used as the triplet quencher and the nonzero

ee value under triplet conditions accounts for the fact that also the triplet 1,5-biradicals can partly combine to nonracemic products in competition with bond rotation (Scheme 3).



Scheme 3. Memory of chirality effects in the singlet 1,5-photocyclization of the alanine derivative **6**.^[11]

Photocyclization can proceed with a high degree of chirality memory, not only under singlet conditions.^[12] The decarboxylation of the proline derivatives **8** (initiated by a photo-induced electron transfer) gave the pyrrolobenzodiazepines **9** with high *ee* values, although these reactions involve the triplet-excited phthalimide and consequently also an intermediate triplet 1,7-biradical (Scheme 4). Whereas the conformational flexibility at the stage of the triplet 1,5-biradicals from **6** is too high for efficient chirality-memory effects, the situation is less limited for the biradical from **8**, probably because of the restricted rotations about the amide C–N and the arene–N bonds.



Scheme 4. Memory of chirality effects in the triplet 1,7-photocyclization of the proline derivative **8**.^[12]

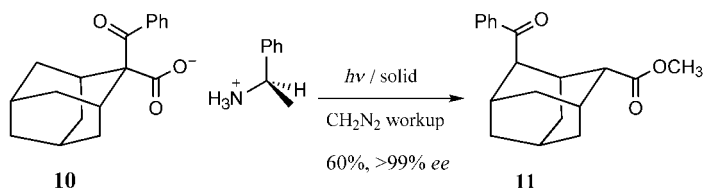
3. Asymmetric Photochemistry in Anisotropic Media

3.1. Solid-State Photochemistry

Similar in many ways to the Pasteur procedure for resolving racemic carboxylic acids and organic amines, the method developed by Scheffer et al. in recent years relies on the use of crystalline organic salts in which the enantioselectivity of a photochemical reaction of an achiral organic ion (for example, an alkyl carboxylate anion) is governed in the solid state by the presence of an optically pure counterion (for example, an optically active ammonium ion). Such optically pure counterions are termed ionic chiral auxiliaries.^[13] Salts containing ionic chiral auxiliaries are required to crystallize in chiral space groups, which provide the asymmetric environ-

ment necessary for chiral induction. Using this methodology, near-quantitative optical yields were obtained in a wide variety of photochemical reactions.

An illustrative example is the solid-state photolysis of the salt of 2-benzoyladamantane-2-carboxylic acid with the phenylethylamine **10**, which results in the formation of the rearrangement product **11** (1,3-acyl shift, Scheme 5) with an

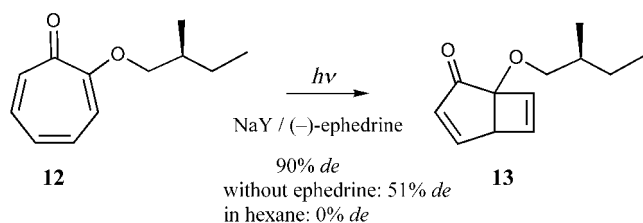


Scheme 5. Enantioselective solid-state photolysis of phenylethylamine/carboxylate salt as an example of the ionic chiral auxiliary concept.^[14]

ee value > 99%.^[14] A further example is the photochemical synthesis of a β -lactam from an achiral *N,N*-dialkylarylglyoxylamide,^[15] a substrate which has also been used frequently in the chiral crystal methodology.^[16]

3.2. Zeolites as Reaction Cavities

Zeolites loaded with a chiral substrate and/or inductor molecule can serve as defined reaction cavities, which can determine the stereochemistry of molecular transformations better than host–guest complexes in isotropic media, and sometimes even better than in the crystalline state. Furthermore, where crystal to crystal photochemical reactions are rare, the reaction cavity does not change during the light-induced process in the zeolite and thus stereoselectivities do not strongly depend on conversions. Zeolites can include a large number of different types of molecules with the main limitation that the dimensions of the guest must be less than the pore dimensions of the zeolite.^[17] Two approaches have been reported for generating a chiral environment in the cavity of zeolite supercages: a) amplification of asymmetric induction using a chiral photoactive substrate and b) the addition of a chiral inductor molecule and/or a chiral sensitizer. The first photosensitized enantiodifferentiating cyclooctene isomerization by an optically active sensitizer immobilized in an NaY zeolite was reported recently.^[18] Ramamurthy and co-workers reported on the photochemistry of a tropolone ether in an NaY zeolite and demonstrated how these two concepts can be linked.^[19] The chiral tropolone **12** undergoes photoinduced electrocyclicization to give racemic product **13** in solution in the absence and in the presence of the chiral inductor molecule ephedrine. Photolysis at room temperature in the zeolite supercage afforded the product with *de* values of 51 % and 92 % in the absence and presence of the chiral inductor, respectively (Scheme 6). Thus, the chirality of the environment, which is generated from the stereogenic center in the substrate as well as from the chiral inductor molecule, is strongly increased in the cavity of the zeolite and weak inductive forces can become dominant.



Scheme 6. Diastereoselective photoelectrocyclization of a tropolone derivative **12**: zeolite effect on the degree of diastereoselection.^[19]

4. Absolute Asymmetric Photochemistry

We have already outlined that biomolecules such as DNA, proteins, and lipids^[20, 21] are composed of homochiral monomers that do not tolerate any pollution by the “wrong” enantiomer. Several controversial theories have been developed to explain the abiotic origin of the biomolecular chiral purity in terms of the physicochemical processes involved. Very recently, a number of these theories have been reexamined experimentally. The theories had been classified into random mechanisms and determinate mechanisms.^[22] Because of the new experimental results, the classification of the origins of biomolecular asymmetry has to be changed in the following way: Random mechanisms are undirected processes that lead to the appearance of the biomolecular asymmetry by mere chance; spontaneous chiral symmetry-breaking in autocatalytic systems is an example of such a mechanism.^[23] Determinate mechanisms exploit the interaction of racemic substances with chiral physical driving forces, which cause the prevalence of one enantiomer. Some examples of such driving forces were reviewed recently^[24] and include the adsorption on enantiomorphic surfaces of quartz^[25] or calcite,^[26] the directed vortex caused by the stirring of a liquid,^[27] weak intermolecular forces,^[28] spin-polarized electrons,^[29] and circularly polarized light (CPL). New concepts and results on absolute asymmetric synthesis induced by photochemical reactions, presented at the Photo-

chirogenesis Symposium in Osaka, Japan, in September 2001, appear to be encouraging. In this section we will outline the context in which absolute asymmetric photochemistry is of interest, summarize recent concepts and advances in the field, and discuss briefly our current understanding of the underlying mechanisms involved. To date, four absolute asymmetric photochemical pathways for the generation of enantiomeric enrichment have been postulated (Figure 1).

4.1. Magnetochiral Photochemistry

Theoretical derivations predict that an enantiomeric enhancement could be induced into chiral or prochiral racemic systems by the interaction with two “pseudochiral” fields, such as unpolarized electromagnetic radiation and a parallel magnetic field.^[30, 31] Until recently, however, convincing experimental verifications for this theorem, though searched for intensively, have been difficult to find.^[32] The first photoresolution of a chiral system (a Cr^{III}–tris(oxalato) complex in aqueous solution) using this method was reported in June 2000.^[33] The model shows that both “pure” and “cascaded” magnetochiral enantioselective photochemistry occur competitively.^[34] The claimed effect, based on magnetochiral dichroism, yielded low *ee* values in the order of 10^{−4}, and required a high magnetic field of about 15 T. In the future, the applications of enantioselective magnetochiral photochemistry to other chiral systems might provide additional convincing arguments that this effect played an active role in the origin of biomolecular homochirality.

4.2. Asymmetric Photolysis

The effect of CPL, which is an example of a “true-chiral” influence^[31, 35] on racemates of organic molecules has been extensively examined since Kuhn et al. achieved the first enantioselective photodecomposition by irradiating solutions

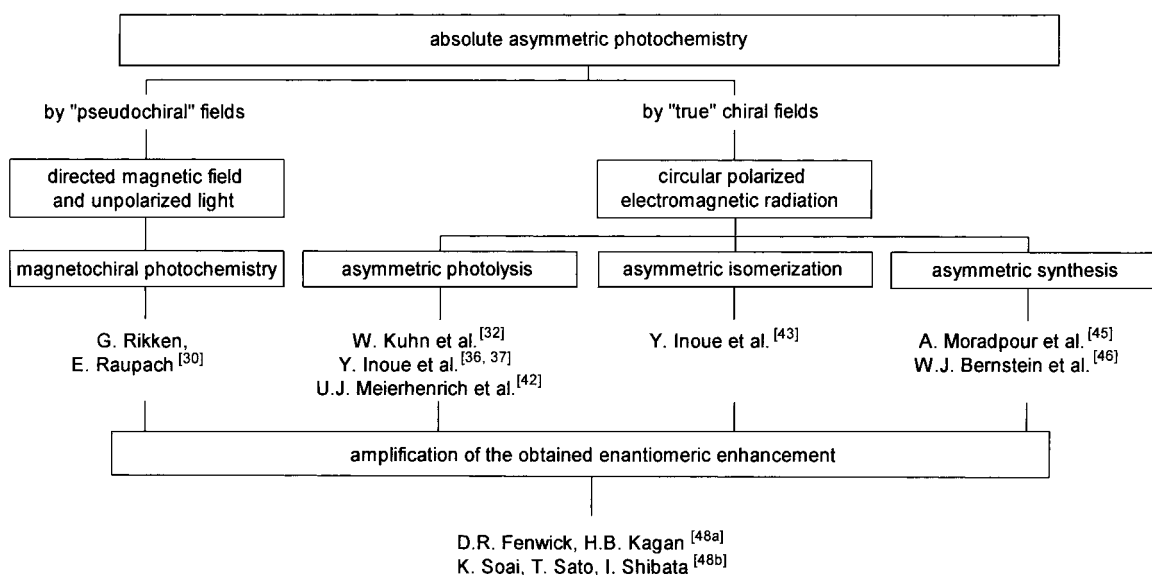


Figure 1. Pathways to inducing enantiomeric enhancements by absolute asymmetric photochemistry.

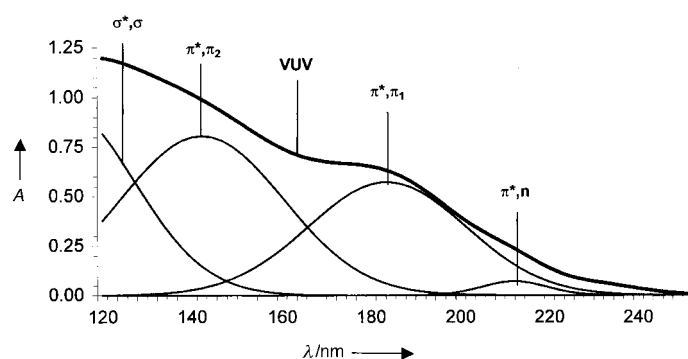


Figure 2. VUV absorption spectrum and electronic transitions of the amino acid leucine, recorded in a solid sample film with synchrotron radiation in LURE, Paris.^[45]

of ethyl- α -bromopropionate and *N,N*-dimethyl- α -azidopropionamide.^[36] In 1974, the irradiation of racemic camphor^[37] was studied, which resulted in the then highest photochemically induced *ee* value (20%), by carrying the photodecomposition to 99% completion. In 1977, molecules of assumed relevance for prebiological pathways, such as the amino acids alanine^[38] and leucine,^[39] were decomposed enantioselectively by irradiating the π^*,n transition at 212 nm in acidic solution. In each case it was demonstrated that the induced enantiomeric enrichments were dependent on the anisotropy factor (*g*), which is the ratio between the circular dichroism ($\Delta\epsilon$) value and the extinction coefficient (ϵ). For the last 25 years, the highest *ee* value for enantioselective photolysis of an amino acid has remained 2.5% in the case of leucine which, among proteinaceous amino acids, also has the highest anisotropy factor.

Very recently, the challenging induction of higher enantiomeric enrichments into amino acids was intensively revisited with the help of innovative ideas, concepts, and instrumentation, and using four main approaches:

- The pH dependence of the chiroptical properties, particularly the anisotropy factor (*g*) (and therefore the ability to induce a high *ee* value), was studied for leucine by subjecting solutions of different acidity to right (*r*-CPL) and left (*l*-CPL) circularly polarized photons and subsequent determination of the yielded *ee* value. It was shown that enantioselective photodecomposition depends strongly on the degree of protonation, such that protonated carboxylic groups at pH values close to 1 generate a higher anisotropy. Based on this effect, which should also be studied for other amino acids, a Norrish Type II mechanism was proposed, which includes γ -H abstraction and Norrish Type II cleavage of the leucine molecule. The obtained *ee* value was, however, close to 0.2%.^[40]
- To increase the anisotropy, two-photon excitation processes were studied. Circularly polarized femtosecond-laser pulses were applied to a modified norbornadiene-quadracyclane system to make use of an additional anisotropy function (g^*) that derives from an electronically excited state. For the chosen system, however, the induction of enantiomeric enrichments during irradiation with two-photon excitation turned out to be very similar to that obtained by one-photon excitation.^[41] Nevertheless, the

principal approach is fascinating and might provide advanced capabilities.

- The potential of right (*r*-EPL) and left (*l*-EPL) elliptically polarized light in asymmetric photolytic reactions was systematically studied by subjecting acidic solutions of leucine to irradiation. It was shown that a decomposition up to 93% lead to a value of close to 3% *ee*. As theory predicts, irradiation with “clean” *r*-CPL and *l*-CPL in parallel experiments gave the higher degree of 4% *ee*.^[42]
- Conventional attempts at enantioselective photolysis were performed by studying the interaction of racemic organic molecules with *r*-CPL and *l*-CPL, in aqueous solution. Single π^*,n electronic transitions of the carboxylic groups of the amino acids were observed here, with values close to 212 nm (5.85 eV), because water absorbs below 200 nm, which makes higher energetic electronic transitions inaccessible. Taking this into account, leucine molecules in their solid state were exposed to synchrotron CPL^[43] of variable polarization^[44] and energy in a newly developed electromagnetic planar/helical-crossed undulator. Using this concept, π^*,π_1 , π^*,π_2 , and even σ^*,σ transitions of amino acids (Figure 2) could be excited below 200 nm,^[45] to provide more effective optical anisotropies.

To make use of this effect, solid films of leucine were deposited onto MgF₂ windows and subjected to irradiation with synchrotron *r*-CPL and *l*-CPL at 180 nm (6.9 eV), which thereby closely matches the desired π^*,π_1 transition. After 70% photodecomposition, analysis of the remaining amino acids resulted in $\pm 2.6\%$ *ee*. The sign of the induced *ee* values was dependent on the direction of circular polarization.^[46] Using this concept the variation of the photon energy enables the determination of the anisotropy factor (*g*) as a function of the wavelength, and from this value the conditions required to obtain enantioenrichments can be determined.

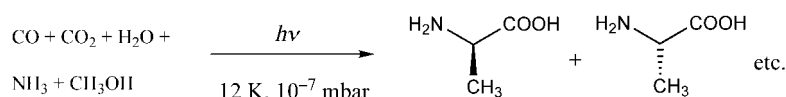
4.3. Asymmetric Photoisomerization

Asymmetric photoisomerizations include processes in which chiral organic molecules undergo enantioselective isomerization induced by CPL. The basic work on this topic was presented by a study of the direct photoderacemization of (*E*)-cyclooctene.^[47] Very recently, functional groups were incorporated along the cyclooctene skeleton, which led to changes in its photochemistry.^[48]

4.4. Asymmetric Synthesis

The pure synthesis of optically active molecules in non-racemic yields induced only by CPL has remained a difficult task. The first successful attempts were reported 30 years ago. In these experiments, the photocyclization of alkenes in solution, which was performed in the presence of iodine, led to the formation of polyaromatic hydrocarbon molecules. By irradiation with CPL, the chiral hexahelicene was synthesized with optical yields below 2%.^[49] The dependence of the reaction on wavelength and substituent structure has also

been examined, and the mechanism was claimed to involve selective excitation of the enantiomeric conformers.^[50] Photo-production of amino acids has been reported to be possible with the help of initial photon acceptors.^[51] Very recently, two groups demonstrated contemporaneously the spontaneous photoformation of a variety of amino acid structures under interstellar conditions.^[52, 53] Because both groups used unpolarized light for the photoreaction, the obtained amino acids were racemic (Scheme 7). In the very near future, similar experiments will be performed with CPL for the direct generation of amino acids showing a considerable enantiomeric enrichment.



Scheme 7. Photochemical formation of amino acids with unpolarized light from C₁ and N₁ components, resulting in the formation of racemic mixtures mimicking the interstellar medium.^[53] Alanine and 15 other amino acids were produced under specific low temperature/low pressure conditions.

4.5. Amplification of Enantiomeric Enrichment

In the amplification of small enantiomeric imbalances obtained by the above-described scenarios, several mechanisms have been proposed and experimentally investigated. Asymmetric amplification can involve enantioenriched aux-

iliaries showing catalytic^[54] or even autocatalytic^[55] function. In 1953, Frank^[56] proposed an autocatalytic kinetic model for spontaneous asymmetric synthesis, which was later modified by Kondepudi^[57] with the help of bifurcation theory, predicting that a laboratory demonstration of this work may not be impossible. However, recently, computer simulations of this sort of stereospecific autocatalytic synthesis have produced promising results;^[58] experimental evidence, however, was difficult to obtain.^[59] The first such system was the asymmetric autocatalysis of 5-pyrimidyl- and 3-quinolylalkanol, which proceeded without the need for any other chiral auxiliaries. In this system, a chiral initiator can determine the absolute configuration of the pyrimidylalkanol with high *ee* values close to enantiomeric purity.^[60]

A slight enantiomeric excess in a mixture of activated amino acid enantiomers was shown to be amplified by a stereoselective polymerization forming α -helical structures. Brack and Spach demonstrated that a right-handed α -helical seed crystal of L-amino acids incorporates L-amino acid monomers 18 times faster than D-amino acids.^[61] A β -sheet conformation of synthetic polypeptides enriched in one enantiomer was found to be more stable than a random coil of racemic amino acids.^[62] Such macromolecular routes show considerable potential in the amplification of enantiomeric enrichments; they were theoretically modelled through the Majority Rule described by Green et al.^[63] Very recently, an enantiomeric enhancement through self-assemblies of amphiphilic, activated amino acid analogues on the surface of water has been reported.^[64]

In this context, it is reasonable to point out that a new field of asymmetric photochemistry studies transfer, memory, and

switching of chiral properties. Chiral information can be transferred from chiral nonracemic organic molecules into liquid crystals and thereby amplified. Such a chirality propagation is usually based on a nematic to cholesteric phase transition of the liquid crystal which depends on the chiral information in the organic dopant.^[65] It was even demonstrated that a chiral bicyclic ketone trigger can induce the reversible switching of a liquid crystal between its nematic and cholesteric form by irradiation with CPL followed by unpolarized light.^[66] The other way round, the transfer from a structural chiral information stored in a liquid crystal can be transferred and amplified into chiral tri(oxalato)chromate guest molecules.^[67]

5. Conclusions and Outlook

Numerous random and determinate mechanisms have been proposed for the induction of the biomolecular parity violation. In the last few years, the hypotheses based on asymmetric photochemistry have been reexamined intensively. At present, the newly obtained results suggest that mainly processes involving CPL or EPL as the external and “true” chiral force are capable of producing significant and reproducible enantiomeric excesses from racemic or prochiral precursors relevant to chemical evolution. These reactions however suffer from the paradoxical condition that, to produce a significant *ee* value which can then be amplified by appropriate mechanisms, large amounts of the amino acids have to be photodecomposed, as determined by the anisotropy factor *g* ($g = \Delta\epsilon/\epsilon$). Both enantioselective, sensitized photochemical reactions, in which chiral or prochiral molecules transfer energy to another prochiral molecule, and the spontaneous photoformation of amino acid structures under interstellar conditions with CPL, might justify higher anisotropies and circumvent this problem. In the field of absolute asymmetric photochemistry it is hard to obtain evidence by laboratory simulation experiments. Because of this, the determination of *ee* values has become part of space scientific programs. Currently, the measurement of enantioenrichment is included for the first time in one of the cornerstone missions of the European Space Agency (ESA) and the Max Planck Institute of Aeronomy (Katlenburg-Lindau, Germany). This program, the cometary mission ROSETTA was designed with the aim of separating chiral organic molecules on the surface of a comet and to determine *ee* values for a wide range of chiral organic molecules.^[68] In addition, NASA has recently demonstrated an interest in measurements of the enantiomeric composition of chiral molecules on Saturn’s moon Titan by launching a special issue of *Enantiomer* focussing on this task.^[69]

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The Scientific and Humane Legacy of Max Perutz (1914–2002)**

John Meurig Thomas*

The son of a prosperous Viennese textile manufacturer, educated first at the Theresianum (a grammar school derived from an officers' academy from the days of the Empress Maria Theresa) and then at the University of Vienna, Max Perutz was to have studied law in preparation for entering the family business. At the Theresianum, he was a small, dreamy, and sleepy boy; and many years later he said: *"I owe my first step to popularity to scarlet fever which I caught when I was fourteen. To disinfect the classroom, my schoolmates got three days off, for which they thanked me solemnly in a letter signed by the entire class"*. At sixteen, he, plus two of his colleagues, won the cup for their school in the skiing competition of the Vienna High Schools, and as a result of that victory his standing at school was transformed. *"For the first time in my life I was treated with a certain degree of respect. From then on our gym teacher always gave me top marks, but they happened to be the only ones in my otherwise mediocre school reports"*.

A good schoolmaster kindled his interest in chemistry, and he made this the subject of his studies at university. Although largely disappointed with the way in which the subject (especially inorganic analysis) was taught, he acquired a special interest in organic biochemistry and heard about the work of the Nobel Prizewinner (and discoverer of vitamins) Sir Gowland Hopkins at Cambridge. His teacher, Herman Mark, the polymer specialist, visited Cambridge and had planned to pave the way for Perutz to join Hopkins' group. But Mark met J. D. Bernal, who said that he would take Perutz as his student.

Writing in the *Scientific American* in 1978, Max Perutz said:

"When I was a student, I wanted to solve a great problem in biochemistry. One day I set out from Vienna, my home town, to find the Great Sage at Cambridge. He taught me that the

riddle of life was hidden in the structure of proteins, and that X-ray crystallography was the only method capable of solving it. The sage was John Desmond Bernal, who had just discovered the rich X-ray diffraction patterns given by crystalline proteins. We really did call him Sage,^[1] because he knew everything, and I became his disciple".

Perutz was admitted as a graduate student^[2] at the oldest college in Cambridge, Peterhouse, on 1 October 1936 and had already begun as a researcher in the Cavendish Laboratory (where Bernal taught and researched in physics) some days earlier. It is hardly necessary to recall that Max Perutz found out how to solve the structure of proteins and used his method for the solution of the structure and mode of action of haemoglobin. However, it is instructive and inspirational for scientists and nonscientists alike to trace the trajectory of his life and to ponder the ingredients of his greatness as a researcher, as a communicator, and as a human being.

A Summary of His Achievements

At the memorial meeting in honour of Sir John Kendrew held in Cambridge, 5 November 1997, Perutz said:

"John and I shared three great scientific adventures: founding the MRC Unit for Molecular Biology,^[3] solving the first protein structure and founding the European Organization for Molecular Biology (EMBO)".

Perutz and Kendrew, who shared the Chemistry Nobel Prize in 1962, for their pioneering work on the elucidation of the structure of the biological macromolecules haemoglobin and myoglobin, the respiratory proteins of red blood cells and of muscles, respectively, were very different from one another. They were phenomenally able and perspicacious individuals (Figure 1), among the greatest scientists ever to be members of their small Cambridge college, Peterhouse,^[4] which boasts as its former students Henry Cavendish, William Thomson (Lord Kelvin), Charles Babbage,^[5] Clerk Maxwell, James Dewar, and Frank Whittle.^[6] Kendrew was a precise organiser and a gifted computer programmer, at a time when that breed of scientist was very rare. He was a man who knew exactly where he was going and how to get there. Although possessed of urbane charm, linguistic fluency, a love of music, and a great sense of humour, Kendrew was always a more distant,

[*] Prof. Sir J. M. Thomas
Dept. of Materials Science
Univ. of Cambridge, Cambridge, CB2 3OZ (UK)
Fax: (+44) 1223-334567
and
Davy Faraday Research Laboratory
Royal Institution of Great Britain
21 Albemarle Street, London, W1X 4BS (UK)
E-mail: dawn@ri.ac.uk

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Figure 1. Max Perutz (right) constructing a model of the first ever protein structure determined by X-ray crystallography, with John Kendrew looking on (1959).

detached character than Perutz. Perutz was a gentle, kindly, and tolerant lover of people (particularly the young), passionately committed to social justice and intellectual honesty; the warmth of his personality radiated a sense of human goodness and decency which induced others to behave sanely, especially because he exuded an inner excitement that stems from a love of knowledge for its own sake. A distinguished American molecular biologist who worked in the Perutz–Kendrew team as Kendrew’s postdoctoral assistant (1957–1958), in a reflective article published in *Protein Science*,^[7] wrote:

“Max and John were utterly different in personality. Kendrew came in two or three mornings a week to discuss the progress of the research, and to give help where help was needed. He was a great mentor for someone who wanted to learn how to be an independent investigator. At other times he was busy as a science advisor to the British government (on the Polaris missile system as I recall), as an administrator of Peterhouse (college), and on other affairs. In contrast, Max was never so happy as when in the laboratory at the bench, doing science. One learned by talking with John, but by watching Max”.

Perutz’s inspirational scientific leadership, more than that of any other, made it possible to unite structural crystallography and molecular pathology and helped to unfold the vast

ramifying fields of present day molecular biology. In communicating knowledge to other scientists and the general public—and as an ambassador for science, its methods and philosophy—few of his contemporaries rivaled him. So central were his interests in the vast corpus of scientific endeavor that he was regularly called upon to address biochemists, physicists, physiologists, pathologists, geneticists, and medical scientists of several other kinds. For the last forty years of his life he maintained a punishing round of lecture commitments: one week it was to school sixth formers or to a University of the Third Age^[8] audience; another it might be to the assembled researchers at places such as Rockefeller University, New York; the next to frontier scientists in the California Institute of Technology—or in Rome (lecturing in Italian), Berlin (in German, Figure 2), or Paris (in French).



Figure 2. Max Perutz lecturing in Berlin, 1999. An enlarged photo of “Sage” (J. D. Bernal) is seen on the screen behind him.

The Road to Haemoglobin

Perutz, on Bernal’s advice, first learned of X-ray crystal-structure analysis in the Department of Mineralogy and Petrology, Cambridge, where he was handed—as he later put it—“a nasty crystalline flake of a silicate mineral picked off a slag heap” to investigate.^[9] This training proved crucial, for he became adept at X-ray crystallography and he set out to pursue his “great problem in biochemistry”. Guided a little later by a cousin, who lived in Prague, he soon convinced himself that an appropriate target for his ambitions was the structure of haemoglobin, especially since it was the protein that was most abundant and easiest to crystallize. It was not until the late 1950s that he finally reached his target of elucidating the structure of haemoglobin; when he did, it made him famous. But his path to success was frequently thwarted by scientific, personal, and political obstacles.

Perutz had obtained tantalizing X-ray diffraction patterns, published in 1938—just as Dorothy Crowfoot (later Hodgkin) and Bernal had earlier with crystals of the enzyme pepsin—and it could then be seen that the thousands of reflections he had obtained could, in principle, lead to the atomically resolved structure of haemoglobin. Unfortunately there was

no way of interpreting these data, because the so-called phase angles of the reflections could not be evaluated. Previous X-ray structural determinations had been limited to molecular entities possessing a small number of atoms, and often with a known chemical composition. The analytical techniques then available in the solution of the structure of, for example, polynuclear aromatic hydrocarbons, carbohydrates, and other “small” molecules, simply could not be applied to proteins with thousands of atoms and an unknown chemical composition. Perutz, however, felt that proteins had to take up well-defined structures within their crystals, as, otherwise, those sharp spots that he, Crowfoot, and Bernal had obtained were altogether inexplicable.

As Bernal’s research student, Perutz was disappointed that Lord Rutherford, then the Head of the Cavendish Laboratory, never looked in to find out what the crystallographers were doing. Perutz later discovered that it was not because of any antipathy towards the X-ray crystallography that Rutherford kept his distance. According to Perutz, “*The conservative and puritanical Rutherford detested the undisciplined Bernal, who was a communist and a woman chaser and let his scientific imagination run wild*”.^[10] Perutz was clearly disappointed when Rutherford died before he had a chance of attending his lectures or getting to know him. After his death, graduate students could help themselves to left-over reprints of Rutherford’s classic scientific papers. Their clarity and rigor, Rutherford’s imaginatively conceived experiments, and his determination to prove every one of his results experimentally beyond any possible doubt convinced Perutz that this was the way to do science.

Perutz finished his PhD in 1940, working with Sir Lawrence Bragg, who succeeded Rutherford as the Cavendish Professor, and who had obtained a small grant for him from the Rockefeller Foundation to enable his research to continue. However, the project was interrupted by Perutz’s internment in 1940, along with several hundred German and Austrian refugee scholars, mostly Jewish and all anti-nazi.^[11] They were rounded up and sent to an internment camp in Quebec, Canada. Fortunately, Perutz’s academic friends rallied round and tried to secure his release. He returned to his studies and to work of national importance, which involved him in an unsuccessful scheme to make ships of ice for refueling aircraft in the North Atlantic.

Perutz returned to Cambridge in 1944, and he was joined in 1945 by Kendrew (whose PhD had started with the physical chemist, E. A. Moelwyn Hughes, and whose interest in protein structure had been kindled first by meeting Bernal during war service in operational research and later reinforced by discussions with Linus Pauling in Pasadena on his return journey to the UK). Bragg continued his enthusiastic support, and in 1947 he approached the secretary of the Medical Research Council (MRC), who made the crucial decision to back this small group despite the continuing lack of tangible results—a far cry from present-day attitudes! Francis Crick, a physicist, joined the group as Perutz’s PhD student in 1948. Jim Watson, a geneticist, came later, in 1951, and was soon working with Crick on DNA.

As Hugh Huxley,^[12] the distinguished muscle biophysicist and molecular biologist, has recently written:^[13]

“Because there was no direct way of calculating protein structure, Perutz and Kendrew used the huge amounts of data (the intensities of all the X-ray reflections) to produce contour maps, known as Pattersons, to display the most frequently occurring distances between high-density regions in a structure. It was hoped that these might enable prominent features of the structure to be identified. To this end, Perutz and Kendrew, aided by Bragg, enumerated various helical configurations into which polypeptide chains might fold, based on stereochemical data”.

However, they made what seemed then the plausible—later found to be erroneous—assumption that the helices would contain an integral number of residues per turn. They also did not take into consideration that the chemical bonds on either side of the peptide bond are coplanar. (Pauling, working independently, made no such assumptions, and it was he who first arrived, in 1951, at the now well-known non-integral α -helical structure of proteins).

In early 1951, Crick showed that the Patterson maps for haemoglobin and myoglobin did not provide support for the view that there was some regular packing arrangement of polypeptide chains. Indeed he demonstrated that any such arrangement must be extremely irregular. This conclusion, in particular that no useful information was extractable from the Patterson maps, made Crick unpopular, and, for a while, depressed Perutz.^[14] However, his resourcefulness as a scientist knew no limits—and it remained thus to the very end of his life.

Just as his two colleagues Watson and Crick were constructing what was later to become their monumental model for the structure of DNA in early 1953, Perutz ruminated on the potential of the heavy-atom substitution method of determining the phases of diffracted X-ray waves. This had its origins in the work of Robertson at the University of Glasgow and that of the Dutch crystallographer Bijvoet in Utrecht; Bernal had suggested in 1939 that it might work for proteins. Crick also made this suggestion somewhat later. Perutz argued that if he could attach a heavy atom to a specific site in the haemoglobin molecule, and if it did not disrupt the structure of the molecule, and if he could make it crystallize in just the same way as ordinary haemoglobin, and if it made changes large enough to be measurable, then if all these conditions were met, Perutz could see a way to use the methods of X-ray crystallography to image the haemoglobin molecule.

What Perutz realized, with increasing clarity and conviction, was that the X-ray diffraction (scattering) intensities from haemoglobin and other proteins were very weak, despite the large number of electrons contributing to them, and that this arose as an inevitable consequence of the fact that the scattering matter was distributed over a relatively large volume. As Huxley recently remarked,^[13]

“Perutz also realized that scattering from a single heavy atom—mercury, say, with its 80 electrons, or gold with its 79 electrons within a single atomic diameter—would be relatively strong. So if such a marker (heavy atom) were

attached at a specific position on each protein molecule in a crystal, it would produce a measurable change in the intensities of the reflections (diffraction spots), and this could be used to obtain (X-ray) phase information necessary for the determination of the structure (the imaging) of the haemoglobin molecule. His peers and contemporaries had wrongly assumed that any such change (to the intensities of X-ray patterns) would be immeasurably small; but Perutz did the experiment carefully, using haemoglobin labelled with mercury, and he found quite measurable changes”.

This constituted a major breakthrough in the methodological approach to the structure of proteins.^[16] When the world's experts on proteins, assembled by Pauling at the California Institute of Technology in September 1953 (Figure 3), heard Perutz adumbrate his method, they were conscious that a major breakthrough in protein science was imminent. Perutz later wrote:

“As I developed my first X-ray photograph of mercury haemoglobin my mood altered between sanguine hopes of immediate success and desperate forebodings of all possible causes of failure. I was jubilant when the diffraction spots appeared in exactly the same positions as in the mercury-free protein, but with slightly altered intensity, exactly as I had hoped”.

For Perutz and Kendrew (who also adopted the heavy-atom approach to the determination of the structure of myoglobin), great difficulties still lay ahead before the new method could lead to an interpretable structure.^[13, 17] First, it was necessary to have several different heavy-atom derivatives before the phases of all the reflections could be reliably assigned. Second, all these derivatives had to crystallize with exactly the same (unit cell) dimensions. Third, appropriate mathematical procedures had to be devised for calculating the phases. Numerous assistants had to make intensity comparisons (using relatively primitive microdensitometers) on hundreds of thousands of diffraction spots; and, in turn, the electron-density distributions had to be calculated on very early—and by present-day standards extremely primitive—computers in the University of Cambridge Mathematics Department.

Kendrew, assisted by two visiting American scientists (Dickerson and Dintzis) who came to the Perutz–Kendrew unit in the Cavendish Laboratory succeeded in obtaining crystals of gold- and palladium-substituted myoglobin. With their resulting X-ray diffraction patterns, Kendrew, who possessed formidable quantitative skills and who took advantage of the emergence in Cambridge of the EDSAC-1 and EDSAC-2 (programable) digital computers, which he exploited for the Fourier analysis of his diffraction data, solved the structure of myoglobin in 1957.^[19] But within two years, Per-

utz, along with his MRC associates Ann Cullis, Hilary Muirhead, Michael Rossmann, and Tony North, had unraveled the architecture of the haemoglobin molecule, which contains four times as many non-hydrogen atoms (10000) as myoglobin.^[20]

Here were two quite independent structural determinations of related proteins, done by pure physics, without any assumptions about the chemical nature of haemoglobin and myoglobin or the relation between them. This exhilarating information revealed that the intrinsic structures of the two proteins, replete with haem groups, numerous folds, and (Pauling's) α -helices, were essentially similar. The inescapable conclusion was that each had to be right. This galvanized activity in molecular biology worldwide. Adolf Butenandt, the eminent German Nobel Laureate, set his colleagues in Munich the task of using chemical methods (such as those pioneered by Frederick Sanger) to trace the sequence of amino acids in the proteins studied by Perutz and Kendrew. The chem-

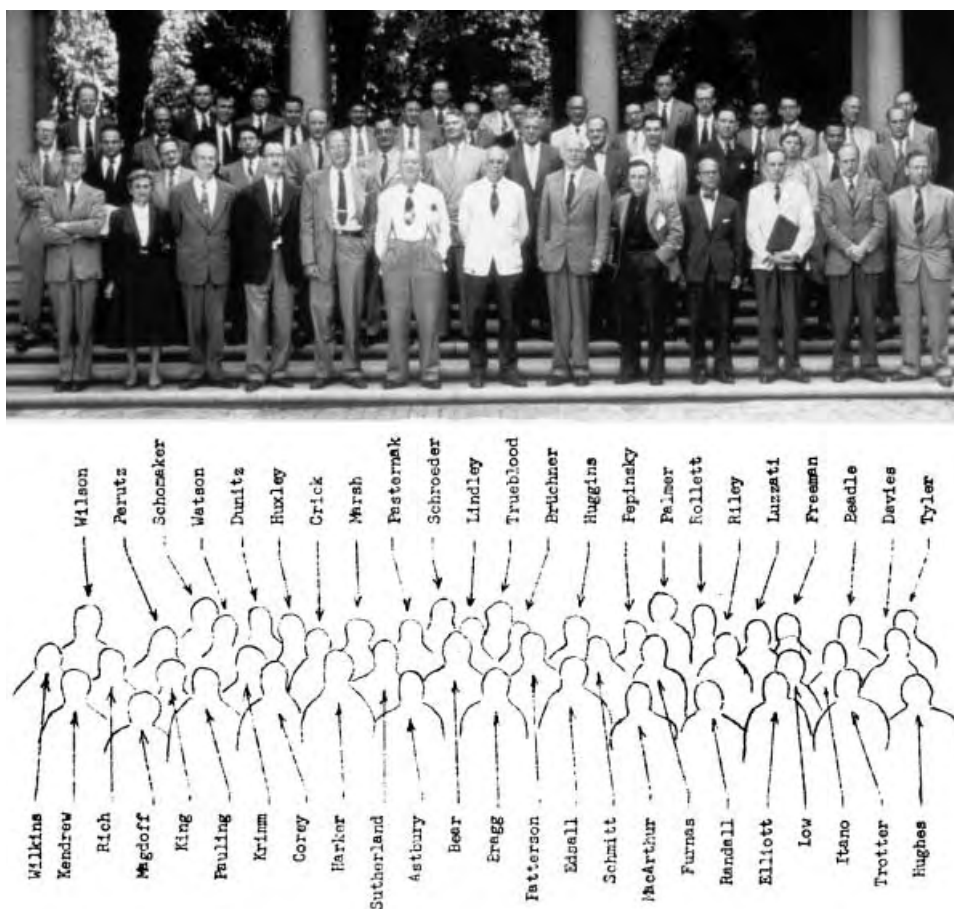


Figure 3. Group photograph taken at the Pasadena Conference on the Structure of Proteins in California, organized by Linus Pauling, 21–25 September 1953.

ical results harmonized beautifully with those of X-ray crystallography. (Butenandt, among others, nominated Perutz and Kendrew for the Nobel Prize^[21].)

The Nobel Prize and Beyond

By 1962, the number of staff of the Perutz–Kendrew MRC unit devoted to molecular biology had grown to ninety. It had long been apparent that the Cavendish Laboratory (now led by Sir Nevill Mott) could no longer satisfactorily house this thriving, expanding community. It seemed eminently sensible that the new breed of biologists, spawned by Perutz's and Kendrew's work, should be accommodated within one of the many existing departments of pure or applied biology of the University of Cambridge. However, cogent though his arguments were, there was little or no enthusiasm in these departments or among the central authorities of the University to welcome Perutz and his colleagues into their fold. Fortunately, the pertinacious and far-sighted Perutz found a ready ally in Sir Harold Himsworth at the MRC Headquarters in London, and, largely through the latter's advocacy, the MRC built the Laboratory of Molecular Biology (LMB) with Perutz as its Chairman on the site of the new Addenbrooke's hospital on the outskirts of the city of Cambridge. This allowed several different aspects of molecular biology to be brought together in one place, along with all the necessary technology. Sanger, who had already won^[22] his first Nobel Prize (in 1958), was invited to join the new laboratory, and he brought with him two bright stars, Brian Hartley and Ieuan Harris (the latter in turn also brought along his outstanding young colleague John (later Sir John) Walker, who was to win the Nobel Prize in Chemistry in 1997).^[23] In 1961, Huxley of University College, London, who had been Kendrew's first research student, came to join the Structural Studies Division of which Kendrew was head. In 1958, with Bernal's retirement looming at Birkbeck College, London, Perutz had invited Aaron Klug and Rosalind Franklin to join the planned new laboratory when their National Institutes of Health (USA) grant ran out. Klug, who also joined Kendrew's Division, came in 1961, bringing Kenneth Holmes (now of the Max-Planck-Institute for Medical Science, Heidelberg) and the expert electron microscopist and all-rounder, John Finch, with him. (Rosalind Franklin, who died in 1958, never came back to Cambridge, from where she had graduated in chemistry many years earlier.)

The LMB was duly opened by Her Majesty Queen Elizabeth one fine day in May, 1962 (Figure 4), and on that occasion Max Perutz took particular pleasure in explaining the significance of the structure of DNA to his Sovereign. In October of that year, the Swedish Academy announced that Perutz and Kendrew were to share the Nobel Prize in Chemistry, and that their two associates, Watson and Crick, along with Maurice Wilkins of King's College, London, were to share the Prize in Medicine and Physiology (Figures 5 and 6).

The unique success of the LMB, measured, for example, by the numerous awards gained by members of this one laboratory—nine Nobel Prizes, four Orders of Merit (the highest civil honour that the British Sovereign can bestow), eight Copley medals (the highest honour of the Royal



Figure 4. Official opening of the Laboratory of Molecular Biology, at which Max Perutz (extreme right) explains the double helix to H.M. Queen Elizabeth II, May 1962.



Figure 5. Photograph taken after the Nobel Prize ceremony, Stockholm: M. F. H. Wilkins, M. F. Perutz, F. H. C. Crick, J. Steinbeck, J. D. Watson, J. C. Kendrew.



Figure 6. Informal photograph (Dec 1962) of Max Perutz (left), Gisela Perutz, and John Kendrew.

Society), and over a hundred Fellowships of the Royal Society conferred upon its staff—merits closer enquiry. An overwhelmingly important factor in all this is the way that Perutz organized the Laboratory and his own role within it.

Perutz, from the outset, adopted a new style of management. Thus he once wrote:

"I persuaded the MRC to appoint me Chairman of a Governing Board, rather than as Director... This arrangement reserved major decisions of scientific policy to the Board, and left their execution to me... The board met only rarely... This worked smoothly and left me free to pursue my own research. Seeing the Chairman standing at the laboratory bench or the X-ray tube, rather than sitting at his desk, set a good example and raised morale. The Board never directed the laboratory's research but tried to attract, or to keep, talented young people and gave them a free hand".

As his former PhD student and distinguished molecular biophysicist, Professor David Blow,^[24] who was a member of the LMB in its early days, said recently of Perutz:

"He always recognized the importance of new instrumental developments, and maintained large mechanical and electronic workshops, to which research workers had full access, directly passing their enthusiasm to the technical staff".

However, over and above these technical features of running a laboratory, Perutz, ably assisted by his devoted and shrewd wife Gisela, made the canteen at the LMB a focal point for intellectual stimulus. It was—and still is—visited three times a day by most scientists and associated staff, and it remains an important center for the exchange of ideas and scientific news. One American molecular biologist^[25] on sabbatical leave in 1985 at the LMB commented that, because the canteen was the intellectual center of the laboratory, one could not stray off course in one's research work for more than a period of three hours! Perutz himself kept abreast of everybody's work, by making a habit of sitting with different groups of people at coffee time, lunch, or tea. (He did likewise whenever he came to lunch at his college, Peterhouse.)

Perutz led by example,^[26] he aimed to spend some 90 % or more of his time working at the bench, and he expected others to do likewise. But he recognized and could cope with differences in individual style. In reflective mood, he once wrote:

"When Crick and Watson lounged around, arguing about problems for which there existed as yet no firm experimental data instead of getting down to the bench and doing experiments, I thought they were wasting their time. However, like Leonardo, they sometimes achieved most when they seemed to be working least, and their apparent idleness led them to solve the greatest of all biological problems, the structure of DNA. There is more than one way of doing good science".

Every now and then, Max Perutz wrote in one of his recent books (I Wish I'd Made You Angry Earlier: Essays on Science, Scientists, and Humanity), I receive visits from earnest men and women armed with questionnaires and tape

recorders who want to find out what made the LMB (where I work) so remarkably creative... I feel tempted to draw their attention to 15th century Florence with a population of less than 50000, from which emerged Leonardo, Michelangelo, Ghiberti, Brunelleschi, Alberti, and other great artists. Had my questioners investigated whether the rulers of Florence had created an interdisciplinary organisation of painters, sculptors, architects, and poets to bring to life this flowering of great art?... My question is not as absurd as it seems, because creativity in science, as in the arts, cannot be organised. It arises spontaneously from individual talent. Well-run laboratories can foster it, but hierarchical organisation, inflexible, bureaucratic rules, and mountains of futile paperwork can kill it. Discoveries cannot be planned; they pop up, like Puck, in unexpected corners".

In an age when the Paladins of accountability and the Funding Councils persist in preaching the necessity for all academic research centers to have a Mission Statement and Strategic Plans, it is prudent to recall how Perutz set about founding and running the extraordinarily successful LMB. The principles he used were: choose outstanding people and give them intellectual freedom; show genuine interest in everyone's work, and give younger colleagues public credit; enlist skilled support staff who can design and build sophisticated and advanced new apparatus and instruments; facilitate the interchange of ideas, in the canteen as much as in seminars; have no secrecy; be in the laboratory most of the time and accessible to everybody where possible; and engender a happy environment where people's morale is kept high.

However, the LMB in Cambridge is not the only major laboratory in which Perutz had a hand in creating. Shortly after the Nobel ceremony in Stockholm in 1962, Leo Szilard and Victor Weisskopf of the United States called to see Watson, Kendrew, and Perutz to discuss the prospects of establishing a European Molecular Biology Organisation (EMBO) like the Nuclear Science Centre (CERN) in Geneva. All three responded enthusiastically. Supported by other European molecular biologists, notably Francois Jacob (France), Friedrich Freska (Germany), Ole Maalo (Denmark), Jeffries Wyman (USA), and, crucially, Ephraim Katchalski-Kazir (Israel), Kendrew led the way, and soon EMBO came into being with Perutz as its Chairman from 1963–1969. In due course, the European Molecular Biology Laboratory (EMBL) at Heidelberg, of which John Kendrew was the founding Director (for ten years), also came into being.^[27]

Haemoglobin and its Impact on Medicine

In 1959 when Perutz and his colleagues first unraveled the architecture of the haemoglobin molecule in outline, it was appreciated by all concerned that it was not the end of their journey. As Perutz put it:

"...our much-admired model (of haemoglobin) did not reveal its inner workings—it provided no hint about the molecular mechanism of respiratory transport. Why not? Well-intentioned colleagues were quick to suggest that our hard-won structure was merely an artefact of crystallisation

and might be quite different from the structure of haemoglobin in its living environment, which is the red blood cell”.

For a long time after Perutz solved the structure of haemoglobin (Figure 7), he zealously pursued the secret of its mode of action. How was it that, in effect, haemoglobin functions as a molecular lung? It was not until early in the 1970s that a satisfactory answer to this question came and the fundamentals of the mechanism were elucidated.^[28]

The firm experimental evidence on which the now accepted (Perutz) mechanism for the so-called allosteric change that accompanies the reaction of haemoglobin with oxygen—an allosteric protein^[29] is one that changes from one conformation to another when it binds another molecule (such as oxygen)—came not only from detailed X-ray crystallographic work but also from Perutz’s imaginative use of other techniques, such as spectroscopy and magnetic measurements. First he recalled the significant earlier work of Faraday (in the 1840s) and Pauling (in 1936) who showed that when haemoglobin binds oxygen it loses its paramagnetism. Then he found that the structural changes in haemoglobin accompanying oxygenation were large. In the “deoxy” form the iron atom of the heme is displaced a little from the plane of the heme group, whereas in the “oxy” structure it lies almost in the plane (Figure 8). Perutz recognized that this is so because of a change in the (electronic) spin state of the iron atom—from so-called “high spin” in the deoxy to “low spin” in the oxy state—and hence to a diminution in the radius of the iron. (This was independently established for heme groups by Leroy Hood.) When the iron center moves closer to the plane of the heme in the oxy state it drags with it the α -helix of the protein to which it is connected; this is the trigger that initiates a sequence of “molecular levers” that loosen and rearrange the subunits in the (tense) deoxy structure into a new (relaxed) oxy structure. This is the basis of the molecular mechanism—“*infinitely rewarding in its simple beauty*” as Perutz used to say—that governs the oxygen affinity of haemoglobin in response to physiological needs, and the release of bound oxygen when it is needed under conditions of oxygen scarcity.

This mechanism was to lead in due course, through work on haemoglobin mutants, to a fuller understanding of several inherited diseases and it opened up the new field of molecular pathology, a subject which relates a structural abnormality to a particular disease. Perutz gained new insights into molecular evolution,^[31] and into the delicate (sometimes major) differences exhibited by haemoglobin in a wide range of living species. For example, the frogs of Lake Titicaca, high in the mountains of Bolivia, have evolved a form of haemoglobin that can absorb oxygen better than that in the frogs of Lake Michigan, at a lower altitude. This enhanced absorbability of oxygen is also a feature of the haemoglobin of migrating geese that fly at high altitudes. Crocodiles are able to remain under water for more than an hour without surfacing to breathe^[32] and often kill their prey by drowning it. How do crocodiles stay under water for so long? Perutz’s colleague, Kiyoshi Nagai, and his associates found that when crocodiles hold their breath, bicarbonate ions—the final products of respiration—accumulate and drastically reduce the oxygen affinity of

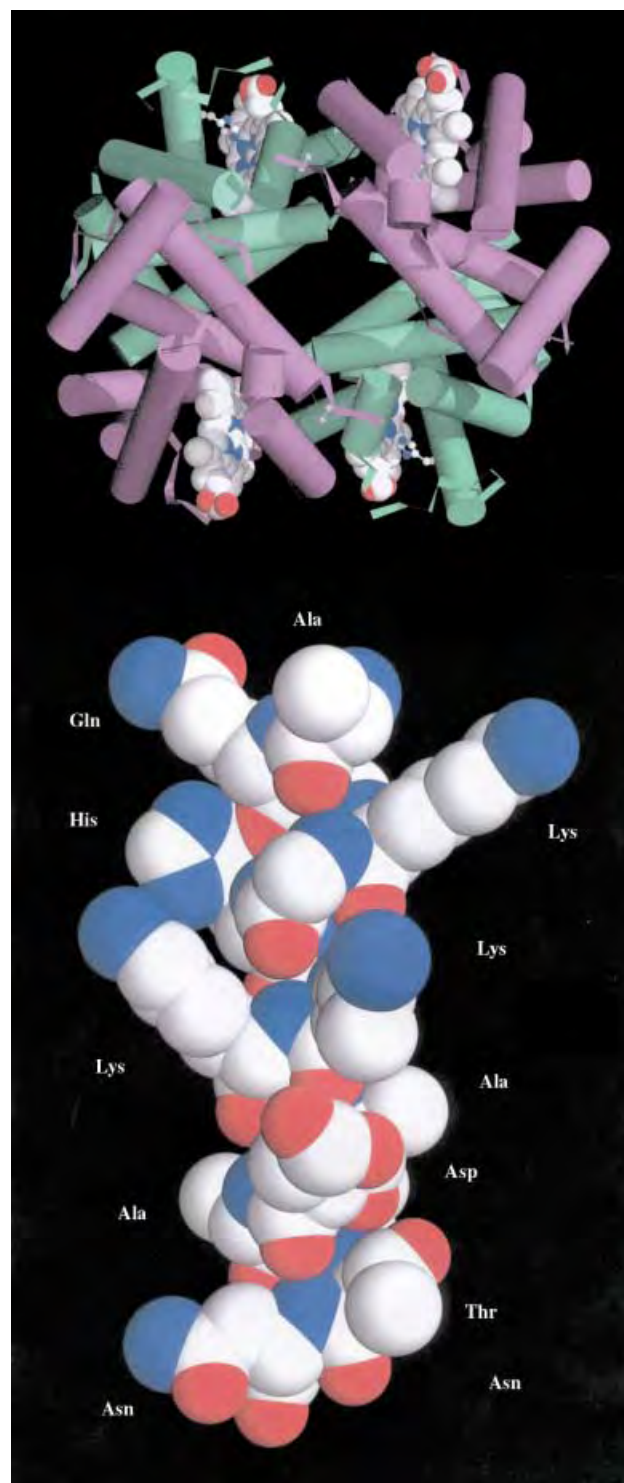


Figure 7. Top: Representation of a molecule of haemoglobin, with the four heme groups shown in atomic detail, and the two pairs (the so-called α and β subunits) of helically arranged amino acid residues shown as colored cylinders: α unit, green; β unit, purple. Bottom: Atomic representation of the amino acid residues that constitute the subunits shown as green and purple cylinders in the top picture. Carbon atoms are in white, nitrogen atoms in blue, and oxygen atoms in red).

their haemoglobin, thereby releasing a large fraction of the oxygen bound to the globin into the tissues of the mammal.^[33] (In collaboration with an American company, Nagai (at the LMB) laid the groundwork for an engineered haemoglobin

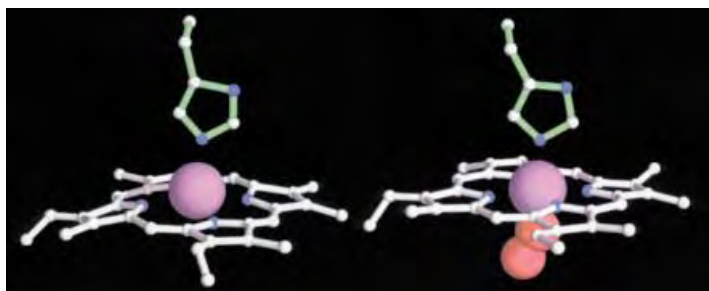


Figure 8. Left: In human deoxy haemoglobin the Fe^{2+} ion, attached to histidine (above), lies slightly above the plane of the heme group. Right: When the Fe^{2+} ion binds oxygen, as in the oxyform, it moves into the plane of the heme. This process is what initiates the sequence of resulting structural changes, see text for further information.

likely to be suitable for use as a cell-free blood substitute. The need to develop a blood substitute is now urgent because of the increasing concern over blood-transmitted viral and bacterial pathogens.)

Earlier, Perutz's pioneering work offered a deeper appreciation of such tragic diseases as thalassemia, which arises because of defective synthesis of haemoglobin, and of sickle-cell anaemia. His colleagues at Cambridge, Vernon Ingram and John Hunt, showed that sickle-cell haemoglobin differed from the normal protein merely by a change of a single amino acid residue, in fact the replacement of glutamic acid by valine.

The Exponential Growth of Protein-Structure Determination

In 1953, when Perutz discovered that the so-called X-ray phase problem of protein crystallography could be solved by the method of isomorphous replacement with heavy atoms, he expected that the structures, not only of haemoglobin, but also of many other proteins, would presently be solved;^[34] but this did not happen. Only three protein structures had been solved by 1965, and only eleven by 1970. The practical difficulties of crystallization, of preparing isomorphous heavy-atom derivatives, and of recording the X-ray diffraction data were so great that determination of each new structure took many years. Besides, most professional crystallographers were reluctant to enter this risky new field. However, the situation has now been fundamentally transformed. Since 1975 there

has been an exponential rise in the annual number of protein structures solved (Figure 9). In 1990 over 100 new structures came to light; but by 2000 approximately 16000 structures were known, and very many of these are of direct practical interest to medicine. If one knows the structure of a protein in atomic detail, then the precise architecture, shape, and dimensions of receptor centers and catalytically active sites are also known. This situation enables the protein engineer to improve the performance of existing proteins by using various modern methods. This is now one of the major growth areas of enzymology.

It is interesting to note that most, but not all, of the first generation protein crystallographers (1960–1980) came out of British laboratories in Cambridge, Oxford, and the Royal Institution, London. (The migration of D. C. Phillips and his former student Louise Johnson to Oxford in the mid-1960s, after they had solved the structure of lysozyme and explained its mode of action, accounts for a shift of the center of excellence in protein crystallography outside Cambridge from London to Oxford, although the towering presence and achievements of Dorothy Hodgkin at Oxford had already established it as a world-renowned X-ray structural laboratory.) It is also interesting to reflect, with the benefit of hindsight, how wrong-headed the eminent biochemist and Nobel Prizewinner Sir Ernst Chain was when, some thirty years ago, he advised the MRC in London that medical research involving crystal-structure analysis was a profligate waste.^[35] Such is the unpredictability of science.

From Glaciers to Huntington Disease: Perutz's Earliest and Latest Research

As a teenager Perutz gained distinction in his school in Vienna as an expert downhill skier. He was also, at that time, an accomplished mountaineer, and his love of mountains and glaciers never left him. He claims to have barged into Sir Lawrence Bragg's office one day in the Cavendish making the untypical claim: "I've had an honour that you can't match—I've had a glacier named after me!" to which Sir Lawrence retorted "I've had a cuttlefish named after me".^[36]

From his early twenties Perutz had a deep interest in glaciers, particularly how they flowed. Did this occur like

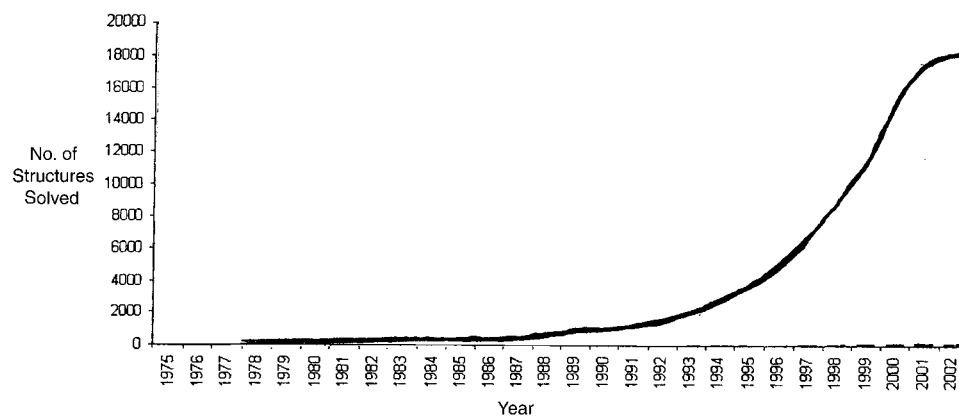


Figure 9. Exponential growth of the number of protein structures determined since 1975. (Adapted from the web site of the Research Collaboratory of Structural Bioinformatics (RCSB).)

treacle or honey flowing out of a tilted container, or was there some other mechanism? More or less as a hobby, Perutz, after conducting measurements perched inside his Alpine igloo on the Jungfrau (Figure 10) for several months in 1938 and again



Figure 10. Max Perutz with a polarizing microscope examining thin sections of glacier ice on the Jungfrauoch in 1938 (Photograph by G. Seligman).

ten years later in a grotto in Eigergletscher, solved the problem of how a glacier flows. It moves, not like treacle, but more like a ductile metal (such as aluminum when it is rolled into a sheet). The process of slip, in the metallurgical sense of the term, is what occurs here. Perutz gave a Friday Evening Discourse on *The Flow of Glaciers* at the Royal Institution on 5 June, 1953, and a summary of his lecture/demonstration appeared in *Nature* later that year.^[37]

In the dining Hall at Peterhouse in October 1936, Perutz made friends (at the research students' table) with a highly gifted, modest, gentle young man named John Carter, whose father, a retired Indian Civil Servant in Budleigh Salterton (a seaside town in Devon), had made a strange discovery. Could Perutz help to explain it? When walking under the red sandstone cliffs to the west of Budleigh Salterton, Carter senior had noticed gray balls of rock of ranging size protruding from the walls of the cliff. They looked like cannon balls and were surrounded by sharply drawn, circular white halos

where the red sandstone had been bleached. Carter senior had himself decided that the bleached halos must have arisen from intrinsic radioactivity. In a fascinating account entitled *My First Great Discovery*, published in the *Peterhouse Annual Record* eight years ago,^[38] Perutz describes how, notwithstanding the obstructionism of the wily old Lincoln (Rutherford's Sergeant Major-like, miserly lab steward), he established that the nodules contained about 0.5 % uranium, concentrated at the borders of dark and light material in the sandstone. Bernal, Perutz's supervisor, thought that the nodules were intriguing enough to be exhibited at the Royal Society Conversazione in June 1937.

Approaching his eightieth birthday, Perutz took an interest in Huntington disease, a neurodegenerative disorder caused by abnormal expansions of glutamine repeats in the mutant protein (later called huntingtin).^[39] In 1994, Perutz and his colleagues showed that polyglutamine polymers could form β sheets in which glutamine residues of neighboring strands are linked by hydrogen bonds between the main chain and side-chain amides. Perutz proposed that proteins with long runs of glutamine residues would form aggregates harmful to the cell. Indeed, aggregates of huntingtin have by now been observed as intranuclear inclusions in the brain of patients suffering from Huntington disease. It has not yet, however, been incontrovertibly established that they are themselves the cause of neuronal deaths. Perutz, in a promising collaboration (started in 2000) with A. H. Windle (a materials scientist), drew parallels between the rates of nucleation of crystals with the random occurrence of neuron deaths.^[40] Their model explains the finding that the age of the patient at the outset of the disease is related exponentially to the length of the glutamine repeats in the pathological protein. Perutz's very last paper,^[41] was finished just ten minutes before he was admitted to Addenbrooke's Hospital for emergency surgery.

A memorable incident took place in the Henry Cavendish dining room at Perutz's College, Peterhouse, on 31st October 2001. At the instigation of the President of the Royal Society of Chemistry, Professor Stephen V. Ley, I organized a small lunch party (Figure 11) to celebrate the award to Perutz of Honorary Fellowship of the Society. Around the table all of us were chemists of various backgrounds. Just as coffee was being served, I asked Max, in a rather public manner, to outline his present research. Those who were privileged to listen to his impromptu, ten-minute exposition of the problems that cause neurodegenerative diseases (Huntington and Alzheimer) will never forget it. First he told us that certain clues were known to some scientists in the early 1930s; then he said that it was less than ten years ago that he himself had tumbled (via so-called "polar zippers") to the enigma of the amyloid proteins. Then he proceeded to proffer the hard experimental evidence that had led him to the structure of amyloid fibres. We listened in awe and exhilaration. Here was this gentle, patriarchal, sparkling, eighty-seven-year-old, who had won his Nobel Prize forty years earlier, flanked by his octogenarian friend Sanger (a double Nobel Laureate), telling us not only a scientifically important, but an absolutely fascinating story—a story which, fortunately for posterity, constitutes his last scientific paper.



Figure 11. Photograph taken at Peterhouse, Cambridge, 31 October 2001, to celebrate Max Perutz's election as Honorary Fellow of the Royal Society of Chemistry (RSC) in which Max Perutz is flanked by Frederick Sanger (right) and John Meurig Thomas (left).

Some fourteen weeks later he passed away, having been visited by a succession of his friends and colleagues, lovingly supported by Gisela his wife (to whom he had been married for sixty years) and by his devoted children—Vivien, a historian of art, and Robin, Head of the Department of Chemistry, University of York—grandchildren, and neighbors.

The Expositor and Critic

Max Perutz was an excellent lecturer, with a gift of perceiving how to put his points so that they would be readily grasped by an audience which was not expert in his own line. His lectures had a wonderful lightness of touch and a mesmeric charm, partly because they were interspersed with unforgettable human incidents involving his friends and scientific adversaries. In a memorable lecture, entitled *Science is No Quiet Life*, (organized by the Kelvin Club, the students' scientific society at Peterhouse at which he was a frequent and highly popular speaker, to mark the 60th anniversary of his arrival at the College), he related how a pugnacious American physicist "burst into my room at the LMB, like a gladiator entering the arena in Rome, telling me that the Perutz picture of haemoglobin is wrong".

Perutz was also a deeply cultured individual, the breadth and depth of whose knowledge was extraordinary. These qualities, along with his magnanimity and generosity to friends and strangers, and his implacable opposition to any unfairness, were particularly evident in the many popular articles that he wrote in limpid prose for the *New York Review of Books* and the *London Review of Books*, with their frequent allusions to characters, incidents, and poems in the works of George Eliot, Tolstoy, Dickens, Shakespeare, Bacon, Donne, Rilke, Hugo, Iris Origo, Lampedusa, and Manzoni.

William Blake claimed that only through three human pursuits could one be brought to the edge of eternity: music, poetry, and painting. With any one of these, said Blake, one could acquire an ineffable sense of ecstasy. Judging by what

Perutz has written over the years, I am sure that he would have wished to add science as a fourth such pursuit. He used to say that: "Scientific research is an exhilarating and imaginative activity depending on qualities of the human mind that are beyond our comprehension".

The pursuit of science frequently entails the fusion of the aesthetic and the intellectual. Like music, poetry and painting its prosecution demands single-minded devotion. In this context two of Max Perutz other favorite sayings are pertinent:

"Haydn rose early each morning to compose; if ideas failed him, he clasped his rosary and prayed until Heaven sent him fresh inspiration";

and

"Renoir painted every day of his life, and, when old age had made his fingers too arthritic to hold a brush, he got someone to tie his brush to his hand".

Max Perutz spoke with the same respect to young students, and to college and laboratory staff, as he did to Prime Ministers and Royalty. He was a citizen of the world, endowed with a great sense of history and of the continuity of existence. It is easy to appreciate why he so much admired the following passage from the *Memoirs* of the ballerina Dame Margot Fonteyn:

"I cannot imagine feeling lackadaisical about a performance. I treat each encounter as a matter of life and death. The important thing I have learned over the years is the difference between taking one's work seriously and taking oneself seriously. The first is imperative and the second disastrous".

Max Perutz was a wonderful human being: the great can also be good.

- [1] Sage was J. D. Bernal (1901–1971), Anglo-Irish crystallographer, who graduated from the University of Cambridge before proceeding to work as a research student of W. H. Bragg at the Davy Faraday Research Laboratory of The Royal Institution, London, where he solved the structure of graphite. He was later appointed Assistant Director of Research at the Cavendish Laboratory, Cambridge (where Dorothy Crowfoot (later Hodgkin), and A. F. Wells of Oxford, Isadore Fankuchen, of Brooklyn Polytechnic, and Max Perutz, joined him). He later became Professor of Physics at Birkbeck College, University of London. During World War II he led a team of operational research and other work of national importance. John Kendrew rubbed shoulders with him during duties in the jungles of Sri Lanka. Max Perutz said that Bernal was the most brilliant conversationalist he had ever met, and that he was a restless genius always searching for something more important to do than the work of the moment. A lifelong member of the British Communist Party, he was much admired by an enormous circle of influential people. Earl Mountbatten of Burma, to whom he reported in the war years, said of him: "Desmond Bernal was one of the most engaging personalities I have ever known... his most pleasant quality was his generosity. He never minded slaving away at other people's ideas, helping to decide what could or could not be done, without himself being the originator of any of the major ideas on which he actually worked". Bernal gave

- laboratory space to Aaron (later Sir Aaron) Klug, Nobel Laureate in Chemistry, 1982, and Rosalind Franklin, while at Birkbeck College. Bernal is widely acknowledged as one of the major pioneers of molecular biology. He and Dorothy Crowfoot published in 1934 (D. Bernal, D. Crowfoot, *Nature*, 1934, 130, 794) the X-ray diffraction photographs of crystals of the enzyme pepsin (in its wet state). Up to then, many felt that large biological molecules had no well-defined structure, certainly not in solution, and believed that they resembled spaghetti with intertwined strands of variable length, bent and folded so as to be difficult to disentangle physically and to defy structural description. Bernal and Crowfoot, however, pointed out that “*from the intensity of the more distant (X-ray diffraction) spots, it can be inferred that the arrangement of atoms inside the protein molecules is also of a perfectly defined kind*”.
- [2] Perutz sought entry as a graduate student to Trinity, King's, Gonville and Caius, and St John's Colleges, but he was turned down. In desperation he asked the crystallographer, W. A. Wooster, an associate of Bernal, for advice. He told him: “*Why not choose the college with the best food, which is the college of which I am a member?*”. And that is how he came to join Peterhouse (where the food is still among the best in Cambridge).
- [3] The Medical Research Council (MRC) is one of Britain's most successful scientific seedbeds. It was set up for practical reasons as a consequence of the 1911 National Insurance Act, when David Lloyd George, as Chancellor of the Exchequer, singled out tuberculosis (TB) as a problem needing special attention. In Great Britain and Ireland this dreadful disease was responsible for one in three deaths among males aged between 15 and 44, and half the deaths among females aged 15 to 24. Germany was making great strides through the building of TB institutions. The Chancellor of the Exchequer felt that something had to be done in Britain. The First World War brought out many other pressing medical problems as well—wound infections (especially tetanus and gangrene), typhoid, cholera, dysentery, civilian malnutrition, and even TNT poisoning in munitions factories. The MRC worked successfully on many of these problems, and when the war ended the first Secretary of the MRC, Sir Walter Fletcher, was able to argue that its work should not be restricted to any particular area such as TB, for which the funds were originally committed. Fletcher defined the primary function of the MRC as promoting fundamental scientific research, since this was essential to the development of clinical treatment. He found a ready ally in the Prime Minister of the day, David Lloyd George, who had been the original architect of the National Insurance Act. The MRC has become one of the great jewels in the crown of British science.
- [4] Of which they were each Honorary Fellows. Perutz, although a member of Peterhouse, with dining rights and some other privileges ever since he entered as a graduate student in 1936, was not made a Fellow until he won the Nobel Prize in 1962. Kendrew, on the other hand, from the time he entered the college in 1947 as a College Lecturer, Official Fellow, and Director of Studies in Natural Sciences, played a leading part in the academic, social, and administrative life of the College for 27 years. He served successively as Librarian, Wine Steward, Steward, and Curator of the College's paintings and portraits.
- [5] Charles Babbage (1792–1871) is best known as the inventor of the so-called “Difference Engine”, a calculating machine that is accepted as the first computer, see Doron Swade, *Charles Babbage and his Calculating Engines*, Science Museum, London, 1991. The inventive Babbage once remarked: “*All of chemistry, and with it crystallography, would become a branch of mathematical analysis which, like astronomy taking its constants from observation, would enable us to predict the character of any new compound and possibly the source from which its formation may be anticipated*”.
- [6] Inventor of the jet engine. Other distinguished living members include the Nobel Laureates A. J. P. Martin (Chemistry, 1952) and Aaron Klug (Chemistry, 1982).
- [7] R. E. Dickerson, *Protein Sci.* **1992**, 1, 182–186.
- [8] The University of the Third Age (U3A), an organization that began in France, caters for retired people, and there are now branches in many British (especially university) towns and cities.
- [9] Rhodonite is a manganese-rich silicate of the pyroxenoid family (Mn,Ca,Fe)SiO₃.
- [10] Perutz subsequently discovered that Rutherford wanted to throw Bernal out of the Cavendish but was restrained from doing so by W. L. (later Sir Lawrence) Bragg, who became Rutherford's successor at Manchester and at Cambridge. Perutz used to say that “*Had Bragg not intervened, Bernal's pioneering work in molecular biology would not have started, John Kendrew and I would not have solved the structure of proteins, and Watson and Crick would never have met*”.
- [11] When Hitler invaded Austria, the family business was expropriated, and his parents became refugees. Perutz brought his parents to Britain, but he and his father were interned in 1940. After his release, his father, who had never worked with his hands before, took a manual job (as a lathe operator in Letchworth) to help the war effort.
- [12] Who also joined the Perutz–Kendrew team in 1948.
- [13] H. E. Huxley, *Nature* **2002**, 415, 851–852.
- [14] Perutz, after six years of labor extracting Patterson maps (which consisted of some 25 million lines between the thousands of atoms in the haemoglobin molecule, felt:^[15] “*elated when they seemed to tell me that the molecule consists simply of bundles of parallel chains of atoms spaced apart at equal intervals. Shortly after my results appeared in print, a new graduate student joined me. As his first job, he performed a calculation which proved that no more than a small fraction of the haemoglobin molecule was made up of the bundles of parallel chains that I had persuaded myself to see, and that my results, the fruits of years of tedious labour, provided no other clue to its structure. It was a heart-breaking instance of patience wasted, an ever-present risk in scientific research. That graduate student was Francis Crick, later famous for his part in the solution of the structure of DNA*”.
- [15] M. F. Perutz, *I Wish I'd Made You Angry Earlier*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 1998, p. XI.
- [16] It is a fortunate fact that complex molecules such as haemoglobin take no more notice of the isomorphous attachment of a heavy atom than (to use Sir Lawrence Bragg's words) “*a Maharaja's elephant would of the gold star painted on its forehead*”.
- [17] The picture was crude, but two years later, by using the linear diffractometer devised and built by Arndt and Phillips^[18] at the Davy Faraday Research Laboratory, London (where Perutz and Kendrew were Honorary Readers, 1954–1968), a much sharper picture of myoglobin, in all its glorious complexity, was obtained, with the identities of the amino acid residues clearly discernible.
- [18] Arndt later moved from the Davy Faraday Laboratory to the LMB in Cambridge, and Phillips (later Sir David, then Lord Phillips of Ellesmere, 1925–1999) was appointed Professor of Molecular Biophysics in the University of Oxford.
- [19] J. C. Kendrew, G. Bodo, H. M. Dintzis, R. G. Parrish, H. W. Wyckoff, D. C. Phillips, *Nature* **1958**, 181, 662–666.
- [20] M. F. Perutz, M. G. Rossman, A. F. Cullis, H. Muirhead, G. Will, A. C. T. North, *Nature* **1960**, 185, 416–422.
- [21] Perutz loved telling the story of how, on hearing so many people predict that he and Kendrew would be awarded the Nobel Prize, one day an excited secretary brought in to them an important-looking envelope bearing an unusual stamp, and they each thought: “*This is it, news of the Prize*”. But the letter had been sent from the Pontifical Academy urgently requesting their reprint order forms, duly completed!
- [22] For his work on the primary structure of proteins, especially that of insulin.
- [23] For elucidating the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP).
- [24] D. M. Blow, *The Independent* (London), 7 February 2002.
- [25] D. Eisenberg, *Protein Sci.* **1994**, 3, 1625.
- [26] In his *Commonplace Book*, Perutz has enumerated his own: “*People are best judged by their actions*”, and that of Albert Schweitzer: “*Example is not the main thing in influencing others; it is the only thing*”.
- [27] K. C. Holmes, *Biogr. Mem. Fellows R. Soc.* **2001**, 47, 311–332. Kendrew's own interest in fundamental research began to wane in the mid 1960s as he gradually turned his brilliant mind to matters of policy. He had already served as Deputy Chief Scientific Advisor to the Ministry of Defence (1960–1965); and then he became Chairman and Secretary General of the International Council of Scientific Unions (ICSU), centred in Paris, a body of which he became President (1988–1990). From 1969 to 1975, Kendrew was Secretary-General of

- the EMBO, and in 1974 he became the (first) Director General of EMBL at Heidelberg, where a splendid new building was opened in May 1978.
- [28] M. F. Perutz, *New Sci.* **1971**, 49, 676–679.
- [29] In some cases, the binding of a molecule to the protein produces little conformational change. Sperm whale myoglobin^[30] is a good example: the oxy and deoxy structures may be superimposed almost exactly.
- [30] A. M. Lesk, *Protein Architecture: A Practical Approach*, Oxford University Press, Oxford, **1991**, p. 121.
- [31] G. Fermi, M. F. Perutz, *Atlas of Molecular Structures in Biology: Haemoglobin and Myoglobin*, Clarendon Press, Oxford, **1981**. The aminoacid sequences in the α and β subunits of the haemoglobin in the following creatures are enumerated in this Atlas: man, rhesus monkey, orang-utan, slow loris, tupai, savannah monkey, capuchin monkey, hanuman langur, spider monkey, rabbit, dog, horse, cat, pig, camel, llama, Indian elephant, opossum, rat, chicken, grey lag goose, carp, goldfish, caiman, Nile and Mississippi crocodile, tadpole, and shark.
- [32] H. T. Andersen, *Acta Physiol. Scand.* **1961**, 53, 24–45.
- [33] N. Hennakas, G. Miyazaki, J. Jame, K. Nagai, *Nature* **1995**, 373, 244–246.
- [34] M. F. Perutz, *Faraday Discuss.* **1992**, 93, 1–11.
- [35] Private communication from Max Perutz to Sir Aaron Klug, July **1993**.
- [36] Neither of these two scientists was given to boasting, idle or otherwise. But the story is undoubtedly true and was told in Perutz's Royal Institution Discourse in 1990 entitled *How W. L. Bragg invented X-ray Analysis* published in M. F. Perutz, *The Legacy of Lawrence Bragg* (Eds.: J. M. Thomas, D. C. Phillips), Science Reviews Ltd, London, **1990**.
- [37] M. F. Perutz, *Nature* **1953**, 172, 929–932.
- [38] M. F. Perutz, *Peterhouse Annual Record*, **1994–1995**, p. 15.
- [39] A. Klug, *Science* **2002**, 295, 2382–2383.
- [40] M. F. Perutz, A. H. Windle, *Nature* **2001**, 412, 143–144.
- [41] M. F. Perutz, J. T. Finch, J. Berriman, A. Lesk, *Proc. Natl. Acad. Sci. USA*, **2002**, 99, 5591–5595.

Biominingalization in Diatoms Mediated through Peptide- and Polyamine-Assisted Condensation of Silica

Georg Pohnert*

Diatoms are unicellular algae with cell walls of amazing variety of shape. Their aesthetic shapes and elaborate patterns have fascinated scientists since the early years of light microscopy (Figure 1). The cell walls of diatoms are predominantly composed of a biomineral derived from hydrated silica (SiO_2), which is associated with peptides and polyamines. Today we know that precipitation of this amorphous material during biogenesis of cell walls is controlled species-specifically, to nanometer resolution.



Figure 1. Transmission electron micrograph of the cell wall of *Cylindrotheca fusiformis*.^[10]

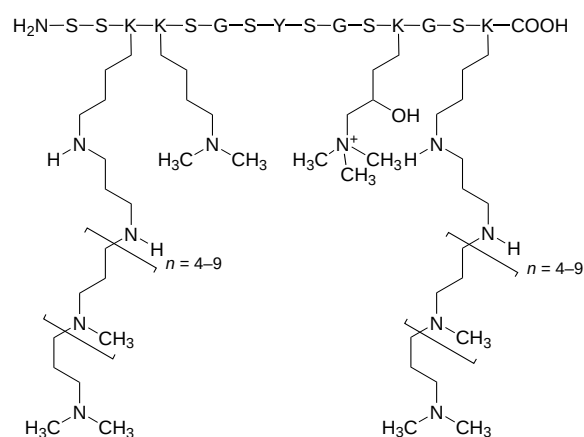
Cell-wall formation occurs primarily in silica deposition vesicles (SDVs); intracellular organelles in which soluble forms of silicate are accumulated by active-transport mechanisms. The directed precipitation and formation of highly differentiated cell walls begins only after accumulation of the silicic acid in the SDV. Different shaping mechanisms are thought to be involved in this process. Silica precipitation may be initiated and controlled by diffusion-limited processes in the SDV,^[1] and shaping mechanisms mediated by spatial restrictions in the cellular environment may also be involved.^[2, 3] Another proposed mechanism involves the presence of an organic matrix in the SDV that promotes and directs silica precipitation. Detailed investigations of organic components in the silica cell walls were carried out to verify this hypothesis.^[4]

Recently, this approach led to the elucidation of universal mechanisms involved in directed biomineralization in diatoms, which are the topic of this highlight. Early on, it was recognized that removal of the mineral content of diatom cell

walls by using hydrogen fluoride (HF) vapors leaves behind organic material “like the ghost of the cell”.^[5] Organic components are found even after pretreatment with ethylenediaminetetraacetate (EDTA) or after oxidative purification of the silica cell wall with NaOCl. This organic material is tightly associated with the remaining SiO_2 and can be separated from the inorganic material only by dissolving it in HF. Purification and characterization of the thus-obtained constituents from cell walls of the diatom *Cylindrotheca fusiformis* resulted in the discovery of two new families of proteins.^[6] The lighter components in the HF extract form a dominant fraction with masses of 4 to 17 kD. Because of their affinity for silica, these peptides were termed silaffins.^[7] Kröger et al. observed precipitation of hydrated silica within seconds of adding these purified proteins to supersaturated silicic acid solutions, while untreated controls remained stable for several hours. The amount of amorphous material formed was directly proportional to the amount of added silaffin, which indicates that the peptides are directly involved in the mineralization process. Remarkably, the structure of the formed silica nanospheres depends on the nature of the added peptide. While addition of a mixture of all the purified silaffins from *C. fusiformis* induces the formation of SiO_2 particles with average diameters of < 50 nm, addition of the smallest silaffin 1A leads to the formation of particles with diameters between 500–700 nm.^[7] N-terminal sequencing of silaffin 1B and cloning of the corresponding gene revealed a coding protein with a modular structure. A signal peptide and a highly negatively charged unit are followed by seven repetitive, strongly basic, units. After endoproteolytic cleavage, these form the corresponding silaffins. Characteristic structural elements of these proteins are regularly arranged lysine–lysine clusters which are modified post-translation. ESIMS-based structure elucidation of the 15 and 18 amino acid peptides silaffin 1A₁ and silaffin 1A₂ shows that the ϵ -nitrogen atoms of the lysine residues bear different modifications (shown in Scheme 1).^[8]

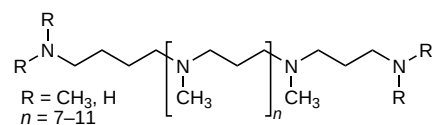
These modifications of lysine play a central role in the formation of silica under intracellular, acidic conditions. While both silaffins and the corresponding nonmodified peptides promote the precipitation of silicic acid in a neutral medium, this process is exclusively accelerated by the post-translational-modified silaffins if the surrounding medium has a pH value of < 6.

[*] Dr. G. Pohnert
Max-Planck-Institut für chemische Ökologie
Winzlerlaer Strasse 10
07745 Jena (Germany)
Fax: (+49) 3641-571-256
E-mail: pohnert@ice.mpg.de



Scheme 1. Structure of silaffin 1A₁ obtained from *C. fusiformis* cell walls treated with HF. The polypeptide is represented in the one-letter amino acid code (S = serine, K = lysine, G = glycine, Y = tyrosine). Only the structures of the post-translatory modified amino acids are shown.^[8]

Newer investigations show that the principles found for the formation of silica in *C. fusiformis* represent, with variations, a general concept for biomineralization in diatoms.^[9] Comparison of the organic constituents of cell walls from six different diatom species revealed that silaffins and related molecules are ubiquitous in this algal class, and may be responsible for the complex pattern formation of morphologically different cell walls. Significantly, these silica-precipitating molecules differ, depending on the species; this is a prerequisite for such a formation mechanism. After treatment with HF and purification, the remaining organic components exhibited differing characteristics for the six different species. Detailed investigations led not only to the identification of species-specific sets of silaffins but also to the characterization of another, non-proteinogenous compound class, which is incorporated into the diatom silica. These cell-wall constituents are complex mixtures of long-chain polyamines with molecular weights of up to 1500 Da. ESIMS shows different patterns and mass distributions of these macromolecules in all of the diatoms investigated.^[9] The amines from *Nitzschia angularis* showed regular mass distributions, which suggests the presence of defined homopolymers. MS-based structure elucidation led to the identification of a polymer formed from *N*-methyl-propylamine monomers (Scheme 2). Comparison of



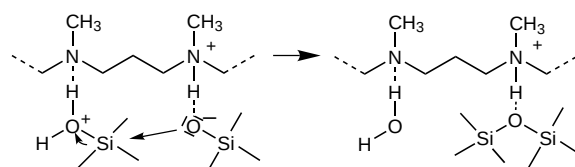
Scheme 2. Polyamines from the diatom *N. angularis*. A family of 25 amines is generated by variation of the chain length and the degree of methylation. Additional variation is achieved by exchange of the butylamine (left) for a propylamine unit.

the mass spectra of macromolecules from other diatom cell walls showed the universal presence of polyamines with an inherently similar structural principle. The amines from *C. fusiformis*, for example, consist of polymers of non-methylated propylamine units of different lengths.^[9] These polymers

can extend by up to 20 repeat units, which makes them the longest linear polyamines found in nature. These amines often comprise the majority of organic material in diatom cell walls.

If purified amines from *N. angularis* are added to metastable solutions of silicic acid, they induce the rapid precipitation of silica and are simultaneously incorporated into the formed biomineral.^[9] As a species-specific influence of the matrix on the silica pattern implies, diameters of the resulting spherical particles depend on the nature of the added amines. If mixtures of silaffins and amines are added to silicic acid solutions, the nature of the precipitate is altered and the composite material forms spherical particles that are arranged in blocklike structures.

A mechanism for the activity of polyamines during silica formation has been suggested, based on the alternating presence of protonated and non-protonated tertiary amine groups in the polyamine chain. These amine groups could form hydrogen bonds to silicic acid and thus facilitate the Si–O bond formation, according to Scheme 3.^[10] The resulting biomineral has a relative composition of 1.25:1 SiO₂/polyamine based on weight, which indicates that the amines interact directly with the silanol functional groups of hydrated SiO₂.^[9]



Scheme 3. Postulated mechanism of the amine-mediated silicic acid condensation.

An elegant model explains how the above-mentioned polyamines and peptides might also be involved in the shaping process during the formation of diatom cell walls.^[11] Based on the assumption that the amphiphilic methylated polyamines form emulsions of microdroplets by phase-separation processes in the SDV, a template mechanism has been suggested that could explain the observed stages of cell-wall development in *Coscinodiscus wailesii* (Figure 2A). In a close-packed arrangement the microdroplets would form a hexagonal monolayer within the flat SDV. Precipitation of silica around this arrangement creates a honeycomb-like framework. The consumption of a part of the polyamine population by coprecipitation could cause dispersion of the original organic droplets that, again, could serve as precipitation templates (Figure 2B). Repetition of this simple iterative mechanism (Figure 2C,D) could explain the pattern observed during electron microscopic investigation of *C. wailesii* cell walls during growth (Figure 2E–H).^[11]

The concepts underlying diatom biomineralization have also inspired research into directed bio- and nanotechnological silica formation.^[3] While diatoms have the ability to create highly complex and intricate silica structures under physiological conditions, laboratory methods often require elevated pH values or temperatures, with long reaction times. It is thus not surprising that possible applications of biochemical

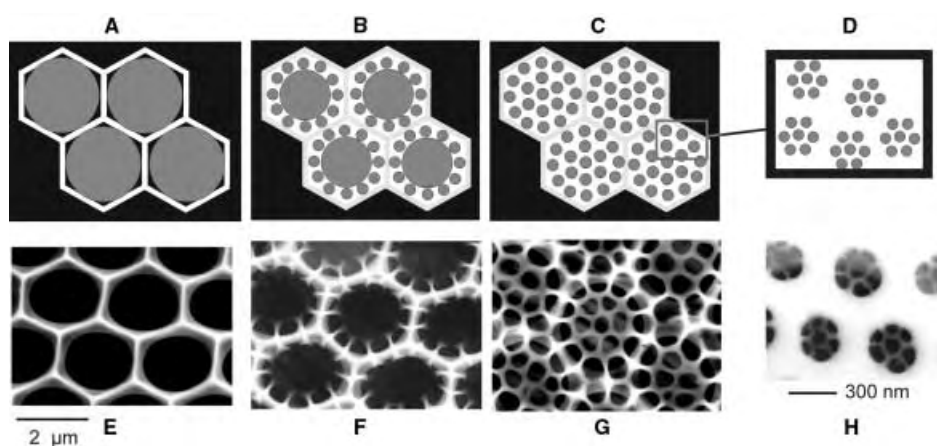


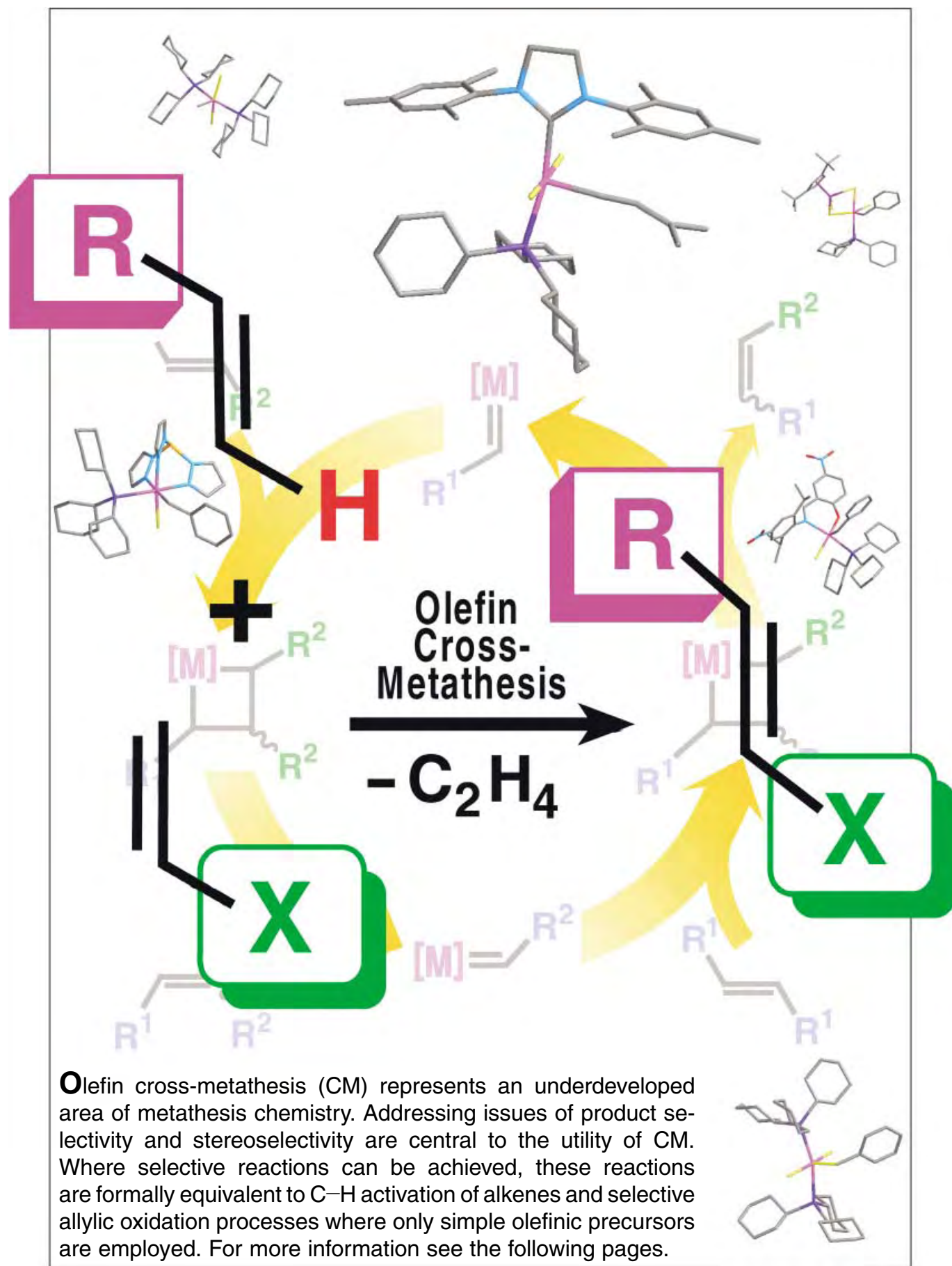
Figure 2. Schematic representation of the phase-separation mediated templating mechanism (A–D) and comparison with different stages of the cell-wall biogenesis of *C. wailesii* (scanning electron micrographs of valves during formation (E–H)). Reproduced with permission from ref. [11], copyright (2002), American Association for the Advancement of Science.

processes have been explored during the search for new ways to create sensitive hybrid materials with silicate minerals. Technical applications that allow ordered, peptide-assisted precipitation of silica onto a polymer hologram were developed following the initial identification of silaffins.^[12] For this purpose, silaffin A₁ was incorporated into a polymer hologram to form a regularly arranged peptide matrix. Treatment of this hologram with a solution of silicic acid for 10 min resulted in the formation of spherical silica nanospheres arranged in a regular two-dimensional array. This process combines the ease of processability of organic polymers with the improved mechanical properties of a composite material. The directed biomineralization results in structures with increased mechanical stability and improved optical properties (up to 50 times increase in surface refractive index), and

may be of practical use in the fabrication of photonic devices.^[12]

Only in recent years have we begun to understand the underlying principles of the formation of complex silica structures in diatoms. The identification of the first matrices for silica precipitation and new models for shaping processes leave the field open for in vivo approaches to clarify the detailed interactions leading to the highly differentiated structures of diatom cells.

- [1] R. Gordon, R. W. Drum, *Int. Rev. Cytol.* **1994**, *150*, 243–372.
- [2] A.-M. M. Schmidt, D. Schulz, *Protoplasma* **1979**, *100*, 267–288.
- [3] S. Mann, *Angew. Chem.* **2000**, *112*, 3532–3548; *Angew. Chem. Int. Ed.* **2000**, *39*, 3393–3406.
- [4] D. M. Swift, A. P. Wheeler, *J. Phycol.* **1992**, *28*, 202–209.
- [5] B. E. Volcani in *Silicon and Siliceous Structures in Biological Systems* (Eds.: T. L. Simpson, B. E. Volcani), Springer, New York, **1981**, pp. 157–200.
- [6] N. Kröger, R. Wetherbee, *Protist* **2000**, *151*, 263–273.
- [7] N. Kröger, R. Deutzmann, M. Sumper, *Science* **1999**, *286*, 1129–1132.
- [8] N. Kröger, R. Deutzmann, M. Sumper, *J. Biochem.* **2001**, *276*, 26066–26070.
- [9] N. Kröger, R. Deutzmann, C. Bergsdorf, M. Sumper, *Proc. Natl. Acad. Sci.* **2000**, *97*, 14133–14138.
- [10] N. Kröger, M. Sumper, in *Biomineralization* (Ed.: E. Baeuerlein), Wiley-VCH, Weinheim, **2000**, pp. 151–170.
- [11] M. Sumper, *Science* **2002**, *295*, 2430–2433.
- [12] L. L. Brott, R. R. Naik, D. J. Pikas, S. M. Kirkpatrick, D. W. Tomlin, P. W. Whitlock, S. J. Clarkson, M. O. Stone, *Nature* **2001**, *413*, 291–293.



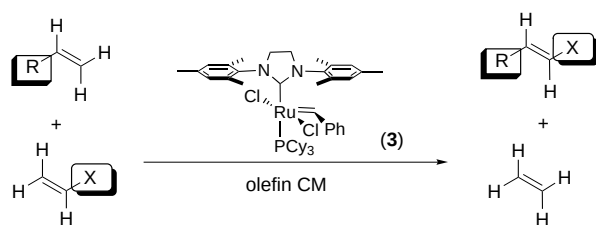
Formal Vinyl C–H Activation and Allylic Oxidation by Olefin Metathesis

Arnab K. Chatterjee and Robert H. Grubbs*

A general process for the substitution of C–H bonds of simple olefins and for the directed allylic oxidation of trisubstituted olefins would provide efficient new methods for the synthesis of complex molecules. Conceptually, many reactions in organic synthesis are analogous to C–H activation and directed oxidation processes. While a substantial amount of research has focused on these reactions, the recognition of (other) known reactions as formal processes towards the same products is also an important undertaking. Herein we describe olefin cross metathesis (CM) as a formal vinylic C–H activation or a formal allylic oxidation reaction.

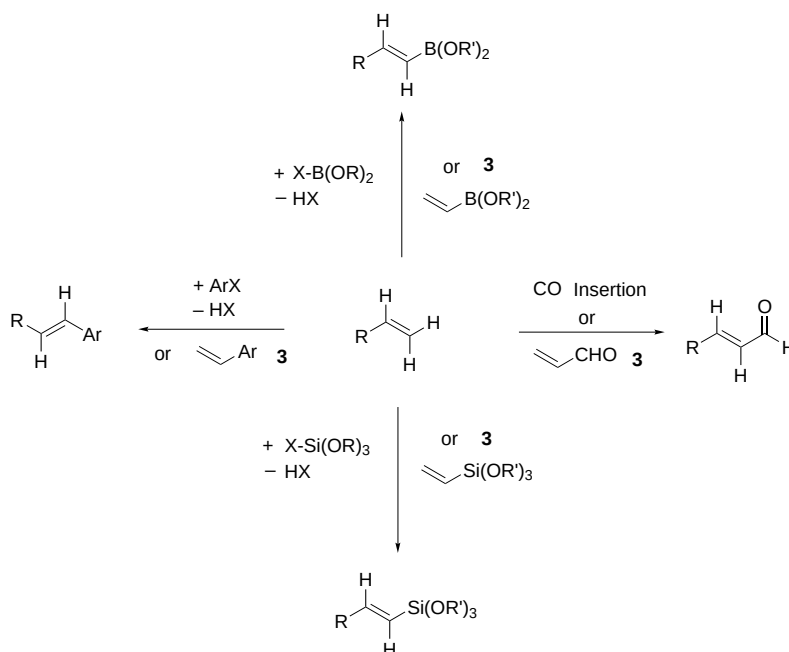
With the advent of single-component functional-group-tolerant catalysts such as $[\text{Mo}(\text{CHCMe}_2\text{Ph})(\text{NAr})\{\text{OCMe}(\text{CF}_3)_2\}_2]$ (**1**) and $[\text{Ru}(\text{CHPh})(\text{PCy}_3)_2\text{Cl}_2]$ (**2**), the olefin metathesis reaction has provided new methods for the construction of complex organic molecules by ring-closing metathesis (RCM) and ring-opening-metathesis polymerization (ROMP) and offers a unique solution for the substitution of alkene C–H bonds.^[1] However, a transformation that is often overlooked is CM^[2] of readily available α -olefins with simple functionalized olefins, and is presumably a consequence of the low catalytic activities of **1** and **2** towards intermolecular metathesis.^[3] The advent of more active catalysts that still retain excellent functional-group compatibility (e.g. **3**),^[4] has led to a reexamination of CM as a general synthetic reaction. With these more active catalysts, the range of functionalized products available by CM has been greatly expanded and a number of highly efficient CM transformations have been described.^[5] For this reaction to reach its full potential, a general way of visualizing the reaction and the factors that control the yield and stereoselectivity of the desired cross products is required.

As shown in Scheme 1, CM affords the same products that would result from an analogous C–H activation/substitution pathway, combining both a α -olefin substituent (R) with a functional group (X). There are several similarities between this interpretation of CM and some C–H activation processes (e.g. arene borylation).^[6] Both reactions can be driven to completion by the loss of a volatile gas: ethylene, propylene, or isobutylene in CM and molecular hydrogen in some cases of arene borylation. Furthermore, both reactions use widely available chemicals to provide synthetically useful functionalized products. It is noteworthy that when very good stereoselectivities are observed in CM,



Scheme 1. Direct cross-coupling of olefins.

the obtained product can be considered formally to as a result of chemoselective C–H activation of a terminal methylene proton. Scheme 2 illustrates a variety of these chemoselective C–H-activation products that can be also accessible by CM, including some that are not accessible by other metal-catalyzed processes such as vinyl siloxane coupling^[7] and CO insertion. The analogy between CM and C–H-activation

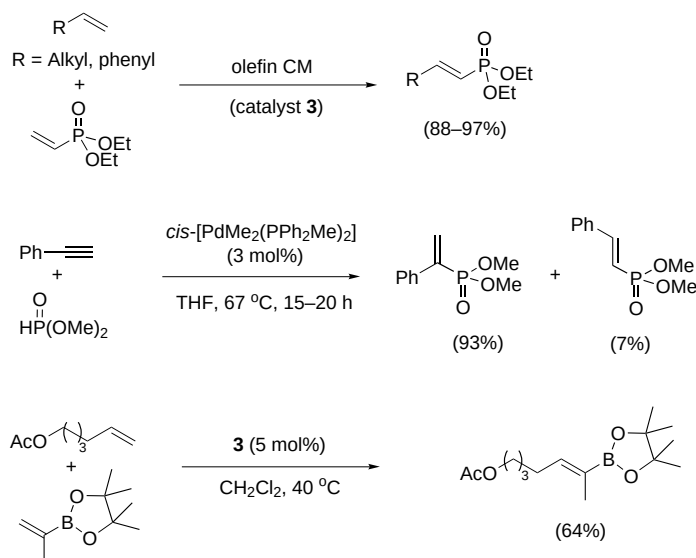


Scheme 2. Substitution and insertion reactions by CM.

processes allows for a conceptually new way of viewing CM, beyond a simple statistically governed scrambling of α -olefins. Additionally, in most cases, the metathesis reaction is milder and produces higher yields of the desired substituted product than of the corresponding C–H-substitution product. Therefore, CM can be viewed as a conceptual equivalent of a selective and general vinyl C–H-activation process to yield highly functionalized products.

By a judicious choice of olefin partners, the regioselectivity of CM can be superior to that of other metal-catalyzed processes. In addition to using readily available olefins as *both* coupling components in place of reactive functionalities such as alkyl halides and aldehydes, these reactions also provide different (and in certain instances improved) regioselectivities that would not be obtained from addition reactions to alkyne functionalities. For example, the resulting regioselectivity

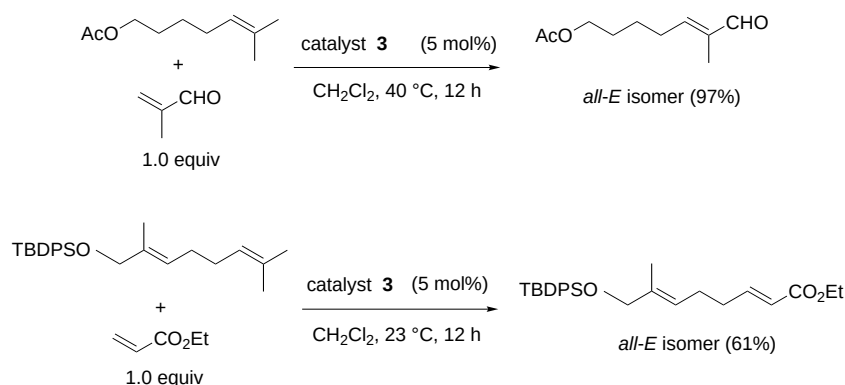
[*] Prof. Dr. R. H. Grubbs, A. K. Chatterjee
Division of Chemistry and Chemical Engineering
Arnold and Mabel Beckman Laboratories for Chemical Synthesis
California Institute of Technology
Mail Code 164-30, Pasadena, CA 91125 (USA)
Fax: (+1) 626-564-9297
E-mail: rhg@caltech.edu



Scheme 3. Unique regioselectivity in olefin CM.

from CM routes is opposite to that from the hydrophosphorylation of alkynes (Scheme 3). The addition across terminal alkynes leads to mainly geminal 1,1-disubstituted product and only a small amount of the 1,2-disubstituted product,^[8] whereas the 1,2-disubstituted product can be directly accessed from CM of commercially available diethylvinylphosphonate with a variety of α -olefins in excellent yield. In addition, CM of 1,1-disubstituted vinyl borates is regioselective, whereas the hydroboration reaction of the corresponding unsymmetrical internal alkyne provides a mixture of regioisomers.^[9]

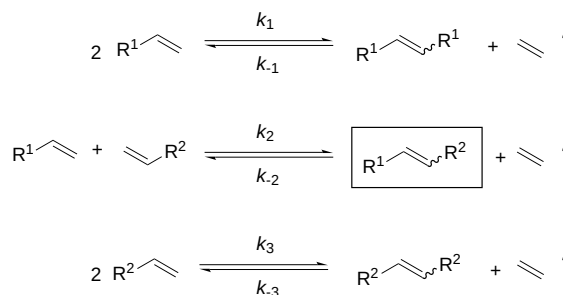
Earlier we demonstrated the CM of vinyl borates and vinyl siloxanes in the presence of catalyst **2**, but the range of substrates amenable to CM has been greatly expanded by using **3**. For example, trisubstituted^[10] and α,β -unsaturated carbonyl-containing olefins are metathesis-active substrates in the presence of the more active catalyst **3**. This reaction provides a route to the apparent selective allylic oxidation of isoprenoid groups. For example, if a prenyl/isoprenoid olefin is treated with a functionalized olefin such as methacrolein, the overall transformation is the apparent oxidation of one of the *trans* terminal methyl groups (Scheme 4). Moreover, since the CM reaction can be conducted with acrylate esters, acids, and allylic alcohols, all oxidation states and desired protecting



Scheme 4. Selective allylic oxidation by olefin CM.

groups can be directly accessed without any protecting-group or oxidation-state adjustments of the products. Furthermore, by using bulky protecting groups within a single CM substrate, certain trisubstituted olefins can remain inert to the CM-reaction conditions.

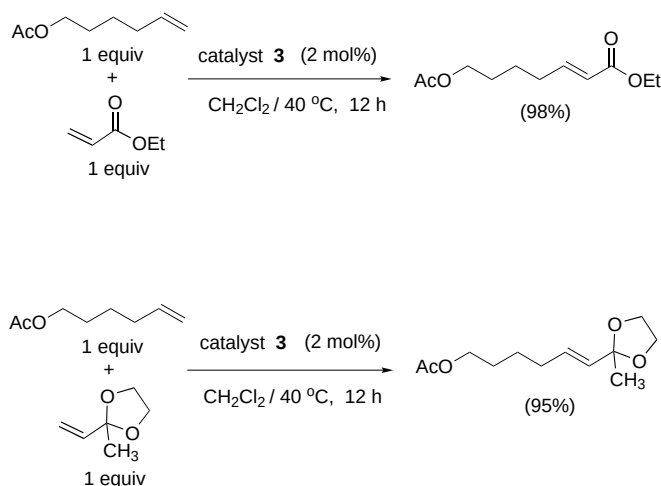
For these CM-functionalization reactions to become generally useful, methods are required to increase the efficiency of these transformations. Traditionally, CM reactions are driven to the desired product by using an excess of the more readily available cross partner. Most other efficient cross-coupling strategies use differentiated functionalities such as vinyl stannanes and alkyl chlorides in Stille couplings to allow equal stoichiometry of reactants in the reaction. However, under certain circumstances CM reactions can be highly efficient with equal stoichiometries of reactants. In CM reactions there are three equilibria and six rate constants (Scheme 5). If the rates of all the reactions are similar or if the reaction is allowed to proceed for a long period of time, statistical ratios are obtained with nearly 50% yield of cross product. However, if one olefin forms the homodimer at a slower rate (k_3) than the other reactions (as a result of either steric or electronic factors) such that $k_1, k_{-1}, k_2 \gg k_3$, and all the possible ethylene is removed from the system such that all



Scheme 5. Equilibria involved in olefin CM.

terminal olefins are consumed, then only the cross product is produced. These reaction conditions would allow much greater yields than the statistically predicted 50% CM product. Since the only pathway for loss of ethylene from the R^2 -containing olefin is by CM with an R^1 olefin. The utility of this approach has been demonstrated in the cross-metathesis of α,β -unsaturated esters (Scheme 6) and quaternary allylic compounds (Scheme 6); steric or electronic factors result in the formation of the cross product in much higher yields than 50%, with excellent olefin stereoselectivity.

Stereoselective and chemoselective olefin CM provide new avenues for olefin metathesis to become useful in organic synthesis. In particular, CM can be viewed as a highly selective and efficient set of reactions that provide the same products as would selective C–H activation and allylic oxidation. As more active catalyst systems are discovered in the future, and thus a wider range of olefins can participate in CM, these reactions will provide an efficient process to functionalized products from readily available olefins.



Scheme 6. Olefin CM with equal stoichiometry of substrates.

Experimental Section

General procedure (Scheme 6): 5-Hexenyl-1-acetate (200 μ L, 1.20 mmol, 1.0 equiv) and ethyl acrylate (130 μ L, 1.20 mmol, 1.0 equiv) were added simultaneously by using a syringe to a stirred solution of **3** (20 mg, 0.024 mmol, 2.0 mol %) in CH_2Cl_2 (2.5 mL, 0.5 N in acrylate) under a nitrogen atmosphere. The flask was fitted with a condenser and heated at reflux under nitrogen for 12 hours. The reaction mixture was then concentrated in vacuo, and the residue was purified directly on a silica-gel column (2×10 cm), eluting with hexane/ethyl acetate (9:1) to provide the CM product as a clear colorless oil (253 mg, 1.18 mmol, 98 %).

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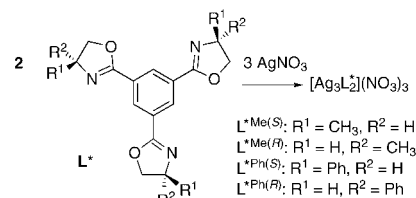
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An Enantiomerically Pure Propeller-Shaped Supramolecular Capsule Based on the Stereospecific Self-Assembly of Two Chiral Tris(oxazoline) Ligands around Three Ag^{I} Ions**

Hae-Jo Kim, Dohyun Moon, Myoung Soo Lah, and Jong-In Hong*

The self-assembly of supramolecular structures by simply mixing ligands and labile metal ions has attracted considerable attention.^[1] Among the self-assembled supramolecular capsules,^[2] a few propeller-shaped structures have been described.^[3] In most cases racemates were obtained; however, recently chiral ligands have been reported to induce enantiomerically pure supramolecular capsules and helical superstructures.^[4] Herein we describe the completely stereospecific self-assembly of a propeller-shaped supramolecular capsule induced by a rigid chiral tris(oxazoline) unit acting as a tris-monodentate ligand and Ag^{I} metal ions having tetrahedral coordination geometry. The stereochemistry arises from the self-recognition of the ligand chirality^[5] during the self-assembly of the supramolecular capsule.

Chiral tris(oxazoline) ligands (L^*) were used to induce a predetermined chiral helicity because it is easy to introduce chirality and rigidity within the self-assembled superstructure from simple chiral amino alcohols.^[6] Simple mixing of Ag^{I} ions and L^* in a 3:2 ratio generated a single set of ^1H NMR resonances, which implies the formation of only one self-assembled structure (Scheme 1). The stoichiometry of the complex was identified by electrospray ionization (ESI) mass spectrometry. In particular, examination of the isotope distribution of the peak at m/z 1101.0, attributable to either $\{[\text{Ag}_3\text{L}_2^*](\text{NO}_3)_2\}^+$ or $\{[\text{Ag}_6\text{L}_4^*](\text{NO}_3)_4\}^{2+}$, showed a peak spacing of one mass unit typical of a +1 charged species; this



Scheme 1. Self-assembly of L^* and Ag^{I} ions into a trinuclear complex.

[*] Prof. J.-I. Hong, H.-J. Kim
School of Chemistry, College of Natural Sciences
Seoul National University
Seoul 151-747 (Korea)
Fax: (+82)2-889-1568
E-mail: jihong@plaza.snu.ac.kr
D. Moon, Prof. M. S. Lah
Department of Chemistry, College of Science
Hanyang University, Ansan
Kyunggi-Do 425-791 (Korea)

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confirms the presence of the former trinuclear complex. Evidence for the formation of a chiral helical superstructure comes from the CD spectra of the enantiomeric complexes $[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}](\text{NO}_3)_3$ and $[\text{Ag}_3\text{L}_2^{*\text{Me}(R)}](\text{NO}_3)_3$. The CD signs are nearly opposite for the two complexes: $\Delta\epsilon(\lambda_{\text{max}}) = -8.1\text{ M}^{-1}\text{ cm}^{-1}(235\text{ nm})$ for the complex with the *S* ligand ($\text{L}^{*\text{Me}(S)}$) and $7.2\text{ M}^{-1}\text{ cm}^{-1}(235\text{ nm})$ for that with the *R* ligand ($\text{L}^{*\text{Me}(R)}$).

X-ray diffraction analysis of crystals of $[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}](\text{NO}_3)_3$, which were obtained by slow diffusion of ether into an acetonitrile solution in a dark room, shows the presence of a D_3 -symmetric, dimeric, trinuclear, propeller-shaped supramolecular capsule with *M* helicity (Figure 1), in which $\text{L}^{*\text{Me}}$ acts as a tris-monodentate ligand.^[7] The complex consists of

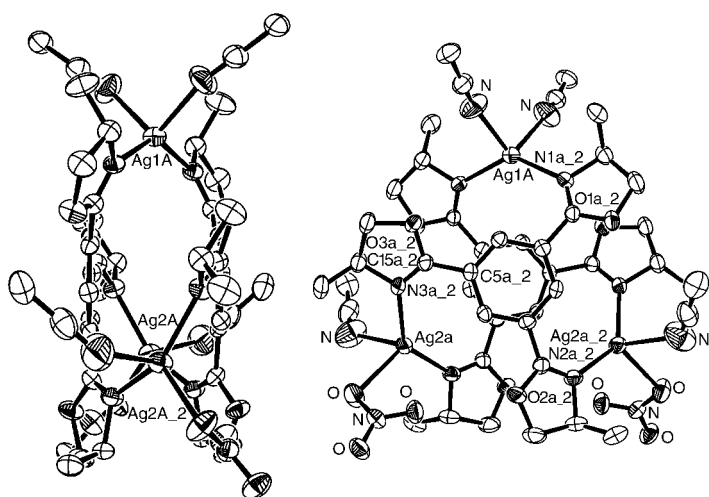


Figure 1. Structure of $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}](\text{CH}_3\text{CN})_4(\text{NO}_3)_2]^+$ in the solid state (ORTEP representations). Side view (left) and top view along pseudo- C_3 symmetric helical axis (right). All hydrogen atoms are omitted for clarity, only the heteroatoms of the upper $\text{L}^{*\text{Me}}$ ligand, the nitrate, and the acetonitrile ligands are indicated in the top view. Selected torsional angles $[\circ]$ (bond lengths $[\text{\AA}]$; bond angles $[\circ]$) for C5a_2, C15a_2, N3a_2, Ag2a: -7.9 (1.480, 1.263, 2.243; 126.99, 131.69).

an equilateral triangle of silver ions (av Ag–Ag distance $7.195\text{ \AA}$). Each silver ion binds to one oxazoline unit of $\text{L}^{*\text{Me}}$ above the plane of the silver atoms and to a second oxazoline unit of $\text{L}^{*\text{Me}}$ below the plane. Thus, the structure may be considered as a supramolecular helical capsule or triply bridged metallocyclophane, in which the silver ions constitute a triangle, with the ligands wrapping around the sides of the triangle.

It is noticeable that the two central phenyl rings lie nearly parallel to each other (interplanar distance $3.585\text{ \AA}$), which results in an aromatic stacking interaction.^[8] This stacking interaction seems to induce formation of the dimeric structure by the coordination of each silver ion to two oxazoline N atoms each linked to one phenyl ring. The silver ions are almost tetrahedrally coordinated by two oxazoline N atoms, CH_3CN , and NO_3^- because of a favorable stacking interaction (av N–Ag–N bond angle 133.68°). The helical chirality of $[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}]^{3+}$ is determined by the configuration of the methyloxazoline moiety of the ligands.

To investigate the origin of the helical chirality in the complex, a model structure of the complex with the *R* ligand,

$(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(R)}]^{3+}$, was compared with the X-ray structure of $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}]^{3+}$ (Figure 2).^[9] Methyl substituents on the oxazoline rings are away from the coordinating Ag^I ions between the two aromatic planes in the crystal structure of $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}]^{3+}$. The average distance between the me-

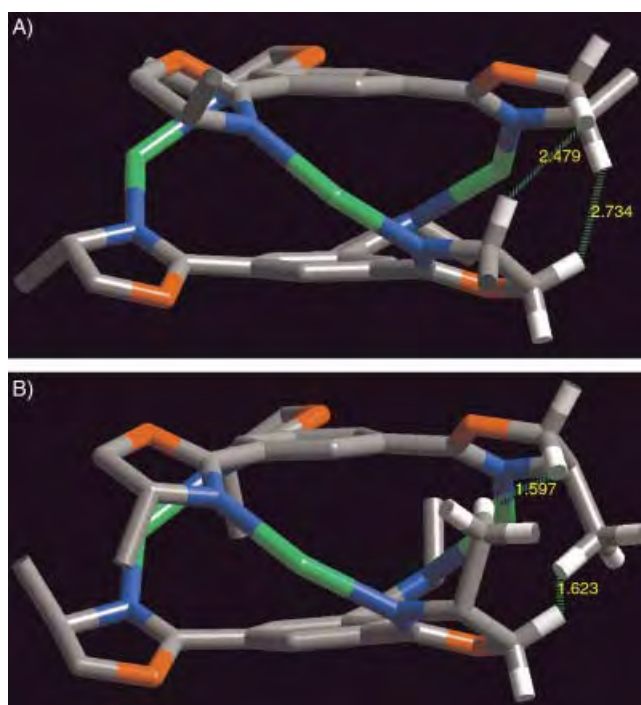


Figure 2. A) Crystal structure of $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}]^{3+}$ and B) model structure of $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(R)}]^{3+}$. All hydrogen atoms except those at interacting sites are omitted for clarity. Atom color code: C (gray), O (red), N (blue), Ag (green), H (white). Both views were generated with the Cerius2 program.

thine hydrogen of the upper oxazoline ring and the methylene hydrogen of the lower oxazoline ring in $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}]^{3+}$ is $2.6\text{ \AA}$ —enough to relax the steric repulsions in the $\pi\text{-}\pi$ stack of the crystal structure. In contrast the average distance between the methylene hydrogen of the upper oxazoline and the methyl hydrogen of the lower oxazoline ring in the model structure $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(R)}]^{3+}$ is $1.6\text{ \AA}$ —far too short for the structure to exist. The resulting van der Waals repulsions at six points prohibit the formation of the complex $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(R)}]^{3+}$, instead causing the exclusive formation of $(P)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(R)}]^{3+}$ with different helicity.

In addition to the completely stereospecific induction of helicity in the dimeric superstructure, the chirality recognition between ligands within the supramolecular helical box is of interest. Two approaches to ligand recognition are possible: ligand self- and hetero-recognition. An equimolar mixture of $\text{L}^{*\text{Me}(S)}$ and $\text{L}^{*\text{Me}(R)}$ in the presence of three equivalents of AgNO_3 was tested because one enantiopure ligand could specifically perceive its enantiomer to generate a *meso* complex, $[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}\text{L}^{*\text{Me}(R)}]^{3+}$ (hetero-recognition), and/or each enantiomeric ligand could selectively recognize itself to give the homochiral complexes $(M)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}]^{3+}$ and $(P)\text{-}[\text{Ag}_3\text{L}_2^{*\text{Me}(S)}]^{3+}$ (self-recognition). A mixture of $\text{L}^{*\text{Me}(S)}$, $\text{L}^{*\text{Me}(R)}$, and AgNO_3 in a 1:1:3 ratio generated a highly symmetric

single set of ^1H NMR resonances, which suggests that either exclusively self-recognition or exclusively hetero-recognition between the chiral ligands takes place. However, it is more likely that the *R* form of the ligand in the dimer recognizes the *R* form and that the *S* form recognizes the *S* form stereospecifically because of the triple steric repulsions between the methylene hydrogens of the upper oxazoline, $\text{L}^{*\text{Me}(\text{S})}$, and the methyl hydrogens of the lower oxazoline, $\text{L}^{*\text{Me}(\text{R})}$ of mesocate, $[\text{Ag}_3\text{L}^{*\text{Me}(\text{S})}\text{L}^{*\text{Me}(\text{R})}]^{3+}$ (vide supra). This high homoleptic diastereoselectivity was also observed in $[\text{Ag}_3\text{L}_2^{*\text{Ph}}]^{3+}$.

Crucial evidence for ligand self-recognition comes from the X-ray structure determination of the colorless crystals obtained from the racemic ligand $\text{L}^{*\text{Me}}$ with three equivalents of Ag^{I} ions. A racemic mixture of the homochiral complexes (*M*)- $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}(\text{CH}_3\text{CN})_2(\text{NO}_3)_3]$ and (*P*)- $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{R})}(\text{CH}_3\text{CN})_2(\text{NO}_3)_3]$ is evident in the unit cell, similar to the structure of the pure enantiomer (*M*)- $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}(\text{CH}_3\text{CN})_3(\text{NO}_3)_3]$ except for the composition of the counteranions and solvents (Figure 3).^[10]

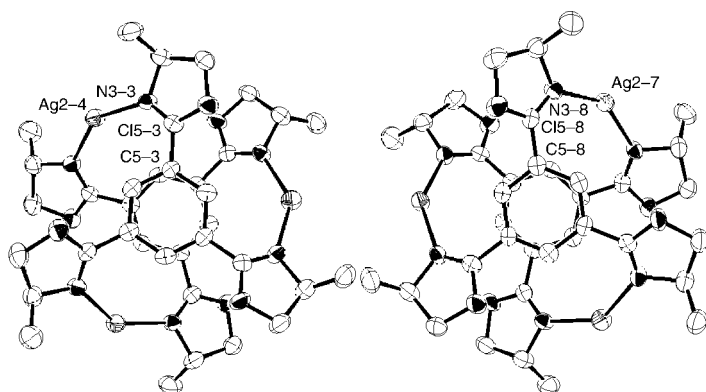


Figure 3. ORTEP representation of the racemic mixture of the homochiral complexes (*M*)- $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}(\text{CH}_3\text{CN})_2(\text{NO}_3)_3]$ (left) and (*P*)- $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{R})}(\text{CH}_3\text{CN})_2(\text{NO}_3)_3]$ (right) in the unit cell. Selected torsional angles $[\circ]$ (bond lengths $[\text{\AA}]$; bond angles $[\circ]$) for C5-3, C15-3, N3-3, Ag2-4 of the *M* form: -10.3 (1.475, 1.264, 2.222; 126.50, 132.22); for C5-8, C15-8, N3-8, Ag2-7 of the *P* form: $+10.3$ (1.475, 1.264, 2.222; 126.50, 132.22).

Next, more evidence for the self-recognition of ligand chirality comes from an equimolar mixture of $\text{L}^{*\text{Me}(\text{S})}$ and $\text{L}^{*\text{Ph}(\text{R})}$ in the presence of three equivalents of Ag^{I} ions. Only two sets of ^1H NMR resonances were observed instead of the plausible three sets of peaks, which would be expected from consideration of all the possible ligand combinations (Figure 4). However, three sets of ^1H NMR resonances appeared when $\text{L}^{*\text{Me}(\text{S})}$ and $\text{L}^{*\text{Ph}(\text{S})}$ were mixed with Ag^{I} ions due to the presence of the heterodimer, $[\text{Ag}_3\text{L}^{*\text{Me}(\text{S})}\text{L}^{*\text{Ph}(\text{S})}]^{3+}$ in addition to the homodimers $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}]^{3+}$ and $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{S})}]^{3+}$ in the ^1H NMR spectra (Figure 4). Further evidence for the heterodimerization of different ligands with the same chirality appeared from ESI mass data of a 1:1:3 mixture of $\text{L}^{*\text{Ph}(\text{S})}$, $\text{L}^{*\text{Me}(\text{S})}$, and AgNO_3 : the peaks from the heterodimer complex $[\text{Ag}_3\text{L}^{*\text{Ph}(\text{S})}\text{L}^{*\text{Me}(\text{S})}](\text{NO}_3)_3$ were observed in addition to those of the homodimers $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}](\text{NO}_3)_3$ and $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{R})}](\text{NO}_3)_3$.^[11]

This study shows a rare example of the formation of enantiomerically pure, propeller-shaped supramolecular cap-

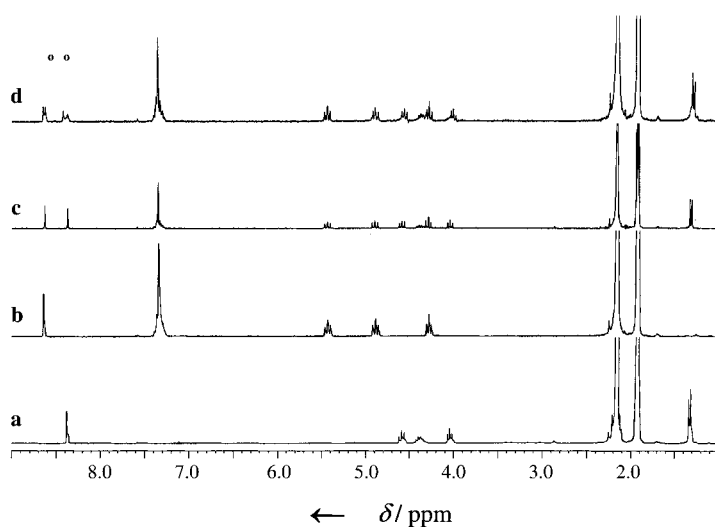


Figure 4. ^1H NMR spectra of chiral complexes (1.0 mM) in $[\text{D}_3]\text{acetonitrile}$. a) $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}](\text{NO}_3)_3$; b) $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{S})}](\text{NO}_3)_3$; c) $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}](\text{NO}_3)_3$ + $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{R})}](\text{NO}_3)_3$; d) $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}](\text{NO}_3)_3$ + $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{S})}](\text{NO}_3)_3$ + $[\text{Ag}_3\text{L}^{*\text{Ph}(\text{S})}\text{L}^{*\text{Me}(\text{S})}](\text{NO}_3)_3$ (open circles).

sules by the stereospecific recognition of enantiopure polynucleating ligands in the presence of metal ions. This is the first systematic study of the self-recognition phenomena of chiral ligands in the self-assembly of supramolecular helical boxes, as was unambiguously proven by both NMR spectroscopy and X-ray diffraction analysis. In an extension of this study modified tris(oxazoline) ligands and Ag^{I} ions could be used to generate a dimeric chiral capsule, which could function as a chiral catalyst.

Experimental Section

$[\text{Ag}_3\text{L}_2^{*\text{Me}}](\text{NO}_3)_3$: During all the reactions involving silver complexes, the reaction flask was wrapped with aluminum foil to shield the visible light. To a solution of $\text{L}^{*\text{Me}}$ (20 mg, 61 μmol) in degassed MeOH (1 mL) was added a solution of 1.5 equiv AgNO_3 in degassed water (1 mL). Stirring for 30 min resulted in a white suspension. The reaction mixture was concentrated to dryness, dissolved in a minimum amount of degassed acetonitrile, filtered through glass wool, and recrystallized in a refrigerator by slow evaporation of ether to give the desired silver complex as a colorless crystalline solid.

^1H NMR (300 MHz, $[\text{D}_3]\text{acetonitrile}$): δ = 8.48 (s, 6H of aromatic H), 4.68 (dd, $^3J(\text{H,H})$ = 9.0 Hz, 8.0 Hz, 6H of CH_2O), 4.46 (m, 6H of chiral C*H), 4.13 (dd, $^3J(\text{H,H})$ = 9.0 Hz, 8.0 Hz, 6H of CH_2O), 1.39 ppm (d, $^3J(\text{H,H})$ = 6.6 Hz, 18H of CH_3); ^{13}C NMR (75 MHz, $[\text{D}_3]\text{acetonitrile}$): δ = 163.8 (oxazoline), 130.3, 127.9 (aromatic), 75.6 (CH_2O), 63.0 (C*HN), 20.9 ppm (CH_3); MS (ESI $^+$, CH_3CN): m/z : 1101.0 ($[[\text{Ag}_3\text{L}_2^{*\text{Me}}](\text{NO}_3)_2]^+$), 930.1 ($[[\text{Ag}_3\text{L}_2^{*\text{Me}}](\text{NO}_3)]^+$), 761.2 ($[\text{AgL}_2^{*\text{Me}}]^+$), 434.1 ($[\text{AgL}^{*\text{Me}}]^+$); $[\alpha]_D^{24}$ = -50.8 for $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{S})}](\text{NO}_3)_3$, +48.5 for $[\text{Ag}_3\text{L}_2^{*\text{Me}(\text{R})}](\text{NO}_3)_3$ (c = 1.0, acetonitrile).

$[\text{Ag}_3\text{L}_2^{*\text{Ph}}](\text{BF}_4)_3$: Similar procedure as above; ^1H NMR (300 MHz, $[\text{D}_6]\text{acetone}$): δ = 8.96 (s, 6H of aromatic H), 7.44 and 7.34 (m, 30H of Ph-H), 5.69 (dd, $^3J(\text{H,H})$ = 9.2 Hz, 8.9 Hz, 6H of CH_2O), 5.30 (dd, $^3J(\text{H,H})$ = 9.2 Hz, 8.9 Hz, 6H of CH_2O), 4.54 ppm (t, $^3J(\text{H,H})$ = 8.9 Hz, 6H of chiral C*H); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{acetone}$): δ = 166.8 (oxazoline), 140.9, 131.5, 129.3, 128.8, 128.3, 127.6 (aromatic), 77.9 (CH_2O), 70.5 ppm (C*HN); $[\alpha]_D^{24}$ = -28.5 for $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{S})}](\text{BF}_4)_3$, +32.2 for $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{R})}](\text{BF}_4)_3$ (c = 1.0, dichloromethane); $\Delta\epsilon$ (λ_{max}) = $-21.4\text{ M}^{-1}\text{ cm}^{-1}$ (241 nm) of $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{S})}](\text{BF}_4)_3$ and $16.7\text{ M}^{-1}\text{ cm}^{-1}$ (240 nm) of $[\text{Ag}_3\text{L}_2^{*\text{Ph}(\text{R})}](\text{BF}_4)_3$ (c = 40 μM , CH_2Cl_2 + CH_3CN , 10:1, v/v).

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Deracemization of α -Methylbenzylamine Using an Enzyme Obtained by In Vitro Evolution**

Marina Alexeeva, Alexis Enright,
Michael J. Dawson, Mahmoud Mahmoudian, and
Nicholas J. Turner*

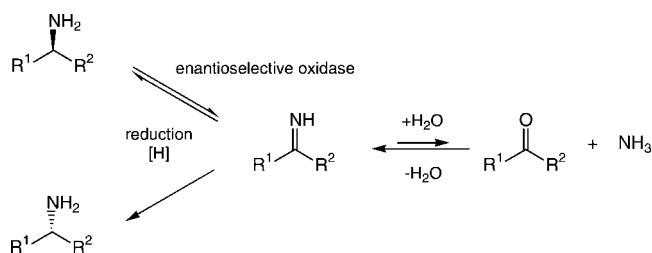
Enantiomerically pure chiral amines are valuable synthetic intermediates, particularly for the preparation of pharmaceutical compounds. Traditionally, chiral amines have been obtained by resolution-based procedures, for example, by kinetic resolution of a racemate using an enzyme^[1,2] or crystallization of a diastereomer using a chiral acid to form a salt.^[3] Increasingly, there is a desire to develop asymmetric approaches, or their equivalents, which can in principal deliver the product in 100 % yield and 100 % *ee*. For example, transaminases have been utilized for the conversion of

[*] Prof. N. J. Turner, M. Alexeeva, A. Enright
Department of Chemistry
Centre for Protein Technology, The University of Edinburgh
King's Buildings, West Mains Road, Edinburgh EH9 3JJ (UK)
Fax: (+44) 131-650-4717
E-mail: n.j.turner@ed.ac.uk
Dr. M. J. Dawson, Dr. M. Mahmoudian
GlaxoSmithKline R&D, Medicines Research Centre
Gunners Wood Road, Stevenage, Hertfordshire, SG1 2NY, (UK)

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ketones into chiral amines^[4] and chiral ruthenium catalysts have been used for the asymmetric reduction of imines.^[5] Alternative strategies are based upon the dynamic kinetic resolution of amines, for example, by using *Burkholderia plantarii* lipase^[6] or *Candida antarctica* lipase^[7] with appropriate in situ racemization protocols.

Recently we described a method for the deracemization of a range of α -amino acids that gave high yields and optical purities^[8,9] (Scheme 1, $R^2 = \text{CO}_2\text{H}$). This deracemization method involves the stereoinversion of one enantiomer to the other by repeated cycles of enzyme-catalyzed oxidation to



Scheme 1. Process for the deracemization of chiral amines by employing a cyclic sequence of enantioselective oxidation using an amine oxidase coupled with a nonselective reducing agent.

the imine, followed by nonselective reduction back to the amino acid.^[10] We demonstrated that both L- and D- α -amino acids can be prepared in this way by employing enantioselective D-^[8] and L-amino acid oxidases,^[9] respectively. A key factor that determines the efficiency of the deracemization process is the choice of reducing agent. In the early reports^[11] sodium borohydride was employed, although the instability of this reagent at pH 7 precludes its use on a practical scale. However, this problem can be overcome by switching to alternative, stable reductants such as sodium cyanoborohydride,^[8] ammonium formate with Pd/C,^[9] and also amine–borane complexes.^[9] Herein we report a significant new extension of the deracemization strategy by applying the method for the first time to the deracemization of chiral amines.^[12]

The key issue at the outset was the identification of enantioselective amine oxidases that would be suitable for the oxidation–reduction cycle. Amine oxidases have been classified into two groups, namely, Type I (Cu/TOPA-dependent) and Type II (flavin-dependent).^[13] In the catalytic cycle of the Type I enzyme the intermediate imine remains covalently bound to the protein and hence these enzymes were deemed unsuitable for our use. The Type II enzymes generate “free” imines, and although they are well known from mammalian sources,^[14] their microbial counterparts are poorly documented; indeed at the outset of this work there were no reports of enantioselective transformations. Schilling and Lerch^[15] reported the cloning and expression of a Type II monoamine oxidase from *Aspergillus niger* (MAO-N), and Sablin et al.^[16] subsequently purified the enzyme to homogeneity and carried out substrate-specificity and kinetic studies. The enzyme was reported to have high activity towards simple aliphatic amines (for example, amylamine, butylamine) but was also active, albeit at a lower rate, towards benzylamine. We decided to select α -methylbenzylamine (AMBA, Scheme 1, $R^1 = \text{Ph}$,

$R^2 = \text{Me}$) as a model system for study in view of its importance as a chiral amine.^[6] Our initial studies revealed that the *A. niger* MAO-N enzyme possessed very low, but measurable, activity towards L- α -methylbenzylamine and even slower oxidation of the D enantiomer (see below). We reasoned that such activity represented a viable starting point for improvement of both the catalytic activity and enantioselectivity using in vitro evolution methods.^[17]

The MAO-N gene from *A. niger* was obtained from Schilling and Lerch^[15] and subcloned into the *E. coli* PET16b vector. Sequencing of the gene revealed four differences in the amino acid sequence compared to the published sequence (A300V, L304V, K348M, and R450G). Two of these differences (K348M and R450G) had previously been noted by Sablin et al.^[16] However, the activity of the enzyme (see below) was found to be comparable to published data and hence we used this plasmid as the starting point for the in vitro evolution experiments. The initial priority was the development of an effective high-throughput screen for amine oxidase activity and, in this respect, we focussed on a method that would allow approximately 2000–3000 colonies per plate to be visualized. Amine oxidases are typical of all members of the oxidase family in that they evolve hydrogen peroxide as a by-product. Many of the reported assays for oxidase activity are based upon capture of the peroxide by a peroxidase in the presence of a substrate that yields a highly colored product upon oxidation. Use of 3,3'-diaminobenzidine (DAB) as the peroxidase substrate gave rise to a dark pink, insoluble product that gave both very high definition and contrast of the active colonies (Figure 1).

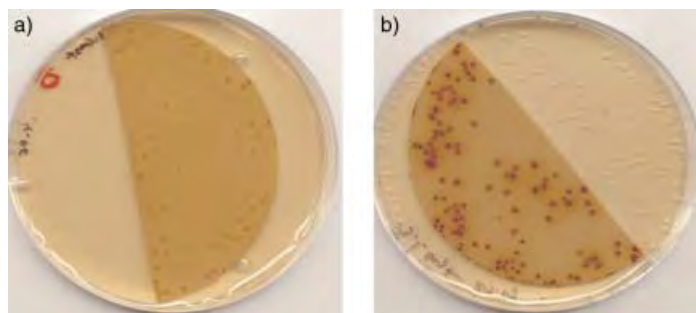


Figure 1. Colorimetric plate based screening assay for amine oxidase activity by capture of the hydrogen peroxide produced using 3,3'-diaminobenzidine with peroxidase: a) colonies with D- α -methylbenzylamine and b) identical clones with the L enantiomer.

The library of variants was generated by carrying out multiple cycles of mutagenesis using the *E. coli* XL1-Red mutator strain^[18] followed by transformation of the plasmid library into *E. coli* BL21. The library was plated out directly onto nitrocellulose filters on agar plates (ca. 3000 colonies per plate) and, following partial lysis of the cells, each plate was treated with a cocktail containing both the assay mixture (L- or D-AMBA, DAB) and also 2% agarose. The plates were incubated at 37 °C after which they were inspected for positive clones. By using this colorimetric assay we were able to identify clones that possessed higher activity towards L-AMBA than the D enantiomer (Figure 1).

The result of screening a subset (ca. 150 000 clones) of the library led to the identification of 35 clones with improved activity towards L-AMBA compared to the wild-type enzyme. Each of these clones was grown on a small scale and assayed against both L- and D-AMBA as cell-free extracts, which resulted in the best 27 clones being selected for further study. Each of these 27 clones was assayed against amylamine, L-AMBA, and D-AMBA (Figure 2).

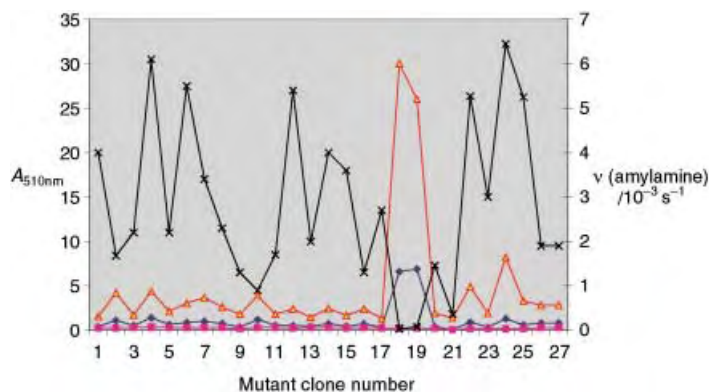


Figure 2. Activity of the best 27 clones identified from screening ca. 150 000 colonies. Blue line: L-AMBA as substrate, pink: D-AMBA, orange: ratio of activity towards L- versus D-AMBA, black: amylamine. The left-hand y axis corresponds to absorbance data (recorded at 510 nm) for L-AMBA, D-AMBA, and the ratio of L/D-AMBA. The absorbance was recorded after incubation for 96 h. The right-hand y axis corresponds to data for amylamine. Initial rates were measured.

Examination of the polyacrylamide gels showed that several of these 27 clones appeared to be “expression mutants”, as evidenced by increased levels of protein expression. However two (identical) clones were clearly superior in terms of their selectivity and activity towards L- versus D-AMBA and appeared not to have increased levels of expression of MAO-N. This clone was therefore selected for more detailed examination.

Both the wild-type and mutant MAO-N were purified by a modification of the literature procedure to give protein of approximately 10% purity. Each enzyme was then assayed against L-AMBA, D-AMBA, benzylamine, and amylamine as the substrate (Table 1).

The data revealed that the activity of the mutant towards L-AMBA ($k_{\text{cat}} = 8.0 \text{ min}^{-1}$) was 47-fold higher than the wild-type enzyme ($k_{\text{cat}} = 0.17 \text{ min}^{-1}$). Moreover, the selectivity of the mutant for the L enantiomer versus D-AMBA (ca. 100:1) had also increased (5.8-fold) relative to the wild-type enzyme

Table 1. K_m and k_{cat} values for wild-type and best mutant monoamine oxidase enzymes using L-AMBA, D-AMBA, benzylamine, and amylamine as substrates.

Substrate	Wild-type		Mutant	
	K_m [a] [mM]	k_{cat} [min^{-1}]	K_m [mM]	k_{cat} [min^{-1}]
L-AMBA	ND	0.17	0.4	8.0
D-AMBA	ND	0.01	ND[a]	0.08
benzylamine	ND	371	ND[a]	196
amylamine	ND	1000	0.4	116

[a] ND = not determined.

(ca. 17:1). Thus, the outcome of the in vitro evolution experiments had been to simultaneously improve both the enantioselectivity and catalytic activity of the enzyme. For comparison, the activity towards the best substrate for the wild-type enzyme, namely amylamine, and also benzylamine, is presented. Sequencing of the mutant revealed a single change in the amino acid sequence (Asn336Ser).

The substantial improvement in activity and selectivity of the mutant was confirmed by chiral HPLC (Chiralcel CrownPak CR+) in which complete oxidation of the L enantiomer was apparent after 24 h, whereas there was no detectable conversion of the D enantiomer. The final objective became the application of the mutant enzyme to the deracemization of DL-AMBA. A range of reducing agents was screened (sodium borohydride, catalytic transfer hydrogenation, amine–borane complexes) using 1 mM DL-AMBA as the substrate in the presence of the mutant MAO-N. This screen identified the ammonia–borane complex as the optimal reagent which gave a 77% yield of D-AMBA with an *ee* value of 93%. Greater optical purities of the product (up to 99% *ee*) could be achieved although at the expense of yield. We also carried out the stereoinversion of L- to D-AMBA (18% yield, 99% *ee*) and showed that under identical conditions there was no conversion of D- into L-AMBA.

In conclusion we have successfully achieved the “directed evolution” of an enzyme to meet the specific requirements of a novel biotransformation. The decision to select the *A. niger* MAO-N gene for in vitro evolution was based upon the observation that the wild-type MAO-N enzyme showed inherent selectivity for L- over D-AMBA (ca. 17:1), although the overall rate was very low. An interesting aspect of the present work is the identification of a mutant with enhanced enantioselectivity by using a single enantiomer substrate in the screen (L-AMBA). There is currently much effort directed towards the development of truly enantioselective screens in which racemates are used, thereby mimicking the real-life situation found in a kinetic resolution in which the two enantiomers compete for the enzyme.^[19] It may be that if one is able to screen large enough libraries of variant genes (ca. 10^6), by using inherently simpler screens, then enzymes with improved enantioselectivity can be identified in the manner described here.

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Fabrication of Carbohydrate Chips for Studying Protein–Carbohydrate Interactions**

Sungjin Park and Injae Shin*

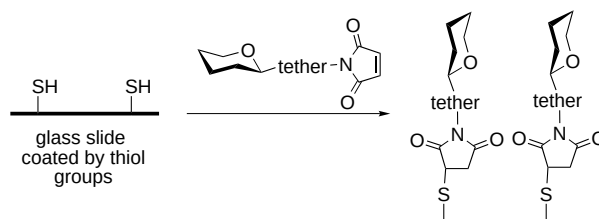
Carbohydrates play a central role in living organisms as recognition markers to enable cell adhesion, fertilization, differentiation, development, and tumor-cell metastasis through carbohydrate–protein interactions.^[1] Interestingly, it is through these biomolecular interactions that bacteria and viruses adhere to the host cells and confer pathogenic properties.^[1] Therefore, it is important to determine the molecular basis for specific protein–carbohydrate recognition events. Details of carbohydrate–protein interactions have

been investigated mainly by biophysical and biochemical approaches, including X-ray crystallography and NMR spectroscopic studies of carbohydrate–protein complexes, mutagenesis, and synthesis of nonnatural sugar analogues.^[2] Despite the established approaches to investigate carbohydrate–protein interactions, high-throughput methods have not been developed.

In the last decade, biological microchips (biochips) have been fabricated for a variety of applications. For instance, DNA chips (gene chips) are extensively used for tracking the activity of many genes at once and for studying changes in gene expression in diseased states.^[3] Additionally, protein chips have been exploited for the high-throughput study of molecular interactions and biochemical activities,^[4,5] and profiling protein expression in normal and diseased states.^[6] Ziauddin and Sabatini have developed cell microarrays for the functional analysis of gene products in parallel.^[7] Analogously, carbohydrate-based arrays may provide a new tool for the high-throughput study of carbohydrate–protein interactions.^[8]

In many cases, carbohydrate-binding proteins recognize terminal and/or penultimate saccharides. Furthermore, they exhibit a strong affinity for multivalent carbohydrates with suitable spacing and orientation (cluster effect) but bind to monovalent oligosaccharides weakly.^[9] Thus, we reasoned that carbohydrate chips that contain immobilized mono- and disaccharides with suitable distances between the carbohydrate probes on the glass surface could provide a useful tool for elucidating recognition events between carbohydrates and proteins at a molecular level.

An efficient immobilization technique of carbohydrates on the surface is essential for successful fabrication of carbohydrate chips. Recently, we prepared glycopeptides/glycoproteins by chemoselective ligation of maleimide-linked sugars to cysteine-possessing peptides/proteins.^[10,11] Herein we report how this method was applied to immobilize carbohydrates on glass microscope slides (7.5 cm × 2.5 cm). As shown in Scheme 1, maleimide-linked sugars are attached through stable thioether linkages to the slide coated with thiol groups.

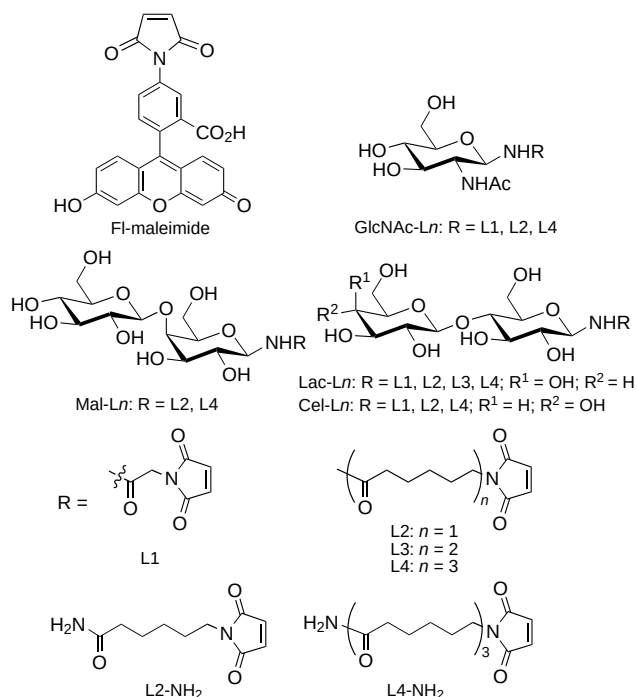


Scheme 1. Immobilization of maleimide-linked carbohydrates on thiol-derivatized slides.

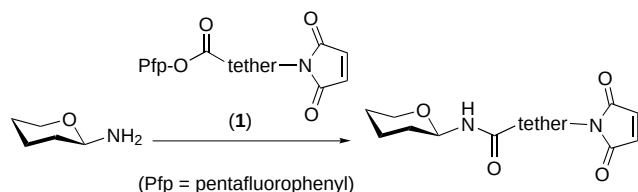
Carbohydrates were appended to linkers *L_n* of various lengths (*L*₁, *L*₂, *L*₃, and *L*₄) by coupling glycosylamines obtained from one-pot amination of carbohydrates to bifunctional cross-linkers such as **1** (Schemes 2 and 3).^[10] Furthermore, we also prepared *L*₂-NH₂ and *L*₄-NH₂, which lack the carbohydrate moiety, to examine the nonspecific binding of lectins to linkers (Scheme 2).

[*] Prof. Dr. I. Shin, S. Park
Department of Chemistry, Yonsei University
Seoul 120-749 (Korea)
Fax: (+82)2-364-7050
E-mail: injae@yonsei.ac.kr

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Scheme 2. Structure of carbohydrate probes and linkers.

Scheme 3. Glycosylamines were coupled to bifunctional cross-linkers such as **1** to produce carbohydrate probes, which were immobilized on the thiol-derivatized glass slides.

We immobilized maleimide-conjugated carbohydrate probes (GlcNAc, lactose (Lac), cellobiose (Cel), or maltose (Mal)) on glass slides derivatized with thiol groups. A high-precision pin-type microarrayer was used to microspot carbohydrate probes (100–120 μm in diameter). Carbohydrate probes were dissolved in phosphate-buffered saline (PBS)/glycerol (1:1) to avoid undesired evaporation of the nanodroplets during spotting and ligation reactions. To examine the effect of the concentration of immobilized carbohydrates on the subsequent protein binding, we printed carbohydrates at various concentrations (5.0, 1.0, 0.5, and 0.1 mM) on the slide. After the coupling reaction (5 or 10 h), the unreacted thiols on the slide were capped with *N*-ethylmaleimide (NEM; 1%) to prevent disulfide-bond formation of the surface thiol groups with cysteine residues of proteins used in the subsequent step through air oxidation. Next, we treated the slide with a solution of bovine serum albumin (BSA; 3%) in PBS buffer that contained Tween 20 (0.2%) to reduce background fluorescence caused by non-specific binding of fluorophore-labeled proteins. Subsequently, the microspotted slides were probed with fluorescein-labeled lectins (FITC-lectins) such as Concanavalin A (ConA), *Erythrina cristagalli* (EC), and *Triticum vulgaris*

(TV) in PBS buffer that contained Tween 20 (0.1%) for 1 h.^[12] After extensive washing of the lectin-treated slides with the same buffer, the fluorescence intensity of microspots on the slides was determined by using a laser scanner.

Interestingly, carbohydrate chips obtained after a coupling reaction of either 5 h or 10 h exhibited similar lectin-binding patterns. The results showed that 5 h was adequate for efficient immobilization of carbohydrate probes onto the glass slides. In contrast, washing the slides thoroughly after incubation with FITC-lectins was critical to reduce background fluorescence. For example, short washes (3×1 min) of the slide gave rise to a high background, whereas three washes for 5–10 min consistently resulted in a low background. The microspots that contained L2-NH₂ and L4-NH₂ were used as negative controls and did not show any fluorescent signal after incubation with FITC-lectins, thus demonstrating that lectins do not bind to the linkers alone (data not shown).

As shown in Figure 1A, the microspots that contained fluorescein as a positive control exhibited similar fluorescence intensity at carbohydrate concentrations greater than 2 μM ,

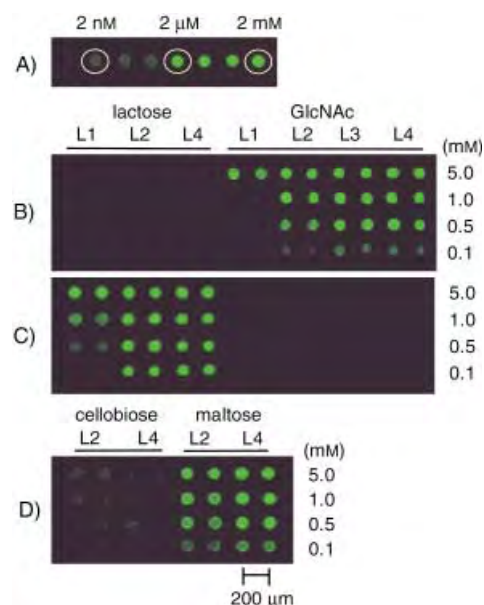


Figure 1. Lectin binding to carbohydrate microarrays. A) Fluorescence image of fluorescein (concentration of immobilized fluorescein decreases 10-fold from right to left); B) fluorescence images of lactose and GlcNAc-containing microspots probed with FITC-TV; C) lactose and GlcNAc-containing microspots probed with FITC-EC; D) cellobiose and maltose-containing microspots probed with FITC-ConA.

but were weakly visible at carbohydrate concentrations lower than 0.2 μM . To investigate the lectin-binding patterns with carbohydrate chips, the slides containing immobilized lactose (Gal β 1,4Glc) and GlcNAc with linkers of various lengths were probed with FITC-TV (a GlcNAc-binding lectin) and FITC-EC (a GalNAc/Ga-binding lectin).^[12] As expected, only the microspots that contained GlcNAc retained fluorescent signals after treatment with FITC-TV, whereas the lactose-bearing microspots specifically bound to FITC-EC (Figures 1B and C). In addition, we found that the binding affinity of TV and EC for carbohydrates on the slide depends on both

the concentration of the immobilized carbohydrate probes and on the length of linkers. The carbohydrates connected by the shortest linker (L1) bound to lectins weakly, unless their concentrations were high (5 mM). However, carbohydrates tethered to longer linkers (L2, L3, or L4) bound to the lectins with similar binding affinity at concentrations above 0.5 mM.

We then examined the difference in binding affinity and selectivity for recognition epitopes that differed in the anomeric configuration. As shown in Figure 1D, the slide with maltose (Glc α 1,4Glc) and cellobiose (Glc β 1,4Glc) was probed with FITC-ConA (an α Man/ α Glc-binding lectin).^[12] As anticipated, maltose with α -glucose at the nonreducing terminus was bound tightly to the ConA; however, cellobiose with β -glucose showed a weak affinity for the lectin. The binding pattern of ConA by the immobilization concentration and the length of linkers (L2 and L4) is similar to that of TV. Overall, we demonstrated that immobilized carbohydrate probes (0.5–5 mM) connected by long linkers (L2–L4) bind to lectins with high specificity and strong affinity. Based on these observations, immobilized GlcNAc-L4 and lactose-L4 (5 mM) were printed on a slide to produce 12 000 microspots (60 $\times$ 200) and subsequently probed with FITC-TV. As shown in Figure 2, only the microspots that contained GlcNAc were visible.

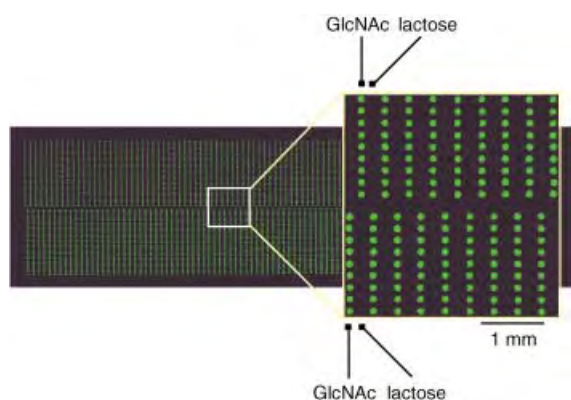


Figure 2. Carbohydrate microarrays consisting of 12 000 microspots (60 $\times$ 200).

In summary, we have developed carbohydrate chips with mono- and disaccharides that are covalently immobilized on glass slides and can be recycled without detaching carbohydrate probes from the slide. Linkers of suitable lengths and the concentration of the immobilized carbohydrate probes are important for strong binding to proteins. The specificity of protein–carbohydrate interactions on carbohydrate chips resembles that in solution. The results described herein demonstrate that carbohydrate chips are practical for evaluating high-throughput protein–carbohydrate interactions. We believe that they could be useful for high-throughput screening of inhibitors of carbohydrate-binding proteins to develop novel therapeutic agents.

Experimental Section

Microchip production: Thiol-derivatized glass slides and FITC-lectins were purchased from Biometrix Technology (Korea) and Sigma, respectively.

Samples were spotted with a MicroSys 5100 from Cartesian Technologies and the slides probed with FITC-lectins were scanned with a Scanarray 5000 from Packardbiochip.

Microspotting of carbohydrates: The carbohydrate probes (1 nL with concentrations of 5.0, 1.0, 0.5, 0.1 mM) dissolved in PBS/glycerol (1:1) from a 384-well plate were printed on a thiol-coated glass slide with a distance of 200 μ m between the centers of adjacent spots by using a MicroSys 5100 (spot size: 100–120 μ m in diameter). Subsequently, the slides were left at room temperature for 5 h and then the unreacted thiols were capped by immersing them into a solution of PBS buffer (pH 6.8) that contained *N*-ethylmaleimide (1 %) for 15 min with gentle shaking. The slides were then washed with PBS buffer (pH 6.8) that contained Tween 20 (0.1 %) for 1 h followed by doubly distilled H₂O (three times) and then dried by purging with Ar gas. Subsequently, the slides were treated with buffer that contained Tween 20 (0.2 %) and BSA (3 %) for 1 h and then rinsed with the same buffer without BSA.

Detection of protein–carbohydrate interactions: The slides were probed with FITC-lectin (1 μ g mL^{−1}) in PBS buffer that contained Tween 20 (0.1 %) for 1 h at room temperature. For FITC–ConA binding, MnCl₂ and CaCl₂ were added at with final concentrations of 1 mM. After incubation, unbound lectins were removed by gentle shaking in the same buffer (3 $\times$ 5–10 min). The slides were scanned by using a Scanarray 5000.

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Vapor-Induced Luminescence Switching in Crystals of the *Syn* Isomer of a Dinuclear (Bipyridine)platinum(II) Complex Bridged with Pyridine-2-Thiolate Ions**

Masako Kato,* Ai Omura, Asami Toshikawa, Shinobu Kishi, and Yukihiro Sugimoto

Assembled metal complexes of platinum(II) and gold(I) ions often exhibit a characteristic color and intense luminescence based on electronic metal–metal interactions. Such complexes have recently attracted particular interest as sensor materials.^[1] Herein, we report a new dinuclear platinum(II) complex, *syn*-[Pt₂(bpy)₂(pyt)₂][PF₆]₂ (bpy = 2,2'-bipyridine, pyt = pyridine-2-thiolate ion), which exhibits a remarkable change in its luminescence in the presence of organic vapors such as acetonitrile or ethanol.

Dark-red polyhedral crystals of *syn*-[Pt₂(bpy)₂(pyt)₂][PF₆]₂·CH₃CN were isolated from an acetonitrile/ethanol solution as the minor component of two geometrical isomers containing the [Pt₂(bpy)₂(pyt)₂]²⁺ ion. The *syn* isomer has a head-to-head configuration of two bridging pyridine-2-thiolate ions (Figure 1), with the platinum ions adopting different

coordination environments: Pt1 is bonded to four nitrogen atoms, whereas Pt2 has N₂S₂ coordination. This arrangement is in contrast to the *anti* isomer, which has a head-to-tail configuration (Figure 2), and is obtained as orange needlelike crystals. The Pt···Pt separations for the *syn*- and *anti* isomers are 2.923(1) and 2.997(1) Å, respectively. These separations are amongst the shortest Pt···Pt interactions observed in divalent platinum complexes.^[2] Similar dinuclear complexes have been reported by Che and co-workers.^[3]

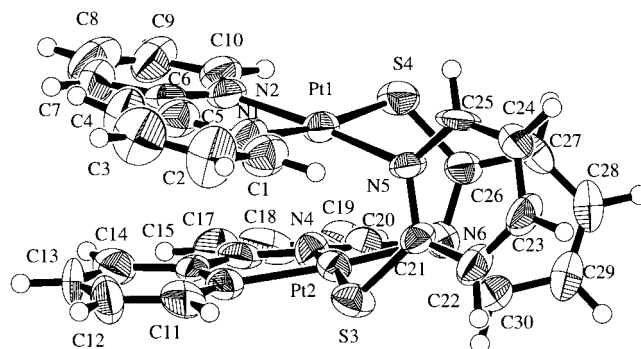


Figure 2. Single-crystal X-ray structure of the *anti* isomer.

Crystals of the *anti* isomer exhibit very intense orange luminescence ($\lambda_{\text{max}} = 603 \text{ nm}$), even at room temperature (Figure 3a). On the basis of the spectral profile and the

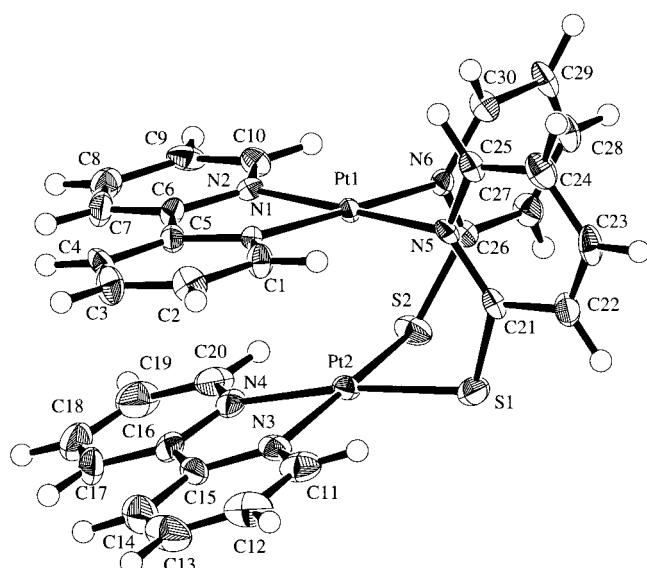


Figure 1. Single-crystal X-ray structure of the *syn* isomer.

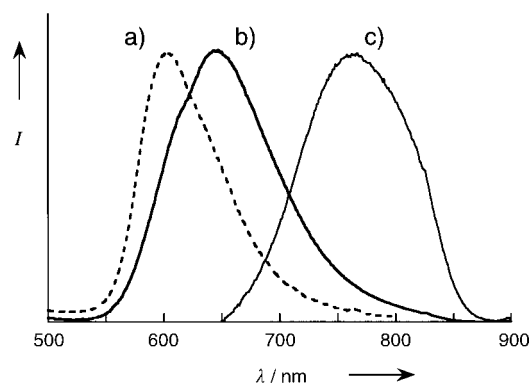


Figure 3. Luminescence spectra at room temperature for a) the *anti* isomer, b) the light-red (desolvated) form of the *syn* isomer, and c) the dark-red (solvated) form of the *syn* isomer.

[*] Dr. M. Kato, A. Omura, A. Toshikawa, S. Kishi
Division of Material Science
Graduate School of Human Culture
Nara Women's University, Nara 630-8506 (Japan)
and PRESTO, JST, Kawaguchi 332-0012 (Japan)
Fax: (+81)742-20-3393
E-mail: kato@cc.nara-wu.ac.jp

Dr. Y. Sugimoto
Arid Land Research Center
Tottori University, 1390 Hamasaka
Tottori 680-0001 (Japan)

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emission lifetime ($\tau = 240 \text{ ns}$), the luminescence can be assigned as emission from the triplet metal–metal-to-ligand charge-transfer state, which has been observed in diimineplatinum(II) complexes with short Pt···Pt separations.^[4] The emission state is thought to also include a contribution from the sulfur orbitals of the pyridine-2-thiolate ligands.^[3a,5]

Crystals of the *syn* isomer are initially dark-red in appearance, but appear to become lighter in color upon standing in air for several hours at room temperature (Figure 4). Luminescence spectroscopy of these materials shows the generation of a concomitant emission (Figure 3b and c). It is noteworthy that the luminescent light-red form reverts back to the nonemissive darker immediately upon exposure to acetonitrile or ethanol vapor, from which could be monitored

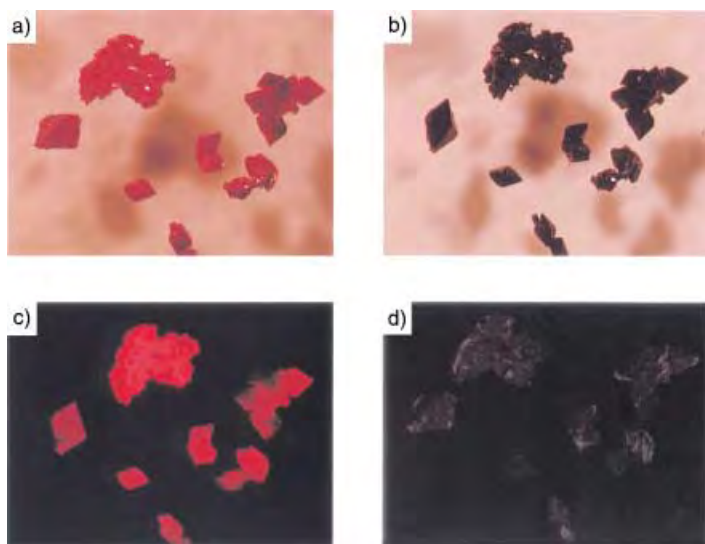


Figure 4. Photographic images of crystals of the *syn* isomer, illustrating vapo-chromic effects: a) the light-red (desolvated) form in air and b) the dark-red form after exposure of (a) to acetonitrile vapor. Luminescence images of c) the light-red and d) dark-red forms.

spectroscopically: the IR spectrum of the dark-red form possesses a band corresponding to acetonitrile at 2248 cm^{-1} which disappears after standing in air. In addition, ^1H NMR spectroscopy gives evidence that acetonitrile (or ethanol) is inherent to the complex after exposure to the vapor (see Supporting Information). Thus, crystals of the *syn* isomer exhibit vapor-induced luminescence switching. Such vapo-chromic behavior is characteristic of the *syn* isomer in the presence of particular organic vapors such as nitriles and alcohols. However, the sensitivity is reduced with increasing size and bulkiness of vapor molecules. For example, the *syn* isomer is less sensitive to isopropanol than ethanol, but exhibits no sensitivity at all to *tert*-butanol despite their similar vapor pressures (see Supporting Information). In addition, the *syn* isomer is also very sensitive to dichloromethane, while no changes are observed on exposure to either chloroform or carbon tetrachloride. Thus the observed vapo-chromism of this system is also unique from the viewpoint of sensitivity.

The luminescence spectra of the two *syn*-isomeric forms indicate that the light-red form (that is, without solvent) has an intense luminescence at a slightly longer wavelength than that of the *anti*-isomer ($\lambda_{\text{max}} = 644\text{ nm}$, $\tau = 170\text{ ns}$), while the dark-red form emits light at a wavelength almost beyond the visible region ($\lambda_{\text{max}} = 766\text{ nm}$).

To clarify the origin of such a remarkable vapor-induced change in luminescence, we investigated the crystal structure of the dark-red, acetonitrile-solvated form in detail. The molecules are arranged co-planar to the N_2S_2 coordination plane, thus forming a tetranuclear motif within the crystal structure (Figure 5 (top)). The $\text{Pt2}\cdots\text{Pt2}^*$ separation is $3.384(1)\text{ \AA}$, which is short enough to suggest that intermolecular (metal–metal) electronic interactions could occur between stacked complexes. In fact, the $\text{Pt}\cdots\text{Pt}$ separation for the emissive red form of $[\text{PtCl}_2(\text{bpy})]$ is reported to be $3.449(1)\text{ \AA}$ at room temperature.^[6] A channel can be observed within the

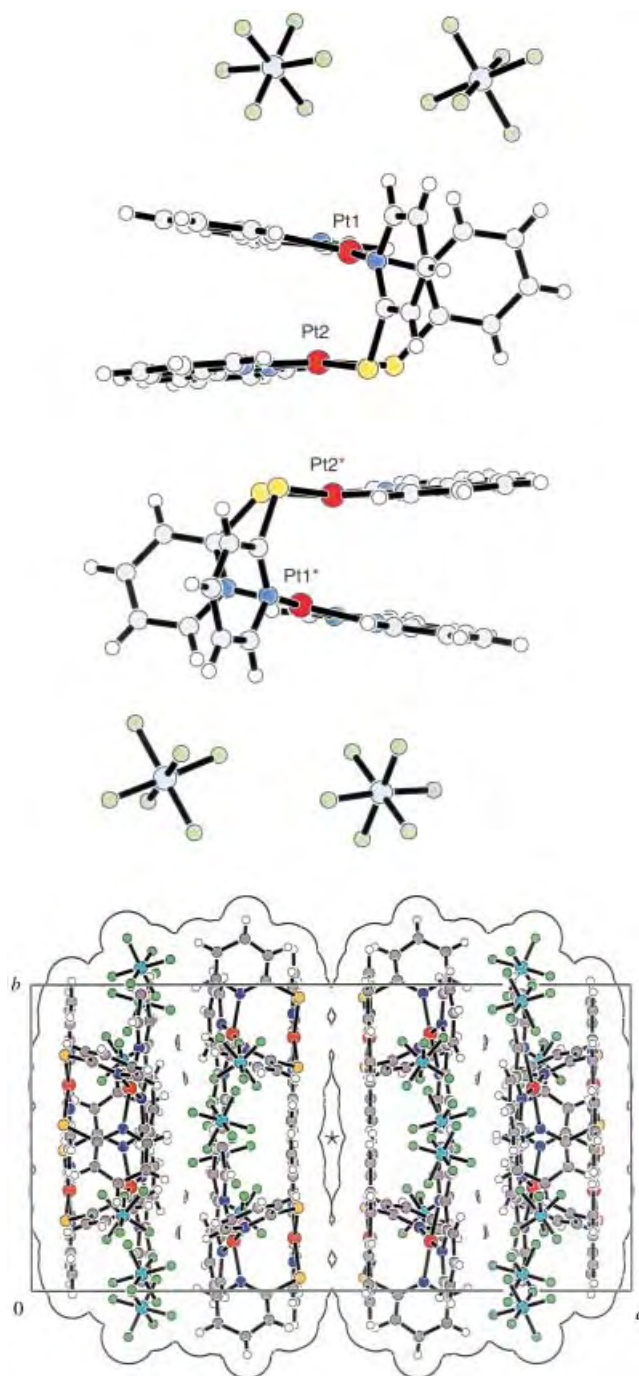


Figure 5. Top: X-ray structural diagram indicating the tetranuclear motif found in the *syn* isomer; bottom: X-ray packing diagram of the *syn* isomer at room temperature with van der Waals outline.

crystal structure, as indicated by the asterisk in Figure 5 (bottom). The structure should contain one acetonitrile molecule per complex within this channel, as suggested by NMR spectroscopy and the crystal density. In fact, the Fourier map of the X-ray analysis indicated several peaks of electron density in the channel. However, the atomic coordinates for the acetonitrile molecule could not be determined with certainty, even at -150°C , because of the level of disorder. Nevertheless, this indicates that there are no distinct interactions between the main body of the complex and the

acetonitrile solvate molecule, and also suggests that there is a pathway that allows the organic vapor to easily penetrate the crystal through the channel. Thus, vapochromism may occur as a result of changes in Pt···Pt interactions as the channel fills with organic vapor molecules. The fact that the *anti* isomer possesses no channels within its crystal structure, and does not exhibit vapochromism, lends support to this conclusion.

Experimental Section

[PtCl₂(bpy)] was prepared according to the literature method.^[7] Pyridine-2-thiol was purchased from Aldrich. A suspension of [PtCl₂(bpy)] (421 mg, 1 mmol) and pyridine-2-thiol (114 mg, 1 mmol) in water (40 mL) was heated at 70 °C for 24 h. After filtration, an excess of NH₄PF₆ was added to the dark-brown solution to yield an orange-red precipitate. Yield 98 %. The ratio of *syn* to *anti* isomers in the precipitate was approximately 1:3, based on ¹H NMR spectral data. Recrystallization from CH₃CN/EtOH gave orange needlelike crystals of the *anti* isomer. ¹H NMR (300 MHz, [D₆]DMSO): δ = 7.26 (t, 1H), 7.42 (dd, 1H), 7.57 (t, 1H), 7.68 (t, 1H), 7.99 (d, 1H), 7.83 (d, 1H), 8.21 (d, 2H), 8.26 (t, 1H), 8.33 (d, 1H), 8.78 (d, 1H), 9.02 ppm (d, 1H). Elemental analysis calcd for Pt₂C₃₀H₂₄N₆S₂P₂F₁₂: C 29.71, H 1.99, N 6.93; found: C 29.69, H 1.87, N 6.96.

Dark-red (solvated) polyhedral crystals of the *syn* isomer were obtained from the filtrate by slow evaporation. ¹H NMR (300 MHz, [D₆]DMSO, dark-red form): δ = 2.06 (CH₃CN, s, 1.5H), 7.26 (t, 1H), 7.30 (t, 1H), 7.64 (m, 2H), 7.83 (t, 1H), 7.88 (d, 1H), 8.22 (t, 1H), 8.25 (d, 1H), 8.35 (d, 1H), 8.40 (t, 1H), 8.75 (d, 1H), 8.84 ppm (d, 1H). For the light-red form, the spectrum is identical except that the resonance at 2.06 ppm is absent, which indicates that no CH₃CN was present. Elemental analysis (for the unsolvated light-red form) calcd for Pt₂C₃₀H₂₄N₆S₂P₂F₁₂: C 29.71, H 1.99, N 6.93; found: C 29.58, H 2.22, N 7.13.

Crystal data for *syn*-[Pt₂(bpy)₂(pyt)₂][PF₆]₂·CH₃CN. Pt₂C₃₂H₂₇N₇S₂P₂F₁₂, *M*_r = 1253.84, orthorhombic, space group *Pbcn* (no. 60), *a* = 26.475(7), *b* = 13.863(4), *c* = 20.454(5) Å, *V* = 7507(3) Å³, *Z* = 8, *T* = −150 °C, ρ_{calcd} = 2.22 g cm^{−3}, μ(MoKα) = 77.14 cm^{−1}. The final *R* indices: *R*(*F*) = 0.056 based on 8266 reflections (*I* > 2σ(*I*)), *wR*(*F*²) = 0.130 based on 8573 observed reflections (all data) and 487 parameters, GOF = 1.27. Lattice constants and density of the same crystal at 25 °C: *a* = 27.270(5), *b* = 13.930(2), *c* = 20.660(3) Å, *V* = 7848(2) Å³, ρ_{calcd} = 2.12 g cm^{−3}, ρ_{measured} = 2.13 g cm^{−3}. Crystal data for *anti*-[Pt₂(bpy)₂(pyt)₂][PF₆]₂. Pt₂C₃₀H₂₄N₆S₂P₂F₁₂, *M*_r = 1212.79, triclinic, space group *P* $\bar{1}$ (no. 2), *a* = 12.738(7), *b* = 20.11(1), *c* = 7.405(4) Å, α = 99.26(1), β = 100.34(2), γ = 95.50(2)°, *V* = 1826(1) Å³, *Z* = 2, *T* = 25 °C, ρ_{calcd} = 2.21 g cm^{−3}, ρ_{measured} = 2.22 g cm^{−3}, μ(MoKα) = 79.16 mm^{−1}. The final *R* indices: *R*(*F*) = 0.077 based on 5183 reflections (*I* > 2σ(*I*)), *wR*(*F*²) = 0.163 based on 7912 observed reflections (all data) and 487 parameters, GOF = 1.12. CCDC-181956 and -181957 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Ruthenium Photocatalysts Capable of Reversibly Storing up to Four Electrons in a Single Acceptor Ligand: A Step Closer to Artificial Photosynthesis**

Rama Konduri, Hongwei Ye, Frederick M. MacDonnell,* Scolastica Serroni, Sebastiano Campagna, and Krishnan Rajeshwar

Dedicated to the memory of Hongwei Ye

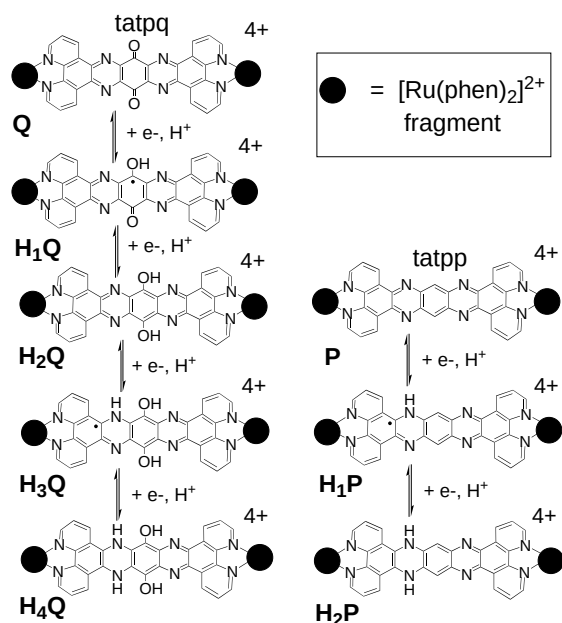
Artificial photosynthesis occupies a central focus of chemical research. Natural systems provide useful guidelines for the design of efficient artificial photosynthetic systems that function at the molecular level: complimentary functionally organized components are needed, such as 1) antennas, 2) reaction centers, and 3) light-driven multielectron catalysts.^[1] While research on synthetic analogues of components 1) and 2) is relatively well-developed,^[2,3] efficient photoactivated synthetic multiredox catalysts are very rare.^[4] Here we report the first example, to the best of our knowledge, of an artificial system which, upon visible irradiation, is capable of reversibly storing up to four electrons in a molecularly localized fashion.

Ru^{II} polypyridyl complexes have long been studied because of their favorable stability and photophysical properties, however the vast majority of these species are only capable of catalyzing one-electron processes.^[5] In the ruthenium polypyridine family, only [(bpy)₂Ru(2,3-bis(pyridyl)-benzoquinoxaline)]₂IrCl₂⁴⁺ forms a stable doubly reduced product upon irradiation,^[6] and the two electrons are stored on different acceptor ligands. Herein, we describe a photoactive ruthenium(II) dimer, [(phen)₂Ru-tatpq-Ru(phen)₂]⁴⁺ (**Q**),^[7] which reversibly stores up to four electrons in the central bridging ligand (Scheme 1).

The photoreduction process is relatively rapid and easily monitored by absorption spectroscopy. A degassed solution of

[*] Prof. Dr. F. M. MacDonnell, R. Konduri, H. Ye, Prof. Dr. K. Rajeshwar
Department of Chemistry and Biochemistry
The University of Texas at Arlington
502 Yates Street
Arlington, TX 76019 (USA)
Fax: (+1) 817-272-3808
E-mail: macdonn@uta.edu
Dr. S. Serroni, Prof. Dr. S. Campagna
Dipartimento di Chimica Inorganica, Chimica Analitica e Chimica Fisica
University of Messina, Messina (Italy)

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Scheme 1. Structures and redox reactions for **Q** and **P**? phen = 1,10-phenanthroline.

Q (16 μM) and 0.35 M triethylamine (TEA) in acetonitrile is irradiated with visible light^[8] and monitored periodically (Figure 1 A,B). We first observe appearance of a peak at 630 nm (Figure 1 A), assigned to a two-electron reduction of **Q** $\rightarrow$ **H₂Q**. Subsequently, this peak diminishes with concomitant growth of the peak at 1070 nm (Figure 1 B (blue to red)), assigned as the **H₂Q** $\rightarrow$ **H₃Q** transformation. Finally, the peak at 1070 nm diminishes with the gradual appearance of the final three peaks at 650, 725, and 790 nm assigned to the **H₃Q** $\rightarrow$ **H₄Q** reduction (also shown in Figure 1 B (red to green)). These assignments are made with a combination of data from cyclic voltammetry (CV), spectroelectrochemistry

(SEC), as described below, and by comparison with a related two-electron photocatalyst, $[(\text{phen})_2\text{Ru}-\text{tatpp}-\text{Ru}(\text{phen})_2][\text{PF}_6]_4$ (**P**; Scheme 1).

The cyclic voltammetric scan of **Q** (MeCN/1 % acetic acid) shows two reversible one-electron reductions at 0.01 V and -0.18 V versus Ag/Ag^+ quasi-reference. Controlled potential spectral scans in a spectroelectrochemical thin-layer cell^[9] at 0.0, -0.4 , and -0.8 V resulted in the absorption spectra shown in Figure 1 C. The peak at 630 nm is associated with a two-electron reduction and is consistent with formation of the hydroquinone species (**H₂Q**). Unfortunately, the redox behavior of this complex at more negative potentials is obscured by H_2 evolution and other interfering processes at the electrode surface. We note, however, that a similar spectral change (appearance of a peak at 630 nm) upon photoirradiation of the hydrocarbon 5,7,12,14-tetraazapentacene-6,13-quinone (which is closely related to tatpq in terms of the structure) was also assigned to a doubly reduced product of which the hydroquinone was one possible tautomer.^[10] The assignment of **H₂Q** as the hydroquinone follows from the discussion below.

The related tatpp complex (**P**)^[7] offers valuable insight into the photochemistry of **Q**. Irradiation of **P** under similar conditions^[11] as for **Q** results in the appearance of two photoproducts, observed sequentially. First, a band at 970 nm grows in (Figure 2 A) and finally this decreases and three new peaks at 725, 660, and 590 nm concomitantly appear (Figure 2 B). The cyclic voltammetric scan of **P** (MeCN) shows two reversible one-electron reductions at -0.18 V and -0.56 V versus Ag/Ag^+ . Spectroelectrochemistry at set potentials of 0, -0.4 , and -0.9 V (Figure 2 C,D) clearly shows that the spectral changes in Figure 2 A and 2 B are associated with two one-electron reductions of **P**^[12] As shown in Scheme 1, these reductions are assigned to the formation of a hydro-pyrazine-benzene-pyrazine radical (**H₁P**) and the dihydro-pyrazine-benzene-pyrazine (**H₂P**), respectively. The ^1H NMR

and absorption spectra of the related hydrocarbon dihydro-5,7,12,14-tetraazapentacene (**1**), which exists as the benzoid tautomer, support this structure for **H₂P** but we cannot rule out the quinoid tautomer.^[12] Importantly, the visible spectrum of **1** shows a characteristic three-peak spectral signature (at 490, 510, and 560 in dimethylacetamide (DMA)) which is remarkably similar to the spectra observed for the final (most reduced) forms of **Q** and **P**.

Remarkably, the entire process is reversible upon exposure of **H₄Q** to air as shown in Figure 1 D and, upon degassing with N_2 , the entire photocatalytic cycle can be repeated. Complex **H₂P** is similarly re-oxidized to **P** by air, however, some irreversible oxidation is observed.

Molecular orbital calculations^[7] for tatpq show two orbitals, the LUMO

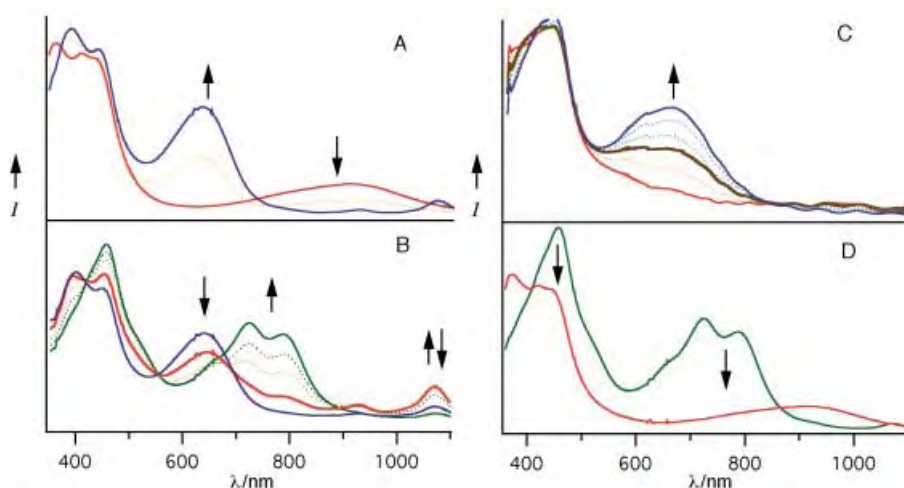


Figure 1. Evolution of the visible spectrum of **Q** (16 μM) observed during photoirradiation^[8]: A) 0 to 3 min; note: the broad band at 920 nm for **Q** is presumably a charge-transfer band between TEA and **Q** as it is not observed in the absence of TEA, B) 3 to 12 min. Conditions: MeCN, 0.25 M TEA, 23 °C. C) The spectral changes observed during controlled potential electrolysis (SEC) of **Q** (0.2 mM): 0.0 to -0.4 V (red to brown), -0.4 to -0.8 V (brown to blue). Conditions: MeCN, 2.5 % HOAc/5 % TEA, 0.1 TBAPF₆, 23 °C. D) Regeneration of **Q** from **H₄Q** by exposure to air. TBA = tetrabutylammonium.

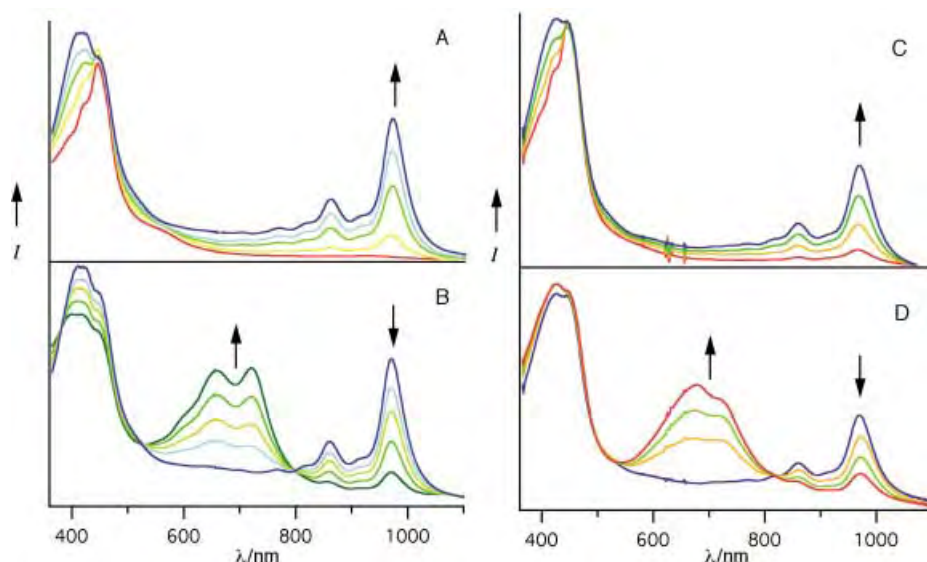


Figure 2. Evolution of the visible spectrum of **P** (50 μM) observed during photoirradiation^[8]: A) 0 to 2 min, B) 2 to 10 min. Conditions: MeCN, 0.25 M TEA, 23 °C. Spectral changes observed during controlled potential electrolysis (SEC) of **P** (0.5 mM): C) 0.0 to -0.4 V, D) -0.4 to -0.9 V Conditions: MeCN, 0.1 TBAPF₆, 23 °C.

(quinone-like) and the LUMO + 1 (centered on the pz-bz-pz unit), below the phenanthroline-like LUMO + 2 which is initially populated by a metal-to-ligand charge-transfer (MLCT) transition. Similar calculations on tatpp show one orbital, the pz-bz-pz like LUMO, below the phenanthroline-like LUMO + 1. This MO picture, along with the CV and SEC data, collectively yields a simple picture of the photoreduction processes involved in **Q** and **P**. Thus, **P** undergoes two sequential one-electron reductions (by electron transfer from the initially populated MLCT states), to fill the pz-bz-pz LUMO and is readily identified by the characteristic visible spectrum of the benzoid form of the dihydrotetraazapentacene unit.^[13] On the other hand, **Q**, with an additional lower-lying orbital, accepts two electrons to first fill the quinone-based LUMO and subsequently accepts two more electrons in the pz-bz-pz LUMO + 1. For both **Q** and **P**, TEA serves as a sacrificial reductant and proton donor by restoring the Ru^{II} chromophore(s) after each electron-transfer event.^[14] The various absorption peaks observed between 500 and 1100 nm are ligand-centered transitions associated with the multiple oxidation states of the bridge.

Interestingly, each photoinduced electron-transfer process is coupled with protonation of the reduced site, a feature which has been proposed to be essential in most natural light-activated energy-storing processes.^[15] Currently, the exact protonation states of the central bridging ligands are speculative but we believe they are essential to avoid excessive build-up of negative charge on the ligand. The presence of two Ru²⁺ ions in **P** and **Q** may be necessary to stabilize the charge-separated state (Ru^{III}-BL⁻-Ru^{II}) and is being investigated further. Indeed, the influence of internal electric fields on the stabilization of electron-transfer products has already been reported.^[16]

To the best of our knowledge, **Q** is the first synthetic species capable of a storing more than two electrons in its structure,

and the localization of these electrons in two "overlapping" MOs on the tatpq ligand suggests that they may be delivered to substrates in a concerted fashion, mimicking one essential property of natural photosynthetic systems.

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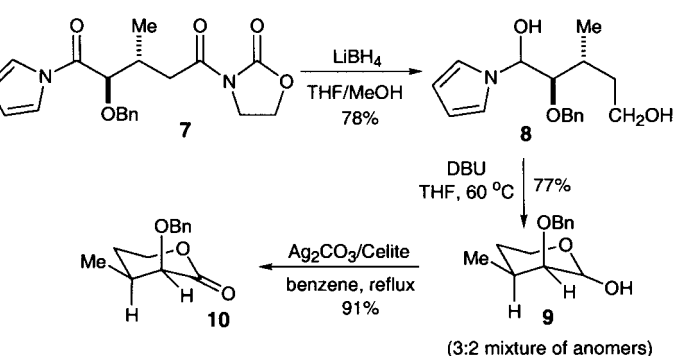
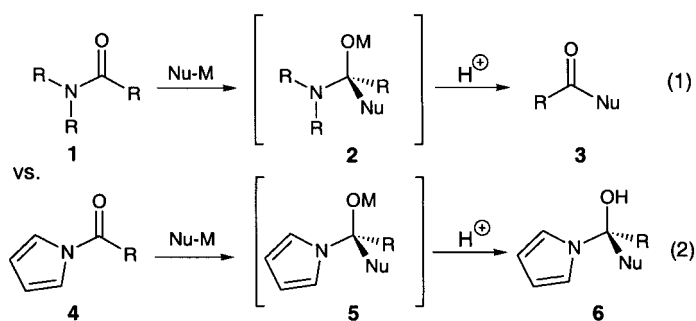
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- [11] A lower concentration of TEA (0.25 M) was required for complete conversion of **P** to **H₂P** in a similar time frame than that of **Q** to **H₂Q**.
- [12] Our assignment is in agreement with the very recently reported spectroelectrochemistry of a dinuclear Ru^{II} compound containing a bridging ligand which is related to that which is present in **P** (see: M. Staffilani, P. Belser, L. De Cola, F. Hartl, *Eur. J. Inorg. Chem.* **2002**, 335).
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Remarkably Stable Tetrahedral Intermediates: Carbinols from Nucleophilic Additions to *N*-Acylpyrroles**

David A. Evans,* George Borg, and Karl A. Scheidt

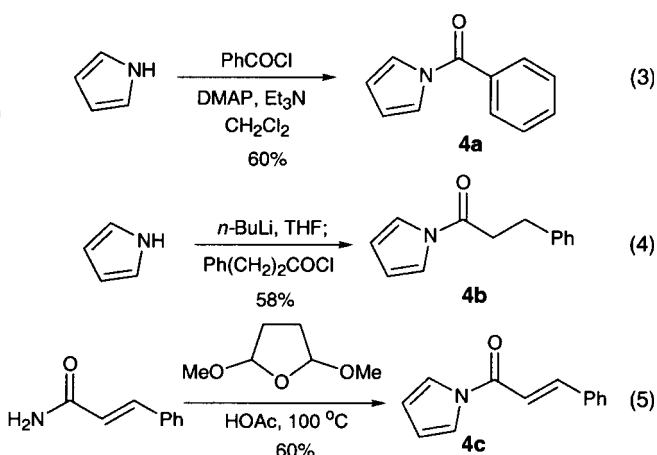
Tetrahedral intermediates resulting from the addition of nucleophiles to carboxylic acid derivatives are important, short-lived species in acyl-transfer reactions.^[1] As a result of their transient nature, the utility of these compounds in organic chemistry remains limited. The isolation of tetrahedral intermediates could provide insight into the acyl-transfer process as well as useful compounds for organic synthesis. While the adducts formed by the addition of organometallic reagents to *N*-methoxy-*N*-methylamides^[2] and tertiary amides^[3] are relatively stable as their corresponding metal alkoxides (**2**),^[4] their protonated counterparts rapidly decompose to the derived carbonyl derivative **3** [Eq. (1)].^[5] Herein, we report a study of the stability and synthetic utility of the exceptionally stable tetrahedral intermediates **5** and **6** resulting from the addition of nucleophiles to *N*-acylpyrroles **4** [Eq. (2)].



Scheme 1. Isolation of pyrrolyl carbinol **8** (see reference [10] for abbreviations), and subsequent reaction to give **10**.

presence of DBU the lactol **9** was obtained and characterized as the lactone **10**. We felt that the high stability of these tetrahedral intermediates, as well as their potential synthetic utility as masked aldehyde or ketone equivalents, warranted further investigation.

Several methods were used to prepare *N*-acylpyrroles for this study. Aryl and alkyl *N*-acylpyrroles were synthesized by the acylation of pyrrole with acid chlorides (Scheme 2, Eqs. (3) and (4)).^[11,12] *N*-Cinnamoylpyrrole (**4c**) was prepared by the condensation of cinnamamide with 2,5-dimethoxy-tetrahydrofuran in acetic acid [Eq. (5)].^[13]



Scheme 2. Synthesis of *N*-acylpyrroles.

A few examples documenting the isolation of tetrahedral intermediates from nucleophilic additions to *N*-acylpyrroles have been reported.^[6] In an early report, Brandange and co-workers demonstrated that the adducts derived from lithium enolate additions to *N*-acylpyrroles could be protonated to afford isolable "pyrrolyl carbinols".^[6d,e] In a later study, Fukuyama and co-workers reported the isolation of several tetrahedral intermediates from the reduction of indolylamides with DIBAL-H.^[7,10]

Our own interest in the chemistry of *N*-acylpyrroles began with the initial observation that the LiBH₄ reduction of compound **7**,^[8] prepared from our previously reported Cu^{II}-catalyzed Mukaiyama–Michael reaction,^[9] afforded the carbinol **8** in 78% yield (Scheme 1). When **8** was heated in the

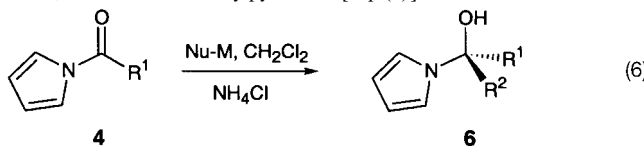
We began our study by investigating the scope of organometallic additions to *N*-acylpyrroles (Table 1, Eq. (6)). Carbinol stability was found to be quite general, as aromatic (**4a**), alkyl (**4b**), and α,β -unsaturated (**4c**) *N*-acylpyrroles all afforded stable adducts **6a–g** after aqueous workup. Moreover, all the pyrrolyl carbinols could be purified by flash column chromatography. Grignard reagents were found to be competent nucleophiles. For example, the addition of MeMgCl and PhMgBr to **4a** and **4b** at –48 °C afforded the tertiary carbinols **6b,c** and **6e,f**, respectively, in good yields (76 to 86%). The reduction of *N*-acylpyrroles **4a** and **4b** with LiBH₄ afforded the secondary carbinols **6a** and **6d**, respectively, in high yields (94–95%). The facile reduction with LiBH₄ highlights the enhanced electrophilicity of these carbonyl derivatives, as LiBH₄ normally does not react with

[*] Prof. D. A. Evans, G. Borg, Dr. K. A. Scheidt
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-1460
E-mail: evans@chemistry.harvard.edu

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

Table 1. 1,2-Additions to *N*-acylpyrroles **4** [Eq. (6)].



Entry	4	R ¹	Nu-M	R ²	T [°C]	t [h]	Product	Yield [%]
1	4a	Ph	LiBH ₄ ^[a]	H	0	1	6a	95
2	4a	Ph	MeMgCl	Me	-48	10	6b	81
3	4a	Ph	PhMgBr	Ph	-48	6	6c	80
4	4b	CH ₂ CH ₂ Ph	LiBH ₄ ^[a]	H	0	3	6d	94
5	4b	CH ₂ CH ₂ Ph	MeMgCl	Me	-48	8	6e	76
6	4b	CH ₂ CH ₂ Ph	PhMgBr	Ph	-48	4	6f	86
7	4c	(<i>E</i>)-CH=CHPh	DIBAL-H	H	-78	2	6g	86

[a] Et₂O as solvent.

tertiary aliphatic amides.^[14] Although the LiBH₄ reduction of *N*-cinnamoylpyrrole (**4c**) afforded a mixture of products, reduction with DIBAL-H afforded carbinol **6g** in 86 % yield (Table 1, entry 7).^[15]

These results illustrate the reactivity conferred by the pyrrole ring, which provides activation for nucleophilic addition yet is deactivated as a leaving group. The ketone-like reactivity of *N*-acylpyrroles may be attributed to nitrogen lone pair delocalization in the aromatic system reducing donation into the carbonyl moiety.^[16] The stability of the protonated adducts may also be attributed to pyrrole aromaticity, as the lack of an accessible lone pair prevents nitrogen protonation and ensuing decomposition to the carbonyl derivative.

The structure of **6b** was confirmed by X-ray crystallography (Figure 1).^[17,18] Interestingly, the C6–N1 bond length of 1.478 Å is longer than previously reported C_{sp}³–N_{pyrrole} bond lengths, which range from 1.412 to 1.458 Å.^[19] Conversely, the C6–O1 bond length of 1.411 Å is shorter than the average C_{sp}³–OH bond length of 1.432 Å.^[20] The C6–C5 bond length is 1.522 Å, shorter than the average C_{sp}³–C_{sp}³ bond length of 1.530 Å. The C6–C7 bond length is 1.527 Å, longer than the average C_{sp}³–C_{aryl} bond length of 1.513 Å.^[20] The elongated C6–N1 bond and the shortened C6–O1 bond are consistent with an anomeric effect resulting from the interaction of the oxygen lone pairs with the C–N σ* orbital.^[21]

The stability of pyrrolyl carbinols **6** encouraged us to investigate additions to 1,1'-carbonyldipyrrole (**11**)

[Eq. (7)].^[22] Although the bis(pyrrolyl) carbinols **12** resulting from the addition of PhMgBr and MeMgCl to **11** could be isolated and characterized, they were found to be considerably less stable than the corresponding pyrrolyl carbinols **6**. In addition, the quality of the Grignard reagent significantly affected the outcome of the addition. New or freshly prepared Grignard reagent afforded intermediate **12** as the major product, while older Grignard reagent provided mainly the *N*-acylpyrrole **4** resulting from decomposition of **12**.

The instability of carbinols **12** prompted us to examine the preparation of *N*-acylpyrroles directly from **11**. The addition of organometallic reagents to **11** followed by brief treatment of the unpurified material with 5 mol % DBU afforded *N*-acylpyrroles **4a** and **4e–h** in moderate to good yields (55 to

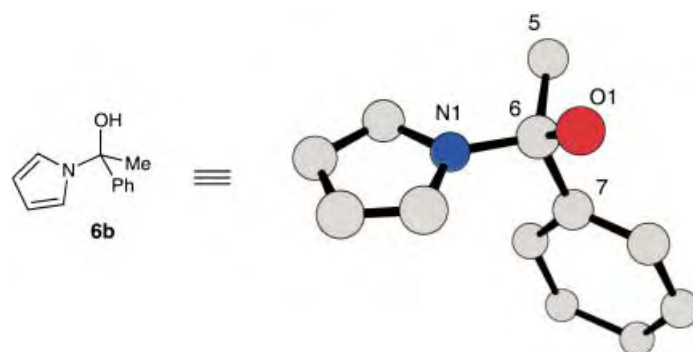
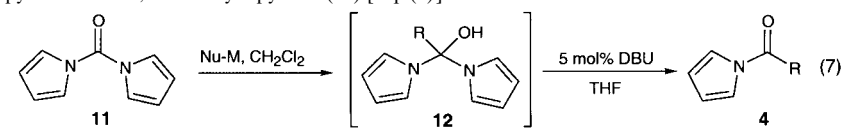


Figure 1. Structure of **6b**. Selected bond lengths [Å] and angles [°]: C6–N1 1.478, C6–O1 1.411, C6–C5 1.522, C6–C7 1.527; N1–C6–O1 108.2, N1–C6–C5 109.2, N1–C6–C7 110.4, C5–C6–C7 110.7.

87 %; Table 2, Eq. (7)). Notably, this procedure provided access to *trans*-*N*-crotonylpyrrole (**4f**), which could not be prepared by using the previously described methods (see above).

Selected experiments were performed to probe the stability of **6**. Carbinol **6c** was found to be stable for extended periods (> 10 h) under mildly acidic (PPTS, 2:1 THF/H₂O) and mildly basic conditions (pyridine, Et₃N) at ambient temperatures, but quickly decomposed to pyrrole and benzophenone when treated with a catalytic amount of DBU in THF. The conversion of **6a–c** to their derived carbonyl compounds was monitored by in situ IR spectroscopy. Following addition

Table 2. Synthesis of *N*-acylpyrroles from 1,1'-carbonyldipyrrole (**11**) [Eq. (7)].



Entry	Nu-M	T [°C]	t [h]	Carbinol	Yield [%]	<i>N</i> -Acylpyrrole	Yield [%]
1	PhMgBr	-48	7	12a	77 ^[b]	4a	83
2	MeMgCl	-30	24	12b	92	4d	–
3	<i>n</i> -BuMgCl	-48	7	12c	–	4e	69
4	vinylMgBr	-78	21	12d	–	4f	58 ^[c]
5	<i>trans</i> -1-propenylLi ^[a]	-78	1.5	12e	–	4g	87 ^[c]
6		-78	0.5	12f	–	4h	55

[a] THF as solvent. [b] Yield for addition at -30 °C. [c] The *N*-acylpyrrole was obtained directly without treatment with DBU.

of DBU (0.05 equiv) to a solution of the carbinol in THF, an absorption appeared corresponding to the newly formed C=O stretching frequency of carbonyl derivatives **13a–c** [Eq. (8)]. The time-dependent increase in the carbonyl absorption was used to determine the decomposition of the carbinol as a function of time (Figure 2).^[23] The data document that steric

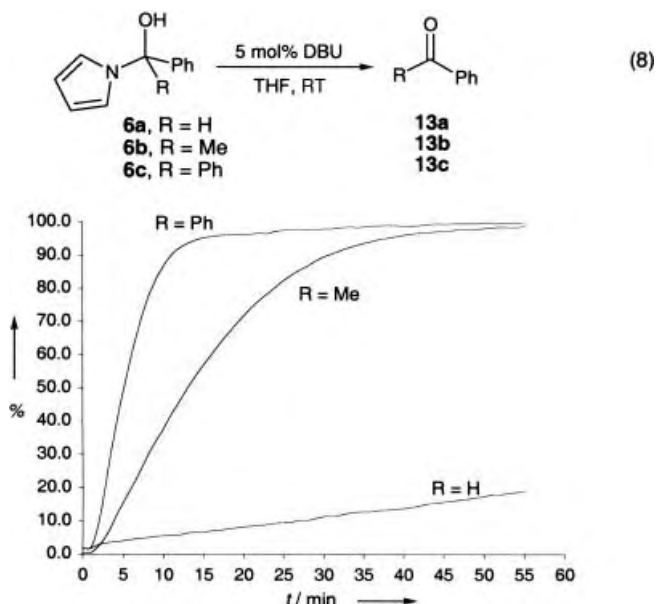


Figure 2. Conversion [%] of the carbinols **6a**, **6b**, and **6c** as a function of time.

congestion in the substrate accelerates the rate of conversion to **13**. Whereas **6a** (R = H) decomposes slowly over a 13-hour period, **6b** (R = Me) and **6c** (R = Ph) decompose completely in 40 and 15 minutes, respectively.

The effect of temperature and counterion on the stability of the deprotonated carbinols was also investigated. Three different bases (EtMgBr, *n*BuLi, NaHMDS) were used to

deprotonate **6c** (R = Ph). The rate of conversion of the resulting metal alkoxide **5c** into benzophenone was monitored at -78 , -30 , and 0°C using in situ IR spectroscopy (Figure 3, Eq. (9)). In a representative experiment, EtMgCl (1.2 equiv) was added to a solution of **6c** in THF at -78°C . The carbinol O–H stretch at 3300 cm^{-1} immediately disappeared, which indicated complete deprotonation. No new IR absorptions were detected at -78°C or upon warming to -30°C .^[24] However, upon continued warming to 0°C , a new absorption at 1664 cm^{-1} corresponding to the benzophenone carbonyl stretching frequency was observed, which signaled slow decomposition of the magnesium alkoxide (**5c**, M = Mg^{II}) at 0°C . In similar experiments, the lithium alkoxide decomposed at -30°C , and the sodium alkoxide at -78°C . Thus, the thermal stability of the alkoxide correlates well with the electronegativity of the counterion, with the stability decreasing in the order $\text{Mg}^{\text{II}} > \text{Li}^{\text{I}} > \text{Na}^{\text{I}}$.

The potential synthetic utility of pyrrolyl carbinols lies in their ability to function as masked carbonyl equivalents whose carbonyl functionality is revealed under suitably basic conditions. For example, treatment of **6f** with MeLi at 0°C resulted in deprotonation and elimination of pyrrole to afford the ketone intermediate **14**, which was then intercepted by another equivalent of MeLi to afford the tertiary alcohol **15** in 98% yield (Scheme 3, Eq. (10)). Alternatively, pyrrolyl carbinols may be protected from base by silyl ether formation. The secondary carbinol **6d** was silylated with TBSCl to afford the TBS ether **16** in 84% yield [Eq. (11)]. The tertiary carbinol **6f** was silylated with TMSOTf to afford the TMS ether **17** in 86% yield [Eq. (12)]. The silylated carbinols **16** and **17** were stable in the presence of *n*BuLi, MeMgCl, DIBAL-H, and DBU.^[25] Deprotection of silyl ether **17** with *n*Bu₄NF at -78°C afforded **14** in 83% yield.

In summary, the addition of organometallic reagents to *N*-acylpyrroles to afford stable, isolable tetrahedral intermediates is a general process. *N*-Acylpyrroles undergo additions with hydride and Grignard reagents to provide pyrrolyl

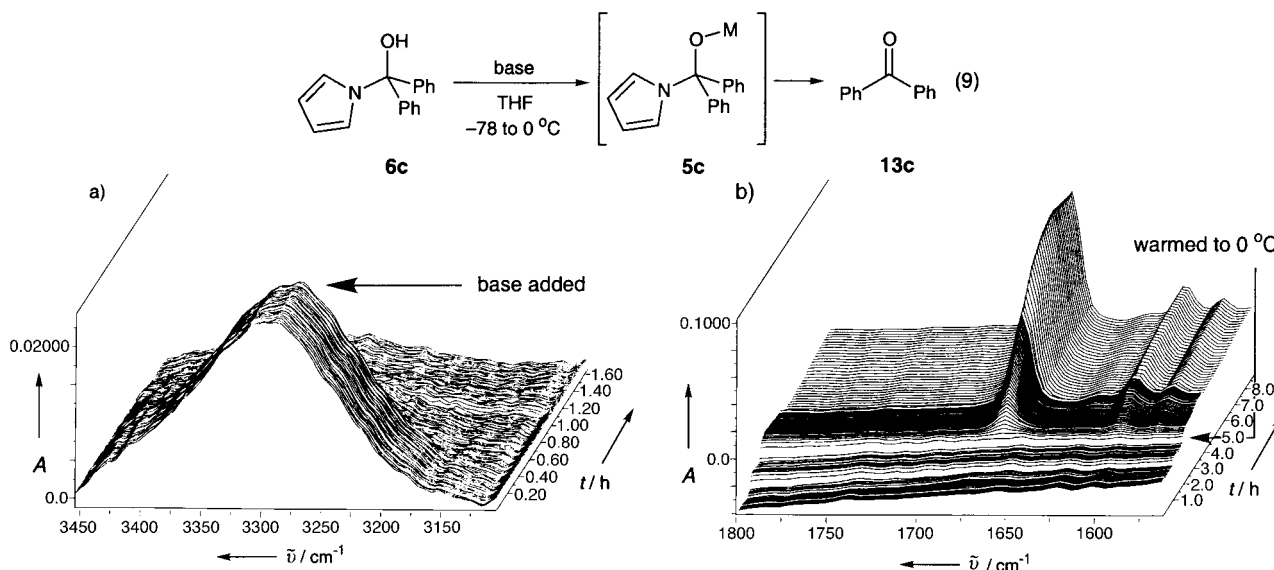
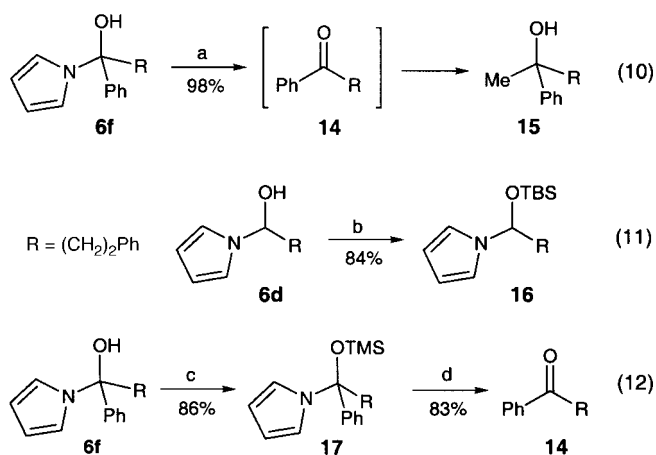


Figure 3. Monitoring the conversion of **6c** to benzophenone by in situ IR spectroscopy: a) Disappearance of the O–H stretch upon addition of EtMgCl. b) A benzophenone carbonyl absorption appears upon warming to 0°C .



Scheme 3. Transformations of carbinols **6**. a) MeLi, THF, 0°C; b) TBSCl, imidazole, CH₂Cl₂; c) TMSOTf, 2,6-lutidine, DMF; d) *n*Bu₄NF, THF, –78°C.

carbinols in good to high yields. The stability of the alkoxides generated by deprotonation of the carbinols depends on the electronegativity of the counterion in the order Mg^{II} > Li^I > Na^I. Conversion of the carbinols into the corresponding carbonyl compounds can be achieved with catalytic DBU. In addition, we have demonstrated that pyrrolyl carbinols are useful synthetic intermediates that are stable enough to undergo further synthetic transformations.

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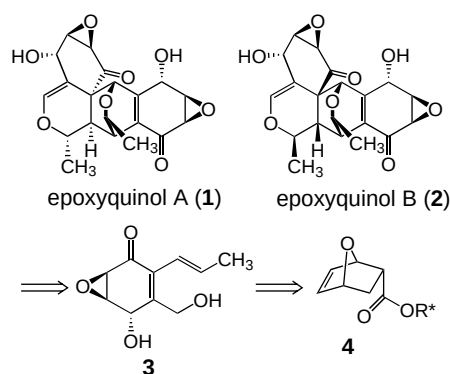
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Total Synthesis of (+)-Epoxyquinols A and B**

Mitsuru Shoji, Junichiro Yamaguchi,
Hideaki Kakeya, Hiroyuki Osada, and
Yujiro Hayashi*

Angiogenesis inhibitors are promising drugs for the treatment of angiogenesis-related diseases such as cancer.^[1] We have recently reported the isolation and structural determination of unique pentaketide dimers, epoxyquinols A (**1**)^[2] and B (**2**; Scheme 1),^[3] which show anti-angiogenic activity, but have different structural properties from the known



Scheme 1. Retrosynthesis of epoxyquinols A (**1**) and B (**2**).

angiogenesis inhibitors. To facilitate elucidation of the mechanism of action of epoxyquinols A and B, the development of a method for their total synthesis and derivatization is highly desirable. Though structurally epoxyquinols A and B have a highly functionalized and complicated heptacyclic ring system containing 12 stereocenters, biosynthetically it is proposed they are formed by an unusual oxidative dimerization of the much simpler epoxycyclohexenone **3** (Scheme 1).^[2,3] Herein we report the first total synthesis of the naturally occurring enantiomers of (+)-epoxyquinols A and B using the postulated biomimetic oxidative dimerization, along with determination of their absolute stereochemistry.

The monomer **3** of epoxyquinols A and B was the initial target. The synthesis starts from the Diels–Alder reaction between furan and a chiral dienophile,^[4] which is planned in such a way to establish the correct stereochemistry and

introduce all the carbon atoms except those in the side chain. Though there are a number of methods for the diastereoselective Diels–Alder reaction of a chiral acrylate ester with furan,^[5] few of these are synthetically useful with high *endo/exo* selectivities and diastereoselectivities. The low selectivities can be attributed to rapid *endo/exo* isomerization and/or to a retro-Diels–Alder reaction, which occurs at around -20°C .^[5c] Recently we have found that HfCl_4 is a highly efficient Lewis acid in the Diels–Alder reaction of furan, and enables the reaction to proceed at low temperature.^[6] Thus, the HfCl_4 -mediated Diels–Alder reaction of furan was applied to the chiral acrylate ester derived from Corey's chiral auxiliary ((-)-(1*R*,2*R*)-2-(naphthalene-2-sulfonyl)cyclohexanol),^[7] in the expectation of high selectivity. In fact, in the presence of HfCl_4 , the chiral acrylate ester **5** reacted with furan in toluene at low temperature (-45°C) over 48 h to give the cycloadducts **4** in good yield with moderate *endo/exo* selectivities and high diastereoselectivities (Scheme 2).

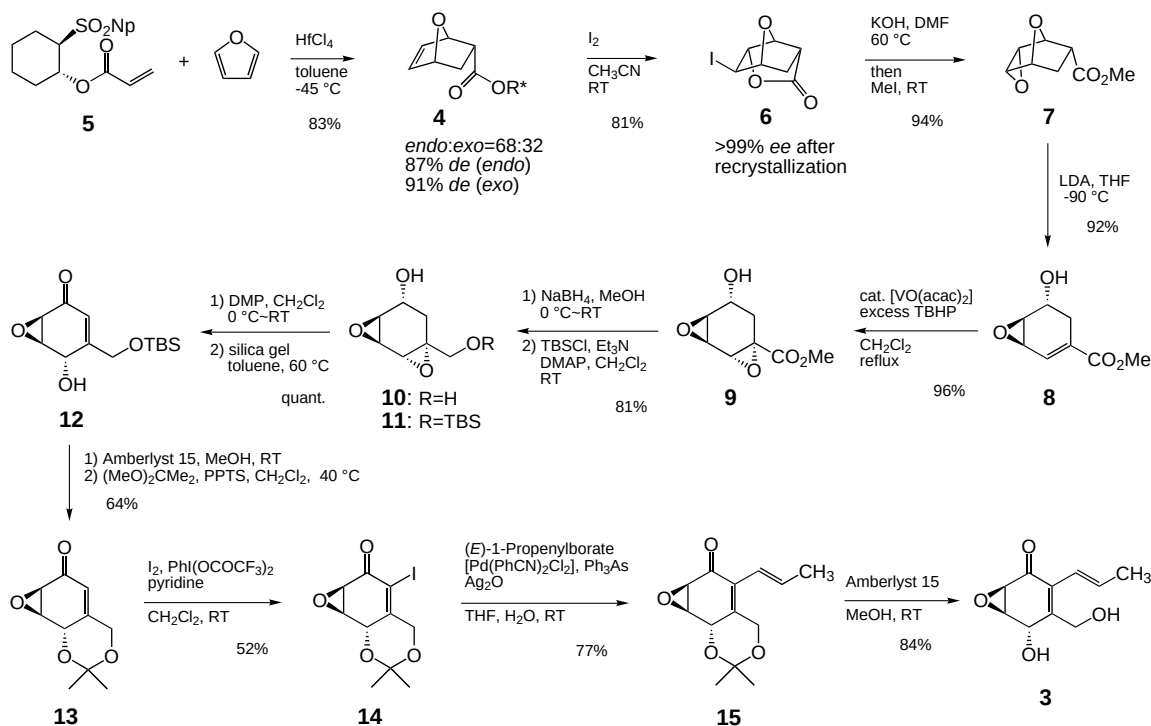
The next stage was the preparation of *endo*-epoxide **7**. As an *exo*-epoxide was obtained by the direct epoxidation reaction of **4**,^[8] a novel method was developed for the selective formation of the *endo*-epoxide via the iodolactone **6**. Though the usual two-step procedure (hydrolysis and iodolactonization) afforded iodolactone **6** in good yield, the chiral auxiliary was recovered in only 40% yield along with 55% of 1-(naphthalene-2-sulfonyl)cyclohexene. On the other hand, direct treatment of the *endo* isomer with I_2 in aqueous CH_3CN afforded iodolactone **6** in 81% yield with recovery of the chiral auxiliary in 94% yield. After recrystallization, optically pure lactone **6** was obtained, and its absolute stereochemistry was determined by comparing its optical rotation with that in the literature.^[9] Though the direct transformation of iodolactone **6** to epoxy methyl ester **7** in MeOH under a variety of basic conditions was unsuccessful, a two-step conversion (hydrolysis and esterification) worked well: Treatment of **6** with KOH in DMF at 60°C for 10 h, followed by esterification with MeI under sonication conditions for 1 h, furnished **7** in one pot, in high yield (94%).

Exposure of **7** to lithium diisopropylamide (LDA) at -90°C for 30 min led to β -elimination, affording hydroxy ester **8**. An excess of LDA should be avoided owing to Michael addition of diisopropylamine to **8**, which provides a β -amino ester as a side product. Hydroxyl-directed epoxidation of homoallylic alcohol **8** using a catalytic amount of $[\text{VO}(\text{acac})_2]$ (acac = acetylacetonate) and excess *tert*-butyl hydroperoxide (TBHP) under reflux in CH_2Cl_2 ^[10] proceeded to give diepoxide **9** as a single isomer in high yield. Although reduction of ester **9** with diisobutylaluminum hydride (DIBAL) proceeded smoothly, the yield of the diol **10** was quite low owing to its water solubility. Thus, a nonaqueous workup was examined: Reduction with NaBH_4 in MeOH at room temperature for 15 min, removal of solvent, and flash column chromatography afforded the diol **10**. The primary alcohol of the diol **10** was selectively protected with *tert*-butyldimethylsilyl chloride (TBSCl), affording **11** in 81% yield over two steps. Though the oxidation of **11** with SO_3 ·pyridine^[11] afforded an epoxyquinone,^[12] the over-oxidation product of **12**, the use of the Dess–Martin periodinane^[13] gave the desired β,γ -epoxyketone without formation of this by-product. Isomerization

[*] Prof. Dr. Y. Hayashi, Dr. M. Shoji, J. Yamaguchi
Department of Industrial Chemistry
Faculty of Engineering
Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
Fax: (+81)3-5261-4631
E-mail: hayashi@ci.kagu.sut.ac.jp

Dr. H. Kakeya, Prof. Dr. H. Osada
Antibiotics Laboratory, RIKEN
2-1 Hirosawa, Wako, Saitama 351-0198 (Japan)

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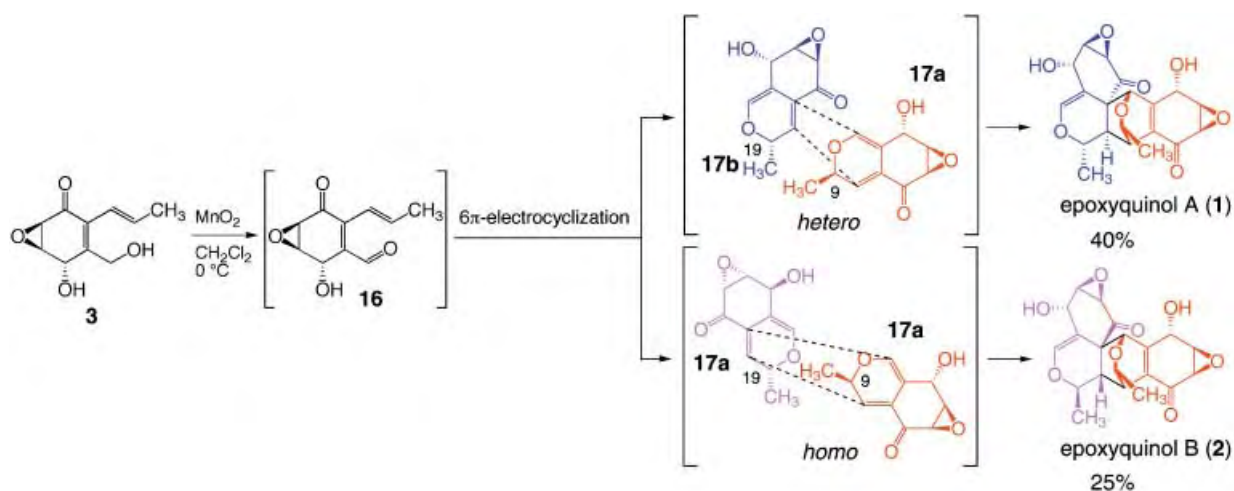
Scheme 2. Synthesis of the monomeric precursor **3** of epoxyquinols A (**1**) and B (**2**). DMAP = 4-dimethylaminopyridine; PPTS = pyridinium toluenesulfonate; for other abbreviations see text.

occurred on treatment of β,γ -epoxyketone with silica gel at 60°C in toluene for 4 h,^[14] affording α,β -unsaturated ketone **12** quantitatively over two steps.

The α -iodination of cyclohexenone **12** was problematic, and the choice of diol protecting group and iodination reagent was found to be important for the success of this reaction: None of the desired product was obtained on treatment of hydroxy ketone **12** with I_2/DMAP ^[15] or $\text{I}_2/\text{trimethylsilylazide}$ (TMSN_3)^[16] and only a low yield was observed in the reaction using $\text{I}_2/\text{PhI}(\text{OCOCF}_3)_2/\text{pyridine}$.^[17] On the other hand, the reaction of $\text{I}_2/\text{PhI}(\text{OCOCF}_3)_2/\text{pyridine}$ with the corresponding acetone **13** (prepared in 64% yield from **12** over two steps: 1) deprotection of the *tert*-butyldimethylsilyl group with

Amberlyst in MeOH, and 2) protection of the resulting 1,3-diol with 2,2-dimethoxypropane) gave the iodinated cyclohexenone **14** in moderate yield. As **14** is labile, it was immediately subjected to the Suzuki coupling reaction with *trans*-1-propenylborate^[18] under Johnson's conditions,^[19] affording dienone **15** in 77% yield. Cleavage of the acetone group under acidic conditions provided monomer **3** in 84% yield.

Next the biomimetic oxidative dimerization was examined. After several experiments, it was found that the monomer **3** could be directly oxidized without protection of the secondary hydroxy group. That is, the oxidation proceeded on treatment of epoxycyclohexenol **3** with excess MnO_2 ^[20] in CH_2Cl_2 for



Scheme 3. Biomimetic dimerization approach towards epoxyquinols A (**1**) and B (**2**).

40 min at 0 °C (Scheme 3), affording hydroxyaldehyde **16** and 2H-pyran derivatives **17a** and **17b** which would be formed by 6 π -electrocyclization reaction of the former. The dimerization reaction proceeded when the crude oxidized mixture was allowed to stand at room temperature without solvent. After 4 h, epoxyquinols A (**1**) and B (**2**) were isolated in 40 and 25 % yields, respectively. Epoxyquinol A (**1**) is a heterodimer of **17a** and **17b**, which would be generated by an *exo* intermolecular Diels–Alder reaction with the *anti* stereochemistry at the C₉ and C₁₉ methyl positions to reduce the steric hindrance at these positions.^[2] On the other hand, epoxyquinol B (**2**) is a homodimer of **17a**, which would be generated by an *endo* intermolecular Diels–Alder reaction, also with the sterically favored *anti* stereochemistry at the C₉ and C₁₉ methyl positions.^[3] In their recent elegant total synthesis of torreyanic acid^[21] and jesterone dimer (unnatural product),^[22] Porco, Jr. et al. have demonstrated the oxidative dimerization of epoxyquinones, in which only heterodimers were formed. As shown by the dimerization of **3**, not only epoxyquinones, but also epoxycyclohexenones can be oxidatively dimerized to form highly functionalized heptacyclic ring systems, in which both hetero- and homodimerizations occur.

Synthetic epoxyquinols A (**1**) and B (**2**) exhibited identical properties to those of the natural substances (¹H NMR, ¹³C NMR, IR). Comparison of the optical rotation (synthetic epoxyquinol A; [α]_D²⁵ = +60 (*c* = 0.17, MeOH), natural epoxyquinol A;^[2] [α]_D²¹ = +61.0 (*c* = 0.146, MeOH), synthetic epoxyquinol B; [α]_D²¹ = +150 (*c* = 0.060, MeOH), natural epoxyquinol B;^[3] [α]_D²¹ = +153.0 (*c* = 0.315, MeOH)) determined the absolute stereochemistry to be as shown in **1** and **2**.

In summary, the first total synthesis of epoxyquinols A (**1**) and B (**2**) has been achieved, and their absolute stereochemistry has been determined. The combination of HfCl₄ and the chiral acrylate ester of Corey's auxiliary enables the highly diastereoselective Diels–Alder reaction of furan, which established the correct stereochemistry. All 12 chiral centers of epoxyquinols A and B are controlled by the highly diastereoselective reactions in the route from the initial Diels–Alder product. A diastereoselective synthesis of *endo*-epoxide **7** via iodolactone **6**, and a biomimetic oxidative 6 π -electrocyclization, followed by Diels–Alder reaction of the nonprotected diol monomer **3** are other noteworthy features of the synthesis.

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Novel Glycodendrimers Self-Assemble to Nanoparticles which Function as Polyvalent Ligands In Vitro and In Vivo**

Gebhard Thoma,* Andreas G. Katopodis, Nicolas Voelcker, Rudolf O. Duthaler, and Markus B. Streiff

The recognition of oligosaccharides by proteins represents the basis of many biologically important events.^[1] Individual protein–carbohydrate interactions are generally weak ($K_D = 10^{-3}$ – 10^{-4} M⁻¹).^[2] To overcome this, such processes often involve polyvalent binding, which is characterized by the simultaneous contact of multiple ligands (oligosaccharides) on one biological entity to multiple receptors (proteins) on another.^[3] Polyvalent carbohydrate–protein interactions occur frequently in recognition events on cellular membranes. Collectively, they can be much stronger than corresponding monovalent interactions rendering it difficult to control them with individual small molecules.^[4] Therefore, complex macromolecules have been used as polyvalent antagonists, however, both characterization and preparation of these nonuniform entities is demanding.^[4] Here we present an alternative concept for the polyvalent presentation of ligands based on the supramolecular chemistry^[5] of small molecules that fulfil single-molecule entity criteria (Figure 1). Novel dendrons capped with carbohydrate ligands (glycodendrimers^[6]) were found to self-assemble to noncovalent nanoparticles which function as polyvalent ligands. We demonstrate that these particles—not the individual molecules—efficiently inhibit polyvalent interactions, such as IgM binding (IgM = immunoglobulin), to the α Gal-epitope^[7] (α -D-Gal-(1 $\rightarrow$ 3)- β -D-Gal-(1 $\rightarrow$ 4)-D-GlcNAc), both in vitro and in vivo. As self-assembly is dynamic, optimization of size and shape of the polyvalent ligand could occur utilizing the receptor as a template.

Dendrimer cores were prepared by a convergent “outside-in” approach^[8] based on a single building block **1a** which was obtained from methyl 3,5-diaminobenzoate and 4-(*tert*-butoxycarbonylaminomethyl)benzoic acid (Scheme 1a). Selective deprotection furnished **1b** and **1c** (first-generation dendrimer core, two end-groups). A one-pot procedure comprising coupling of **1c** (1 equiv) and **1b** (0.5 equiv) followed by methyl ester cleavage gave **2c** (second-generation dendrimer core, four end-groups).^[9] The third-generation dendrimer **3c** (eight end groups) was obtained from **2c** (1 equiv) and **1b** (0.5 equiv).^[9] Applying the same procedure repetitively gave

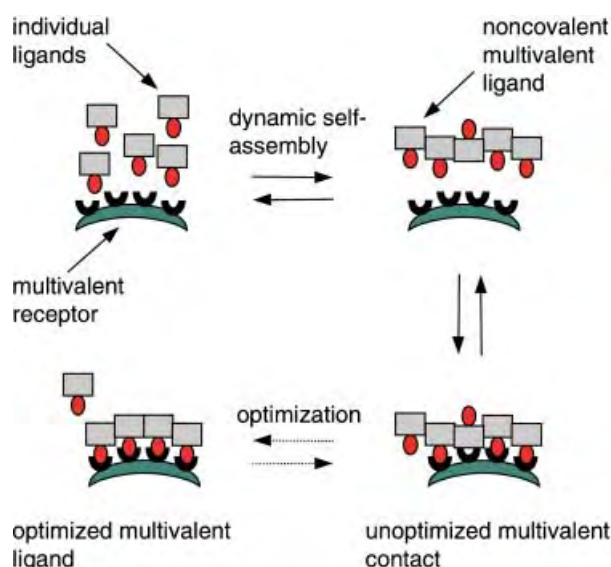


Figure 1. Individual molecules, comprised of both a ligand and a self-assembling moiety, form noncovalent nanoparticles which function as multivalent ligands. If self-assembly is a dynamic process natural polyvalent receptors could serve as templates optimizing size and shape of their own polyvalent inhibitors.

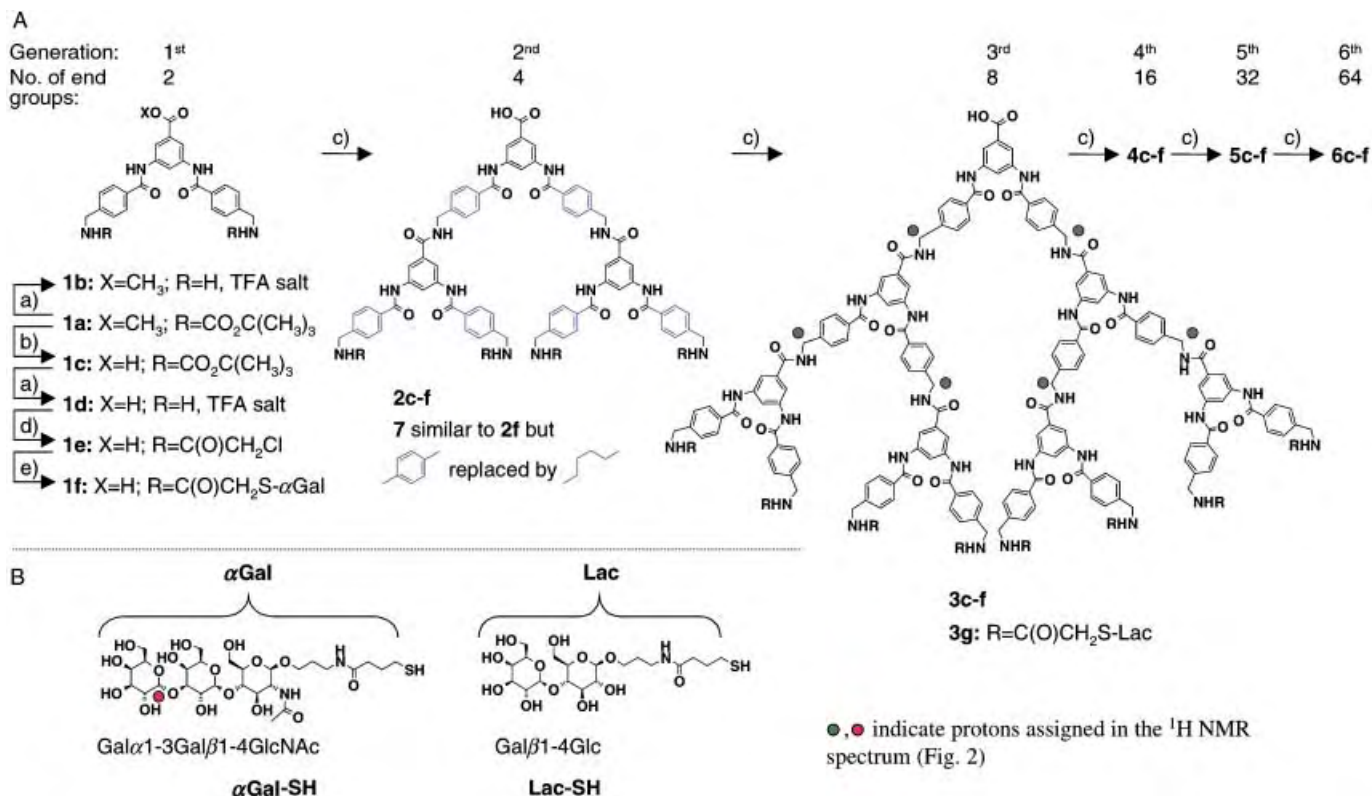
dendrimers with up to 64 end groups (**4c**, fourth generation, 16 end groups; **5c**, fifth generation, 32 end groups; **6c**, sixth generation, 64 end groups). Dendrimers **1c–6c** were deprotected ($\rightarrow$ **1d–6d**) and transformed into their chloroacetamide derivatives (**1e–6e**) to allow subsequent introduction of thiolated oligosaccharides such as α Gal-SH^[10] and Lac-SH (Figure 2b) furnishing water-soluble glycodendrimers **1f–6f** and **3g** which were purified by ultrafiltration. Compound **7**, which is similar to **2f** but contains butylene chains instead of the disubstituted aromatic rings, was also prepared (Scheme 1a). The integrity of all compounds was established by ¹H NMR spectroscopy. Accordingly, the first- to third-generation dendrimers exist as single molecules (purity > 95 %). The fourth- to sixth-generation dendrimers possibly contain minute quantities of smaller fragments. The 500 MHz ¹H NMR spectra of compound **3f** in [D₆]DMSO demonstrates the remarkable purity of these compounds (Figure 2).

The first indication that our glycodendrimers were aggregating in water came from ¹H NMR spectroscopy of **2f** in D₂O. At ambient temperature, we observed very broad signals which sharpened at elevated temperatures. The aggregation was quantified using multiangle light scattering (MALS; Table 1). The first-generation dendrimer **1f** forms small aggregates (50 kDa) whereas **2f** forms large particles of 7000 kDa (more than 1500 individual molecules per particle). Interestingly, the particle weight obtained for **3f–6f** drops (2200 to 200 kDa) with increasing mass of the individual molecule. The root-mean-square radii of the particles formed by **2f–6f** showed the same trend (for **2f**, **3f**, and **4f** 49, 34, and 12 nm, respectively; for **5f** and **6f** the radii were below the detection limit of 10 nm). Core-modified second-generation glycodendrimer **7** ($4 \times \alpha$ Gal), which is of comparable size and lipophilicity as **2f** but contains butylene chains instead of the disubstituted aromatic rings, does not form aggregates. The third-generation compounds **3g** ($8 \times$ Lac; 1900 kDa) and **3f**

[*] Dr. G. Thoma, Dr. A. G. Katopodis, Dr. R. O. Duthaler, Dr. M. B. Streiff
Novartis Pharma AG
P.O. Box, 4002 Basel (Switzerland)
Fax: (+41) 61 324 6735
E-mail: gebhard.thoma@pharma.novartis.com

Dr. N. Voelcker[†]
The Scripps Research Institute
Beckman Centre for Chemical Sciences
10550, N. Torrey Pines Rd., La Jolla, CA 92034 (USA)

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Scheme 1. A) Reaction conditions: a) TFA, Et₃SiH, H₂O (95:2.5:2.5), 3 h, RT (> 80 %); b) 1N NaOH/dioxane (1:1), 16 h, RT (82 %); c) 1) **1a** (0.5 equiv), HBTU (1.0 equiv), DMF/Pr₂NEt (4:1), 6–16 h, RT (> 75 %); 2) LiOH, H₂O (> 75 %); d) chloroacetic acid anhydride (3.0 equiv), DMF/2,6-lutidine (3:1), 3 h, RT (50–95 %); e) αGal-SH or Lac-SH (1.5 equiv per end group), DMF, DBU, 1 h, RT; B) structures of αGal-SH and Lac-SH. TFA = trifluoroacetic acid, HBTU = *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, DMF = *N,N*-dimethylformamide

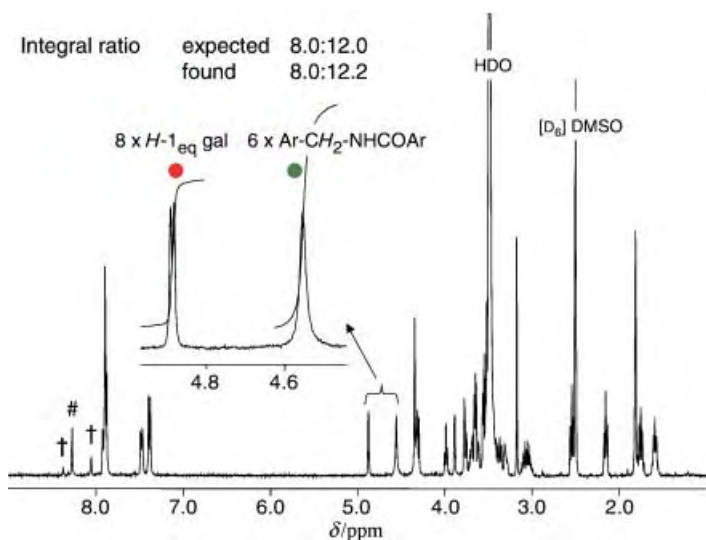


Figure 2. 500 MHz ¹H NMR spectrum of **3f** (third generation, eight end groups) recorded in [D₆]DMSO/D₂O (5:1) at 75 °C. The spectrum demonstrates the remarkable purity (> 95 %) of this compound. The indicated signals represent 8 × H-1 of the terminal α-linked galactose residue (see Scheme 1b, red) and 6 × Ar-CH₂-NHCO-Ar of the dendrimer core (see Scheme 1a, green). Their relative intensities (8.0:12.2; expected 8.0:12.0) proves the quantitative functionalization with αGal. The small signals (indicated by †) at δ = 8.05 ppm (intensity 1H) and δ = 8.38 ppm (intensity 2H) can be assigned to the protons of the terminal trisubstituted ring of the dendrimer core structure, bearing the carboxylic acid functionality. The signal at δ = 8.26 ppm (intensity 6H, indicated by #) reflects the protons between the N substituents of the six internal trisubstituted rings.

Table 1. Properties of Dendrimers.

Compound (end groups)	<i>M_r</i> ^[a] (individual molecule) [kDa]	(aggrega-IgM ^[c] te) [kDa]	Hemolysis ^[c] IC ₅₀ [μM]	IC ₅₀ [μM]
1f (2)	1.908	50 ± 5	> 10	> 100
2f (4)	4.198	7100 ± 250	0.025	0.035
3f (8)	8.779	2200 ± 70	0.010	0.010
4f (16)	17.941	1200 ± 50	0.019	0.180
5f (32)	36.264	270 ± 10	> 1	0.550
6f (64)	72.911	200 ± 10	> 1	2.240
3g (8)	7.154	1900 ± 100	> 100	n.d.
7 (4)	4.078	7 ± 1	> 100	> 100

[a] Satisfactory MALDI mass spectra were obtained for all compounds with the exception of **5f** and **6f**. Interestingly, intense fragmentation was observed for all compounds, even for the first-generation glycodendrimer **1f**. [b] All determinations of the weight-average molar mass (*M_r*) were performed by Wyatt Technology Deutschland GmbH by multi-angle light scattering (MALS) using a DAWN EOS and a Wyatt Optilab 903 refractometer; at 20 °C; concentration 0.3 mg mL⁻¹ (0.06 mg mL⁻¹ for **2f** as the signal intensity was too high at 0.3 mg mL⁻¹ because of high-molecular-weight particles); refractive index increment (dn/dc) values were between 0.18 and 0.22 mL g⁻¹. [c] Average of at least two experiments (variations within a factor of 2.5). For assay conditions see bioassays. Concentrations refer to equivalent concentration of trisaccharide but not to the concentration of oligovalent glycodendrimer.

(8 × αGal; 2200 kDa), with identical backbones but different carbohydrate end groups, form aggregates of very similar size. Thus, the particle weight strongly depends on the dendrimer core structure but less on the size of the hydrophilic end groups. Intermolecular hydrogen bonds seem not to be significantly involved in self-assembly since particle weights

are not reduced by the H-bond-disrupting reagent guanidinium hydrochloride (1.5 M), as determined by light scattering. Most probably, the highly aromatic core induces aggregation as a result of π stacking and/or rigidity. The core of **1f** seems to be too small for efficient core–core interactions whereas the second-generation core of **2f** is optimal for self-assembly. The decreasing particle weight obtained for higher generation glycodendrimers (**3f–6f**) could be explained by the increasing number of large end groups per individual molecule inducing a more globular shape. As a consequence, the core is more efficiently shielded by carbohydrates, which renders intermolecular core–core contact more difficult. The particle weight does not substantially depend on the concentration, as shown for dendrimer **2f** (7000 kDa at 0.06 mg mL⁻¹, 6000 kDa at 0.03 mg mL⁻¹, 3700 kDa at 0.01 mg mL⁻¹), but is significantly affected by temperature (Table 2); it drops ten fold with an increase in temperature to 70 °C, but increases as the temper-

Table 2. Effect of temperature on the weight of nanoparticles formed by **2f**.

<i>T</i>	Heating period ^[a] <i>M_r</i> [kDa]	Cooling period ^[b] <i>M_r</i> [kDa]
30 °C	5000 ± 500	4600 ± 500
50 °C	2200 ± 300	2600 ± 500
70 °C	550 ± 100	350 ± 50

[a] A cold solution of **2f** (0.03 mg mL⁻¹) was slowly heated to the indicated temperature and after 15 min equilibration time was injected into a thermostat-controlled cell. [b] A hot solution of **2f** (0.03 mg mL⁻¹) was slowly cooled down to the indicated temperature and after 15 min equilibration time was injected into a thermostat-controlled cell.

ature is lowered. Comparable particle weights were determined at identical temperatures for both the heating and the cooling period which indicates there is a dynamic self-assembly process which rapidly reaches thermodynamic equilibrium. Both the shape and size of the formed nanoparticles was investigated by atomic force microscopy (AFM). Aqueous solutions of **2f–6f** were applied to mica surfaces and the solvent evaporated. The observed particles have a disklike morphology (Figure 3), and their average diameters decrease with increasing mass of the individual molecules (61 nm, **2f**; 13 nm, **6f**), thus showing the same trend as the molecular weights in solution. The size distribution for the individual generations was found to be remarkably homogenous (within a factor of two).

To exemplify the use of our glycodendrimers as noncovalent multivalent ligands we selected the inhibition of decavalent IgMs directed against the α Gal xenoantigen.^[7] This epitope is expressed on the cells of mammals, with the exception of humans and Old World monkeys. Anti- α Gal antibodies are the most abundant natural human antibodies and cause the hyperacute rejection of pig organs transplanted into primates. They include IgG, IgM, and IgA classes with the IgM class being dominant in the immediate, complement-dependent, hyperacute destruction of the xenograft. Currently there are no pharmacological agents that affect the production of this class of antibodies and research efforts have focused on blocking or removing anti- α Gal antibodies prior to pig-to-primate xenotransplantation. Recently, it has

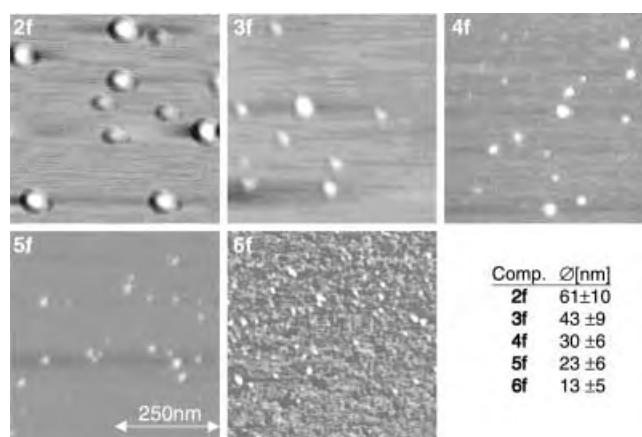


Figure 3. AFM images of particles formed by compounds **2f–6f**. The size of the particles decreases with increasing molecular weight of the individual glycodendrimer. Aqueous solutions (10 μ L; 2 μ g mL⁻¹ for **2f–5f**, 0.2 μ g mL⁻¹ for **6f**) were spotted on freshly cleaved mica. The solvent was allowed to evaporate for at least 120 min. A Nanoscope III microscope (Digital Instruments) was used to generate the images. The microscope was operated in tapping mode in air with Olympus etched silicon probes (cantilever length 120 μ m, tip height 10 μ m). The particles exhibit disklike morphologies. Their flatness (1–5 nm) might be caused by interactions with the mica surface. The diameters ($\varnothing$) were determined by measuring over 30 randomly selected particles.

been demonstrated that polymers providing multiple copies of the α Gal epitope can inhibit IgM binding in vitro.^[10,11] To assess our compounds as polyvalent IgM ligands we employed two in vitro assays in which the inhibition of both the anti- α Gal IgM binding to the xenoantigen^[12a] and the α Gal-mediated lysis of pig erythrocytes^[13a] were measured (Table 1). In both assays monomeric α Gal was inactive at 100 μ M, which is in agreement with the finding that individual carbohydrate–protein interactions are often weak.^[2] Divalent first-generation dendrimer **1f** which forms small aggregates (50 kDa) also showed no effect in the binding assay. The second- and third-generation dendrimers **2f** and **3f**, which form large nanoparticles, were highly potent in both assays (0.025, 0.035 μ M and 0.010, 0.010 μ M, respectively).^[14] Compound **4f** also showed high potency in the binding assay (0.019 μ M) but was significantly less potent in the hemolysis assay (0.18 μ M). Potency dropped even more for the larger dendrimers **5f** and **6f** which do not aggregate. Thus, especially in the more relevant hemolysis assay, potency clearly correlates with the size of the aggregates but not with the size of the individual molecules. The inhibition data suggest that the optimal particle weight and size for IgM inhibition are obtained with **3f**. The particles formed by **2f** might be larger than the optimum, but still displayed high potency. The aggregates formed by **1f**, **4f**, **5f**, and **6f** are apparently too small to accomplish polyvalent amplification of IgM inhibition. Further evidence for the involvement of polyvalent aggregates (but not oligovalent dendrimers) in antibody binding stems from the observation that backbone-modified tetravalent α Gal dendrimer **7** (size and lipophilicity comparable to **2f**), which does not aggregate, was found to be inactive whereas **2f** was highly potent.^[15] Nonspecific interactions of the dendrimer backbone can be excluded because dendrimer **3g** (identical backbone and similar aggregation

properties as **3f** but Lac instead of α Gal) did not inhibit binding. The most potent compound **3f** was selected for in vivo profiling in cynomolgus monkeys (1 mg kg⁻¹, intravenous, $n=3$; Figure 4). Within five minutes after injection the anti- α Gal IgMs, as detected by enzyme-linked immuno

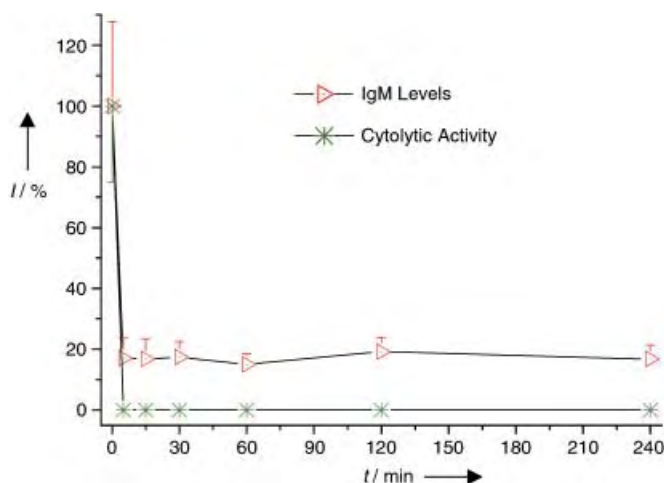


Figure 4. Effects of **3f** on anti- α Gal IgM levels and cytolytic activity of the sera of cynomolgus monkeys ($n=3$; 1 mg kg⁻¹; intravenous; plasma concentration approximately 10 μ M assuming all of **3f** is present). Prior to injection ($t=0$) the IgM 100% level (I) was 2.3 times higher than the IgM level of pooled human sera.

sorbent assay (ELISA), were reduced to 20% of the initial value and remained at low levels for more than 4 h.^[12b] Most importantly, anti- α Gal antibody-mediated haemolytic activity was completely eliminated.^[13b]

In conclusion, we have described novel, self-assembling glycodendrimers which form noncovalent nanoparticles in water. The particle sizes are remarkably homogenous and can be varied over a broad range by the appropriate choice of the dendrimer generation. The particles can be deposited on surfaces by evaporation of the solvent. In solution, they function as noncovalent polyvalent inhibitors both in vitro and in vivo. The self-assembly of the glycodendrimers is a dynamic equilibrium process. Thus, it is conceivable that noncovalent polyvalent ligands are optimized with respect to size and shape in the presence of natural polyvalent receptors. The control of a broad variety of physiologically relevant polyvalent interactions should be possible.

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- [9] Ethyl diisopropylamine (3 mL) was added to a mixture of **1b** (0.50 equiv), **1c–5c** (1.00 g; 1.00 equiv), and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) (1.00 equiv) in dry DMF (10 mL). The solution was stirred for 16 h at room temperature. DMF (5 mL), water (3 mL, dropwise), and LiOH monohydrate (approximately 50 equiv) were added and the mixture was stirred for an additional 16 h at room temperature. The solution was added dropwise to a mixture of acetone and 0.2N HCl (250 mL, 1:3). The precipitate formed was filtered off and washed with water, acetone, and dichloromethane. Products **2c–6c** (all yields greater than 80%) were isolated as beige solids.
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- [12] ELISAs: a) Human serum: Wells on plate A were coated with 0.5 μ g of α Gal-HSA (HSA = human serum albumin) conjugate in NaHCO₃ (100 μ L, 100 mM; pH 9.6) for 2 h at 37°C. Blocking with phosphate buffer saline (PBS, 250 μ L) containing 0.5% Tween20 for 2 h at ambient temperature was followed by removal of the liquid. On plate B pooled human serum was diluted (1:20) with PBS containing 10% Seablock and 0.2% Tween20 and incubated for 30 min with serial dilutions of dendrimers or other inhibitors. Samples (100 μ L) from each well on plate B were transferred to plate A, incubated for 1 h at ambient temperature, and washed three times with PBS containing 0.15% Tween20. They were then incubated with PBS containing anti-IgM secondary antibody peroxidase conjugate (1/2000 diluted, 100 μ L), 10% Blocker-BSA, and 0.2% Tween20. After washing with PBS containing 0.1% Tween20 (6 $\times$ 300 μ L), color development was initiated by adding TMB substrate solution (100 μ L, a mixture of 3,3',5,5'-tetramethylbenzidine, H₂O₂, and stabilizers) and stopped after 5 min with 1M H₂SO₄ (50 μ L). The absorbance at 450 nm (A_{450}) was measured; b) Cynomolgus monkey serum: wells were coated with α Gal-polymer^[10] (0.5 μ g) in PBS (100 μ L) overnight at 4°C. Blocking with PBS containing 10% Seablock (300 μ L) for 2 h at ambient temperature was followed by removal of the liquid. The wells were incubated for 30 min with 100 μ L of serially diluted serum sample in PBS containing 10% Seablock and 0.2% Tween20 and, subsequently, washed three times with PBS containing 0.15% Tween20. Incubation with a secondary antibody and color development were performed as described above.
- [13] Hemolysis assays. a) Human serum: pig erythrocytes were obtained from heparinized pig blood, washed three times with CFD buffer (3.1 mM diethyl barbituric acid, 0.9 mM sodium barbitone, 145 mM NaCl, 0.83 mM MgCl₂, 0.25 mM CaCl₂; pH 7.4), and suspended in CFD at a concentration of 1×10^9 mL⁻¹. Seven serial dilutions of inhibitor were prepared on low-bind U-shaped plates in CFD (50 μ L). Human serum was serially diluted in CFD (50 μ L, 10 dilutions assayed for each inhibitor concentration). Then, pig erythrocyte solution (50 μ L) was added to each well and the plate incubated for 60 min at 37°C with mild shaking. Plates were centrifuged for 10 min at 2000g to precipitate the unlyzed erythrocytes, the supernatant was transferred to a flat-bottomed plate, and the released hemoglobin (A_{420}) was measured; b) Cynomolgus monkey serum: the assay was carried out as above, but with the addition of baby rabbit complement (50 μ L, heterologous complement source at a final dilution of 1:10) in CFD and pig erythrocyte solution (50 μ L) to each well.
- [14] Polyvalent amplification was found to be less pronounced for the inhibition of divalent IgG binding. Compounds **1f–6f** showed very similar IC₅₀ values in the range of 0.45–0.85 μ M. Compound **3g** gave no inhibition at 10 μ M whereas **7** showed an IC₅₀ value of 1.80 μ M.
- [15] It also has to be considered that the individual molecules **2f** (M_r 4 kDa) and **3f** (9 kDa) are too small to allow for simultaneous contact of several oligosaccharide ligands with several binding sites of an individual IgM molecule (900 kDa).

Molecular Composition of Liquid Sulfur**

Ralf Ludwig,* Jörg Behler, Björn Klink, and F. Weinhold

The structure determination of liquids is still a challenge. This in particular holds for the complex system of liquid sulfur.^[1–4] Liquid sulfur exhibits a wide range of colors and structures with change in temperature.^[5] In the solid state, sulfur adopts three allotropes of cycloocta-S_{8c} which are well-known as orthorhombic α -sulfur, monoclinic β -sulfur, and monoclinic γ -sulfur. It is possible that these structures may also be present in the liquid phase. Two basic models have been proposed for the liquid. One claims predominantly S_{8c} rings^[6] and the other proposes mainly polymeric chains for the liquid.^[7] In spite of the large amount of experimental data reported, there is little direct information to differentiate among the models for the structure. A detailed understanding of this liquid is also highly desirable as there is a peculiar phase λ -transition at 432 K that results in drastic changes in the physical properties, such as viscosity and structure.^[6] Most of the experimental studies suffer because the thermodynamic and spectroscopic properties of various chain and cyclic molecules do not differ significantly and/or cannot be resolved in the liquid phase and thus not allow any conclusion to be drawn for the structure. In detailed experimental studies, Steudel et al.^[5,6] quenched liquid sulfur in liquid nitrogen, extracted the sulfur species with CS₂, and could characterize several ring structures (S_{6c} to S_{20c}) by high-performance liquid chromatography (HPLC) and Raman spectroscopy. But one question still remains: Are the detected structures constituents of the liquid phase or are they developed during preparation?

Neutron-scattering experiments^[7] tell us that liquid sulfur and rapidly quenched liquid sulfur provide different structure factors indicating to different compositions in both systems. These studies yield numbers of nearest neighbors in the pair-correlation function of about 1.8 ± 0.1 , which is less than the value of 2.0 expected for cyclic molecules. The determined number of neighbors suggests that short linear molecules must be the main components of liquid sulfur. On the other hand ESR studies of liquid sulfur have shown that the concentration of free radicals is low over the whole temperature range, which suggests long polymer chains.^[8,9] Thus from the

experimental viewpoint the structure determination of liquid sulfur is somewhat controversial.

In general, theoretical methods should be helpful to predict the structure of liquid sulfur and to disprove one of the models. Classical molecular-dynamics (MD) calculations suffer from the difficulty of constructing an empirical interatomic potential that could describe the many different structures and valence states of sulfur.^[10] Probably the best choice to determine the complicated structure of liquid sulfur is to apply first-principle theoretical methods. Thus Car-Parrinello ab initio molecular dynamics simulations^[11] have been performed by Tse et al.^[12] to predict the structure, vibrational spectrum, and dynamics of liquid sulfur over a wide range of temperature. But this particular covered only about 72 sulfur atoms and had short simulation runs of about 5 ps. Thus only crude predictions about the existence of cyclic and/or linear structures can be made.

Herein quantum cluster equilibrium (QCE) theory^[13] is used to provide a detailed picture of the equilibrium cluster structures and thermodynamic properties of liquid sulfur. Developed for describing the equilibrium structures of H-bonded liquids this method is now applied for the first time to a covalently bonded system. QCE theory is based on a full quantum treatment of the geometries, binding energies, and vibrational frequencies for molecular structures that are considered to be constituents of the gaseous and liquid phases. The cluster equilibria that dictate phase composition are determined by rigorous techniques of quantum statistical thermodynamics in the canonical ensemble, based on the ab initio or density functional (DFT) partition functions for each cluster.

Thus we carried out supermolecular calculations at the uncorrelated Hartree-Fock (HF) level ($n=2-20$), density-functional (B3LYP) level ($n=2-20$), and Møller-Plesset second-order perturbation theory (MP2; $n=2-8$) for molecular structures of sulfur S_n using 6-31 + G* basis set as implemented in Gaussian 94.^[14] For all optimized structures frequency calculations were performed. Recently, Wong^[15] calculated vibrational frequencies for a large number of molecules, which included sulfur compounds, by using a smaller basis (6-31G*) set and by several different methods. The data set gave strong support to hybrid density functionals versus MP2. Thus we think that B3LYP is an appropriate method and 6-31 + G* a well balanced basis set to calculate sulfur clusters. We also want to emphasize that a uniform level of theory must be applied to all candidate clusters ($n=2-20$). Frequencies for MP2/6-31 + G* and higher are simply impractical for the largest clusters considered ($n=9-20$).

There have been several theoretical studies on sulfur clusters, which range from empirical to ab initio studies. Most have considered only specific molecular systems though there have also been a few systematic studies on a range of cluster size.^[10,16–21] The most detailed and probably the most accurate studies to date have been the DFT calculations performed by Hohl et al.^[19] and ab initio calculations on RHF/3-21G* geometries up to the cyclic 12mer by Raghavachari et al.^[20] Recently, Cioslowski et al.^[21] calculated conformations and thermodynamic properties of small sulfur molecules S_{5c}, S_{6c}, S_{7c}, and S_{8c} on higher levels of theory (B3LYP/6-311G* and

[*] Priv.-Doz. Dr. R. Ludwig, J. Behler, B. Klink
Physikalische Chemie, Fachbereich Chemie
Universität Dortmund
Otto-Hahn-Strasse 6, 44221 Dortmund (Germany)
Fax: (+49)231-755-3937
E-mail: ludwig@pc2a.chemie.uni-dortmund.de
Prof. Dr. F. Weinhold
Theoretical Institute and Department of Chemistry
University of Wisconsin
Madison 53706 (USA)

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MP2/6-311G*). The calculations on both levels of theory disagreed only in minor details supporting our choice for B3LYP as an appropriate method. Unfortunately no frequency calculations were performed. Thus for comparison with our results only studies presenting all properties including frequencies were considered.

Our fully optimized 34 structures comprise singlet-state chains S_{ns} and triplet-state chain S_{nt} , as well as cyclic sulfur molecules S_{nc} . The most stable molecules are shown in Figure 1. For all calculated structures we obtained positive frequencies. The polymeric chains are twisted in a helical

manner and closely resemble the well-known structure of sulfur S_8 . The geometry and vibrational spectrum of the isolated S_{8c} molecule and other small-ring structures are in good agreement with observed values^[1–5,22,23] and previous theoretical studies.^[16–21] In Table 1 our calculated vibrational frequencies for S_{8c} are given in comparison to experimental results and other theoretical work. The data show that our choice of methods and basis set is appropriate to tackle the problem. For the cyclic 18mers we calculated the known crystal structures α - S_{18} and β - S_{18} . The α - S_{18} molecule shows C_{2h} symmetry which is by far the most stable structure and thus considered here.

The calculated average energies per sulfur atom for both theoretical methods are shown in Figure 2a and 2b referred to the energetically most favorable S_{8c} ring structure. It can be seen that except for the trimer, all chain molecules are energetically more favorable in the triplet rather than the singlet state. But even the largest triplet-state structure containing 17 sulfur atoms is higher in energy than S_{8c} . The structures of the cyclic sulfur molecules are calculated for S_{5c} to S_{20c} . The ring structures S_{6c} , S_{7c} , S_{9c} , S_{10c} , and S_{12c} are slightly weaker, whereas S_{14c} and S_{20c} are bonded slightly stronger than S_{8c} . For both methods the energy differences relative to S_{8c} range between -0.2 and 5 kJ mol^{-1} . These values are close to the estimates obtained experimentally from enthalpies of formation and equilibria constants for these species^[5] (between 1 and 4 kJ mol^{-1} ; Table 2).

The liquid-phase cluster populations for sulfur obtained from thermodynamic calculations for temperatures in the range of 389.5 (melting point) to 717.6 K (boiling point) are shown in Figure 3a,b and 4a,b. Over the whole temperature range the populations are dominated by cyclic rings S_{8c} . For the QCE(34)/RHF/6-31 + G* and QCE(34)/B3LYP/6-31 + G* models we obtained percents by weight of 98.2% and 99.8% , respectively, which is close to the experimental value of about 93.6% , a little above the melting point. Considering that in the experiment up to 5% of all molecules could not be detected, this was caused by undissolved species and weighing errors, this agreement is quite remarkable. From the theoretical viewpoint this result is also not obvious. Using smaller basis sets, such as 3-21G, leads to populations of only 50% S_{8c} and larger amounts of cyclic S_{6c} to S_{12c} structures (see Supporting Information). Clearly a 6-31 + G* basis set is needed and sufficient to obtain reasonable bond energies and frequencies.

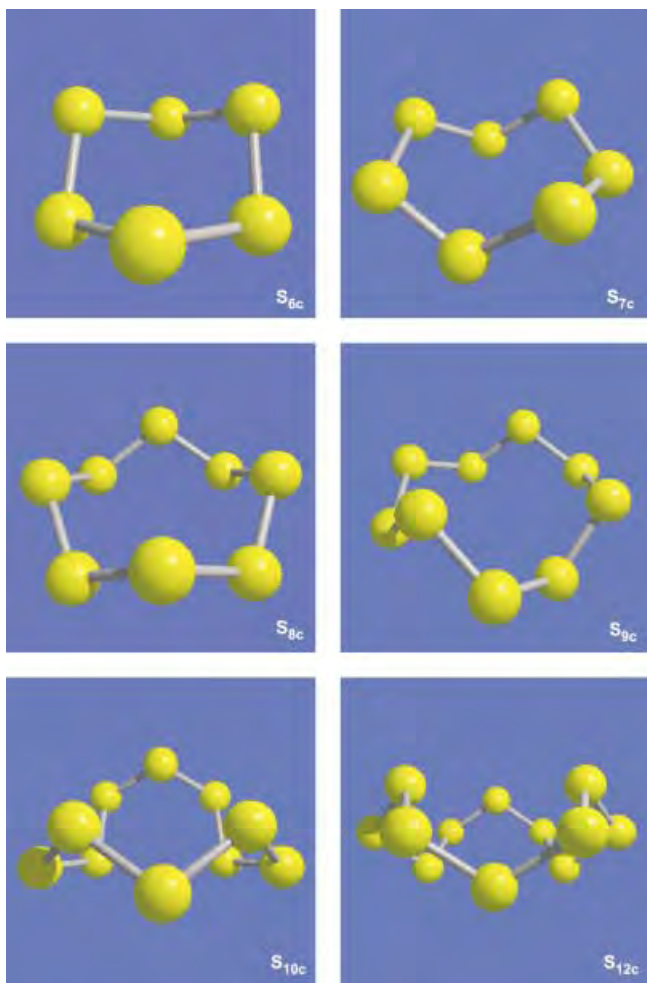


Figure 1. Enthalpically and entropically favored cyclic sulfur molecules.

Table 1. Experimental and scaled calculated vibrational frequencies $\tilde{\nu} [\text{cm}^{-1}]$ for the cyclic molecule S_{8c} .

HF/3-21G*[a]	HF/6-31 + G*[b]	B3LYP/6-31 + G*	MP2/6-31 + G*[c]	AIMD[d]	Exp.[23]
468	484	459	464	480	475
465	482	451	462	476	437
462	481	448	420	474	415
454	460	446	411	435	475
450	459	397	427	408	471
256	252	245	239	247	239
243	240	240	237	243	248
214	212	212	196	218	218
192	189	190	187	187	186
156	153	143	144	140	152
61	62	73	68	59	86

[a] Scale factor of 0.89 .^[19] [b] Scale factor of 0.89 . [c] Scale factor of 0.95 . [d] AIMD = Ab initio molecular dynamics.^[12]

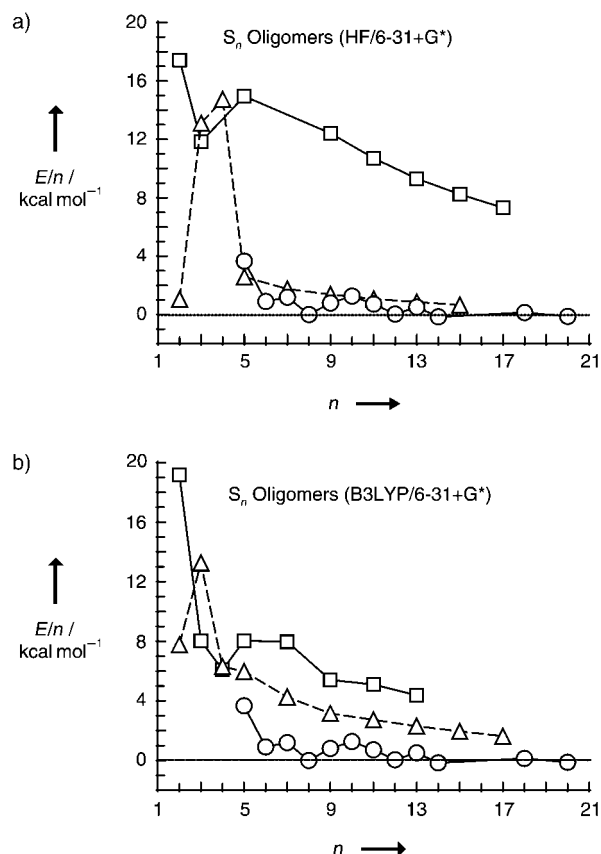


Figure 2. a) Calculated (HF/6-31 + G*) average energy per sulfur atom in singlet-state S chains ($\square$), triplet-state S chains (Δ), and cyclic sulfur molecules S_n ($\circ$; $n=2-20$). b) Calculated (B3LYP/6-31 + G*) average energy per sulfur atom in singlet-state S chains ($\square$), triplet-state S chains (Δ), and cyclic sulfur molecules S_n ($\circ$; $n=2-20$).

Table 2. Calculated average bond energies per atom E_{bon} [kJ mol $^{-1}$] for selected cyclic S_n clusters in comparison to calculated bond energies E_{bon} [kJ mol $^{-1}$] derived from reaction enthalpies.

Cluster	HF/6-31 + G*	B3LYP/6-31 + G*	MP2/6-31 + G*	Exp. ^[5]
S_{6c}	3.775	6.799	6.265	3.7
S_{7c}	5.009	4.462	5.067	3.0
S_{9c}	3.350	3.328	2.280	3.1
S_{10c}	5.283	3.756	4.458	3.0
S_{12c}	-0.187	0.468	-1.423	1.0

Up to the λ -transition at 432 K the S_{8c} contribution is reduced only slightly as found in the experiment. Beside the dominant species S_{8c} other cyclic ring structures, such as S_{6c} , S_{7c} , S_{9c} , S_{10c} , and S_{12c} , show up in trace amounts. These species were also found by Steudel et al., who rapidly quenched the liquid sulfur, solved it in CS_2 , and investigated the sulfur structures by HPLC and Raman spectroscopy.^[5,6] From our DFT studies we obtain the same relative populations: S_{7c} , S_{6c} as well as trace amounts of S_{9c} , S_{10c} , and S_{12c} . In our HF population S_{6c} is favored over to S_{7c} . The S_{7c} structure used for the HF calculations is lower in symmetry (C_2) and higher in energy than the experimentally found molecule (C_s),^[24,25] which is also a true minimum structure in the DFT calculations.

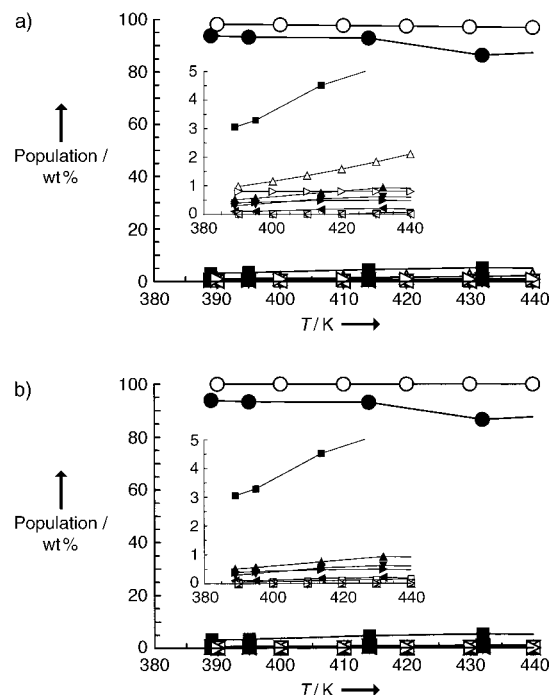


Figure 3. QCE(34)/HF/6-31 + G* (a) and QCE(34)/B3LYP/6-31 + G* (b) cluster populations of sulfur as a function of temperature: $\circ$: S_{6c} ; $\square$: S_{7c} ; $\circ$: S_{8c} ; ∇ : S_{9c} ; $\triangleleft$: S_{10c} ; $\triangleright$: S_{12c} . For comparison experimental populations of sulfur molecules (filled symbols) are given^[6]: $\blacktriangle$: S_{6c} ; $\blacksquare$: S_{7c} ; $\bullet$: S_{8c} ; $\blacktriangledown$: S_{9c} ; $\blacktriangleleft$: S_{10c} ; $\blacktriangleright$: S_{12c} .

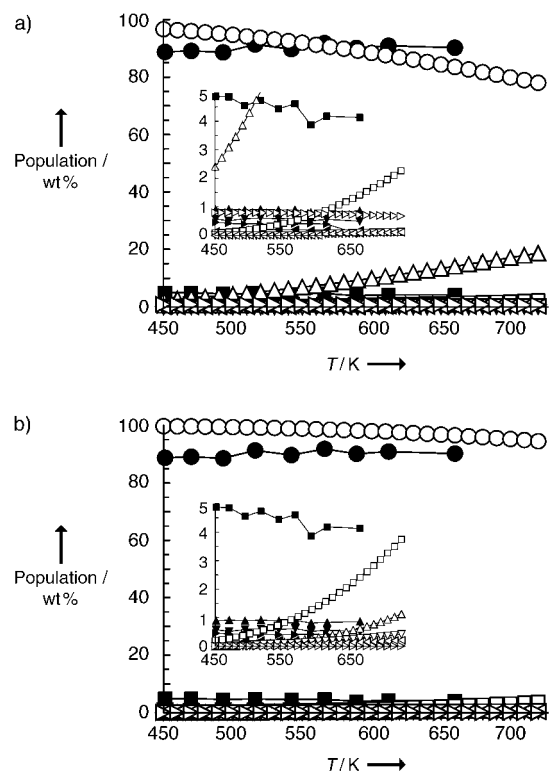


Figure 4. QCE(34)/HF/6-31 + G* (a) and QCE(34)/B3LYP/6-31 + G* (b) cluster populations of sulfur as a function of temperature: $\triangle$: S_{6c} ; $\square$: S_{7c} ; $\circ$: S_{8c} ; ∇ : S_{9c} ; $\triangleleft$: S_{10c} ; $\triangleright$: S_{12c} . For this temperature range no linear sulfur molecules could be found by the QCE model. For comparison with experimental populations of sulfur molecules^[6] (filled symbols) the measured S_{8c} and S_{μ} contributions are included in the total contribution S_{8c} : $\blacktriangle$: S_{6c} ; $\blacksquare$: S_{7c} ; $\bullet$: S_{8c} ; $\blacktriangledown$: S_{9c} ; $\blacktriangleleft$: S_{10c} ; $\blacktriangleright$: S_{12c} .

But why is S_{7c} favored over the other cyclic structures S_{6c} , S_{9c} , S_{10c} , and S_{12c} which mostly show higher symmetry and larger bond energies? The answer is given by the calculated vibrational frequencies. The five lowest wavenumbers for the cyclic species as given in Table 3 show clearly that S_{7c} is

Table 3. Low-lying vibrational frequencies $\tilde{\nu}_{1-5}$ [cm^{-1}] and zero-point energies E_{ZPE} [kJ mol^{-1}] per atom for selected cyclic S_{nc} clusters (B3LYP/6-31 + G*).

Cluster	$\tilde{\nu}_1$	$\tilde{\nu}_2$	$\tilde{\nu}_3$	$\tilde{\nu}_4$	$\tilde{\nu}_5$	E_{ZPE}
S_{6c}	161.7	162.5	198.7	199.1	258.6	3.796
S_{7c}	56.2	124.1	150.7	165.4	190.8	3.761
S_{9c}	51.5	59.3	62.8	94.4	150.7	3.798
S_{10c}	39.3	56.5	58.2	74.2	113.5	3.822
S_{12c}	42.6	43.4	43.9	45.0	68.7	3.913

entropically favored. A larger number of lower frequencies determine the vibrational partition function in our model and thus the equilibrium distribution of the molecules. Subtleties of the energetics of various sulfur ring and chain conformations are largely associated with the torsional dependencies of hyperconjugative interactions (vicinal delocalizations from sulfur lone pairs to vicinal sulfur–sulfur antibonds).^[26–28] Interestingly, S_{7c} is known to be responsible for the deep yellow color of liquid sulfur.^[5]

For the temperature range between 389.5 and 432 K, QCE populations do not show any evidence for the linear molecules predicted by neutron-scattering experiments. The number of 1.8 ± 0.1 nearest neighbors suggests, on average, pure linear 10mers, or if any cyclic or longer linear molecules are present even smaller linear structures.

Above the λ -transition temperature (432 K) no linear sulfur molecules could be found. Clearly our calculated clusters up to the synthetic 37mers are still too small compared to presumed structures built upon 10^3 to 10^6 sulfur atoms.^[5] Thus, in our model larger linear or cyclic molecules are incorporated in the total contribution of the most favorable S_{8c} . Adding the experimentally found S_{8c} and S_{μ} contributions gives absolute values and temperature behavior comparable to our S_{8c} population (Figure 3b and 4b). Clearly the regime above the λ -transition cannot be simulated by any theoretical model. In classical and moreover in ab initio MD studies the small system size as well as too-short simulation runs prevent such a viscous system being characterized. For QCE calculations bond energies and vibrational frequencies for such large molecules are not available.

Concerning the cyclic structures our results are essentially in agreement with the findings of Steudel et al. For both theoretical methods rising temperature leads to slightly smaller contributions of S_{8c} (5–15%) in favor of the neighboring cyclic structures S_{7c} and S_{6c} (2–10%), whereas the amounts of the larger species S_{9c} , S_{10c} , and S_{12c} do not show significant changes with temperature at all. This change in population is mainly caused by entropic effects. This result can be demonstrated by using the same energy per sulfur atom for all structures as that found for S_{8c} ; immediately the dominant S_{8c} is replaced by S_{7c} and S_{6c} .

The present QCE model provides a new type of ab initio theoretical support for the general picture of sulfur polymer

distributions that has emerged from experimental studies spanning more than 100 years. While certain novel observations could be offered concerning detailed enthalpic and entropic origins of cluster stability, it is gratifying that the overall QCE results are generally “unsurprising”. These results yield satisfactory overall agreement with a multitude of crystallographic, spectroscopic, and thermodynamic measurements on individual cluster species and complex liquid mixtures. This general concordance also suggests how a combined theoretical and experimental approach can elucidate additional details of the complex phase behavior of sulfur and other substances.

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Towards A DNA-Like Duplex without Hydrogen-Bonded Base Pairs**

G rald Mathis and J rg Hunziker*

The creation of alternative base pairs to expand the genetic alphabet has recently been the focus of intensive research.^[1–13] Initial work was based on the systematic permutation of hydrogen bond donor and acceptor arrangements within the pyrimidine and purine nuclei.^[1–3] In subsequent studies the Watson–Crick complementarity paradigm was abandoned altogether.^[4–9] It was shown that aromatic entities devoid of hydrogen bonding functional groups can satisfy at least part of the criteria for replicable base pairs, that is, thermodynamic stability of the resulting duplex, orthogonality to natural nucleobases, and enzymatic processability. Such nonpolar base pair isosteres are held together by hydrophobic dispersion forces which act predominantly along the base stack but less so at the interface between the bases. In an attempt to orient the base–base attraction perpendicular to the helix axis, chelating nucleosides have been developed.^[10–13] However, such metal-mediated base pairs can hardly be amenable to enzymatic replication.

In the search for alternative base pair design principles we were particularly intrigued by the interaction between benzene and hexafluorobenzene.^[14–18] The two compounds, both liquids at room temperature, form a solid aggregate^[19,20] which is characterized not only by π stacks of alternating components but by the lateral alternation between hexafluorobenzene and benzene rings as well (Figure 1). The inverse quadrupolar moments of benzene and hexafluorobenzene lead to edge-to-edge attractive intermolecular forces which could be utilized in designing novel base pairs, such as the one formed between C-nucleosides **1** and **2** (Scheme 1). Here we report on the synthesis and the promising pairing properties of oligonucleotides containing **1** and **2**.

The synthesis of phenyl-2-deoxyribose **2** and its incorporation into oligonucleotides has been described.^[21] The novel pentafluorophenyl congener **1** was prepared from 2-deoxyribonolactone following a literature strategy (Scheme 2).^[22] Commercially available bromopentafluorobenzene (**4**) was lithiated and then the silyl-protected 2-deoxyribonolactone **3**^[22] was added. The resulting hemiacetal was reduced in situ with Et_3SiH to give an inseparable 9:1 mixture of the two anomers **5** (β) and **6** (α) in low yield. These compounds could be separated by chromatography after deprotection of the deoxyribose moiety and reprotection as 5'-dimethoxytrityl ethers. At this stage the configuration of the two isomers could be assigned by ^1H NMR NOE experiments.^[23] The pentafluorophenyl- β -D-ribose phosphoramidite **8** was then obtained by standard phosphitylation.^[24] Oligonucleotides

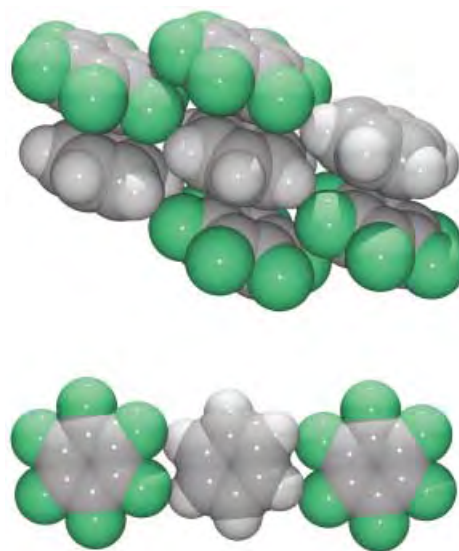
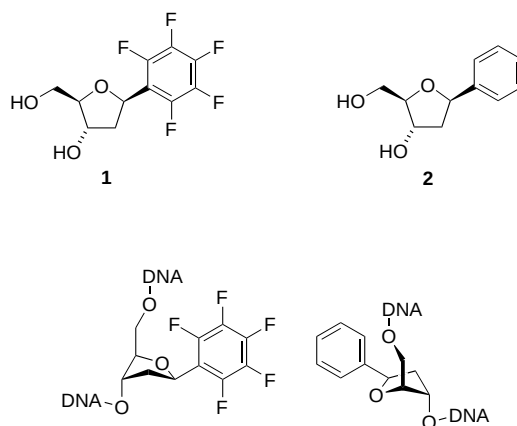


Figure 1. Details of the X-ray crystal structure of the solid 1:1 complex formed from benzene and hexafluorobenzene (grey: carbon, white: hydrogen, green: fluorine). The side view (top) shows the stacks of alternating composition. The aromatic molecules are tilted with respect to the stack axis, which leads to lateral alternation within the plane of individual benzene or hexafluorobenzene molecules (bottom).



Scheme 1. Structures of the pentafluorophenyl- β -D-deoxyribose (F^5 , **1**) and phenyl- β -D-deoxyribose (**P**, **2**) used to investigate the stability of F^5 –**P** base pairs in oligonucleotide duplexes.

containing **1** and **2** (Tables 1 and 2) were prepared using a regular solid-phase DNA synthesis protocol.^[24,25]

When incorporated into a 10-mer duplex, a single pentafluorophenyl–phenyl pair (F^5 –**P**) leads to a strong decrease in duplex stability, as judged by the melting temperature T_m (Table 1). The stability of the novel base pair is intermediate to that of the relatively well-tolerated mismatched pairs A–G and G–G as well as the wobble pair G–T and all other more deleterious mismatches between natural bases. The interaction between the phenyl and the pentafluorophenyl units is stronger than those with any of the natural bases. Unfortunately, there is no or only a slight discrimination between F^5 –**P** and the corresponding self-pairs **P**–**P** and F^5 – F^5 in this sequence context.

Moving to a self-complementary 10-mer duplex with several F^5 –**P** base pairs dramatically changes the picture.

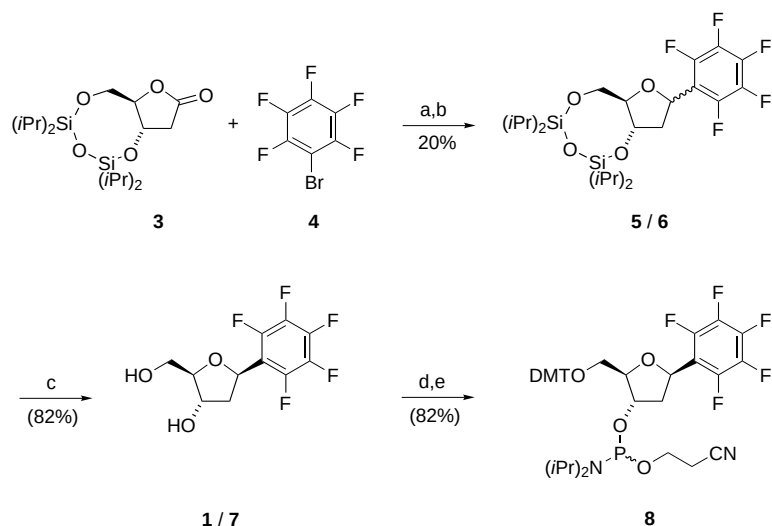
[*] Priv.-Doz. Dr. J. Hunziker, Dipl.-Chem. G. Mathis
Department of Chemistry and Biochemistry
University of Bern
Freiestrasse 3, 3012 Bern (Switzerland)
Fax: (+41)31-631-8057
E-mail: juerg.hunziker@ioc.unibe.ch

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Table 1. The T_m values [°C] determined from UV melting experiments for the 10-mer DNA duplex **9** with varying bases in positions **X** and **Y**.^[a]

		5' -CTGAXTCGAC-3' 3' -GACTYAGCTG-5' 9					
		d (CTGAXTCGAC)					
		A	T	G	C	F ⁵	P
d (GTCGAYTCAG)	A	29.0	44.3	36.2	28.1	25.0	25.1
	T	45.0	27.1	35.5	27.1	22.0	21.1
	G	35.6	36.1	38.9	49.0	25.0	23.0
	C	29.8	28.0	50.0	25.1	24.1	24.1
	F ⁵	25.0	22.0	28.7	21.1	29.9	30.6
	P	25.1	21.0	27.2	17.6	30.0	30.0

[a] Duplex concentration: 4 μ M; buffer: 10 mM NaH₂PO₄, 150 mM NaCl, pH 7.0; detection at 260 nm, T_m = mean value of three melting curves, heating rate = 0.5 °C min⁻¹.



Scheme 2. a) Compound **4** (2.0 equiv), BuLi (1.8 equiv), Et₂O, -78 °C, 1 h, then **3** (1.0 equiv) in Et₂O, -78 °C, 2.5 h; b) Et₃SiH, BF₃·Et₂O, CH₂Cl₂, -78 °C, 12 h; c) Bu₄NF, THF, RT, 2 h; d) DMT-Cl, *N,N*-dimethylaminopyridine, pyridine, RT, 3 h; e) [(iPr₂N)(NCCH₂CH₂O)P]Cl, iPr₂NEt, THF, RT, 1 h. DMT = 4,4'-dimethoxytrityl.

With two such pairs in a central position (duplex **12**₂) there is still a decrease in thermal stability (ΔT_m /mod. -4.0 K compared to A-T, Table 2), however, to a considerably lower degree than in the case of a single substitution (ΔT_m /mod. -15 K). Introducing four consecutive F⁵-P pairs (**13**₂) leads to

a duplex which is more stable than its natural counterpart with four A-T pairs (ΔT_m /mod. +1.5 K). The beneficial mutual interaction is unique to the phenyl and pentafluorophenyl residues in this system. The duplexes **15**₂ and **16**₂ with four F⁵-G and F⁵-A pairs, respectively, are destabilized in comparison.

The differences in duplex stability of sequences with one, two, or four consecutive F⁵-P base pairs may reflect the altered geometry of this artificial base pair. The contact between phenyl and pentafluorophenyl in an optimal orientation likely requires a backbone distance shorter than the 11 Å of a standard pyrimidine-purine base pair. The backbone may only adapt to this if several F⁵-P pairs are arranged in a row.^[26]

Measuring the thermal stability of 10-mer duplexes containing more than four F⁵-P pairs meets technical hurdles. The UV absorption of C-nucleosides **1** and **2** is weak over the wavelength range of the melting experiments. In essence, only the destacking of natural bases is detected, as can be seen from the drop in hyperchromicity in duplexes **12**₂ (14.5 %, Table 2), **13**₂ (8 %), **18**₂ (7.5 %), and **21**₂ (-1 %). In addition, duplex **18**₂ with six alternating F⁵-P base pairs does not show a sigmoidal curve indicative of a cooperative transition.

The strength and the directionality of the interaction between the phenyl and pentafluorophenyl residues is revealed in concentration variation experiments, which also yield the thermodynamic parameters of duplex formation (Table 3). A single F⁵-P base pair in the duplex d(CTGAPTCGAC)-d(GTCGAF⁵TCAG) (**24-25**) leads to a decrease in the enthalpy of duplex formation compared to the unmodified reference, which cannot be compensated by a more favorable pairing entropy. The situation is different in the self-complementary duplex d(CTGF⁵PF⁵PCAG)₂ (**13**)₂. The pairing enthalpy in this system is almost 40 % higher than for the reference d(CTGATATCAG)₂ (**10**)₂, which can most likely be attributed to the extraordinarily strong stacking interactions between alternating phenyl and pentafluorophenyl bases. Support for this notion stems from the following observations. The oligonucleotide d(CTGF⁵PF⁵PCAG) (**13**) forms a duplex at concentrations above 3 μ M; below this threshold a monomolecular structure—presumably a hairpin—is predominant

Table 2. The T_m values [°C] determined from UV melting experiments for the 10-mer oligonucleotides **10-21** with several F⁵-P pairs.^[a]

Oligonucleotide	T_m [°C]	ΔT_m /mod. [K]	Hyperchromicity
d(CTGATATCAG) (10)	38.0	—	27 %
d(CTGAGCTCAG) (11)	48.5	+5.3	23 %
d(CTGAF ⁵ PTCAG) (12)	30.0 ^[b]	-4.0	14.5 %
d(CTGF ⁵ PF ⁵ PCAG) (13)	44.0	+1.5	8 %
d(CTGF ⁵ PP ⁵ PCAG) (14)	44.7 ^[b]	+1.7	8 %
d(CTGF ⁵ GF ⁵ GCAG) (15)	35.8	-1.1	6 %
d(CTGF ⁵ AF ⁵ ACAG) (16)	37.7	-0.2	6.5 %
d(CF ⁵ GPATF ⁵ CPG) (17)	— ^[c]	—	2.5 %
d(CTPF ⁵ PF ⁵ PF ⁵ AG) (18)	— ^[d]	—	7.5 %
d(CTF ⁵ F ⁵ F ⁵ PPPAG) (19)	— ^[d]	—	5 %
d(CF ⁵ PF ⁵ GC PF ⁵ PG) (20)	23.1 ^[b]	-2.5	9 %
d(CF ⁵ PF ⁵ PF ⁵ PF ⁵ PG) (21)	— ^[c]	—	-1 %

[a] Duplex concentration: 4 μ M; buffer: 10 mM NaH₂PO₄, 150 mM NaCl, pH 7.0; detection at 260 nm, T_m = mean value of three melting curves, heating rate = 0.5 K min⁻¹. [b] Monomolecular hairpin at 4 μ M. [c] No melting transition observed. [d] No sigmoidal (cooperative) melting transition.

Table 3. Thermodynamic data for 10-mer DNA duplexes containing F⁵-P base pairs and the corresponding references.^[a]

Oligonucleotide	ΔH° [kcal mol ⁻¹]	ΔS° [cal mol ⁻¹ K]	ΔG° (25 °C) [kcal mol ⁻¹]
d(CTGAATCGAC)- d(GTCGATTCAG) (22-23)	-77.6	-213	-13.8
d(CTGAF ⁵ TCGAC)- d(GTCGAF ⁵ TCAG) (24-25)	-61.5	-175	-9.1
d(CTGATATCAG) ₂ (10) ₂	-67.5	-192	-10.1
d(CTGAGCTCAG) ₂ (11) ₂	-82.3	-231	-13.3
d(CTGF ⁵ PF ⁵ PCAG) ₂ (13) ₂	-94.3	-273	-13.0

[a] Duplex concentration: 1–32 μ M; buffer: 10 mM NaH₂PO₄, 150 mM NaCl, pH 7.0.

(Figure 2). In contrast, the sequences d(CTGF⁵F⁵PPCAG) (**14**) as well as d(CTGAF⁵PTCAG) (**12**) prefer a monomolecular structure with constant T_m up to much higher concentrations (> 10 μ M). In the case of **13** the central portion of the oligonucleotide seems to be rigidified by the alternating F⁵-P-F⁵-P stack, which is absent or smaller in **12** and **14**.^[27] The intramolecular stacking interaction between the phenyl and pentafluorophenyl residues is therefore more stabilizing than the lateral, intermolecular one. This is not surprising given the different sizes of the contacting surfaces in the two dimensions.

In conclusion, complementary charge distribution as in the pentafluorophenyl-phenyl C-nucleosides **1** and **2** represents a novel design principle for artificial base pairs. The results from this study highlight the importance of favorable intrastrand stacking interactions in the thermodynamic stabilization of oligonucleotide duplexes. On the other hand, interstrand stacking has recently been exploited in a base pair formed between two bipyridine residues.^[13] A combination of these two features could lead to orthogonal, non-hydrogen bonded, non-shape complementary base pairs. Experiments towards this end as well as attempts to replicate the pentafluorophenyl-phenyl pair by polymerases are currently under way.

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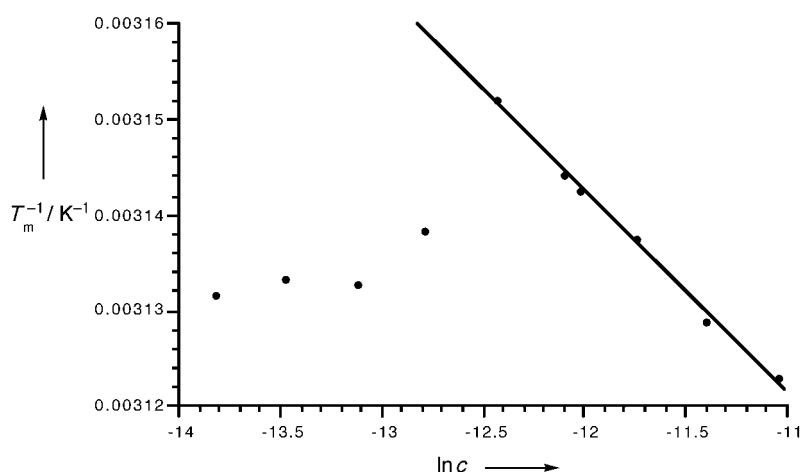


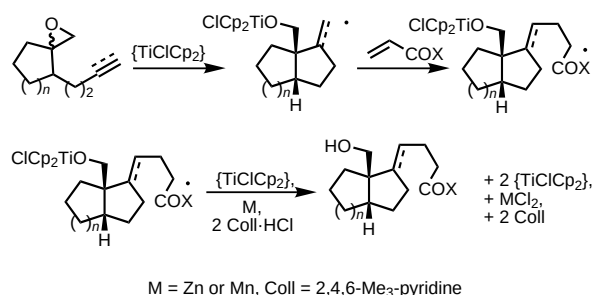
Figure 2. Van't Hoff plot of $1/T_m$ vs. $\ln(c)$ (c in mol L⁻¹) for oligonucleotide d(CTGF⁵PF⁵PCAG) (**13**). Sequence **13** with four alternating F⁵-P base pairs in the middle forms duplexes at concentrations above 3 μ M (sloped region, linear regression indicated). In contrast, sequences d(CTGAF⁵PTCAG) (**12**) and d(CTGF⁵F⁵PPCAG) (**14**) form a duplex only at much higher concentrations.

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- The tritylated pentafluorophenyl- β -D-deoxyriboside was deprotected under acidic conditions (CHCl₃COOH, pyrrole, CH₂Cl₂, RT, 20 min) to give anomerically pure **1**. ¹H NMR NOE (400 MHz, [D₆]DMSO): irradiation of the signal for H-C(1') (5.30 ppm) leads to enhancement of the signal for H-C(4') (3.75 ppm), and vice versa.
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- The identity of the oligonucleotides synthesized was confirmed by ESI mass spectrometry.
- Substituting the phenyl part of a F⁵-P base pair by a naphthalene or indole unit could possibly resolve this problem. Experiments with the corresponding modified oligonucleotides are under way.
- Experiments with the non-self-complementary 10-mer duplexes d(CTGF⁵PF⁵PGAC)-d(GTCF⁵PF⁵PCAG) and d(CTGF⁵F⁵F⁵GAC)-d(GTCPPPCAG) were inconclusive since they showed melting temperatures below 10 °C.

Stereoselective Synthesis of Tri- and Tetrasubstituted Olefins by Tandem Cyclization Addition Reactions Featuring Vinyl Radicals**

Andreas Gansäuer,* Marianna Pierobon, and Harald Bluhm

Reactions leading to structurally complex molecules by transformation of simple precursors with high mass transfer under catalytic conditions are attractive for synthesis.^[1] A promising candidate in this respect is the combination of our titanocene-catalyzed cyclization^[2] of suitably unsaturated epoxides with intermolecular additions to α,β -unsaturated carbonyl compounds (Scheme 1).^[3] The resulting transforma-



Scheme 1. General concept for the titanocene-catalyzed tandem reactions involving vinyl radicals.

tion is an example of a tandem radical sequence with a cyclization addition.^[4] An especially attractive feature of this reaction is the possibility of generating vinyl radicals as intermediates for the intermolecular synthesis of olefins. To the best of our knowledge this latter transformation has only rarely been realized stereoselectively, especially in the case of tetrasubstituted alkenes. We are only aware of the use of tributylstannyl- and phenylselenyl-substituted vinyl radicals in this context.^[5]

We started our investigation with olefins as radical acceptors in cyclizations. Some of our results are summarized in Table 1. The epoxides were synthesized according to reference [2e].

The tandem reaction yielded the desired products in reasonable to high yields. Noticeable amounts of undesired product resulting from intermolecular addition without cyclization (13 %) were only formed with **3** as substrate (Table 1, entry 2). In terms of kinetics, this is remarkable since the intermolecular additions of simple radicals to α,β -unsaturated carbonyl compounds should compete substantially with simple 5-*exo* cyclization reactions.^[3,7] The absence of this type

Table 1. Titanocene-catalyzed tandem reactions with alkenes in THF.^[a]

Entry	Substrate	Product	Yield [%]
1			51, ^[b] d.r. > 97:3
2			51, ^[c] d.r. = 55:45
3			68, ^[d] d.r. = 55:40:5
4			78, ^[e] d.r. = 56:39:5

[a] For the synthesis and experimental details, see [6] and the Supporting Information. [b] **1**: d.r. > 98:2, 5 mol % cat., 9 equiv of acrylate. [c] **3**: d.r. = 90:10, 10 mol % cat., 5 equiv of acrylate. [d] **5**: d.r. = 56:44, 10 mol % cat., 9 equiv of acrylate, minor isomer: *cis* orientation of CH₂OH and alkyl chain. [e] **5**: d.r. = 56:44, 10 mol % cat., 9 equiv of acrylonitrile, minor isomer: *cis* orientation of CH₂OH and alkyl chain.

of product in the reaction of **5** with acrylonitrile, the most reactive radical trap employed, is especially noteworthy (Table 1, entry 4). We suggest that the β -titanoxy radicals are conformationally predisposed for cyclization and that the inductive effect of the CH₂OTiCp₂Cl group retards additions to the electron-deficient α,β -unsaturated carbonyl compounds. The diastereoselectivities of the two-step process are in the same range as for simple cyclizations.^[2e]

The chemoselectivity of the tandem reaction is expected to be even lower in the case of alkynes as radical acceptors, because their cyclizations are about one order of magnitude slower than those of the corresponding alkenes.^[8] Our results with these substrates are summarized in Table 2. The epoxides were synthesized according to reference [2e].

Epoxide **8** gave the desired product **9** in good yield and with high diastereoselectivity (diastereomeric ratio d.r. > 97:3; Table 2, entry 1). Basically no products (< 3 %) resulting from intermolecular addition without cyclization or from simple cyclization were observed. Remarkably, preorganization and electron deficiency of the β -titanoxy radicals allow for a successful tandem reaction even in the case of the slower cyclization.

A key characteristic of this reaction is the necessity to use a solvent with a lower hydrogen donor propensity than THF, which reduces highly reactive vinyl and aryl radicals by hydrogen atom abstraction to yield the products of simple cyclization.^[9] The general ease of reduction has probably precluded the use of vinyl radicals for intermolecular additions in typical chain reactions in the presence of stannanes or silanes.

In addition to displaying a low hydrogen donor ability, the substitute for THF must also enable a fast reduction of

[*] Prof. Dr. A. Gansäuer, Dr. M. Pierobon, Dr. H. Bluhm
Kekulé-Institut für Organische Chemie und Biochemie
Universität Bonn
Gerhard Domagk Strasse 1, 53127 Bonn (Germany)
Fax: (+49)228-73-4760
E-mail: andreas.gansaueuer@uni-bonn.de

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

Table 2. Titanocene-catalyzed tandem reactions with alkynes in ethyl acetate.^[a]

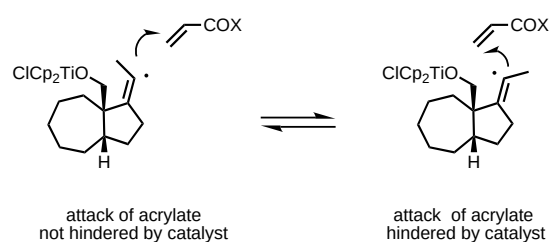
Entry	Substrate	Product	Yield [%]
1			69, ^[b] d.r. > 97:3
2			67, ^[c] d.r. = 92:8
3			54, ^[d] d.r. = 95:5
4			58, ^[e] d.r. > 97:3
5			55, ^[f] d.r. > 97:3
6			68, ^[g] d.r. = 96:4

[a] d.r. refers to the *E*:*Z* ratio of the olefins. For the assignment of the configuration by NOE measurements, see the Supporting Information. [b] **8**: d.r. = 97:3, 20 mol % cat., 9 equiv of acrylate. [c] **8**: d.r. = 97:3, 20 mol % cat., 9 equiv of amide. [d] **11**: d.r. = 97:3, 20 mol % cat., 1.5 equiv of acrylate. [e] **13**: d.r. = 97:3, 10 mol % cat., 9 equiv of acrylate. [f] **13**: d.r. = 97:3, 20 mol % cat., 9 equiv of amide. [g] **16**: d.r. = 86:14, 20 mol % cat., 9 equiv of amide.

[Cp₂TiCl₂] by Zn in order to maintain the catalytic cycle. In this process the titanium reagents and ZnCl₂ must be solvated. We found that benzene, diethyl ether, and *tert*-butyl acetate did not fulfill the requirement of fast reduction. Of the polar solvents investigated—those which dissolved the salts and reduced titanium(IV)—EtOAc gave the best yields and lowest amounts of side products formed upon simple cyclization. Acetonitrile, acetone, *N*-methylpyrrolidone (NMP), and γ -butyrolactone gave distinctly inferior results.

Therefore, our modified reaction allows the formation of vinyl radicals under conditions that enable intermolecular C–C bond formation. The results observed so far suggest that vinyl radicals are well suited for the highly stereoselective synthesis of unfunctionalized tri- and tetrasubstituted olefins. Tetrasubstituted olefins are often difficult to prepare stereoselectively by other methods. A rationale for the origin of the selectivity in the reaction of the rapidly inverting vinyl radicals is presented in Scheme 2.

It is of interest to note that the reduction of the same vinyl radicals proceeds with varying selectivities (between 65:35 and 77:23). Therefore, the steric interactions of the catalyst and the acrylates as radical traps are essential for high stereoselectivity.



Scheme 2. Possible explanation for the origin of diastereoselectivity in vinyl radical additions.

Only during the synthesis of trisubstituted olefins were we able to detect minor amounts (3–10 %) of the cyclization product. In these cases the more reactive disubstituted vinyl radical is formed. Our reaction is not confined to acrylates as radical traps; acrylamides are also useful. Tetrahydrofurans, for example, **17**, can be efficiently synthesized. The formation of **12** proceeds smoothly in reasonable yield. Compounds of this type may serve as models for the C and D rings of modified steroids with a double bond that can be further functionalized. They should thus be of general interest for the synthesis of important biologically active compounds.

In summary, we have devised a radical tandem reaction based on titanocene-catalyzed epoxide opening. This reaction features the use of vinyl radicals in the highly stereoselective intermolecular synthesis of tri- and tetrasubstituted olefins.

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- [6] Typical experimental procedure: Preparation of **7**: Collidine hydrochloride (394 mg, 2.50 mmol), zinc (131 mg, 2.00 mmol), [TiCl₂Cp₂] (25 mg, 0.10 mmol), acrylonitrile (0.60 mL, 9.00 mmol), and epoxide **5**

(180 mg, 1.00 mmol) were mixed in THF (10 mL). The mixture was stirred for 65 h at room temperature and then heated at reflux for 15 h. Purification by SiO₂ flash chromatography (22 cm, Ø 2 cm, AcOEt:cyclohexane (97:3)→(20:80), 20 mL) allowed the partial separation of three diastereoisomers of the desired product as pale yellow oils: *cis*-**7** (71 mg, 30%) and *trans*-**7** (112 mg, 48%, d.r. = 92:8). Combined yield: 78%, d.r. = 56:39:5. Starting material (25 mg, 14%) was also recovered. See the Supporting Information for spectroscopic details.

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Do Isopropyl and *tert*-Butyl Cations Form π Complexes with Benzene?*

Dietmar Heidrich*

The question of formation of π complexes in electrophilic aromatic substitution (EAS) has been debated for a long time.^[1–4] The answer to this question is fundamental for setting up the mechanism of EAS and, therefore, for the interpretation of the kinetic data. Quantum chemistry plays a key role in the assessment of the complex formations. Herein we deal with the identification of π complexes that may be formed from benzene and carbocations.

If we initially consider the structure of protonated benzene, π complexes of benzene with H⁺ are not found by using the potential energy surface of the benzene–H⁺ system. The only minimum is formed by the σ complex (benzenium ion).^[5,6] The latter is also observed under mass spectrometric conditions^[7] as well as in superacidic acids.^[8] A “face” protonation is strongly disfavored.^[5,6] The question arises, whether the knowledge about the protonation is qualitatively also valid for the carbocation attack on benzene.

The attack of CH₃⁺ on benzene leads barrierless to a σ complex.^[9] Our quantum-chemical studies on the interaction of the isopropyl cation with benzene do not give a π -complex intermediate (without the inclusion of electron correlation a conflicting result is obtained^[10]). Like CH₃⁺, the naked isopropyl cation approaches the benzene molecule barrierless to form the σ complex **1a** (Figure 1). In a recent theoretical paper on the alkylation of naphthalene,^[11] π -complex formation was not included. We do find a π complex (**3**) for the attack of the *tert*-butyl cation (*t*Bu⁺) on benzene preceding the σ complex **4** (Figure 2). In contrast to the results in reference [10], the cationic electrophile is not centered above the

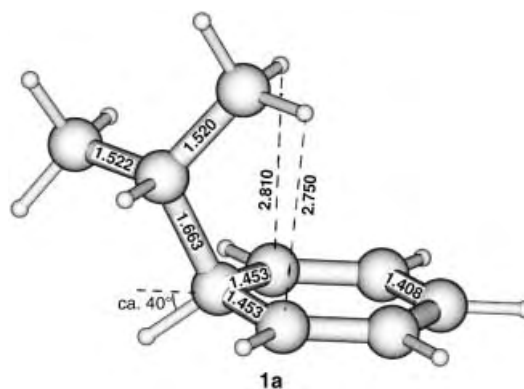


Figure 1. The σ complex **1a** of the isopropyl cation with benzene (C_1 symmetry).

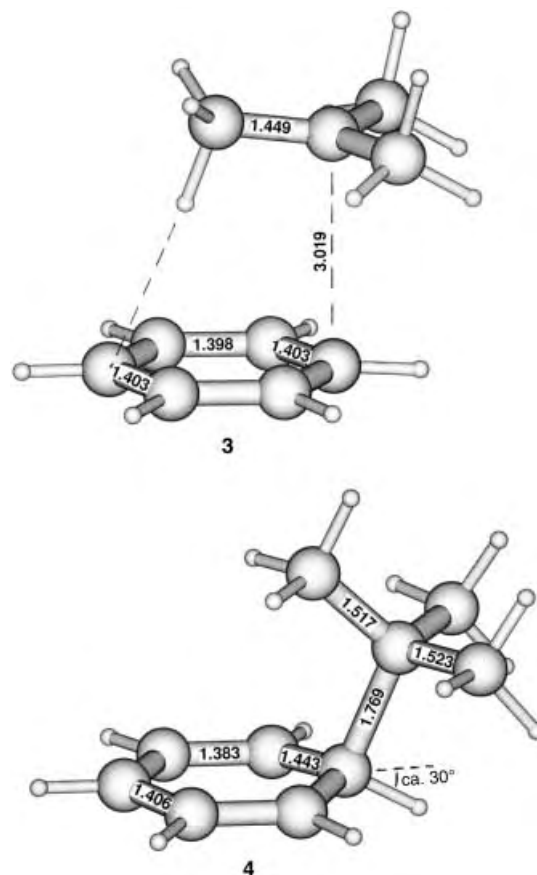


Figure 2. The π complex **3** (C_s) and the σ complex **4** (C_s) of the system [benzene + *tert*-butyl cation] (numbering according to Table 1; bond lengths [Å], angles [°]).

ring centroid. The “face” structure **5a** (C_3) is, analogously to benzene–H⁺, a saddle point of index 2 and is $\Delta H^\circ(0) = 2.5$ kcal mol^{−1} higher in energy than the σ complex (≈ 7 kcal mol^{−1} with respect to ΔE_{pot} , Table 1). Another three quasi-“face” structures **5b** (C_s) are saddle points of index 1. They are $\Delta H^\circ(0) = 2.1$ kcal mol^{−1} more unstable than the σ complex (6 kcal mol^{−1} with respect to ΔE_{pot}). The most probable position of the *t*Bu⁺ (defined by the position of the central C(δ^+) atom, C_{*t*Bu⁺) is calculated to be along the ring carbon atoms and their C–C bonds. Directly over the ring carbon atoms (distance C_{*t*Bu⁺–C_{benzene} = 3.02 Å) there is a}}

[*] Prof. Dr. D. Heidrich
 Wilhelm-Ostwald-Institut für Physikalische und Theoretische Chemie
 Universität Leipzig
 Johannisallee 29, 04103 Leipzig (Germany)
 Fax: (+49)341-97-36099
 E-mail: heidrich@informatik.uni-leipzig.de

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Table 1. Selected total energies E_t and relative energies ΔE_{pot} and $\Delta H^{\circ}(0)$.^[a]

Structure/Compound	Symmetry	E_t [Hartree] (index) ^[b]	$E(\text{ZPV})$ [kcal mol ⁻¹]	$\Delta H^{\circ}(0)/\Delta E_{\text{pot}}$ [kcal mol ⁻¹]	
benzene	C_{6h}	-231.519173 (0)	62.7	PA ^[c]	174.6/181.9
propene	C_s	-117.510856 (0)	51.1	PA	176.5/182.1
isobutene	C_{2v}	-156.699867 (0)	69.2	PA	192.0/196.1
isopropyl cation	C_2	-117.801025 (0)	56.7		
<i>tert</i> -butyl cation	C_1 $C_1^{[d]}$	-157.012347 (0) -157.012367 (0)	75.0 75.1		
<i>benzene + isopropyl cation:</i>					
σ complex ^[f]	1a C_1	-349.372478 (0)	125.1	σ -mon ^[f]	-27.1/-32.8
	1b C_s	-349.371103 (0)	125.4		
TS (σ - σ)	2 C_s	-349.356516 (1)	124.4	barr ^[f]	9.3/10.0
<i>benzene + <i>tert</i>-butyl cation:</i>					
π complex	3 C_s	-388.556170 (0)	139.8	π -mon ^[f]	-13.4/-15.5
				π -mon ^[g]	-9.9/-12.1
σ complex	4 C_s	-388.561898 (0)	142.9	σ -mon ^[f]	-13.9/-19.1
				π - σ	0.6/3.6
face structure	5a C_3	-388.550995 (2)	138.6	face- σ	2.5/6.8
quasi-face ^[h]	5b C_s	-388.552265 (1)	139.0		
TS (π - σ)	6 C_1	-388.554350 (1)	140.4	barr (π - σ) ^[f]	1.7/1.1
				barr (σ - π)	2.2/4.7
TS (π - π) ^[i]	7 C_s	-388.555902 (1)	139.8	barr (π - π)	0.2/0.2

[a] $\Delta H^{\circ}(0)$ includes zero-point vibrational energies E_{ZPV} with MP2/6-31 + G** (fc);^[12] the method is found to be sufficiently reliable for calculations in carbocation chemistry.^[11] [b] Index of the stationary point (number of negative eigenvalues of the force constant matrix). [c] Proton affinities. [d] Pyramidal *t*Bu group. [e] **1a**: Figure 1; **1b**: both CH₃ groups of the isopropyl group point symmetrically away from the ring. [f] $\Delta H^{\circ}(0)/\Delta E_{\text{pot}}$ values are given by short-hand notation of the energy differences, for example face- σ means: $E(\text{face structure}) - E(\sigma\text{-complex})$; barr: barrier, mon: monomer, etc. [g] BSSE corrected. [h] In addition to the face structure **5a** (C_3), there are further so-called quasi-face structures (C_s , **5b**) which are also no minima. In **5b** C_{tBu^+} is shifted from the ring center towards a C-C bond of the ring by about 0.3 Å. [i] The energy of the π - π transition structure (TS) is nearly identical with that of **3**; the barrier is negligible (0.2 kcal mol⁻¹, $\nu_1 = 23\text{ i cm}^{-1}$). Between two σ complexes there is no direct TS; *t*Bu⁺ follows the MEW over the TS(σ - π) into the π -complex orbit and can reach any σ -complex from there by passing the TS(π - σ).

negligible higher stability of -0.2 kcal mol⁻¹ (Table 1) compared with arrangements of C_{tBu^+} over benzene C-C bonds (distance 3.10 Å). In other words, the center of *t*Bu⁺ is not fixed along the π -electron belt around the benzene ring. Hence, the present π complex is well represented by the description frequently used for putative or real π complexes of cations with benzene (cf. ref. [1]).

The formula demonstrates the great mobility of the *t*Bu⁺ group along the benzene periphery (the formula cannot be used in the same sense for H⁺ which does not form a π complex with benzene). The “ π -complexation” energy with the *t*Bu⁺ group is $\Delta H^{\circ}(0) = -13.4$ ($\Delta E_{\text{pot}} = -15.5$) kcal mol⁻¹ and is corrected for the basis set superposition error to give -10 (-12) kcal mol⁻¹ (Table 1). The *t*Bu⁺ subunit remains nearly planar, the positive charge is still located at this group, which explains the isomerizations of the alkyl side chain.^[14]

π -Complex formation proceeds as follows: If C_{tBu^+} , with a charge of approximately +0.5 (Mulliken population analysis), approaches the π -electron belt of benzene up to about 3 Å, the system gains energy which is essentially electrostatic in nature (ion-molecule interaction!). Here, the polarization of the π -electron cloud plays an important role. However, the bonding is further enforced and stabilized at the given distance by the formation of a single hydrogen bond (2.35 Å) between one of the (positive) H atoms of the *t*Bu⁺ CH₃ groups and the π -overlap region (cf. Figure 1). This single

hydrogen bond may be lost by rotation of the corresponding CH₃ group (Figure 3) and now C_{tBu^+} is able to further approach the benzene carbon atom by forming the σ complex (C_{tBu^+} -C_{benzene} distance: 1.77 Å). However, the energy gain is limited due to the increasing steric hindrance and the increasing zero-point vibrational energy.

Importantly, the formation of the σ complex gives, in comparison to the π complex, a similar binding energy and therefore, a sufficient equalization of the stability of both complexes (despite of the very different distances between the

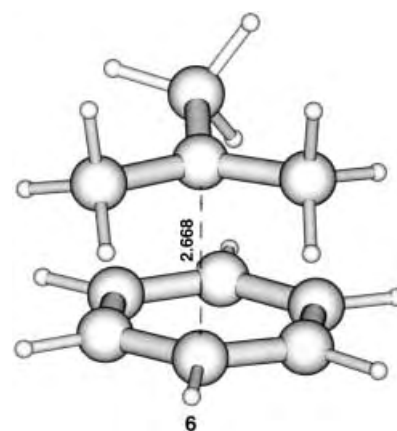
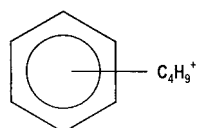


Figure 3. Benzene + *tert*-butyl cation: Transition structure **6** (C_1) between π and σ complexes viewed from the right on **3** (Figure 2) to indicate the rotation of CH₃ group at the back.

subunits of the complexes). As expected, σ complexation with the isopropyl cation shows much larger binding energy, $\Delta H^{\circ}(0) = -27.1$ and $\Delta E_{\text{pot}} = -32.8$ kcal mol⁻¹ (Table 1). Here, the π complex disappears in the steep energy descent towards the σ complex. In electron-deficient arenes the probability of π -complex formation could be increased for the isopropyl cation.^[14b] The transition structure (Figure 3) between the π and σ complex of the [C₄H₉-C₆H₆]⁺ system occurs at R(C_tBu⁺-C_{benzene}) = 2.68 Å with $\Delta H^{\ddagger}(0) = 1.7$ and $\Delta E_{\text{pot}} = 1.1$ kcal mol⁻¹, respectively. In the opposite direction, the barrier is somewhat larger: 2.2(4.7) kcal mol⁻¹. The results indicate a short-lived π -complex intermediate. The *t*Bu⁺ shifts from one *ipso*- σ -complex to the next require the intermediate change of *t*Bu⁺ back into the π -complex region. From there, each of the six σ complexes can be reached by passing the π - σ barrier. Figure 4 illustrates the energy profile.

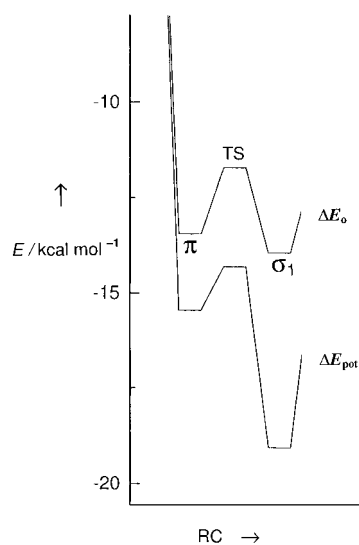


Figure 4. Energy profile of the gas-phase reaction of benzene with C₄H₉⁺ starting from the π complex formation and the subsequent transition structure to the σ complex; $E(\text{benzene} + t\text{Bu}^+) = \text{zero}$. The upper curve represents the zero-point energies (good approximation to the relative enthalpies); the potential energies below are shown for comparison.

Summarizing the results, we find an early π -complex during the attack of the *tert*-butyl cation on benzene which shows a high extent of nonrigidity along the ring periphery of benzene. The interactions are realized by electrostatic forces and a single hydrogen bond which keeps *t*Bu⁺ at a distance of 3 Å to the benzene ring. The barrier for the *t*Bu⁺ transition from the π complex to the σ complex essentially results from the loss of the hydrogen bond between the reactants by rotation of the H donor, the CH₃ group of the *t*Bu⁺.

Our results show a remarkable relation with those of gas-phase electrophilic aromatic substitution of alkyl cations with arenes studied by mass spectrometric^[14–16] and radiolytic techniques.^[17] Holman and Gross showed that σ and π complexes coexist as interconvertible species where the existence of π complexes is unambiguous for the interaction with large carbocations such as butyl and pentyl cations.^[14a] The considerable π -complex stabilization of carbocations (here about 10 kcal mol⁻¹) at a large distance from the benzene ring has also importance for the formation of

carbocation intermediates in enzymatic reactions.^[9] It remains to note that the existence of π complexes in condensed-phase electrophilic aromatic substitution cannot be determined unambiguously based on results of gas-phase ion chemistry. However, the extensive indirect evidence found by Olah^[2] provides a strong indication for the existence of π complexes also in solution, that is we can suppose that there is frequently a qualitative similarity between the structure formation in ion-molecule reactions (gas) and the corresponding electrophilic attack in certain solutions.

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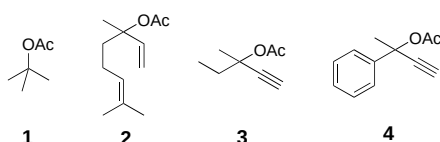
Activity of Lipases and Esterases towards Tertiary Alcohols: Insights into Structure–Function Relationships**

Erik Henke, Jürgen Pleiss, and Uwe T. Bornscheuer*

Dedicated to Professor Rolf D. Schmid on the occasion of his 60th birthday

Hydrolytic enzymes are versatile biocatalysts and find increasing applications in organic synthesis.^[1] A considerable number of industrial processes using these enzymes have been commercialized.^[2] Within this class, lipases (E.C. 3.1.1.3) and carboxy esterases (E.C. 3.1.1.1) are frequently used as they accept a broad range of non-natural substrates, are usually very stable in organic solvents, and exhibit good to excellent stereoselectivity. However, the vast majority of (chiral) substrates are secondary alcohols, followed by carboxylic acids and primary alcohols. Chiral tertiary alcohols (TA) and their esters (TAEs) are a group of important compounds, which can be found in a number of natural products (e.g., α -terpineol, linalool) and represent a group of useful building blocks.^[3] Unfortunately, only very few hydrolases accept them as substrates.^[4] Furthermore, reaction rates and/or enantioselectivities were quite low and consequently applications are rather unlikely. Structural reasons for the lack of activity—except for the expected lower chemical reactivity compared to secondary alcohols—and enantioselectivity of hydrolases towards these compounds have not been revealed so far, although the 3D structures of several lipases and esterases have been known for more than a decade.

Initially, we checked 25 commercially available enzyme preparations for their activity towards the four model acetates **1–4** (Scheme 1). In accordance with the literature, we found that only a lipase from *Candida rugosa* (CRL)^[4c,d] and lipase A from *Candida antarctica* (CAL-A)^[4e] are active.



Scheme 1. Esters of tertiary alcohols (TAEs) used as model substrates.

The protein structure of CAL-A is unknown and sequence analysis shows no major similarity to known protein structures.^[5] Thus, further investigations concentrated on the well-characterized CRL. Comparison of the 3D structure of CRL with those enzymes not active towards TAEs revealed that the alcohol binding pocket in CRL is 1.5–2 Å wider (Table 1), which thus allows the binding of the nearly spherical TA

Table 1. Comparison of the distances between the proton at the active-site histidine and the carbonyl oxygen atom at the indicated oxyanion hole residue ($N_{\epsilon, \text{His}}$ H-O_{Carb.}) for various GX and GGGX-type α/β hydrolases.

Hydrolase	PDB entry ^[a]	Type	Oxyanion hole residues	$N_{\epsilon, \text{His}}$ H-O _{Carb.} [Å]
PCL	4LIP	GX	G L17	5.88
PAL	1EX9	GX	G M15	6.00
CVL	1CVL	GX	G L17	4.06
CAL-B	1TCA	GX	G T65	6.29
HLL	1TIB	GX	G S83	6.44
CRL	1LPM	GGGX	FGG G134 F	7.76
BsubpNBE	Homology model	GGAX	FGG A107 F	7.67
hAChE	1CLJ	GGGX	YGG G122 F	7.48
eeAChE	1C2B	GGGX	YGG G121 F	7.83
BACHe	Homology model	GGGX	YGG G123 F	7.25

[a] PDB = protein data bank (<http://www.resb.org/pdb/>).

moiety. The amino acid sequence of CRL contains a GGGX motif that is positioned in the active center of the enzyme.^[6] This pattern of amino acids, located on a protein loop near the binding site of the substrate ester's carboxylic group, is involved in the formation of the so-called oxyanion hole. This involvement stabilizes the anionic carbonyl oxygen atom of the tetrahedral intermediate during the catalytic cycle of ester hydrolysis by use of two H bonds which are provided by two amide groups of the protein backbone. In contrast, most commercial lipases and esterases have a GX motif in this particular part of the active site.^[6] Here a bulky residue (labeled X) forms the H-bond. So far, the GX and GGGX motifs and their occurrence in α/β -hydrolases have been reported upon only as phenomena, but no direct linkage to catalytic properties of these enzymes has been identified.

Based on the structural differences of the GGGX and GX-type α/β -hydrolases, a computer model was developed (see Supporting Information for details). A thorough comparison of structural data of CRL with that of inactive GX hydrolases (e.g. lipase from *Pseudomonas cepacia*; PCL) revealed that in GX-type hydrolases the backbone carbonyl oxygen atom of the X residue (leucine in PCL) is orientated into the binding pocket at a location incorporating the C_α atom of the alcohol moiety of the substrate (Figure 1a). In the case of a quaternary C_α atom, which is present in TAEs, a repulsive interaction occurs between the carbonyl oxygen atom and the spherically arranged substituents of this C_α atom. In CRL, the GGGX loop should provide a most flexible conformation, because of the small hydrogen residue in glycine, (Figure 1b). Moreover, the carbonyl oxygen atoms are arranged parallel to the binding pocket, thus providing sufficient space at this critical part of the enzyme structure for the bulky tertiary alcohol group. This finding was verified first by computer simulation of substrate–enzyme complexes with GX and

[*] Prof. Dr. U. T. Bornscheuer, Dr. E. Henke
Institute of Chemistry & Biochemistry
Dept. of Technical Chemistry & Biotechnology
Greifswald University
Soldmannstr. 16, 17487 Greifswald (Germany)
Fax: (+49)3834-86-4346
E-mail: bornsche@uni-greifswald.de

Dr. J. Pleiss
Institute of Technical Biochemistry
Stuttgart University, Allmandring 31
70569 Stuttgart (Germany)

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

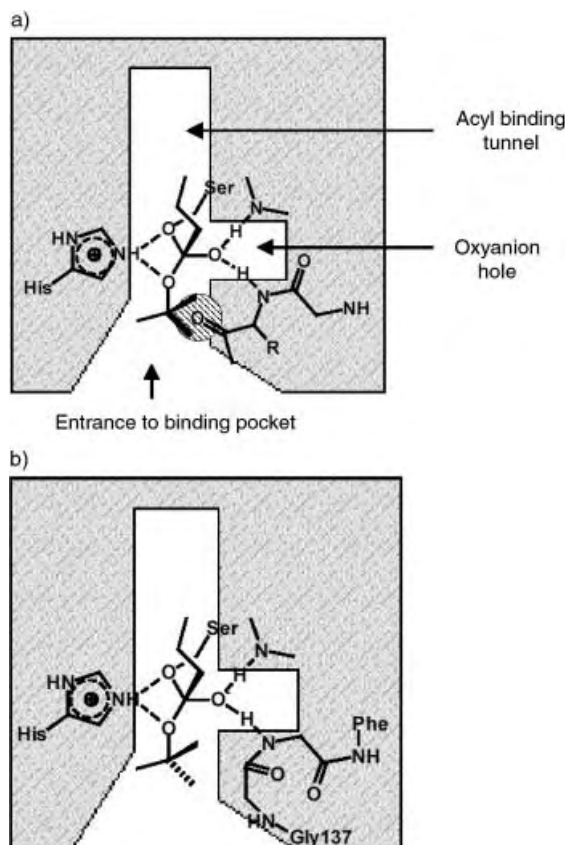


Figure 1. a) Schematic view into the binding pocket of GX-type hydrolases. The carbonyl oxygen atom of the oxyanion hole residue faces in, towards the binding pocket of the alcohol moiety. Thus interaction of this oxygen atom with the quaternary C_q atom of a TAE disables an appropriate binding of the substrate. b) Schematic view into the binding pocket of GGGX-type hydrolases (i.e. CRL). The carbonyl backbone of the flexible triple glycine motif is parallel to the limiting wall of the binding pocket. This yields an increased capability to incorporate space-demanding substrates.

GGGX-type esterases and lipases followed by experimental confirmation using a range of GGGX-type α/β -hydrolases, which were identified by amino acid sequence comparison using internet-based public databases.

Thus discovered, acetylcholine esterases from three species (electric eel (*Electrophorus electricus*; eeAChE), banded krait snake (*Bungarus fasciatus*, bAChE), and human (hAChE)), carboxylesterases (*p*-nitrobenzylesterase from *B. subtilis* (BsubpNBE) and pig liver esterase (PLE)), and an additional lipase (from *Geotrichum candidum* (GCL)) were checked for

activity in the hydrolysis of model acetates **1–4**. All PLE and eeAChE were used as commercial-grade lyophilized powders; GCL,^[7] bAChE, and hAChE^[8] were expressed in the methylotrophic yeast *Pichia pastoris*. The gene encoding BsubpNBE was cloned from genomic DNA from *B. subtilis* DSM 402 and expressed in high yields in *E. coli* (see Supporting Information for details).

With the exception of GCL, all these GGGX type α/β -hydrolases hydrolyzed the model esters (Table 2). Only eeAChE showed no measurable activity towards *tert*-butyl

Table 2. Activity of hydrolases towards **1** compared to natural substrates. Activity was determined by pH-stat assay at pH 7.5 and 40 °C (eeAChE: 25 °C).

Hydrolase		Specific activity (natural substrate) [mU mg ⁻¹ Protein]	Specific activity towards 1 [mU mg ⁻¹ Protein]
CRL	(Amano AYS)	44 000 ^[a]	10
GCL-B		83 000 ^[a]	— ^[e]
EeAChE		200 000 ^[b]	— ^[e]
CAL-A	(Chirazyme L5, Iyo)	117 000 ^[c]	50
PLE	(Chirazyme E1, Iyo)	157 000 ^[d]	80
	(Chirazyme E2, Iyo)	103 000 ^[d]	160
BsubpNBE		170 000 ^[c]	230

[a] Triolein. [b] Acetylthiocholine. [c] Tributyrin. [d] Ethyl butyrate. [e] No activity.

acetate (**1**), but this was also a poor substrate for the other biocatalysts. In contrast, substrates **2–4** were converted at high rates (up to 77 % conversion; Table 3). The activity of BsubpNBE towards **4** was 3890 mU mg⁻¹ protein; the activity of the PLE preparation Chirazyme E-1 was 1640 mU mg⁻¹ protein, which is thus 17 and 20 times more active towards **4** than towards **1**. Although activities and conversions were high, enantioselectivities of all hydrolases towards **2–4** never exceeded *E* = 10 (bAChE) and were mostly in the range of *E* = 1.5–4 (data not shown).

An additional hint that the GGGX motif is crucial for activity towards tertiary alcohols are our unsuccessful experiments to create activity by directed evolution^[9] experiments based on GX-type esterases. For this, enzyme libraries of two genes encoding esterases from *Pseudomonas fluorescens*^[10] and *Bacillus stearothermophilus*^[11] were built using error-prone polymerase chain reaction (PCR)^[12] and DNA shuffling^[13] methods, and the proteins were then expressed in *E. coli* using a strong rhamnose-inducible promoter.^[14] However, no active mutants were identified after screening a library of approximately 15 000 esterase variants.

Table 3. Activity of GGGX-type hydrolases towards substrates **2–4**. Reactions were carried out at pH 7.5, 40 °C (AChEs 25 °C).

Enzyme ^[a]	<i>t</i> [h]	Substrate					
		2	3	4	2	3	4
		Conversion [%]	Conversion [%]	Conversion [%]	<i>t</i> [h]	<i>t</i> [h]	<i>t</i> [h]
PLE, Chirazyme E-1, 390 U	2	53	48	50	8	0.5	0.5
PLE, Chirazyme E-2, 270 U	2	69	72	n.b. ^[b]	8	n.b. ^[b]	n.b. ^[b]
CRL-CLEC, 10 mg	2	56	23	77	8	0.5	0.5
hAChE, 37.5 U	24	17	5	39	48	4	4
eeAChE, 100 U	24	26	10	50	48	4	4
bAChE, 100 U	8	57	6	66	48	4	4
CAL-A, 480 U	24	41	71	59	48	2	2
BsubpNBE, 350 U	0.8	50	50	50	0.6	0.3	0.3

[a] Units refer to the activity towards the natural substrates, see Table 2. [b] Not determined.

We have provided strong evidence that the GGGX motif described for some lipases not only plays a role in stabilizing the tetrahedral intermediate during catalysis, but also governs activity towards TAs. With the exception of GCL, all tested esterases and lipases bearing the GGGX motif hydrolyzed the model acetates. In the case of GCL, we assume that this lipase will accept other TAEs.

The overall amino acid sequence similarity between these hydrolases originating from bacteria, yeast, and mammalian sources is rather low and only small regions around the GGGX motif and the active serine residue are conserved. This structure dissimilarity is also reflected by the large differences between the substrates normally accepted by these hydrolases,^[15] which means, in turn, that knowledge about their usual biocatalytic activity would not suggest that these enzymes would have activity towards TAs in common.

Furthermore, our computer model also allows the prediction of mutants with enhanced or even inverse stereoselectivity in the resolution of the model acetates of TAs.^[16]

Experimental Section

All experimental details can be found in the Supporting Information.

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¹[HgGe₉]²⁻—A Polymer with Zintl Ions as Building Blocks Covalently Linked by Heteroatoms**

Anke Nienhaus, Ralf Hauptmann, and Thomas F. Fässler*

Dedicated to Professor Dr. Gottfried Huttner on the occasion of his 65th birthday

Homoatomic-element polyhedra of the type E_n^{x-} (E = Group 14 element) are promising candidates for the formation of complex structures with interesting electronic properties. The polyhedra E_n are stable with different charges so they can be employed as electron reservoirs and suitable coupling of the clusters can lead to unexpected properties. The alkali-metal fulleride phases are a particularly impressive example of this. They contain C₆₀³⁻ ions and become superconducting at relatively high critical temperatures.^[1] The structural characterizations of the linear polymer anions with C₇₀^[2] and Ge₉^[3] as building blocks show new possibilities for obtaining complex structures by covalent linking of the polyhedra. Recently we have pointed out parallels between fullerides and homoatomic polyhedra of the heavier elements of Group 14, the latter are known as Zintl ions.^[4] Such homoatomic Zintl ions have been known since 1891 when their formation by dissolving elementary tin or lead in a solution of sodium in liquid ammonia was reported,^[5] however, there is still little known about their chemical reactivity.^[6]

During our examinations of semiconductors and metal clusters as building blocks for ordered structures, we successfully coupled Ge₉ clusters with Hg atoms for the first time.^[7] The compound [K(crypt)]₂[HgGe₉](en)₂ (**1**) can be prepared by the reaction of a solution of the binary alloy K₄Ge₉ in ethylenediamine (en) with elementary mercury in the presence of [2.2.2]cryptand (crypt).^[8] As expected the Hg atoms appear as bridges between the E₉ clusters forming a linear polymer of the composition ¹[HgGe₉].

Single-crystal structure determination of **1** shows that the Hg atoms are connected to two Ge atoms situated opposite of the open rectangular face of the Ge₉ cluster.^[9] The shortest Hg–Ge separations (Figure 1) are 2.543(1) Å (Hg–Ge3) and 2.606(1) Å (Hg–Ge4). There are significantly longer separations from the Hg atom to two more sets of Ge atoms 3.049(1) Å (Hg–Ge5) and 3.120(1) Å (Hg–Ge6) as well as 4.096(1) Å (Hg–Ge7) and 4.043(1) Å (Hg–Ge8). The shorter distances to the atoms Ge5 and Ge6 means that the Ge₉ cluster is tilted with respect to the Hg–Hg vector.

The bond angle Ge3–Hg–Ge4 is 172.2(3)° and points to a coordination number of two for the Hg atom and thus to a covalent interaction between Hg and the Ge atoms. The

*] Prof. Dr. T. F. Fässler, A. Nienhaus, Dr. R. Hauptmann
Technische Universität Darmstadt
Anorganische Chemie II
Petersenstrasse 18, 64287 Darmstadt (Germany)
Fax: (+49) 6151-16-6029
E-mail: faessler@ac.chemie.tu-darmstadt.de

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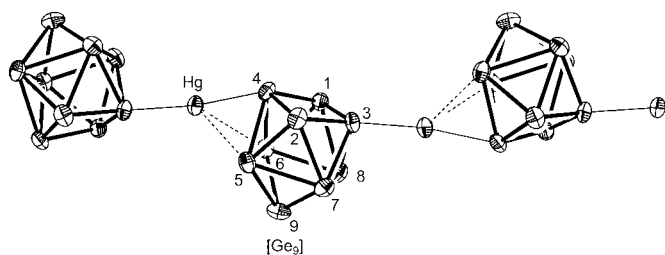


Figure 1. Section of the molecular structure of the linear polymer $[1][\text{HgGe}_9]$ in **1** (thermal ellipsoids set at 50% probability). Interatomic distances [Å]: Ge1–Ge3 2.555(2), Ge1–Ge4 2.583(1), Ge1–Ge6 2.550(1), Ge1–Ge8 2.682(1), Ge2–Ge3 2.555(1), Ge2–Ge4 2.575(2), Ge2–Ge5 2.537(1), Ge2–Ge7 2.643(1), Ge3–Ge7 2.606(1), Ge3–Ge8 2.590(1), Ge4–Ge5 2.726(1), Ge4–Ge6 2.725(1), Ge5–Ge6 2.904(1), Ge5–Ge7 2.750(1), Ge5–Ge9 2.560(1), Ge6–Ge8 2.756(1), Ge6–Ge9 2.567(1), Ge7–Ge8 2.776(1), Ge7–Ge9 2.589(1), Ge8–Ge9 2.587(1), Hg–Ge3 2.543(1), Hg–Ge4 2.606(1).

shortest Ge–Hg separations are in the range of the sum of covalent radii which again indicate a covalent bond ($r_{\text{Hg}} = 1.30 \text{ Å}$, $r_{\text{Ge}} = 1.22 \text{ Å}$).^[10] Comparable bond parameters are observed in the organometallic compound $\text{Ph}_3\text{Ge–Hg–GePh}_3$ with Ge–Hg separations of 2.543(1) and 2.514(2) Å and a Ge–Hg–Ge bond angle of 178.68° .^[11]

There are two $[\text{K}(\text{crypt})]^+$ ions for each $[\text{HgGe}_9]$ unit which leads to a charge of -2 for the monomer of the polymer chain (Figure 2). The Ge–Ge bond lengths range from 2.537(1) to 2.904(1) Å and are in accordance with those known in other Ge_9 clusters.^[12] Here the longest bond, 2.904 Å, is between Ge5 and Ge6, which have weak interactions with the Hg atom. Depending on how the charges are allocated, the polymer can be formulated as $-(\text{Ge}_9)^{2-}\text{–Hg–}(\text{Ge}_9)^{2-}\text{–Hg-}$ with covalent bonds between the Ge and Hg atoms, or with the formal charges of $(\text{Ge}_9)^{4-}\text{–Hg}^{2+}\text{–}(\text{Ge}_9)^{4-}\text{–Hg}^{2+}$. The clusters possess 22 skeletal electrons independent of charge allocation. From Wade rules a *nido* structure in form of a mono-capped square-antiprism with C_{4v} symmetry is expected. The geometric bond parameters in **1** point to a C_s symmetric body with a structure between the *nido* and *closo*

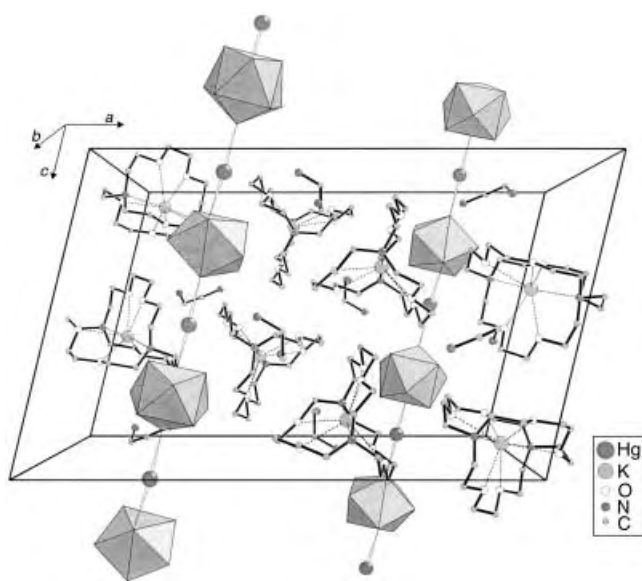


Figure 2. Unit cell of **1** with projection along the *b* axis.

(tri-capped trigonal-prism, D_{3h} symmetry) type. The *closo* structure is expected for 20 skeletal electrons. The open rectangular face of the underlying C_{4v} symmetric polyhedra in **1** is clearly a distorted rhombus with the shorter diagonal parallel to the polymer axis ($d(\text{Ge1}\cdots\text{Ge2}) = 4.049(2) \text{ Å}$, $d(\text{Ge3}\cdots\text{Ge4}) = 3.149(1) \text{ Å}$). Assuming a trigonal prism of the atoms Ge3 to Ge8, the prism edge ($\text{Ge3}\cdots\text{Ge4}$) is extended by 14% compared to the edges Ge5–Ge7 and Ge6–Ge8. The nearly C_{2v} symmetric topology of clusters is common and observed in a large number of Ge_9 clusters with 22 and 21 skeletal electrons.^[12]

The $[1][\text{HgGe}_9]$ chains in **1** are separated from each other by $[\text{K}(\text{crypt})]^+$ ions and arranged parallel to the *c* axis in the form of a distorted hexagonal-close packing of rods (Figure 3). There are no bonding interactions between the $[1][\text{HgGe}_9]$

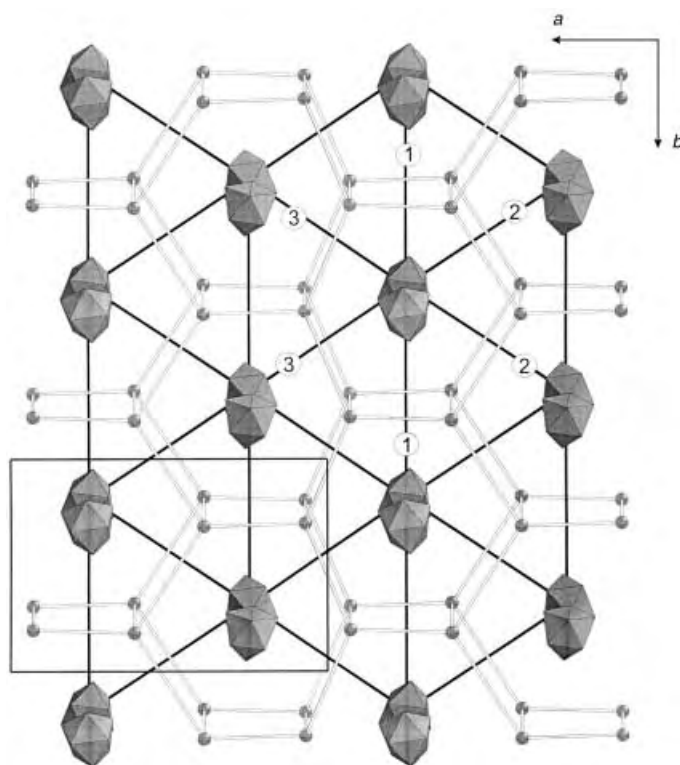


Figure 3. Crystal structure of **1** with projection along the *c* axis. The polymer chains are ordered analogously to a hexagonal close-packing of rods. Distances between the centers of gravity of the clusters: ① 16.242, ② 15.084, and ③ 14.736 Å. The $[\text{K}(\text{crypt})]^+$ ions form a strongly distorted lattice of hexagons. For the reason of clarity the $[\text{K}(\text{crypt})]^+$ units are represented by the central K atoms alone.

chains and the cations. The distances between the centers of gravity of the clusters of neighboring chains are in the range from 14.736 to 16.242 Å. The en molecules occupy the space between the $[1][\text{HgGe}_9]$ chains showing no bonding interactions to the chains or to the cations (Figure 2).

Compound **1** is synthesized from $[\text{Ge}_9]^{4-}$ ions and Hg^0 without using an oxidant. The comparable formations of $[1][\text{Ge}_9]^{2-}$,^[3] $[\text{Ge}_9\text{–Ge}_9]^{6-}$,^[13] $[\text{Ph}_2\text{Bi–Ge}_9\text{–BiPh}_2]$,^[14] and the paramagnetic ions $[\text{Ge}_9]^{3-}$ ^[15–17] using $[\text{Ge}_9]^{4-}$ ions as precursors also proceed without oxidizing agents. For the present reaction

which uses an excess of mercury, oxidation might occur through impurities, but also by the reduction of mercury.

Synthesis of compound **1** shows the possibility to use Zintl ions as building blocks to construct complex structures. In agreement with the structural results and charge allocation, crystals of **1** shows no signal in the EPR spectrum.^[18] Partial oxidation or reduction of the polymer chain—which corresponds to an insertion of paramagnetic clusters into the chain—should lead to interesting magnetic properties. Each homoatomic cluster of the one-dimensional polymer in **1** has two more reactive sites. In principle, these sites hold the possibility to build two-dimensional polymers by repeated oxidative coupling in presence of atoms able to build bridges. In attempts to prepare analogues of **1**, syntheses using Sn₉ clusters instead of Ge₉, up to now, simply lead to the decomposition of the solution and formation of elementary tin. A comparable synthesis to link Sn₉ clusters with Te atoms leads to the break down of the cluster and formation of the heteroatomic ions [Te₂Sn(μ₂-Te)₂SnTe₂]⁴⁻ and [Sn(μ₂-Te)₃Sn]²⁻.^[19]

Experimental Section

The synthesis of compound **1** was carried out under argon atmosphere using a glove-box or Schlenk line. Toluene (Merck) and en (Merck) were dried over CaH₂ (Fluka), freshly distilled and degassed. The binary phase of the formal composition “K₄Ge₉” was prepared by high-temperature reaction (650 °C) from the elements K and Ge (Chempur) in the ratio 4:9. K₄Ge₉ (200 mg, 0.25 mmol) was dissolved in en (3 mL) in a Schlenk tube and stirred for 5 min in an ultrasonic bath. The resulting dark green solution was filtered onto to Hg (300 mg, 1.5 mmol). Afterwards the reaction mixture was treated for 20 min in an ultrasonic bath, filtered, and added to [2.2.2]crypt (376 mg, 1 mmol). The resulting solution was layered with toluene (3 mL). After about three days compound **1** crystallized as red brown columnar crystals with a yield of 90 mg (20 % with respect to K₄Ge₉). Elemental analysis (%) calcd: C 26.61, H 4.91, N 6.21; Found: C 26.82, H 4.95, N 6.04.

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- [8] [2.2.2]crypt = 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo-[8.8.8]hexacosane.
- [9] Crystal structure determination: Crystals of **1** were mounted in glass capillaries. Structure solution (SHELXS-97) and refinement (SHELXL-97) was carried out with direct methods and full-matrix least-square methods based on *F*² for all non-hydrogen atoms except those of the en molecules, with anisotropic displacement parameters. Crystal dimensions 0.17 × 0.42 × 0.46 mm³, lattice constants at 150 K:

a = 24.994(5), *b* = 16.242(3), *c* = 16.062(3) Å, β = 103.51(3)°, *V* = 6340(2) Å³; space group *P*2₁/c (No. 14), *Z* = 4, ρ_{calcd} = 1.891 g cm⁻³, μ = 6.800(2) mm⁻¹; data collection: STOE-IPDS2, MoK_α-radiation, 2θ_{max} = 50.02° (imaging-plate distance 120 mm); of 49959 total reflections, 11123 were independent (*R*_{int} = 0.108); *R*₁ = 0.061 and *R*_w = 0.102 for 609 parameters and 8619 reflections with *I* > 2σ(*I*), *R*₁ = 0.081 and *R*_w = 0.108 for all data, respectively. CCDC-182906 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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A Further Step towards Single-Molecule Sequencing: *Escherichia coli* Exonuclease III Degrades DNA that is Fluorescently Labeled at Each Base Pair**

Susanne Brakmann* and Sylvia Löbermann

The international race to sequence the human genome as well as the genomes of other model organisms encouraged efforts to realize “single-molecule sequencing”—an idea which nourishes the hope to simplify and speed up the task of sequencing DNA segments as long as 50 000 base pairs (bp) and joining the sequence information of genome fragments.^[1–5] The different strategies to realize single-molecule sequencing are based on that single fluorescent molecules can be identified within milliseconds,^[6] and they combine sequential enzymatic hydrolysis of individual DNA molecules with subsequent identification of the released monomers by their

[*] Dr. S. Brakmann
Applied Molecular Evolution
Institute for Zoology, University of Leipzig
Talstrasse 33, 04103 Leipzig (Germany)
Fax: (+49) 341-97-36848
E-mail: sbrakma@rz.uni-leipzig.de

S. Löbermann
Max Planck Institute for Biophysical Chemistry, Am Fassberg, 37077 Göttingen (Germany)

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fluorescence characteristics, either wavelengths, or fluorescence lifetimes, or both.^[7,5]

Two unusual enzymatic activities are required for this technique, 1) the complete and faithful synthesis of DNA copies exclusively from fluorescently labeled analogues of the four types of bases (A, G, C, and T), and 2) the exonucleolytic degradation of the completely labeled DNA. Recently, we presented a solution to the problem of complete enzymatic labeling by identifying the wildtype Klenow fragment (KF) of *E. coli* DNA polymerase I as the first natural polymerase which retains full activity and fidelity in the sole presence of rhodamine-labeled deoxynucleoside triphosphates.^[8] We demonstrated that the complete substitution of all the pyrimidine bases of one DNA strand and thus, complete labeling of every base pair by the respective fluorescent analogues can be achieved using KF in a primer-extension reaction.^[9]

That a natural DNA polymerase exhibited full performance with bulky rhodamine-labeled substrates and was also capable of accommodating the sterically and electronically demanding DNA product stimulated us to screen a series of natural exonucleases for activity on substrate DNA that was completely rhodamine-labeled at all the pyrimidine bases of one strand (fluorescent nucleotides: Tetramethylrhodamine-dUTP, and Rhodamine-Green-dCTP). In preliminary experiments which were based on the online monitoring of fluorescence intensity in a fluorimeter (LS-50; Perkin-Elmer) we assessed the acceptance of completely rhodamine-labeled DNA by bacteriophage λ exonuclease, snake venom phosphodiesterase, as well as two DNA polymerases known to possess 5'→3' exonuclease activity, bacteriophage T7 DNA polymerase, and KF. Since DNA that harbors a very high density of rhodamine labels usually is nonfluorescent (except those sequences which contain homopolymeric regions of A:T (A:U) base pairs), we expected to observe a substantial increase in fluorescence intensity upon release of fluorescent monomers by an exonucleolytically active enzyme. However, the fluorescence behavior of the reaction systems studied did not change, which indicated that none of the enzymes showed activity with the highly modified substrate, no hydrolytic reaction occurred. Because labeled DNA tends to aggregate in aqueous solution, we added various organic solvents (e.g. acetonitrile, or DMSO) to a maximum of 10 % (v/v). Although these were known to increase the solubility of the highly modified DNA^[9] they did not enhance the targeted reaction because their denaturing, or toxic effect on the enzymes prevailed. An important hint towards a solution of this problem came from the observation that a high degree of fluorescence labeling could promote the transition of a portion of right-handed B-form DNA to left-handed Z-form DNA:^[9] In accord with observations made by Ogilvie and Hruska for snake venom phosphodiesterase,^[10] we assumed that the labeled DNA which possibly contains syn-oriented nucleosides was not accepted as a substrate by the enzymes studied. In further tests, we employed *E. coli* exonuclease III because this enzyme had been useful in searching for potential Z-DNA regions within genomic DNA.^[11] Indeed, we observed a substantial increase in rhodamine fluorescence upon addition of exonuclease III to an aqueous solution of labeled

DNA (no co-solvents present). In attempting to optimize the performance of this reaction, we tested a variety of additives, such as bovine serum albumin (BSA), glycerol, spermidine, sarcosine, DMSO, or Triton-X-100, all of which did not increase the turnover of substrate DNA. The addition of a maximum of 25 % 1,4-dioxane, however, enhanced the DNA-degradation reaction substantially by supporting the solution of the dye-labeled DNA without affecting the natural enzyme.

Since sequential degradation of completely rhodamine-labeled DNA by exonuclease III could be the key to a future single-molecule sequencing, we examined the action of this enzyme in detail. Using equilibrium kinetic analysis, we varied a series of rate-determining factors, which include enzyme concentration, temperature, or presence of organic co-solvent, and we compared the results gained with the labeled DNA to a standard reaction of exonuclease III and natural DNA of the same sequence (with only rhodamine label at the 5'-terminal for detection). Quantitative fragment analysis by using an automated fluorescence-based sequencing system (ABI 373A) enabled us to determine fragment lengths of educt and product(s) relative to an internal standard, as well as fluorescence intensities (relative concentrations) of all the fragments present. Evaluation of the electropherograms permitted the estimation of apparent hydrolysis rates in terms of nucleotides per second, as well as the determination of second-order reaction rates (see Supporting Information for details).

Processivity: The most striking difference between the degradation reactions of natural and completely dye-labeled substrate with or without dioxane could be recognized by visual inspection of the electropherograms. We observed that exonuclease III degraded the fluorescent substrate DNA in dioxane-containing solutions without showing intermediates (that is, processively) at the time intervals chosen (earliest point = 0.3 min after addition of enzyme). Even at a 280-fold molar excess of exonuclease III over substrate, this degree of processivity was not achieved with natural DNA or in the absence of 1,4-dioxane. Instead, we observed—in accordance with other investigations^[12]—that progressively shortened intermediates appeared with increasing reaction time (usually more than one species centering around a predominant fragment length) while the respective precursor(s) disappeared (*distributive* mode).

High processivity of exonuclease III at rhodamine-labeled DNA is related to the reaction conditions being different from the “natural reaction”. The limited availability of substrate within the aqueous phase requires the presence of solubility-mediating 1,4-dioxane. Association of enzyme and substrate to the active complex therefore might take place in “solvent cages” where the reaction into products comes to an end before enzyme and substrate dissociate.

Apparent rate of hydrolysis: The activity of exonuclease III at fluorescently labeled DNA appeared to be independent of enzyme concentration and temperature when the reaction was performed with the organic co-solvent. Because no intermediates were present, and because the electropherograms of samples taken after increasing periods of time differed in the relation of educt and product only, a maximal rate was presumed. According to this assumption, the rate of

Table 1. Apparent rate of hydrolysis, $\bar{v}$, and processivity of exonuclease III as derived by visual evaluation of electropherograms.^[a]

Entry	DNA label	[E_0] [U]	T [°C]	1,4-dioxane	Substrate turnover [%]	t [min]	$\bar{v}$ [nt s ⁻¹]	Processivity
1	TMR, RG	5	37	+	26	0.3	16.5	+
2	TMR, RG	50	37	+	72	0.3	16.5	+
3	TMR, RG	250	37	+	67	0.3	16.5	+
4	TMR, RG	50	10	+	38	0.3	16.5	+
5	TMR, RG	50	20	+	68	0.3	16.5	+
6	TMR, RG	50	37	+	72	0.3	16.5	+
7	TMR, RG	25	20	+	56	0.3	16.5	+
8	TMR, RG	25	20	–	15	5.0	1.1	–
9	none ^[b]	25	20	–	98	0.2	4.1	–

[a] TMR = tetramethylrhodamine; RG = rhodamine–green. [b] 5'-Terminal RG label.

processive hydrolysis reached a value of 16.5 nucleotides per second (nts⁻¹). Intermediate degradation products of both, dye-labeled and natural DNA, arose when no 1,4-dioxane was present. Whereas natural DNA was hydrolyzed at a rate of ≈ 4 nts⁻¹ (this value is in good agreement with published data of ≈ 5 nts⁻¹ at 37°C),^[12,13] the rate decreased to about 1 nts⁻¹ with dye-labeled DNA.

Enzyme concentration and temperature, however, influenced the extent of substrate turnover at the time of first product appearance. This finding reflects that 1) an increase of temperature enhances the solubility of substrate DNA, and 2) elevated enzyme concentrations increase the probability for the association of enzyme and substrate (Table 1). Of note is that the activity of exonuclease III is strongly dependent on the incubation temperature under natural conditions (rate duplication every 6°C between 22 and 46°C).^[12]

Regarding our aim to investigate the biochemical requirements for a single-molecule sequencing, we now can conclude that the fundament has been built: Although it will probably be necessary to label all four bases of one strand of DNA with a fluorescent label, and to then digest the labeled strand, it could, in principle, be sufficient to only label two nucleotides, and then repeat the experiment with all possible permutations.^[7,14] This “minimal”, or two-color, approach could be accomplished with our findings that DNA can be copied into two daughter strands with complete tagging of each pyrimidine base, and that the heteroduplex DNA with one strand of natural origin, the complementary strand being labeled, serves as a template for the sequential hydrolytic degradation by exonuclease III of *E. coli* if 1,4-dioxane is added. The solvent not only facilitates the solubility of the labeled DNA but also changes the microscopic behavior of the enzyme from the distributive to a highly processive mode. Thus, we are confident that the “proof-of-concept” of single-molecule sequencing will now become feasible.

Experimental Section

Steady-state kinetic analysis: A solution of dsDNA template (40 fmole) with one strand completely rhodamine-labeled at each pyrimidine (ca. 370 bp; fragment of HIV reverse transcriptase coding sequence) was prepared in reaction buffer (75 μ L) composed of Tris-HCl (66 mM, pH 8.0), MgCl₂ (0.66 mM), dithiothreitol (DTT; 50 mM), BSA (0.5 mg mL⁻¹), and 25% (v/v) 1,4-dioxane. Exonucleolytic degradation of the substrate was started by addition of exonuclease III (2 μ L; dilutions containing the amounts of enzyme units as indicated in Table 1; United States Biochemicals) and incubation at 20°C. Samples (7 μ L) were taken prior to the addition of enzyme (0 min), as well as after 0.2, 2, 5, 10, 15, 20, 30, 60, 120 min, and the reaction was stopped with ethylenediaminetetraacetate

(EDTA; 1 μ L; 0.5 M). Following lyophilization, samples were dissolved in loading buffer (4 μ L; formamide:25 mM EDTA = 5:1 (v/v) containing 50 mg mL⁻¹ blue dextrane), supplied with 1 μ L internal fragment length standard ROX-1000 (Applied Biosystems), and analyzed using sequencing gels (6% polyacrylamide, 8.3 M urea) with resolution on an ABI 373A sequencer. Fragment lengths and their relative concentrations were determined by employing GeneScan 672 software (ABI).

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Ligand Design and Bioconjugation of Colloidal Gold Nanoparticles**

Andrea Schroedter and Horst Weller*

The binding of inorganic nanoparticles to biological molecules has created a rapidly expanding field of research that deals with numerous aspects of biosensors, medical diagnostics, and drug delivery up to fundamental investigations on the sector of self-organizing nanoelectronics.^[1] An example is the labeling of biological substrates with noble metal nanoparticles or fluorescent semiconductor particles.^[2,3] To prepare such conjugates from nanoparticles and biomolecules, the surface chemistry of the nanoparticles must be such that the stabilizing ligands are fixed to the nanoparticle and possess terminal functional groups that are available for biochemical coupling reactions if required. The binding to the particle surface is frequently done through thiol groups.^[4-6] In the case of gold nanoparticles, thiolated DNA quasi serve as ligands.^[7-10] In most cases, however, a simple thiol bond to the particle surface is not sufficient to accomplish a permanent linkage. Instead an equilibrium is established with dynamic ligand exchange. To avoid this, a shell of silica is often grown on the particle itself by means of the sol-gel technique^[11-14] and the linkage groups pointing outwards are added as functionalized alkoxy silanes during the polycondensation process.^[15,16] The result is relatively compact silica shells and a tight coating of the surface with coupling groups.

In an ideally designed surface the number of linkage groups should be adjustable and inert functional groups should be added which determine the solubility and the surface potential of the particles. The linkage groups of the ligands should adhere to the crystallite surface as much as possible and the ligands should be covalently linked together to completely avoid exchange. The crystallite surface should be tightly covered to terminate all free valence states. The thickness of the total linked ligand shell should preferably be small to keep the mass fraction of the nanoparticle core as high as possible.

Herein we describe how to synthesize such an optimized ligand shell and explain the coupling to biotin and the conjugative effect of the particles bound to biotin with avidin. Owing to the high chemical resistivity we initially developed this synthesis for gold nanoparticles; however, preliminary investigations revealed that semiconductor nanoparticles can be synthesized in an analogous way.

The schematic structure of the ligand shell is shown in Figure 1. First gold nanoparticles were prepared by reduction

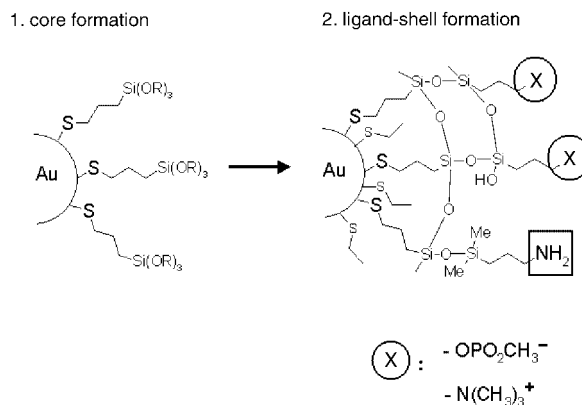
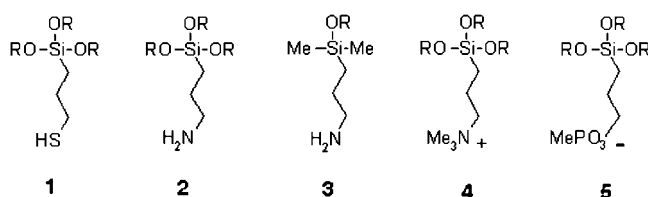


Figure 1. Schematic composition of the ligand shell.

of KAuCl₄ with NaBH₄ in propanol in the presence of the ligand 3-sulfanypropyltrimethoxysilane (**1**). We obtained



particles with an average diameter of about 2.2 nm and a standard deviation of 21 %. The thiol group of ligand **1** binds very tightly to the particle surface and the trimethoxysilyl group allows further functionalization and cross linkage of the ligands. If the polycondensation necessary took place in the presence of excessive aminopropyltrimethoxysilane (**2**), it was followed by relatively quick coagulation. From this we conclude that the trialkoxysilyl groups of the ligands **1** and **2** have formed extensive interparticular networks. We were able to avoid this coagulation step by carrying out polycondensation in the presence of 3-aminopropyldimethylethoxysilane (**3**). Ligand **3** has only one condensable alkoxy group and therefore has a terminating effect during the polycondensation process. This results in a precipitation of hydrophilic colloids which readily redissolve in H₂O. After washing with propanol, the particles can be redispersed in H₂O. Figure 2 shows a transmission electron microscopy (TEM) image with the appropriate histogram. Crystalline, well-separated particles can be discerned, their minimum distance is about 1.5 nm which corresponds to the length of twice the sum of ligands **1** and **3**. The cross-linked ligands presumably prevent the external

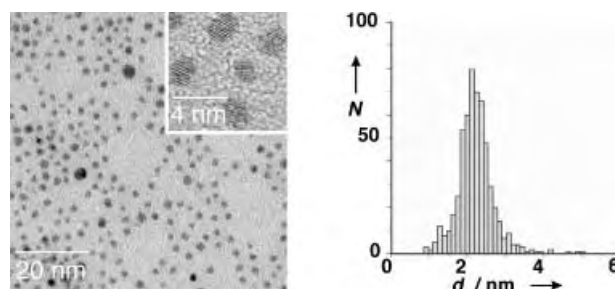


Figure 2. TEM image of the silica-coated amino-functionalized gold nanocrystals and the respective histogram.

[*] Prof. Dr. H. Weller, A. Schroedter
Institute of Physical Chemistry
University of Hamburg
Bundesstrasse 45, 20146 Hamburg (Germany)
Fax: (+49)40-42838-3452
E-mail: weller@chemie.uni-hamburg.de

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

amine ligands from binding to the surface of a second particle thus causing coagulation.^[17] This assumption is confirmed by the absorption spectrum (Figure 3) which would display an additional band at $\lambda > 600$ nm if interparticular binding was occurring. The IR spectrum of the cleaned particles shows all vibrations of the coupled ligand shell expected; detailed assignments are given in the Supporting Information.

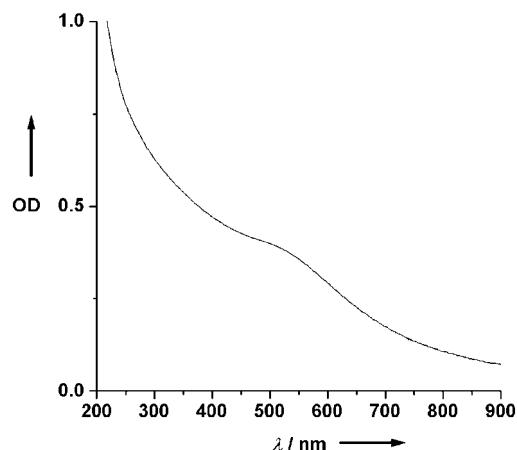


Figure 3. UV/Vis spectrum of a colloidal solution of the silica-coated and amino-functionalized gold nanoparticles in water. OD = optical density.

We determined the number of the freely accessible amino groups at the surface of the particles by using the fluorescence indicator fluorescamine.^[18–19] Figure 4a shows the number of amino groups translated into number per gold particle as a

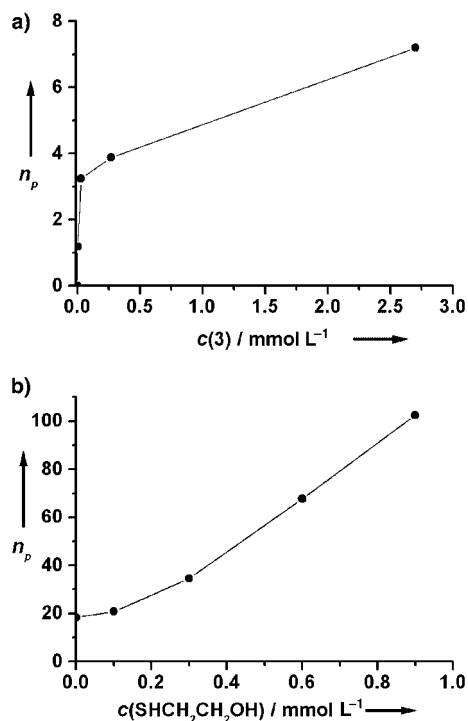


Figure 4. Number of amino groups per particle (n_p) determined with fluorescamine a) as a function of the concentration of compound **3** presented during condensation, and b) as a function of the 2-sulfanylethanol concentration. The latter compound was added as a supplementary ligand before the condensation with compound **3**.

function of the quantity of the ligand **3** added during polycondensation. It can be seen that already relatively small concentrations of **3** are sufficient to verify three to four amino ligands per particle and that the number of detectable amino ligands increases only slightly after further increasing the concentration of **3**. Owing to the relatively small required surface area of the ligands chosen, the small number of amino groups per particle is hard to understand, one may, moreover, suspect that during polycondensation the aminopropyl group is not only incorporated in a way that the amino groups point outwards, but also that backbonding to the particle surface takes place. This is readily explained as the voluminous trimethoxysilyl end groups of the originally used ligands **1** prevent the gold particles from being completely covered by thiolate groups. Back-bonded amino groups which are fixed to the particle surface cannot be detected with fluorescamine as this molecule only reacts with free primary amines and hardly reaches the particle surface.

To support the theory of amino backbonding and to possibly prevent the latter, we added the short-chained ligand 2-sulfanylethanol during polycondensation. We intended to block the free coordinating sites at the particle surface thus impeding amino backbonding. Figure 4b shows the number of amino groups detectable by fluorescamine, this time as a function of the 2-sulfanylethanol concentration. One can clearly recognize that the 2-sulfanylethanol molecules quasi force the amino groups outwards.

With the synthesis described one obtains water-soluble nanoparticles with a tightly bound ligand shell and amino groups pointing outwards which are particularly suitable for coupling reactions with biological molecules. The amino group can be brought to react with the activated ester of biotin,^[20–22] a molecule that conjugates with outstanding selectivity and specificity with avidin proteins. Biotin–avidin coupling represents an extraordinary example for the molecular key-and-lock system in biological processes. With increasing biotinylation the formerly hydrophilic nanoparticle surface becomes more and more hydrophobic and the biotinylated particles precipitate gradually in aqueous media. We solved this problem by adding during polycondensation besides the ligand **3**, the ligand **4** functionalized with quaternary ammonium. Quaternary ammonium groups cannot bind to biotin, they only cause a positive surface charge of the particles over the entire pH range and give rise to the desired water solubility of the particles during the biotinylation of the amino ligands. It is possible to adjust the number of coupling groups at the surface by varying the ratio of ligands **3** and **4**.

To achieve a possible coupling of negatively charged biomolecules such as DNA, ligand **4** can be exchanged for ligand **5** which results in a negative surface charge of the particles preventing coagulation due to Coulomb attraction. Preliminary experiments with DNA were successful, and details will appear in a future article. To prove the conjugation of biotinylated particles, we mixed fluorescently labeled avidin with varying quantities of biotinylated particles. The resulting conjugates have a molar mass of such a magnitude that they can easily be separated from the solution by centrifugation. The fluorescence intensity F of the super-

natant solution is shown in Figure 5 as a function of the added quantity of biotinylated particles. The ratio of biotinylated particles to the avidin substrate is indicated on the x axis (r). It can be seen that already from about two gold particles per

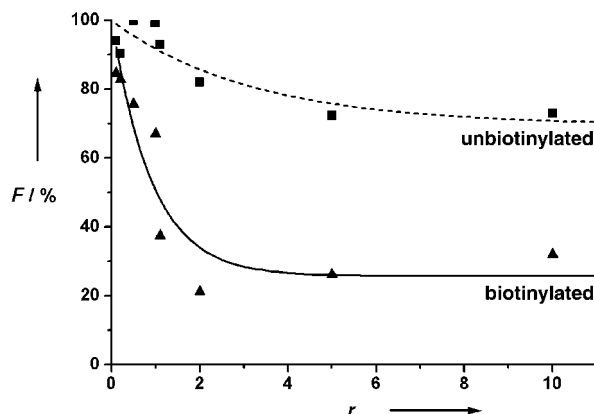


Figure 5. Decrease of fluorescence by FITC-avidin in the supernatant solution after the centrifugation of the mixtures of FITC-avidin with biotinylated and unbiotinylated particles as a function of the molar particle/avidin ratio.

avidin molecule the fluorescence intensity of the supernatant solution has decreased to about 20% of the original value, which suggests a specific coupling. From the fact that the fluorescence intensity does not decrease completely we conclude that either some of the avidin is not able to link, a certain percentage of the conjugates could not be separated by centrifugation, or that a small quantity of the fluorescence probe molecules are available as monomers and are not coupled to avidin. To further elucidate this phenomenon, we added to an identical avidin substrate the respective quantity of unbiotinylated (but in other respects identical) gold particles. We observed a slight decrease of fluorescence after centrifugation which may be explained by the small degree of nonspecific adsorption.

In summary, we present for the first time a synthesis for functionalized nanoparticles that allows one to covalently link the ligand shell at minimum thickness, thus binding it statically to the particle surface. Furthermore, the total amine ligand shell is provided in such a way that it points outward into the solution with an adjustable number of functional coupling groups and at the same time the solubility and surface charge can be adjusted by additional covalently bound auxiliary ligands. The particles surface-modified in such a way remained stable for months and did not show any signs of coagulation before and after biotinylation. The outstanding suitability for specific bioconjugation is confirmed by the biotin-avidin coupling.

Experimental Section

All chemicals used were of highest available purity, and were supplied by Merck, Sigma, Aldrich, Fluka, and ABCR. The Millipore water had a specific resistance of 18.2 MΩ cm.

UV/Vis absorption spectra were recorded with a Varian Cary 50 single beam spectrometer. Fluorescence spectra were measured at room temperature with a FluoroMax-2 ISA Instruments Inc. fluorescence spectrometer.

High-resolution transmission electron microscopic images were recorded with a Philips CM 300 UT microscope, which operates with an LaB₆ cathode at 300 KV and is equipped with an EDX detector (EDAX) and a CCD camera type Gatan 694.

Particle synthesis: For the synthesis of the gold nanocrystals stabilized with ligand **1**, KAuCl₄ was reduced with NaBH₄ in the presence of **1**. Accordingly, KAuCl₄ (1.5 mg) was dissolved in H₂O (80 μL) and then 2-propanol (20 mL) was added, thereafter ligand **1** (0.58 μL) and NaBH₄ (0.2 mg, dissolved in H₂O (240 μL)) were added under stirring. The surface of the resulting 2.2 nm gold colloids was condensed in the presence of various alkoxysilanes.

For the amino functionalization four freshly prepared 20 mL aliquots of gold colloids were mixed with compound **3** (x μL) each replenished to 10 μL by addition of dry DMF (x μL (equivalent to *c*(**3**) in the reaction mixture); 0.01 μL (2.7 μM); 0.01 μL (27 μM); 1 μL (270 μM); 10 μL (2.7 mM)), with a 50% solution of compound **4** (40 μL) in methanol, and 25% aqueous NH₃ (1.5 mL) and then stirred for 16 h. The resulting colloidal precipitate was washed three times in propanol and redispersed in H₂O (10 mL). The number of NH₂ groups was determined with sols cleaned in this way.

In a further series of experiments the surface of the gold particles was protected with 2-sulfanylethanol before the condensation step. Directly after reduction 2-sulfanylethanol (x μL (equivalent to *c* in the reaction mixture); 0.14 μL (100 μM); 0.42 μL (300 μM); 0.84 μL (600 μM); 1.26 μL (900 μM)) were added to 20 mL aliquots of freshly prepared colloidal solution followed by condensation in the presence of compound **3** (10 μL) and 25% aqueous NH₃ (1.5 mL). The colloids were cleaned as described above and redissolved in H₂O (10 mL).

In a blank experiment we added the respective amounts of 2-sulfanylethanol to the readily formed colloidal solutions after shell preparation and determined the number of NH₂ groups. No increase was found.

Determination of the NH₂ groups with fluorescamine: To each cleaned colloidal solution (600 μL), H₂O (400 μL), 50 mM borate buffer pH 9 (1 mL), and a fluorescamine solution (100 μL, 2.8 mg in 1 mL of acetone) were added and stirred for 30 min. Absorption spectra and emission spectra (λ_{ex} = 390 nm) of the solutions diluted to 1/5 were recorded.

The negatively charged, amino-functionalized gold nanocrystals were synthesized in methanol. The reduction took place using the same quantities as described above. Successively, a 50% methanolic solution of ligand **5** (45 μL), ligand **3** (10 μL), H₂O (500 μL), and a 50% methanolic solution of tetramethylammonium hydroxide (500 μL) were added under stirring and refluxed for 25 min. After the mixture had been allowed to cool, trimethylchlorosilane (26 μL) was added and the mixture was further refluxed for 10 min. A 5-mL sample of the resulting clear solution was mixed with H₂O (1.5 mL), concentrated to 1 mL using a rotary evaporator, and then purified by using a Sephadex G-25 column.

Biotinylation: The colloids from a 20-mL preparation, which had been condensed with a mixture of ligand **3** (10 μL) and ligand **4** (40 μL), were redissolved in H₂O (3 mL) and intensively dialyzed against a 5 mM K₂HPO₄ buffer. Succinimidyl 6-(biotinamido)hexanoate (0.7 mg) was dissolved under dry N₂ in dry DMF (140 μL) and then added to the gold colloids under stirring. After 14 h the resulting clear solution was purified by dialysis.

The quantitative determination of the NH₂ groups before and after the biotinylation served as an indicator for the success of biotinylation and resulted in an average covering of two biotin groups per particle.

FITC-avidin-particle conjugates: For a series of experiments with various particle/avidin ratios we replenished x μL of the purified solution of biotinylated colloids (x μL (particle/avidin ratio); 7.5 μL (0.25); 15 μL (0.5); 30 μL (1); 75 μL (2.5); 150 μL (5); 300 μL (10)) to 300 μL with H₂O, added an FITC-avidin solution (15 μL, 0.15 mg protein mL⁻¹) and shook the mixture for 20 min.

The mixtures were filled up with H₂O to 3 mL and centrifuged at 13000 rpm for 5 min. Emission spectra of the supernatant solutions were recorded at an excitation wavelength of 495 nm.

An identical series of experiments was carried out with the same, but unbiotinylated particles.

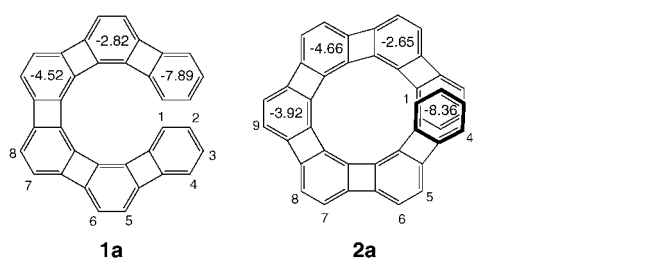
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Total Syntheses and Structures of Angular [6]- and [7]Phenylene: The First Helical Phenylenes (Heliphenes)**

Sangdon Han, Andrew D. Bond, Raymond L. Disch, Daniel Holmes, Jerome M. Schulman, Simon J. Teat, K. Peter C. Vollhardt,* and Glenn D. Whitener

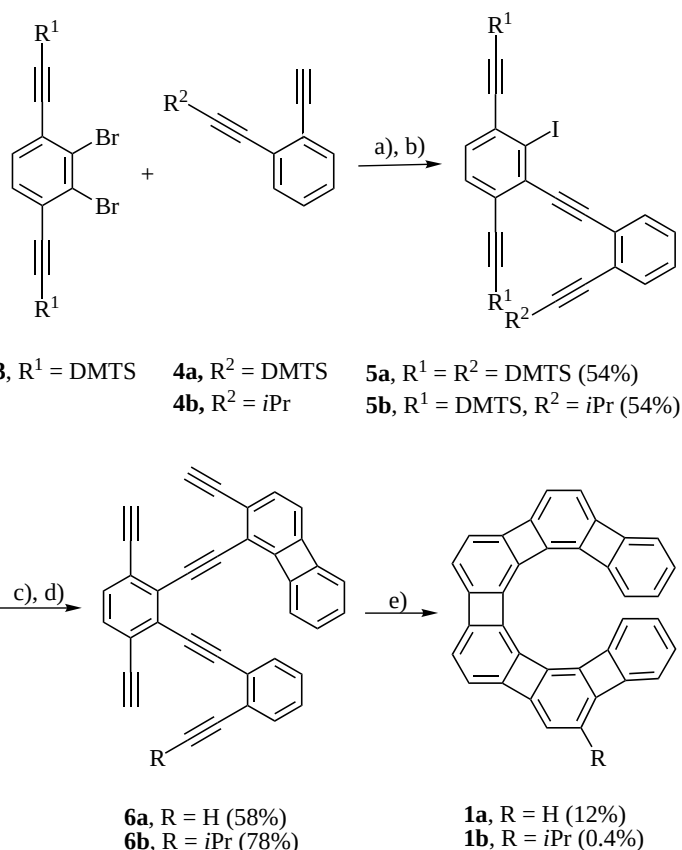
Helically extended conjugated π systems are of great interest in the design and synthesis of novel molecules and materials with a variety of unusual properties and applications.^[1] The $[N]$ phenylenes,^[2] comprised of alternating N benzene units fused to $N-1$ cyclobutadiene rings, can be regarded as highly σ - and π -activated “spacer” polycyclic benzenoid hydrocarbons, long arrays of which may furnish interesting structures endowed with small band gaps.^[3] Among their various topologies, the angular variant is unusual, in as much as it becomes helical for $N > 5$, a feature that has attracted the attention of theoretical chemists.^[4] So far, unbranched phenylenes could be synthesized only up to $N=5$.^[2,5] We disclose herein the synthesis of the next two higher members of the series, the first helical phenylenes (heliphenes), **1a**, $N=6$, and **2a**, $N=7$ [nucleus-independent



chemical shift (NICS)(0) values are given inside the rings], their X-ray structures (and comparison with the structure of

angular [5]phenylene, **11**), and their ease of enantiomerization.

Consideration of a cobalt-based cyclization strategy^[2a,5,6] to the target molecules ruled out an adaptation of the single-cyclotrimerization approach used in the construction of their lower benzocyclobutadienologues, because of the absence of suitably functionalized angular [3]phenylene derivatives. Instead, a double-cyclization protocol was followed, in which the requisite hexaynes were derived by judicious Pd-catalyzed alkynylations of the readily available central core building block **3**.^[7] For **1** (Scheme 1), appendages **4a** and **7** had been made previously,^[2a,5b] and **4b** was prepared by employing 3-

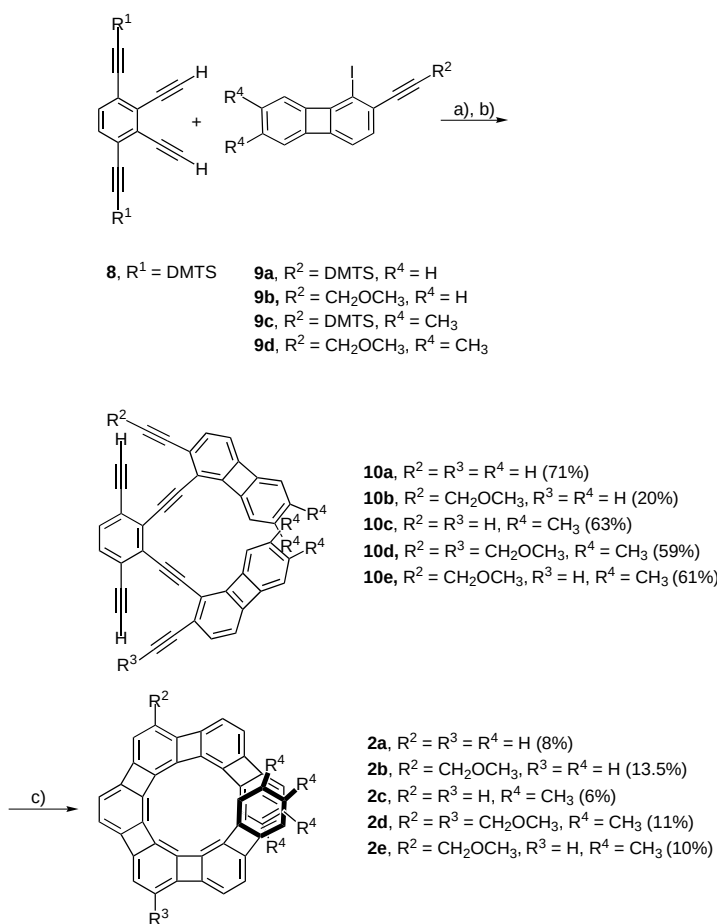


Scheme 1. a) 4–6% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 4–6% CuI , Et_3N , 70–85 °C, 14–22 h; b) 1) BuLi , Et_2O , –78 °C, 2) I_2 , Et_2O , –78 °C; c) 1-ethynyl-2-(2-DMTS-ethynyl)biphenylene (**7**), 10% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 10% CuI , Et_3N , 85 °C, 22 h; d) $\text{Bu}_4\text{N}^+\text{F}^-$ (5–7 equiv), THF , 23 °C, 40 min; e) $[\text{CpCo}(\text{CO})_2]$ (2.5–3.5 equiv), *m*-xylene, $h\nu$, Δ , 30 min. DMTS = $\text{SiMe}_2(\text{CMe}_2\text{CHMe}_2)$ (dimethylthexylsilyl).

methyl-1-butyne as one of the alkyne units (78% from 1-bromo-2-iodobenzene). For **2** (Scheme 2), **8**^[7] and **9a**^[5b] were known, **9b** was constructed using 3-methoxy-1-propyne (77%), and **9c** and **9d** were the end result of the same sequence of steps that lead to **9a**, but starting from commercial 1,2-dibromo-4,5-dimethylbenzene (seven steps, 4.6% and 3.9% yield, respectively). The assembly of **10e** by the method used for **10b** failed. A modified protocol was successful in which the first biphenylene appendage was introduced by coupling silyl-protected 1,2,4-triethynyl-3-iodobenzene^[7] with 1-ethynyl-2-(2-DMTS-ethynyl)-6,7-dimethylbiphenylene (made in two steps from **9c**, 74%) in 72% yield, and reacting the product (after desilylation) with **9d** as in Scheme 2 (three

[*] Prof. K. P. C. Vollhardt, Dr. S. Han, Dr. D. Holmes, G. D. Whitener
Center for New Directions in Organic Synthesis
Department of Chemistry, University of California at Berkeley
and the Chemical Sciences Division, Lawrence Berkeley National Laboratory
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-643-5208
E-mail: kpcv@uclink.berkeley.edu
Dr. A. D. Bond
University of Cambridge, Department of Chemistry
Lensfield Road, Cambridge, CB2 1EW (UK)
Prof. R. L. Disch, Prof. J. M. Schulman
Department of Chemistry
The City University of New York, Queens College
Flushing, NY 11367 (USA)
Dr. S. J. Teat
CLRC Daresbury Laboratory, Warrington
Cheshire, WA4 4AD (UK)

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Scheme 2. a) For **10a**, **c**, and **d**: **9** (2 equiv), 5–16% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 5–20% CuI , Et_3N , 50–75 °C, 5–22 h; for **10b**: same conditions, but 1) **9a** (1 equiv), 2) **9b** (1 equiv); for **10e**: see text; b) $\text{Bu}_4\text{N}^+\text{F}^-$ (5–7 equiv), THF, 23 °C, 40 min; c) $[\text{CpCo}(\text{CO})_2]$ (4–15 equiv), *m*-xylene, *hν*, Δ , 30 min.

steps, 64%). Noteworthy is the desymmetrization of the ultimate starting material, 1,2,3,4-tetrabromobenzene, to the hexaalkynyl systems **6** and **10**. Angular [5]phenylene (**11**) was resynthesized^[5b] according to the double-cyclization strategy in Scheme 1 starting from **3** and **4a** (three steps, 18%).

Systems **1** and **2** are orange solids,^[8] moderately stable to air (except in solution, but sufficiently stable to be isolable by column chromatography on silica with hexane/ CH_2Cl_2 gradient), and moderately soluble in ordinary organic solvents. The spectral data (Table 1) highlight some of their extraordinary features. Thus, in the EI mass spectra of **1a** (and **1b**) diagnostic single and double dehydrogenations [M^+ , $M^+ - 2$, $M^+ - 4$] are evident (unique for the entire series), suggesting potentially facile annealing to antikekulene.^[7] The electronic spectra reveal the same characteristic patterns as those of the lower phenylene homologues^[2a] but shifted to increasingly longer wavelengths. Thus, the longest wavelength peaks along the series angular [3]- to [6]phenylene are displaced by relatively constant increments of about 20–22 nm. Interestingly, this value is approximately halved (12 nm) when going from **1a** to **2a**, perhaps an indication of convergence with the effective conjugation length in polyheliophene.^[9]

The ^1H NMR spectra could be assigned by comparison with those of the lower angular phenylenes^[2a,5b] and calculated spectra,^[4,10,12] and utilizing the simplifying effects of substitu-

Table 1. Selected physical data for **1a**, **2a**, and **2c**.^{[8][a]}

1a: light orange solid; MS (70 eV): m/z (%): 448 ($[M^+]$, 100), 446 (46), 444 (25); ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 7.00$ – 6.95 (m, 2H, H3), 6.88 (td, $J = 7.2$, 0.8 Hz, 2H, H1), 6.84– 6.82 (m, 4H, H2, H4), 6.49 (s, 4H, H7, H8), 6.34 ppm (s, 4H, H5, H6); ^1H NMR (400 MHz, C_6D_6): $\delta = 6.74$ – 6.66 (m, 4H), 6.61– 6.54 (m, 4H), 6.20 (d, $J = 6.8$ Hz, 2H), 6.16 (d, $J = 6.8$ Hz, 2H), 6.09 ppm (s, 4H); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 236 (sh, 4.46), 272 (sh, 4.43), 281 (4.66), 309 (4.35), 321 (4.32), 350 (4.19), 374 (4.02), 444 (3.61), 470 (3.57), 491 nm (sh 3.40). High-resolution MS calcd for $\text{C}_{36}\text{H}_{16}$: 448.1252; found: 448.1240.

2a: orange solid; MS (70 eV): m/z (%): 522 ($[M^+]$, 100); ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 6.77$ (dt, $J = 6.8$, 0.8 Hz, 2H, H1), 6.64 (m, 2H, H3), 6.63 (m, 2H, H4), 6.54 (m, 2H, H2), 6.49 (s, 4H, H7, H8), 6.42 (s, 2H, H9), 6.32 (d, $J = 6.8$ Hz, 2H, H6), 6.27 ppm (d, $J = 6.8$ Hz, 2H, H5); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 247 (5.03), 292 (sh, 4.95), 306 (5.16), 367 (4.44), 389 (4.39), 430 (3.99), 457 (3.99), 485 (3.86), 503 nm (sh, 3.48). High-resolution MS calcd for $\text{C}_{42}\text{H}_{18}$: 522.1408; found: 522.1403.

2c: orange solid; MS (70 eV): m/z (%): 578 ($[M^+]$, 100); ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 6.62$ (s, 2H, H1), 6.45 (s, 4H, H7, H8), 6.42 (s, 2H, H4), 6.37 (s, 2H, H9), 6.24 (d, $J = 6.8$ Hz, 2H, H6), 6.11 (d, $J = 6.8$ Hz, 2H, H5), 1.91 (s, 6H), 1.87 ppm (s, 6H); UV/Vis (CH_2Cl_2): λ_{max} ($\lg \epsilon$) = 253 (5.11), 266 (sh, 5.06), 291 (5.04), 312 (5.15), 377 (4.56), 393 (4.49), 459 (4.08), 486 (3.91), 505 nm (sh, 3.70); High-resolution MS calcd for $\text{C}_{46}\text{H}_{26}$: 578.2034; found: 578.2049.

[a] For the labeling of the protons see the structural formulae.

tion in the alkylated derivatives (Schemes 1 and 2). Two observations are noteworthy. First, as in all angular phenylenes, the terminal six-membered rings are the most diatropic (aromatic), the penultimate rings the most cyclohexatrienic. However, while the proximity of the former in **1** ($\delta_{\text{avg}} = 6.88$ ppm; cf. **11**, $\delta_{\text{avg}} = 6.95$ ppm) has an almost negligible effect on chemical shifts (pointing to the presence of a nonplanar structure), in **2** all terminal hydrogens are significantly shielded ($\delta_{\text{avg}} = 6.64$ ppm) due to the overlap stacking of the corresponding rings, as in the helicenes.^[11] Second, we had noted previously^[2a,5] that the internal benzene units reveal attenuated ring currents, the degree of which seems to alternate, in agreement with NICS data.^[10,12] A didactically useful interpretation takes recourse to Clar's notion of the electron sextet.^[13] Thus, to maximize aromaticity in the six- and minimize antiaromaticity in the four-membered rings, the extent of bond localization should alternate, starting from a minimum value at the termini. This picture explains why angular [3]phenylene has the most shielded internal (cyclohexatrienic) hydrogens in the series ($\delta = 6.18$ ppm), why in **11** the hydrogens of the central ring resonate at lower field ($\delta = 6.51$ ppm) than their neighbors ($\delta = 6.29$ ppm), and why the internal hydrogens in angular [4]phenylene have chemical shifts that are intermediate ($\delta = 6.31$ ppm). Gratifyingly, this simple model is consistent with the data for **1** and **2** (Table 1). Perhaps most impressive is that in **2** (as opposed to **11**) the central benzene ring hydrogens are *shielded* (for **2a**: $\delta = 6.42$ ppm) relative to their neighbors ($\delta = 6.49$ ppm).

The X-ray crystal structures of **1a**, **2a**, and **11** are shown in Figure 1.^[14] The compounds exhibit bond parameters that are in excellent agreement with calculations.^[4,10] Visually most dramatic is the sudden topological change from relatively planar to helical on going from **11** to **1a** and then **2a**. The phenylenes are readily deformed^[15] and, consequently, the calculated “helical strain” in **1a** (BLYP/6-31G*,

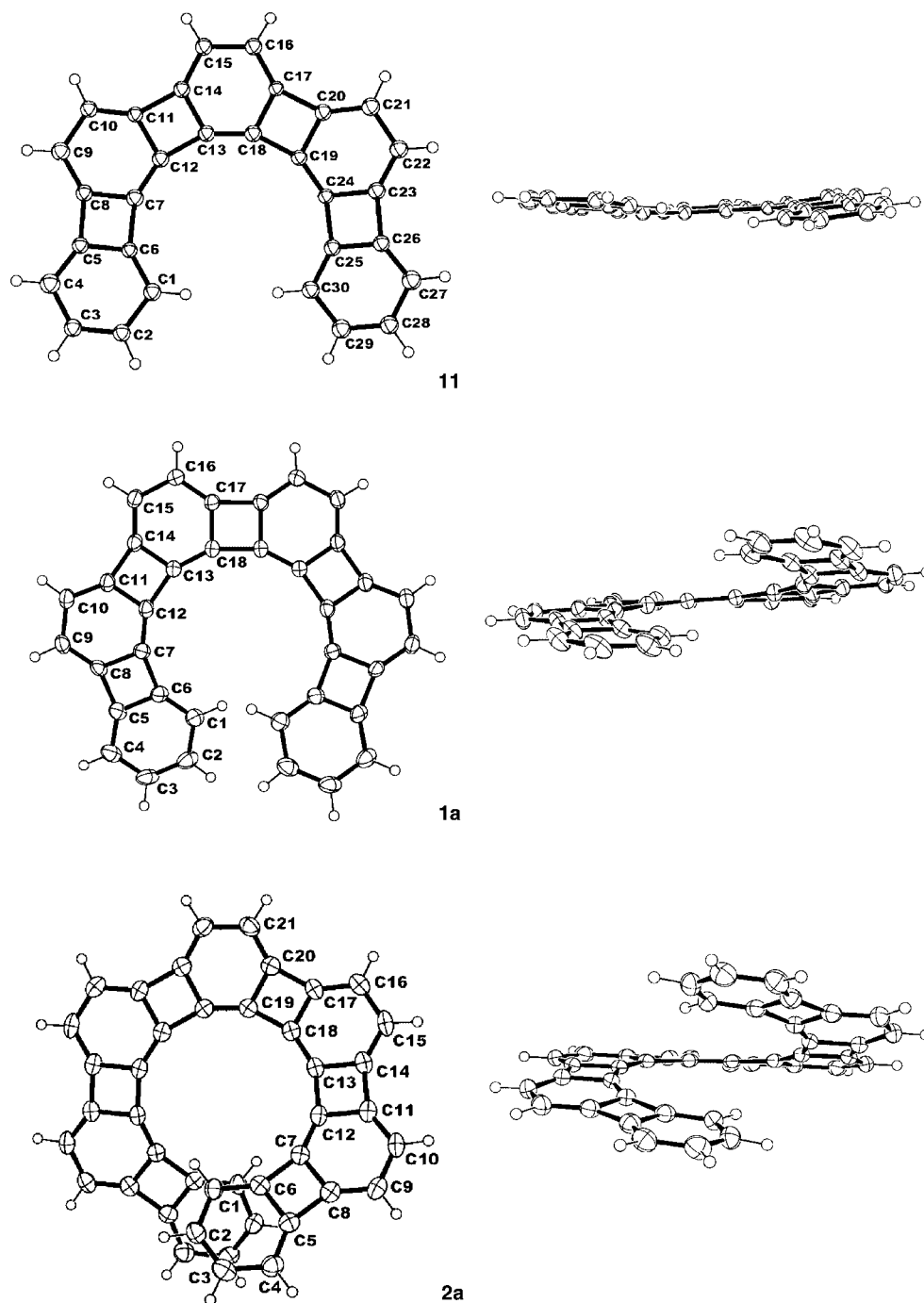


Figure 1. X-ray crystal structures of **11** (from $\text{CH}_2\text{Cl}_2/m$ -xylene by diffusion), **1a** (from CH_2Cl_2 /benzene by diffusion), and **2a** (from CH_2Cl_2 /benzene by diffusion); views from above (left) and the side (right).

$3.2 \text{ kcal mol}^{-1}$) and **2a** ($5.4 \text{ kcal mol}^{-1}$) is small.^[4] In agreement with the NMR data, the extent of bond localization alternates. Using 1,2-dimethylenecyclobutene as a 100% reference,^[16] the percent bond fixations in the six-membered rings (starting from the terminus) amount to (for **11**) 31, 68, 48% [shortest bond $1.33(1) \text{ \AA}$, longest bond $1.46(1) \text{ \AA}$], (for **1a**) 15, 55, 51% [$1.346(4)$, $1.449(3) \text{ \AA}$], and (for **2a**) 23, 53, 47, and 50% [$1.348(3) \text{ \AA}$, $1.460(3) \text{ \AA}$]. In **11**, the distance between H1 and H30 (numbering in Figure 1) is $2.68 \text{ \AA}$, beyond van der Waals contact, yet the molecule is not completely planar but adopts a prehelical conformation with dihedral angles between the

planes of adjacent rings ranging from 0.82° to 5.18° . The calculated lowest-frequency vibrational mode is $a_2 = 18 \text{ cm}^{-1}$,^[10] hence this observed distortion is certainly due to crystal packing forces.^[15] The terminal ring centroids are separated by $7.41 \text{ \AA}$, the corresponding interplanar angle is 14.3° . Taking the central six-membered ring as a reference, the inner prehelix (C1, C6, C7, C12, C13, etc.) climbs $0.64 \text{ \AA}$ and turns in plane by 305.9° .

Helical **1a** has twofold symmetry and crystallizes as stacked pairs of each enantiomer. The closest contact is between H1 and H1' at $2.36 \text{ \AA}$ (calculated $2.42 \text{ \AA}$),^[10] considerably more than that in the planar structure (calculated $1.85 \text{ \AA}$).^[4] The terminal ring centroids are separated by $5.62 \text{ \AA}$ ($5.87 \text{ \AA}$),^[10] and the corresponding interplanar angle is 22.8° (27.2° ; cf. these values for [6]helicene: $4.44 \text{ \AA}$, 58.5° ^[17]). The interplanar angles between consecutive six- and four-membered rings are 1.49 , 3.35 , 2.41 , 3.28 , and 3.28° , describing a slightly uneven helical turn. Taking the central four-membered ring as a reference, the inner helix climbs $2.16 \text{ \AA}$ ($2.30 \text{ \AA}$) and turns in plane by 337.3° (332.4°) (for [6]helicene: $3.20 \text{ \AA}$, 314.3°).^[17]

Heliphen **2a** is centrosymmetric and crystallizes as alternating right- and left-handed helices. The closest contact is between C1 and C1' [$3.31 \text{ \AA}$ ($3.64 \text{ \AA}$)] with a terminal ring centroid distance of $4.07 \text{ \AA}$ ($4.54 \text{ \AA}$) and corresponding interplanar angle of 30.1° (40.6° ; cf. [7]helicene, $3.83 \text{ \AA}$, 32.3° ^[18]). The interplanar angles between consecutive six- and four-membered rings are 2.25 , 2.99 , 4.01 , 6.66 , 4.50 , and 3.88° , more uneven and larger in size than those in **1a**. Taking the central six-membered ring as a reference, the inner helix climbs $3.29 \text{ \AA}$ ($3.64 \text{ \AA}$) and turns in plane by 361.3° (361.6° ; [7]helicene $3.75 \text{ \AA}$ and 380.8° ^[18]).

The unusual electronic nature of the heliphenes suggests exceptional chiroptical properties of the enantiomers.^[1,11,19] Therefore, the feasibility of resolving **1a** and **2a** was probed.

While the barriers to enantiomerization in the related [6]- (36.2 kcal mol⁻¹) and [7]helicene (41.7 kcal mol⁻¹)^[11] are relatively high, the bond length patterns in the angular phenylenes are distorted from perfect symmetry in such a way as to spread the termini (Figure 1).^[7] That effect, in conjunction with the phenylenes' flexible frames,^[15] suggests lesser configurational stability. Indeed, the calculated inversion barrier for **1a** (BLYP/6-31G*) is low—3.6 kcal mol⁻¹.^[4] For **2a**, AM1 calculations, which reproduce experimental findings well in the helicenes,^[20] gave a more encouraging 17.0 kcal mol⁻¹ (*C*_s symmetry). To obtain experimental numbers, the heliphene backbones were decorated with substituents bearing potentially diastereotopic units for ¹H NMR experiments (Schemes 1 and 2). In accord with the theoretical estimate above, the two methyl groups in **1b** did not decoalesce at the (solubility) limiting temperature of -75 °C (400 MHz, [D₈]toluene). We then turned to the more promising [7]phenylene derivative incorporating a synthetically more readily accessible methoxymethyl group. Heliphene **2b** showed decoalescence of the methylene hydrogen signals to an AB quartet at -27 °C (400 MHz, Δ*ν*_{max} = 13.5 Hz, [D₈]toluene), corresponding to Δ*G*[‡] = 12.6 ± 0.4 kcal mol⁻¹, a surprisingly low value (cf. [6]- and [7]helicene: Δ*G*[‡]_{-27 °C} = 36.2 and 41.7 kcal mol⁻¹, respectively),^[11c] obviating attempts to resolve the molecule.

Helicenes with methyl substituents on the terminal rings exhibit higher barriers to enantiomerization than the parent systems.^[11,20] Consequently, the tetramethylated **2c** and, subsequently, its methoxymethyl derivatives **2d** and the less symmetrical **2e** were constructed (Scheme 2).^[8] To our astonishment, the NMR spectra of **2d** and **2e** did not exhibit any changes in the appearance of the methylene singlet at temperatures as low as -70 °C (400 MHz, [D₈]toluene). An explanation for this behavior may be that in the flexible heliphenes methyl repulsion raises the ground state energy more than that of the transition state along the pathway to enantiomerization by effectively enlarging the helical climb.^[21] This consideration and the fact that **1** and **2** constitute only the first two members of the helical series provided the impetus for tackling the synthetic challenge of assembling higher heliphene systems.^[22]

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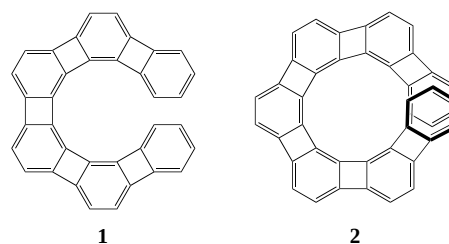
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Total Syntheses of Angular [7]-, [8]-, and [9]Phenylene by Triple Cobalt-Catalyzed Cycloisomerization: Remarkably Flexible Heliphenes**

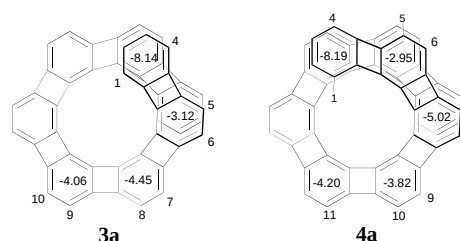
Sangdon Han, D. Ryan Anderson, Andrew D. Bond, Hiufung V. Chu, Raymond L. Disch, Daniel Holmes, Jerome M. Schulman, Simon J. Teat, K. Peter C. Vollhardt,* and Glenn D. Whitener

We have reported on the total syntheses of the first helical phenylenes (heliphenes), angular [6]- (**1**) and [7]phenylene (**2**), by a double cobalt-catalyzed cyclotrimerization strategy.^[1] These hydrocarbons are the highest members of the, so far, five angular phenylene systems and, with **2**, match the current size limit of all phenylenes.^[2] Their properties are intriguing, including unusual mass spectrometric fragmentations for **1**, a



strongly attenuated bathochromic increment in the UV spectrum of **2**, shielding of the terminal rings in **2** as a result of spatial overlap, alternating ring current intensities along the angular frame, X-ray crystallographic data that detail the helical and σ - π distortive features, and, most surprisingly, an unusually low barrier for the enantiomerization of **2**, which decreases on introduction of terminal substituents. To better understand these results, the construction of even higher members of the series was deemed imperative.

Here, we describe the total synthesis of angular [8]- (**3a**) and [9]phenylene (**4a**) [nucleus-independent chemical shift



(NICS)(0) values are given inside the rings], together with another assembly of [7]phenylene (**2**), by an unprecedented triple cobalt-catalyzed cycloisomerization protocol, the X-ray structure of **3a**, and experiments addressing the conformational flexibility of the targets.

Retrosynthetic analysis of **3** and **4** along the lines used in the formation of the lower benzocyclobutadienologues **1** and **2**^[1] proved problematic because of the absence of suitably functionalized angular [3]phenylene building blocks. As a result, a challenging disconnection of three inner benzene rings was contemplated. This approach would require the stitching together of the corresponding nonayne precursors and was first tested on a known final product, **2** (Scheme 1). For this purpose, the scaffold of the crucial intermediate **7** was put together by linking two units of **5**^[1] with a C_2 bridge in a stepwise manner via **6**.^[3] Gratifyingly, cobalt-catalyzed cyclization of **7** gave **2**. While the yield of this transformation is modest, it should be viewed within the context of what it accomplishes, namely the generation of the desired helical topology by forming nine rings in one step, including all six of the component cyclobutadienes with an associated estimated strain of about 300 kcal mol⁻¹!^[4]

Encouraged by these results, we employed the same strategy en route to **3** (Scheme 2) and **4** (Scheme 3). Triyne **8**^[5] and the requisite biphenylene reagents **11**,^[6] **12**,^[1] and **16**^[6] were known, allowing for the iterative Pd-catalyzed build-up of the target nonaynes **10** and **15**. Attempts to shorten the sequences depicted (in particular, exploiting the symmetry inherent in **7** and **15**) were less effective.

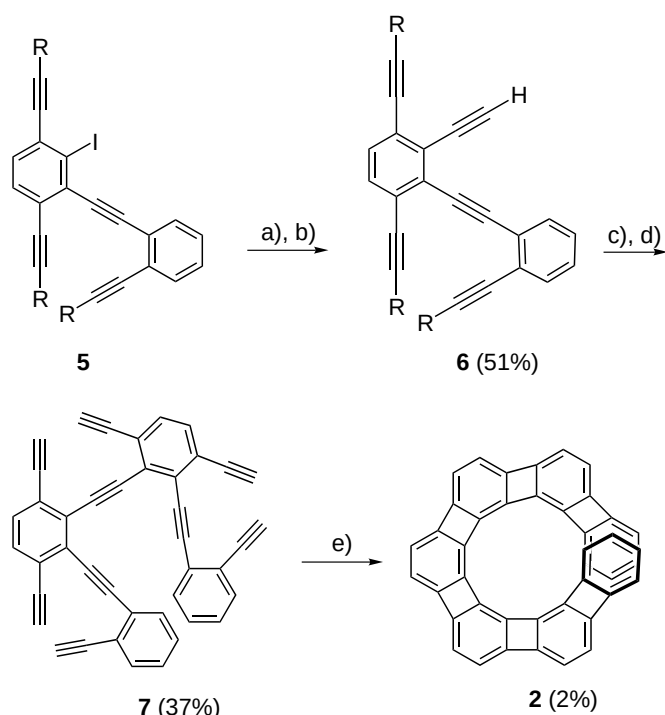
[*] Prof. K. P. C. Vollhardt, Dr. S. Han, D. R. Anderson, H. V. Chu, Dr. D. Holmes, G. D. Whitener
Center for New Directions in Organic Synthesis
Department of Chemistry, University of California at Berkeley
and the Chemical Sciences Division, Lawrence Berkeley National Laboratory
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-643-5208
E-mail: kpcv@uclink.berkeley.edu

Dr. A. D. Bond
University of Cambridge, Department of Chemistry
Lensfield Road, Cambridge, CB2 1EW (UK)

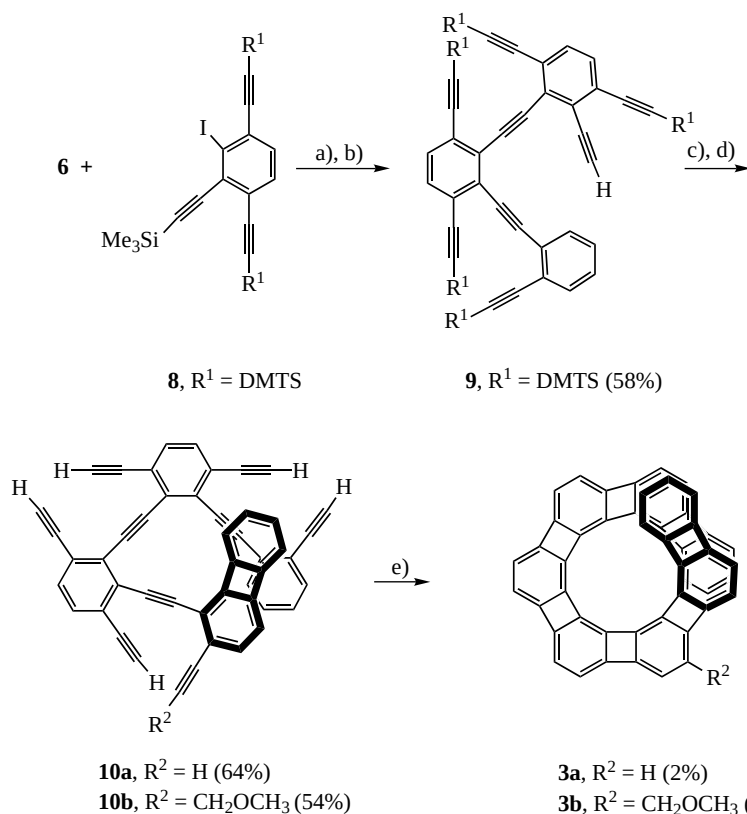
Prof. R. L. Disch, Prof. J. M. Schulman
Department of Chemistry
The City University of New York, Queens College
Flushing, NY 11367 (USA)

Dr. S. J. Teat
CLRC Daresbury Laboratory, Warrington
Cheshire, WA4 4AD (UK)

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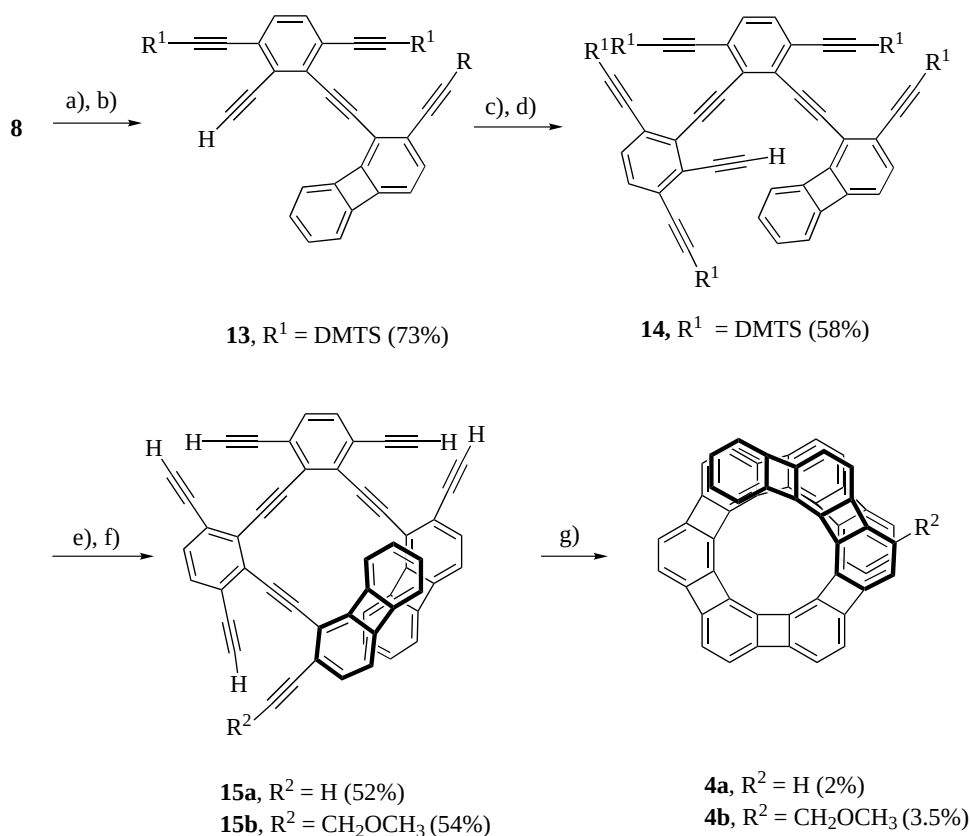
Scheme 1. a) Trimethylsilyl ethyne (2 equiv), 5% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 6% CuI , Et_3N , 85°C , 14 h; b) K_2CO_3 (0.5 equiv), THF, MeOH, 30 min; c) **6** (1 equiv), 8% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 8% CuI , Et_3N , 65°C , 17 h; d) $\text{Bu}_4\text{N}^+\text{F}^-$ (7 equiv), THF, 23°C , 1 h; e) $[\text{CpCo}(\text{CO})_2]$ (5 equiv), *m*-xylene, $h\nu$, Δ , 1 h. $\text{R} = \text{DMTS} = \text{SiMe}_2(\text{CMe}_2\text{CHMe}_2)$ (dimethylthexylsilyl).



Scheme 2. a) 12% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 9% CuI , Et_3N , 80°C , 16 h; b) K_2CO_3 (3 equiv), Et_2O , MeOH, 23°C , 15 h; c) for **10a**: 2-(DMTS-ethynyl)-1-iodobiphenylene (**11**, 1 equiv), 25% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 18% CuI , Et_3N , 85°C , 20 h; for **10b**: 1-iodo-2-(3-methoxy-1-propynyl)biphenylene (**12**, 1 equiv), 22% $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 17% CuI , Et_3N , 85°C , 16 h; d) $\text{Bu}_4\text{N}^+\text{F}^-$ (12–13 equiv), THF, 23°C , 1–2 h; e) $[\text{CpCo}(\text{CO})_2]$ (8–10 equiv), *m*-xylene, $h\nu$, Δ , 30 min.

Systems **3** and **4**, the largest phenylenes known, are orange-red solids, stable to air for one to two days (in solution for several hours, requiring rapid column chromatography on silica with hexane/ CH_2Cl_2 gradient), and moderately soluble in common solvents.^[7] The spectral data (Table 1) reflect the novel topology and electronic features of the systems. Thus, the mass spectra show the molecular ion as the base peak, typical of polycyclic aromatic hydrocarbons,^[8] but no discernible M^{2+} peaks or (for the parent compounds) significant fragmentations. The electronic spectra continue to show the typical patterns of the lower angular phenylenes, with a set of high-intensity peaks at lower wavelengths, followed by a corresponding group of weaker absorptions at higher wavelengths.^[1,9] Significantly, in light of the attenuated (from a $\Delta\lambda = 20$ – 22 nm in the lower analogues) incremental bathochromic shift of the longest-wavelength band of **2** ($\Delta\lambda = 12$ nm), the corresponding data for **3** ($\Delta\lambda \sim 10$ nm) and **4** ($\Delta\lambda \sim 9$ nm) seem to confirm a trend to smaller values. Indeed, a plot of the corresponding λ_{max} values versus $1/(N+0.5)$ ^[10] for $N = 2$ – 9 , where N is the number of six-membered rings, provides a straight line ($R^2 = 0.9954$) that extrapolates to 578 nm (2.14 eV), a possible measure of the solution band gap for the hypothetical polyheliophene. A similar graph for the helicenes gives 505 nm (3.24 eV), a clear reflection of the relative electronic activation of the phenylenes.

The assignments of the ^1H NMR spectra were consistent with those made for the lower angular phenylenes^[1,9] and with calculated spectra,^[11,12] and used the simplifying effects of substitution in the alkylated derivatives (Schemes 2 and 3). Nevertheless, the correlations of the close-lying signals for H5, H6, and H7 in **4a** are tentative. As is typical for the series,^[1,9] the terminal rings are most diatropic (aromatic), the penultimate ones the least (most cyclohexatrienic). Interestingly, however, in comparing the spectrum of **3a** with that of **2**,^[1] we note that the resonances for H1, H2, and H3 have moved slightly downfield, and those for H4, H5, and H6 upfield. A possible rationale for this behavior is found on inspection of the structure of **3a** (Figure 1), in which the former hydrogens are placed above the cyclohexatrienoid, and hence relatively less diatropic, penultimate ring of the opposite helical frame. Conversely, the latter hydrogens are now located above and relatively closer to the corresponding terminal ring, thus experiencing relatively increased shielding. Noteworthy is also the position of the peak for the internal hydrogens H9/H10 at higher field than those of their neighbors H7 and H8, in accord with the alternation of cyclohexatrienoid and aromatic character discussed previously, and nicely reproduced by the NICS(0) data (see structural drawing).^[1] The spectrum of **4a** reveals similar trends, particularly in comparison to that of **3a**, notably pronounced relative shielding of H7 and H8,



Scheme 3. a) 2-(DMTS-ethynyl)-1-ethynylbiphenylene (**16**) (1 equiv), 22 % $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 16 % CuI , Et_3N , 75°C , 17 h; b) K_2CO_3 (2 equiv), Et_2O , MeOH , 23°C , 2 h; c) **8** (1 equiv), 25 % $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 19 % CuI , Et_3N , 80°C , 15 h; d) K_2CO_3 (3 equiv), Et_2O , MeOH , 23°C , 18 h; e) for **15a**: **11** (1 equiv), 23 % $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 17 % CuI , Et_3N , 85°C , 1.5 d; for **15b**: **12** (1 equiv), 23 % $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, 18 % CuI , Et_3N , 85°C , 1 d; f) $\text{Bu}_4\text{N}^+\text{F}^-$ (12–13 equiv), THF , 23°C , 1–2 h; g) $[\text{CpCo}(\text{CO})_2]$ (8–10 equiv), *m*-xylene, $h\nu$, Δ , 25 min.

Table 1. Selected physical data for **3a** and **4a**.^{[7][a]}

3a: orange-red solid; MS (70eV): m/z (%): 596 ($[M^+]$, 100); ^1H NMR (400 MHz, CD_2Cl_2): δ = 6.92 (d, J = 6 Hz, 2H, H1), 6.69 (t, J = 6.8 Hz, 4H, H2, H3), 6.54 (d, J = 6.4 Hz, 2H, H4), 6.49 (d, J = 6.8 Hz, 2H, H7), 6.47 (d, J = 6.8 Hz, 2H, H8), 6.44 (s, 4H, H9, H10), 6.13 (d, J = 6.4 Hz, 2H, H6), 5.98 ppm (d, J = 7.2 Hz, 2H, H5); UV/Vis (CH_2Cl_2): λ_{max} (lg ϵ) = 235 (4.81), 264 (4.81), 320 (4.83), 387 (4.10), 416 (4.01), 465 (3.64), 498 (3.42), 515 nm (sh, 2.79). High-resolution MS calcd for $\text{C}_{48}\text{H}_{20}$: 596.1565; found: 596.1559.

4a: orange-red solid; MS (70eV): m/z (%): 670 ($[M^+]$, 100); ^1H NMR (400 MHz, CD_2Cl_2): δ = 6.95 (d, J = 6.4 Hz, 2H, H1), 6.61 (m, 4H, H2, H3), 6.59 (m, 2H, H4), 6.43 (s, 2H, H11), 6.39 (AB m, 4H, H9, H10), 6.23 (d, J = 6.8 Hz, 2H, H8), 6.06 (d, J = 6.4 Hz, 2H, H7), 6.04 (d, J = 6.4 Hz, 2H, H6), 5.99 ppm (d, J = 6.4 Hz, 2H, H5); UV/Vis (CH_2Cl_2): λ_{max} (lg ϵ) = 240 (4.45), 273 (4.50), 315 (4.33), 408 (sh, 3.69), 460 (sh, 3.36), 507 (sh, 3.04), 524 nm (sh, 2.72). High-resolution MS calcd for $\text{C}_{54}\text{H}_{22}$: 670.1721; found: 670.1715.

[a] For the labeling of the protons see the structural formulae.

and the occurrence of the peak for the internal hydrogens H11/H12 at lower field than that of their neighbors H9/H10.

The X-ray crystal structure of **3a**· $[\text{CH}_2\text{Cl}_2]_{0.5}$ is depicted in Figure 1.^[13] The molecule is unsymmetrical (because of the cocrystallizing CH_2Cl_2) and crystallizes as alternating enantiomers. The bond parameters are in excellent agreement with calculations.^[11,12] Unlike the lower analogues and not reflecting the NMR data, the percent bond fixation^[1] does not alternate on proceeding from the least bond-alternated terminal to the internal benzene rings, but remains essentially

constant [averaged for twofold symmetry: 29 %, 54 %, 52 %, 54 %; shortest bond 1.344(6) Å, longest bond 1.459(6) Å], perhaps reflecting the limiting value for polyheliophene. The closest intramolecular contact is between C37 and H5 [2.888 Å (calculated^[12] 3.043 Å), numbering in Figure 1]. The terminal ring centroids are separated by 4.41 Å (5.49 Å), and the corresponding interplanar angle is 23.6° (41.1°). The interplanar angles between consecutive six- and four-membered rings starting from the terminus defined by C1–C2–C3–C4–C5–C6 are 1.51, 1.60, 2.93, 6.02, 6.94, 5.99, 4.83, 4.76, 5.01, 5.15, 2.64, 2.98, 3.60, and 3.61° , describing an uneven and unsymmetrical helical turn, presumably affected by the presence of the solvating CH_2Cl_2 . Taking the central four-membered ring as a reference, the inner helix climbs 3.35 Å (4.24 Å) and turns in plane by 393.0° (389.1°). Unfortunately, crystals suitable for X-ray analysis could not be obtained for **4a** (or **4b**). However, the calculated structure^[12] gives an impression of its molecular topology. As in **3a**, the inner six-membered rings maintain

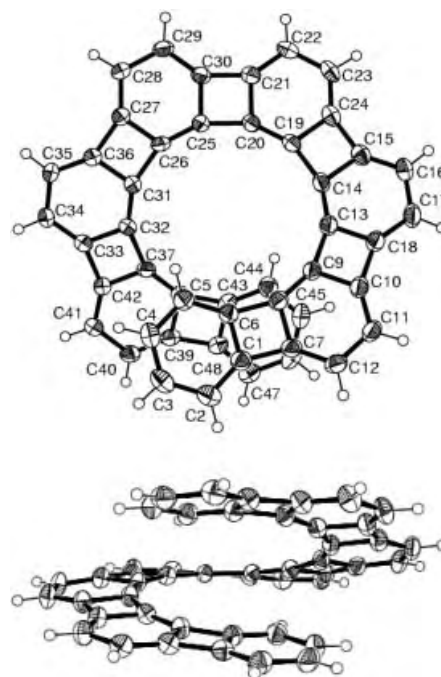


Figure 1. Structure of **3a**· $[\text{CH}_2\text{Cl}_2]_{0.5}$ (from CH_2Cl_2) in the crystal: views from above (top) and the side (bottom). Solvent of crystallization has been omitted for clarity.

approximately the same level of bond fixation (23 %, 53 %, 48 %, 48 %, 49 %, shortest bond 1.358 Å, longest bond 1.456 Å). The interplanar angles between consecutive six- and four-membered rings starting from the terminus are 1.31, 2.98, 3.61, 4.67, 3.84, 5.47, 4.50, and 4.99°, a smoother progression than that of **3a**, likely due to the absence of crystal lattice forces.^[14] The closest contact is between H1 and C22f (2.99 Å), the terminal ring centroids are separated by 7.48 Å, with an interplanar angle of 33.2°. Taking the central six-membered ring as a reference, the inner helix climbs 5.07 Å and turns in plane by 415.7°.

Are heliphenes **3** and **4** sufficiently extended to render their enantiomers amenable to resolution? The answer is provided by variable-temperature NMR experiments carried out on derivatives **3b** and **4b**. Remarkably, decoalescence of the potentially diastereotopic methylene hydrogens of the substituent in **3b** occurred only on cooling, providing $\Delta G^\ddagger_{-45^\circ\text{C}} = 13.4 \pm 0.4 \text{ kcal mol}^{-1}$ (400 MHz, $\Delta\nu_{\text{max}} = 12.6 \text{ Hz}$, $[\text{D}_8]\text{toluene}$). This value is less than 1 kcal mol⁻¹ higher than that of the corresponding [7]heliphenes **2**.^[1] To our further surprise, [9]heliphenes **4b** did not show any change in the shape of the corresponding methylene singlet signal down to the (solubility) limiting temperature of -45°C (400 MHz, $[\text{D}_8]\text{toluene}$), suggesting a lower barrier to enantiomerization, less than around 12 kcal mol⁻¹. As proposed previously,^[1,15] it appears that steric activation of the helical ground state toward unwinding the helix is responsible for the observed dynamic behavior. Structural elements, such as additional stereocenters biasing the helix or steric blockers locking it, will have to be introduced to render the heliphenes frame configurationally robust. Finally, it is evident that extensions of the “stitching” procedures outlined in Schemes 1–3 should provide access to even higher members of the heliphenes series. Such is the focus of future research.

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- [13] X-ray structure analysis: **3a**·[CH₂Cl₂]_{0.5} (synchrotron radiation, Station 9.8, SRS Daresbury): crystal size 0.08 × 0.06 × 0.01 mm³, space group *P2₁/c* (no. 14), scan range 4.80 < 2θ < 47.7°, *a* = 8.2710(6), *b* = 23.1799(18), *c* = 16.2279(13) Å, *V* = 3090.5(4) Å³, *Z* = 4, $\rho_{\text{calcd}} = 1.374 \text{ g cm}^{-3}$, $\mu(\lambda = 0.6880 \text{ Å}) = 0.78 \text{ cm}^{-1}$, 15 619 total reflections, 5266 unique reflections (*R*_{int} = 0.0411) at -53°C, of which 4062 were taken as observed [*F*² > 2.00σ(*F*²)], conventional *R*₁ = 0.0878, *R*_w = 0.2369 (on all 5266 *F*² data). CCDC-183203 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit @ccdc.cam.ac.uk).
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A New Pd⁰–Cu^I Bimetallic Catalyst for the Synthesis of Indoles from Isocyanates and Allyl Carbonates**

Shin Kamijo and Yoshinori Yamamoto*

In the research field of transition-metal-catalyzed organic synthesis, one of the modern trends is to use a bimetallic catalyst system to explore not only more efficient but also entirely new transformations. Representative examples of such bimetallic catalysis in palladium-catalyzed reactions^[1] are the following: 1) cat.Pd⁰/Cu^I in the Sonogashira coupling reaction, in which a catalytic amount of Cu salts activate terminal acetylenes to form copper–acetylide species;^[2] 2) cat Pd⁰/Cu^I in the Stille coupling reaction, in which organostannanes are transmetalated to give organocoppers which

[*] Prof. Dr. Y. Yamamoto, Dr. S. Kamijo
Department of Chemistry
Graduate School of Science, Tohoku University
Sendai 980-8578 (Japan)
Fax: (+81)22-217-6784
E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp

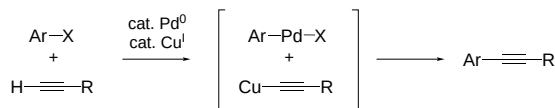
[**] We thank faculties in the Instrumental Analysis Center, Department of Chemistry at Tohoku University, for measurement of mass spectra and elemental analysis. S.K. is also thankful for fellowship support from the Japan Society of Promotion of Science for Young Scientists.

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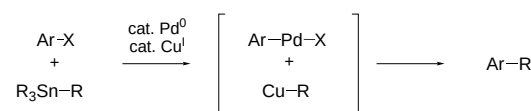
accelerate the coupling;^[3] 3) cat.Pd⁰/excess Ag^I in the Heck reaction, in which Ag salts abstract the halide ion to produce a reactive cationic Pd intermediate;^[4] 4) cat.Pd⁰/Rh^I in the asymmetric Tsuji–Trost reaction, in which Rh activates pronucleophiles by coordinating to a cyano group.^[5] Accordingly, the above examples 1) and 2) are categorized into the Pd⁰–M group, while examples 3) and 4) belong to the Pd⁰–LA

Pd⁰–M: A starting substrate is converted into a more reactive organometallic reagent

1) Sonogashira coupling reaction

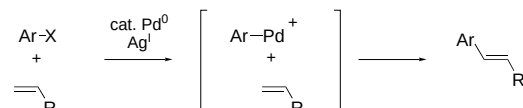


2) Stille coupling reaction

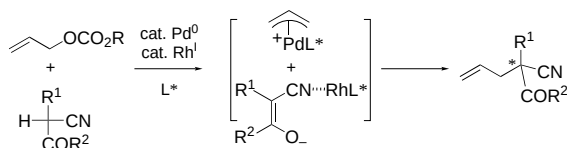


Pd⁰–LA: Lewis acid activates a starting substrate or intermediate

3) Heck reaction

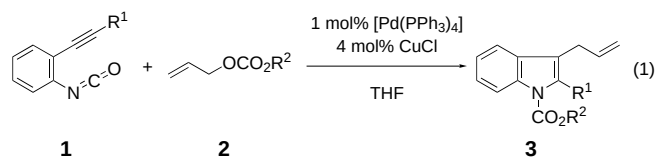


4) Asymmetric Tsuji–Trost reaction



Scheme 1. Bimetallic catalyst systems in Pd-Catalyzed Reactions. Pd⁰–M: A starting material is converted into a more reactive organometallic complex. 1) Sonogashira coupling reaction; 2) Stille coupling reaction. Pd⁰–LA: LA acts as a Lewis acid to activate a starting substrate or an intermediate. 3) Heck reaction; 4) Asymmetric Tsuji–Trost reaction.

family (LA = Lewis acid, Scheme 1). We now report that the coupling of the (2-alkynyl)phenylisocyanate **1** and the allyl carbonate **2** proceeds using a palladium–copper bimetallic catalyst system to afford indoles **3**^[6–9] in high yields [Eq. (1)],



in which Cu^I ions most probably act as π -coordinative Lewis acids.^[10]

We first investigated several catalytic systems for the reaction of **1** with **2**. The results are summarized in Table 1. The reaction of 2-(1-pentynyl)phenyl-1-isocyanate (**1a**) and allyl methyl carbonate (**2a**) in the presence of a catalytic amount of [Pd(PPh₃)₄] gave the *N*-allylaniline derivative **4aa** in 83 % yield (entry 1). After intensive investigations, we

Table 1. Effect of the additive.^[a]

Entry	Additive	NMR yield (isolated) [%] ^[b]	
		3aa	4aa
1	none	0	89 (83)
2	CuCl	78 (73)	0
3	CuBr	70	trace
4	CuI	27	20
5	[(CuOTf) ₂ ·C ₆ H ₆] ^[c]	37	0
6	CuOAc	26	37
7	Cu ₂ O	0	69
8 ^[d]	CuCl ₂	0	0
9	ZnCl ₂	62	0
10	AgCl	0	70
11	PdCl ₂	0	74
12 ^[e]	LiCl	0	0
13	<i>n</i> Bu ₄ NCl	0	80

[a] **2a** (2 equiv) was added to a solution of **1a**, [Pd(PPh₃)₄] (5 mol %), and additive (20 mol %) in THF, and the mixture was heated at 100 °C for 1 h. [b] Yields were determined by ¹H NMR spectroscopy with *p*-xylene as an internal standard (yield is shown in parentheses). [c] 10 mol % additive was used. [d] The starting material **1a** was recovered in 29 % yield, as suggested by NMR spectroscopy. [e] The starting material **1a** was recovered in 69 % yield, as suggested by NMR studies.

found that Cu^I species effectively catalyze the cyclization to form the indole **3aa**. Of the additives we tested, CuCl showed the best catalytic activities and gave the desired indole **3aa** in 73 % yield (entry 2), while CuBr showed a comparable activity to CuCl (entry 3). Other Cu^I catalysts such as CuI, [(CuOTf)₂·C₆H₆], and CuOAc gave lower yields of **3aa** (entries 4–6) and Cu₂O displayed no catalytic activity for the cyclization (entry 7). However, Cu^{II} catalysts inhibited the formation of both **3aa** and **4aa** (entry 8). Among the other metal-based catalysts, ZnCl₂ was found to catalyze the cyclization to form **3aa** in 62 % yield and did not give **4aa** at all (entry 9). AgCl and PdCl₂ did not catalyze the cyclization and gave only **4aa** (entries 10 and 11). LiCl inhibited the formation of both **3aa** and **4aa** and resulted in the recovery of the starting material **1a** in 69 % yield (entry 12), while tetrabutylammonium chloride did not yield **3aa** (entry 13). We found after further optimization of the reaction conditions that the reaction proceeds efficiently in THF by using 1 mol % of [Pd(PPh₃)₄] and 4 mol % of CuCl as cocatalysts [Eq. (1)].

We investigated the scope and limitations of the indole synthesis based on the bimetallic catalyst system. We first treated the (2-alkynyl)phenylisocyanate **1a** [R¹ = Pr in Eq. (1)] with various allyl carbonates **2** (Table 2). The reaction of **1a** and allyl methyl carbonate (**2a**) was conducted in the presence of catalytic amounts of [Pd(PPh₃)₄] (1 mol %) and CuCl (4 mol %) in THF (1M) at 100 °C for 1 h. The desired 3-allyl-*N*-(methoxycarbonyl)-2-propylindole (**3aa**) was obtained in 81 % yield (entry 1). The reaction with bulky allyl carbonates **2b** and **2c** also proceeded smoothly to give the corresponding indoles **3ab** and **3ac** in 69 and 72 % yields, respectively (entries 2 and 3). Even allyl phenyl carbonate

Table 2. Indole synthesis from **1a** and various allyl carbonates.^[a]

Entry	2	R ²	3	Yield [%]
1	2a	Me	3aa	81
2	2b	<i>i</i> Pr	3ab	69
3	2c	<i>t</i> Bu	3ac	72
4	2d	Ph	3ad	86
5	2e	Bn	3ae	83

[a] **2** (1.2 equiv) was added to a solution of **1a**, [Pd(PPh₃)₄] (1 mol %), and CuCl (4 mol %) in THF, and the mixture was stirred at 100 °C for 1 h.

(**2d**) and allyl benzyl carbonate (**2e**) gave the corresponding indoles **3ad** and **3ae** in good yields (entries 4 and 5).

We next treated allyl methyl carbonate (**2a**) [R² = Me in Eq. (1)] with isocyanate **1** having various acetylenic terminal groups (Table 3). The isocyanates with propyl (**1a**) and cyclopentyl (**1b**) substituents afforded the corresponding

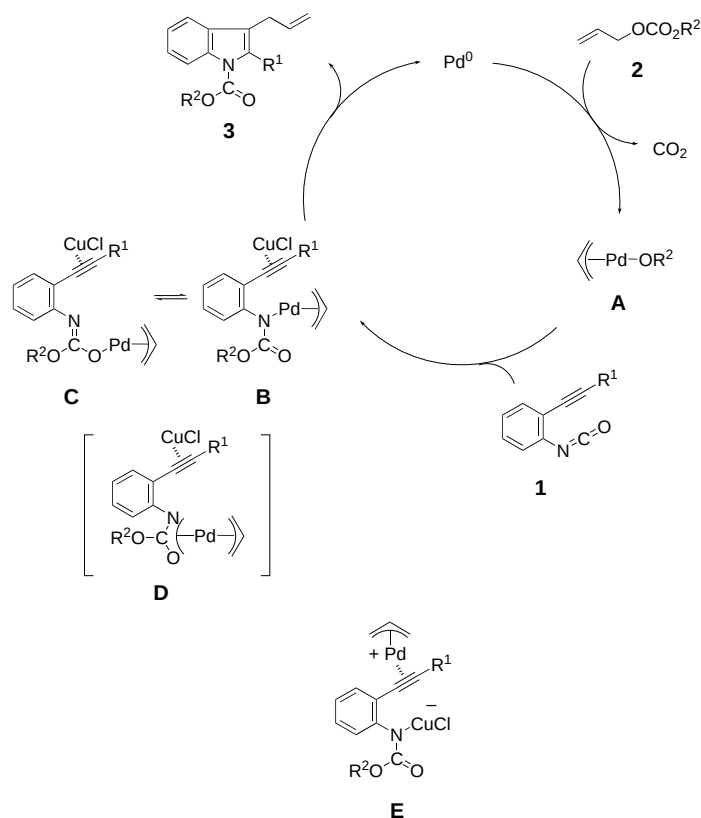
Table 3. Indole synthesis from **2a** and various isocyanates.^[a]

Entry	1	R ¹	Reaction time [h]	3	Yield [%]
1	1a	Pr	1	3aa	81
2 ^[b]	1b	cyclopentyl	3	3ba	71
3	1c	<i>t</i> Bu	5	3ca	0 ^[c]
4 ^[b]	1d	Ph	2	3da	62
5 ^[d]	1e	<i>p</i> -MeOC ₆ H ₄	6	3ea	62
6 ^[d]	1f	<i>p</i> -CF ₃ C ₆ H ₄	7	3fa	65

[a] The reaction was conducted with **1** and **2a** (1.2 equiv) in the presence of [Pd(PPh₃)₄] (1 mol %) and CuCl (4 mol %) in THF (1 M) at 100 °C for the time displayed in Table 3. [b] The reaction was conducted in 0.5 M THF solution. [c] **4ca** was obtained in 42 % yield. [d] Two equivalents of **2a** were used.

indoles **3aa** and **3ba** in 81 and 74 %, respectively (entries 1 and 2). However, the isocyanate with a terminal *tert*-butyl group (**1c**) afforded the corresponding *N*-allylaniline derivative **4ca** in 42 % yield and did not give the corresponding indole **3ca** at all (entry 3). The phenyl-substituted isocyanates **1d–1f** gave the corresponding indoles **3da–3fa** in good yields (entries 4–6). The above results indicate that the reaction proceeds irrespective of the electronic nature of the aromatic ring.

A proposed mechanism is shown in Scheme 2. Initially, the Pd⁰ center reacts with allyl carbonates **2** to give the π -allylpalladium alkoxide complex **A** with extrusion of CO₂. Then, the insertion of isocyanates **1** into complex **A** would form the π -allylpalladium intermediate **B**. This intermediate, with Pd–N bonding, could be in equilibrium with the Pd–O-bonded intermediate **C**, which should more probably be represented as the bis- π -allylpalladium analogue **D**.^[11] Insertion of the alkyne then occurs to form indole **3** and the Pd⁰ species is regenerated. The key step in this proposed mechanism is the insertion of the alkyne into the π -allylpalladium intermediates **B–D**, which occurs to give the *trans* indoles **3**. The role of CuCl is not understood completely at present, but we believe that the Cu^I center behaves as a Lewis acid for the C≡C bond to activate the alkyne through π coordination and catalyze the insertion of the alkyne into intermediates **B–D**, that is, it acts as a catalyst for the carboamination of the alkyne.^[12] An alternative mechanism through the intermediate **E** can be proposed, in which copper



Scheme 2. Proposed mechanism for the formation of indoles.

activates the nitrogen nucleophile and the alkyne bond coordinates to a π -allylpalladium cationic species.^[17] At the present time, it is impossible to distinguish between the two mechanisms; the alkyne bond is activated by copper or by palladium species. It should be emphasized that no carboamination takes place at all in the absence of CuCl.

In conclusion, we have developed a new [Pd(PPh₃)₄]/CuCl bimetallic catalyst system for the synthesis of indoles **3** from isocyanates **1** and allyl carbonates **2**. This is the first example of a palladium-catalyzed indole syntheses from isocyanates. Various kinds of indoles are now available, and deprotection of the alkoxycarbonyl group is relatively easy.^[18] Further studies on synthetic applications and a mechanistic investigation are now in progress.

Experimental Section

Allyl methyl carbonate (**2a**, 69 μ L, 0.6 mmol) was added to a solution of 2-(1-pentynyl)phenyl-1-isocyanate (**1a**, 92.7 mg, 0.5 mmol), [Pd(PPh₃)₄] (5.8 mg, 0.005 mmol), and CuCl (2.0 mg, 0.02 mmol) in THF (0.5 mL) under an argon atmosphere, and the mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to room temperature, filtered through a short Florisil pad, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 100/1 to 20/1) to afford 3-allyl-*N*-(methoxycarbonyl)-2-propylindole (**3aa**) in 81 % yield (104.2 mg).

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Fluorescence Enhancement through Enzymatic Cleavage of Internally Quenched Dendritic Peptides: A Sensitive Assay for the AspN Endoproteinase**

John M. Ellard, Thomas Zollitsch, W. Jon Cummins, Alan L. Hamilton, and Mark Bradley*

Fluorescence resonance energy transfer (FRET) systems in which a peptide sequence contains both a fluorophore and an internal quencher are amongst the best methods available for protease analysis and characterization. Numerous proteases have been studied using this method, including trypsin which cleaves the FRET-based system Dabcyl-Gly-Pro-Ala-Lys-Leu-Ala-Ile-Gly-Edans,^[1] cathepsin B which cleaves Abz-Lys-Leu-X-Phe-Ser-Lys-Gln-EDDnp (where X is Cys(SBz), Thr(OBz), or Ser(OBz) and EDDnp is 2,4-dinitrophenylthylenediamine),^[2] leukotriene D₄ hydrolase which cleaves ϵ -DNP-L-Lys-D-Amp^[3] (where Amp is 2-amino-3-(7-methoxy-4-coumaryl)propanoic acid) and caspase 1 and 3 which cleave the FRET systems BFP-Tyr-Val-Ala-Asp-GFP and BFP-Asp-Glu-Val-Asp-GFP, respectively (where BFP is blue fluorescent protein and GFP is green fluorescent protein)^[4] to name but a few. A host of methods have been developed using this methodology to determine the most appropriate substrate for a particular protease. For example, Meldal et al. have reported a powerful general method for the use of a split-and-mix approach to libraries of FRET-based peptides for on-bead screening to determine optimal substrates for a range of proteases including subtilisin carlsberg,^[5] FRET-based hexapeptide libraries have been used to map the S'-subsite specificity of serine proteases using solution-based assays,^[6] and a positional scanning substrate library has been used to determine the specificity of ICE (= interleukin-converting enzyme).^[7]

In this paper a new method for the detection of proteolytic activity is presented using internal fluorescence quenching between fluorophores of the same type. These are attached to a dendrimer-type structure, thereby giving a high local concentration of fluorophore needed for quenching yet eliminating the need for a separate quenching moiety. This method simplifies the synthesis of substrates for assay compared to traditional FRET, while being very sensitive due to the amplification nature of the assay as multiple

[*] Prof. M. Bradley, Dr. J. M. Ellard
Department of Chemistry
University of Southampton
Highfield, Southampton SO17 1BJ (UK)
Fax: (+44)23-80596766
E-mail: mb14@soton.ac.uk
Dr. W. J. Cummins, Dr. A. L. Hamilton
Amersham Biosciences
Amersham Place, Little Chalfont, Buckinghamshire HP79NA (UK)
T. Zollitsch
Current address: Infineon Technologies AG
Wernerwerkstrasse 2, 39049 Regensburg (Germany)

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cleavage sites are available. This self-quenching phenomenon was first observed in a series of dibranched, tribranched, and hexabranched dendrimeric structures, terminally loaded with fluorophores, that showed significantly reduced fluorescence with increasing branching. Thus at equal concentrations of the labeled dendrimer (determined by absorbance) the fluorescence output decreased as shown in Figure 1. This fluorescence quenching is even more significant when one considers that identical molar ratios of the dendrimers were used and that the number of fluorophores is actually increasing along the series.

For these experiments and subsequent loading with labeled peptides “dendrimers” were prepared on the solid phase

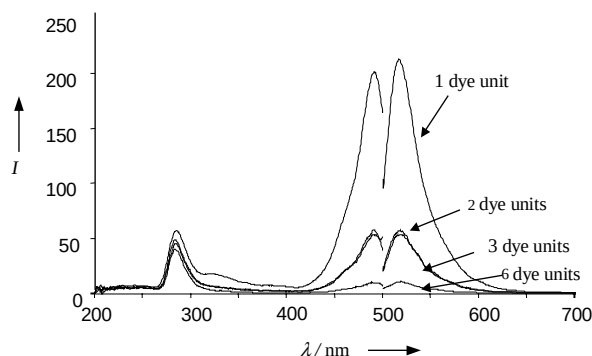
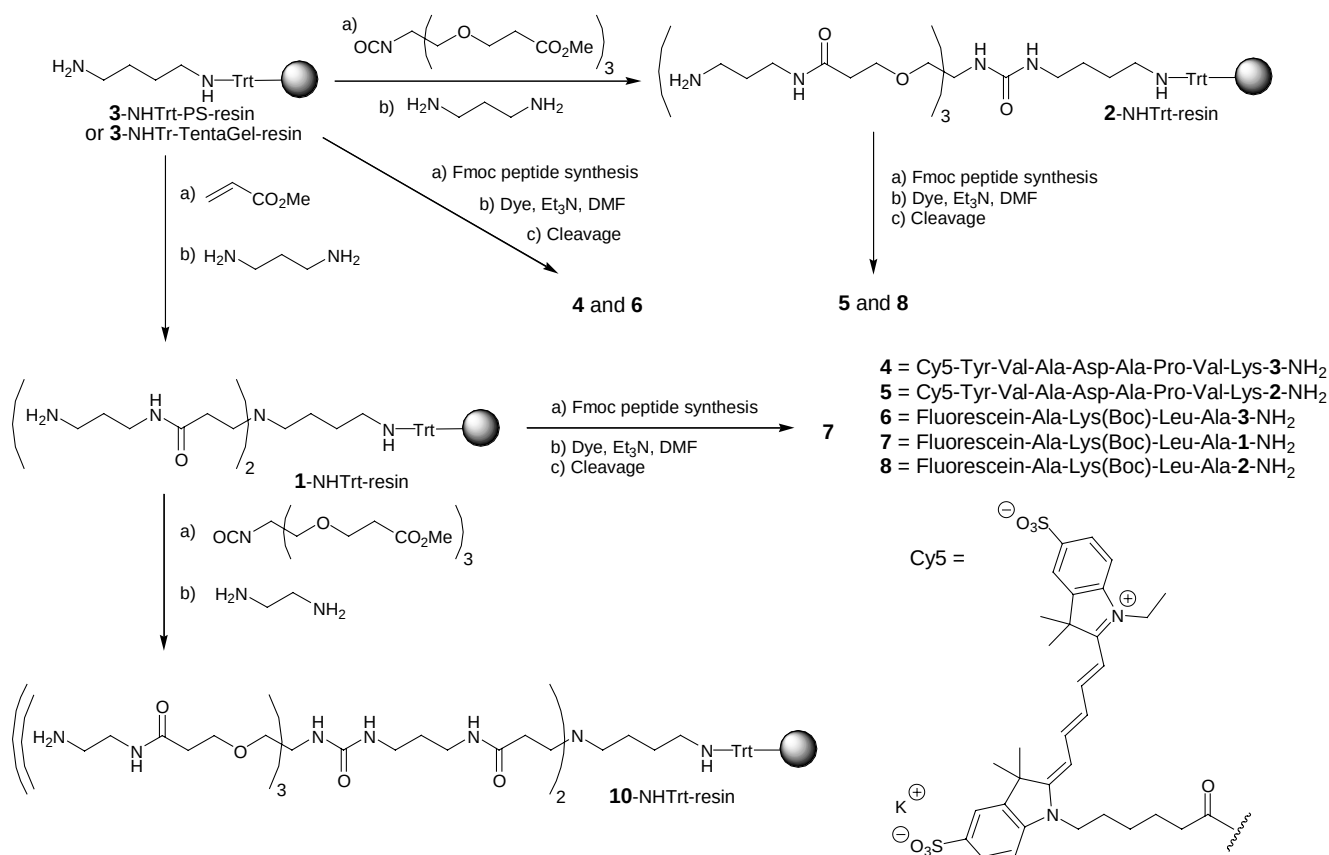


Figure 1. Fluorescence spectra (excitation 492 nm, emission 520 nm) of fluorescein-labeled constructs **3** (1 dye unit), **1** (2 dye units), **2** (3 dye units), and **10** (6 dye units) all at 0.25 μM .

(Scheme 1). Thus resin-bound 1,3-diamino-PAMAM-type dendrimer (**1**-NHTrt-resin) was prepared from 1,4-diaminobutane loaded onto TentaGel resin by a trityl (Trt) linker (0.22 mmol g^{-1} , 90 μm beads) by sequential treatment with methylacrylate and 1,3-diaminopropane.^[8a] **2**-NHTrt-resin was prepared from 1,4-diaminobutane loaded onto polystyrene resin again by a trityl linker (1.5 mmol g^{-1}) by treatment with dimethyl 6-isocyanato-6-(4-carbomethoxy-2-oxabutyl)-4,8-dioxaundecanedioate and 1,3-diaminopropane.^[8b]

The peptide Tyr-Val-Ala-Asp-Ala-Pro-Val-Lys-OH, which is specific for the protease endoprotease AspN, was constructed on the diamine resin **3**-NHTrt-resin and the dendrimer resin **2**-NHTrt-resin (Scheme 1) using standard Fmoc peptide synthesis.^[9] After the final Fmoc deprotection step the amino termini of the peptides were labelled with an *N*-hydroxysuccinimide activated ester of sulfonated Cy5. Finally the peptides were cleaved from the resin by 50% TFA and 3% TIS in CH_2Cl_2 , precipitated with ether, and purified by reversed-phase HPLC (details in Supporting Information) to afford the fluorescent peptides **4** and **5**, respectively (TFA = trifluoroacetic acid, TIS = triisopropylsilane).

Initial enzyme cleavage experiments were carried out on the linear peptide **4** and showed complete and rapid cleavage of the starting peptide. Dendritic peptide **5** was also rapidly consumed affording a fluorescent product with an identical retention time to that previously obtained from **4** (Figure 2), indicating identical cleavage sites of the two peptides. As expected, fluorescence monitoring of the enzymatic cleavage



Scheme 1. Synthesis of dendrimers **1**, **2**, and **10** and peptides **4**–**8**.

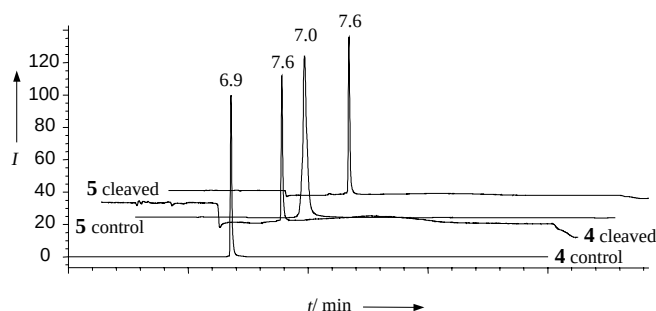


Figure 2. HPLC traces of AspN cleavage of peptides **4** and **5**.

of the linear substrate **4** revealed no increase in fluorescence, while treatment of **5** revealed a fivefold enhancement of fluorescence upon cleavage (Figure 3). From the cleavage

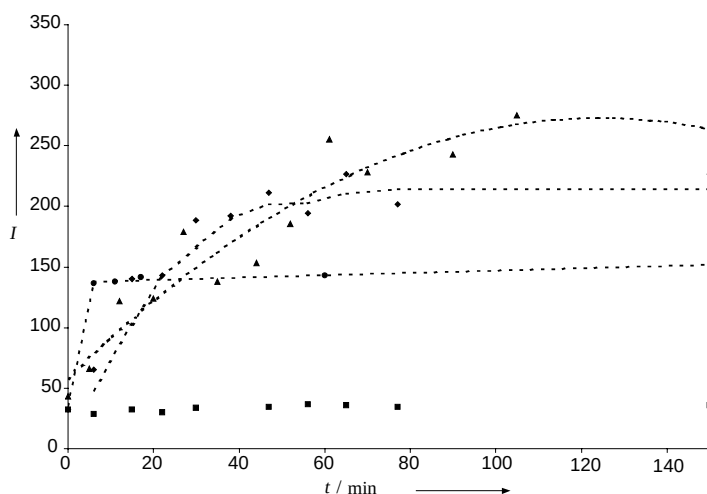


Figure 3. Fluorescence emission over time during AspN cleavage (excitation 640 nm, emission 670 nm) of peptide **5** (●) and chymotrypsin cleavage (excitation 492 nm, emission 520 nm) of peptides **7** (◆) and **8** (▲); ■ controls.

kinetics of substrate **5** a K_m of 4 μM was deduced (Figure 4). However it should be borne in mind that this value is complicated as the tribranched, dibranched and monobranched materials are all substrates for the enzyme.

In order to illustrate the generality of this new technique a second example was sought using a different fluorophore. The peptide Ala-Lys-Leu-Ala-OH was constructed on the diamine resin 3-NHTrt-resin and the two dendrimer resins 1-NHTrt-resin and 2-NHTrt-resin (Scheme 1). Following Fmoc deprotection, fluorescein was introduced by treatment of the resin with fluorescein isothiocyanate and triethylamine. Attempts at TFA-mediated cleavage resulted in decomposition of the peptides (through a typical Edman sequencing cleavage). Resin cleavage was accomplished with 30% HFIP (= 1,1,1,3,3,3-hexafluoro-2-propanol) in CH_2Cl_2 affording the protected peptides **6**, **7**, and **8** (details in Supporting Information).

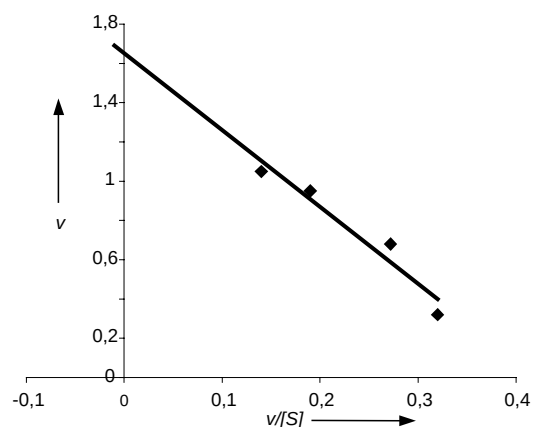


Figure 4. Eadie-Hofstee plot for AspN cleavage of **5**.

The treatment of peptide **6** with chymotrypsin, monitored by HPLC, led to the formation of peptide **9** (FITC-Ala-Lys(Boc)-Leu-OH) by cleavage between the leucine and alanine residues. On the other hand no increase or decrease in fluorescence was observed. Attention was then turned to the cleavage of peptides **7** and **8**. When monitored by HPLC an identical fluorescent peak to that previously obtained was produced (Figure 5) thus indicating that all peptides were cleaved at an identical position.

The fluorescence emission over time for the cleavage of both the PAMAM-peptide dendrimer **7** and the tris(dendrimer) **8** was measured (Figure 3). As can be seen both enzymatic reactions led to a dramatic increase in fluorescence: for **7** there was a six- to sevenfold increase, while for **8** an almost ninefold enhancement was observed.

In conclusion, internally quenched fluorescently labeled dendritic peptides (**5**, **7**, and **8**) have been prepared. Enzymatic cleavage caused a large increase in fluorescence emission, and in the case of dendrimer **8** almost a ninefold fluorescence enhancement was observed. Internally quenched dendritic peptides of this type thus represent a new assay method for proteases avoiding much of the synthetic complexities of FRET-based systems yet with good sensitivity and signal-to-noise ratios.

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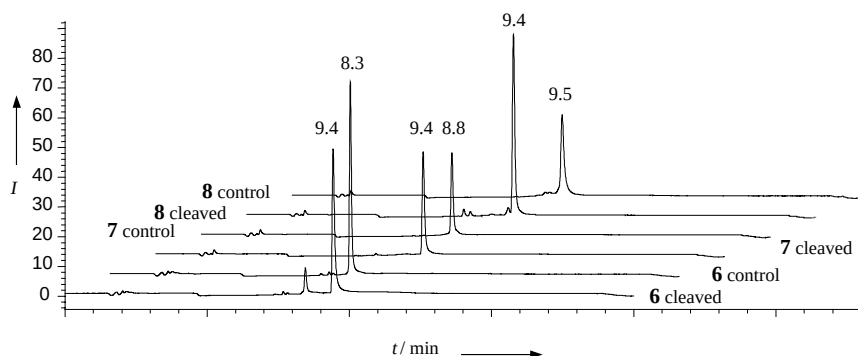


Figure 5. HPLC traces of chymotrypsin cleavage of peptides **6-8**.

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Layer-By-Layer Deposition and Ordering of Low-Molecular-Weight Dye Molecules for Second-Order Nonlinear Optics**

Kevin E. Van Cott,* Matthew Guzy, Patrick Neyman, Charles Brands, J. R. Heflin, Harry W. Gibson, and Richey M. Davis

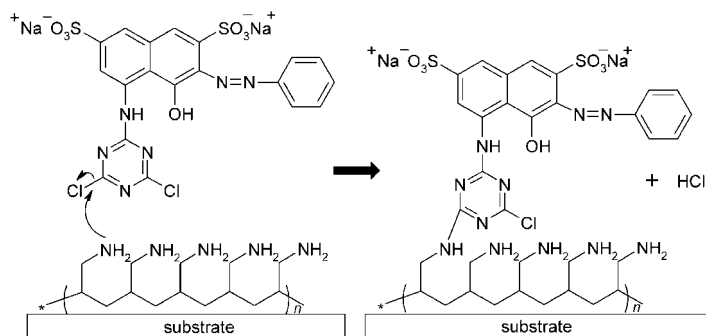
Materials that exhibit second-order nonlinear optical (NLO) properties are key components in electrooptic modulators and frequency-doubling devices.^[1] Second-harmonic generation (SHG), in which incident light at one frequency is converted into light at twice that frequency, is one example of second-order NLO phenomena and is often used as an experimental probe of the second-order susceptibility ($\chi^{(2)}$). A material must have a non-centrosymmetric structure to possess a nonzero $\chi^{(2)}$. Electrooptic modulators have traditionally employed ferroelectric inorganic crystals, such as lithium niobate or potassium dihydrogen phosphate, which are formed at high temperatures. However, organic NLO materials offer several advantages in performance, such as higher nonlinear susceptibilities, higher modulation rates, and potentially lower device fabrication costs.^[2] Organic films

exhibiting nonzero $\chi^{(2)}$ values have been fabricated using a variety of methods, including electric field poling,^[3] Langmuir–Blodgett (LB) films,^[4] and covalent self-assembly.^[5] Both poled polymer systems and LB films have been made with non-centrosymmetric structures that exhibit relatively high values for $\chi^{(2)}$, but poor temporal or mechanical stability restrict their potential applications.^[6] Deposition processes using reactive silane compounds require organic solvents and high temperatures.^[5]

There is a large and growing body of literature on the use of layer-by-layer (LBL) methods for fabricating nanostructured films for a variety of applications. The LBL technique, which relies on purely electrostatic interactions, was first developed by Iler^[7] and further elaborated upon by Decher et al.^[8] Several research groups have demonstrated that the NLO films made by this technique have greater thermal and temporal stability than poled polymer systems.^[9] A related approach that could be employed to fabricate NLO materials involves the use of low-molecular-weight dye molecules and polyelectrolytes as film constituents. Yamada et al. made films of poly(diallyldimethylammonium chloride) and Erichrome Black T that exhibited an SHG intensity that increased only for the first five bilayers and then reached a plateau.^[10] Other research groups, including ourselves, have found that ionic interactions alone are not sufficient for constructing LBL films with low-molecular-weight chromophores.^[11] A combination of low-molecular-weight chromophoric molecules and polyelectrolytes that could be used to construct stable NLO films with the large number of bilayers needed for electro-optic devices is yet to be demonstrated.

The objective of this work was to demonstrate that LBL films made under ambient conditions with a water-soluble, monomeric chromophoric molecule can possess high net polar ordering in each bilayer. By alternating the methods of deposition for each monolayer (covalent reaction and electrostatic interaction) and decoupling the chromophore orientation from the steric constraints of a polymer chain, we hypothesized that the non-centrosymmetric orientation required for nonzero $\chi^{(2)}$ values could be achieved.

The model anionic/reactive species used in this study was Procion Red MX-5B (PR), and the NLO-inactive polycation was poly(allylamine hydrochloride) (PAH, Scheme 1). The pH values of the dipping solutions determine the ionization state of the amine moieties on PAH, which affects both the conformation of the polymer upon adsorption and its



Scheme 1. Reaction between PR and a previously adsorbed monolayer of PAH.

[*] Prof. K. E. Van Cott, M. Guzy, Prof. R. M. Davis
Department of Chemical Engineering
133 Randolph Hall, Virginia Tech
Blacksburg, VA 24061 (USA)
Fax: (+1) 540-231-5022
E-mail: kvancott@vt.edu
P. Neyman, C. Brands, Prof. J. R. Heflin
Department of Physics
Virginia Tech
Blacksburg, VA 24061 (USA)
Prof. H. W. Gibson
Department of Chemistry
Virginia Tech
Blacksburg, VA 24061 (USA)

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Peter Göllitz, Editor

Layer-By-Layer Deposition and Ordering of Low-Molecular-Weight Dye Molecules for Second-Order Nonlinear Optics**

Kevin E. Van Cott,* Matthew Guzy, Patrick Neyman, Charles Brands, J. R. Heflin, Harry W. Gibson, and Richey M. Davis

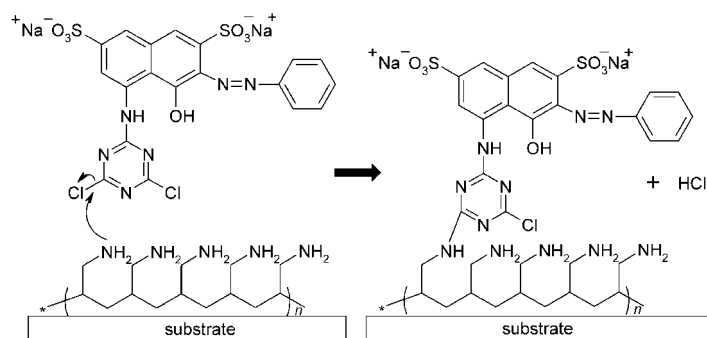
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Scheme 1. Reaction between PR and a previously adsorbed monolayer of PAH.

[*] Prof. K. E. Van Cott, M. Guzy, Prof. R. M. Davis
Department of Chemical Engineering
133 Randolph Hall, Virginia Tech
Blacksburg, VA 24061 (USA)
Fax: (+1) 540-231-5022
E-mail: kvancott@vt.edu

P. Neyman, C. Brands, Prof. J. R. Heflin
Department of Physics
Virginia Tech
Blacksburg, VA 24061 (USA)
Prof. H. W. Gibson
Department of Chemistry
Virginia Tech
Blacksburg, VA 24061 (USA)

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(8.7),^[12] where the majority of the NH₂ groups will be protonated and available for interaction with negative charges on the substrate or the PR molecule. The pH value of the PR solution must be near or above the pK_a value of the PAH amine groups for efficient covalent attachment of the chromophore to the dichlorotriazine ring at room temperature.^[13]

In situ measurements of SHG intensity during PR deposition showed that each monolayer was deposited within two minutes at room temperature. Successful film growth was characterized by a linear increase in the absorbance and thickness with the number of bilayers deposited (Figure 1 and Table 1). The pH value of the PAH solutions in these experi-

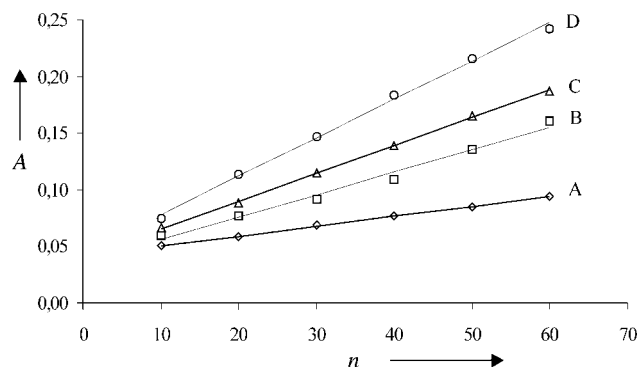


Figure 1. Absorbance (*A*) at 538 nm as a function of the number of bilayers (*n*) in PR-PAH films. Experimental conditions for A–D correspond to entries in Table 1. Lines are obtained by linear regression analysis. ◇: PAH pH 4.5/PR pH 7.0, □: PAH pH 4.5/PR pH 10.5, △: PAH pH 7.0/PR pH 7.0, ○: PAH pH 7.0/PR pH 10.5.

ments was held at either 4.5 or 7.0. The positive charges along the PAH chain strongly repel each other and are strongly attracted to the negatively charged surface. These two effects lead to the deposition of PAH in layers with a bilayer thickness less than 1 nm.

The pH value of the PR solution has a significant effect on the amount of chromophore incorporated into the film. When the pH value of the PAH solution was held constant at 4.5 or 7.0 and that of the PR solution was increased from 7.0 to 10.5, the amount of PR deposited per bilayer increased, which is

Table 1. Properties of films made by a hybrid deposition process from Procion Red (PR) and poly(allylamine hydrochloride) (PAH).

Expt	PAH pH	PR pH	$An_b^{-1[a]}$	t_b [nm] ^[b]	$\chi^{(2)}$ [$\times 10^9$ esu] ^[c]	Rel. $An_b^{-1[c]}$	Rel. $(I_{2\omega})^{1/2}n_b^{-1[c]}$
A	4.5	7.0	$(8.9 \pm 0.1) \times 10^{-4}$	[d]	–	–	–
B	4.5	10.5	$(2.0 \pm 0.1) \times 10^{-3}$	0.34 ± 0.02	11.2 ± 0.1	1.00	1.00
C	7.0	7.0	$(2.3 \pm 0.4) \times 10^{-3}$	0.55 ± 0.05	1.2 ± 0.01	1.15	0.17
D	7.0	10.5	$(3.3 \pm 0.3) \times 10^{-3}$	0.52 ± 0.06	11.3 ± 0.1	1.63	1.55

[a] *A* = absorbance at 538 nm; *n_b* = number of bilayers as determined by linear regression analysis. [b] *t_b* = thickness per bilayer as determined by ellipsometry. [c] Relative values of the slopes obtained by linear regression analysis of each series in Figure 1 and 2 relative to experiment B. [d] Too thin to measure. [e] For quartz, $\chi^{(2)} = 1.92 \times 10^{-9}$ esu.

consistent with the increased covalent-coupling efficiency. When the pH value of the PR solution was 10.5 and that of the PAH solution was increased from 4.5 to 7.0 (compare experiments B and D), a statistically insignificant increase in the film thickness per bilayer ($p > 0.05$) was observed. However, this also resulted in a small but significant increase in the amount of PR deposited per bilayer ($p < 0.05$), as measured by the absorbance per bilayer.

Importantly, the pH value of the PR solutions affects the degree of ordering of the chromophore molecules in the film. When the film thickness is much less than the SHG coherence length (typically a few microns), the SHG should have a quadratic dependence on the film thickness. The linear dependence of the square root of the SHG intensity ($(I_{2\omega})^{1/2}$) on the number of bilayers for the films fabricated with a PR solution at pH 10.5 thus demonstrates there is equivalent polar ordering in each successive bilayer (Figure 2: lines B and D). When the pH value of the PR solution is held

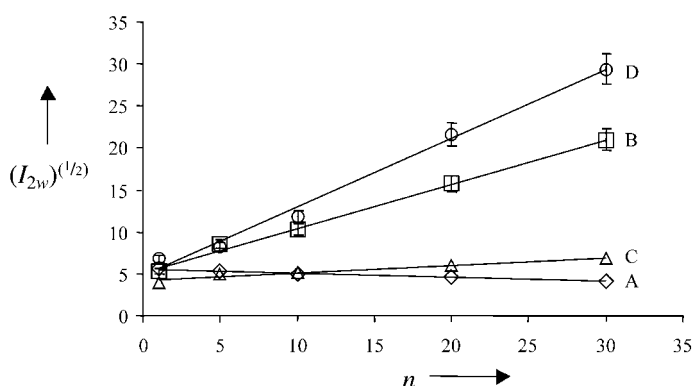


Figure 2. Square root of the SHG intensity ($(I_{2\omega})^{1/2}$) as a function of the number of bilayers for films with experimental conditions for A–D corresponding to Table 1. Lines are obtained by linear regression analysis. ◇: PAH pH 4.5/PR pH 7.0, □: PAH pH 4.5/PR pH 10.5, △: PAH pH 7.0/PR pH 7.0, ○: PAH pH 7.0/PR pH 10.5.

constant at 10.5, an increase in the pH value of the PAH solution from 4.5 to 7.0 results in an increase in the absorbance per bilayer (Figure 1 and Table 1, lines B and D). The value of $(I_{2\omega})^{1/2}$ per bilayer also increases by a similar relative amount and the $\chi^{(2)}$ value of the films is similar, which indicates that for these conditions the increase in SHG is simply a result of the incorporation of more PR. When the pH value of the PAH solution is held constant at 7.0 and that of the PR solution changes from 7.0 to 10.5, the bilayer thickness is similar, but the absorbance per bilayer and the $\chi^{(2)}$ value all increase. While 42 % more PR is incorporated per bilayer, the values of $(I_{2\omega})^{1/2}$ per bilayer and $\chi^{(2)}$ increase approximately eightfold. The $\chi^{(2)}$ values for films made with the PR solution at pH 10.5 are six times greater than that of quartz.

The dependence of the values of $\chi^{(2)}$ and $(I_{2\omega})^{1/2}$ per bilayer on the pH value of the PR solution indicates that the mechanism of PR deposition has a dramatic effect on the orientation of the PR molecules in the film. For the films made with a PR solution at pH 7.0 (experiments A and C), there is a much weaker dependence of the SHG intensity on the number of bilayers and a much lower $\chi^{(2)}$ value, which

indicates a lower degree of molecular ordering of the PR molecules. At pH 7, the reactivity of the PAH amine groups with the triazine ring of the PR is lower, and PR may be incorporated by a combination of electrostatic, hydrogen-bonding, and covalent interactions. Thus at conditions favoring a covalent reaction between PR and PAH, a high degree of ordering of the PR molecules results, while under unfavorable conditions, the PR deposited within the films has a more random orientation.

We interpret the larger $\chi^{(2)}$ value and SHG observed in the deposition of PR at pH 10.5 as confirmation of our hypothesis that alternating the mechanism of deposition in these films and decoupling of the chromophore from steric constraints of a polymer backbone provides a route to low-molecular-weight chromophores. In our earlier studies with polymeric dyes bearing NLO-active chromophores as charged pendant groups, films were made under deposition conditions leading to relatively thin bilayers (ca. 0.2 nm).^[14] We found by measuring SHG intensity in situ during deposition that the polar ordering of an adsorbed chromophore layer is reduced by subsequent adsorption of the next polyelectrolyte monolayer.^[15] Decoupling the NLO-active chromophore from a polymer chain reduces the steric constraints for ordering that are present when using a large chromophoric side group. Additionally, competing intermolecular interactions that prevent the achievement of a high net polar ordering of the chromophore within the film can be minimized by using a “bifunctional” chromophore with which the mechanism for deposition (covalent bonding) differs from the deposition of the polymeric component (electrostatic interaction).

In conclusion, we have demonstrated a new methodology for making organic LBL films with non-centrosymmetric ordering of low-molecular-weight chromophores in each bilayer. Any chromophore with dichlorotriazine and ionic moieties can potentially be used in this scheme. While the initial $\chi^{(2)}$ values are significant, they are far from optimized because Procion Red is not an ideal NLO chromophore. We are currently testing other commercially available reactive dyes and developing new triazine-functionalized NLO chromophores with larger hyperpolarizability values.

Experimental Section

PR (Aldrich) and PAH (M_w = ca. 70 000, Aldrich) were used as received. Glass microscope slides (Fisher Scientific) were used as the substrates and prepared by using the RCA cleaning procedure.^[16] Solutions of PAH (10 mM, based on the monomer) and solutions of PR (25 mM) in deionized water were used in all experiments. The pH values of the solutions were adjusted with HCl or NaOH. The immersion time in PAH was 5 min, with the exception of the first layer, which was immersed for 10 min. The immersion time in PR was 10 min. The substrates were rinsed thoroughly with deionized water between immersions. The slides were dried after every ten bilayers with N_2 . For each set of conditions, a series of five slides was made with a total of 2, 10, 20, 40, and 60 bilayers (counting both sides). Absorbance and SHG measurements took into account the films deposited on both sides of the substrate, while ellipsometry measurements were made with films deposited on only one side. Absorption measurements were made with a Hitachi U-2000 spectrophotometer at a wavelength of 538 nm and were taken every ten bilayers during the deposition process. Film thicknesses were measured with a variable-angle spectroscopic ellipsometer (J. A. Woolam Ellipsometer VB-200). Ellipsometric data were ob-

tained from the unfrosted face of the slide, as the scattering eliminates backside reflections and simplifies data analysis. The amplitude factor (ψ) and phase factor (Δ), which are related to the complex Fresnel coefficients for any given film,^[17] were measured for wavelengths from 350 to 1000 nm at 10 nm intervals. This wavelength range was repeated for angles ranging from 55 to 75° in 5° intervals.

SHG measurements were performed with a standard setup using a 10-ns pulse-width, Q-switched Nd:YAG laser with a fundamental wavelength of 1064 nm. The SHG data were averaged over 100 shots per data point, and the uncertainty in the relative $\chi^{(2)}$ values is 10%. Typical spot radius and pulse energy values were 30 μ m and 7 mJ pulse⁻¹, respectively. The film was deposited on both sides of the substrate. As a result, as the sample was rotated with respect to the incident beam, the path length between the films on opposite sides was varied, which led to interference fringes of the SHG intensity. The sample was rotated from 30 to 60° away from normal incidence using a stepper-motor-controlled rotation stage. The $\chi^{(2)}$ values were determined from the peak of the interference fringe in the vicinity of 45°. By comparison to Maker fringes in a quartz crystal wedge, the $\chi^{(2)}$ value

of a film was obtained from $\frac{\chi_{\text{film}}^{(2)}}{\chi_{\text{q}}^{(2)}} = \frac{2l_{\text{eq}}}{\pi l_{\text{film}}} \sqrt{\frac{l_{\text{eq}}}{l_{\text{q}}}}$ where l_{film} is the total path length through the film, the coherence length of quartz ($l_{\text{c,q}} = \lambda/4(n^{2\omega} - n^{\omega})$) is 22.4 μ m, and the $\chi^{(2)}$ value of quartz is 1.92×10^{-9} esu.

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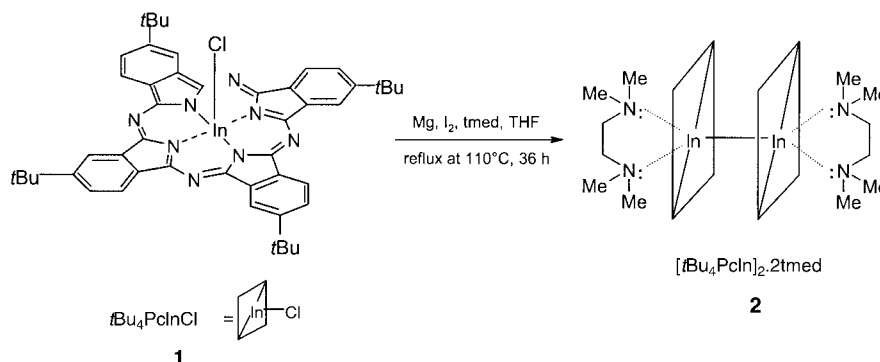
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An Axially Bridged Indium Phthalocyanine Dimer with an In–In Bond**

Yu Chen, Markus Barthel, Michael Seiler,
L. R. Subramanian, Helmut Bertagnolli, and
Michael Hanack*

New nonlinear optical (NLO) materials are essential to the development of optoelectronic technologies, such as optical communications, high-speed electrooptical information processing, short optical-pulse generation, and all-optical switching.^[1] For practical NLO devices, such as optical limiting devices, only a few appropriate nonlinear materials are currently available. This has been a primary barrier to the development of these optical devices, which can control the amplitude, phase, polarization, or direction of optical beams.^[2–4]

Among the large number of NLO absorbers that have been identified, metallophthalocyanines and related compounds have emerged as the most promising materials owing to their large nonlinearities (originating from optical pumping of low-lying electronic states), ultrafast response times, and easy processability.^[2,4] $[\text{tBu}_4\text{PcInCl}]$ (Pc = phthalocyanine) has been used to prepare optical limiters,^[4] which can reduce optical damage to elements that are sensitive to sudden high-intensity light, such as sensors or human eyes. The effect of axial substitution on the optical properties of indium(III) phthalocyanines was studied systematically in our research group, and by Shirk and co-workers.^[3] The optical-limiting properties of the axially substituted indium phthalocyanine monomers were surprisingly robust to structural changes in the axial position.^[3] Dimers, in comparison with monomeric phthalocyanines (Pcs), may show increased third-order nonlinearities as a result of intramolecular π – π interactions of the Pc units. Additionally, the optical-limiting properties of these compounds are influenced by the dimeric structure. In this regard, we report here for the first time an axially linked indium phthalocyanine dimer with a direct In–In bond.



Scheme 1. Synthesis of **2**.

Organometallic compounds containing metal–metal single bonds between the metallic elements of Group 3A (Al, Ga, In, and Tl) are quite unusual,^[5a] but also of great interest in materials science.^[5] So far, only metallophthalocyanine dimers with transition-metal–transition-metal bonds, for example, $\text{Ru}=\text{Ru}$,^[6,7] $\text{Os}=\text{Os}$,^[8] $\text{Mo}=\text{Mo}$,^[9] $\text{Rh}=\text{Rh}$,^[10] $\text{Ir}=\text{Ir}$,^[11] and $\text{Re}=\text{Re}$ ^[12] are known. Kobayashi et al claimed to have prepared $(\text{PcSiX})_2$ with a direct Si–Si bonding interaction^[13a] but this has since been proved to be incorrect.^[13b] Very recently, however, the same research group have again reported to have obtained Pc dimers linked by an Si–Si bond.^[13c]

We attempted to prepare a dimeric indium phthalocyanine complex with an In–In bond, by the reaction of soluble $[\text{tBu}_4\text{PcInCl}]$ (**1**)^[3a] with activated magnesium turnings in freshly dried THF in the presence of a catalytic amount of iodine, but all efforts were unsuccessful. Further investigations showed that the pure dimer $[\text{tBu}_4\text{PcIn}(\text{InPc}(\text{tBu}_4))]_2$, that is, without an associated N donor ligand, is unstable in solution under the classical Wurtz coupling conditions. These findings are in agreement with the observations of Tuck and co-workers,^[14] who successfully prepared stable N,N,N',N' -tetramethylethylenediamine (tmed) adducts of In_2X_4 ($\text{X} = \text{Br}, \text{I}$), which possess In–In bonds. The role of the neutral tmed ligand in stabilizing In_2X_4 or In_2XY_3 molecules is mainly to promote maximum coordinative saturation at the indium center.^[14] Accordingly, we successfully prepared $[\text{tBu}_4\text{PcIn}(\text{tmed})]_2$ (**2**) by a Wurtz coupling reaction of **1** in the presence of tmed (Scheme 1). To remove any inorganic impurities, the crude product was dissolved in anhydrous toluene, stirred, filtered (this procedure was repeated several

times), and dried at 80°C in vacuo to afford a blackish-green powder in 93 % yield.

The formation of an indium–indium bond in **2** was confirmed by Raman spectroscopy and by transmission extended X-ray absorption fine structure (EXAFS) spectroscopy. The strong peak at 110 cm^{-1} in the Raman spectrum of **2** (Figure 1) is ascribed to an In–In bond vibration,^[14b] but suggests that the In–In interaction is rather weak. The band at 148 cm^{-1} is assigned to the isotopic peak of the $\nu(\text{In}(\text{In}))$ mode.

Despite several attempts, compound **2** could not be obtained as a single crystal for an X-ray structural determination. EXAFS is considered to be a powerful technique for determining the local atomic environment of a specific atom,

[*] Prof. Dr. Dr. h.c. M. Hanack, Prof. Dr. Y. Chen, Dr. M. Barthel, Dr. L. R. Subramanian
Institut für Organische Chemie
Universität Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49)07071-295268
E-mail: hanack@uni-tuebingen.de

Dr. M. Seiler, Prof. Dr. H. Bertagnolli
Institut für Physikalische Chemie
Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)

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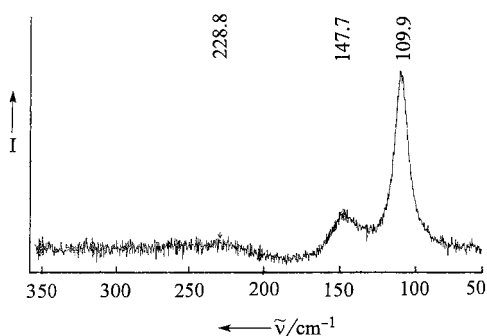


Figure 1. Resonance Raman spectrum ($\lambda_{\text{exc}} = 647.10 \text{ nm}$) of $[\text{tBu}_4\text{PcIn}(\text{tmed})]_2$ (**2**).

regardless of the state of the sample. EXAFS analysis provides information on the bond distance, the coordination number, the Debye–Waller factor, and the nature of the scattering atoms that surround the excited atom.^[15] Thus, EXAFS measurements were performed on **2** at the In–K edge at 27940 eV and 20 °C with an Si(311) double-crystal monochromator under ambient conditions (5.46 GeV, beam current 115 mA) and an inert atmosphere (beamline X1.1 at the Hamburger Synchrotron-Strahlungslabor (HASYLAB) at DESY, Hamburg). Data were collected in transmission mode with ion chambers. Energy calibration was monitored using 20- μm thick indium metal foil, also at the In–K edge at 27940 eV.

The experimental data and the fitted functions of **2** are shown in k space as well as by Fourier transformations in real space in Figure 2. The structural parameters and the EXAFS-determined molecular structure of **2** are given in Table 1 and Figure 3, respectively. In agreement with the well-known

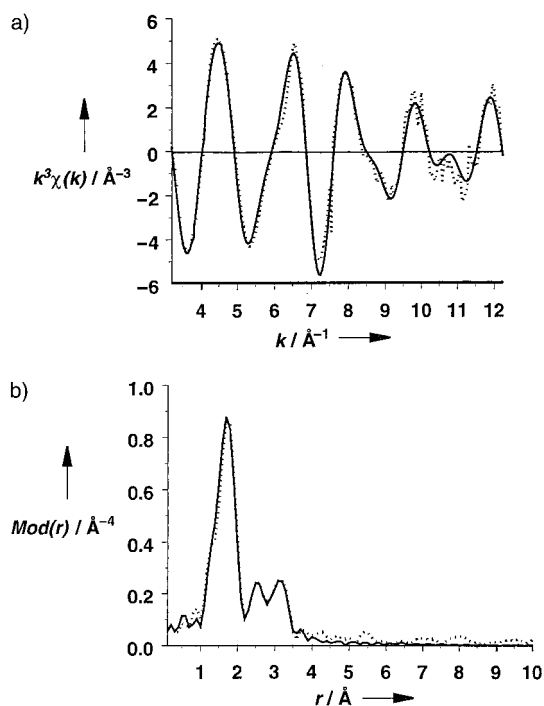


Figure 2. Experimental (dotted line) and calculated (solid line) $k^3\chi(k)$ functions (a) (k range = 3.18–12.29 $\text{\AA}^{-1}$, fit-index = 16.30, $E_0 = 18.78 \text{ eV}$) and their Fourier transforms (b) for $[\text{tBu}_4\text{PcIn}(\text{tmed})]_2$ (In–K edge, see Table 1 for fit parameters).

Table 1. EXAFS-determined structural data of $[\text{tBu}_4\text{PcIn}(\text{tmed})]_2$ (**2**). The letters in parentheses refer to **2** and indicate the molecule where the back-scattering atom is located.

	$N^{[a]}$	$r \text{ [\AA]}^{[b]}$	$\sigma \text{ [\AA]}^{[c]}$
In–(N ₁)	4	2.12 ± 0.02	0.067 ± 0.010
In–(N ₂)	2	2.59 ± 0.03	0.050 ± 0.005
In–(C ₂)	8	2.90 ± 0.03	0.102 ± 0.025
In–(N ₃)	4	3.05 ± 0.03	0.074 ± 0.011
In–(In')	1	3.24 ± 0.03	0.092 ± 0.002
In–(N ₁ ')	4	3.40 ± 0.03	0.122 ± 0.018
$\eta \text{ [}^\circ\text{]}^{[d]}$			14.5 ± 2.0
$\text{In}_{\text{out}} \text{ [\AA]}^{[e]}$			0.78 ± 0.3

[a] N = coordination number. [b] r = Absorber–backscatterer distance. [c] σ = Debye–Waller factor with calculated standard deviations. [d] η = tilting angle. [e] In_{out} = the out-of-plane displacement of the In atom.

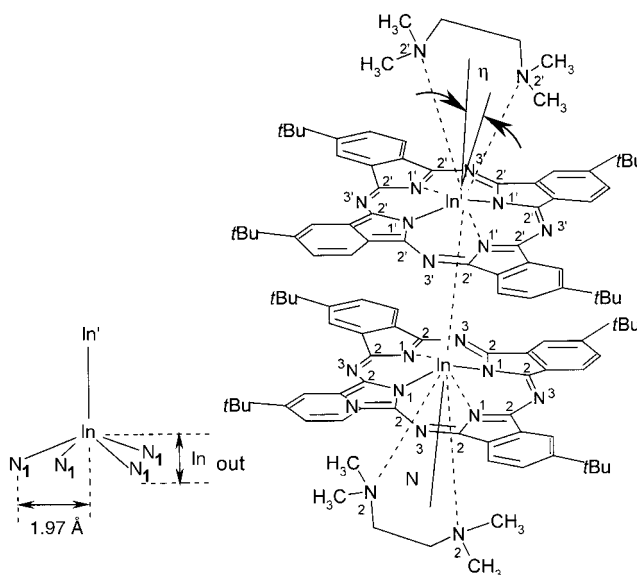


Figure 3. EXAFS-determined molecular structure of $[\text{tBu}_4\text{PcIn}(\text{tmed})]_2$.

structure of phthalocyanine complexes, we found four equivalent indium–nitrogen atomic separations of 2.12 and 3.05 $\text{\AA}$, and two equivalent indium–nitrogen atomic separations of 2.59 $\text{\AA}$. An additional shell, consisting of eight equivalent indium–carbon atomic separations at 2.90 $\text{\AA}$ gives good agreement between the experimental and the calculated parameters for **2**. The fit is significantly improved using an indium–indium separation of 3.24 $\text{\AA}$ (for comparison, reported In–In bond lengths are, for example, 2.775,^[16] 2.828,^[17] 3.631,^[18] and 3.952 $\text{\AA}$ ^[19]), and an additional indium–nitrogen interaction at 3.40 $\text{\AA}$. This is the shortest separation observed between an indium atom and a nitrogen atom situated in the neighboring phthalocyanine moiety within the dimer. The structural data acquired by the fitting procedure of **2** are listed in Table 1. Since an intermolecular In–In' separation was found, it can be deduced that two phthalocyanine molecules are arranged as a dimer. The relative orientation of the neighboring molecules can be calculated from the determined separations and the length of the intramolecular In–N₁ interaction. The molecular planes are tilted, with respect to the axis connecting the center of the molecules, by an angle of 14.5°. To check this result we calculated the shortest

intermolecular In–(N') distance, which is 3.87 Å for a parallel arrangement of the molecular planes perpendicularly oriented to the axis connecting the molecular centers. This separation, however, was not found in the spectra. If we assume a rigid phthalocyanine molecule, which is not deformed by the metal atom, the shortest indium–nitrogen distance amounts to 1.97 ± 0.02 Å;^[20–22] our results indicate an In–N₁ separation of 2.12 Å. We therefore conclude that the indium center is located 0.78 Å out of the plane described by the four nitrogen atoms directly bonded to it (In_{out}).

The IR spectrum of **2** is similar to that of **1**, and gives little structural information. As expected, the weak absorption band of the In–Cl stretching mode at 336 cm^{-1} is absent in the IR spectrum of the dimer; a new pair of split, low-intensity peaks are observed, centered at 368 and 399 cm^{-1} . Some characteristic absorption peaks, for example, at 1613, 1087, 1023, and 568 cm^{-1} appear to increase in intensity. A new intense peak at 802 cm^{-1} was also observed, and may be associated with the coordination of the tmed ligands to the indium centers.

Field-desorption mass spectrometry (FDMS) of $[(t\text{Bu}_4\text{PcIn}(\text{tmed}))_2]$ (**2**) (m/z calcd for $\text{C}_{108}\text{H}_{128}\text{N}_{20}\text{In}_2$: 1935) only shows a single peak at m/z 978, whereas the m/z value of a singly charged monomer, that is, $[\text{tBu}_4\text{PcIn}]^+$, is 851. In general, peaks containing ^{23}Na are always detected because of its ubiquitous nature. Hence, the peak at m/z 978 can be logically assigned to $[\text{M}^{2+} + ^{23}\text{Na}]$. We also employed FDMS to investigate the in situ hydrolyzed product of **2** in analytically pure THF containing a trace of water, and found that the original signal at m/z 978 disappears, followed by the appearance of a new strong peak at m/z 1703, which can be unambiguously attributed to $[\text{tBu}_4\text{PcIn}]_2$. This pure Pc dimer, without tmed ligands, is extremely unstable in solution and, thus, can not be obtained from the hydrolyzed product of **2**.

A series of highly soluble axially substituted or bridged phthalocyanine compounds have been prepared under mild conditions utilizing the chemical reactivity of M–Cl (M = Ga^{3+} , In^{3+}) and M=O (M = for example, Ti^{4+}) bonds.^[3,23] The axial ligands did not affect the linear optical properties; in fact the Q and B bands in the UV/Vis spectra are shifted only by a few nanometers on exchanging the axial ligands.^[3] Similarly, the formation of the axial In–In bond in the phthalocyanine dimer **2** displayed similar linear optical properties as the starting material **1**. The observed red-shifts of the Q and B bands in the UV/Vis spectrum of **2** in anhydrous THF are only of the order of 4–5 nm relative to **1**.^[3a] This observation can be explained by the fact that the average mutual polarization effect is close to zero as a result of near free rotation of the two Pc macrocycles around the In–In single bond. Consequently, the spectrum of **2** is similar to that of Pc monomer **1**. In addition, we measured the UV/Vis spectra of compounds **1** and **2** in anhydrous THF and analytically pure THF containing a trace amount of water. No matter what type of THF was used, the UV/Vis spectrum of **1** was the same. However, the UV/Vis spectrum of **2** in analytically pure THF is apparently shifted to short wavelengths relative to **1**. This blue-shift is related to protonation of the coordinated tmed.

The UV/Vis absorption bands of a thin film of **2** are marginally broader, but the position of the Q band is only slightly shifted (1–2 nm) towards longer wavelengths, compared to a dilute solution in anhydrous THF. This result is suggestive of only weak aggregation of **2**. Dimer **2** is susceptible to photochemical degradation in common organic solvents, for example, THF, CH_2Cl_2 , and CHCl_3 . After exposure of the solution of **2** in THF to daylight for 48 h, the B and Q bands of **2** decrease significantly in intensity, the Q band is blue-shifted by approximately 7–8 nm, and a new, weak absorption peak near 740 nm is observed. However, in the absence of light, the solution of **2** in THF does not show a significant or apparent decrease in absorbance for up to 72 hours.

The ^1H NMR spectrum of **2** is more complicated than that of **1** because of ring-current effects^[24] caused by the two macrocycles and the existence of possible rotational isomers. The spectrum shows two broad groups of multiplet signals for the aromatic protons and one intense singlet for the *t*Bu protons, a slight downfield shift is observed for the aromatic protons in the plane of the macrocycle relative to those of **1**.^[3a] A slight deshielding effect is also observed in the ^{13}C NMR spectrum of **2** for the carbon atoms close to the indium atom. The presence of coordinated ligands is apparent from the NMR spectra of **2**. In comparison with the ^{13}C NMR spectrum of free tmed, which displays resonances at 57.34 (CH_2N) and 45.53 ppm (NCH_3), the equivalent signals for coordinated tmed in **2** are shifted upfield to $\delta = 54.75$ and 44.72 ppm, respectively. ^1H NMR signals for free tmed appear at $\delta = 2.23$ (CH_2) and 2.09 ppm (CH_3), whereas the corresponding proton signals for the coordinated tmed ligands in **2** are located at $\delta = 2.91$ and 2.50 ppm. The observed downfield shift would not normally be expected; here it may be explained by the fact that the coordinating molecules do not fit into the cone of the ring-current.^[24] In addition, the possible protonation of the coordinated tmed during measurement also leads to a downfield shift of its proton signals. To provide evidence for this, we have measured the ^1H NMR spectrum of protonated tmed, and found that after treatment of free tmed with HCl, the measured ^1H NMR signals are shifted downfield, and appear at $\delta = 2.39$ and 2.23 ppm, respectively.

Excitation of **1** and **2** in toluene with a nanosecond laser at 355 nm results in almost identical transient absorption spectra being observed. The transient absorption bands appearing at about 520 nm can be attributed to the transition from the lowest triplet excited state to the upper triplet excited states (T–T absorption).^[25] The triplet-state-maximum of each sample occurs in the region of 400–610 nm, which is located just inside the high-transmission region between the intense Q and B bands in the UV/Vis absorption spectra (of all samples). This region is of great interest for optical limiting based on reverse saturable absorption^[3b,4] since it ensures that the excited-state absorption always exceeds the ground-state absorption cross-section.^[26]

The Z scans for all samples in toluene at 532 nm indicate that **2** shows a much stronger positive NLO response at relatively low powers than starting material **1**. This NLO response can be attributed to reverse saturable absorption.^[3b] The optical-limiting properties of **1** and **2**, as well as the tmed

adduct of **1** [*t*Bu₄PcInCl(tmed)], have been studied in toluene with laser pulses at 410 nm. These preliminary results show that **2** exhibits good optical-limiting response at this laser wavelength, whereas no response was found for compound **1** and its tmed adduct. Further studies on the NLO properties (including optical-limiting properties) displayed by **2** are currently in progress.

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Samarium Diiodide-Mediated Reductive Coupling of Epoxides and Carbonyl Compounds: A Stereocontrolled Synthesis of C-Glycosides from 1,2-Anhydro Sugars**

Jose Luis Chiara* and Esther Sesnilo

Dedicated to Professor Antonio Gómez-Sánchez on the occasion of his 75th birthday

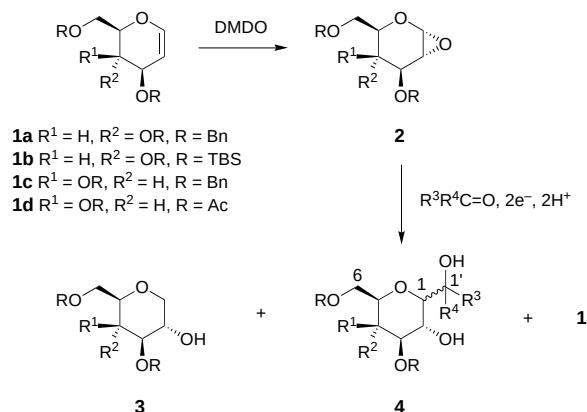
The significant advances in the understanding of the biological function of carbohydrates and glycoconjugates achieved during the last two decades have stimulated the development of glycomimetics as fundamental tools for biological research and as potential agents for therapeutic intervention.^[1] C-Glycosides are of special relevance in this context because of their resistance to hydrolysis and their occurrence in a number of natural products with interesting biological activities. Methods for their preparation using anomeric anions, cations, radicals, and carbenes have been extensively studied.^[2] 1,2-Anhydro sugars, readily available and well-known donors for the stereoselective preparation of O-glycosides,^[3] have also found application in the stereoselective synthesis of C-glycosides.^[2] Because of their electrophilic nature, in all examples described to date, 1,2-anhydro sugars have reacted with metalated C-nucleophilic partners, which are often unstable and not readily available with a wide range of functionality. The regioselective and stereodefined umpolung of 1,2-anhydro sugars into nucleophilic C-glycosyl donors by reductive metalation could greatly extend the scope of these useful donors, by allowing the introduction of an expanded set of substituents at the anomeric position in a stereoselective way.^[4,5]

To test the feasibility of this approach, we performed exploratory experiments with epoxide **2a**, readily available from the protected D-glucal **1a** by oxidation with DMDO

[*] J. L. Chiara, Dr. E. Sesnilo
Instituto de Química Orgánica General, CSIC
Juan de la Cierva, 3, 28006 Madrid (Spain)
Fax: (+34) 91-564-4853
E-mail: jl.chiara@iqog.csic.es

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(Scheme 1).^[10] Initial attempts to couple **2a** to isobutyraldehyde^[11] in the presence of $[\text{Cp}_2\text{TiCl}]_2$ ^[11i,12] as the reducing agent produced only minor amounts (<20%) of the C-glycoside **5a** (see Table 1 for structure)^[6,9] as a 1:1 mixture of



Scheme 1. Synthesis of C-glycosides from glycals by a one-pot DMDO oxidation and intermolecular reductive coupling reaction with carbonyl compounds. DMDO = dimethyl dioxirane, TBS = *tert*-butyldimethylsilyl.

α diastereoisomers, irrespective of temperature (-78°C to RT) and the order of addition of reagents (Table 1, entry 1). The major products obtained under these conditions were the corresponding glycal **1a** (35–45%) and the 1-deoxy pyranose **3a** (25–40%). We next tried samarium(II) diiodide as the reducing agent. Gratifyingly, addition of isobutyraldehyde (4 equiv) to a THF solution of SmI_2 containing a catalytic amount of NiI_2 (1 mol %),^[7g,h,13,14] at -78°C , followed immediately by dropwise addition of a THF solution of crude **2a** afforded the α -C-glycoside **5a** in 60% overall yield, as a 4:1 mixture of diastereoisomers^[15] together with minor amounts of **1a** and **3a** (Table 1, entry 1). This two-step/one-pot DMDO oxidation– SmI_2 reduction sequence was successfully applied to the coupling of differently protected glycals **1a–d** with a series of simple aldehydes and ketones to yield C-glycosides of D-*gluco* and D-*galacto* configuration in moderate to good overall yields (Table 1).

Some unique features of this new reductive coupling process are worth emphasizing. First, it shows wide protecting-group compatibility because of the very mild reaction conditions. Thus, apart from benzyl and silyl ethers, ester groups on the glycal are completely stable under the reaction conditions (Table 1, entries 4, 6, 15, 18). Second, the α/β stereoselectivity of the reaction is subtly sensitive to steric effects. In contrast to other reductive samariumation procedures,^[7] α -C-glycosides are predominantly or exclusively obtained with aldehydes (Table 1, entries 1–4, 6), independent of the protecting-group arrangement and the configuration of the starting glycal, while ketones give the corresponding β isomers as the major products (Table 1, entries 7, 9, 10, 12, 14, 15, 18).^[16]

The new reductive coupling procedure was also successfully applied to the β epoxide **17**^[17] affording C-glycosides of D-*manno* configuration in good yields (Table 2). In this case, α -C-glycosides are selectively obtained both with aldehydes and ketones.

A series of control experiments was carried out for mechanistic studies. First, fair yields of C-glycosides were still obtained by performing the reaction in the presence of a large excess (10 equiv) of D_2O (Table 1, entries 5, 8, 11, 13, 16; Table 2, entries 2, 4). This result is not consistent with the involvement of an anomeric organosamarium species in the C–C bond-forming step. Unexpectedly, the proton source affected the diastereoselectivity of the reaction. Thus, 1,2-*cis* C-glycosides are selectively formed under these protic conditions in all cases.^[18] Second, addition of 10 equiv of *t*BuSH, a good hydrogen donor, severely affected the yield of C-glycoside (<7%), giving the corresponding 1-deoxy-pyranose as the major product.

A possible mechanistic rationalization for the above observations is illustrated in Scheme 2 for the case of 1,2-anhydro sugars **2**. Single electron transfer (SET) from SmI_2 to the epoxide group^[19] of **2** regioselectively leads to an α -anomeric radical intermediate in the form of a solvated samarium(III) alkoxide **A**. Intermolecular radical addition of **A** to the Lewis acid- (Sm^{2+} or Sm^{3+}) activated carbonyl group^[20] and subsequent (or concomitant) kinetic trapping of the generated alkoxyl radical (**B** or **D**) by a second SET from another molecule of SmI_2 (possibly by inner-sphere ET^[21] from a chelated Sm^{2+} ion) produces the C-glycoside after hydrolysis. Destabilizing steric interactions between the solvated samarium(III) alkoxide at the C-2 atom in **A** and the incoming complexed carbonyl moiety along the kinetically favored axial trajectory of attack^[22] (Path b) is more severe in the case of ketones, which could explain a preferential 1,2-*trans* approach in their case (Path a). Under protic conditions (Path c), fast protonation of the samarium alkoxide at the C-2 atom of **A** allows a hydroxy-directed^[7d,23] approach of the Lewis acid-activated carbonyl compound **F**, generating predominantly the 1,2-*cis* C-glycoside **H**. A similar mechanistic rationalization can be proposed for the couplings of the 1,2-anhydro-D-*manno*-pyranose **17**. The glycal and 1-deoxypyranose are probably formed by competitive reduction of the anomeric radical **A** to an anomeric carbanion followed by β elimination or protonation, respectively.^[24,25]

In summary, we have developed an efficient preparation of C-glycosides by a new intermolecular reductive coupling reaction of 1,2-anhydro sugars with carbonyl compounds, promoted by samarium(II) diiodide. Outstanding features of the new approach are the following: 1) the starting 1,2-anhydro sugars are readily available with different stereochemistry, 2) good overall yields of C-glycoside are obtained, independent of the configuration of the starting 1,2-anhydro sugar, 3) the very mild reaction conditions allow a wide O-protecting group compatibility, 4) the stereoselectivity of the reaction is complementary to other syntheses of C-glycosides mediated by SmI_2 , 5) C-glycosides with a free hydroxy group at C-2 are directly obtained, which facilitates further selective functionalizations, and 6) the stereoselectivity of the reaction can be significantly modified by adding a proton source. The extension of this process to other radical acceptors and its application to the solution- and solid-phase synthesis of C-glycosidic analogues of biologically important natural glycosides are being actively pursued in our laboratory.

Table 1. One-pot DMDO oxidation–SmI₂ reductive coupling synthesis of C-glycosides from glycals and carbonyl compounds.

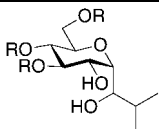
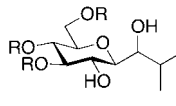
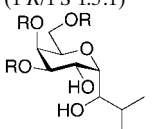
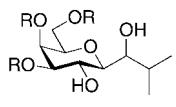
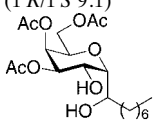
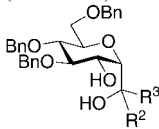
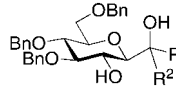
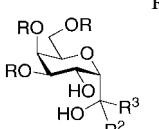
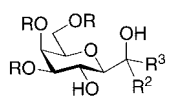
Entry	Glycal	Carbonyl compound	C-Glycoside Yield [%] ^[a] (diastereoisomer ratio)	Glycal	1-Deoxypyranose
					
1	1a	isobutyraldehyde	5a ^[b] 60 (1' <i>R</i> /1' <i>S</i> 4:1)	5b ND ^[c]	1a 12 3a 15
2	1b	isobutyraldehyde	6a 67 (1' <i>R</i> /1' <i>S</i> 1.5:1)	6b ND	1b 27 3b ND
					
3	1c	isobutyraldehyde	7a ^[d] 76 (1' <i>R</i> /1' <i>S</i> 2.5:1)	7b ND	1c 6 3c 14
4	1d	isobutyraldehyde	8a 73 (1' <i>R</i> /1' <i>S</i> 5:1)	8b ^[e] 9	1d 8 3d 7
5			61 ^[f] (1' <i>R</i> /1' <i>S</i> 9:1) 	ND ^[f]	12 ^[f] 14 ^[f,g]
6	1d	1-octanal	9a 52 (1' <i>R</i> /1' <i>S</i> 6:1) 	9b ^[h] 18 	1d 16 3d 2
7	1a	acetone	10a 12 53 ^[f] (R ² = R ³ = Me)	10b 64 10 ^[f]	1a 3 3a 8
8					23 ^[f] 13 ^[f,g]
9	1a	3-pentanone	11a 5	11b 60 R ² = R ³ = Et	1a 13 3a 22
10	1a	cyclohexanone	12a ^[i] 12	12b ^[i] 48	1a 3 3a 32
11			51 ^[f] R ² , R ³ = (CH ₂) ₅ 	8 ^[f] 	20 ^[f] 17 ^[f,g]
12	1c	acetone	13a ND	13b 70 2 ^[f] R ² = R ³ = Me	1c 2 3c 16
13			40 ^[f]		42 ^[f] 2 ^[f,g]
14	1c	cyclohexanone	14a ND	14b ^[i] 77 R ² , R ³ = (CH ₂) ₅	1c 3 3c 18
15	1d	acetone	15a 15	15b 46	1d 9 3d 9
16			40 ^[f]	6 ^[f]	15 ^[f] 24 ^[f,g]
17			44 ^[j] R ² = R ³ = Me	8 ^[j]	19 ^[j] 12 ^[j]

Table 2 (Continued)

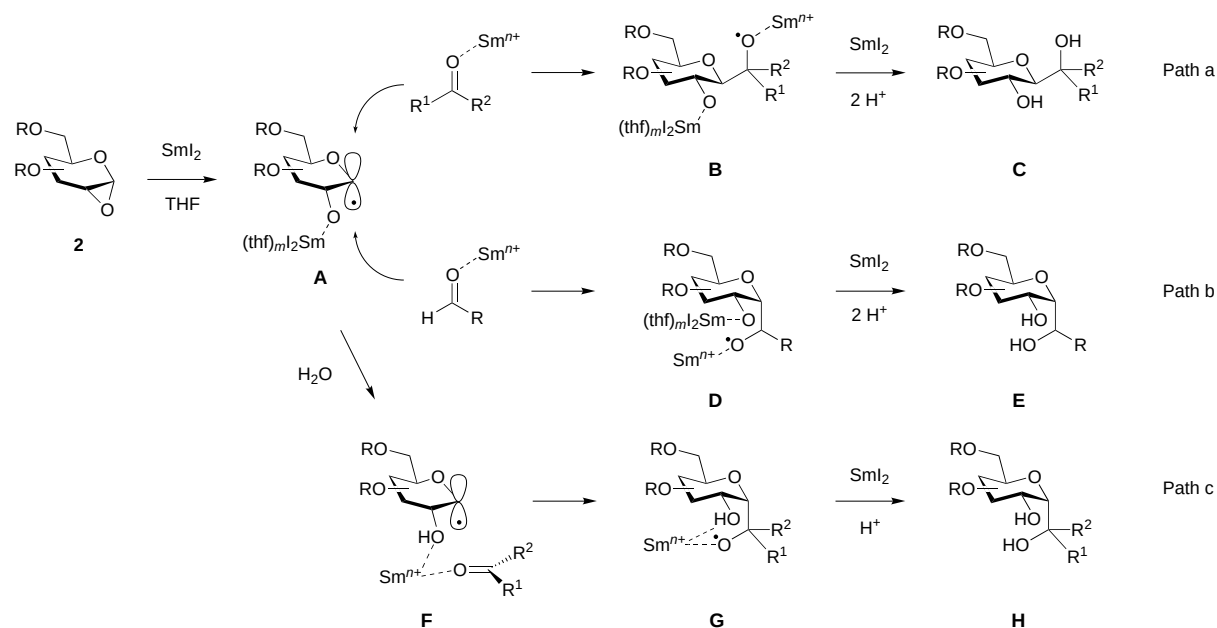
Entry	Glycal	Carbonyl compound	C-Glycoside Yield [%] ^[a] (diastereoisomer ratio)	Glycal	1-Deoxypyranose
18	1d	3-pentanone	16a 8 $R^2 = R^3 = \text{Et}$	1d 14	3d 15

[a] Overall yields of isolated products from starting glycal; diastereoisomeric ratios as determined by ¹H NMR spectroscopy of the crude reaction mixtures. [b] Ref. [6a,9]. [c] ND = Not detected. [d] Ref. [6b]. [e] Single diastereoisomer (stereochemistry at the C-1' atom not determined). [f] Reaction performed in the presence of 10 equiv of D₂O. [g] ¹H NMR spectroscopic analysis showed that compound **3** was >80 % α-monodeuterated at the C-1 atom. [h] 1:1 mixture of diastereoisomers at the C-1' atom. [i] Ref. [7b,d]. [j] Reaction performed in the presence of 2 equiv of D₂O.

Table 2. SmI₂-promoted synthesis of C-glycosides from glycal **17**.

Entry	Carbonyl compound	C-Glycoside Yield [%] ^[a] (diastereoisomer ratio)	Glycal	1-Deoxy sugar
1	isobutyraldehyde	19a ^[b] 68 8 ^[c]	1a 9 9 ^[c]	18 12 34 ^[c,e]
2	acetone	20a 63 11 ^[c]	1a 9 9 ^[c]	18 11 26 ^[c,e]

[a] Overall yields of isolated products from crude mixture; diastereoisomeric ratios as determined by ¹H NMR spectroscopy of the crude reaction mixtures. [b] Single diastereoisomer at the C-1' atom (ref. [7d]). [c] Reaction performed in the presence of 10 equiv of D₂O. [d] 1:1 mixture of diastereoisomers at the C-1' atom. [e] ¹H NMR spectroscopic analysis showed that compound **18** was >80 % β-monodeuterated at the C-1 atom.



Scheme 2. Proposed mechanistic pathway for the reductive coupling of 1,2-anhydro sugars with carbonyl compounds, promoted by SmI₂.

Experimental Section

General procedure for the preparation of C-glycosides: To a freshly prepared solution of SmI_2 (6 equiv) in THF, containing 1 mol % of NiI_2 at -78°C under argon, a carbonyl compound (4 equiv) was added in one portion, followed immediately by dropwise addition of a 0.1 M THF solution of the crude 1,2-anhydro sugar^[10,17] (1 equiv) over 30 min. After stirring at -78°C for 1.5 h, the reaction mixture was allowed to attain RT slowly (1 h). A 10:1 mixture of saturated aqueous Rochelle salt (potassium sodium tartrate) and saturated aqueous NaHCO_3 was added and the mixture was extracted with EtOAc ($3 \times$). The combined organic phases were washed with brine, dried over Na_2SO_4 , filtered, and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel to obtain the products.

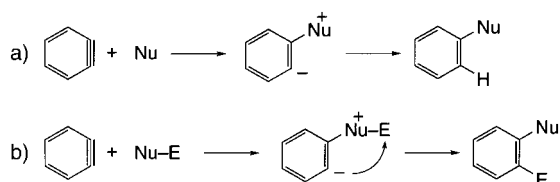
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- [24] 1-Monodeuterated 1-deoxypyranose (> 80 % deuterium incorporation by ^1H NMR spectroscopic analysis) is obtained when the coupling is performed in the presence of D_2O . Interestingly, deuterium incorporation is stereospecific. Thus, α -deuterated **3** and β -deuterated **18** are exclusively formed from α epoxides **2** and β epoxide **17**, respectively, as expected for deuteration of a (chelated) 1,2-*cis* anomeric organosamarium intermediate. The corresponding 1,2-*trans* organosamarium compound should undergo a fast β elimination to give the glycal. We believe that these observations cast doubt on the commonly accepted carbanionic nature of other C-glycoside syntheses mediated by SmI_2 ^[7] and the assumption of a preferred *syn*-elimination pathway^[7b,d] for organosamarium compounds, which is unprecedented for other metal carbanions.
- [25] A referee has argued that a mechanism involving anions may still be plausible, which suggests that carbonyl addition could be faster than protonation at -78°C . However, we think this is unlikely since previous work from our group^[23b] has shown that primary radicals are not readily reduced by SmI_2 at -78°C and that intermolecular addition of a postulated organosamarium intermediate to acetone is efficiently suppressed in the presence of an excess of D_2O (see also ref. [24]). In spite of recent progress,^[20] the nature of the intermediate involved in the key carbon–carbon bond-forming step of samarium Barbier reactions remains elusive.

Addition of Ureas to Arynes: Straightforward Synthesis of Benzodiazepine and Benzodiazocine Derivatives**

Hiroto Yoshida, Eiji Shirakawa,* Yuki Honda, and Tamejiro Hiyama*

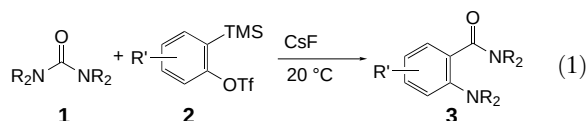
The reaction of arynes with nucleophiles is a unique, straightforward method for the synthesis of substituted arenes.^[1] Owing to the marked electrophilicity of arynes, even neutral nucleophiles that are inert toward alkynes are applicable to such a reaction. In most cases, however, an initially formed zwitterion abstracts a proton from the surroundings, which results in the formation of a monosubstituted arene (Scheme 1a). Although insertion of an aryne into a single bond between a nucleophile and an electrophile (Nu–E) should be more beneficial from the standpoint of organic synthesis (Scheme 1b), examples of this are limited to such activated species as Te–Te,^[2a] S–S,^[2b] C–Si,^[2c] and C–Sn^[2d] bonds.



Scheme 1. The reaction of arynes with nucleophiles.

Herein we report that an N–CO bond of ureas **1** readily adds to arynes to provide, in one step, a wide variety of 1-amino-2-(aminocarbonyl)arenes, including 1,4-benzodiazepine and 1,5-benzodiazocine derivatives. These heterocycles are an important group of therapeutic agents: 1,4-benzodiazepines, for example, diazepam and flurazepam, have been used as antianxiety drugs, sedatives, anticonvulsants, or hypnotics, whereas 1,5-benzodiazocines have attracted much interest as homologues of 1,4-benzodiazepine drugs.^[3a,b] Furthermore, some of the products exhibited characteristic fluorescence comparable to that of anthranilic acid derivatives, which are well-known fluorophores.^[4,5]

The novel synthetic reaction was discovered when we generated arynes by treatment of precursors **2** with cesium fluoride in 1,3-dimethyl-2-imidazolidinone (DMI, **1a**) [Eq. (1)].



For example, treatment of **1a**, 2-(trimethylsilyl)phenyl triflate (**2a**),^[6,7] and CsF at 20 °C for 2 h gave 1,4-dimethyl-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one (**3a**) in 62 % yield (Table 1, entry 1).^[8] Worthy of note is the perfect regioselectivity observed in the reaction of 3-substituted

Table 1. Reaction of arynes with DMI.^[a]

Entry	1	2	Product(s)	<i>t</i> [h]	Yield [%] ^[b]
1				2	62
2				3	77
3				15	66
4				7	89
5				5	73
6				17	73

[a] The reaction was carried out in **1a** (0.75 mL) at 20 °C using **2** (0.34 mmol) and CsF (0.69 mmol). [b] Yield of isolated product, based on **2**.

benzyne. Thus, the 3-methoxybenzyne derived from **2b** or 3-phenylbenzyne from **2c** reacted smoothly with **1a**, giving **3b** or **3c** as a single isomer, respectively (entries 2 and 3). The reaction of 1-(trimethylsilyl)-2-naphthyl triflate (**2d**), a 1,2-naphthalene precursor, proceeded regioselectively to afford solely **3d** in 89% yield (entry 4). Exclusive formation of **3d** was also observed in the reaction of 2-(trimethylsilyl)-1-naphthyl triflate (**2e**; entry 5), which indicates that both reactions proceed through the 1,2-naphthalene intermediate. Products **3b–3d** contain the amide moiety at the more sterically hindered position.^[9] In contrast, 4-methylbenzyne prepared from **2f** gave almost equal amounts of regioisomeric

[*] Prof. Dr. E. Shirakawa
Graduate School of Materials Science
Japan Advanced Institute of Science and Technology
Asahidai, Tatsunokuchi, Ishikawa 923-1292 (Japan)
Fax: (+81)761-51-1631
E-mail: shira@jaist.ac.jp

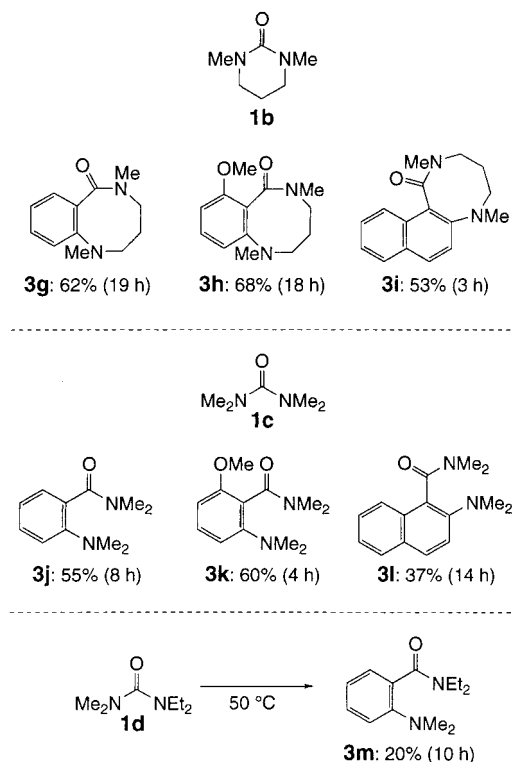
Prof. Dr. T. Hiyama, Dr. H. Yoshida, Y. Honda
Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81)75-753-5555
E-mail: thiyama@npc05.kuic.kyoto-u.ac.jp

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

products **3e** and **3f**,^[10] which suggests that a substituent at the 4-position of the benzyne exerts little influence on the regioselectivity (entry 6).

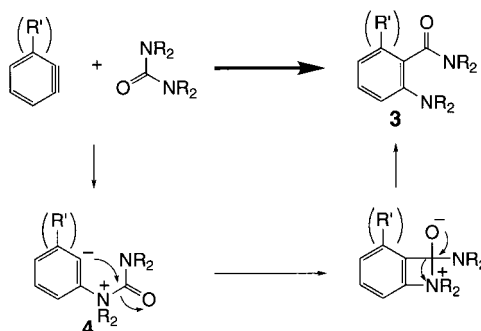
N,N-Dimethylpropyleneurea (DMPU, **1b**) also reacted readily with **2a** to give 1,5-dimethyl-1,2,3,4,5,6-hexahydro-1,5-benzodiazocin-6-one (**3g**) in 62 % yield (Scheme 2). As



Scheme 2. Products of the reaction of arynes with ureas.

was the case with **1a**, the reaction of **1b** with **2b** or **2d** produced the corresponding 1,5-benzodiazocine derivatives **3h** or **3i** as a single isomer. In addition to cyclic ureas, an acyclic urea, *N,N,N',N'*-tetramethylurea (TMU; **1c**), also reacted with the formed arynes, which gave 2-aminobenzamides **3j** and **3k**, and 2-amino-1-naphthamide **3l**.^[11] An unsymmetrical urea, *N,N*-diethyl-*N',N'*-dimethylurea (**1d**), reacted with **2a** to afford *N,N*-diethyl-2-(dimethylamino)benzamide (**3m**) as the sole insertion product.^[12]

Although the mechanism of the reaction is not clear at present, the susceptibility of arynes to addition of nucleophilic heteroatoms^[1] prompted us to consider a plausible mechanism, depicted in Scheme 3. A urea nitrogen atom adds to an aryne to give the zwitterion **4**, which furnishes the product by the intramolecular nucleophilic substitution at the carbonyl carbon atom.^[13] The perfect regioselectivities observed in the reaction of **2b–2d** can be rationally explained by steric considerations: a urea molecule attacks the aryne carbon atom *meta* to the substituent *R'*, which avoids steric repulsion.^[14] On the other hand, steric effects would be less pronounced in the addition of a urea to 4-methylbenzyne, resulting in the formation of a mixture of regioisomers (entry 6, Table 1). Exclusive formation of **3m**, which was observed in the reaction of **1d**, can be attributed to the regioselective



Scheme 3. A plausible mechanism for the reaction of arynes with ureas.

nucleophilic addition to benzyne at the sterically less congested dimethylamino moiety.^[15]

Seven- or eight-membered products derived from DMI or DMPU, respectively, showed fluorescence in solution. The excitation and emission wavelengths and fluorescence quantum yields are summarized in Table 2. For example, the benzodiazepine derivative **3a** emitted fluorescence ($\lambda_{\text{ex}} = 324\text{ nm}$; $\lambda_{\text{em}} = 436\text{ nm}$) with a quantum yield (Φ_f) of 0.07 in MeOH (entry 1, Table 2). In contrast, the fluorescence of TMU-derived products was hardly detectable. Detailed investigation of the relationship between fluorescence behavior and structure is underway.

Table 2. Fluorescence properties of products **3**, recorded in MeOH.

Entry	Product	λ_{ex} [nm]	λ_{em} [nm]	Φ_f [a]
1	3a	324	436	0.07
2	3c	325	430	0.02
3	3d	355	427	0.07
4	3g	326	421	0.03

[a] Measured relative to quinine sulfate in H_2SO_4 .

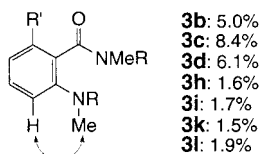
In conclusion, a general and efficient approach to 1,4-benzodiazepines, 1,5-benzodiazocines, and 2-aminobenzamides has been developed, based upon the novel reaction of arynes with ureas. 1,4-Benzodiazepines and 1,5-benzodiazocines prepared in this study, which are hardly accessible by conventional methods, would be valuable for their fluorescence properties as well as for their potential for pharmaceutical application. Further studies on the synthetic application of the reaction and details of the reaction mechanism are in progress.

Experimental Section

3a: To a solution of CsF (0.11 g, 0.69 mmol) in **1a** (0.75 mL) was added **2a** (0.10 g, 0.34 mmol); the mixture was stirred for 2 h at 20 °C before dilution with ethyl acetate. The resulting mixture was filtered through a celite plug and evaporated. Bulb-to-bulb distillation to remove the excess urea, followed by gel-permeation chromatography, gave **3a** as a colorless oil (0.040 g, 62 % yield); ^1H NMR (270 MHz, CDCl_3 , 20 °C): $\delta = 2.83$ (s, 3 H), 3.21 (s, 3 H), 3.31 (t, $J = 5.5\text{ Hz}$, 2 H), 3.43 (t, $J = 5.5\text{ Hz}$, 2 H), 6.87 (d, $J = 8.3\text{ Hz}$, 1 H), 6.99 (t, $J = 7.6\text{ Hz}$, 1 H), 7.37 (t, $J = 8.3\text{ Hz}$, 1 H), 7.63 ppm (dd, $J = 7.6$, 1.3 Hz, 1 H); ^{13}C NMR (67.8 MHz, CDCl_3 , 20 °C): $\delta = 34.5$, 40.0, 48.1, 58.0, 117.4, 121.0, 129.2, 130.0, 131.7, 146.7, 170.5 ppm; elemental analysis (%) calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$: C 69.45, H 7.42; found: C 69.26, H 7.43.

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- [5] Fluorescence properties of representative compounds: Anthranilic acid ($\lambda_{\text{ex}} = 327 \text{ nm}$; $\lambda_{\text{em}} = 392 \text{ nm}$; $\Phi_{\text{f}} = 0.01$); ethyl anthranilate ($\lambda_{\text{ex}} = 339 \text{ nm}$; $\lambda_{\text{em}} = 404 \text{ nm}$; $\Phi_{\text{f}} = 0.11$).
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- [7] The aryne precursors used in this study are readily available from the corresponding 2-halophenols or phenols. For detailed procedures, see Supporting Information.
- [8] Although the reaction of benzyne (from **2a** and CsF) with a small excess of ureas in THF also gave moderate yields of products (e.g. with 2 equiv of **1a**, 20°C, 27 h, 41 % yield of **3a**), we employed ureas as a solvent, as the yields were considerably improved.
- [9] The structure of the products was determined by NOE in ^1H NMR spectra (Scheme 4). Furthermore, the crystal structure of **3b** was determined by an X-ray diffraction study. CCDC-185541 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
- [10] Although the regioisomeric ratio of **3e** and **3f** was elucidated to be 52:48 by ^1H NMR, we did not pursue the exact position of the methyl substituent of each compound, because separation of the regioisomers was difficult.
- [11] 2-Amino-1-naphthamide **3l** was produced solely, regardless of the precursor (**2d** or **2e**) employed, which indicates that the reaction of an acyclic urea also proceeds through an aryne intermediate.
- [12] In this reaction, 2-(dimethylcarbamoyl)phenyl triflate, which should be produced by the reaction of **1d** with the aryl anion derived from Ar-TMS and a fluoride ion, was also formed as a by-product.
- [13] Because the urea oxygen atom is often considered to be more nucleophilic than the urea nitrogen atom, we cannot rule out the possibility that the reaction proceeds through other pathways, triggered by the nucleophilic addition of the urea oxygen atom to an aryne.
- [14] It is well-known that electronic effects also favor nucleophilic attack at this *m*-position (see ref. [1]).
- [15] The generation of 2-(dimethylcarbamoyl)phenyl triflate (see ref. [12]) may imply that the reaction of **1d** proceeds through a pathway which does not involve an aryne intermediate: The reaction of the primarily formed aryl anion (from Ar-TMS with a fluoride ion) with **1d** and subsequent aromatic nucleophilic substitution at a C-OTf moiety with an amide anion (R_2N^-). However, this pathway can be discounted, at least in the case of **1a**, because, according to this pathway, the reaction of **1a** with a 1,2-naphthalene precursor (**2d** or **2e**) should afford the corresponding regioisomeric product. This conclusion contrasts with the results in entries 4 and 5 of Table 1.



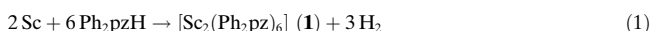
Scheme 4. Determination of the structures of **3** by measuring the magnitude of the NOE denoted by the double-headed arrow.

Pyrazolate Coordination Continues To Amaze—The New $\mu\text{-}\eta^2\text{:}\eta^1$ Binding Mode and the First Case of Unidentate Coordination to a Rare Earth Metal**

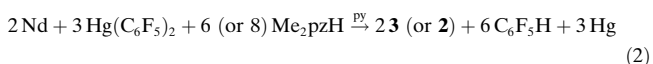
Glen B. Deacon,* Craig M. Forsyth, Alex Gitlits, Rita Harika, Peter C. Junk, Brian W. Skelton, and Allan H. White

Despite the recent transformations of pyrazolate coordination chemistry by the discovery of a range of new binding modes^[1–4] and by extension of η^2 -bonding from f-block elements^[5] to early^[6] and mid^[7] d-block transition elements and main group metals,^[8] surprising discoveries are still possible. Thus, we now report the preparation of $[\text{Sc}_2(\text{Ph}_2\text{pz})_6]$ (**1**; $\text{Ph}_2\text{pz} = 3,5$ -diphenylpyrazolate) with the new pyrazolate coordination mode, $\mu\text{-}\eta^2\text{:}\eta^1$, which is intermediate between the common $\mu\text{-}\eta^1\text{:}\eta^1$ ^[9] and the recently reported $\mu\text{-}\eta^2\text{:}\eta^{2,3a}$ ligation, and the first example of $\eta^1(\text{N})$ coordination of a pyrazolate to a lanthanoid ion in $[\text{Nd}(\eta^2\text{-Me}_2\text{pz})_2(\eta^1\text{-Me}_2\text{pz})(\text{Me}_2\text{pzH})_2\text{py}]$ (**2**; $\text{Me}_2\text{pz} = 3,5$ -dimethylpyrazolate; py = pyridine). Normally and expectedly, the large size and high Lewis acidity of Ln^{3+} favor chelation (η^2) and/or double bridging ($\mu\text{-}\eta^1\text{:}\eta^1$, $\mu\text{-}\eta^2\text{:}\eta^2$, $\mu\text{-}\eta^2\text{:}\eta^5$ etc.).^[2,3a,9]

Compound **1** was synthesized by the direct reaction between scandium metal and 3,5-diphenylpyrazole at 270–300°C [Eq. (1)], and was isolated by extraction with toluene from which single crystals were obtained.



On the other hand, **2** was a minor product of the redox transmetalation/ligand exchange reaction between neodymium metal, $\text{Hg}(\text{C}_6\text{F}_5)_2$, and 3,5-dimethylpyrazole in pyridine, a reaction giving $[\text{Nd}(\text{Me}_2\text{pz})_3(\text{py})]$ (**3**) as the main product [Eq. (2)].



A few single crystals of **2** deposited amidst bulk impure **3** and were separated for structure determination.

The structure of **1**^[10a] comprises a dimer (Figure 1). Each scandium center is seven-coordinate with two terminal η^2 - Ph_2pz ligands and two bridging Ph_2pz ligands, one of which ($3n$) is η^1 -bonded by N(32) to Sc(1) and η^2 -linked through

[*] Prof. Dr. G. B. Deacon, Dr. C. M. Forsyth, Dr. A. Gitlits, R. Harika, Dr. P. C. Junk
School of Chemistry
Monash University
Victoria, 3800 (Australia)
Fax: (+61) 3-9905-4597
E-mail: glen.deacon@sci.monash.edu.au
Dr. B. W. Skelton, Prof. Dr. A. H. White
Chemistry
University of Western Australia
Crawley WA, 6009 (Australia)

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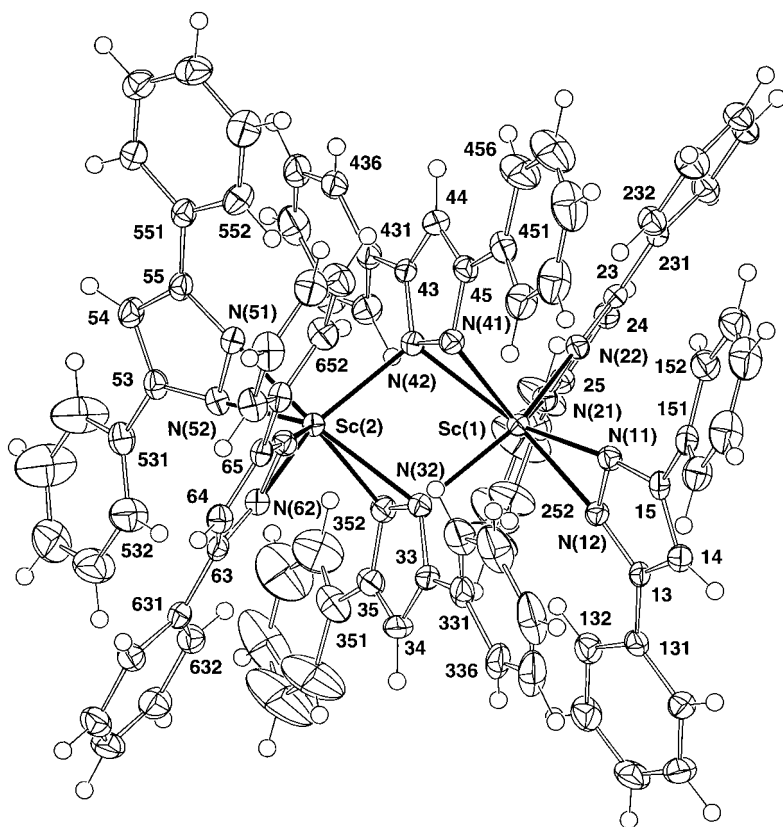


Figure 1. Projection of **1**, with the Sc $\cdots$ Sc vector in the page, showing the inclinations of the central planes of ligands 3 and 4. Selected bond lengths [Å] and angles [°]: Sc(1)–N(11,12,21,22,31*,32,41,42) 2.126(2), 2.116(2), 2.145(2), 2.114(2) 3.011(2), 2.250(2), 2.226(2), 2.349(2); Sc(2)–N(31,32,41*,42,51,52,61,62) 2.222(2), 2.365(2), 3.092(2), 2.271(2), 2.112(2), 2.135(2), 2.125(2), 2.128(2); Sc(1)–N(31,32,41,42)–Sc(2) 85.37(6), 102.27(7), 83.34(6), 102.14(7) Sc(1) $\cdots$ Sc(2)* 3.5943(6). * Nonbonding separations.

N(31,32) to Sc(2) and the other (4*n*) η^2 -bonded by N(41,42) to Sc(1) and η^1 -linked through N(42) to Sc(2). As the Sc(2) $\cdots$ N(41) and Sc(1) $\cdots$ N(31) separations are 0.76–0.82 Å longer than the bonding Sc(2)–N(42) and Sc(1)–N(32) distances (Figure 1), they are convincingly nonbonding, thereby establishing μ - η^2 : η^1 ligation. Moreover, the nonbonding separations are greater by over 0.3 Å than the average bonding distances for the bridging ligands of eight-coordinate [La₂(η^2 -*t*Bu₂pz)₄(μ - η^2 : η^2 -*t*Bu₂pz)₂] (**4**; *t*Bu₂pz = 3,5-di-*tert*-butylpyrazolate)^[3a] despite the much smaller size (ca. 0.3 Å) of Sc³⁺ than La³⁺.^[11] For each μ - η^2 : η^1 ligand, the Sc– η^1 (N) length lies between the two Sc– η^2 (N) distances, the latter two differing by 0.12–0.15 Å, slightly more than the differences between each pair of bridging Sc(1,2)–N(*n*2) (*n* = 4,3) distances. The C₃N₂ planes of the bridging ligands are near parallel (dihedral angle 1.8(1)°) and they intersect the Sc $\cdots$ Sc axis at 62.69(8) and 60.96(7)° (cf. parallel with Sc $\cdots$ Sc for μ - η^1 : η^1 - or 90° for μ - η^2 : η^2 -ligation). Parallel stacking of ligand Ph substituent planes about *x* = 0, 0.5 is a significant lattice motif.

Although the ¹H NMR spectrum of **1** in C₆D₆ differs significantly from that in coordinating (and presumably bridge splitting) C₄D₈O, only one H4(pz) resonance signal was observed by contrast with two for the μ - η^2 : η^2 bridged **4**.^[3a] Possibly the chemical shifts of the terminal and bridging ligands overlap (difference only 0.24 ppm for **4**).^[3a] but

cleavage of the η^1 bridge or exchange cannot be ruled out. Two C4(pz) resonance signals are observed in the solid-state ¹³C NMR spectrum of **1**, but the solubility in C₆D₆ was insufficient for a satisfactory spectrum.

The structure of **2** (Figure 2) features an eight-coordinate neodymium center with two η^2 -Me₂pz, one η^1 -Me₂pz, one η^1 -py, and two η^1 -Me₂pzH ligands. For the unidentate ligand (3*n*), the Nd–N(31) bond length is 0.83 Å shorter than the Nd $\cdots$ N(32) separation, completely excluding the latter as a bonding contact, and establishing η^1 -ligation. Stronger (by ca. 0.15 Å) bonds are observed for η^2 -binding than the η^1 -linked Nd–N(31) which is only 0.05–0.08 Å shorter than the Nd–N(Me₂pzH) distances. Location of the H(N) atoms of the Me₂pzH ligands provides a clear reason for noncoordination of N(32) of the η^1 -bonded Me₂pz, as it is held in a hydrogen-bonding chelate by cisoid pyrazole hydrogen atoms H(12, 22) (Figure 2).

Overall, the structure of **1** with μ - η^2 : η^1 -Ph₂pz groups results from effective steric engineering. Seven-coordination by comparison with six-coordination in monomeric [Sc(η^2 -*t*Bu₂pz)₃]^[3a] can be attributed to the lower bulkiness of Ph₂pz than *t*Bu₂pz (e.g. *t*Bu₂pz gives the eight-coordinate dimer **4**,^[3a] but Ph₂pz gives the ten-coordinate trimer [La₃(Ph₂pz)₉]^[12]). However, Sc³⁺ is too small to sustain eight-coordination which would result from μ - η^2 : η^2 bonding, as observed for a larger metal in **4** (or the isostructural Lu ana-

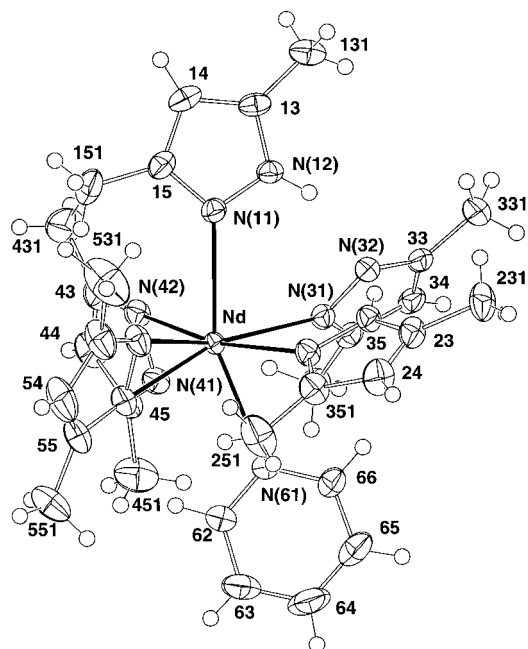


Figure 2. Projection of **2** normal to the Nd–N(11) vector. Selected bond lengths [Å] and angles [°]: Nd–N(11,21,31,32*,41,42,51,52,61) 2.621(1), 2.649(1), 2.564(1), 3.398(1), 2.412(1), 2.428(1), 2.447(1), 2.434(1), 2.626(1); N(12)–H(12) 0.88(2); N(22)–H(22) 0.85(3); N(32) $\cdots$ H(12,22) 1.96(2), 1.97(3); H(12)–N(32)–H(22) 88(1). * Nonbonding separations.

logue^[3a]). On the other hand, the η^1 -Me₂pz coordination of **2** is mainly a fortuitous result of a composition permitting significant hydrogen bonding to the uncoordinated nitrogen atom. This factor is far more important than the small reduction in crowding^[13] caused by η^1 - rather than η^2 -Me₂pz bonding, and the sum of steric coordination numbers of the ligands^[14] is not overlarge at 7.4 (or 7.6 with three η^2 -Me₂pz groups).^[15] Indeed the structure of **2** is so unusual as to confirm the normal unlikelihood of η^1 -pyrazolate coordination to large Ln³⁺ ions.

Experimental Section

1: A mixture of Sc chunks (0.40 g, 8.90 mmol), Ph₂pzH (Lancaster) (0.66 g, 3.00 mmol), and mercury metal (two drops) was heated in a sealed tube between about 270 and 300 °C for a total of 111 h (minimum time for visual disappearance of Ph₂pzH). The reaction mixture was extracted twice with hot toluene (80 and 20 mL) and filtered giving a colorless solution which deposited some colorless single crystals of [Sc₂(Ph₂pz)₆] for the structure determination. The solution was then concentrated to 5 mL yielding large colorless crystals which were dried at 100 °C under vacuum affording [Sc₂(Ph₂pz)₆] (0.58 g, 83 %). M.p. (sealed tube/N₂): 318–321 °C (sublimation ~180 °C); IR (Nujol): $\tilde{\nu}$ = 1604m, 1535m, 1422s, 1313m, 1283m, 1244m, 1164m, 1135w, 1100w, 1071m, 1020m, 985w, 965s, 952m, 910m, 814m, 803m, 757s, 686s cm⁻¹; ¹H NMR ([D₈]THF): δ = 7.10–7.22 (m, 36H; *m,p*-H(Ph)), 7.26 (s, 6H; H-4(pz)), 7.71 ppm (dd, ³J = 8.2 Hz, ⁴J = 1.2 Hz, 24H; *o*-H(Ph)); ¹H NMR ([D₆]benzene): δ = 6.56 (s, 6H; H-4(pz)), 6.89–6.92 (m, 36H; *m,p*-H(Ph)), 7.54 ppm (d, ³J = 7.9 Hz, 24H; *o*-H(Ph)); ¹³C NMR (75.48 MHz CPMAS): δ = 105.4 (s, C4; terminal-Me₂pz), 123.6–133.0 (complex m, *o,m,p*-Ph of terminal-/bridging-Me₂pz), 149.1 ppm (s, C4; bridging-Me₂pz), *ipso*-C unresolved; elemental analysis calcd (%) for C₉₀H₆₆N₁₂Sc₂: C 76.9, H 4.7, N 12.0, Sc, 6.4; found: C 76.7, H 5.0, N 12.0, Sc 6.6.

2: Neodymium metal powder (0.93 g, 6.45 mmol), Me₂pzH (1.08 g, 11.23 mmol), and Hg(C₆F₅)₂ (2.78 g, 5.20 mmol) were stirred and heated in pyridine (50 mL) at 70 °C. Filtration through a Celite pad, evaporation to about 5 mL, addition of hexane (40 mL), and standing at 30–35 °C produced a blue product containing brown impurities and some blue crystals of **2** (IR (Nujol): $\tilde{\nu}$ = 3289w, 1570w, 1518vs, 1415s, 1310s, 1296s, 1242s, 1131m, 1026w, 1008m, 983w, 801w, 780w, 726w cm⁻¹), which were used for the structure determination.^[10b] Addition of toluene dissolved the brown impurity leaving **3** as the bulk product (0.77 g, 44 %). M.p. (sealed tube/N₂): 213–215 (initial decomp at ca. 156 °C); IR (Nujol): $\tilde{\nu}$ = 1597vs, 1513vs, 1481s (sh), 1444vs, 1417vs, 1363vs, 1351s (sh), 1333s, 1242s, 1218s, 1152s, 1096m, 1070s, 1035s, 1007vs, 961s, 809s, 778vs, 764vs, 755vs, 730vs, 696vs, 676m, 668m, 656m cm⁻¹; Vis/near IR (in PhMe λ_{max} (ε)) = 352 (10), 515 (12), 529 (5), 587 (9), 685 (33), 740 (1), 794 (11), 805 (22), 881 (14) nm; elemental analysis (%) calcd for C₂₀H₂₀N₇Nd: Nd 28.35; found: Nd 28.61. Deliberate syntheses of **2** have not yet succeeded.

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Singlet Delta Oxygen Production from a Gas–Solid Reaction**

Angelo J. Alfano and Karl O. Christe*

Dedicated to Dr. Robert Corley

The long and interesting history of singlet delta ($^1\Delta_g$) oxygen, including its discovery, study, understanding, and applications, has been described in several publications.^[1–4] The singlet delta state is the lowest lying excited electronic state of oxygen and it differs from the triplet ground state, $^3\Sigma_g^-$, in spin multiplicity. The generation of $^1\Delta_g$ O₂ from ground state $^3\Sigma_g^-$ O₂, using direct electronic excitation, is spin forbidden and inherently inefficient.^[5] Therefore, either complex chemical reactions that produce intermediates capable of spontaneously eliminating electronically excited O₂, or compounds that can decompose directly to produce excited state oxygen have been studied for $^1\Delta_g$ O₂ production. Typical examples include: hydrogen peroxide with aqueous hypochlorite,^[6] basic hydrogen peroxide (BHP) with molecular halogens or phenols,^[7] the superoxide anion with water,^[4,8] ozone with organic substrates such as triaryl phosphates,^[9] alkaline peroxy acids,^[7,10] organic peroxides,^[11] and transition-metal–oxygen complexes.^[12] Although some of these reactions efficiently generate $^1\Delta_g$ O₂, they are all carried out in liquid-phase systems that cause quenching of the excited oxygen. The required rapid extraction of the gaseous singlet delta oxygen is very difficult. Furthermore, molecules capable of spontaneous elimination of electronically excited oxygen are thermodynamically unstable and, therefore, can present serious handling problems. Similar arguments may also apply to some of the precursors, such as the basic hydrogen peroxide in the BHP/Cl₂ system.^[13] In view of the significance of an efficient and safe $^1\Delta_g$ O₂ generator for the chemical oxygen iodine laser (COIL)^[14] and other chemical and biochemical applications,^[1,4] the development of new methods that can overcome these problems is of great importance.

Herein, we describe chemical reactions that spontaneously and efficiently produce singlet delta oxygen from solid alkali metal or alkaline-earth metal peroxides and dry hydrogen-(deuterium) halide gases at room temperature. The reactions do not require external energy sources, such as heat, light, or

electricity (discharge), and they avoid liquid-phase quenching and dangerous reagents.

The apparatus for generating and monitoring O₂ $^1\Delta_g$ from solid peroxides and gaseous hydrogen(deuterium) halides is depicted in Figure 1. The reaction/observation cell consisted

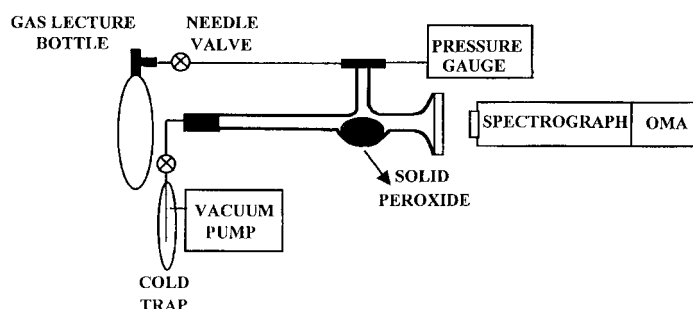


Figure 1. Apparatus for generating singlet delta oxygen and observing its emission.

of a 5 mm (i.d.) Pyrex glass tube that was attached to a 5 mm O-ring seal joint and a perpendicular sidearm. Opposite from the sidearm, the diameter of the tube was increased to provide a repository for the solid peroxide samples. A sodium chloride or an S-1 UV quartz window was clamped to the O-ring joint, and the whole assembly was placed 3 cm in front of an optical multichannel analyzer (OMA) spectrograph combination with the optical window facing the entrance slit. No collection optics were used.

In a typical experiment, 400 mg of a solid alkali metal or alkaline-earth metal peroxide was added to the cell within the dry nitrogen atmosphere of a glove box. The cell was installed into the test apparatus, evacuated, and dry hydrogen(deuterium) halide gas was added through the sidearm up to a maximum total pressure of 760 Torr. The OMA was kept at 160 K and an uninterrupted sequence of ten emission spectra (120 s collection time each) was recorded. Background subtraction was performed on all data. Several combinations of solid peroxide and gaseous hydrogen halide were tested: sodium peroxide/hydrogen(deuterium) chloride, sodium peroxide/hydrogen(deuterium) bromide, sodium peroxide/hydrogen iodide, barium peroxide/hydrogen chloride, barium peroxide/hydrogen bromide, and lithium peroxide/hydrogen chloride.

The O₂ $^1\Delta_g$ generation was monitored by the emission from its A→X ($^1\Delta_g \rightarrow ^3\Sigma_g^-$) spin-forbidden transition at 1.27 microns using a 0.3 m Czerny–Turner spectrograph with a 600 groove per mm grating blazed at 1 micron and a near-IR sensitive OMA. The emission was identical in wavelength and contour to those produced by either a microwave discharge of an oxygen–helium mixture^[15] or a BHP–chlorine sparger^[16] (see Figure 2 a and b, respectively).

All the above listed combinations of peroxide and gaseous hydrogen halide produced readily observable O₂ $^1\Delta_g$ emissions, except when hydrogen iodide was used. Figure 2 c shows the results obtained from sodium peroxide and 580 Torr of hydrogen chloride. The data represent an OMA exposure time of 120 s. Singlet delta oxygen emission from the Na₂O₂/HCl reaction was recorded for ten consecutive 120 s exposures

[*] Dr. K. O. Christe, Dr. A. J. Alfano
ERC, Inc. and Propulsion Sciences and Advanced Concepts Division
Air Force Research Laboratory (AFRL/PRSP)
Edwards Air Force Base, CA 93524 (USA)
Fax: (+1) 661-275-5471
E-mail: karl.christe@edwards.af.mil
and
Loker Hydrocarbon Research Institute
University of Southern California
Los Angeles, CA 90089-1661 (USA)

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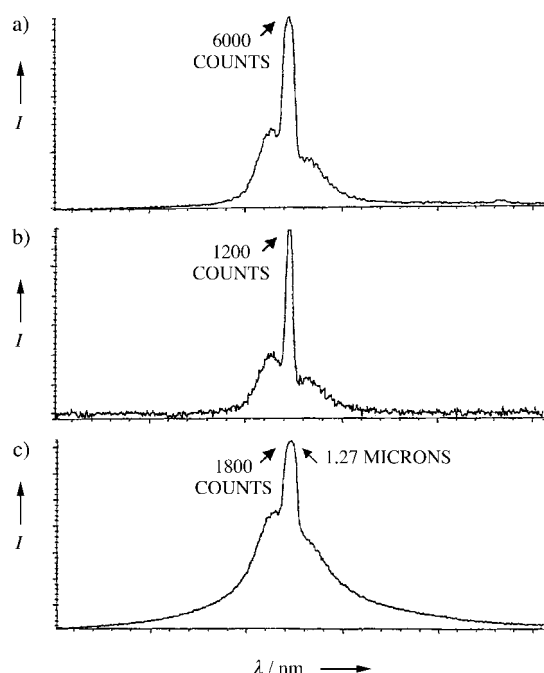
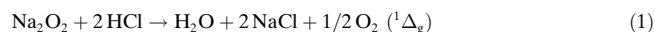


Figure 2. Emission spectra of singlet delta oxygen from a helium–oxygen microwave discharge (a; exposure time 1 s), a basic hydrogen peroxide/chlorine sparger (b; exposure time 1 s), and the $\text{Na}_2\text{O}_2/\text{HCl}$ reaction system (c; exposure time 120 s).

under three different reaction pressure conditions. The pressure of the reaction cell was either maintained constant by repeated addition of HCl, allowed to fall as HCl was consumed, or increased by continuous addition of HCl. In the latter case, the emission increased logarithmically with pressure. Constant or decreasing cell pressures resulted in exponentially decreasing emission signals over a 20-minute period. At a constant cell pressure of 450 Torr, the observed decay of the excited state emission over a 20-minute observation period was four orders of magnitude slower than that predicted from the known quenching rates of HCl and water vapor.^[18,19] These results demonstrate that the loss of emission due to quenching is largely offset by the continuous production of $\text{O}_2\ ^1\Delta_g$.

The stoichiometry of the sodium peroxide/HCl reaction was experimentally established by quantitatively analyzing the material balance on a vacuum line. The results are in excellent agreement with Equation (1).

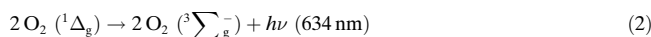


Equation (1) is also consistent with the condensation of some water vapor on the cell walls, the conversion of the yellow peroxide starting material to a white solid (NaCl), and a decrease in pressure as the emission data were recorded.

In Figure 2, the $\text{O}_2\ ^1\Delta_g$ emission signals from the microwave discharge, the BHP sparger, and the $\text{Na}_2\text{O}_2/\text{HCl}$ system are compared. The discharge was operated with a flow rate of 1×10^{-5} mol of O_2 per second plus helium, and the sparger could produce a maximum of 1.2×10^{-4} mol of O_2 per second, assuming 100% chlorine utilization. A single sample of 5×10^{-3} mol of sodium peroxide was recharged ten times with 500

to 700 Torr of HCl and produced $\text{O}_2\ ^1\Delta_g$ emission for a total of 200 minutes. Although a quantitative comparison of these three $\text{O}_2\ ^1\Delta_g$ production methods is difficult due to the differences in exposure times, observation geometries, and signal durations, the gas–solid reaction must be considered a highly efficient source of excited oxygen based upon the duration and strength of the emission signal in nearly one atmosphere of a quenching gas.

An additional experiment was conducted with the sodium peroxide/hydrogen chloride pair to check for potential emission at 634 nm from the energy-pooling reaction [Eq. (2)]. At sufficiently high $\text{O}_2\ ^1\Delta_g$ concentrations, this



energy-pooling process is known to produce a visible red glow.^[20] In our study, a separate OMA system sensitive in this region was used, but no evidence for this transition was found, possibly due to the dilution imparted by the high HCl pressure.

The other gas–solid reaction systems were tested in a larger cell that consisted of a 10 mm O-ring seal joint connected to a 7 inch length of 1/2 inch (o.d.) Pyrex tubing with 1/4 inch (o.d.) sidearms for gas inlet and evacuation. Larger amounts of sample were spread over a longer reaction zone, thus increasing the gas–solid contact time over that allowed by the cell of Figure 1. The listed reagent pairs were tested in a qualitative fashion. Typically, a one gram sample of solid peroxide was slowly pressurized with the hydrogen(deuterium) halide gas to 300 to 400 Torr. The gas was allowed to flow into the cell during the measurement so that the net pressure rose during the recording of the emission data. The emission from the sodium peroxide/hydrogen bromide system was especially strong and OMA saturation was experienced at exposure times of 120 s. The results from these tests are summarized in Table 1. The emission signal intensities varied

Table 1. Solid peroxides and gaseous hydrogen halides yielding singlet delta oxygen.

Peroxide	Hydrogen halide	Qualitative emission strength
Na_2O_2	HCl	strong
Na_2O_2	DCl	strong
Na_2O_2	HBr	very strong
Na_2O_2	DBr	very strong
BaO_2	HCl	medium
BaO_2	HBr	medium
Li_2O_2	HCl	strong

somewhat from experiment to experiment. This was partially due to small changes in the positioning of the sample cell after cleaning and reloading with fresh solid peroxide. The reactions with the deuterated halides are of special interest since deuterated compounds are significantly weaker quenchers than their hydrogen-containing counterparts.^[21] Other simple systems were also tested. For example, potassium superoxide, KO_2 , was allowed to react with hydrogen chloride, and a weak emission signal due to $\text{O}_2\ ^1\Delta_g$ was observed.

However, these systems are inferior to those involving the alkali metal and alkaline-earth metal peroxides.

In summary, the results of this study demonstrate the feasibility of efficiently generating singlet delta oxygen from gas–solid reactants without the problems associated with liquid-phase quenching. Furthermore, the required starting materials are commercially available, moderately priced, and safe to handle.

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Controlled Release of a Dendritically Encapsulated Template Molecule**

Graham M. Dykes, David K. Smith,* and Gordon J. Seeley

Over the past few years there has been intense interest in the unique properties exhibited by molecules with branched superstructures (namely, dendrimers).^[1] In particular, there has been a focus on the effect of dendritic encapsulation on a variety of physical and chemical properties—for example, the optical, redox, and catalytic behavior of core units have all been modified by dendritic functionalization.^[2]

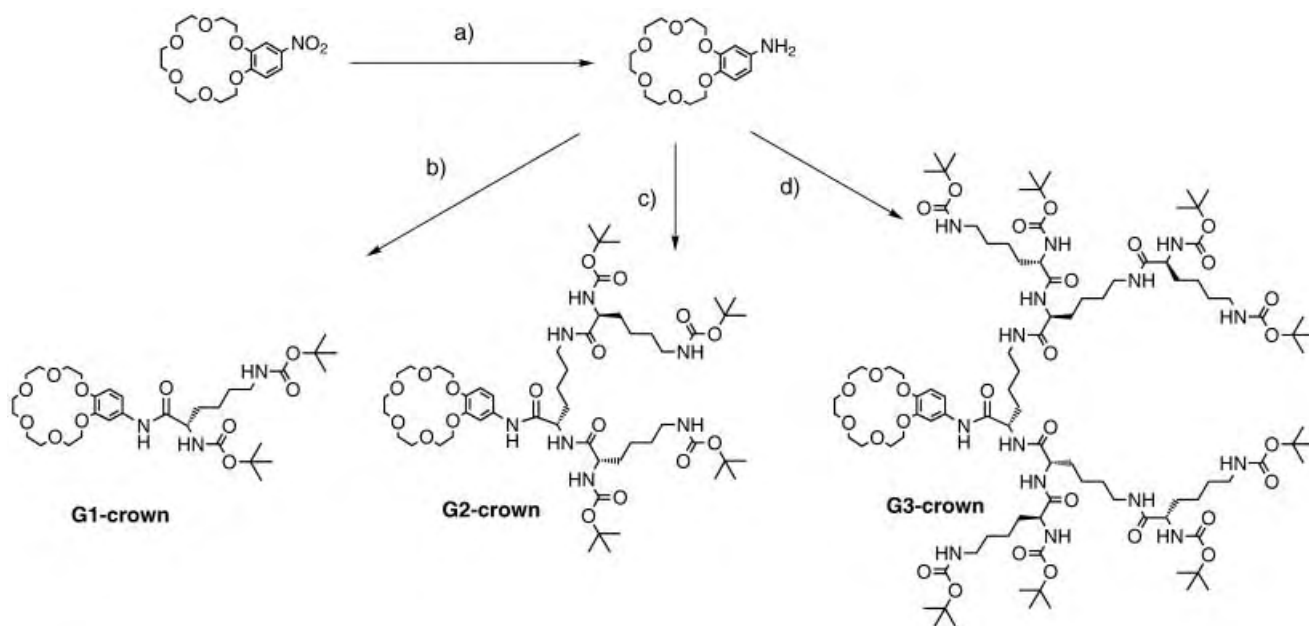
Chemists have increasingly begun to focus on the assembly of dendritic structures in which the core unit is held in place by noncovalent interactions rather than by covalent bonds.^[3] Zimmerman et al. published reports of dendritically functionalized rosettes, assembled through hydrogen-bond formation,^[4] as well as other hydrogen-bonded assemblies.^[5] Hydrogen bonds have also been used by other research groups for dendritic assembly.^[6] Kenda and Diederich reported well-defined “dendrophane” assemblies based on hydrophobic interactions,^[7] whilst Percec et al. have used similar forces to assemble distinctive architectures from dendritic building blocks.^[8] A wide range of dendrimers assembled around metal ions have also been reported.^[9] Gibson and co-workers have used interactions between secondary amines and dibenzo[24]crown-8 to assemble dendrimers with rotaxane-like mechanical branching.^[10] Recently, we used COOH⋯NH₂ hydrogen bonds at the focal point of individual dendritic branches to assemble them around hydrophilic dyes, thus modulating the solubility profiles and optical properties.^[11]

Herein we report a novel series of dendritic branches based on L-lysine, in which the focal point has been functionalized with benzo[18]crown-6. We have characterized the strength and stoichiometry of binding with potassium and benzylammonium cations, and report the effect of dendritic branching on the host–guest binding process. In addition, we have assembled dendritic branches around a bis-ammonium cation, thus encapsulating it within a supramolecular dendritic shell. We were able to achieve controlled release of the encapsulated template molecule by the addition of potassium ions. In this way, we have achieved the controlled assembly and disassembly of a supramolecular dendrimer in solution for the first time.

[*] Dr. D. K. Smith, G. M. Dykes
Department of Chemistry
University of York
Heslington, York, YO10 5DD (UK)
Fax: (+44) 1904-432-516
E-mail: dks3@york.ac.uk
Dr. G. J. Seeley
ICI Technology
PO Box 90, Wilton Centre
Middlesbrough, Cleveland, TS90 8JE (UK)

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Scheme 1. Synthesis of the crown ether functionalized dendritic branches: a) Pd/C, EtOH, 99 %; b) **G1-COOH**, DCC, HOBt, Et₃N, EtOAc, 87 %; c) **G2-COOH**, HATU, Et₃N, EtOAc, 91 %; d) **G3-COOH**, HATU, Et₃N, EtOAc, 63 %.

The dendritic crowns **G1-crown**, **G2-crown**, and **G3-crown** were synthesized according to Scheme 1. Preformed dendritic branches based on L-lysine^[12] which possess a carboxylic acid at the focal point were coupled to 4'-aminobenzocrown-6.^[13] As expected in convergent synthesis,^[1c] the reaction became less favored with increasing dendritic generation, which necessitated a change in the coupling reagent from 1,3-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/HOBt) to the more active *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) uronium salt for the synthesis of **G2-crown** and **G3-crown**.^[14] Yields of 87, 91, and 63 % were obtained for **G1-crown**, **G2-crown**, and **G3-crown**, respectively. The dendritic crowns were characterized by all standard methods, and data were in full agreement with the proposed structures.^[15]

The ability of these receptors to bind K⁺ ions was monitored by ¹H NMR titrations in MeOD solution. The chemical shift of the aromatic protons was followed during the addition of K⁺ ions, and in all cases 1:1 complexes were formed (Figure 1). The binding for **G1-crown** and **G2-crown** was on the upper limits of determination by NMR methods, and log *K* values (Table 1) were estimated as ≥ 5. By inspection of the data, it appeared that **G1-crown** binds K⁺ ions more strongly than **G2-crown**. **G3-crown** binds K⁺ ions slightly less strongly, with the log *K* value calculated as 4.1 (HypNMR).^[16] The change in chemical shift of the aromatic protons induced by K⁺ ions decreased as the dendritic generation of the receptor increased. Host–guest chemistry inside dendrimers is of considerable current interest,^[2] and it has been previously observed that binding strengths (and induced shifts) decrease with increasing generation as a consequence of small amounts of nonselective binding within the dendritic branching.^[17] In our case, the C=O groups within the branches may bind weakly to K⁺ ions, thus competing with the crown ether at the focal point. Alternatively, the build-up of charge within the

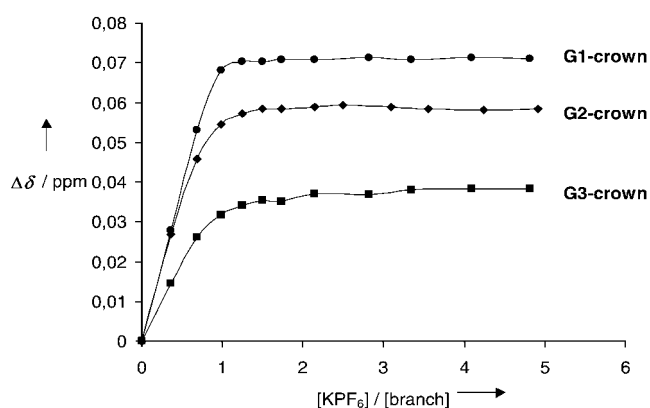


Figure 1. NMR titration curves for **G1-crown**, **G2-crown**, and **G3-crown** with K⁺ ions in which the shift of the aromatic signal (at ca. δ = 6.9 ppm) is monitored.

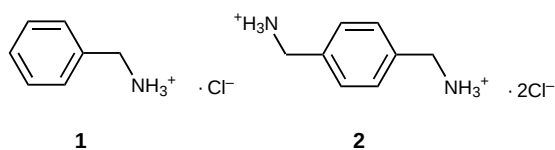
Table 1. Binding constants (log *K*_a, MeOD, *T* = 300 K) elucidated by ¹H NMR titration methods for 1:1 complexes of dendritic crown ethers with K⁺ ions and **1**.

Receptor	Guest cation	log <i>K</i> _a	Standard deviation ^[a]	$\Delta\delta_{\text{sat}}$ [ppm]
G1-crown	K ⁺	≥ 5	excessive	0.070 ^[b]
G2-crown	K ⁺	≥ 5	excessive	0.058 ^[b]
G3-crown	K ⁺	4.10	0.14	0.038 ^[b]
G1-crown	1	3.58	0.14	0.115 ^[c]
G2-crown	1	3.28	0.23	0.104 ^[c]
G3-crown	1	2.31	0.12	0.108 ^[c]

[a] The standard deviation gives the +/− error for 67 % confidence. [b] Saturation shift in the aromatic peak (at ca. δ = 6.9 ppm) of the benzocrown ether induced by the addition of potassium cations. [c] Saturation shift in the CH₂ (benzyl) signal (at δ = 4.10 ppm) of guest **1** induced by the addition of the dendritic crown ether.

dendritic structure may be disfavored as a consequence of increasing amounts of branching shielding the charge from the polar solvent.

The ability of the receptors to bind the benzylammonium cation **1** was also investigated in MeOD. Binding constants



(Table 1) were elucidated by NMR titrations in which the perturbation of the benzyl CH₂ protons of **1** on the addition of **Gn-crown** was monitored. The strength of binding decreased as the dendritic generation increased. As a control experiment, the dendritic branch functionalized with a methyl ester group, **G3-COOMe**,^[18] was titrated with **1**. There was only a very small perturbation of the NMR signals of **1**, which is indicative of very weak, nonselective binding in the branches. As expected, therefore, the crown ether is the primary site for binding these cationic guests.

The ability of the more strongly binding potassium ion to trigger the release of the more weakly bound ammonium cation **1** from the complex was then investigated. A fivefold excess of **G1-crown** was mixed with **1** and the NMR signal of the benzyl CH₂ protons was monitored on the addition of K⁺ ions. The addition of one equivalent of K⁺ ions was sufficient to completely displace the benzylammonium guest (**1**) from the complex (Figure 2).^[19]

The relatively strong crown⋯NH₃⁺ interactions were then used to assemble a supramolecular dendrimer. The interaction between protonated 1,4-bis(aminomethyl)benzene (**2**) and **G2-crown** was monitored in MeOD by using NMR methods, and a Job plot analysis was performed to monitor the stoichiometry of the complex formed (Figure 3, ■). This plot was compared to the Job plot for the binding of **1** to **G2-crown** (Figure 3 ▲), and clearly illustrates the difference in stoichiometry between the two complexes. Hence, a 2:1 assembly was formed between **G2-crown** and compound **2** (Scheme 2), namely, formation of a supramolecular dendrimer takes place. The HypNMR program was used to elucidate the binding constants for the formation of 1:1 and 2:1 complexes, and values of log *K*₁₁ = 2.06 (0.37) and log *K*₂₁ = 1.27 (0.16) were obtained. The results indicate a noncooperative binding process in polar MeOH solution. Once again, this supramolecular dendrimer was smoothly disassembled by the addition of K⁺ ions to the solution—releasing template **2** into solution—a process which was monitored by NMR methods. In a very recent paper,^[10b] Gibson et al. reported the cooperative assembly of related dendritic structures in nonpolar solvents. In the future, the assembly process reported here will also be investigated in nonpolar solvents to determine whether there are any cooperative binding effects in this case.

In conclusion, we can assemble dendritic structures in competitive solvents such as methanol, and then disassemble them in a controlled manner. This approach is of general importance: it obviates the need for time-consuming covalent synthesis, and also has the advantage that compounds containing ammonium ions

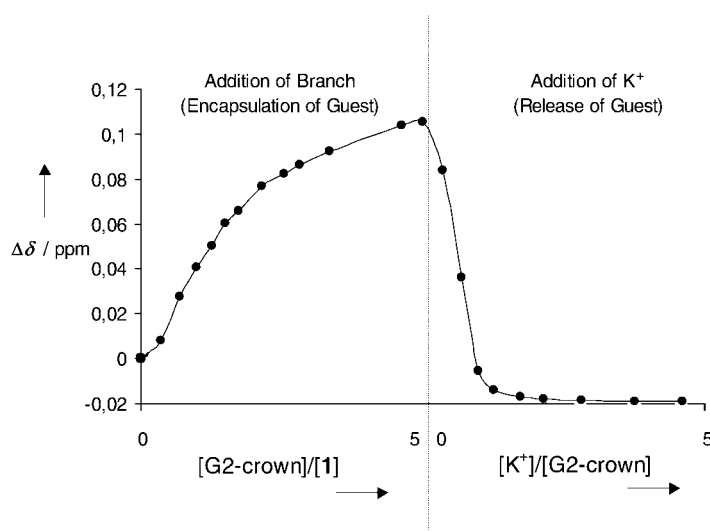


Figure 2. NMR shift of the ArCH₂ peak (at $\delta = 4.10$ ppm) of guest **1** on the addition of **G2-crown** followed by the addition of KPF₆.

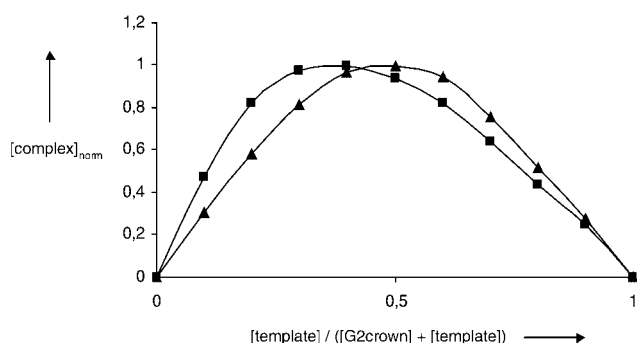
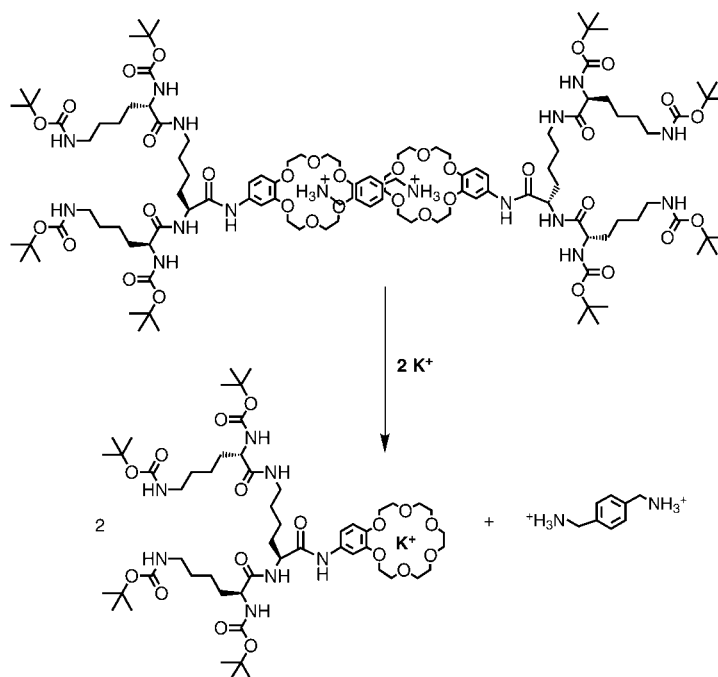


Figure 3. Job plot determined by ¹H NMR spectroscopy indicating the 2:1 stoichiometry of the complex formed between **G2-crown** and **2** (■), and the 1:1 stoichiometry of the complex formed between **G2-crown** and **1** (▲).



Scheme 2. Proposed structure of the supramolecular dendrimer generated by mixing **G2-crown** with compound **2**, and the disassembly process induced by the addition of KPF₆.

which could act as potential templates are fairly common. This reversible dendritic encapsulation will be of particular use when the template is a functional molecule derivatized with NH_3^+ groups. The function will then be dendritically modified (or shielded) until such a point as K^+ ions are added, when controlled release of the functional template would be achieved. Investigations of the reversible encapsulation and controlled release of functional template molecules are currently in progress.

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- [18] **G3COOMe** is the third-generation lysine-based dendritic branch in which the carboxylic acid at the focal point has been protected as a methyl ester. The full characterization of this compound has previously been published in reference [11b].
- [19] The chemical shift of the benzyl peak after K^+ -triggered release of the guest from the complex is not the same as at the start of the experiment because of the change in counter anion (from Cl^- to PF_6^-) and the increase in ionic strength of the solution.

Phosphite Dehydrogenase: A Versatile Cofactor-Regeneration Enzyme**

Jennifer M. Vrtis, Andrea K. White, William W. Metcalf, and Wilfred A. van der Donk*

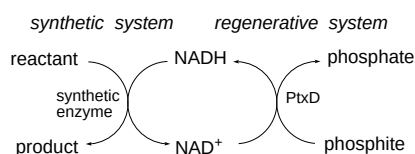
The potential of enzyme-catalyzed transformations in organic synthesis is well recognized.^[1] Oxidoreductases make up an important class of enzymes as they can perform highly stereoselective reductions of a variety of functional groups.^[2] A drawback of the nicotinamide-dependent oxidoreductases is the prohibitively high expense of the cofactor for stoichiometric use. This impediment has been overcome by using a second enzyme system that can continuously replenish a catalytic amount of the active form of the cofactor.^[3] Cofactor regeneration also simplifies product isolation and can influence the position of the equilibrium of the synthetic enzyme system, that is, the regeneration system may drive the reaction to completion when product formation would be unfavorable in its absence. The efficiency of a regeneration system is determined by the expense and stability of the regeneration enzyme and its substrate, the ease of product purification, the kinetic parameters of the regeneration enzyme (k_{cat} , K_M), and the thermodynamic driving force.

We recently described the unusual enzyme phosphite dehydrogenase (PtxD).^[4,5] This protein catalyzes the oxidation of phosphite to phosphate with the concomitant reduction of NAD^+ to NADH. The enzyme can also use NADP^+ as the oxidant, albeit less effectively.^[4] The equilibrium constant for the oxidation of phosphite by NAD^+ can be estimated as 10^{11} by using the reported redox potentials at pH 7.0 for

[*] Prof. W. A. van der Donk, J. M. Vrtis
Department of Chemistry, Box 38-5
University of Illinois at Urbana-Champaign
600 S. Mathews Ave., Urbana, IL 61801 (USA)
Fax: (+1) 217-244-8068
E-mail: vddonk@uiuc.edu
A. K. White, Prof. W. W. Metcalf
B103 Chemical and Life Sciences Laboratory
Department of Microbiology, University of Illinois at Urbana-Champaign
601 S. Goodwin, Urbana, IL 61801 (USA)

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NAD^+/NADH (-0.32 V)^[6] and phosphite/phosphate (-0.65 V)^[7]. For comparison, the equilibrium constant for NAD^+ reduction by the industrially used formate dehydrogenase (FDH) from *Candida boidinii* is 7×10^5 .^[8] The k_{cat} of recombinant phosphite dehydrogenase (7.3 s^{-1})^[4] is slightly higher than that of FDH (2.5 s^{-1}),^[9] and the protein has a K_{m} of $\sim 50\text{ }\mu\text{M}$ for both NAD^+ and phosphite,^[4] assuring use of the cofactor in low concentrations. Moreover, phosphite is inexpensive and a phosphite buffer is simply converted into a phosphate buffer during the reaction.^[10] Importantly, it has been shown previously that phosphate does not inhibit PtxD, even at high concentrations, and that the enzyme displays a broad pH-rate maximum.^[4] Collectively, these properties imply that the enzyme has great potential as an NADH-regenerating system (Scheme 1).



Scheme 1. Schematic representation of the use of phosphite dehydrogenase (PtxD) as an NADH-regeneration enzyme.

The time course of the reduction of pyruvate to L-lactate by L-lactate dehydrogenase (LLDH) in the presence of NAD^+ (0.05 %) and PtxD (0.002 %) at relatively high concentrations of pyruvate (200 mM) and phosphite (500 mM) is shown in Figure 1. During the process, the rate of the synthetic system (LLDH) did not decrease over a time span of more than 70 h. At this timepoint, the substrate was completely converted into product, resulting in total turnover numbers (TTNs) of 2000 for the cofactor and 5×10^4 for phosphite dehydrogenase. The apparent robustness was not anticipated as it has been

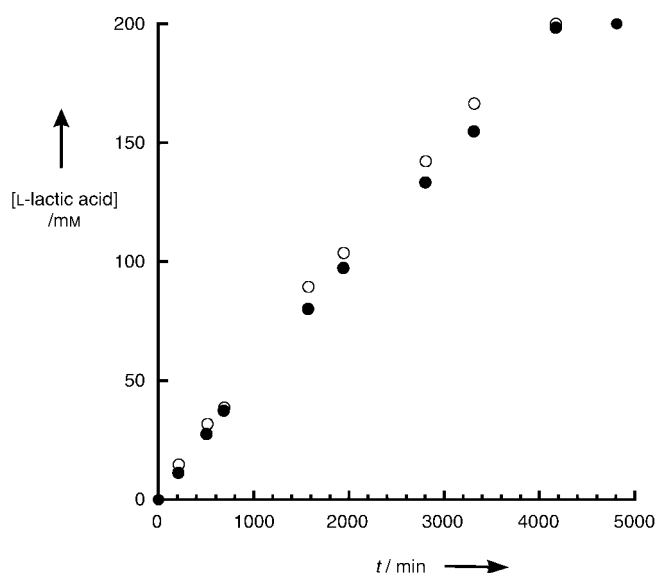
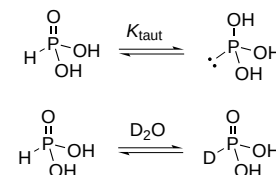


Figure 1. Time dependence of the production of L-lactate in a reaction mixture that contains phosphite (500 mM), pyruvate (200 mM), NAD^+ (0.1 mM), commercial LLDH (0.25 U mL^{-1}), and MBP-PtxD ($3\text{ }\mu\text{M}$). The progress of the reaction was monitored by ^1H NMR (pyruvate) and ^{31}P NMR spectroscopy (phosphite).

reported that among various buffers, phosphate is the most effective in accelerating the decomposition of NADH ($t_{1/2}$ 27 h at 0.1 M).^[11] It appears that in this system, however, the buffer-catalyzed breakdown of the cofactor is not a limiting factor. The regeneration enzyme consisted of phosphite dehydrogenase fused at its N-terminus to maltose-binding protein (MBP) (obtained on a large scale from a 30-L fermentation of *E. coli* that contained a pMAL-derived expression vector). A one-step purification protocol using an amylose affinity column yielded $\sim 70\text{ mg}$ of purified protein per liter of culture.^[12]

A convenient feature of the use of phosphite as the reductant involves the ease by which the reaction progress can be followed. A sensitive colorimetric assay allows the quantification of the phosphate produced,^[4] or alternatively, the diagnostic doublet of phosphite in the ^{31}P NMR spectrum can be monitored ($\delta = 3.58\text{ ppm}$, $J_{\text{P-H}} = 581\text{ Hz}$). The latter method is noninvasive and the amounts of both phosphite remaining and phosphate produced can be determined. After establishing that PtxD can be used for NADH regeneration with LLDH, a series of other dehydrogenases were investigated. PtxD was utilized in transformations catalyzed by D-lactate dehydrogenase (DLDH), horse liver alcohol dehydrogenase (HLADH), and malate dehydrogenase (MDH). In the case of HLADH, trifluoroacetaldehyde monohydrate was used as its nonphysiological substrate.^[13] For all four synthetic enzyme systems, TTNs of 10^2 – 10^3 were observed for NAD^+ and TTNs for PtxD ranged from 10^4 to 10^5 .^[14]

Perhaps the most valuable aspect of using phosphite dehydrogenase as a cofactor-regeneration system is the ease by which it can be used for the preparation of deuterated products. Phosphite exists in two different equilibrating isomers, of which the tetracoordinated tautomer **1** is favored by a factor of 10^{21} at pH 7.0. At pH 2, however, K_{eq} for phosphorous acid is increased to 10^{-10} .^[15] Hence, equilibration of phosphorous acid in D_2O followed by lyophilization provides facile access to labeled substrate (Scheme 2).^[16] The rate of exchange is slow at pH 2 ($t_{1/2} = 500\text{ min}$), and becomes essentially negligible at pH 7.^[17] Therefore, deuterium-labeled phosphite can be used for the in situ preparation of NAD^2H and thereby for the enzymatic preparation of labeled compounds.^[18] We have previously shown that PtxD displays only a moderate primary kinetic isotope effect (KIE) on k_{cat} (2.0) and $k_{\text{cat}}/K_{\text{m,phosphite}}$ (1.8),^[5] and hence the use of labeled substrate should not prohibit cofactor regeneration. Indeed, (*S*)-2-[D]lactate was obtained in high isotopic purity ($> 98\%$) when LLDH and PtxD were used in the presence of [D]phosphite. This methodology allows a low-cost alternative to existing methods for the enzymatic preparation of labeled compounds.^[19]



Scheme 2. The equilibrium between the two tautomeric forms of phosphorous acid can be exploited for the production of deuterium-labeled phosphite.

In summary, we report the use of a new NADH-regeneration system based on phosphite dehydrogenase. This enzyme has much potential owing to a larger thermodynamic driving force for NADH production than any of the previously

reported regeneration systems. The products can be readily separated from the phosphate by-product, and this technology can be conveniently and economically adapted for the production of deuterium-labeled products.

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Guest Preorganization: An Alternative “Bioinspired” Paradigm in Host–Guest Chemistry**

Brian S. Hammes, Xuemei Luo, Mary W. Carrano, and Carl J. Carrano*

The tris(pyrazolyl)borate ligands pioneered by Trofimenko in the late 1960s, have arguably become the preeminent platform for metal binding in coordination, organometallic, and bioinorganic chemistries.^[1] Indeed, complexes of this ligand with almost every metal in the periodic table are known.^[1] Modifications to the parent ligand over the last few decades have been primarily directed towards the synthesis of highly sterically congested analogues that have allowed the stabilization of species not previously accessible.^[2–5] Another possible application for this anionic, three-fold-symmetric class of molecule, namely as a “host” to something other than a metal ion, seems to have been largely unexplored. Recently, by using ester- or amide-containing R groups at the 3-position of the pyrazole ring to provide an additional set of sites for secondary interactions, we have begun to explore the host–guest chemistry of the tris(pyrazolyl)borates. Whilst trying to use various transamidation reactions to convert 3-ester-substituted Tp (tris(pyrazolyl)borates) ligands into 3-amido-substituted ligands we isolated complexes of the general stoichiometry [Tp*][NH₃R], where Tp* = tris(3-carboxyethyl-5-methylpyrazolyl)borate. That these species were not simple salts but true host–guest complexes was revealed by an X-ray crystal structure of the *tert*-butylammonium analogue, **1**.^[6] The structure of **1** (Figure 1) reveals the expected complementarity of fit between the anionic tris(pyrazolyl)borate and the cationic three-fold symmetric protonated amine which is lodged in the “metal-binding” cavity of the former. In addition to the electrostatic attraction, the protonated amine group makes three strong, bifurcated hydrogen bonds with the pyrazole nitrogen atoms and the ester carbonyl groups. The hydrogen atoms of the ammonium ion, which were all easily located and refined in the structure, are at an average of 2.16(6) Å from the pyrazole nitrogen atoms and 2.54(16) Å from the carbonyl oxygen atoms, with 71.6(26)° N–H···O angles. Two sharp N–H proton resonances

[*] Dr. C. J. Carrano, Dr. X. Luo, M. W. Carrano
Department of Chemistry and Biochemistry
Southwest Texas State University
San Marcos, TX 78666 (USA)
Fax: (+1) 512-245-2374
E-mail: cc05@swt.edu
Dr. B. S. Hammes
Department of Chemistry
St. Joseph's University
Philadelphia, PA (USA)

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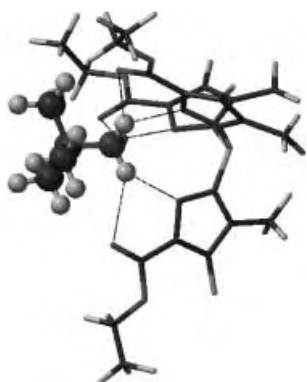


Figure 1. The structure of $[(\text{CH}_3)_3\text{CNH}_3][\text{Tp}^{\text{CO}_2\text{EtMe}}]$ (**1**). The host $\text{Tp}^{\text{CO}_2\text{EtMe}}$ is depicted as a tube model while the guest $(\text{CH}_3)_3\text{CNH}_3$ is shown as a ball-and-stick structure. Dotted lines indicate the bifurcated hydrogen bonds.

corresponding to free and bound alkyl ammonium ion in slow exchange are observable by NMR spectroscopy in CDCl_3 for methylamine, while a single broad resonance, indicative of intermediate exchange, is seen with *tert*-butylamine, which reveals that there is thermodynamic and/or kinetic discrimination between amines. While this type of host-guest interaction promises to provide possible applications for Tp-based hosts in the sensing of, for example, amino acids and neurotransmitters, it is not in any way unique in supramolecular chemistry. It follows the accepted paradigm in that the host is preorganized to accept a particular guest based on size, shape, and electrostatic complementarity.^[7] However, this paradigm requires that a new host be designed and synthesized for each guest or at least each class of guest. Nature often takes a different approach to the question of recognition. For example, iron uptake in microbes is a receptor-mediated event but the metal cation is first attached to a siderophore molecule which serves not only to solubilize the iron but also to provide the recognition sites.^[8] These recognition sites arise because the siderophore adopts a specific 3D structure, based on the coordination preferences of the iron center (in some cases the siderophore itself may also be preorganized to provide high thermodynamic stability). In general, neither the metal ion nor the siderophore itself are recognized, but only the complex of the two. In this way, a single receptor is able to recognize iron complexes based on a variety of siderophores; possibly a competitive advantage to some organisms. That, in this case, the desired guest is the metal ion rather than the ligand does not detract from the basic concept. Another relevant example concerns the so-called zinc fingers. These are small metal-binding peptide units that function in gene regulation by promoting protein-nucleic acid binding and recognition.^[9] All these proteins contain a core of histidine and cysteine residues which, when coordinated to a zinc center in a tetrahedral fashion, are stabilized in a variety of folding motifs critical to DNA recognition. In this case, the protein ligands themselves have no DNA-binding specificity in the absence of the metal ion. It is only after they are “preorganized” by metal coordination that interaction is observed. To illustrate the utility of this approach, we have taken the guest molecule 3-methylcarboxamido-5-methylpyrazole, which has no affinity for the Tp^* host, and preorganized it for recognition by taking advantage of the coordination preferences of Ni^{II} centers. Thus, reaction of Ni^{II} with three equivalents of the pyrazole produces the dicationic tris octahedral complex, in which the pyrazole functions as a bidentate ligand, coordinating through a pyrazole nitrogen

atom and the amide carbonyl group. In this way, the remaining three uncoordinated pyrazole nitrogen atoms have their protons arranged in a trigonal array that is highly complementary to the pyrazole nitrogen atoms of the Tp^* “host”. An X-ray structure of **2** (Figure 2) reveals a host-guest complex stabilized by both electrostatic interactions and hydrogen

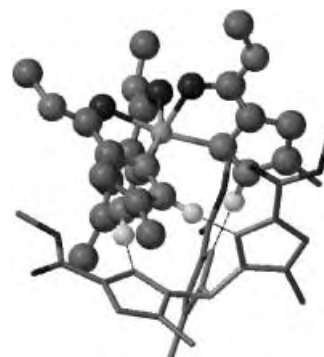


Figure 2. The structure of the cationic portion of $[\text{Ni}(\text{pz}^{\text{CONHMeMe}})_3][\text{Tp}^{\text{CO}_2\text{MeMe}}]\text{ClO}_4$ (**2**). The host $\text{Tp}^{\text{CO}_2\text{MeMe}}$ is depicted as a tube model while the guest $[\text{Ni}(\text{pz}^{\text{CONHMeMe}})_3]^{2+}$ is shown as a ball-and-stick structure. All hydrogen atoms, except those involved in H-bonding (dotted lines), have been removed for clarity.

bonding, with an average $\text{N}\cdots\text{N}$ distance of $2.87(3)$ Å and a $\text{N}_{\text{pz}}\cdots\text{H}\cdots\text{N}_{\text{Tp}}$ angle of $172(1)$.^[10] The perchlorate counterion needed for the charge balance of the $[[\text{Ni}(\text{pz}^{\text{CONHMeMe}})_3][\text{Tp}^{\text{CO}_2\text{MeMe}}]]^+$ complex unit does not interact.

In conclusion, we have shown for the first time that an elaborated version of the widely utilized tris(pyrazolyl)borate class of ligand can function as a host for something other than a metal cation. In addition, we show an example of an alternate paradigm in host-guest chemistry in which a simple pyrazole guest with no inherent affinity is preorganized, by coordination to a metal ion, to bind to a Tp host.

Experimental Section

Complex **1** was isolated during the attempted aminolysis of potassium tris(3-carboxyethyl-5-methylpyrazolyl)borate (5.1 g, 0.1 mol) with $\text{Al}(\text{CH}_3)_2\text{NH}_2\text{Bu}$ in refluxing dichloromethane. Acidic workup, extraction, and recrystallization from diethyl ether gave large crystals of **1** (1.0 g) suitable for crystallographic analysis. Elemental analysis (%) calcd for $[(\text{CH}_3)_3\text{CNH}_3][\text{Tp}^{\text{CO}_2\text{EtMe}}]$, $\text{C}_{25}\text{H}_{40}\text{N}_7\text{O}_6\text{B}\cdot 0.5\text{H}_2\text{O}$: C 54.59, H 7.44, N 17.83; found C 54.51, H 7.39, N 17.84; ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 8.10 (br s, 3H; NH_3), 6.37 (s, 3H; PzH), 4.28 (q, J = 7 Hz, 6H; $-\text{OCH}_2-$), 2.32 (s, 9H; $\text{Pz}-\text{CH}_3$), 1.54 (s, 9H; *tert*-butyl- CH_3), 1.31 ppm (t, J = 7 Hz, 9H; $-\text{CH}_2-\text{CH}_3$); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): δ = 164.30, 144.70, 142.89, 106.92, 60.12, 51.31, 27.02, 14.41, 12.79 ppm; FTIR (KBr): $\tilde{\nu}$ = 2497 (B-H), 1714 cm^{-1} (C=O). Pz = pyrazolyl.

Compound **2** was prepared by a one-pot reaction by adding 3-methylcarboxamido-5-methylpyrazole (0.204 g, 1.5 mmol) to the complex $[\text{Tp}^{\text{CO}_2\text{EtMe}}\text{Ni}(\text{H}_2\text{O})_3]\text{ClO}_4$ ^[11] (0.31 g, 0.5 mmol) in methanol, followed by overnight stirring. After evaporation of the solvent under reduced pressure, the light-blue solid was dissolved in acetonitrile. Slow diffusion of diethyl ether into a concentrated acetonitrile solution produced crystals suitable for X-ray diffraction. Caution! The perchlorate salt is potentially explosive and should be handled with care. Elemental analysis (%) calcd for $[(\text{pz}^{\text{CONHMeMe}})_3\text{Ni}][\text{Tp}^{\text{CO}_2\text{MeMe}}]\text{ClO}_4\cdot\text{ACN}\cdot 3\text{H}_2\text{O}$, $\text{C}_{38}\text{H}_{57}\text{N}_{16}\text{O}_{16}\text{BClNi}$: C

41.55, H 5.23, N 20.42; found C 41.31, H 4.70, N 20.34; FTIR (KBr): $\tilde{\nu}$ = 2564 (B-H), 1722, 1634 cm^{-1} (C=O); λ_{max} (CH₃CN, ϵ , $\text{M}^{-1}\text{cm}^{-1}$): 378 (20).

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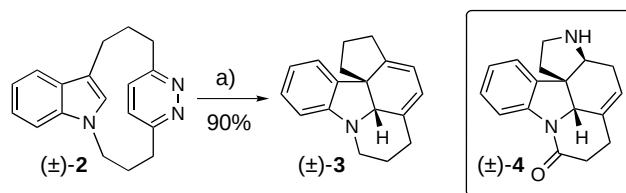
A Concise Formal Total Synthesis of (±)-Strychnine by Using a Transannular Inverse-Electron-Demand Diels–Alder Reaction of a [3](1,3)Indolo[3](3,6)pyridazinophane**

Graham J. Bodwell* and Jiang Li

Owing to its level of complexity for its size, strychnine (**1**) presents a most formidable synthetic challenge.^[1] The first total synthesis, one of the most significant achievements in the history of organic synthesis, was reported by Woodward^[2] in 1954 and it wasn't until the early 1990s that a series of other

successful syntheses, both racemic and enantioselective, began to appear. There are now ten reported total syntheses of strychnine^[2–11] and each of them features an elegant application of one or more reactions that bring about a substantial increase in molecular complexity, for example, the Mannich reaction combined with a sigmatropic rearrangement (Overman and co-workers,^[3] Kuehne et al.^[4,5]), the intramolecular Diels–Alder reaction (Rawal et al.^[6] Martin and co-workers^[7]), intramolecular Heck reactions (Rawal et al.^[6] Bonjoch, Bosch, and co-workers^[8]), the cobalt-mediated [2 + 2 + 2] cycloaddition (Vollhardt and co-workers^[9]), skeletal rearrangements (Stork,^[10] and Martin and co-workers^[7]) and transannular oxidative cyclization (Magnus et al.^[11]). The shortest synthesis reported to date is that of Vollhardt (14 steps from propiolic acid), but the highest overall yield (10 %) belongs to Rawal's synthesis.^[6,12]

We recently reported the synthesis of cyclophane (±)-**2** and its efficient transannular inverse-electron-demand Diels–Alder (IEDDA) reaction to afford pentacycle (±)-**3** (Scheme 1).^[13] The similarity of (±)-**3** to the key pentacyclic amine (±)-**4** (ABCEG rings of strychnine) described by Rawal^[6] prompted us to attempt to apply our “cyclophane approach” to a formal total synthesis of (±)-strychnine.



Scheme 1. Conversion of (±)-**2** into (±)-**3**. Reagents and conditions: a) *N,N*-diethylaniline, Δ , 48 h.

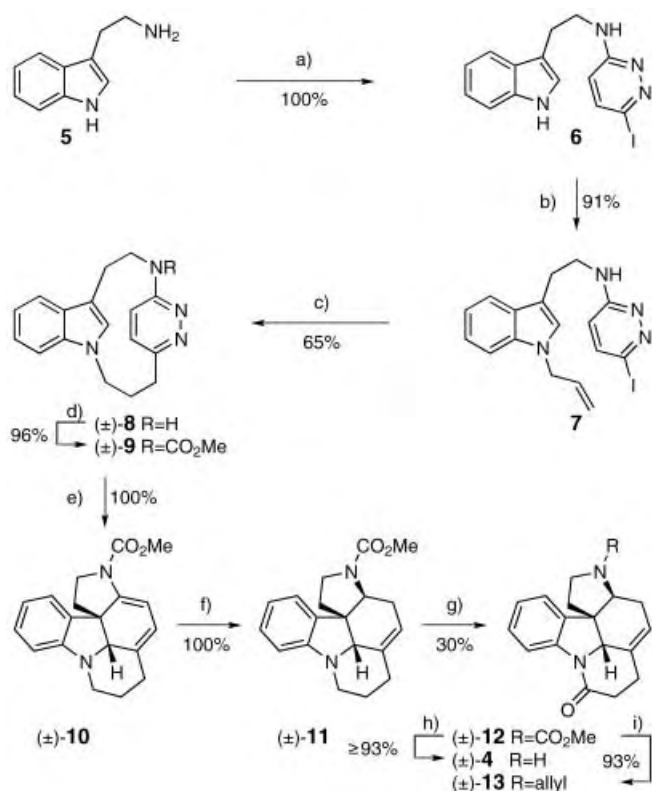
The synthesis (Scheme 2) commenced with the reaction of the tryptamine **5** with 3,6-diiodopyridazine^[14] to afford iodide **6** (100 %). *N*-Allylation of the indole moiety yielded **7** (91 %), which was subjected to a sequential hydroboration/intramolecular B-alkyl Suzuki–Miyaura cross-coupling reaction^[15] to give cyclophane (±)-**8** (65 %). The secondary amine was protected as a methyl carbamate and the resulting cyclophane (±)-**9** (96 %) was heated in *N,N*-diethylaniline to induce the key transannular IEDDA reaction. Pentacycle (±)-**10**, the product of the transannular IEDDA reaction followed by the expulsion of N₂ from the initially formed adduct,^[13] was obtained quantitatively. This very productive step resulted in the generation of two stereogenic centers (including the key quaternary center^[1b]) with the correct relative stereochemistry^[13] and the simultaneous construction of the C, E, and G rings.

Having rapidly constructed the ABCEG framework, a short series of functional group interconversions were required to prepare (±)-**4**. Reduction of (±)-**10** with NaBH₄/CF₃CO₂H occurred with complete chemo- and stereoselectivity to afford (±)-**11** (100 %). The tertiary amine was then oxidized with PDC^[16] to give the amide (±)-**12** (30 %) and removal of the carbamate protecting group delivered Rawal's

[*] Dr. G. J. Bodwell, J. Li
Department of Chemistry
Memorial University of Newfoundland
St. John's, NF, A1B 3X7 (Canada)
Fax: (+1) 709-737-3702
E-mail: gbodwell@mun.ca

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Scheme 2. Synthesis of Rawal's key intermediate (±)-4. Reagents and conditions: a) 3,6-diiodopyridazine, *sec*-butanol, Δ , 4 days; b) KOH, DMF, RT, 1 h, then allyl bromide, RT, 2 h; c) 9-BBN, THF, 0°C–RT, 12 h, then Pd(PPh₃)₄, Cs₂CO₃, THF, Δ , 2 days; d) NaHMDs, THF, –78°C, 1 h, then ClCO₂Me, –78°C–RT, 3 h; e) *N,N*-diethylaniline, Δ , 1 h; f) NaBH₄, CF₃CO₂H, benzene, 0°C–RT, 12 h; g) PDC, celite, CH₂Cl₂, RT, 3 d; h) TMSI, CHCl₃, Δ , 6 h; i) TMSI, CHCl₃, Δ , 6 h, then allyl bromide, Li₂CO₃, DMF, RT, 24 h. DMF = *N,N*-dimethylformamide, 9-BBN = 9-borabicyclo[3.3.1]nonane, PDC = pyridinium dichromate, TMS = trimethylsilyl.

key intermediate (±)-4. The crude yield of this latter reaction was typically over 100% and attempts to purify the product chromatographically led to substantial losses and little improvement in the quality of the NMR spectra. Rawal^[6] also noted (in his Supporting Information) that this compound was not very stable. Consequently, he used the crude product immediately in the following step, which was the attachment of the side chain by N-alkylation of the secondary amine with an allylic bromide. Accordingly, the crude product of the reaction of (±)-11 with TMSI was treated immediately with allyl bromide and Li₂CO₃. This reaction afforded (±)-13 in 93% yield, which established a lower limit of 93% for the yield of (±)-4.

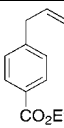
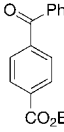
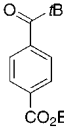
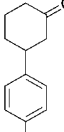
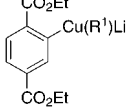
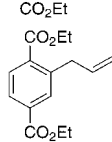
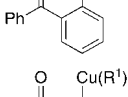
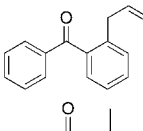
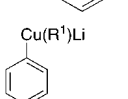
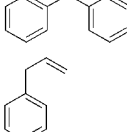
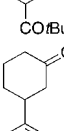
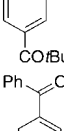
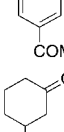
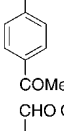
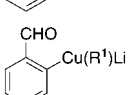
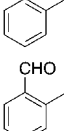
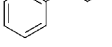
The overall yield of (±)-4 from 5 is 15.8% over eight steps, with the majority of the losses occurring during the conversion of (±)-11 into (±)-12 (30% yield). All attempts to improve this yield have so far been unsuccessful, as have attempts to introduce the carbonyl group prior to the key transannular IEDDA reaction. Applying Rawal's yields^[6] for the conversion of (±)-4 into isostrychnine and Kuehne's yield^[4] for the conversion of isostrychnine into strychnine, our formal overall yield of (±)-strychnine from tryptamine is 2.6% over 12 steps. Thus the synthesis described here is the shortest route to strychnine yet reported. However, the best overall yield still belongs to Rawal.^[6]

Until recently, the use of cyclophanes in the synthesis of natural products was unheard of. The synthesis described above adds to the still small, but growing, number of syntheses that employ cyclophanes.^[17] Future work in this area will be aimed at the modification of the existing synthesis to avoid the use of isostrychnine as an intermediate and development of an enantioselective route to strychnine.^[18]

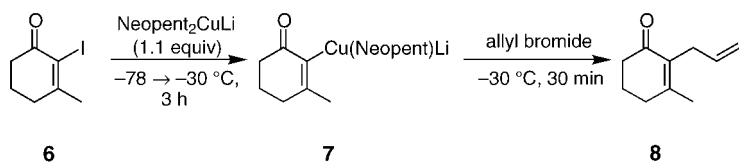
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Table 1. Reaction of functionalized lithium cuprates **4** with electrophiles to give **5**.

Entry	Cuprate 4 ^[a]		Electrophile	Product 5	Yield [%] ^[b]
1	Cu(R¹)Li 	4a	allyl bromide	 5a	95 90 ^[c]
2	Cu(R¹)Li 	4a	PhCOCl	 5b	87 95 ^[c]
3	Cu(R¹)Li 	4a	<i>t</i> BuCOCl	 5c	83
4	Cu(R¹)Li 	4a	cyclohexenone	 5d	70
5	 Cu(R¹)Li	4b	allyl bromide	 5e	76
6	 Cu(R¹)Li	4c	allyl bromide	 5f	80
7	 Cu(R¹)Li	4c	MeI	 5g	80
8	Cu(R¹)Li 	4d	allyl bromide	 5h	93
9	Cu(R¹)Li 	4d	cyclohexenone	 5i	60
10	Cu(R²)Li 	4e	PhCOCl	 5j	77 ^[c]
11	Cu(R²)Li 	4e	cyclohexenone	 5k	68 ^[c]
12	 Cu(R¹)Li	4f	CH ₃ COCl	 5l	70
13	 Cu(R¹)Li	4f	allyl bromide	 5m	80

[a] R¹ = neopentyl; R² = neophyl. [b] Yields of isolated analytically pure products. [c] Yields obtained by performing the I/Cu exchange with **2**.



Scheme 2. Iodine-copper exchange with 2-iodo-3-methyl-2-cyclohexenone.

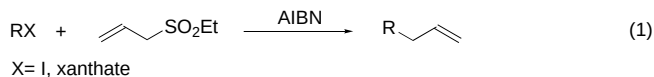
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Tin-Free Radical-Mediated C–C-Bond Formations with Alkyl Allyl Sulfones as Radical Precursors**

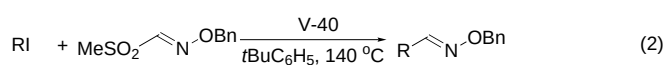
Sunggak Kim* and Chae Jo Lim

The synthetic importance of tin-free radical reactions has been well recognized in recent years.^[1] Among several

approaches, an organosulfone-mediated approach is very effective for allylation,^[2] vinylation,^[3] and azidation^[4] [Eq. (1), AIBN = 2,2'-azobisisobutyronitrile]. However, the reported methods did not work well with primary alkyl iodides and xanthates owing to inefficient iodine-atom transfer and xanthate-group transfer, respectively. Recently, we also reported a tin-free acylation approach

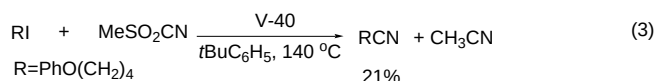


using methanesulfonyl oxime ether, in which primary alkyl iodides and xanthates caused the same problem as a result of the small energy difference between the methyl radical and the primary alkyl radical [Eq. (2), V-40 = 1,1'-azobis(cyclohexane-1-carbonitrile)].^[5]



As our extensive efforts to generate primary alkyl radicals from primary alkyl iodides and xanthates were unsuccessful, we have been interested in developing a new reliable method to generate primary alkyl radicals by using new types of radical precursors that do not require an atom- or a group-transfer step. In this regard, we have studied the possibility of using an alkyl allyl sulfone as a radical precursor. Alkyl allyl sulfones have been widely used as radical acceptors to transfer an allyl group to a radical precursor.^[6] Although alkyl allyl sulfones have been used once as the radical precursor in an allylation reaction,^[2a] primary alkyl allyl sulfones have not been examined. To the best of our knowledge, S-alkoxycarbonyl dithiocarbonates are the only generators of primary alkyl radicals from alcohols, but they cannot be applied to C–C-bond formations owing to the rapid formation of the corresponding xanthates.^[7] We have found that alkyl allyl sulfones are highly efficient and reliable radical precursors for the generation of primary alkyl radicals under tin-free conditions and can be successfully applied to various C–C-bond-formation reactions.

Initially, we focused on radical cyanation,^[8] and began our study with a primary alkyl iodide and methanesulfonyl cyanide.^[9] The reaction of 4-phenoxybutyl iodide with methanesulfonyl cyanide (2 equiv) and V-40 (0.2 equiv) in *tert*-butylbenzene at 140 °C for 5 h afforded 4-phenoxybutyl cyanide in only 21 % yield together with recovered 4-phenoxybutyl iodide (77 %). Notably, methanesulfonyl cyanide was completely consumed, with acetonitrile as the major product [Eq. (3)].^[10] However, allyl sulfone **1** was an effective

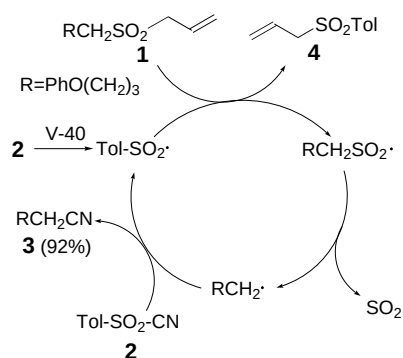


precursor for radical cyanation, and our approach is outlined in Scheme 1. We envisaged that the addition of a *p*-toluenesulfonyl radical to **1** would produce an alkyl sulfonyl radical as well as *p*-tolyl allyl sulfone **4**. Although the alkyl sulfonyl

[*] Prof. Dr. S. Kim, C. J. Lim
 Center for Molecular Design and Synthesis
 and Department of Chemistry, School of Molecular Science
 Korea Advanced Institute of Science and Technology
 Taejon 305-701 (Korea)
 Fax: (+82)42-869-8370
 E-mail: skim@mail.kaist.ac.kr

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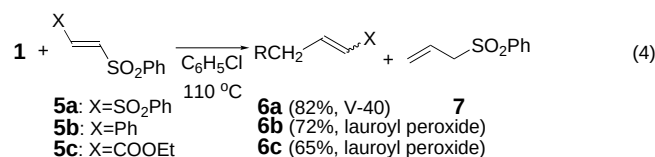
Scheme 1. Pathway for radical cyanation of an alkyl allyl sulfone with *p*-toluenesulfonyl cyanide.

radical could add to **1** and **4**, the former is a degenerate process, and the latter produces the *p*-toluenesulfonyl radical. Thus, neither of the reactions interferes with the desired process. As the addition of an alkyl radical to **4** and **1** is relatively slow,^[11] the alkyl radical that is generated from the thermal decomposition of the alkyl sulfonyl radical, should preferentially add to *p*-toluenesulfonyl cyanide (**2**) and regenerate the *p*-toluenesulfonyl radical for propagation of the radical chain reaction.

The reaction of **1** with **2** (1.5 equiv) in the presence of V-40 initiator (0.2 equiv) in chlorobenzene at 110 °C for 6 h proceeded cleanly, yielding **3** in 92 % yield. The high-yielding formation of **3** indicates that the primary alkyl radical is generated cleanly under tin-free conditions (Scheme 1).^[12] As shown in Table 1, the present method worked well with primary and secondary alkyl allyl sulfones as well as with a benzyl allyl sulfone.

The present approach can be further applied to radical vinylation and allylation reactions. For radical vinylation,^[3,13] we found that (*E*)- and (*Z*)-1,2-bis(phenylsulfonyl)ethylene (**5a**)^[14] are excellent radical acceptors and transfer a vinyl

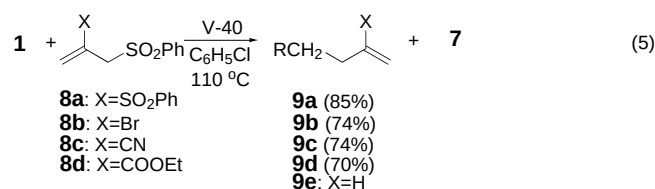
sulfonyl group to an alkyl group.^[15] Treatment of **1** with **5a** and V-40 in chlorobenzene at 110 °C for 6 h afforded **6a** in 82 % yield [Eq. (4)].^[16] Apparently, the addition of the primary



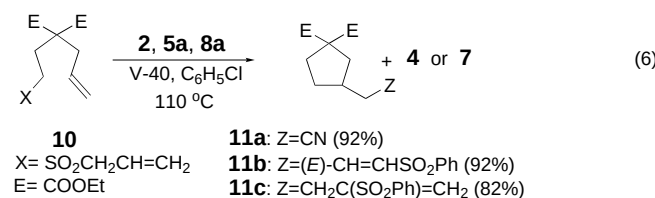
alkyl radical derived from **1** to activated vinyl sulfone **5a** is much faster than the addition to unactivated allyl sulfone **1** and **7**. When (*Z*)-1,2-bis(phenylsulfonyl)ethylene was used, various alkyl allyl sulfones worked equally well, yielding (*E*)-1-phenylsulfonyl alkenes as a major product in high yields (Table 1).^[16]

However, the reaction of **1** with **5b** under similar conditions gave the desired alkene **6b** in 21 % yield. A similar result was also obtained with **5c** (18 %). However, when the reactions were performed with lauroyl peroxide as initiator, much better results were obtained with **5b** and **5c**, showing the generality of vinylation.

We next studied radical allylations with several C2-substituted allyl sulfones [Eq. (5)]. Radical reaction of **1** with **8a**



(1.5 equiv) in chlorobenzene in the presence of V-40 (0.2 equiv) for 6 h afforded 2-phenylsulfonyl alkene **9a** in 85 % yield. Additional experimental results with **8a** clearly demonstrate the synthetic efficiency of the present method (Table 1). When allylations were carried out with other functionalized allyl sulfones (**8b**, **8c**, **8d**) under similar conditions, the corresponding allylated products were isolated in high yields without the formation of **9e**, which results from the concomitant addition of the alkyl radical to **1** and **7**. Finally, when tandem radical reactions involving cyclization and C–C-bond formation were briefly studied with **10**, the reactions worked well, yielding **11** in high yield [Eq. (6)].



In conclusion, we have found that primary alkyl allyl sulfones are one of the most useful and reliable sources of primary alkyl radicals under tin-free conditions and developed highly efficient tin-free radical-mediated cyanation, vinylation, and allylation reactions, which we believe have great synthetic potential.

Table 1. Tin-free cyanation, vinylation and allylation.^[a]

Alkyl allyl sulfone (1) RY (Y = SO ₂ CH ₂ CH=CH ₂)	3 ^[c]	Yields [%] ^[b] 6a ^[d]	9a ^[e]
EtO ₂ C(CH ₂) ₃ Y	93	88	84
	96	94	85
	98	96	90
	98	98	88
		98	98
	98	97	97

[a] The reaction was carried out with V-40 in chlorobenzene at 110 °C for 4–6 h. [b] Yield of isolated products. [c] **3**: Obtained from the reaction of **1** and **2**. [d] (*E*)-**6a**: Obtained from the reaction of **1** and (*Z*)-**5a**. [e] **9a**: Obtained from the reaction of **1** and **8a**.

Experimental Section

Typical procedure: A solution of **1** (0.2 mmol), **2** (0.3 mmol), and V-40 (0.04 mmol) in chlorobenzene (1 mL) was degassed with nitrogen for 10 min and the solution was then heated at 110 °C under nitrogen for 6 h. The solvent was evaporated under reduced pressure and the residue was separated by silica-gel column chromatography (Et₂OAc/*n*-hexane 1:3) to give **3**. ¹H NMR (CDCl₃, 400 MHz): δ = 1.85–1.95 (m, 4H), 2.43 (t, *J* = 7.0 Hz, 2H), 4.00 (t, *J* = 5.6 Hz, 2H), 6.86–6.96 (m, 3H), 7.24–7.29 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ = 17.0, 22.5, 28.2, 66.5, 114.4, 119.5, 120.9, 129.5, 158.6; IR (polymer): $\tilde{\nu}$ = 2927, 1601, 1586, 1497, 1474, 1247, 757, 693 cm⁻¹; HRMS [*M*⁺] calcd for C₁₁H₁₃NO: 175.0997, found: 175.0997.

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Chirality Induction through the Reversible Catenation of Coordination Rings**

Akiko Hori, Akihiko Akasaka, Kumar Biradha, Shigeru Sakamoto, Kentaro Yamaguchi, and Makoto Fujita*

Although oligo(*m*-phenylene)s and their isostructural compounds containing heteroatoms often adopt helical conformations spontaneously,^[1] formation of their double-helical assembly requires interstrand noncovalent interactions such as metal coordination^[2,3] or complementary hydrogen bonding.^[4] Pentakis(*m*-phenylene) can be one of the smallest units of choice for forming double-helical assemblies, as predicted by calculation ($\Delta H = -36.2 \text{ kcal mol}^{-1}$).^[5] However, nonfunctionalized oligo(*m*-phenylene)s have never favored double-helical stacking because of the high entropic cost of this process (Figure 1 a). If the ligand motif is preorganized into a

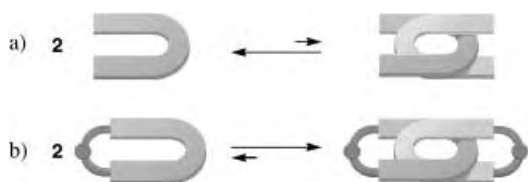


Figure 1. Schematic representation showing double helical stacking of a) open and b) metal-linked pentakis(*m*-phenylene) strands.

cyclic form by metal coordination, the entropy cost will be significantly reduced and the metal-linked cyclic oligo(*m*-phenylene) strands can assemble into a metal-linked catenane^[6] through double-helical stacking of the nonfunctionalized organic strands (Figure 1 b). This idea prompted us to design a pentakis(*m*-phenylene) compound **1** that contains pyridine units at both ends of the strand. Here we show that a coordination ring derived from ligand **1** is reversibly catenated through efficient aromatic stacking (Scheme 1). The catenated structure is characterized by the helical chirality and by the ancillary chiral unit on the metal ion. Molecular chirality is observed by circular dichroism only if the coordinated rings are catenated.

The monomer ring **3** was obtained by treating the ligand **1** with the metal unit **2** in DMF. Typically, **1a** and **2a** were combined in DMF at 60 °C. The formation of **3a** as a single product was confirmed by NMR spectroscopy (Figure 2 a) and cold spray ionization mass spectrometry (CSI-MS).^[7] The proton NMR spectrum of **3a** in $[D_7]$ DMF showed nine signals in the aromatic region. Major ion peaks in the CSI-MS spectrum were assigned as $[(M-(NO_3)_n) + (dmf)_m]^{n+}$ ($m = 0-2$, $n = 1-2$). The crystal structure was solved for the analogous Pt^{II} ring **3a'** which was prepared in a similar way and recrystallized from DMF/MeOH (Figure 3).^[8] The macrocyclic framework of **3a'** was achiral.

In aqueous conditions, the monomer ring **3a** equilibrated with another compound. This new product was assigned as catenane **4a** based on NMR and CSI-MS, analogous to previous work on “molecular magic rings”.^[9-11] Thus, the equilibrium between **3a** and **4a** was shifted toward **4a** with the increase of D_2O in the solvent (Figure 2 b–f). In 2:1 $D_2O/[D_7]$ DMF, **4a** was quantitatively formed because of an enhanced hydrophobic effect which drives the catenation. The NMR spectrum of **4a** was qualitatively the same as that of **3a**, but featured the outstanding upfield shifts of the signals arising from the central aromatic protons, caused by inter-strand contact between the two component rings. The CSI-MS spectrum of **4a** in an H_2O/DMF 2:1 solvent showed prominent peaks for $[(M-(NO_3)_n) + (dmf)_m]^{n+}$: for example, m/z 510 $[(M-(NO_3)_4) + (dmf)_4]^{4+}$, 653 $[(M-(NO_3)_3) + (dmf)_2]^{3+}$, 937 $[M-(NO_3)_2]^{2+}$, 1936 $[M-NO_3]^+$. Compound **4a** was precipitated from solution as a colorless powder in 90 % yield by adding a large amount of water. The elemental analysis was consistent with the formula of **4a**·6 H_2O .

The ratio of **3a** and **4a** also depended on the concentration of the species. In 1:1 $D_2O/[D_7]$ DMF, the ratios **3a**:**4a** were 1:2.5 at 1 mM, 1:11 at 20 mM, and 1:16 at 50 mM. An exchange spectroscopy (EXSY) spectrum indicated clear correlations between the corresponding protons of **3a** and **4a**, which shows rapid equilibration between **3a** and **4a** on the EXSY time-scale (300 ms).^[12] When the non-fluorinated ligand **1b** was employed, a mixture of monomer ring **3b** and catenane **4b** was formed similarly, in which the equilibrium was largely in favor of the monomer ring formation: for example, under the same conditions (10 mM, $D_2O/[D_7]$ DMF 1:1), ratios **3a**:**4a** and **3b**:**4b** were 15:85 and 90:10, respectively. Because catenane **4b** was less soluble than **4a** in aqueous media, **4b** was not formed exclusively under any conditions.

The crystal structure was obtained of **4a***,^[13] which is an alkoxy derivative of **4a** (Figure 4). As expected, efficient aromatic contacts are observed between two rings, which keeps the two ionic Pd^{II} centers as far apart as possible ($Pd \cdots Pd$ 18 Å). The mean planes of the two rings, defined by the centers of alkoxy-attached phenylene groups and a Pd cation in each ring, are associated with a cross angle of 64°. The two aromatic ligands efficiently interact with each other with interatomic distances of 2.9–3.5 Å. As a result, two aromatic strands are double-helicated, giving molecular chirality to the resulting catenated assembly.^[14,15]

We expected that the molecular chirality induced by the catenation could be observed if a chiral ancillary ligand were placed on the component ring. Thus, (*R,R*)-1,2-diaminocyclo-

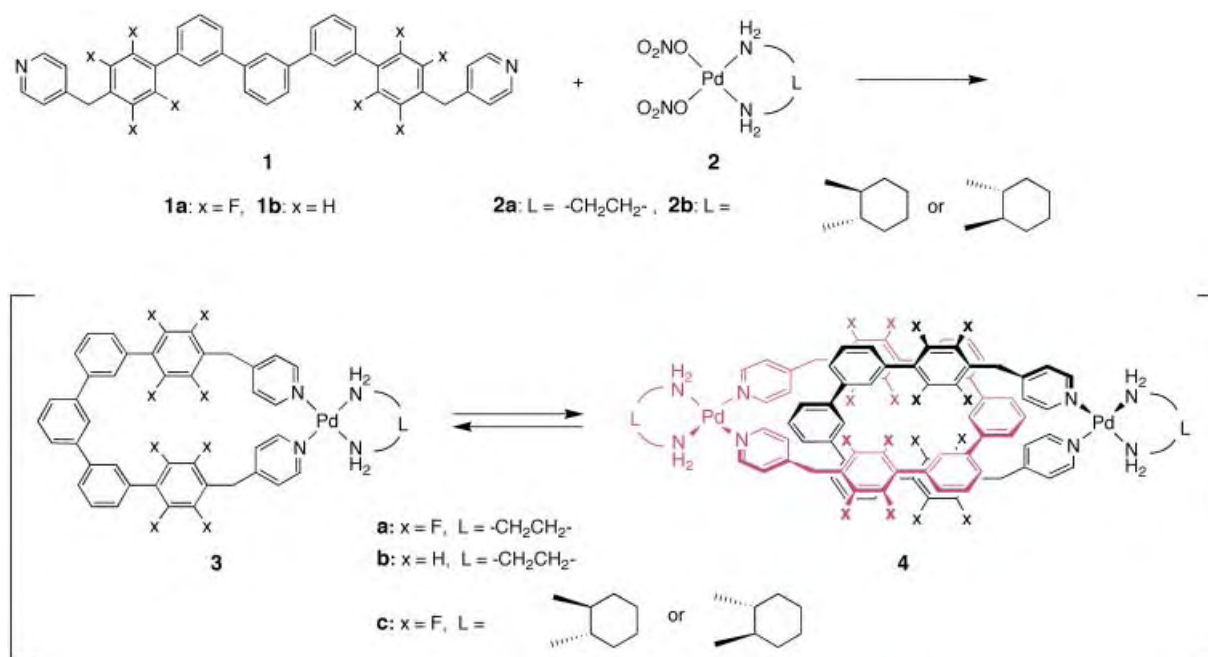
[*] Prof. Dr. M. Fujita,⁺ Dr. A. Hori,⁺ A. Akasaka, Dr. K. Biradha
Department of Applied Chemistry, Graduate School of Engineering
Nagoya University
Furocho, Chikusa-ku, Nagoya 464-8603 (Japan)
E-mail: mfujita@appchem.t.u-tokyo.ac.jp

Dr. S. Sakamoto, Prof. Dr. K. Yamaguchi
Chemical Analysis Center, Chiba University
Yayoicho, Inage-ku, Chiba 263-8522 (Japan)

[⁺] Current address:
Department of Applied Chemistry, Graduate School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81)3-5841-7257

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



Scheme 1. Self-assembly of double helical [2]catenanes and the component rings.

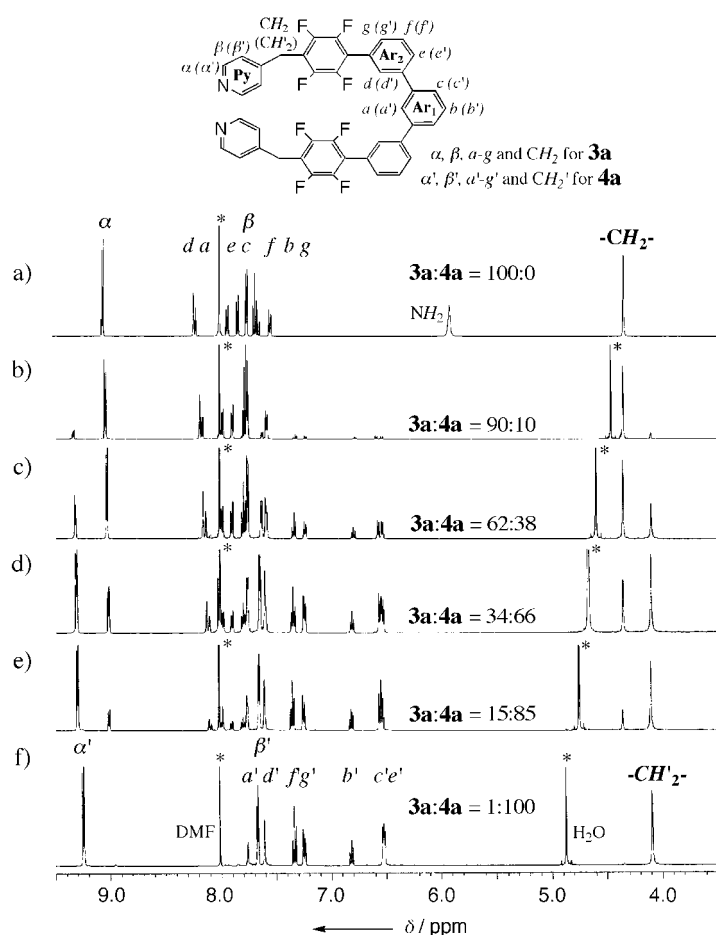


Figure 2. Equilibrium between **3a** and **4a**, monitored by ^1H NMR spectroscopy (aromatic region, 500 MHz, 25 °C, 10 mm, DMF formyl proton at $\delta = 8.05$ as an internal standard). Spectra were obtained by treating **1a** with **2a** for 30 min at 60 °C in a) $[D_7]DMF$; b) $D_2O/[D_7]DMF$ 1:3; c) $D_2O/[D_7]DMF$ 1:2; d) $D_2O/[D_7]DMF$ 2:3; e) $D_2O/[D_7]DMF$ 1:1, and f) $D_2O/[D_7]DMF$ 2:1 solution. Asterisk (*): solvent.

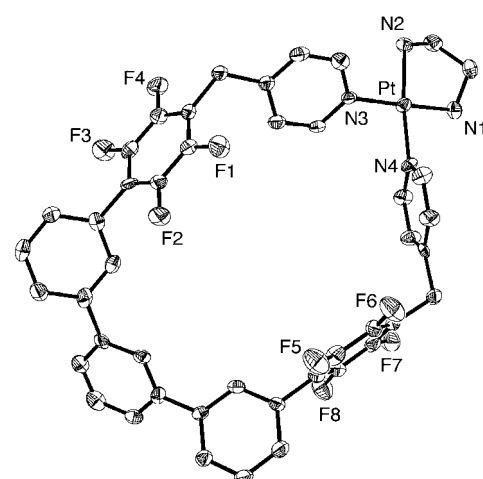


Figure 3. The ORTEP diagram of the crystal structure of **3a'** showing 40% probability thermal ellipsoids.

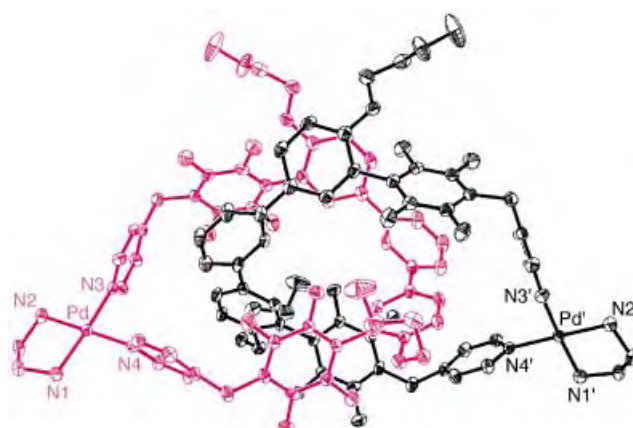


Figure 4. The ORTEP diagram of the crystal structure of **4a*** showing 40% probability thermal ellipsoids.

hexane was substituted onto the Pd^{II} center. The chiral Pd^{II} unit (*R,R*)-**2b** was treated with ligand **1a** to afford the monomer ring (*R,R*)-**3c** and the catenane (*R,R,R,R*)-**4c** in organic and aqueous media, respectively. The crystal structure of (*R,R*)-**3c** again displayed the planar conformation of the central-(C₆H₄)₃-site, despite the presence of a chiral ligand on the Pd^{II} center.^[16] In CD (circular dichroism) spectroscopy, both (*R,R*)-**2b** and (*R,R*)-**3c** were almost silent. These results showed that the chiral ligand on the Pd^{II} center induced no chirality in the macrocycle framework of (*R,R*)-**3c** in solution, which is in good accordance with the X-ray result. In striking contrast, (*R,R,R,R*)-**4c** showed clear induced circular dichroism (ICD) (Figure 5a).^[17] As the chiral auxiliary on the Pd^{II} ion is silent to CD spectroscopy, the observed ICD is ascribed to the chiral orientation of two aromatic strands, which is probably double-helical stacking, as suggested by the X-ray analysis. The clear temperature dependence of the ICD also supported the chiral aromatic stacking which should be less obvious at high temperature (Figure 5b).^[18]

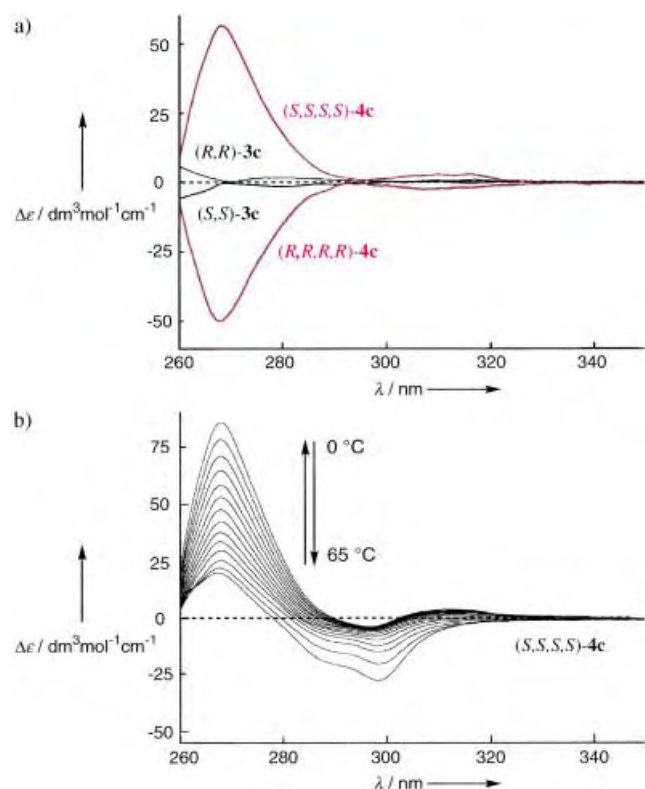


Figure 5. a) CD spectra of **3c** and **4c**; b) temperature dependent ICD of (*S,S,S,S*)-**4c**. $\Delta\epsilon$: molar circular dichroism.

Experimental Section

Syntheses and physical properties of ligands **1a**, **1b**, and **1a*** (methoxyethoxy substituted derivative of **1a**) are summarized in the Supporting Information.

Self-assembly of 3a and 4a. 3a: To a solution of **1a** (9.9 mg, 0.010 mmol) in DMF (1 mL), **2a** (2.9 mg, 0.010 mmol) was added and the mixture was stirred for 15 min at 60 °C to obtain a colorless solution. The monomer ring **3a** was isolated as pale yellow crystals by adding a large amount of diethyl ether to the reaction solution. Yield 80%; m.p. 200 °C dec.; ¹H NMR (500 MHz, [D₇]DMF, reference TMS, 25 °C): δ = 9.59 (d, *J* = 6.5 Hz, 4H; PyH_a), 8.76 (s, 2H; ArH_d), 8.74 (s, 1H; ArH_a), 8.46 (d, *J* =

8.2 Hz, 2H; ArH_e), 8.37 (d, *J* = 7.8 Hz, 2H; ArH_c), 8.28 (d, *J* = 6.5 Hz, 4H; PyH_b), 8.21 (t, *J* = 7.8 Hz, 2H; ArH_f), 8.18 (t, *J* = 7.8 Hz, 1H; ArH_b), 8.07 (d, *J* = 8.2 Hz, 2H; ArH_g), 4.87 (s, 4H; -CH₂-), 3.46 ppm (brs, 8H; *H*-ethylene diamine); ¹³C NMR (125 MHz, [D₇]DMF, reference CDCl₃, 25 °C): δ = 153.0 (CH_a), 152.0 (Cq), 145.5 (d, *J* = 248 Hz, CF_i), 144.2 (d, *J* = 248 Hz, CF_j), 141.6 (Cq), 141.0 (Cq), 130.5 (CH_l), 130.1 (CH_g), 130.0 (CH_h), 129.2 (CH_d), 128.7 (CH_e), 128.2 (Cq), 127.4 (CH_f), 127.1 (CH_c), 126.0 (CH_a), 120.4 (t, *J* = 16.9 Hz, CF_k), 116.6 (t, *J* = 18.3 Hz, CF_k), 47.9 (en), 28.0 ppm (CH₂); ¹⁹F NMR (300 MHz, [D₇]DMF, CF₃COOH): δ = -66.02 (m, 4F, ArF), -66.20 ppm (m, 4F, ArF); IR (KBr) $\tilde{\nu}$ = 1664, 1615, 1480, 1280, 1332, 1174, 998, 788 cm⁻¹; CSI-MS *m/z*: 509.9 [(*M*-(NO₃)₂) + (dmf)₂]²⁺, 546.4 [(*M*-(NO₃)₂) + (dmf)₃]²⁺, 936.1 [*M*-(NO₃)₃]⁺; elemental analysis: calcd for C₄₄H₃₂N₆F₈PdO₆·3.5H₂O (%): C 49.75, H 3.70, N 7.91; found: C 49.80, H 3.89, N 7.92. Similarly, **3c** was obtained by the reaction of **1a** with **2b** in DMF.

4a: Water (0.8 mL) was added dropwise to a DMF (0.4 mL) solution of **1a** (9.9 mg, 0.010 mmol) and **2a** (2.9 mg, 0.010 mmol), and the mixture was stirred for 1 h at 60 °C. Catenane **4a** was isolated as a white powder by adding a large amount of water to the reaction solution. Yield 90%; m.p. 200 °C dec.; ¹H NMR (500 MHz, D₂O/[D₇]DMF (2:1), TMS): δ = 9.25 (d, *J* = 6.5 Hz, 8H; PyH_a), 7.81 (s, 2H; ArH_d), 7.71 (d, *J* = 6.5 Hz, 8H; PyH_b), 7.64 (s, 4H; ArH_d), 7.44 (t, *J* = 8.0 Hz, *J* = 7.5 Hz, 4H; ArH_f), 7.35 (d, *J* = 7.5 Hz, 4H; ArH_e), 6.85 (d, *J* = 8.0 Hz, *J* = 7.5 Hz, 2H; ArH_b), 6.63 (d, *J* = 8.0 Hz, 4H; ArH_c), 6.62 (d, *J* = 8.0 Hz, 4H; ArH_e), 4.16 (s, 8H; -CH₂-), 3.03 ppm (brs, *H*-en); ¹³C NMR (125 MHz, D₂O/[D₇]DMF (2:1), CDCl₃): δ = 152.1 (CH_a), 152.0 (Cq), 144.7 (dd, *J* = 249 Hz, CF_i), 143.0 (dd, *J* = 249 Hz, CF_j), 138.7 (Cq), 138.6 (Cq), 129.5 (CH_l), 129.4 (CH_g and CH_h), 128.2 (CH_d), 127.2 (Cq), 126.6 (CH_e), 126.1 (CH_a), 125.0 (CH_c), 123.0 (CH_a), 118.3 (CF_k), 115.3 (d, *J* = 18.6 Hz, CF_k), 47.0 (en), 27.6 ppm (CH₂); ¹⁹F NMR (300 MHz, D₂O/[D₇]DMF (2:1), CF₃COOH): δ = -66.00 (brs, 4F, ArF), -66.46 ppm (brs, 4F, ArF); IR (KBr) $\tilde{\nu}$ = 1625, 1601, 1480, 1375, 997, 788 cm⁻¹; CSI-MS *m/z*: 510.4 [(*M*-(NO₃)₄) + (dmf)₄]⁴⁺, 653.2 [(*M*-(NO₃)₃) + (dmf)₃]³⁺, 936.2 [*M*-(NO₃)₂]²⁺, 1936.3 [*M*-(NO₃)₃]⁺; elemental analysis: calcd for C₈₈H₆₄N₁₂F₁₆PdO₁₂·6H₂O (%): C 50.18, H 3.64, N 7.98; found: C 50.34, H 3.65, N 7.91. Similarly, **4c** was obtained by the reaction of **1a** with **2b** in a 1:2 DMF/H₂O solution.

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- [13] Crystal data for **4a**·6H₂O (C₁₀₀H₁₀₀F₁₆N₁₂O₂₆Pd₂, *M_w* = 2402.72):^[19] orthorhombic, *Pbcn*, *a* = 37.176(3), *b* = 15.2673(11), *c* = 18.2484(13) Å, *V* = 10357.5(13) Å³, *T* = 193 K, *Z* = 4, *R* = 0.0526, *R_w* = 0.1364, GOF = 0.929. Catenane **4a*** was obtained by the reaction of an alkoxy-attached derivative ligand **1a*** with **2a** in D₂O.
- [14] Very similar orientations were observed in optimized structures which follow annealing by molecular dynamics simulations. Thus, the chiral orientation is considered to be unaffected by crystal-packing effects.
- [15] The chiral orientation was not observed by NMR spectroscopy, which indicates that two enantiomeric *P* and *M* forms rapidly interconvert in solution.
- [16] A single crystal of (*R,R*)-**3c** was obtained by slow diffusion of diethyl ether into the DMF/MeOH solution. Crystal data for **3c**·1.5dmf·0.5MeOH (C₅₃H_{50.5}F₈N_{7.5}O₈Pd, *M_w* = 1178.91):^[19] triclinic, *P1*, *a* = 11.6595(14), *b* = 12.0387(14), *c* = 20.209(2) Å, *α* = 82.508(2), *β* = 83.352(2), *γ* = 68.841(2)°, *V* = 2615.5(5) Å³, *T* = 193 K, *Z* = 2, *R* = 0.0883, *R_w* = 0.2154, GOF = 1.560.
- [17] CD spectra of monomer ring (*R,R*)-**3c** and [2]catenane (*R,R,R,R*)-**4c** were measured in DMF (0.125 mm) and D₂O/[D₇]DMF 2:1 (0.056 mm), respectively, at 25.0 °C.
- [18] The optical purity of the catenane has been not determined.
- [19] CCDC-189501 (**3c**·1.5dmf·0.5MeOH), CCDC-189502 (**3a**·2H₂O), and CCDC-189503 (**4a**·6H₂O) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).



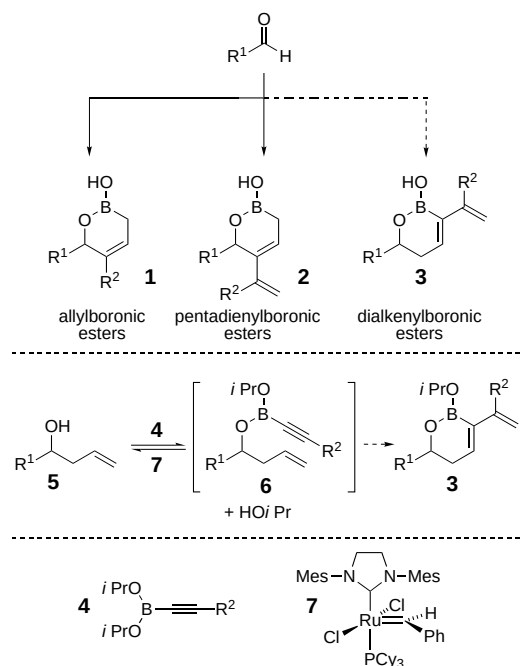
An Alkynylboronic Ester Annulation: Development of Synthetic Methods for Application to Diversity-Oriented Organic Synthesis**

Glenn C. Micalizio and Stuart L. Schreiber*

Dedicated to Professor William R. Roush

Diversity-oriented synthesis aims to prepare complex and diverse small molecules efficiently. These molecules can be used to explore biology—our goal is to be able to do so in a systematic way.^[1] Whereas complex molecules can be synthe-

sized efficiently using coupled complexity-generating reactions,^[2] the goal of developing diversity-generating pathways yielding products with a high degree of skeletal diversity has not yet been realized. The development of synthetic pathways incorporating branch points holds promise as an effective route to skeletal diversity.^[1] One such pathway, which diverges from common starting materials, aims to exploit the diverse reactivity of alkyl-, allyl-, pentadienyl-, alkenyl- and dialkenylboronic acids (Scheme 1).^[3] This approach should enable the branching architecture of diversity-oriented synthesis pathways by using the diverse reactivity associated with these classes of reagents.^[4]



Scheme 1. Development of branching reaction pathways for diversity-oriented organic synthesis; proposed alkynyl-boronic ester annulation. Mes = 2,4,6-trimethylphenyl, Cy = cyclohexyl.

Previously we reported annulation reactions of allylboronic esters with allylic and propargylic alcohols that stereospecifically provide allylboronic acids **1** and pentadienylboronic acids **2**.^[3] Here we report new annulation reactions of electron-deficient alkynylboronic esters with homoallylic alcohols that provide functionalized dialkenylboronic acids **3**. In addition, we demonstrate oxidation and allene-forming hydroxyalkylation reactions of the resulting cyclic alkenyl boronic acids that further illustrate diversity-generating, branching reaction pathways.

Based on our earlier work on the allylboronic ester annulation,^[3] we anticipated that the transesterification of an alkynylboronic ester **4** and a homoallylic alcohol **5** would afford a transient, mixed organoboronic ester **6** (Scheme 1), which could be trapped using ring-closing ene-yne methathesis to afford cyclic dialkenylboronic esters **3**. As expected, treatment of the homoallylic alcohol **8** with the *n*-propyl-substituted alkynylboronic ester **9**^[5] and the Grubbs catalyst **7**^[6] in benzene at 65 °C afforded the cyclic dialkenylboronic acid **12** in 69 % yield (Table 1, entry 1). The annulation

[*] Prof. S. L. Schreiber, Dr. G. C. Micalizio
Howard Hughes Medical Institute
Department of Chemistry and Chemical Biology, and
Harvard Institute of Chemistry and Cell Biology (ICCB)
Harvard University, 12 Oxford St.
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-0751
E-mail: sls@slsiris.harvard.edu

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

Table 1. Alkynylboronic ester annulation.

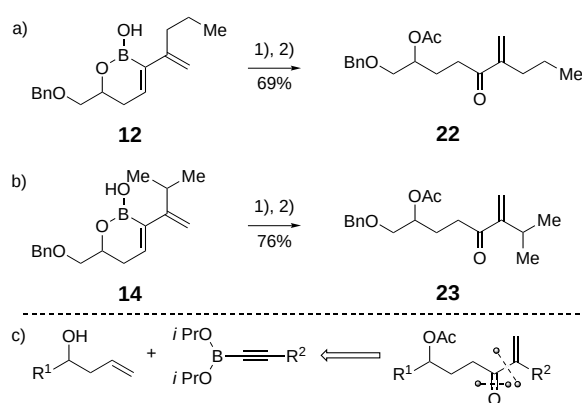
Entry	Substrate	Alkynylboronic ester	Annulation product	Yield [%]
1				69
2				66
3				73
4				72
5				72
6				66
7				67

[a] TIPS = triisopropylsilyl.

reaction was similarly effective with the substituted alkynylboronic esters **10**^[5] and **11**^[5] (Table 1, entries 2 and 3).^[7] Aromatic substitution on the homoallylic alcohol is tolerated in the reaction, as annulation with the benzylic homoallylic carbinol **15** provided the substituted dialkenylboronic acids **16** and **17** (Table 1, entries 4 and 5).

Coupling of the alkynylboronic ester annulation with an additional ring closing ene-yne metathesis^[8] affords bicyclic dialkenylboronic acids. For example, annulation of the homoallylic alcohols **15** and **18** with the allyloxy-substituted alkynylboronic acid **19**^[5] provides the bicyclic heterocycles **20** and **21** in 66 % and 67 % yield respectively (Table 1, entries 6 and 7).

We anticipated that oxidative cleavage of the dialkenylboronic acid products would provide a transient enol which, after tautomerization, would yield substituted enones.^[9] As expected, oxidation of the cyclic dialkenylboronic acids **12** and **14** afforded the sensitive γ -hydroxy enones which, following acetylation afforded the γ -acetoxy enones **22** and **23** (Scheme 2 a,b).^[10] Overall, the two-step sequence of alkynylboronic ester annulation followed by oxidation represents a new convergent strategy for the transformation of homoallylic alcohols to functionalized enones (Scheme 2 c).



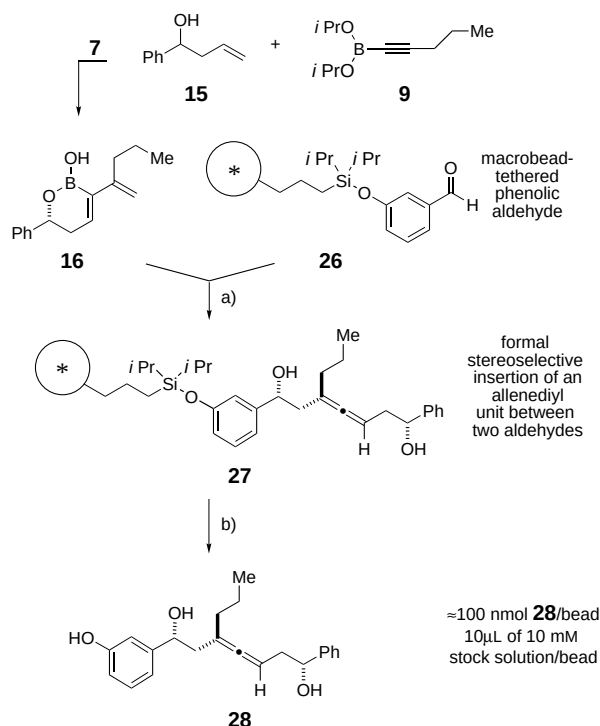
Scheme 2. Manipulation of the cyclic vinylboronic acids via oxidation—acetylation. 1) H_2O_2 , NaOH, THF; 2) Ac_2O , DMAP, Et_3N . DMAP = 4-dimethylaminopyridine. a) and b) show formation of specific functionalized enones, while c) is a retrosynthetic analysis of the product type.

The cyclic dialkenylboronic acids can be transformed efficiently into small molecules with completely different skeletons. For example, when the annulation products **14** and **16** are heated with trioxane they are converted into the trisubstituted allenes **24** and **25** ($\geq 78\%$; d.r. 4–6:1) (Sche-

me 3 a,b).^[11,12] The major product observed in this allenylation process is consistent with reaction via the closed transition structure **A**.^[13] We note that in the closed transition structure leading to the major product (**A**), the developing σ_{B-O} bond is stabilized by two anomeric interactions, whereas in the closed transition structure **B** (leading to the minor diastereomer) the developing σ_{B-O} bond is stabilized by a single anomeric interaction. The new allenylation reaction can be performed without purification of the intermediate cyclic dialkenylboronic acid. For example, following alkynylboronic ester annulation of homoallylic alcohol **15** and hydrolysis of the boronic acid **16** was hydroxymethylated to yield the trisubstituted allene **25** (see Scheme 3 b, 56 % yield, d.r. 6:1).^[14] This two-step sequence (alkynylboronic ester annulation—allenylation) provides a new convergent approach to the diastereoselective synthesis of trisubstituted allenes from homoallylic alcohols (Scheme 3 d).^[15]

The allenylation reaction leading to **28**^[16] was performed efficiently using phenolic aldehyde-loaded macrobeads (Scheme 4). This is an especially promising result as it demonstrates the feasibility of performing this chemistry on the high-capacity macrobead-linker reagent used in a one-bead, one-stock solution platform for chemical genetics.^[17]

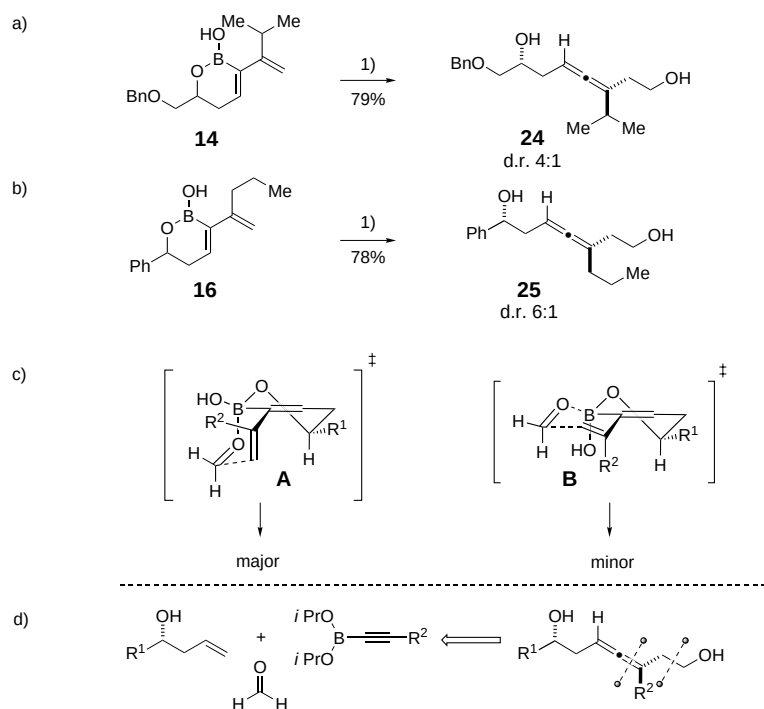
The goal of diversity-orientated synthesis is to synthesize complex and diverse small molecules efficiently. Herein, we have demonstrated the development of a new alkynylboronic ester annulation that provides mono- and bicyclic dialkenylboronic acids. Oxidation of the dialkenylboronic acid products provides a new route to functionalized enones, whereas treatment with trioxane promotes a novel and diastereoselective allene-forming reaction. Together with our previous



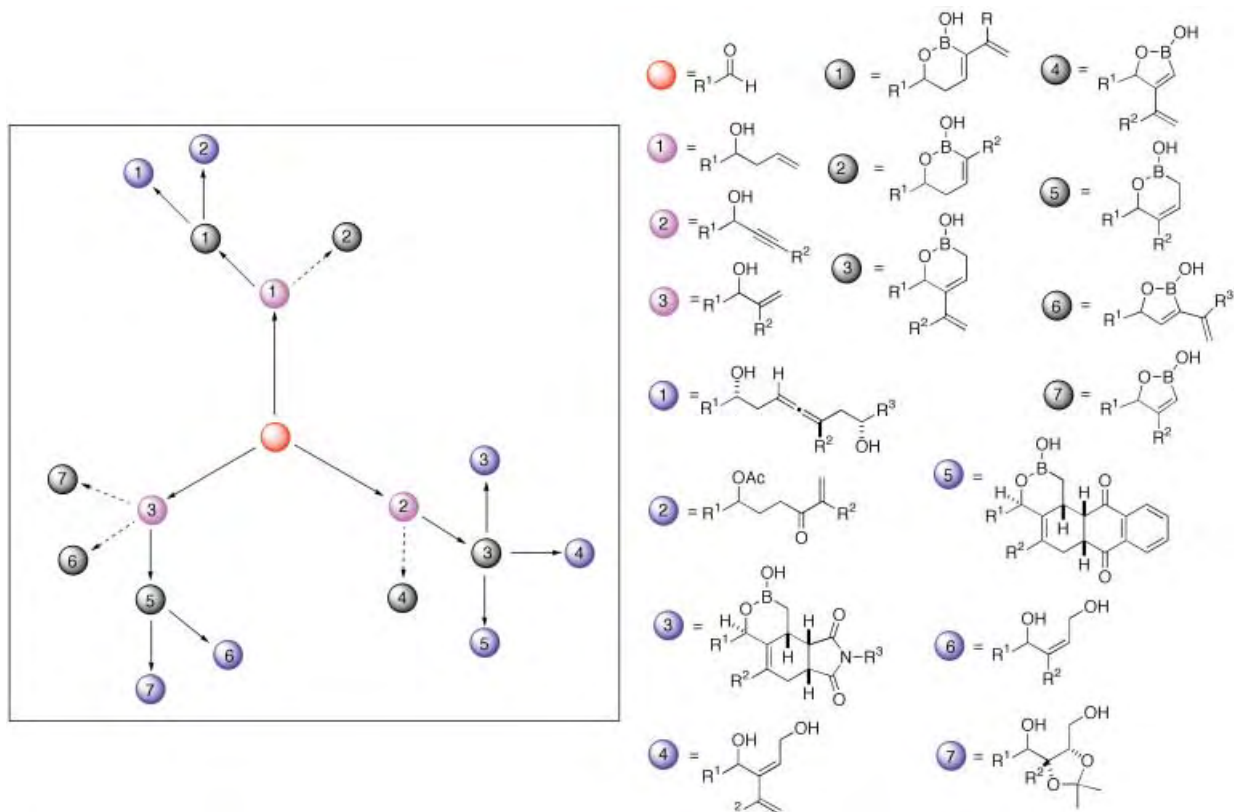
Scheme 4. Allenylation reaction performed on the high capacity bead-linker reagent used in a one-bead, one-stock solution platform for chemical genetics. a) PhMe, 80 °C; b) HF-pyr/pyr, THF.

study, we demonstrate the design of synthetic pathways that diverge from readily available aldehydes in just two steps and provide stereospecific access to allylboronic, pentadienylboronic, and dialkenylboronic acids. Exploiting the reactivity differences inherent to these classes of compounds provides access to saturated and unsaturated diols (including allenic diols), acyclic enones, and polycyclic heterocycles (Scheme 5).

This study is indicative of many diversity-oriented synthesis pathways that are being driven by our knowledge of synthetic chemistry and yet that have not taken into account the range of anticipated molecular properties of the products. To address this shortcoming, we are integrating information science with this diversity-oriented synthesis network, first to populate multidimensional descriptor space (“chemical space”) in a more targeted way. We ultimately hope to populate the chemical space which is likely to overlap effectively with the biological descriptor space most relevant to a given area of biological interest.^[18] This future challenge aside, the reported studies already highlight several issues of relevance to synthetic chemistry. Consideration of the goals of diversity-oriented synthesis provides an intellectual framework for the development of novel synthetic methods. Investigations of diversity-oriented synthesis pathways provide opportunities to discover new patterns of reactivity in organic chemistry. We hope that the current study, together with our earlier report, specifically illustrates these



Scheme 3. Allenylation reaction of cyclic boronic acids. a) Reaction conditions: 1) 1,3,5-trioxane, PhMe, 80 °C; b) reaction conditions: 1) 1,3,5-trioxane, PhMe, 60 °C; c) rationalization of d.r. obtained from proposed transition states; d) retrosynthetic analysis.



Scheme 5. Synthetic pathway incorporating a branched network of reactions based on the boronic ester annulation chemistry presented here and in our earlier report.^[3]

points and generally illustrates the use of branched networks of reactions as a step toward realizing the goals of diversity-oriented synthesis in the context of chemical genetics (Scheme 5).

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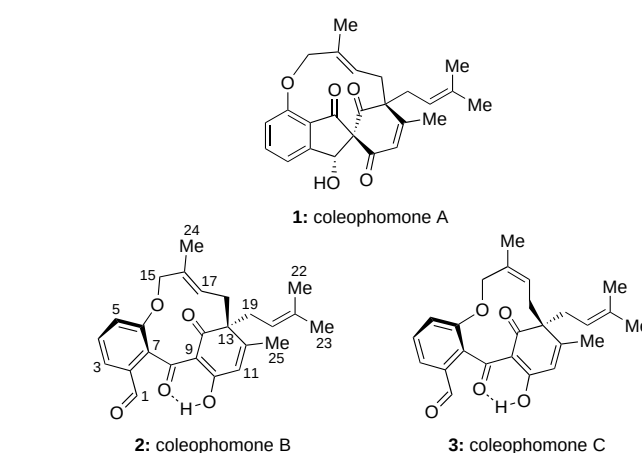


The Total Synthesis of Coleophomones B and C**

K. C. Nicolaou,* Georgios Vassilikogiannakis, and Tamsyn Montagnon

*Dedicated to Professor Thomas J. Katz
on the occasion of his 65th birthday*

In 1998, a patent^[1] from a group at Shionogi disclosed the structures and biological activity of three novel natural products, designated I-1 (**1**), I-2 (**2**), and I-3 (**3**), which had been isolated from a broth produced by the fungus *Stachybothys cylindrospora* RF-5900. Two of these compounds later re-emerged in the literature when a group at Merck discovered them in extracts from the fermentation of *Coleophoma* sp. fungi and named them coleophomones A (**1**) and B (**2**).^[2] The biological profile of the coleophomone family includes



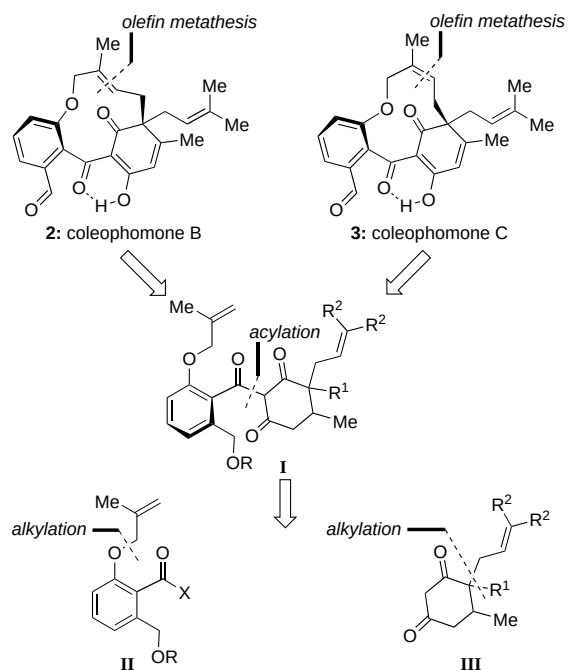
antifungal activity,^[1] inhibition of human heart chymase,^[1,3] and antibiotic properties.^[2] In addition, their unique molecular architectures are laden with unusual and challenging features: The strained and rigid framework of the coleophomones possesses a sensitive tricarboxyl moiety tethered into an 11-membered macrocycle whose strain is derived from the incorporation of a fused aryl ring and a highly unsaturated bridging six-membered carbocycle with the point of attachment being a quaternary carbon atom. Herein we report the total synthesis of coleophomones B (**2**) and C (**3**)^[4] by a route that pushes the frontiers of the olefin metathesis reaction as a means to construct challenging molecular complexity.

Coleophomone A (**1**) is related to coleophomone B (**2**) by an aldol reaction that affords, from the latter, the unique spirocycle seen in the former. In view of the reported^[2] interconversion of **1** and **2**, our approach to the coleophomone family initially focused on the total synthesis of **2** and **3**. These differ only in the configuration of the double bond ($\Delta^{16,17}$) that is *E* in **2** and *Z* in **3**. From all the possible retrosynthetic disconnections we therefore chose the one dissecting this double bond by the olefin metathesis reaction (Scheme 1). This disconnection, which led to the general precursor **I**, promised an exciting synthetic adventure because of the unprecedented nature of the challenge, made even more acute by the requirement to control the geometrical outcome of the projected ring-closing metathesis to deliver either isomer at will and the possible occurrence of atropisomers within the targeted frameworks. Our second major retrosynthetic disconnection operated on precursor **I** at the C8–C9 bond to generate the key building blocks **II** and **III**. This left the considerable hurdle of their union to be negotiated in the synthetic direction.

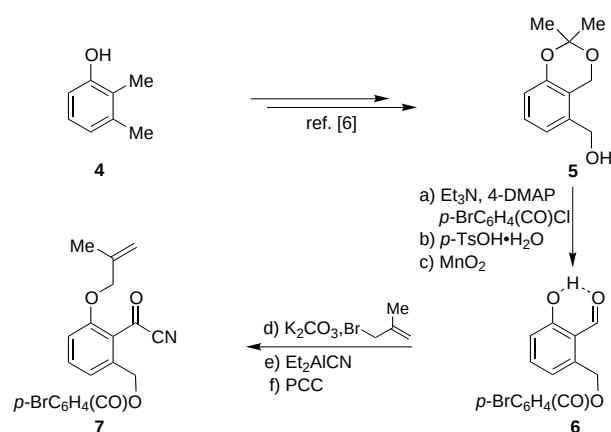
Scheme 2 summarizes the construction of the requisite aromatic building block **7**. The preference for the cyano group in **7** was based upon literature precedent regarding our subsequent intentions to effect preferential C-acylation over the usually more facile O-acylation in the coupling step,^[5] while the *p*-bromobenzoate group was chosen as a protecting group to enhance the chances for crystalline derivatives to be obtained for X-ray crystallographic analysis purposes. Thus, beginning with commercially available 2,3-dimethyl phenol (**4**) and following a five-step literature procedure,^[6] we arrived at hydroxy acetone **5**, whose conversion to benzaldehyde

[*] Prof. Dr. K. C. Nicolaou, Dr. G. Vassilikogiannakis, Dr. T. Montagnon
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093

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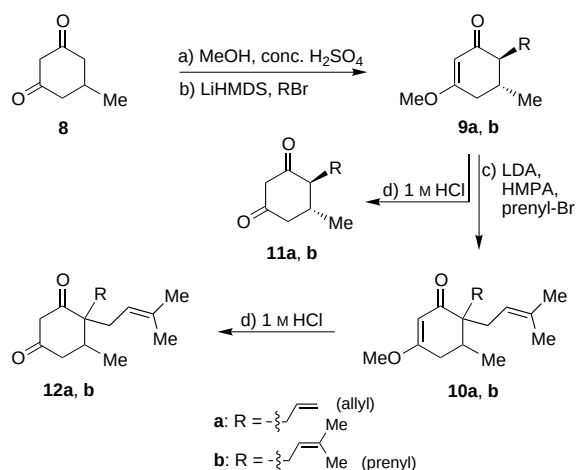


Scheme 1. Retrosynthesis of coleophomones B (2) and C (3).


 Scheme 2. Construction of acyl cyanide 7. a) Et₃N (1.5 equiv), *p*-BrC₆H₄(CO)Cl (1.05 equiv), 4-DMAP (0.05 equiv), CH₂Cl₂, 25 °C, 20 min, 97%; b) *p*-TsOH·H₂O (0.3 equiv), THF/H₂O (3/2), 75 °C, 10 h, 85%; c) MnO₂ (10 equiv), EtOAc, 25 °C, 1.5 h, 87%; d) K₂CO₃ (2.0 equiv), 3-bromo-2-methylpropene (1.5 equiv), acetone, 56 °C, 2 h, 91%; e) Et₂AlCN (1.1 equiv), toluene, 0–25 °C, 1 h, 82%; f) PCC (4.0 equiv), CH₂Cl₂, 40 °C, 12 h, 73%. 4-DMAP = 4-dimethylaminopyridine; *p*-TsOH = *p*-toluenesulfonic acid; PCC = pyridinium chlorochromate.

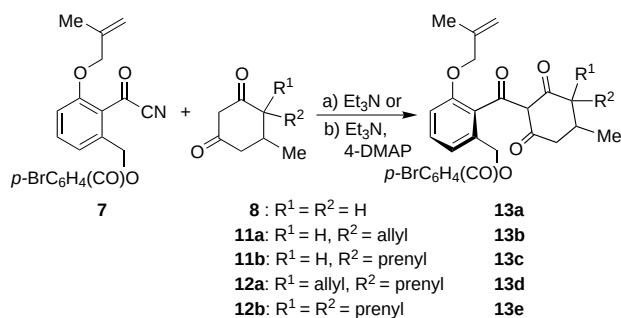
derivative 6 entailed sequential *p*-bromobenzoylation, acetonide removal, and MnO₂ oxidation (72 % yield over the three steps). Aldehyde 6 was then smoothly alkylated with 3-bromo-2-methylpropene in the presence of K₂CO₃ (91 % yield) and subsequently converted to the desired acyl cyanide 7 by a two-step sequence involving initial addition of Nagata's reagent followed by PCC oxidation of the resulting cyanohydrin, events which proceeded in 60 % overall yield.

The desired 1,3-cyclohexadiones (**11a**, **11b**, **12a**, and **12b**) were synthesized starting with C₃-symmetrical 5-methyl-1,3-cyclohexadione (**8**) and following the divergent pathway shown in Scheme 3. Thus, methylation of **8** followed by


 Scheme 3. Synthesis of substituted 1,3-cyclohexadiones **11a**, **11b**, **12a**, and **12b**. a) conc. H₂SO₄ (cat.), MeOH, 65 °C, 12 h, 85%; b) LiHMDS (1.05 equiv), THF, -78 °C, 1 h; then allyl- or prenyl-Br (1.1 equiv), -78→0 °C, 3 h, 80–85%; c) LDA (1.1 equiv), THF, slow addition of a solution of **11a** or **11b** in THF/HMPA (7/1), -78 °C, 1 h; then prenyl-Br (2.0 equiv), -78→20 °C, 12 h, 89%; d) 1 M HCl/THF (10/1), 25 °C, 14 h, 95–98%. LiHMDS = lithium bis(trimethylsilyl)amide; LDA = lithium diisopropylamide.

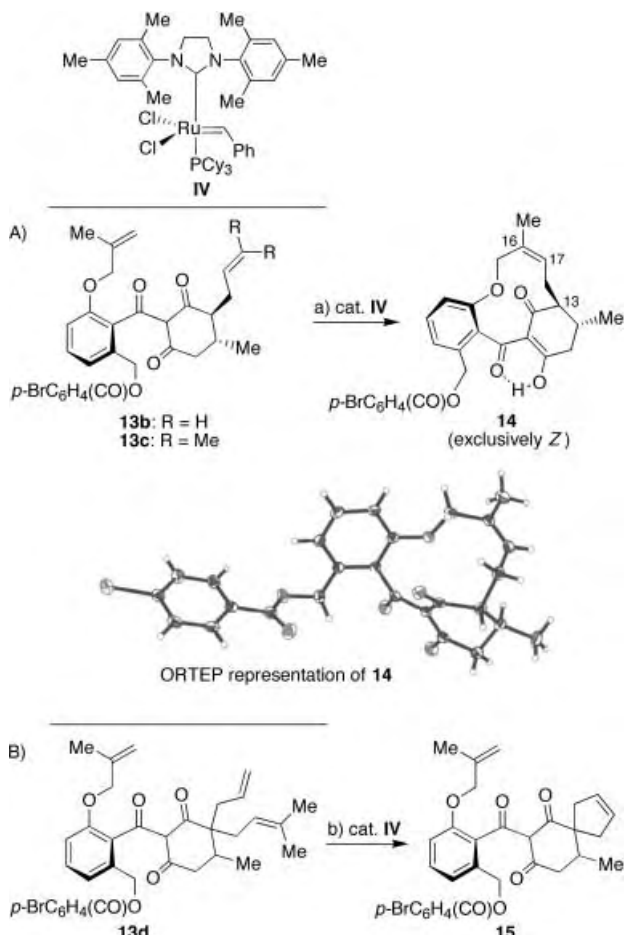
alkylation of the LiHMDS-derived enolate with either allyl or prenyl bromide afforded the *anti* alkylated products **9a** and **9b**, respectively (80–85 % yield). The bisalkylated congeners (**10a** and **10b**) were prepared by a second alkylation that proved more demanding than the first. These compounds were obtained in good yield (89 %) by using HMPA as an additive and LDA as the base to generate the corresponding enolate (-78 °C) followed by addition of the allylic bromide (-78 °C) and slow warming of the reaction mixture to ambient temperature. Finally, deprotection of the resulting vinylogous methyl esters (**9a**, **9b**, **10a**, and **10b**) by aqueous acid hydrolysis furnished the coveted 1,3-cyclohexadiones (**11a**, **11b**, **12a**, and **12b**) in 95–98 % yield.

With all of the requisite building blocks in hand, the task now confronting us was the development of appropriate conditions to achieve the desired C-acylation reaction. Whilst smooth coupling took place (see Scheme 4) when the unsubstituted and monosubstituted 1,3-cyclohexadiones **8**, **11a**, and **11b** were combined with acyl cyanide **7** in the presence of Et₃N at ambient temperature to furnish **13a**


 Scheme 4. Coupling of acyl cyanide 7 with various 1,3-cyclohexadiones. a) **8**, **11a**, or **11b** (1.2 equiv), Et₃N (2.0 equiv), THF, 25 °C, 6–12 h, 91–98%; b) **12a**, **12b** (1.2 equiv), Et₃N (2.0 equiv), 4-DMAP (1.0 equiv), THF, 25 °C, 72–96 h, 83–86%.

(98%), **13b** (94%), and **13c** (91%), respectively,^[7] the disubstituted substrates **12a** and **12b** proved recalcitrant, refusing to react even after prolonged reaction times under similar conditions. However, upon modification of the above protocol to include 4-DMAP, the coupled products **13d** and **13e** could be isolated after 72–96 h, in 83–86% yield (Scheme 4).

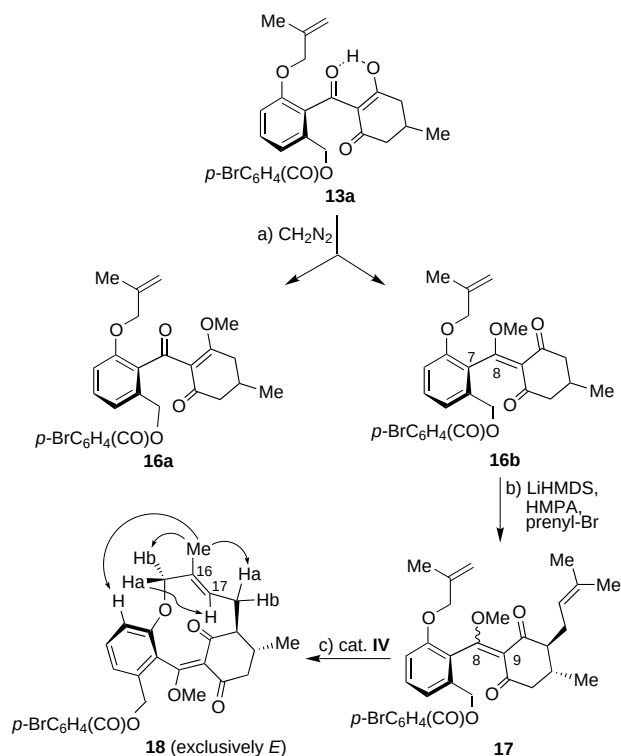
The scene was now set for the exploration to begin into the feasibility of the crucial olefin-metathesis-based step to forge the challenging 11-membered ring;^[8] we started with the simplest substrate, compound **13b**. While the early Grubbs' ruthenium catalyst^[9] failed to induce ring closure within this substrate, our ambition in this regard was realized when diolefin **13b** was subjected to the newest Grubbs^[10] catalyst, **IV** (20 mol%, Scheme 5) in dichloromethane at reflux, conditions that afforded a single macrocyclic product (**14**, Scheme 5A) in 60% yield. X-Ray crystallographic analysis^[11] of **14** (see ORTEP representation) revealed its complete structure, including the *Z* configuration of the $\Delta^{16,17}$ double bond and the arrangement of the enol within the tricarbonyl subunit. Having established the viability of macrocycle formation by olefin metathesis, we then proceeded to investigate the simplest bisalkylated substrate, **13d** (Scheme 5B),



Scheme 5. A) Forging a *Z*-configured 11-membered ring by an olefin metathesis reaction involving disubstituted and trisubstituted double bonds. B) Selective formation of a spirocyclic product from triolefin **13d**. a) cat. **IV** (0.2 equiv), CH₂Cl₂, 40°C, 5 h, 60% for **13b**; cat. **IV** (0.3 equiv), CH₂Cl₂, 40°C, 18 h, 30% for **13c**; b) cat. **IV** (0.1 equiv), CH₂Cl₂, 40°C, 1 h, 85%. Cy = cyclohexyl; Ph = phenyl.

as a substrate for this ring-closing reaction. As we had feared, when this compound was treated with catalyst **IV** (10 mol%), it was rapidly converted to spirocyclic **15** in 85% yield as shown in Scheme 5B. The formation of **15** provoked us to increase the substitution on the terminal olefin to the *gem*-dimethyl level to relocate the metathesis initiation site to the less substituted olefin appended to the aromatic portion of the molecule. We, therefore, subjected substrate **13c** (Scheme 5A) to the same catalyst (**IV**, 30 mol%) and remarkably once again, observed the formation of macrocycle **14**, albeit in reduced yield (30%).

While these results served as a proof of principle for our initial premise that ring-closing metathesis would be a powerful tool to forge the challenging macrocycle of the coleophomones, the tricarbonyl substrates employed left much to be desired in terms of stability and ease of manipulation. To improve upon these two aspects of the sequence we moved to protect the troublesome tricarbonyl moiety, only to discover that the new substrates harbored additional advantages. Thus, exposure of **13a** to excess diazomethane in diethyl ether resulted in the formation of the vinylogous methyl esters **16a**, which precipitated out from the reaction mixture in 48% yield, and **16b**, which could be isolated from the remaining solution in 48% yield (Scheme 6). The latter compound (**16b**) was alkylated with prenyl bromide, after enolate generation with LiHMDS and HMPA, to afford alkylated product **17** (63%) as a 1:1 mixture of geometrical isomers ($\Delta^{8,9}$), each of which existed as a 1:1 pair of atropisomers as revealed by ¹H



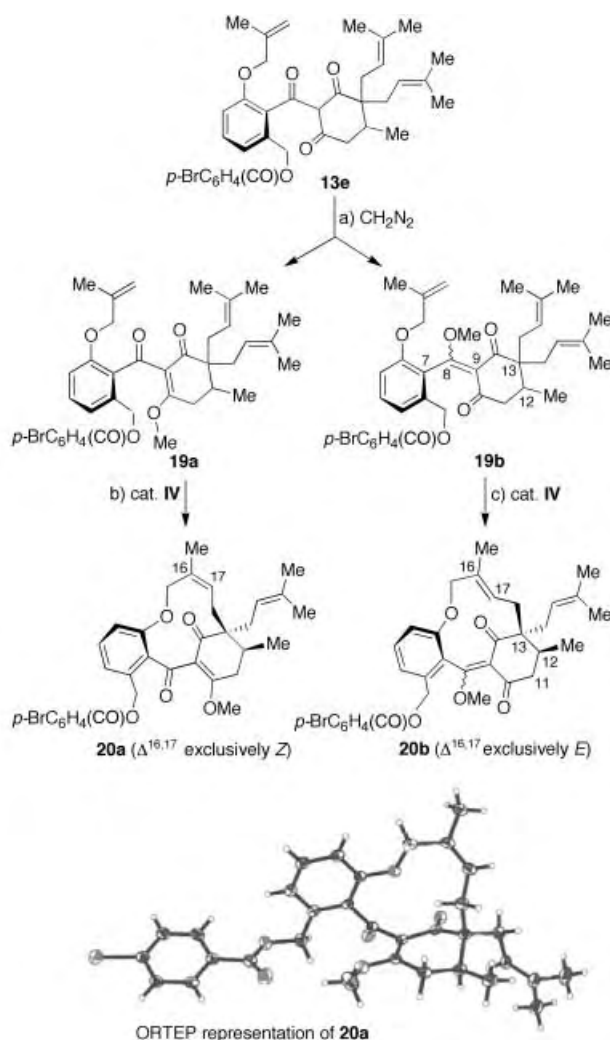
Scheme 6. Protection of the tricarbonyl moiety and reversal of the geometrical outcome of the olefin metathesis reaction leading to an (*E*) $\Delta^{16,17}$ containing 11-membered ring. a) Excess CH₂N₂, Et₂O, 0°C, 30 min, 48% of **16a** plus 48% of **16b**; b) LiHMDS (1.05 equiv), THF, –78°C, 1 h; then prenyl-Br (2.0 equiv), –78→0°C, 5 h, 63%; c) cat. **IV** (0.2 equiv), CH₂Cl₂, 40°C, 20 h, 30% of **18** plus 35% recovered starting material **17**.

NMR spectroscopy. When **17** was subjected to the action of Grubbs' catalyst **IV** (20 mol %) in refluxing dichloromethane for 20 h, a single macrocycle (**18**) was isolated, in 30% yield, and proven to be of the *E* configuration at $\Delta^{8,9}$. Under these conditions, a considerable amount (30%) of the starting material (**17**) was recovered and, interestingly, found to be enriched in the *Z* isomer ($\Delta^{8,9}$). The most tantalizing feature elucidated at this juncture was, however, the fact that the macrocyclic double bond ($\Delta^{16,17}$) bore exclusively the *E* configuration (see NOE effects on structure **18**, Scheme 6). We had now unearthed pathways that led us to both diastereoisomers of the coleophomone macrocyclic skeleton in a specific manner.

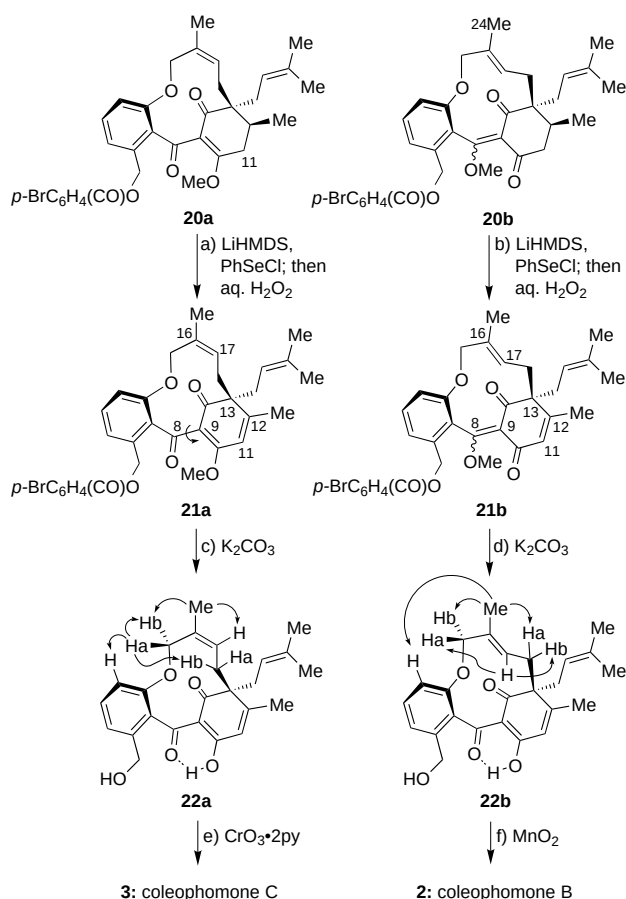
With these results providing the foundation for the next phase, we proceeded to exploit the full potential of our intelligence gathering for the final solution of the coleophomone problem. Thus, fully substituted precursor **13e** (see Scheme 7) was treated with diazomethane under the established conditions and, following flash column chromatography, methoxy derivatives **19a** (32%) and **19b** (48%) were isolated along with a small quantity of the third possible

regioisomer (not shown). As expected, **19a** was a single compound, while **19b** proved to be a mixture of geometrical isomers around the $\Delta^{8,9}$ bond (ca. 1.3:1), each of which again consisted of a pair of atropisomers (ca. 1:1 by ^1H NMR spectroscopy). Upon exposure of the two regioisomers **19a** and **19b**, independently, to the catalyst **IV** (10 mol %) we observed the most pleasing results. Both **19a** and **19b** succumbed to regio- and stereospecific ring-closing metathesis to furnish, in high yields, the corresponding macrocycles **20a** (80%, exclusively *Z*-configured at $\Delta^{16,17}$, ca. 4:1 ratio of atropisomers in CDCl_3 , single atropisomer in CD_3CN) and **20b** (86%, exclusively *E*-configured at $\Delta^{16,17}$, ca. 1:1 *E*:*Z* isomers at $\Delta^{8,9}$). The structures of **20a** and **20b** were established on the basis of nOe studies and, in the former case (**20a**), confirmed by an X-ray crystallographic analysis^[11] (see ORTEP representation). Thus, with exquisite specificity, the olefin metathesis reaction furnishes the two macrocycles processing the opposite configuration at the $\Delta^{16,17}$ bond, each corresponding to a different coleophomone framework. Furthermore, and in contrast to the reaction of the mono-prenylated compound **17** (see Scheme 5), both $\Delta^{8,9}$ diastereoisomers of **19b** reacted smoothly, presumably because the second prenyl group forced the molecule to adopt a more favorable and rigid conformation. The rigidity and, therefore, reduced entropy^[12] of **19a** and **19b** is also presumed to be responsible for the apparent irreversibility of the ring-closing metathesis as evidenced by the absence of any spirocyclopentene products in the reaction mixture and the high yields of the desired macrocycles (**20a** and **20b**). Another fascinating feature of these ring-closing metatheses is their exquisite diastereoselectivity, that is, only the prenyl group occupying the *cis* position to the adjacent methyl group (C12) participates in the reaction. This preference presumably results from the fact that it places the remaining prenyl side chain *trans* to the C12 methyl group, an arrangement that allows both groups to occupy the lower-energy equatorial positions on the cyclohexane ring. Finally, we were able to confirm our earlier hypothesis that the unprotected tricarbonyl system was detrimental to the olefin metathesis reaction by comparing the poor performance (<20% yield of cyclized product) of **13e** (Scheme 7) under the same cyclization conditions with the stellar showing of its protected derivatives **19a** and **19b**.

As a prelude to the final drive toward the coleophomones, the introduction of the $\Delta^{11,12}$ bond was accomplished in both series by a one-pot phenylselenide formation/oxidation/syn-elimination sequence to afford **21a** as a single compound and **21b** as a mixture of geometrical isomers (61 and 53% overall yield, respectively, Scheme 8). This transformation increased the ratio of geometrical isomers ($\Delta^{8,9}$) in **21b** in favor of the *E* isomer (**20b** *E*:*Z* ca. 1:1 $\rightarrow$ **21b** *E*:*Z* ca. 3:1), presumably owing to the apparent steric encumbrance of the C11 methylene group caused by the direct positioning of the C24 methyl group above it in the *Z* isomer (molecular modeling and nOe studies). The recovered starting material **20b** (15%) was enriched in the *Z* isomer. Exposure of **21a** and **21b** to K_2CO_3 in methanol at ambient temperature led to global deprotection and afforded **22a** (90% yield) and **22b** (96% yield), respectively, both as single compounds (see Scheme 8 and Table 1 for spectroscopic data). At this juncture, the



Scheme 7. Stereospecific olefin metathesis reactions leading to (*Z*) and *E* isomers of 11-membered rings en route to the coleophomones. a) Excess CH_2N_2 , Et_2O , 0°C , 1 h, 32% of **19a** plus 48% of **19b**; b) cat. **IV** (0.1 equiv), CH_2Cl_2 , 40°C , 3 h, 80%; c) cat. **IV** (0.1 equiv), CH_2Cl_2 , 40°C , 3 h, 86%.



Scheme 8. Completion of the total synthesis of coleophomones B (2) and C (3). a) LiHMDS (1.3 equiv), THF, $-78 \rightarrow -10^\circ\text{C}$, 1 h; then PhSeCl (1.4 equiv), $-78^\circ\text{C} \rightarrow 20^\circ\text{C}$, 30 min; then sat. NH_4Cl (excess), 31% aq. H_2O_2 (excess), 25°C , 1 h, 61%. b) LiHMDS (1.3 equiv), THF, $-78 \rightarrow 25^\circ\text{C}$, 1 h; then PhSeCl (1.4 equiv), $-60 \rightarrow 25^\circ\text{C}$, 30 min; then sat. NH_4Cl (excess), 31% aq. H_2O_2 (excess), 25°C , 1 h, 53%, plus 15% recovered 20b; c) K_2CO_3 (3.0 equiv), MeOH, 25°C , 3 h; then H_2O (excess), 24 h, 90%; d) K_2CO_3 (3.0 equiv), MeOH, 25°C , 40 min; then H_2O (excess), 30 min, 96%; e) py (12 equiv), CrO_3 (6.0 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 20 min; then 22a, 25°C , 2 h, 81%; f) MnO_2 (20 equiv), Et_2O , 36°C , 8 h, 73%. py = pyridine.

coalescence to a single isomer in each series allowed additional and unequivocal confirmation of our earlier distinction between *Z/E* isomerism and atropisomerism by using nOe studies (see structures 22a and 22b, Scheme 8). Oxidation of 22b with MnO_2 in diethyl ether produced, cleanly^[13] and in 73% yield, coleophomone B (2) whose spectroscopic data matched those of the natural product.^[1,2] Likewise, coleophomone C (3) was accessed by oxidation of 22a, this time with Collins' reagent (this isomer reacts sluggishly with MnO_2) in 81% yield and, once again, the spectroscopic data of the synthetic sample proved to be identical to those of an authentic sample.^[1] Despite the reported equilibrium^[2] between 1 and 2 we choose to refrain from declaring a formal total synthesis of coleophomone A (1) pending further experimentation.

In conclusion we have developed an expedient and stereocontrolled total synthesis of coleophomones B (2) and C (3) through an initially convergent route that diverges at a late stage to allow stereospecific construction of the highly

Table 1. Selected data for compounds 22a and 22b.

22a: yellow oil; $R_f = 0.44$ (silica gel, hexane/EtOAc, 1/1); IR (film): $\tilde{\nu}_{\text{max}} = 3436, 2920, 1651, 1549, 1449, 1261, 1008, 914, 726 \text{ cm}^{-1}$; ^1H NMR (600 MHz, CDCl_3): $\delta = 15.71$ (s, 1H), 7.38 (t, $J = 7.7 \text{ Hz}$, 1H), 7.11 (d, $J = 7.7 \text{ Hz}$, 1H), 6.89 (d, $J = 7.7 \text{ Hz}$, 1H), 6.29 (s, 1H), 5.28 (dd, $J = 11.0, 6.6 \text{ Hz}$, 1H), 4.56 (d, $J = 12.1 \text{ Hz}$, 1H), 4.51 (d, $J = 12.1 \text{ Hz}$, 1H), 4.50 (br dd, $J = 6.5, 5.5 \text{ Hz}$, 1H), 4.34 (d, $J = 8.7 \text{ Hz}$, 1H), 4.10 (d, $J = 8.7 \text{ Hz}$, 1H), 2.84 (dd, $J = 14.8, 6.0 \text{ Hz}$, 1H), 2.69 (dd, $J = 14.3, 11.0 \text{ Hz}$, 1H), 2.22 (m, 2H), 2.08 (s, 3H), 1.82 (s, 3H), 1.55 (s, 3H), 1.50 ppm (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): $\delta = 198.8, 181.0, 164.1, 156.4, 139.8, 136.0, 134.4, 131.9, 131.7, 131.4, 124.1, 123.6, 122.2, 117.8, 115.1, 113.1, 69.7, 64.2, 59.2, 39.0, 37.1, 25.7, 23.2, 20.1, 18.1 \text{ ppm}$; HRMS (MALDI): calcd for $\text{C}_{25}\text{H}_{27}\text{O}_4$ [$\text{MH} - \text{H}_2\text{O}$]: 391.1904; found: 391.1905; MS (ESI): 409 [MH^+], 431 [MNa^+]

22b: amorphous solid; $R_f = 0.32$ (silica gel, hexane/EtOAc, 1/1); IR (film): $\tilde{\nu}_{\text{max}} = 3412, 2920, 1651, 1556, 1455, 1262, 997, 866, 736 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 16.54$ (s, 1H), 7.29 (t, $J = 8.2 \text{ Hz}$, 1H), 7.12 (d, $J = 8.2 \text{ Hz}$, 1H), 7.09 (d, $J = 7.4 \text{ Hz}$, 1H), 6.38 (s, 1H), 5.41 (br d, $J = 12.0 \text{ Hz}$, 1H), 4.66 (d, $J = 12.3 \text{ Hz}$, 1H), 4.56 (d, $J = 11.4 \text{ Hz}$, 1H), 4.55 (br dd, $J = 7.4, 5.5 \text{ Hz}$, 1H), 4.49 (d, $J = 12.3 \text{ Hz}$, 1H), 4.31 (d, $J = 11.4 \text{ Hz}$, 1H), 2.99 (dd, $J = 14.2, 6.8 \text{ Hz}$, 1H), 2.44 (t, $J = 12.8 \text{ Hz}$, 1H), 2.33 (br d, $J = 13.8 \text{ Hz}$, 1H), 2.25 (dd, $J = 14.6, 6.4 \text{ Hz}$, 1H), 2.11 (s, 3H), 1.58 (br s, 3H), 1.57 (br s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 200.0, 198.6, 183.0, 164.9, 153.5, 139.6, 135.7, 134.9, 132.2, 129.6, 128.1, 123.3, 122.9, 118.3, 118.0, 114.2, 76.3, 63.7, 58.8, 38.3, 34.4, 25.7, 20.1, 19.7, 18.0 \text{ ppm}$; HRMS (MALDI): calcd for $\text{C}_{25}\text{H}_{27}\text{O}_4$ [$\text{MH} - \text{H}_2\text{O}$]: 391.1904; found: 391.1898; MS (ESI): 409 [MH^+], 431 [MNa^+]

strained and synthetically challenging macrocyclic scaffolds associated with these molecules via an olefin metathesis reaction. This unprecedented accomplishment bodes well for this venerable reaction that is becoming increasingly enabling for organic synthesis through the discovery of new catalysts to initiate it and the design of novel strategies to apply it.

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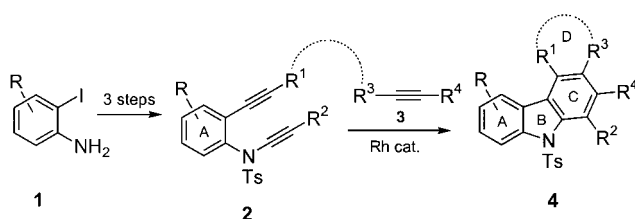
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A Highly Efficient and Flexible Synthesis of Substituted Carbazoles by Rhodium-Catalyzed Inter- and Intramolecular Alkyne Cyclotrimerizations**

Bernhard Witulski* and Carole Alayrac

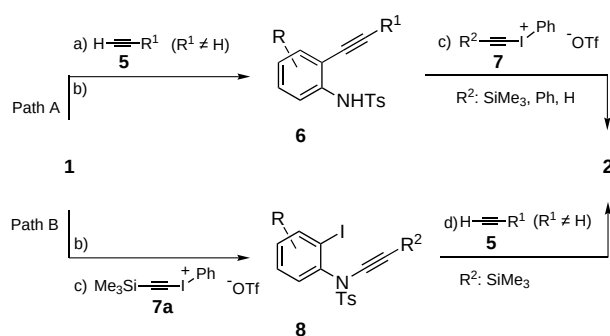
Syntheses of substituted carbazoles have attracted considerable attention because carbazole alkaloids are a growing class of natural products that exhibit a variety of biological activities.^[1,2] Moreover, annelated carbazoles structurally related to the natural indolocarbazole staurosporine have gained significance because of their protein kinase C (PKC) and topoisomerase inhibitory activity.^[3]

Although several syntheses of substituted carbazoles as well as chemical modifications of the carbazole nucleus are established,^[1,4] the major challenge in carbazole chemistry arises from the question of how to functionalize regioselectively up to eight aromatic ring positions. We have designed a strategy for the assembly of the carbazole nucleus by an A→ABC or A→ABCD ring-formation approach that is based on the reliability of the Sonogashira reaction,^[5] our previously reported synthesis of functionalized ynamides,^[6] and the efficiency of transition-metal-catalyzed alkyne cyclotrimerizations (Scheme 1).^[7]



Scheme 1. A→ABC or A→ABCD ring-formation approach to substituted carbazoles by rhodium-catalyzed alkyne cyclotrimerization.

The diynes **2** were prepared in three steps starting from readily available 2-iodoanilines **1**. Sonogashira reactions between **1** and terminal alkynes **5** followed by N-tosylation of the aniline functionality gave alkynes **6**, which thereafter underwent N-ethynylation with alkynylidonium salts **7** to give the diynes **2** in good overall yields (Scheme 2, path A).



Scheme 2. a) **5** (1.3 equiv), 5 mol % $[\text{PdCl}_2(\text{PPh}_3)_2]$, 10 mol % CuI, NEt_3 , DMF, room temperature, 60–98%; b) TsCl, pyridine, THF, 70–92%; c) potassium hexamethyldisilazane (KHMDs), toluene, 0°C, then addition of **7** (1.4 equiv), room temperature, 52–93% for **6**→**2**, 87–98% for **8**; d) **5** (1.4 equiv), 5 mol % $[\text{PdCl}_2(\text{PPh}_3)_2]$, 10 mol % CuI, 10 mol % PPh_3 , NEt_3 , DMF, 80°C, 54–68%.

Alternatively, N-ethynylation reactions with **7a** were carried out with tosylated **1** to give the ynamides **8**, which were then converted to **2** through Sonogashira reactions (Scheme 2, path B). While the conversion of **1** to **6** proceeded readily at room temperature, cross-coupling reactions with **8** to give **2** required heating to 80°C, probably because of an increase of steric hindrance. Notably, the use of trimethylsilylacetylene in the Sonogashira reaction, or the use of **7a** for the N-ethynylation reaction following either path A or B in Scheme 2 allowed further manipulations of the diynes **2** through protective group strategies.

Crossed alkyne cyclotrimerizations between diynes **2** and monoalkynes **3** promoted by Wilkinson's catalyst^[6b,8] proceeded under very mild conditions (3–5 mol % $[\text{RhCl}(\text{PPh}_3)_3]$, 5–6 equivalents of **3**, toluene as solvent) to give the carbazoles **4** in high yields (Scheme 1, Table 1). Notably, the additional triple bond in **2e** did not interfere with the formation of carbazole **4e** (80% yield, Table 1, entry 5). The outstanding efficiency of the carbazole formation by crossed alkyne cyclotrimerizations is presumably a consequence of conformational restrictions present in the diynes **2**. A conformation in which both alkyne moieties are close to each other appears likely and therefore favors the overall catalytic process.

[*] Priv.-Doz. Dr. B. Witulski, Dr. C. Alayrac
Fachbereich Chemie der Universität Kaiserslautern
Erwin-Schrödinger-Strasse, 67663 Kaiserslautern (Germany)
Fax: (+49)631-205-3921
E-mail: witulski@rhrk.uni-kl.de

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Table 1. Functionalized carbazoles **4** through rhodium-catalyzed crossed alkyne cyclotrimerizations (3–5 mol % [RhCl(PPh₃)₃], 5–6 equivalents of monoalkyne **3**, toluene, room temperature, 1–12 h).

Entry	Diyne 2	Monoalkyne 3	Carbazole 4	Isomer ratio	Yield [%]
1	2a : R ¹ = H; R ² = H	3a :	4a : R ¹ = H; R ² = H		90
2	2b : R ¹ = CH ₂ OTHP; R ² = H	3a	4b : R ¹ = CH ₂ OTHP; R ² = H		95
3	2c : R ¹ = H; R ² = Ph	3a	4c : R ¹ = H; R ² = Ph		98
4 ^[b]	2d : R ¹ = CH ₂ OTHP; R ² = SiMe ₃	3a	4d : R ¹ = CH ₂ OTHP; R ² = SiMe ₃		90
					80
5 ^[c]	2e	3b	4e		
6	2c	3c :	4f :	(5:1)	95
		3c	4g :	toluene: (3.5:1) ethanol: (1.4:1)	89 71
7	2f	3c	4g		
8	2g :	3c	4h :	toluene: (1.5:1) ethanol: (5.8:1)	97 68
			4i :		
9	2a	3d	4i	(4:1)	72
10	2h :	3d	4j :	(3.8:1)	78
			4k :	(6:1)	91
11	2c	3e	4k		
12	2c	3f :	4l :	(1:1)	98

[a] THP = tetrahydropyran. [b] *T* = 80 °C, 17 h. [c] *T* = 40 °C, 19 h.

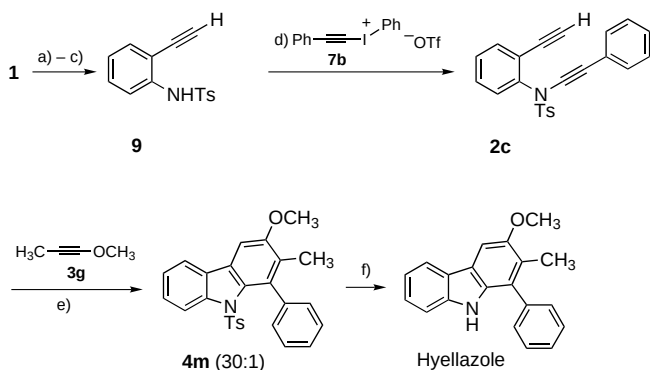
Cyclotrimerizations of diynes **2** with the terminal monoalkyne **3c** afforded one major regioisomer of **4** (Table 1, entries 6–8).^[9] In agreement with previously reported crossed alkyne cyclotrimerizations utilizing Wilkinson's catalyst,^[8e,g] regioselectivities observed in the carbazole series were based on a complex interplay between steric factors and on solvent effects. In the case of **4g**, for which the *ortho* isomer was favored, the regioselectivity was best in toluene (Table 1, entry 7), whereas in the case of **4h**, for which the *meta* isomer was favored, the selectivity could be significantly improved by

using ethanol as solvent (Table 1, entry 8). Furthermore, regioselectivity was influenced by electronic parameters. Although electron-deficient monoalkynes are poor cyclotrimerization partners, the reaction of propiolic ester **3d** with the diynes **2a** and **2h** afforded the carbazoles **4i** (72% yield, ratio of isomers 4:1) and **4j** (78% yield, ratio of isomers 3.8:1), respectively, as major isomers. Using the electron-deficient disubstituted monoalkyne **3e** a high selectivity was achieved in the preparation of carbazole **4k** (Table 1, entry 11). The latter result was again driven by electronic effects

as revealed by the lack of regioselectivity observed with the electron-neutral disubstituted monoalkyne **3f** (Table 1, entry 12).

To illustrate the applicability of our method in natural product synthesis, the target-oriented syntheses of two naturally occurring carbazole alkaloids—clausine C and hyellazole—were investigated. Clausine C,^[10] which was recently isolated from the stem bark of *Clausena excavata*, a wild shrub that has been claimed to be a useful folk medicine in the treatment of snake bites, was readily accessible after deprotection of carbazole **4j** (Table 1, entry 10) with tetrabutylammonium fluoride (TBAF) in refluxing THF (98% yield).^[11] Clausine C was thus obtained in six steps from 2-iodo-5-methoxyaniline with an overall yield of 40%.

Further potential of our methodology was demonstrated through the straightforward synthesis of hyellazole, a marine carbazole alkaloid isolated from the blue-green algae *Hyella caespitosa*.^[12] The key step of our synthesis resides in the regioselective alkyne cyclotrimerization of diyne **2c** with 1-methoxy-propyne **3g** (Scheme 3). Based on previous results with electron-deficient monoalkynes, we expected that the use of an electron-rich monoalkyne as cyclotrimerization partner would invert the regioselective outcome of the reaction as observed with **3e** (Table 1, entry 11). Indeed,



Scheme 3. Synthesis of hyellazole: a) trimethylsilylacetylene (1.3 equiv), 5 mol % $[\text{PdCl}_2(\text{PPh}_3)_2]$, 10 mol % CuI , Et_3N , DMF, room temperature, quant.; b) TsCl , pyridine, THF, 89%; c) TBAF, THF, 0°C , 90%; d) KHMDs , toluene, 0°C , then addition of **7b** (1.4 equiv), 56%; e) **3g** (10 equiv), 10 mol % $[\text{RhCl}(\text{PPh}_3)_3]$, toluene, room temperature, 89%; f) TBAF, THF, reflux, 98%.

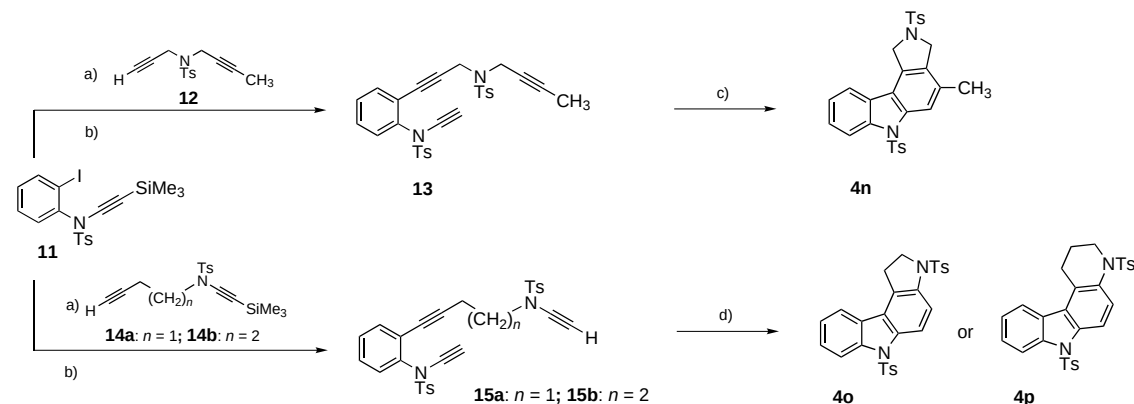
carbazole **4m** was obtained with excellent chemo- and regioselectivity by utilizing the electron-rich monoalkyne **3g** and Wilkinson's catalyst (89% yield, isomer ratio = 30:1, toluene, 20°C). Isomerically pure hyellazole was thereafter obtained through deprotection of the tosyl group (Ts) with TBAF in refluxing THF followed by crystallization. With only six steps starting from commercially available 2-iodoaniline and an overall yield of 39%, this synthesis of hyellazole becomes the most efficient one in terms of conciseness and overall yield.^[13]

Finally, the intramolecular version of this new carbazole synthesis offered a straightforward access to annelated carbazoles (Scheme 4). Although intramolecular alkyne cyclotrimerizations are completely regioselective due to an additional tether, the synthesis of the corresponding triynes is normally much more demanding. However, in the carbazole series this could be easily solved by using the Sonogashira reaction for the assembly of the triynes **13**, and **15a** and **15b**. They were obtained in 80, 71, and 66% overall yield, respectively, starting from **11**. Intramolecular cyclotrimerizations in the presence of 2–5 mol % Wilkinson's catalyst afforded then the annelated carbazoles **4n**, **4o**, and **4p** (77–99% yield). Notably, the intramolecular version not only allowed the use of two ynamide moieties, it also offered the possibility for a six-membered-ring annelation that cannot be achieved easily in the corresponding crossed version of this reaction.

In conclusion, we have developed a novel synthesis of substituted carbazoles based on *inter*- and *intramolecular* alkyne cyclotrimerizations. The flexibility of this approach and the diversity of the carbazole substitution pattern that can be reached now permits application of this methodology in the synthesis of natural products and drug-related targets.

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Scheme 4. Annelated carbazoles by intramolecular alkyne cyclotrimerization. a) terminal alkyne **12** or **14a** or **14b** (1.3 equiv), 5 mol % $[\text{PdCl}_2(\text{PPh}_3)_2]$, 10 mol % CuI , 10 mol % PPh_3 , Et_3N , DMF, 80°C , 2 h, **13** (89%), **15a** or **15b**, (79–84%); b) TBAF, THF, 0°C , 10 min., 85–90%; c) 2 mol % $[\text{RhCl}(\text{PPh}_3)_3]$, toluene, room temperature, 12 h, 99%; d) 5 mol % $[\text{RhCl}(\text{PPh}_3)_3]$, CH_2Cl_2 , 40°C , 15 h, **4o** (95%), **4p** (77%).

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Transannular Radical Cascade as an Approach to the Diastereoselective Synthesis of Linear Triquinane**

Anne-Lise Dhimane, Christophe Aïssa, and Max Malacria*

Diastereoselective constructions of polycyclic structures such as triquinanes by 5-*exo*-radical-cyclization cascade reactions that start from a templating ring are well-known;^[1] from acyclic systems only a few such reactions involve diastereoselective processes.^[2] However, transannular cyclizations, which are nowadays frequently used as a key step in the synthesis of polycyclic frameworks,^[3] have been poorly described as an efficient means of reaching linear triquinane systems diastereoselectively. There is only one specific example reported by Winkler in which linear triquinanes were obtained as a mixture of diastereomers, from suitably substituted cycloocta-1,5-dienes, by a unique transannular process.^[4]

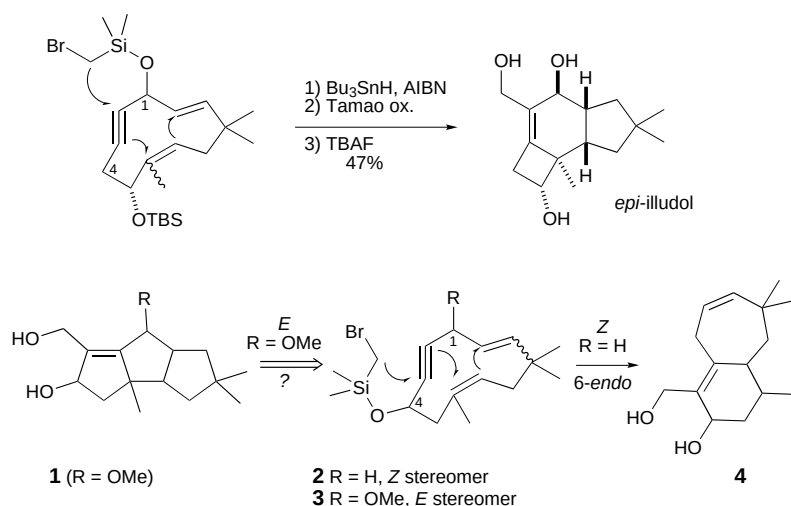
During the last decade, we have been interested in the development of highly chemo-, regio-, and stereoselective cascade processes which rely on radical transannular reactions.^[5] The diastereoselective total synthesis of the proto-illudane *epi*-illudol, which has an angularly fused 4,6,5-tricyclic framework, was achieved by a cascade of radical transannular cyclizations from a (bromomethyl)dimethylsilyl (BMDMS) ether of a cycloundeca-4,8-dien-1-yne (Scheme 1).^[5b] By following the same type of cascade, we believed that switching the BMDMS-ether tether from the C-1 atom to the C-4 atom should now lead to a triquinane skeleton of type **1**. We anticipated that the disubstituted double-bond geometry would be crucial for the behavior of the transannular cascade. In fact, when the *Z,E* precursor **2** was submitted to radical cyclization conditions, the generated vinyl radical cyclized regioselectively in a 6-*endo* mode, leading to the 6,7-bicyclic compound **4** (Scheme 1).^[5c] In contrast, we report herein the stereoselective construction of a linear triquinane through an unprecedented cascade of diastereoselective transannular cyclizations from an *E,E* precursor.

Access to precursor **3** was envisaged by following a similar strategy to that developed for the eleven-membered ring **2**, by using Nozaki-Hiyama-Kishi-Takai (NHKT) macrocyclization as the key step. Thus, *E*-heptenal **6** (as a common precursor),^[6] was subjected to the mild Horner-Wadsworth-Emmons olefination conditions described by Masamune and Roush^[7] to furnish, after tetrabutylammonium fluoride (TBAF) mediated cleavage of the resulting silylated ether, the *E*- α,β -unsaturated ester **7**. Dess-Martin oxidation^[8] of the homoal-

[*] Prof. M. Malacria, Dr. A.-L. Dhimane, Dr. C. Aïssa
Laboratoire de Chimie Organique de Synthèse
UMR 7611, CNRS- Université Pierre et Marie Curie
4, place Jussieu, Tour 44-54, Case 229, 75252 Paris Cedex 05 (France)
Fax: (+33)1-44-27-73-60
E-mail: malacria@ccr.jussieu.fr

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



Scheme 1. Transannular radical cyclizations cascade reactions. TBS = *tert*-butyldimethylsilyl.

lylic alcohol moiety, followed by condensation of the in situ generated organocerium derivative of trimethylsilylacetylene,^[9] with the crude β,γ -unsaturated aldehyde thus provided yno 8. A sequential deprotection of the alkyne/O-silylation led to the propargylic silyl ether 9. Reduction of 9 and subsequent oxidation of the resulting allylic alcohol gave the expected undecadienynal, which was submitted to mild iodination conditions^[10] to give the iodoalkyne 5 (Scheme 2).

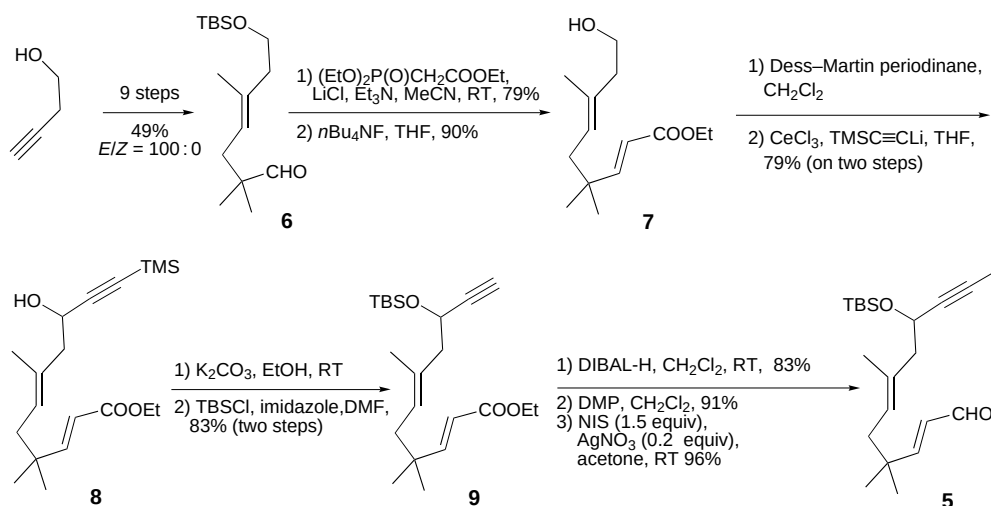
Carefully controlled slow addition of iodoalkyne 5 in THF to a suspension of chromium chloride (7 equiv) in THF produced the desired macrocyclic propargylic alcohol 10 as a

2:1 mixture of diastereomers in 88% yield (Scheme 3). These diastereomers were particularly difficult to separate, however, we could enrich the mixture to a 3:1 ratio. Then, a methylation–desilylation sequence afforded the expected propargylic alcohol.

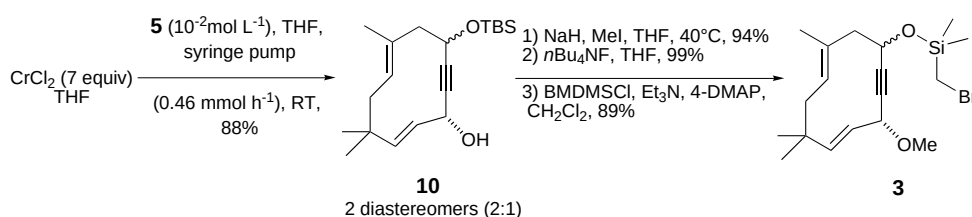
The BMDMS ether 3, prepared under classical silylation conditions, was subjected to reaction with Ph_3SnH –AIBN (AIBN = azobisisobutyronitrile), followed by Tamao oxidation to lead to the 5,5,5-tricyclic triquinane framework 1 in 45% yield diastereoselectively (Scheme 4), along with a bicyclic diol 11 as a 2:1 mixture of diastereomers in 12% yield.

Full characterization by ^1H and ^{13}C NMR spectroscopy, COSY, NOE (Scheme 5), IR, MS, HRMS, and elemental analysis unambiguously supports the proposed structures for 1 and 11.

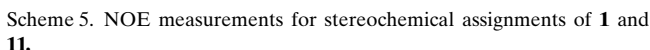
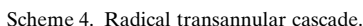
The formation of triquinane 1 results from the now well-established 5-*exo-dig* process^[5] from the initial α -silyl radical A to the vinyl radical B, which then undergoes the transannular tandem [5-(π -endo)-*exo-trig*/8-(π -*exo*)-*endo-trig*]/[5-*exo-trig*/5-*endo-trig*], allowing the consecutive formation of the tricyclic radical C; this finally cyclizes to form the expected tetracyclic radical D. The latter follows two competitive processes: a stannane reduction–Tamao oxidation sequence leading to 1 or, alternatively, a minor β -fragmentation process provides the stabilized α -methoxy and allylic radical E. This latter is reduced in an *endo* mode to give the



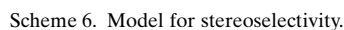
Scheme 2. Synthesis of precursor 5. DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, NIS = *N*-iodosuccinimide



Scheme 3. NHKT macrocyclization of precursor 5 and functional modifications to precursor 3.



A model accounting for the stereoselectivity is proposed in Scheme 6. First, cyclization from the major diastereomer **3** leads to the formation of **B**, in which the heterosilane is *anti* to



The difference of regioselectivity between the cyclizations of vinyl radicals created from precursor **2** and **3** undoubtedly results from the geometric strain generated by the stereochemistry of the double bond. The 6-*endo* transannular cyclization, which creates a seven-membered unsaturated ring, is al-

In summary, we have reported the first example of a triquinane generation by a diastereoselective series of transannular radical cyclizations. Our synthetic transannular strategy was so efficient that, by using the same cycloundecadienyne framework and just moving the radical trigger from one propargylic position to the other, we have a completely selective entry to either the protoilludane^[4b] or the triquinane family.

1: To a degassed solution of the BMDMS ether **3** (154 mg, 0.4 mmol) as a 3:1 mixture of diastereomers in 14 mL of dry benzene heated under reflux, was added a solution of Ph_3SnH (182 mg, 0.52 mmol) and AIBN (20 mg, 0.12 mmol) in 4 mL of dry and degassed benzene by syringe pump (2.12 mL h^{-1}). At completion of the addition, and when all starting material was consumed, the benzene was removed under vacuum and the stannylated derivatives were precipitated by stirring in pentane at 0°C . Filtration twice through celite furnished a residue, which was poured into a mixture of THF/MeOH (1:1, 6 mL) with of KHCO_3 (248 mg,

2.48 mmol), KF (93 mg, 1.6 mmol), and a solution of H₂O₂ (35 %, 4 mL). After heating for 1 h at 70 °C, the reaction mixture was cooled to room temperature, filtered through Celite, and rinsed 3 times with ethyl acetate. The aqueous phase was extracted twice more with ethyl acetate. The organic layers were washed with brine, dried over MgSO₄, and the solvent removed under reduced pressure. The residue was purified on a silica-gel column, eluting with 3 % MeOH in CH₂Cl₂ to afford 47 mg of **1** (45 %) and 13 mg of cyclopentane **11** (12 %).

1: Yield: 45 %; ¹H NMR (200 MHz, CDCl₃, 25 °C): δ = 5.27 (t, *J* = 6.6 Hz, 1H; H-2), 4.47 (d, *J* = 12.6 Hz, 1H; CH₂OH), 4.32 (d, *J* = 12.6 Hz, 1H; CH₂OH), 4.03 (d, *J* = 6.4 Hz, 1H; H-7), 3.15 (s, 3H; OMe), 2.88 (m, 1H, H-6a), 2.38 (dd, *J* = 11.3 Hz, *J* = 9.5 Hz, 1H; H-3b), 2.36 (dd, *J* = 12.1 Hz, *J* = 6.4 Hz, 1H; H-3), 1.68 (dd, *J* = 12.1 Hz, *J* = 10.7 Hz, 1H; H-6), 1.53 (dd, *J* = 11.9 Hz, *J* = 7.8 Hz, 1H; H-3'), 1.32 (d, *J* = 9.6 Hz, 2H; H-4), 1.24 (dd, *J* = 8.4 Hz, *J* = 3.5 Hz, 1H; H-6), 1.07 (s, 3H; H-5a), 1.00 (s, 3H; H-3a), 0.92 ppm (s, 3H; H-5β); ¹³C NMR (CDCl₃, 50 MHz, 25 °C) δ = 154.8 (C-7a), 135.4 (C-1), 81.3 (C-7), 75.6 (C-2), 58.3 (CH₂OH), 56.3 (CH₃O), 55.0 (C-3), 53.6 (C-3b), 50.8 (C-3a), 49.9 (C-6a), 43.2 (C-5), 41.2 (C-6), 38.2 (C-4), 29.2 (CH₃-5), 27.4 (CH₃-5), 23.4 ppm (CH₃-3a); IR (neat) $\tilde{\nu}$ 3450 (br), 2940, 2850, 1650 (br), 1455, 1360, 1090, 995, 760 cm⁻¹; elemental analysis calcd (%) for C₁₆H₂₆O₃ (*M* = 266.381 g mol⁻¹): C 72.14, H 9.83; found : C 72.11, H 9.80; MS (CI, CH₄): *m/z* (%) 266 (M⁺, 4 %), 265 (M⁺-1, 7 %), 249 (M⁺-OH, base peak), 231 (47 %), 217 (35 %).

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COVER PICTURE

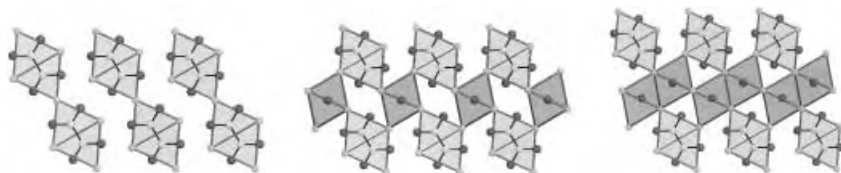
The cover picture shows the newest member of an “elite” club of aromatic molecules. The platinabenzene, in which a benzene methine (CH) unit has been replaced by an isoelectronic platinum fragment, completes the series of metalla-aromatics containing third row, Group VIII metals (Os, Ir, Pt). Previously excluded, the molecule gains admittance to this select club because it exhibits properties similar to other six-membered ring heteroaromatic compounds (e.g., pyridine), such as ring planarity, delocalized bonding, and downfield shifts in the ^1H NMR spectrum. The platinabenzene shares a feature unique for the third period transition metals in that it requires no further stabilization by coordination to an additional metal center. More on the structure and properties of this molecule can be found in the communication by Haley et al. on p. 3470 ff.



REVIEWS

Contents

Between molecular and solid-state chemistry: the nitridoborates of the lanthanides form both saltlike and metal-rich compounds, and are synthesized through solid-state metathesis reactions with dinitridoborate ions. They contain ions such as $[\text{BN}]^{n-}$, $[\text{BN}_2]^{3-}$, $[\text{B}_2\text{N}_4]^{8-}$, $[\text{B}_3\text{N}_6]^{9-}$, and $[\text{BN}_3]^{6-}$. A characteristic structure principle can be derived for nitridoborates and their nitrides as shown in the picture for structures with B_2N_4 anions.



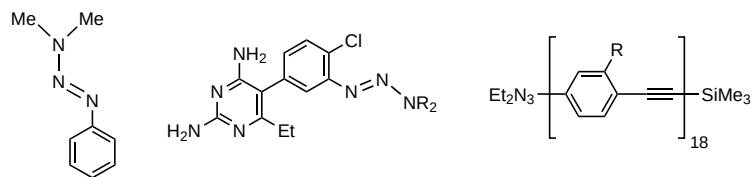
Angew. Chem. **2002**, *114*, 3468–3483

B. Blaschkowski, H. Jing,
H.-J. Meyer* 3322–3336

Nitridoborates of the Lanthanides:
Synthesis, Structure Principles, and
Properties of a New Class of Compounds

Keywords: borates • lanthanide •
nitrides • nitridoborates • solid-state
structures

Extraordinarily versatile best describes triazenes, a class of biologically and synthetically useful molecules (see picture). Triazenes exhibit several types of reactivity depending on the conditions used and can yield a wide variety of functional groups when treated with acids, bases, or iodomethane. Triazenes can form links to solid supports, simplify polymer or macrocycle synthesis, or act as anticancer agents, all of which are described in this review.



Angew. Chem. **2002**, *114*, 3484–3498

D. B. Kimball, M. M. Haley* 3338–3351

Triazenes: A Versatile Tool In Organic Synthesis

Keywords: cross-coupling • cyclization • heterocycles • protecting groups • solid-phase synthesis

ESSAY

Moral justification? How can we choose from the different moral view points, which is correct and which is inappropriate, when the supporters of each view point defend and justify their position with such vehemence. In other words is there a rational basis for norms?

Angew. Chem. **2002**, *114*, 3499–3505

G. Patzig* 3353–3358

Can Moral Norms be Rationally Justified?

Keywords: ethics • norms • philosophy of science

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.org>

Hydroboration of Coordinated Dinitrogen: A New Reaction for the N_2 Ligand that Results in Its Functionalization and Cleavage

M. D. Fryzuk,* B. A. MacKay, S. A. Johnson, B. O. Patrick ◆

Protonated Benzene: IR Spectrum and Structure of $C_6H_7^+$

N. Solcà, O. Dopfer* ◆

Single-Step Assembly of a C_2 -Symmetrical Palladium(IV) Spirocyclic Complex

Y. Yamamoto,* T. Ohno, K. Itoh ◆

Changeable Pore Sizes Allowing Effective and Specific Recognition by a Molybdenum-Oxide Based “Nanosponge”: En Route to Sphere-Surface and Nanoporous-Cluster Chemistry

A. Müller,* E. Krickemeyer, H. Bögge, M. Schmidtman, S. Roy, A. Berkle ◆

Syntheses and Crystal Structures of the New Ag-S Clusters $[Ag_{70}S_{16}(SPh)_{34}(PhCO_2)_4(triphos)_4]$ and $[Ag_{188}S_{94}(PnPr)_3]_{30}$

X.-J. Wang, T. Langetepe, C. Persau, B.-S. Kang, D. Fenske*

A Synthesis Route to Enantiomerically Pure Jasmonoids

M. Ernst, G. Helmchen*

Ethane and Ethylidene Dicarboxylates from the Ruthenium(II)-Catalyzed Disproportionative Addition of Carboxylic Acids to Ethene

T. Funaioli,* F. Marchetti, G. Fachinetti*

Cell-Free Biosynthesis of Fluoroacetate and 4-Fluorothreonine in *Streptomyces cattleya*

C. Schaffrath, S. L. Cobb, D. O'Hagan*

Selective Measurements of a Nitroxide–Nitroxide Distance of 5 nm and a Nitroxide–Copper Distance of 2.5 nm in a Terpyridine-Based Copper(II) Complex by Pulse EPR Spectroscopy

E. Narr, A. Godt, G. Jeschke*

Without large investments in new clean-room facilities, the nano- and micro-structures described here can be achieved by the combination of wet-chemistry with existing conventional lithographic techniques. One of the advantages of the method is that it allows the specific formation of aperiodic patterns, which are of specific interest, since the symmetry that is an intrinsic part of the self-assembly of molecules can be overridden. Another advantage is that the use of organic–inorganic templates allows access to pure inorganic nanostructures.

Angew. Chem. **2002**, *114*, 3507–3510

Moieties that can be cross-linked appear to be the necessary feature of dendrimers that can be used to make poled polymers displaying high chromophore density, excellent electrooptic properties, and good thermal and temporal stability. Such materials could find use in optical telecommunications and public networking.

Angew. Chem. **2002**, *114*, 3511–3514

J. P. Spatz* 3359–3362

Nano- and Micropatterning by Inorganic Templating of Hierarchical Self-Assembled Structures

Keywords: imprinting • lithography • nanotechnology • surface chemistry

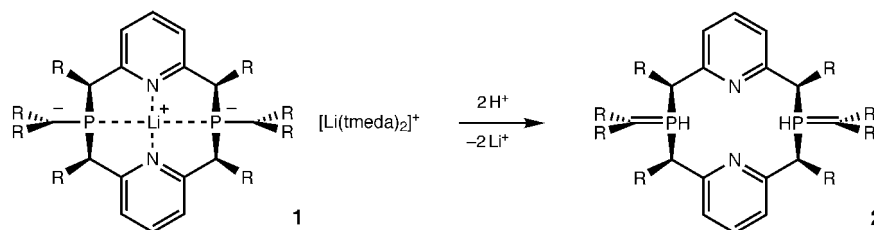
M. E. van der Boom* 3363–3366

Nanostructured Molecular Materials for Device-Quality, Highly Efficient Electrooptic Poled Polymers

Keywords: dendrimers • electrooptic properties • nonlinear optics • organic devices • thin films

COMMUNICATIONS

The thermodynamically less favorable PH-ylide 2, not the corresponding phosphane, is formed in the kinetically controlled protonation of the cyclic phosphamethanide complex **1**. As the electrostatic potential on the surfaces of **1** shows, the attack of the proton on the sterically well shielded methanide carbon atom, and thus the formation of the phosphane form, is hindered. Consequently, a stable phosphonium ylide could be isolated for the first time in the condensed phase and characterized by X-ray crystallography. R = SiMe₃, tmeda = N,N,N',N'-tetramethylethylenediamine.



Angew. Chem. **2002**, *114*, 3515–3519

S. Ekici, D. Gudat, M. Nieger, L. Nyulaszi,* E. Niecke* 3367–3371

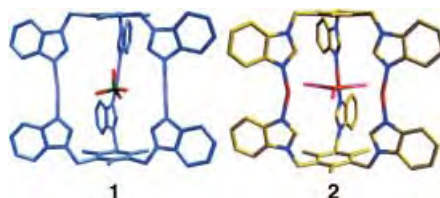
Kinetically Controlled Protonation of a Cyclic Phosphamethanide Complex to a PH-Phosphonium Ylide

Keywords: macrocyclic ligands • P ligands • substituent effects • tautomerism • ylides



Thermodynamically stable, but kinetically labile: Trigonal-prismatic M₃L₂ metallocages occur in [BF₄ C {Ag₃(MsTBim)₂}] (BF₄)₂ (**1**) and [CuI₃ C {Cu₃(MsTBim)₂}]₂ (Cu₂I₄) (**2**), the latter with an unprecedented metal-complex-host/metal-complex-guest arrangement. Large anions such as CF₃SO₃[−] or BPh₄[−] have to reside outside the cage facing its “windows”. MsTBim = 1,3,5-tris-(benzimidazol-1-ylmethyl)-2,4,6-trimethylbenzene.

Angew. Chem. **2002**, *114*, 3519–3523

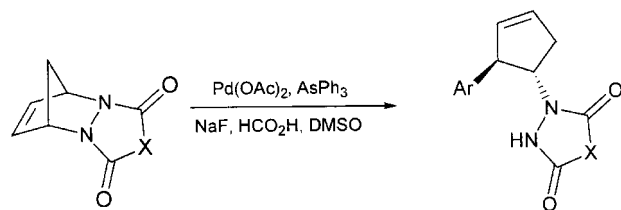


C.-Y. Su, Y.-P. Cai, C.-L. Chen, F. Lissner, B.-S. Kang,* W. Kaim* 3371–3375

Self-Assembly of Trigonal-Prismatic Metallocages Encapsulating BF₄[−] or CuI₃^{2−} as Anionic Guests: Structures and Mechanism of Formation

Keywords: cage compounds • copper • host–guest systems • self-assembly • solid-state structures

The product of a formal hydrazidoarylation of cyclopentadiene was obtained for the first time by palladium-catalyzed reaction of diaza[2.2.1]bicyclic alkenes with aryl halides in the presence of triphenylarsane, sodium fluoride, and formic acid under stereoselective cleavage of a C–N bond (see scheme).



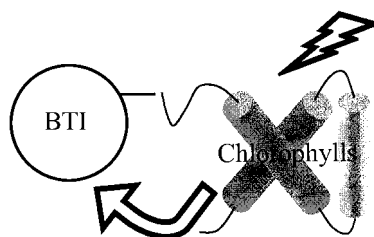
Angew. Chem. **2002**, *114*, 3523–3526

M.-L. Yao, G. Adiwidjaja,
D. E. Kaufmann* 3375–3378

Two-Step, Stereoselective
Hydrazidoarylation of 1,3-
Cyclopentadiene

Keywords: As ligands • fluoride •
hydrazide • hydroarylation • palladium

A simple model of a plant photo-system has been constructed from a recombinant light-harvesting chlorophyll *a/b* protein (LHCIIb) of the plant photosynthetic apparatus and a covalently coupled benzoylterrylene-3,4-dicarboximide dye (BTI) as an artificial energy trap (see picture). Up to 85% of the energy absorbed by LHCIIb are transferred to the acceptor.



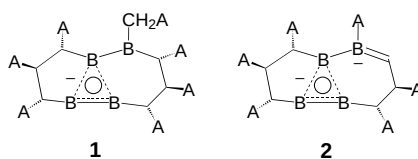
H. Wolf-Klein, C. Kohl, K. Müllen,
H. Paulsen* 3378–3380

Biomimetic Model of a Plant Photosystem
Consisting of a Recombinant Light-
Harvesting Complex and a Terryene Dye

Keywords: chlorophyll • fluorescence
spectroscopy • membrane proteins •
photosynthesis • polycycles

Angew. Chem. **2002**, *114*, 3526–3529

One extremely short and two relatively long B–B bonds are found for the B₃ ring of compounds **1** and **2**. This characteristic of three-membered, two-electron double aromatic compounds was predicted as early as 1994 and has now been experimentally realized for the first time. A = SiMe₃.



C. Präsang, A. Młodzianowska, Y. Sahin,
M. Hofmann, G. Geiseler, W. Massa,
A. Berndt* 3380–3382

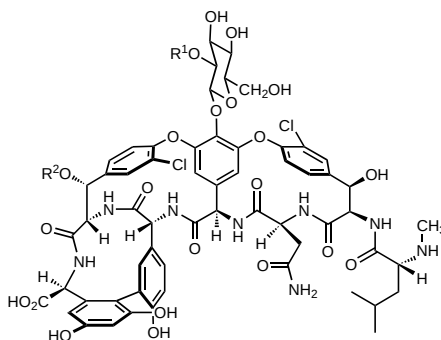
Triboracyclopropanates: Two-Electron
Double Aromatic Compounds with Very
Short B–B Distances

Keywords: aromaticity • boron • density
functional calculations • multicentered
bonds

Angew. Chem. **2002**, *114*, 3529–3531

Mutasynthesis—a very potent tool?

The two chlorine atoms attached to the aglycon of vancomycin-type glycopeptide antibiotics (see structure) have considerable influence on the antibiotic activity of each compound. By combining molecular genetic methods and chemical synthesis these chlorine atoms can be replaced by fluorine atoms. The described approach may also be applicable to modifying other parts of the glycopeptide molecule.



S. Weist, B. Bister, O. Puk, D. Bischoff,
S. Pelzer, G. J. Nicholson, W. Wohlleben,
G. Jung, R. D. Süssmuth* ... 3383–3385

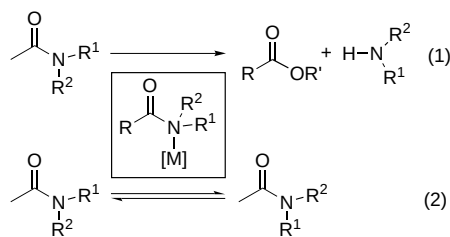
Fluorobalhimycin—A New Chapter in
Glycopeptide Antibiotic Research

Keywords: antibiotics • balhimycin •
glycopeptides • mutasynthesis • structure
elucidation

Angew. Chem. **2002**, *114*, 3531–3534

Unusual coordination compounds:

It has long been postulated that well-known and important reactions of tertiary amides such as C–N cleavage [Eq. (1)] and *cis*–*trans* isomerization [Eq. (2)] may proceed via nitrogen-coordinated metal complexes. We report the first evidence for a well-defined structure–function relationship in these unusual compounds.



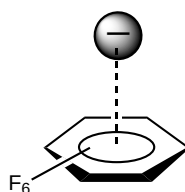
N. Niklas, F. W. Heinemann, F. Hampel,
R. Alsasser* 3386–3388

Activation of the Tertiary Carboxamide
C–N Bond in Werner Complexes:
A Classical Structure–Function
Relationship

Keywords: amides • cadmium • cleavage
reactions • coordination chemistry •
copper • isomerization

Angew. Chem. **2002**, *114*, 3535–3537

Hovering above the π -electron cloud, an anion positioned over hexafluorobenzene along the C_6 axis as shown here interacts with the permanent quadrupole of the arene. Crystallographic and computational evidence demonstrate that anion– π interactions exist and are energetically favorable.



D. Quiñonero, C. Garau, C. Rotger,
A. Frontera,* P. Ballester, A. Costa,
P. M. Deyà* 3389–3392

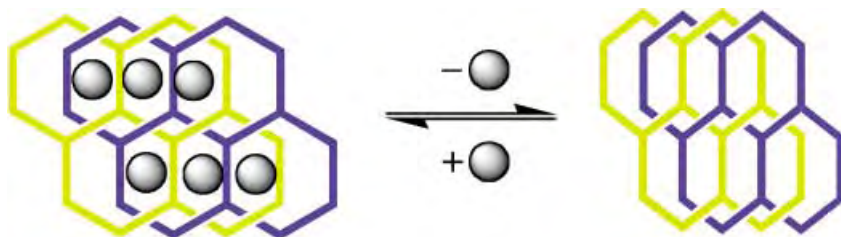
Anion– π Interactions: Do They Exist?

Keywords: ab initio calculations •
anions • noncovalent interactions • π
interactions

Angew. Chem. **2002**, *114*, 3539–3542



Double interpenetration: Guest molecules can control the formation of an unprecedented interlinked network consisting of zinc and a 3D tridentate ligand. The network shrinks when guest molecules are removed and swells when they are returned (see scheme).



K. Biradha, M. Fujita* 3392–3395

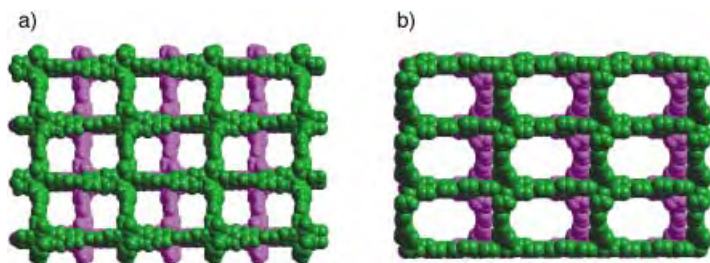
A Springlike 3D-Coordination Network
That Shrinks or Swells in a Crystal-to-
Crystal Manner upon Guest Removal or
Readsorption

Keywords: host-guest systems • solid-
state structures • X-ray diffraction •
zeolite analogues • zinc

Angew. Chem. **2002**, *114*, 3542–3545



Changing channels! The crystal-to-crystal sliding of a 2D network between two packing modes is triggered by the guest exchange of solvent molecules, and results in considerable difference in the channel dimensions ($a \rightarrow b$; see scheme).



K. Biradha, Y. Hongo,
M. Fujita* 3395–3398

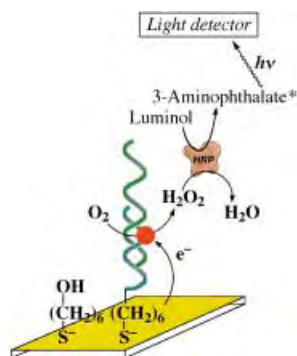
Crystal-to-Crystal Sliding of 2D
Coordination Layers Triggered by Guest
Exchange

Keywords: host-guest systems • nickel •
solid-state structures • X-ray diffraction •
zeolite analogues

Angew. Chem. **2002**, *114*, 3545–3548



Making light work for DNA detection: Amplified DNA detection is accomplished by doxorubicin intercalated into double-stranded DNA assembled on Au-electrodes. Stimulated electrogenerated biochemiluminescence or biocatalyzed precipitation of an insoluble product amplify the DNA sensing that is being transduced by light emission (see picture; HRP = horseradish peroxidase) or Faradaic impedance spectroscopy, respectively.



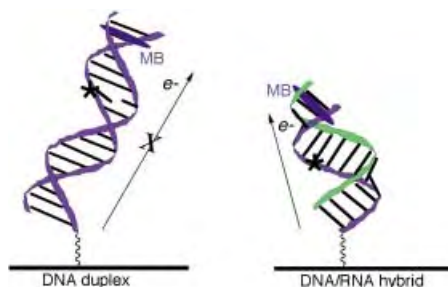
F. Patolsky, E. Katz,
I. Willner* 3398–3402

Amplified DNA Detection by
Electrogenerated Biochemiluminescence
and by the Catalyzed Precipitation of an
Insoluble Product on Electrodes in the
Presence of the Doxorubicin Intercalator

Keywords: biosensors • DNA
recognition • DNA •
electroluminescence • impedance
spectroscopy • intercalations

Angew. Chem. **2002**, *114*, 3548–3552

The preferred base-stacking orientation of a conformationally constrained nucleotide (3'-endo-locked) within DNA/DNA and DNA/RNA duplexes (see picture) was probed by charge transport through DNA-modified gold electrode surfaces. The conformation of the sugar is seen to sensitively determine the local stacking of the duplex. These results illustrate the utility of DNA-mediated charge transport through DNA-modified surfaces in characterizing small perturbations in DNA stacking and structure.



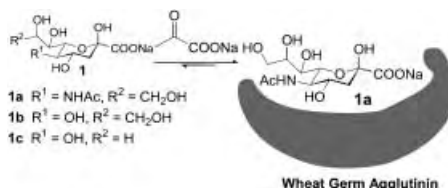
E. M. Boon, J. K. Barton,*
P. I. Pradeepkumar, J. Isaksson, C. Petit,
J. Chattopadhyaya* 3402–3405

An Electrochemical Probe of DNA
Stacking in an Antisense Oligonucleotide
Containing a C3'-endo-Locked Sugar

Keywords: antisense oligonucleotides •
charge transfer • DNA • DNA-modified
surfaces • nucleotides

Angew. Chem. **2002**, *114*, 3552–3555

Reversible formation of carbon-carbon bonds under physiological conditions by enzyme catalysis allows the generation and in situ screening of a dynamic mixture of biologically significant compounds. Generation of the dynamic library by incubation of the three sugars **1a–c** with two equivalents of sodium pyruvate in the presence of *N*-acetylneuraminic acid aldolase and wheat germ agglutinin resulted in amplification of sialic acid **1a** (see scheme).



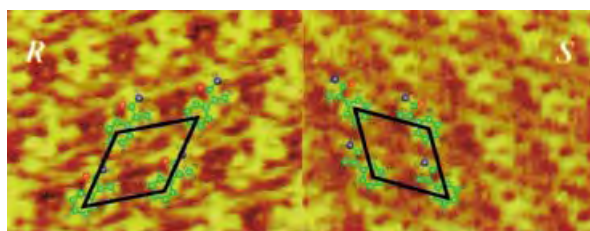
R. J. Lins, S. L. Flitsch,* N. J. Turner,*
E. Irving, S. A. Brown 3405–3407

Enzymatic Generation and In Situ
Screening of a Dynamic Combinatorial
Library of Sialic Acid Analogues

Keywords: aldolase • combinatorial
chemistry • dynamic libraries • enzymes •
sialic acid

Angew. Chem. **2002**, *114*, 3555–3557

Pricking the surface of chirality: The chirality of (*R*)- and (*S*)-2-phenylpropionamide molecules has been directly observed on Cu(111) in solution by using electrochemical scanning tunneling microscopy (see images). Around the chiral center, the methyl and CONH₂ groups maintain the chiral configuration, although the *R* and *S* molecules adsorb onto Cu(111) in the same (4 × 4) symmetry array.



Q.-M. Xu, D. Wang, L.-J. Wan,* C. Wang,
C.-L. Bai,* G.-Q. Feng,
M.-X. Wang* 3408–3411

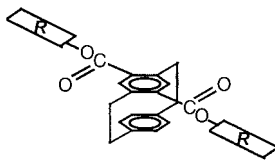
Discriminating Chiral Molecules of (*R*)-
PPA and (*S*)-PPA in Aqueous Solution by
ECSTM

Keywords: adsorption • chirality •
copper • scanning probe microscopy •
surface chemistry

Angew. Chem. **2002**, *114*, 3558–3561



The way in which chirality is introduced in a mesogenic molecule is important for determining the properties of the resultant liquid-crystalline material. The thermotropic liquid-crystalline compounds (see figure) based on planar, chiral [2.2]paracyclophane (PC) exhibit stable mesophases over a wide temperature range, while the mesophase type could be tuned by altering the nature of the substituents in the PC unit. The planar chiral PC derivatives also reveal a sufficiently high twisting ability in a nematic host.



Angew. Chem. **2002**, *114*, 3561–3564

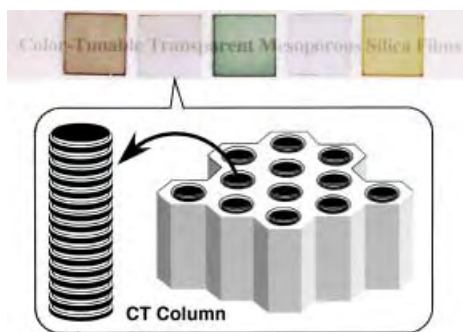
E. L. Popova, V. I. Rozenberg,
Z. A. Starikova, S. Keuker-Baumann,
H.-S. Kitzerow, H. Hopf* ... 3411–3414

Thermotropic Liquid Crystals from Planar Chiral Compounds: Optically Active Mesogenic [2.2]Paracyclophane Derivatives

Keywords: chiral resolution • chirality • cyclophanes • liquid crystals



Physical stabilization of triphenylene-based charge-transfer complexes by hexagonally aligned silica channels enables the preparation of color-tunable, highly transparent mesoporous silica films (see picture). The donor/acceptor molar ratio was varied over a wide range (1:1 to 9:1) with the included charge-transfer complexes exhibiting unique red-shifted absorption bands.



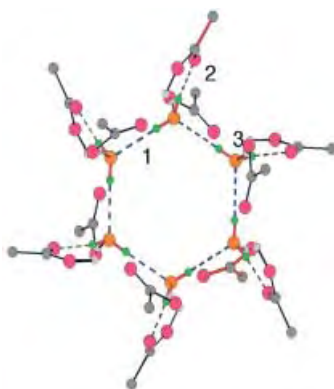
Angew. Chem. **2002**, *114*, 3564–3567

A. Okabe, T. Fukushima, K. Ariga,
T. Aida* 3414–3417

Color-Tunable Transparent Mesoporous Silica Films: Immobilization of One-Dimensional Columnar Charge-Transfer Assemblies in Aligned Silicate Nanochannels

Keywords: charge transfer • donor-acceptor systems • mesoporous materials • silicates • thin films

Trapped water: Six molecules of water are trapped in the crystal lattice of an organic supramolecular complex with bimesityl-3,3'-dicarboxylic acid in the form of a planar cyclic “ring”, which is the basic structural motif of Ice II. The water molecules of the hexamer (see picture) are associated in the crystal lattice by eighteen O–H···O hydrogen bonds.



Angew. Chem. **2002**, *114*, 3567–3570

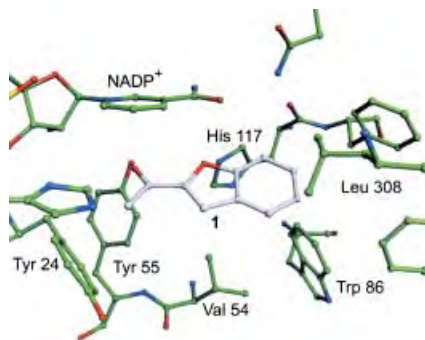
J. N. Moorthy,* R. Natarajan,
P. Venugopalan* 3417–3420

Characterization of a Planar Cyclic Form of Water Hexamer in an Organic Supramolecular Complex: An Unusual Self-Assembly of Bimesityl-3,3'-Dicarboxylic Acid

Keywords: carboxylic acids • cluster compounds • hydrogen bonds • supramolecular chemistry • water chemistry

Binding is good, displacing is better.

By adding a weakly binding reporter ligand to a mixture of protein and test compounds, NMR screening can identify strongly binding ligands by observing the displacement of the reporter ligand. For example, NMR screening identified, as a reporter ligand, a small fragment, 2-acetylbenzofuran (**1**, gray skeleton), which binds to the active site of 3 α -HSD. A molecular model of the complex between 3 α -HSD and **1** is shown.



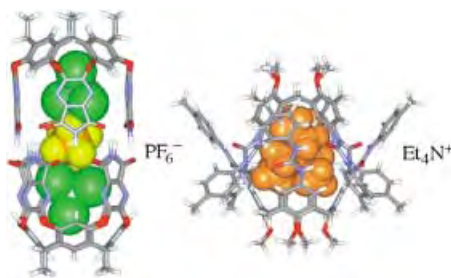
Angew. Chem. **2002**, *114*, 3570–3573

W. Jahnke,* P. Floersheim, C. Ostermeier,
X. Zhang, R. Hemmig, K. Hurth,
D. P. Uzunov 3420–3423

NMR Reporter Screening for the Detection of High-Affinity Ligands

Keywords: drug design • high-throughput screening • inhibitors • NMR spectroscopy • structure–activity relationships

Anions can be “isolated” along with one or two solvent molecules through reversible encapsulation. Cations and anions such as Et_4N^+ and PF_6^- can be further separated in solution by placement in different capsules (see picture).



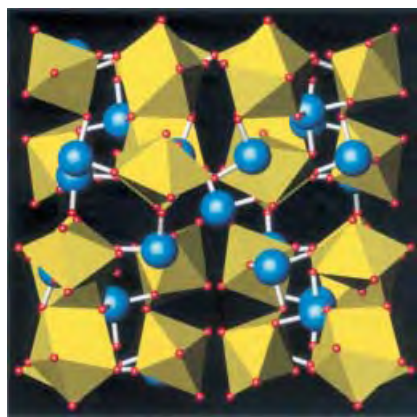
Angew. Chem. **2002**, *114*, 3573–3576

O. Hayashida, A. Shivanyuk,
J. Rebek, Jr. * 3423–3426

Molecular Encapsulation of Anions in a Neutral Receptor

Keywords: anions • host–guest systems • ion pairs • molecular recognition • self-assembly

Under hydrothermal reaction conditions, two new uranyl tellurites, $\text{Ti}_2[\text{UO}_2(\text{TeO}_3)_2]$ (**1**) and $\text{Na}_8[(\text{UO}_2)_6(\text{TeO}_3)_{10}]$ (**2**), have been prepared. These compounds display unusual bonding characteristics in that **1** contains $[\text{Te}_2\text{O}_6]^{4-}$ ions formed from two TeO_3^{2-} ions, and **2** (see picture) possesses a chiral three-dimensional network structure. The bonding and physical properties of these compounds are discussed.



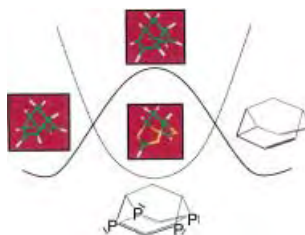
Angew. Chem. **2002**, *114*, 3576–3579

P. M. Almond, M. L. McKee,
T. E. Albrecht-Schmitt * 3426–3429

Unusual Uranyl Tellurites Containing $[\text{Te}_2\text{O}_6]^{4-}$ Ions and Three-Dimensional Networks

Keywords: actinides • hydrothermal synthesis • oxo ligands • tellurium

A homoaromatic C_{2v} -symmetric tetraphosphabarbaralane is the candidate for the first barbaralane derivative with “inverse” barrier to Cope rearrangement according to quantum chemical calculations (see scheme) as its C_s -symmetric form with localized double bonds is higher in energy.



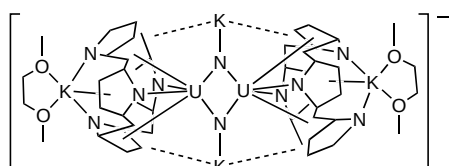
Angew. Chem. **2002**, *114*, 3579–3583

M. Reiher,* B. Kirchner * ... 3429–3433

A C_{2v} -Symmetric Barbaralane

Keywords: ab initio calculations • barbaralanes • fluxionality • rearrangement • phosphorus heterocycles

The importance of atmosphere: The reaction of $[(\text{Et}_8\text{-calix}[4]\text{tetrapyrrole})\text{U}(\text{dme})][\text{K}(\text{dme})]$ and $[\text{K}(\text{naphthalenide})]$ yields remarkable dimeric complexes, the structures of which are dependent on the atmospheric gases employed. Reaction under N_2 leads to dinitrogen cleavage and a $\mu\text{-K-N}$ bridged dimer (see picture). In contrast, reactions performed in an Ar atmosphere promoted solvent deoxygenation, as well as reaction with silicon grease. dme = 1,2-Dimethoxyethane.



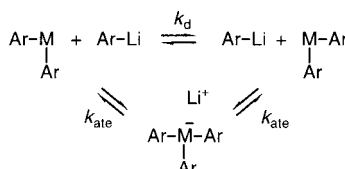
Angew. Chem. **2002**, *114*, 3583–3586

I. Korobkov, S. Gambarotta,*
G. P. A. Yap 3433–3436

A Highly Reactive Uranium Complex Supported by the Calix[4]tetrapyrrole Tetraanion Affording Dinitrogen Cleavage, Solvent Deoxygenation, and Polysilanol Depolymerization

Keywords: cleavage reactions • dimerization • mixed-valent compounds • nitrogen fixation • uranium

Li/Te exchange via the ate complex with no contribution from direct exchange (i.e., $k_d=0$) was demonstrated by NMR studies on an intermolecular reaction (see scheme; $\text{M}=\text{Te}$, $\text{Ar}=5$ -diphenylphosphanyl-2-thienyl). In contrast, in an intramolecular Li/Se exchange reaction, direct exchange bypasses the observable ate complex ($k_d \gg k_{\text{ate}}$).



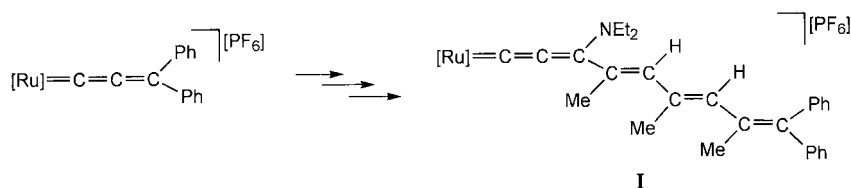
Angew. Chem. **2002**, *114*, 3586–3589

H. J. Reich,* M. J. Bevan,
B. Ö. Gudmundsson,
C. L. Puckett 3436–3439

Are Ate Complexes True Intermediates in Lithium–Metalloid Exchange? Subtle Effects of Ion-Pair Structure in Lithium–Tellurium and Lithium–Selenium Exchange Reactions

Keywords: ate complexes • lithiation • NMR spectroscopy • selenium • tellurium

Three-fold sequential insertion of the ynamine $\text{MeC}\equiv\text{CNEt}_2$ into ruthenium(II) allenylidene complexes leads to the stereoselective formation of the polyunsaturated complex **1**.



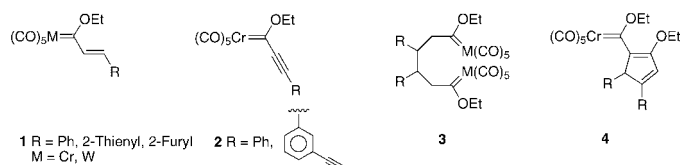
Angew. Chem. **2002**, *114*, 3589–3592

S. Conejero, J. Díez, M. P. Gamasa,
J. Gimeno,*
S. García-Granda 3439–3442

Generation of Polyunsaturated Cumulene Chains by Unprecedented Insertions of the Ynamine $\text{MeC}\equiv\text{CNEt}_2$ in Ruthenium(II) Allenylidene Complexes

Keywords: allenylidene ligands • insertion • ruthenium • cumulenes • ynamines

Cunning carbene chemistry: Potassium-graphite (C_8K) promotes the self condensation (to give compounds **3**) and self-condensation-cycloisomerization (to give compounds **4**) of α,β -unsaturated Fischer carbene complexes **1** and **2**, respectively. The reaction occurs through radical-anion intermediates that dimerize in a tail-to-tail fashion.



Angew. Chem. **2002**, *114*, 3592–3595

M. A. Sierra,* P. Ramírez-López,
M. Gómez-Gallego, T. Lejon,
M. J. Mancheño 3442–3445

C_8K -Promoted Self-Condensation and Self-Condensation-Cycloisomerization Reactions of α,β -Unsaturated Fischer Carbene Complexes

Keywords: carbene ligands • C–C coupling • chromium • dimerization • radical ions • tungsten

A nanometer-sized pipet that really works! A tiny glass pipet (shown in the figure; scale bar = $1\ \mu\text{m}$) filled with an electrolyte solution acts as the tip for scanning electrochemical microscopy. It can be used to evaluate the kinetic behavior of a recycling of charge between two molecular interfaces, such as the immiscible phases water and 1,2-dichloroethane.



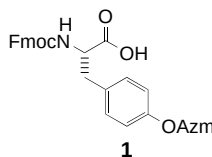
Angew. Chem. **2002**, *114*, 3595–3598

P. Sun, Z. Zhang, Z. Gao,
Y. Shao* 3445–3448

Probing Fast Facilitated Ion Transfer across an Externally Polarized Liquid–Liquid Interface by Scanning Electrochemical Microscopy

Keywords: electrochemistry • interfaces • ion transfer • nanostructures • scanning probe microscopy

Reversible blockage of the tyrosine phenol group leads to an efficient solid-phase strategy for the synthesis of sulfated peptides using an azidomethyl (Azm) protected tyrosine building block (**1**). The protected tyrosine derivative is compatible with standard conditions for amide-bond formation. A monosulfated and a trisulfated octapeptide fragment were assembled using this strategy.



Angew. Chem. **2002**, *114*, 3599–3601

T. Young, L. L. Kiessling* 3449–3451

A Strategy for the Synthesis of Sulfated Peptides

Keywords: lectins • peptides • protecting groups • solid-phase synthesis • sulfonation

Thermal decomposition of the respective trisulfides in a reducing (H_2 /inert gas) atmosphere has enabled nanotubes of HfS_2 , ZrS_2 , and TiS_2 to be synthesized and characterized. The dimensions of the nanotubes formed depend on the Group 4 metal used. The transmission electron micrograph image shows nanotubular structures of HfS_2 with outer diameters of 55–60 nm and inner core diameters of 17–30 nm.



Angew. Chem. **2002**, *114*, 3601–3604

M. Nath, C. N. R. Rao* 3451–3454

Nanotubes of Group 4 Metal Disulfides

Keywords: electron microscopy • hafnium • nanostructures • nanotubes • X-ray diffraction

An exchange is better than a rest: An NMR screening method is described which facilitates the screening of compound mixtures for components that bind protein drug targets. The approach allows detection of active molecules thanks to a “probe” molecule, which competes with a library of potential ligands for binding sites on a targeted protein. The whole spectrum of active ligands, including those displaying either very fast or very slow exchange behavior, are equally susceptible to detection by this method.

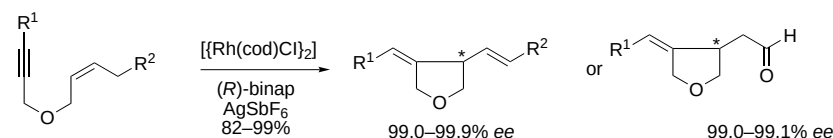
Angew. Chem. **2002**, *114*, 3604–3607

A. H. Siriwardena,* F. Tian, S. Noble, J. H. Prestegard 3454–3457

A Straightforward NMR-Spectroscopy-Based Method for Rapid Library Screening

Keywords: carbohydrates • competitive binding • drug design • high-throughput screening • NMR spectroscopy

Over 99 % ee was obtained for all the tested substrates in a Rh-catalyzed Alder–ene reaction. Simply mixing air-stable, commercially available $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ (cod = 1,5-cyclooctadiene) and 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (binap) at room temperature afforded functionalized and chiral tetrahydrofurans in high yields with high efficiency (turnover frequency: 1500 h^{-1}). The catalyst loading was as low as 0.8 mol %.



R^1 = aryl, alkyl, carbonyl, alkoxy, hydroxy
 R^2 = H, alkyl, acetoxy, alkoxy

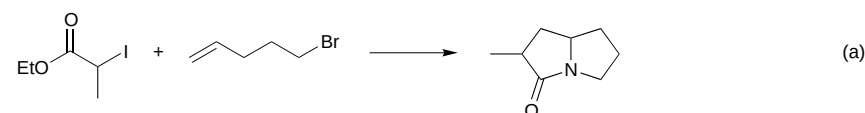
Angew. Chem. **2002**, *114*, 3607–3610

A. Lei, M. He, S. Wu, X. Zhang* 3457–3460

Highly Enantioselective Rh-Catalyzed Intramolecular Alder–Ene Reactions for the Syntheses of Chiral Tetrahydrofurans

Keywords: enantioselectivity • heterocycles • homogeneous catalysis • rhodium • synthetic methods

A one-pot intermolecular radical carboazidation of alkenes is reported. The utility of the reaction is demonstrated by the development of a three-component preparation of pyrrolidinones, pyrrolizidinones [Eq. (a)], and indolizidinones starting from benzenesulfonyl azide, terminal alkenes, and 2-iodoesters.



Angew. Chem. **2002**, *114*, 3611–3612

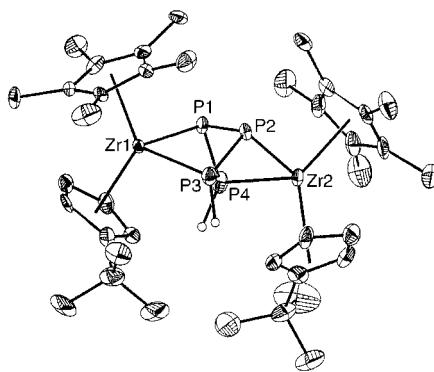
P. Renaud,* C. Ollivier, P. Panchaud 3460–3462

Radical Carboazidation of Alkenes: An Efficient Tool for the Preparation of Pyrrolidinone Derivatives

Keywords: alkaloids • aminations • azides • C–C coupling • radical reactions

Hydrogenation of white phosphorus

(P₄) has been achieved under ambient conditions by reaction with [Zr(η^5 -C₅Me₅)(η^5 -C₅H₄tBu)H₂] to give [[Zr(η^5 -C₅Me₅)(η^5 -C₅H₄tBu)]₂-(P₄)H₂] (see picture). Preliminary data suggest that the reaction proceeds by a cooperative reductive elimination/insertion sequence involving two zirconium centers.



P. J. Chirik,* J. A. Pool,
E. Lobkovsky 3463–3465

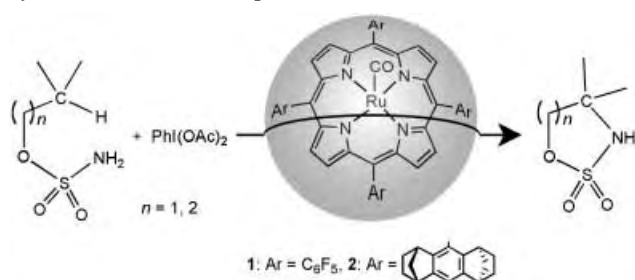
Functionalization of Elemental
Phosphorus with [Zr(η^5 -C₅Me₅)-
(η^5 -C₅H₄tBu)H₂]₂

Keywords: elimination • hydrogenation •
insertion • phosphorus • zirconium

Angew. Chem. **2002**, *114*, 3613–3615



Virtually complete diastereoselectivity is observed in the intramolecular amidation of saturated C–H bonds, catalyzed by the ruthenium porphyrin catalyst **1** or **2**. Reactions of sulfamate esters with PhI(OAc)₂ in the presence of **1** or **2** afforded cyclic sulfamidates in up to 87% ee.



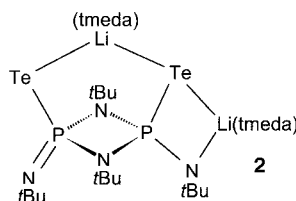
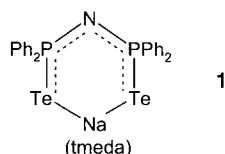
Angew. Chem. **2002**, *114*, 3615–3618

J.-L. Liang, S.-X. Yuan, J.-S. Huang,
W.-Y. Yu, C.-M. Che* 3465–3468

Highly Diastereo- and Enantioselective
Intramolecular Amidation of Saturated
C–H Bonds Catalyzed by Ruthenium
Porphyrins

Keywords: asymmetric catalysis •
cyclization • porphyrinoids • ruthenium •
sulfamidates

Oxidation with elemental tellurium of Na[Ph₂PNPPh₂] and [Li(thf)₂][tBuNP(μ -NtBu)₂PNtBu] in the presence of tetramethylethylenediamine (tmeda) provides access to anionic imido (**1**) and anionic tellurophosphoranes (**2**). Complex **2** displays a novel tetradentate N,Te,Te,Te' bonding mode.



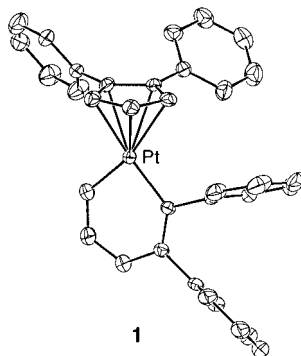
G. G. Briand, T. Chivers,*
M. Parvez 3468–3470

A New Approach to Metalated Imido and
Amido Tellurophosphoranes

Keywords: alkali metals • N ligands •
N,P ligands • tellurium

Angew. Chem. **2002**, *114*, 3618–3620

No longer limited to the classical examples of osmium- and iridium-based metallaaromatics, treatment of [Pt(cod)Cl₂] with a nucleophilic 3-vinylcyclopropene yields platinabenzene **1**, which has been fully characterized by NMR spectroscopy and X-ray crystallography.



V. Jacob, T. J. R. Weakley,
M. M. Haley* 3470–3473

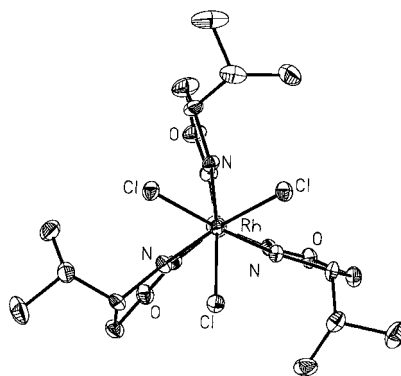
Metallabenzenes and Valence Isomers:
Synthesis and Characterization of a
Platinabenzene

Keywords: aromaticity • metallacycles •
platinum • structure elucidation

Angew. Chem. **2002**, *114*, 3620–3623

A new class of tripodal ligands, chiral 1,1,1-tris(oxazoliny)ethane derivatives, has been synthesized by using a *modular* approach by coupling of mono- with bisoxazoline derivatives. This method allows the facile access to symmetrically (C_3 -chiral, as shown for the rhodium complex) or unsymmetrically substituted (C_1 -chiral) ligands. Their copper(I) complexes have been used as catalysts in the asymmetric cyclopropanation of styrene.

Angew. Chem. **2002**, *114*, 3623–3625

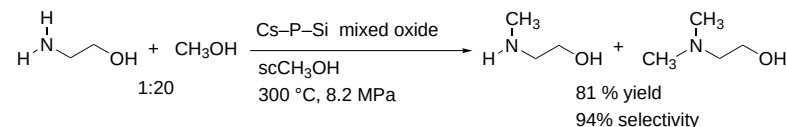


S. Bellemin-Laponnaz,
L. H. Gade* 3473–3475

A Modular Approach to C_1 and C_3 Chiral N-Tripodal Ligands for Asymmetric Catalysis

Keywords: asymmetric catalysis • chirality • N,O ligands • tripodal ligands

The unique properties of supercritical fluids can be exploited for fine-tuning product selectivity. Under the conditions listed for the N-methylation of amino alcohols (see scheme) over solid acid–base bifunctional catalysts, the total yield and product selectivity could be improved. Enhanced product selectivity might be attributed to the milder reaction conditions possible with supercritical methanol, as well as the increased concentration of methanol on the catalyst.



Angew. Chem. **2002**, *114*, 3626–3629

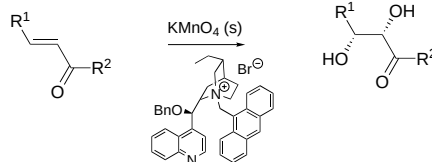
T. Oku, T. Ikariya* 3476–3479

Enhanced Product Selectivity in Continuous N-Methylation of Amino Alcohols over Solid Acid–Base Catalysts with Supercritical Methanol

Keywords: alkylation • amino alcohols • heterogeneous catalysis • supercritical fluids



Enantiomerically enriched 1,2-diols can be prepared, in good enantiomeric excesses, by using a novel asymmetric dihydroxylation of enones with permanganate under phase-transfer conditions (see scheme: e.g. $R^1 = n\text{Bu}$, $R^2 = (p\text{-OMe})\text{C}_6\text{H}_4$).



R. A. Bhunnoo, Y. Hu, D. I. Lainé,
R. C. D. Brown* 3479–3480

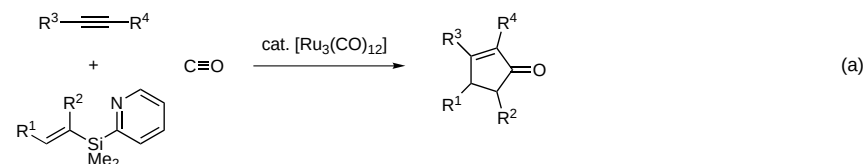
An Asymmetric Phase-Transfer Dihydroxylation Reaction

Keywords: asymmetric synthesis • dihydroxylation • diols • oxidation • phase-transfer catalysis

Angew. Chem. **2002**, *114*, 3629–3630



Now even unstrained alkenes can be used in catalytic intermolecular Pauson–Khand reactions [Eq. (a)]. This is made possible by the use of the directing group dimethyl(2-pyridyl)silyl, which can be easily removed at the end of the reaction. Furthermore, one observes completely regioselective incorporation of substituents at the 4- and 5-positions of the 2-cyclopentenone structure.



Angew. Chem. **2002**, *114*, 3631–3634

K. Itami,* K. Mitsudo,
J.-i. Yoshida* 3481–3484

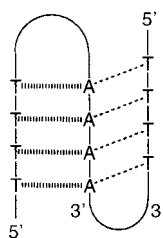
A Pyridylsilyl Group Expands the Scope of Catalytic Intermolecular Pauson–Khand Reactions

Keywords: alkenes • alkynes • cycloadditions • homogeneous catalysis • silanes



Exciting DNA threesome: Time-resolved transient absorption spectroscopy has been used to study electron-transfer processes between an excited-state electron acceptor and a ground-state electron donor, separated by a variable number of T:A·T triplet steps in triplex DNA (see figure). The formation and decay of both the acceptor anion radical and donor cation radical can be resolved. Electron tunneling is more effective at longer acceptor–donor distances in triplex than in duplex DNA.

Angew. Chem. **2002**, *114*, 3635–3637



F. D. Lewis,* Y. Wu, R. T. Hayes,
M. R. Wasielewski * 3485–3487

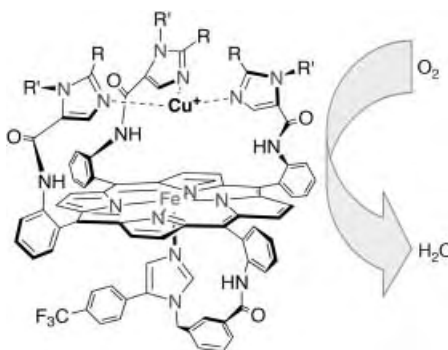
DNA-Mediated Electron Transfer across
Synthetic T:A·T Triplex Structures

Keywords: DNA structures • electron transfer • fluorescence spectroscopy • hole transport • time-resolved spectroscopy



Close structural analogues (see picture) of the O₂-reducing site of terminal oxidases dispersed in a phospholipid reduce O₂ at physiological potentials and do not release toxic partially reduced oxygen by-products, even when electron flux is diffusion-limited.

Angew. Chem. **2002**, *114*, 3637–3639



J. P. Collman,* R. Boulatov 3487–3489

Electrocatalytic O₂ Reduction by
Synthetic Analogues of the Heme/Cu Site
of Cytochrome Oxidase Incorporated in a
Lipid Film

Keywords: bioinorganic chemistry • electrochemistry • oxidoreductases • phospholipids • porphyrinoids



Casting silica nets: By repeated “nanocasting” it is possible to first obtain a negative of the SBA-15 structure, known as CMK-3, which is then used to produce another nanocast by impregnation with tetraethoxysilane and condensation. After calcination to remove the carbon, an ordered mesoporous silica is obtained, called NCS-1 (see scheme). This pathway could be generalized to allow also the synthesis of other ordered oxides.

Angew. Chem. **2002**, *114*, 3639–3642



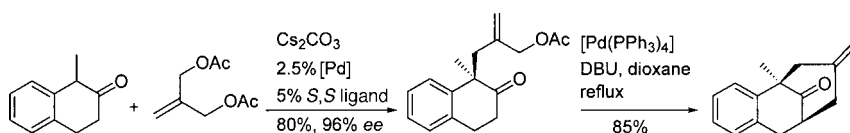
A.-H. Lu, W. Schmidt, A. Taguchi,
B. Spliethoff, B. Tesche,
F. Schüth * 3489–3492

Taking Nanocasting One Step Further:
Replicating CMK-3 as a Silica Material

Keywords: mesoporous materials • nanocasting • silicon • zeolite analogues



Quaternary centers can be created asymmetrically in high enantiomeric excess by the proper choice of ligand and metal cation in the Pd-catalyzed asymmetric allylic alkylation of α -aryl ketones. A broad range of ketone enolates can be tolerated in the reaction, as illustrated by the synthesis of conformationally constrained β -tetralone in 96% *ee* (see scheme, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene).



Angew. Chem. **2002**, *114*, 3642–3645

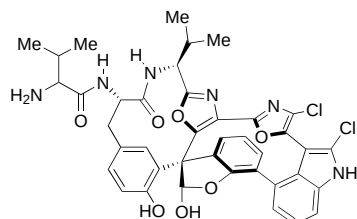
B. M. Trost,* G. M. Schroeder,
J. Kristensen 3492–3495

Palladium-Catalyzed Asymmetric Allylic
Alkylation of α -Aryl Ketones

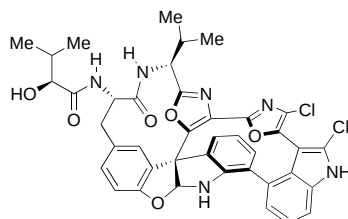
Keywords: aryl ketones • asymmetric catalysis • enantioselectivity • ligand effects • palladium



Ever since its discovery in 1991, diazonamide A (**1**) has been eyed by synthetic chemists as a potential target because of its puzzling molecular architecture and potent biological activity. The race to synthesize this intriguing natural product was further complicated at the end of last year when a synthesis was completed only to prove that the originally proposed structure was in error. The new structural assignment (**2**) required retooling of synthetic strategies toward the new target. A total synthesis of diazonamide A has now been achieved confirming its newly proposed structure.



1: original structure of diazonamide A



2: revised structure of diazonamide A

Angew. Chem. **2002**, *114*, 3645–3649

K. C. Nicolaou,* M. Bella, D. Y.-K. Chen,
X. Huang, T. Ling,
S. A. Snyder 3495–3499

Total Synthesis of Diazonamide A

Keywords: antitumor agents •
cyclization • macrocycles • natural
products • total synthesis



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

* Author to whom correspondence should be addressed



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A Hard Look at Soft Matter

Patricia E. Cladis 3505

• VIPs	3300	• Keywords	3506
• <i>Angewandte's</i> Sister-Journals	3315–3317	• Authors	3507
• Classified	3118	• Preview	3508

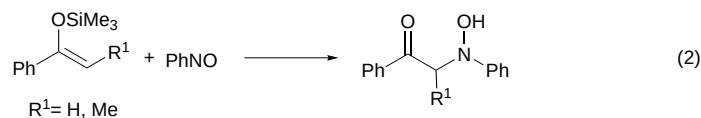
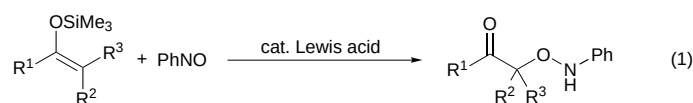
Issue 17, 2002 was published online on August 30.

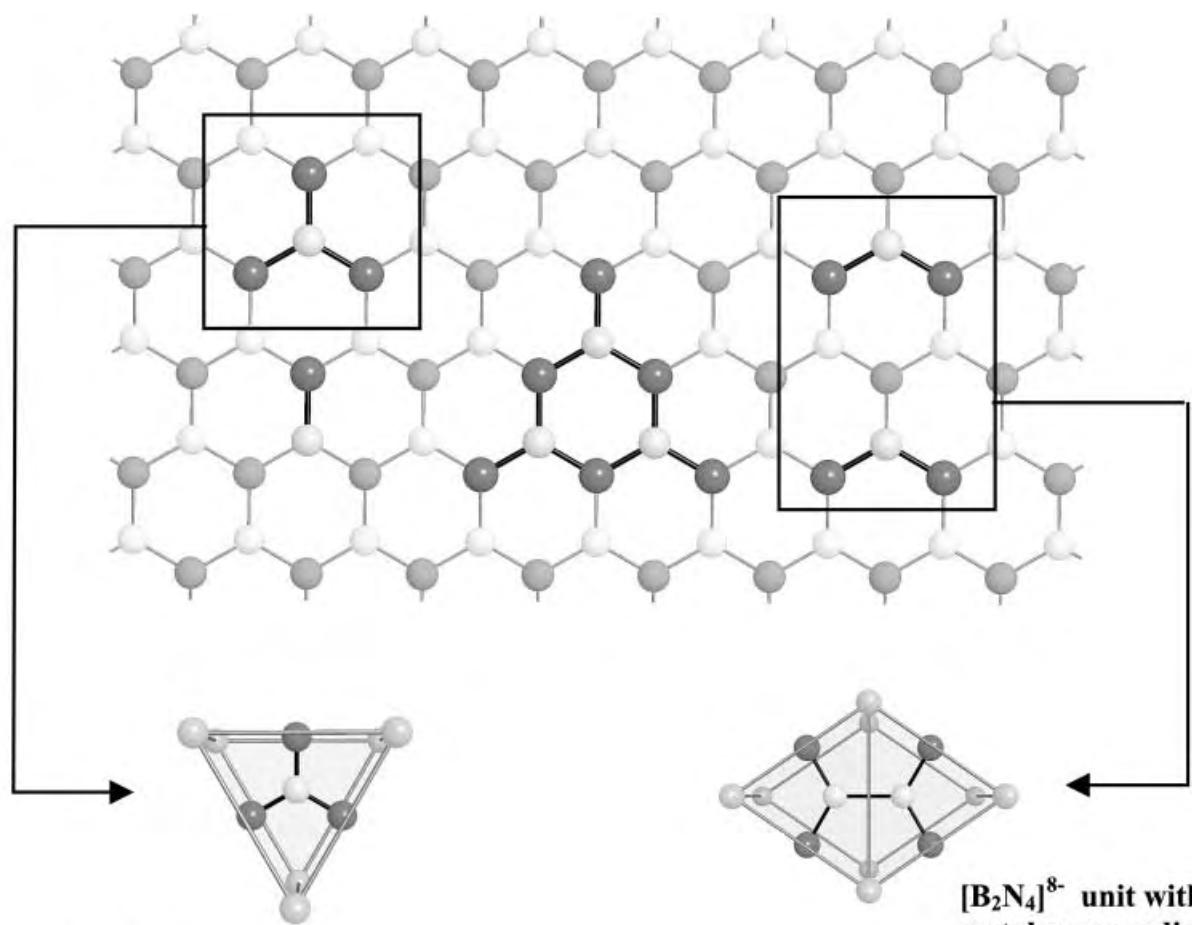
Don't forget all the Tables of Contents from 1998 onwards may be still found on the WWW under:
<http://www.angewandte.org>

CORRIGENDA

In the Communication by **J. Rademann** and **M. Barth** in issue 16, **2002**, pp. 2975–2978, the single-letter codes for the amino acids of peptide **15** (H-Trp-Glu-Ile-His-Asn-Ala-Cys-His-Thr-Ser-Thr-Ala-Gly-OH), WEIHNACHTSTAG, was erroneously printed as “Christmas”. The editorial office apologizes for this error.

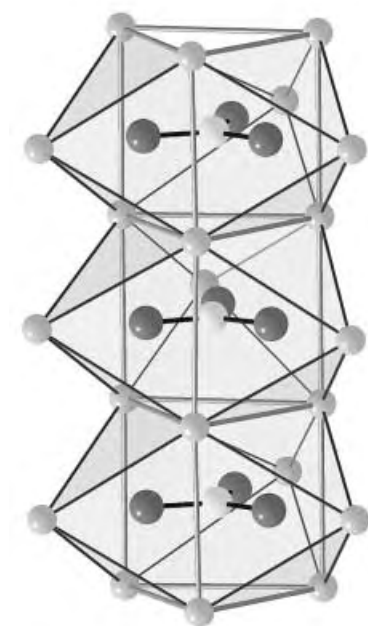
In the Communication by **N. Momiyama** and **H. Yamamoto**, in issue 16, **2002**, pp. 2986–2988, Equations 1 and 2 (shown below) were omitted in the final print version. The correct version of this paper can be found on the Wiley InterScience Website at www.interscience.wiley.com. The editorial office apologizes for this error.



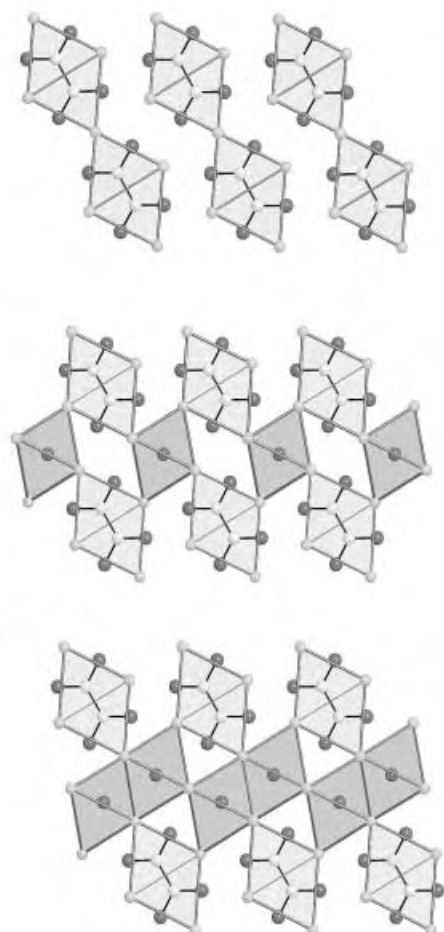
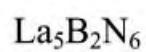
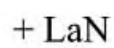
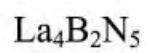
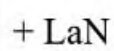
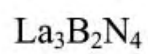


[BN₃]⁶⁻ unit with metal surroundings

[B₂N₄]⁸⁻ unit with metal surroundings



[La_{6/2}La₃(BN₃)] column from La₆(B₃N₆)(BN₃)N



Nitridoborates of the Lanthanides: Synthesis, Structure Principles, and Properties of a New Class of Compounds

Björn Blaschkowski, Haipeng Jing, and H.-Jürgen Meyer*

Investigations of the nitridoborates of lanthanides (Ln) have progressed significantly during the last few years. New compounds have been synthesized and characterized and are presented here together with some of their properties. Currently two distinct methods serve for the preparation of nitridoborate compounds; either hexagonal boron nitride undergoes a fragmentation through the reaction with

LnN, or dinitridoborate ions are converted into other nitridoborate ions. Lanthanide nitridoborates contain molecular anions such as $[\text{BN}]^{n-}$, $[\text{BN}_2]^{3-}$, $[\text{B}_2\text{N}_4]^{8-}$, $[\text{B}_3\text{N}_6]^{9-}$, and $[\text{BN}_3]^{6-}$ which may occur in combinations with other nitridoborates or with additional nitride ions. In crystal structures of lanthanide nitridoborates these anions are arranged in layers and are surrounded by metal atoms in a character-

istic fashion. Terminal N atoms are capped by metal atoms forming a square-pyramid, and B atoms prefer a trigonal-prismatic environment of metal atoms. Nitridoborates form saltlike as well as metal-rich compounds and have the potential to show a lot of what are considered to be important solid-state properties, thus they have a good chance to establish their position within the group of relevant materials.

1. Introduction

The discovery of new materials always raises hopes for improved or combined material properties. Many metal borides and nitrides are chemically, thermally, and mechanically very stable or show good electrical conductivities. What should one therefore expect for ternary compounds in the system metal–B–N?

The first nitridoborate compounds known were Li_3BN_2 and alkaline-earth metal (E) compounds of the type $\text{E}_3(\text{BN}_2)_2$, the BN_2 anions of which were characterized by vibrational spectroscopy.^[1] Several years later single-crystal X-ray investigations were reported for Li_3BN_2 ^[2] and $\text{Sr}_3(\text{BN}_2)_2$.^[3] The alkaline-earth-metal nitrides E_3N were tested (as well as alkaline-earth metals) as catalysts for high-pressure conversions of hexagonal boron nitride (h-BN) into its cubic modification. Because alkaline-earth-metal nitrides (and alkaline-earth metals themselves) react with h-BN to form nitridoborates, the nitridoborates are believed to be particularly important in this conversion as they can form an eutectic mixture with BN.^[4, 5] Since then, numerous phase

equilibria in the ternary system metal–B–N have been examined, also in regard to this application.^[6, 7]

The elements B and N show different coordination geometries in structures. In metal borides the trigonal-prismatic arrangement of metal atoms about the boron atom dominates. In metal nitrides the nitrogen atom is surrounded predominantly octahedrally by metal atoms. A similar picture becomes apparent for the structural preferences of the anions in the system metal–B–N.

For ternary metal–B–N compounds the different interactions between metal and boron, metal and nitrogen, as well as boron and nitrogen have to be considered. Depending on the type of the metal atoms we can distinguish three groups of metal–B–N compounds which are presented here.

1.1 Boride–Nitride Compounds of the Transition Metals

Transition metals are known to form numerous stable binary boride and nitride compounds. However, combinations of transition metals with boron and nitrogen are rare. Solid-state reactions between Ti powder and BN yield TiN and TiB_2 .^[8] Reactions of metal borides with nitrogen, or of metal nitrides with boron lead to compounds similar to alloys with a low degree of substitution.^[9]

Boride–nitride compounds contain no bonds between B and N atoms. Their structures of the formula type M_2BN ($\text{M} = \text{Mo}, \text{Nb}$)^[10] combine structural characteristics typical of

[*] Prof. Dr. H.-J. Meyer, B. Blaschkowski, H. Jing
Institute of Inorganic Chemistry
University of Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49) 7071-29-5702
E-mail: juergen.meyer@uni-tuebingen.de

metal borides and metal nitrides. As in numerous metal nitride compounds the nitrogen atoms occupy octahedral holes (Figure 1), the boron atoms typically reside inside a trigonal-prismatic arrangement of metal atoms. In addition, the boron atoms are arranged to form infinite kinked chains

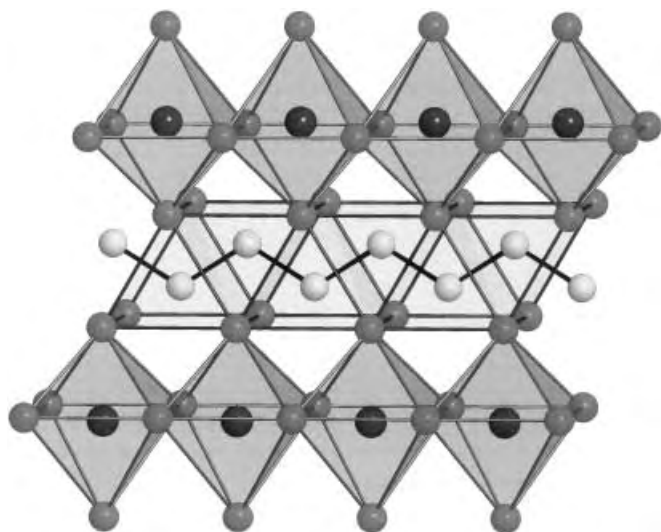


Figure 1. Section from the structure of Nb_2BN with N atoms (black) in the octahedral holes and the trigonal-prismatic arrangement of Nb atoms (gray) around the B atoms (white).

(B–B = 184 pm in Nb_2BN). Similar chains of boron atoms are known from structures of $\text{CrB}^{[11]}$ and FeB .

1.2 Nitridoborates of the Alkaline and Alkaline-Earth Metals

Alkaline and alkaline-earth metals form saltlike compounds with the linear dinitridoborate ion.^[12] The $[\text{NBN}]^{3-}$ ion contains B=N bonds with bond lengths of approximately 135 pm and is isoelectronic to $[\text{C}_3]^{4-}$ (C–C bond length 135 pm in $\text{Ca}_3\text{Cl}_2\text{C}_3^{[13]}$ and 133 pm in $\text{Mg}_2\text{C}_3^{[14]}$), $[\text{CBN}]^{4-}$ (C–B bond length 144 pm, B–N bond length 138 pm in $\text{Ca}_3\text{Cl}_2\text{CBN}^{[15]}$), and CO_2 . Among the simplest examples of compounds with dinitridoborate ions are Li_3BN_2 ,^[2] Na_3BN_2 ,^[16] and compounds with the general formula $\text{E}_3(\text{BN}_2)_2$ with E = Ca, Sr, Ba^[3, 17–19] and Eu^[20] (Figure 2).

The two known phases for Li_3BN_2 differ only by the relative arrangements of their Li^+ and $[\text{BN}_2]^{3-}$ constituents. When $\alpha\text{-Li}_3\text{BN}_2$ is heated to 862 °C it transforms into $\beta\text{-Li}_3\text{BN}_2$ which melts at 916 °C.^[21] Na_3BN_2 was prepared through a high-pressure synthesis. Nitridoborate–nitride compounds of the type $\text{E}_3(\text{BN}_2)\text{N}$ are verified for E = Mg^[22] and Ca.^[23] $\text{Mg}_3(\text{BN}_2)\text{N}$ can be transformed into a high-pressure modification, with a structure (space group $Pmmm$)^[24] topologically identical to the structure of $\text{Ca}_3(\text{BN}_2)\text{N}$ (space group $P4/mmm$) shown in Figure 2.

Björn Blaschkowski, born 1965 in Cologne, studied chemistry in Tübingen, where he finished his degree in 1998 with work on high-temperature superconductors. Afterwards he worked in the group of Professor Sibylle Kemmler-Sack on the development of HTSL bands then in 1999 joined the group of Professor H.-Jürgen Meyer at the Institute for Inorganic Chemistry in Tübingen. There he is working on his PhD thesis in the field of syntheses and characterization of ternary and quaternary nitridoborates.



B. Blaschkowski



H. Jing



H.-J. Meyer

Haipeng Jing, born 1953 in the P.R. of China, studied chemistry first at the Northwest University of Xi'an in China, then at the University of Tübingen in Germany. From 1997 to 2001 he worked on his PhD thesis entitled “Lanthannitridoborate(nitride)s” in the group of Prof. H.-Jürgen Meyer at the Institute of Inorganic Chemistry in Tübingen.

H.-Jürgen Meyer, born 1958 in Braunschweig, received his doctorate in 1987 at the Technical University of Berlin with Professor Joachim Pickardt. In the following two years he worked on metal-rich halides of Lanthanide elements at the Ames Laboratory (Ames, Iowa) with Professor John D. Corbett and on band-structure calculations at the Baker Laboratory of the Cornell University (Ithaca, New York) with Professor Roald Hoffmann. In 1989 he moved as a DFG scholarship holder to the University of Hannover, where he completed his habilitation in 1993. As a Heisenberg fellow he was offered professorships at the Universities of Bonn and Tübingen in 1996 and accepted the position in Tübingen. His research interests include syntheses, reactivities, structures, and electronic properties of solids. Present research topics are metal-rich halides, oxocuprates, and metal-C-B-N compounds.

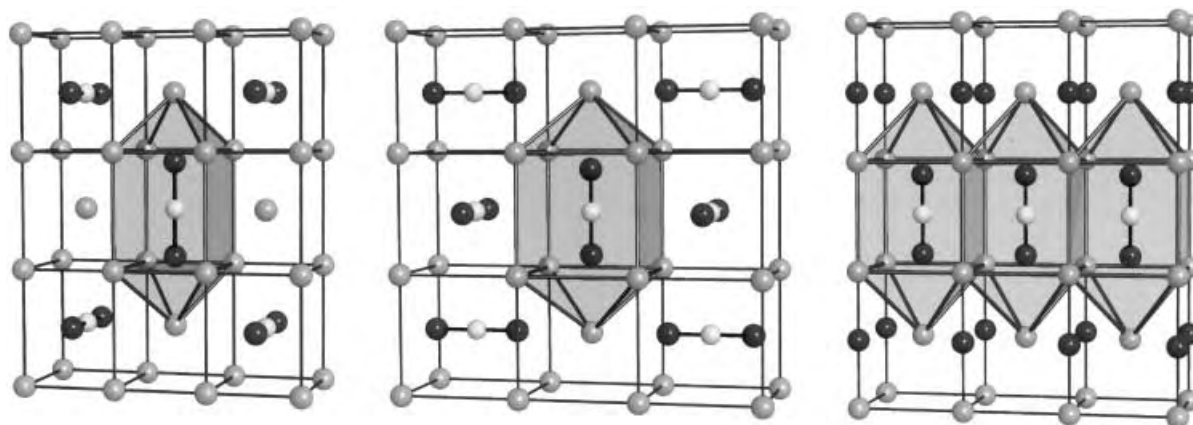


Figure 2. Sections from the structures of α - Li_3BN_2 (left), $\text{E}_3(\text{BN}_2)_2$ with $\text{E} = \text{Ca}, \text{Sr}, \text{Ba}, \text{Eu}$ (center), and $\text{Ca}_3(\text{BN}_2)_2$ (right).

Some of these dinitridoborate compounds have shown their potential as reagents in chemical reactions. Thus $\text{Ca}_3(\text{BN}_2)_2$ and $\text{Mg}_3(\text{BN}_2)_2$ are used as flux catalysts for conversions of h-BN into its cubic modification.^[4, 5] Li_3BN_2 , as shown later, has proven to be worthwhile for the synthesis of nitridoborates of the lanthanides, particularly of lanthanum. Our newest experiments point out that nitridoborates and their derivatives (Li_2CN_2 , $\text{Ca}_3\text{Cl}_2\text{CBN}$) can be considered as suitable starting materials for the synthesis of nonmetallic BN, CN, and CBN materials.^[25]

1.3 Nitridoborate Compounds of Lanthanides

Nitridoborate compounds contain anionic BN_x units with terminal N atoms. Until recently, nitridoborate compounds of the lanthanides were examined only selectively. In this process, the compounds $\text{Ln}_3\text{B}_2\text{N}_4$ ($\text{Ln} = \text{La}, \text{Ce}, \text{Pr}, \text{Nd}$) were characterized by powder neutron diffraction.^[26] For LnBN_2 ($\text{Ln} = \text{Pr}, \text{Nd}, \text{Sm}, \text{Gd}$) only PrBN_2 has been characterized by means of single-crystal X-ray analysis.^[27] Compounds of the type $\text{Ln}_3\text{B}_2\text{N}_4$ contain $[\text{B}_2\text{N}_4]^{8-}$ ions, which are structurally analogous to oxalate ions. The formula type LnBN_2 can be written alternatively as $\text{Ln}_3\text{B}_3\text{N}_6$ to take into account the presence of cyclic $[\text{B}_3\text{N}_6]^{9-}$ ions. Based on a single-crystal X-ray analysis the structure of the nitridoborate nitride $\text{Ce}_{15}\text{B}_8\text{N}_{25}$ ^[28] was determined which (in agreement with the structure of $\text{Ce}_{15}(\text{BN}_3)_8\text{N}$) is constructed from $[\text{BN}_3]^{6-}$ and N^{3-} ions. To balance all the anionic charges tetravalent cerium must be present. For the isotypic compounds $\text{Ln}_{15}\text{B}_8\text{N}_{25}$ with $\text{Ln} = \text{La}$ and Pr substitutions with oxide ions in accordance with $\text{Ln}_{15}\text{B}_8\text{N}_{25-x}\text{O}_x$ were taken into consideration.^[29] Beyond the above mentioned compounds no other nitridoborates of the lanthanide elements were described until 1999.

Syntheses of nitridoborate compounds were straight forward from mixtures of lanthanide powders, their nitrides, and (h-)BN at high temperatures ($>1400^\circ\text{C}$). In this way the preparations always contained a mixture of reaction products as well as residual starting materials; this is why the B and N content of a preparation is not exactly controllable by this method.

2. Preparative Routes

2.1 Reactions at High Temperatures ($>1400^\circ\text{C}$)

$\text{La}_3\text{B}_2\text{N}_4$ is produced from reactions of lanthanum powder, lanthanum nitride, and h-BN by induction heating or by arc-melting. In these reactions the starting materials were pressed to a pellet in the molar ratio 1:2:2 and then melted under Ar for approximately half a minute. A typical X-ray powder pattern of the reaction product shows lines from $\text{La}_3\text{B}_2\text{N}_4$, LaB_4 , and h-BN. Single crystals of $\text{La}_3\text{B}_2\text{N}_4$ with edges of up to 1 mm can be grown by a subsequent annealing in a sealed tantalum ampoule. With Ce, Pr, and Nd isotypic compounds can also be produced in crystalline form.

2.2 Reactions with CaCl_2 as a Flux

A series of interesting compounds in the system alkaline-earth-metal-(B, C, N) have been crystallized from a CaCl_2 flux, which was however, often incorporated into the reaction products.^[30–32] Dry CaCl_2 ^[33] has also been successfully used as a reactive agent for syntheses of several lanthanum nitridoborate compounds. Single-crystalline samples of $\text{La}_3\text{B}_2\text{N}_4$, $\text{La}_5\text{B}_4\text{N}_9$,^[34] $\text{La}_3\text{B}_3\text{N}_6$,^[35] and $\text{La}_5\text{B}_2\text{N}_6$ ^[36] were obtained from reactions of suitable mixtures of La, LaN, and h-BN in a CaCl_2 flux at 1250°C . Reactions were performed using clean tantalum ampoules as reaction containers which were filled under Ar with the respective reaction mixture (and CaCl_2 as a flux). Afterwards the tantalum containers were sealed with an arc-welder and finally sealed into evacuated silica tubes (Figure 3). However, after this method, many compounds still can not be obtained as single-phase products. A prominent side product in several reactions was LaB_4 . Also the N content of the nitridoborates is not so controllable because of reactions with the tantalum ampoule.

The synthesis of $\text{Pr}_3\text{B}_3\text{N}_6$ was reproduced from $\text{BN}_x(\text{NH})_y(\text{NH}_2)_z$ and Pr metal at 1250°C in a NaCl melt.^[37]

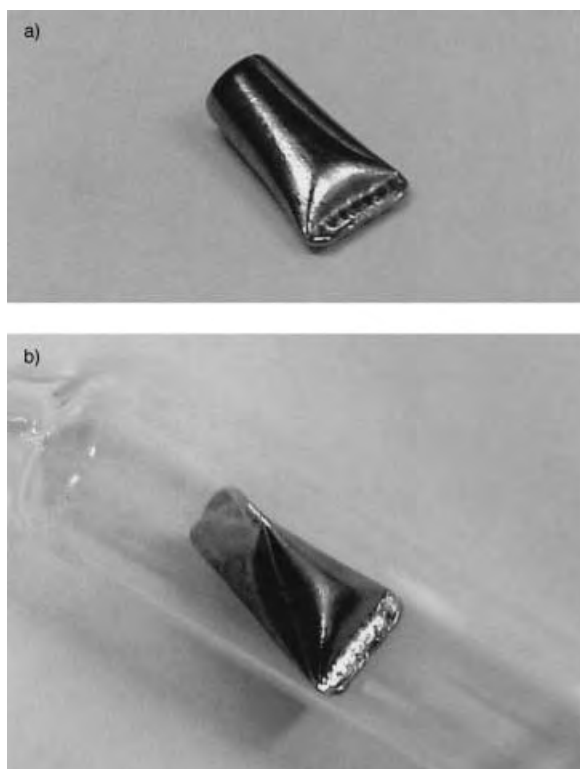


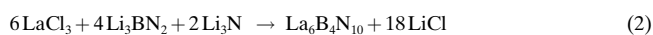
Figure 3. a) tantalum ampoule welded on one side and b) closed tantalum ampoule in an evacuated silica tube.

2.3 Solid-State Metathesis Reactions between LaCl_3 and Li_3BN_2

Metathesis reactions between LaCl_3 and Li_3BN_2 have turned out to be an efficient method for the preparation of nitridoborates of lanthanum.^[38] The Li_3BN_2 , required as starting material is produced from a 1:1 mixture of Li_3N and BN in a tantalum ampoule (at 750°C) or by means of a microwave synthesis in a silica ampoule. Metathesis reactions [Eq. (1)] take place at much lower temperatures than the aforementioned direct syntheses. As can be seen from differential thermal analyses (DTA) the metathesis takes place below 600°C (Figure 4).



For the preparation of nitride-rich compounds the N content can be adjusted in the synthesis with Li_3N [Eq. (2)].



2.4 Reductive Solid-State Metathesis Reactions

The preparation of metal-rich nitridoborate(nitride) compounds $\text{Ln}_{3+x}(\text{B}_2\text{N}_4)_x$ with $x=0, 1, 2$ of $\text{Ln}=\text{La}, \text{Ce}$ was performed by metallothermic reduction reactions. $\text{La}_3\text{B}_2\text{N}_4$ can be synthesized from a reaction of LaCl_3 , Li_3BN_2 , and La powder in a 3:2:1 molar mixture. However, the use of lithium

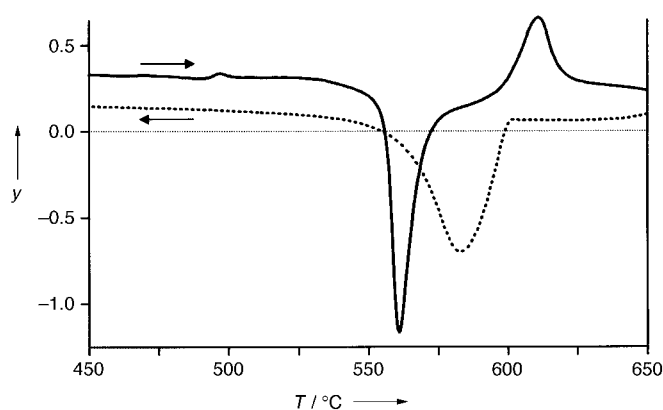
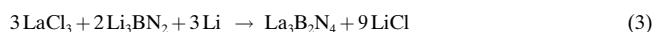
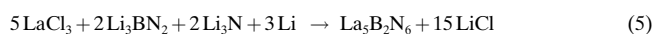
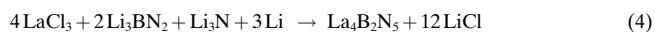


Figure 4. DTA curve (y in $\mu\text{V mg}^{-1}$) for the reaction in Equation (1) with heating and cooling curve (5 K min^{-1}). The strong exothermic reaction begins at approximately 560°C . The endothermic effect above 600°C with heating and the exothermic effect below 600°C with cooling mark the melting and solidifying of LiCl (m.p. 614°C).

as reducing agent has turned out to be more efficient in corresponding reactions [Eq. (3)].



Apart from using lithium as reducing agent for the compositions $\text{La}_4\text{B}_2\text{N}_5$ ^[39] and $\text{La}_5\text{B}_2\text{N}_6$ the nitrogen content can be adjusted by using Li_3N [Eq. (4) and (5)]. After LiCl is removed from the raw products with dry THF, black crystal powders remain as reaction products.



During the past few years single crystals of nitridoborate compounds could be grown and pure bulk samples were obtained particularly from applications of solid-state metathesis reactions with Li_3BN_2 and suitable variations of the reaction conditions. However, the development of a universal synthesis route for the preparation of nitridoborate compounds is still in progress.

3. Nitridoborate Ions

Nitridoborate compounds contain BN_x units in which boron tends to have the coordination number three, as in the structure of hexagonal boron nitride. During the reaction of h-BN with metal nitride compounds ($\text{metal}=\text{Ln}$, alkaline, alkaline-earth metal) the BN layers collapse, and nitridoborate ions are formed. The ions $[\text{BN}]^{n-}$, $[\text{BN}_3]^{6-}$, and $[\text{B}_3\text{N}_6]^{9-}$ can be considered as charged, integral constituents of the h-BN structure (Figure 5).

Following another route the nitridoborate ions $[\text{BN}]^{n-}$, $[\text{B}_2\text{N}_4]^{8-}$, $[\text{B}_3\text{N}_6]^{9-}$, and $[\text{BN}_3]^{6-}$ can be assembled by solid-state metathesis reactions from LnCl_3 with the dinitridoborates Li_3BN_2 or $\text{Ca}_3(\text{BN}_2)_2$. The structures of nitridoborate ions are closely related to those of known molecules or anions. With CO , CO_2 , $[\text{C}_2\text{O}_4]^{2-}$, and $[\text{CO}_3]^{2-}$ the chemistry of the carbon oxides does not have the hypothetical trimer of carbon

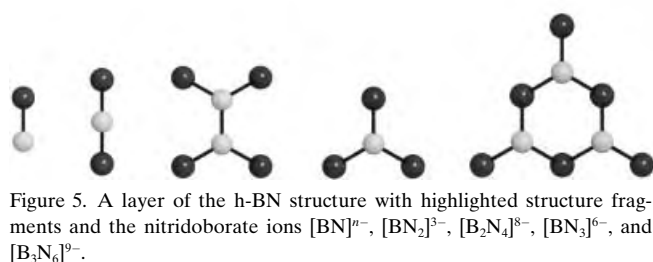
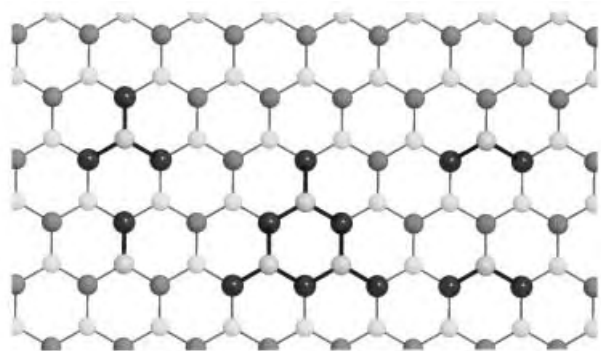
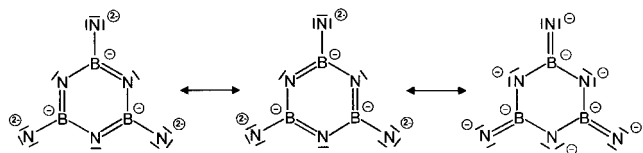


Figure 5. A layer of the h-BN structure with highlighted structure fragments and the nitridoborate ions $[\text{BN}]^{n-}$, $[\text{BN}_2]^{3-}$, $[\text{B}_2\text{N}_4]^{8-}$, $[\text{BN}_3]^{6-}$, and $[\text{B}_3\text{N}_6]^{9-}$.

dioxide C_3O_6 which is known for nitridoborates as $[\text{B}_3\text{N}_6]^{9-}$, for oxoborates as $[\text{B}_3\text{O}_6]^{3-}$,^[40] and for thioborates as $[\text{B}_3\text{S}_6]^{3-}$.^[41] Relationships to these ions (and molecules) as well as the validity of the octet rule characterize the electronic conditions and finally the charges of nitridoborate ions. For the most highly charged ion $[\text{B}_3\text{N}_6]^{9-}$ some resonance structures are shown in Scheme 1.

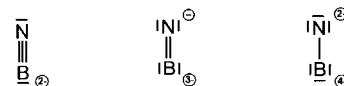


Scheme 1. Selected resonance structures for $[\text{B}_3\text{N}_6]^{9-}$ with D_{3h} symmetry.

Averaged B–N separations were determined to be 148 pm in $[\text{B}_3\text{N}_6]^{9-}$, 145 pm in h-BN,^[42] and 143 pm in solid borazine ($\text{H}_6\text{B}_3\text{N}_3$).^[43] The benzene analogue $\text{H}_6\text{B}_3\text{N}_3$ exhibits, like benzene, six electrons in π states. However, the difference in electronegativity between B and N allows only limited delocalization of the six electrons in the π states. The nine p_z orbitals of the $[\text{B}_3\text{N}_6]^{9-}$ ion combine to form three bonding π (occupied) combinations, as in borazine, three nonbonding π (occupied) combinations which can be regarded as lone electron pairs of the N atoms, and three antibonding π (empty) combinations.^[35]

The chemistry of these highly charged nitridoborate ions in solutions has not been explored to date. This is why the existence of the corresponding nitridoboric acids is in question. Up to now the *ortho*-nitridoboric acid (H_6BN_3), the *meta*-nitridoboric acid (H_3BN_2) and its cyclic trimer ($\text{H}_9\text{B}_3\text{N}_6$) are unknown.

A peculiarity under the nitridoborate(nitride) compounds are metal-rich compounds with B_2N_4 and BN units. Compounds of the formula type $\text{Ln}_3\text{B}_2\text{N}_4$ ($\text{Ln} = \text{La, Ce, Pr, Nd}$) contain $[\text{B}_2\text{N}_4]^{8-}$ ions, isoelectronic to $[\text{C}_2\text{O}_4]^{2-}$ ions, with B–B separations of approximately 180 pm. The $[\text{BN}]^{n-}$ ion may be considered as an intermediate between CO and $[\text{C}_2]^{n-}$. Like $[\text{C}_2]^{n-}$, $[\text{BN}]^{n-}$ can accept different charges depending on the electronic conditions in the respective compound (Scheme 2). Therefore, different bonding conditions with clearly varying bond lengths are expected for B–N bonds in $[\text{BN}]^{n-}$ ions.



Scheme 2. Proposed electronic configurations for $[\text{BN}]^{2-}$, $[\text{BN}]^{4-}$, and $[\text{BN}]^{6-}$ ions.

To date, a tetrahedral $[\text{BN}_4]^{9-}$ ion with coordination number 4 at the boron atom, as in the cubic BN structure, is unknown for nitridoborate compounds. Among the oxoborates BO_4 tetrahedra are known with mean B–O separation of 148 pm. BO_4 tetrahedra in the structure of the luminescence material EuB_4O_7 ^[44] are constituents of a three-dimensional network.

4. Structure Principles for Nitridoborate Compounds

In solid-state structures, nitridoborate ions form unique regular arrangements. Three structure principles are evident, which basically allow crystal structures of new or hypothetical compounds to be accurately predicted.

- Nitridoborate ions are surrounded in a characteristic way by metal atoms. Terminal N atoms are capped by square-pyramidal arrangements of metal atoms, and the boron atom is surrounded preferably by a trigonal-prismatic array of metal atoms. The nitride ions of nitridoborate nitrides occupy octahedral holes (Figure 6).
- Nitridoborate ions have the tendency to arrange in layers so that layers with the successions $\cdots \text{B} \cdots \text{B} \cdots$ or $\cdots \text{B} \cdots \text{N} \cdots$ occur. With compounds containing BN_3 and B_2N_4 units one finds $\cdots \text{B} \cdots \text{B} \cdots$ stacks. The linear units BN and BN_2 form rod packings.
- Nitridoborate ions can be combined in structures with other nitridoborate ions and with N^{3-} ions in a building-block manner.

From systematic combinations of Ln atoms, nitridoborate, and nitride ions a series of compounds may be expected, some of which have been found. Following our classifications, compounds are considered as parent compounds (nitridoborates) and their nitrides (nitridoborate nitrides) as listed in Table 1. For the compositions Ln_2BN_3 and $\text{Ln}_{3+x}(\text{B}_3\text{N}_6)\text{N}_x$ ($x = 1, 2$) specified in Table 1 there is no experimental proof to date. Following the general structure principles for nitridoborate compounds, a crystal structure of the hypothetical compound Ln_2BN_3 is proposed in Figure 7. The central feature of the structure draft are BN_3 units which

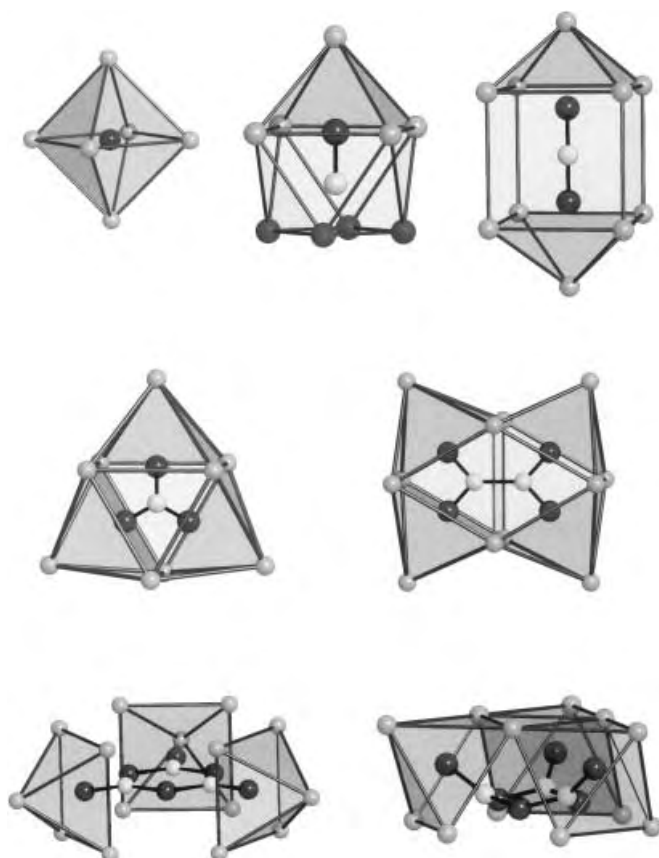


Figure 6. Typical environments of nitride and nitridoborate ions with metal atoms. All N atoms (black) are capped by a (distorted) quadratic-pyramidal formation of metal atoms. For planar and nonplanar B_3N_6 ions two different metal environments occur.

Table 1. Overview of the nitridoborate and nitridoborate nitride compounds of the lanthanides.

Nitridoborate	Ln	Nitridoborate nitride x	Ln
$Ln_3(BN_2)_2$	Eu ^[20]	$Ln_{3+x}(BN_2)_2N_x$ [a]	–
$Ln_2(BN_3)$ [a]	–	$Ln_{2+x}(BN_3)N_x$	1 La ^[25]
$Ln_3(B_3N_6)$ [b]	La, Ce, [35] Pr, Nd, Sm, Gd ^[27]	$Ln_{3+x}(B_3N_6)N_x$ [a]	–
$Ln_5(B_3N_6)(BN_3)$	La ^[34]	$Ln_{5+x}(B_3N_6)(BN_3)N_x$	1 La ^[45]
$Ln_3(B_2N_4)$	La, Ce, Pr, Nd ^[34]	$Ln_{3+x}(B_2N_4)N_x$	1, 2 La, Ce ^[36,39]
$LnNi(BN)$	La, Ce, Pr ^[54]	$Ln_{1+x}Ni(BN)N_x$	$\frac{1}{2}$ La ^[50, 51]

[a] Unknown. [b] Different structures for compounds with La, Ce, and with Pr, Nd, Sm, Gd.

are surrounded by metal atoms in trigonal-prismatic formations and which are stacked along their pseudo-threefold axis to give $[Ln_{6/2}(BN_3)]$ columns. In the next construction step the columns must be joined in a way so that the composition Ln_2BN_3 results.

5. Saltlike Nitridoborate Compounds and Their Nitride Derivatives

The number of compounds in the system La-B-N is larger than it was at first expected because different types of nitridoborate ions can coexist in structures side by side (Table 1). Additional combinations with nitride ions are

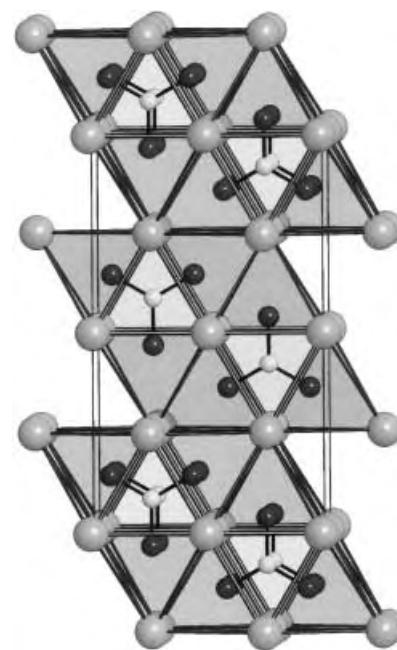


Figure 7. Projection of a structure draft for Ln_2BN_3 .

known for nitridoborate nitride compounds. An example of such combinations is the series of the compounds $La_3(B_3N_6)$, $La_5(B_3N_6)(BN_3)$, and $La_6(B_3N_6)(BN_3)N$ ^[45] which all can be described as saltlike compounds with $[B_3N_6]^{9-}$, $[BN_3]^{6-}$, and N^{3-} ions.

Compounds with the formula $Ln_3(B_3N_6)$ occur with different structures for $Ln = La, Ce$ and for $Ln = Pr, Nd, Gd$. Both structures contain cyclic B_3N_6 ions however, with a planar conformation for the smaller metal atoms $Ln = Pr, Nd, Gd$ and with a significant deviation from planarity in combination for the larger metal atoms $Ln = La$ and Ce . In the structure of $Pr_3(B_3N_6)$ (space group $R\bar{3}c$) planar B_3N_6 ions are stacked to form columns in staggered formation. The stacking sequence of the B_3N_6 ions in the structure corresponds to a section from the h-BN structure having $B \cdots N$ separations of 350.8 pm between B_3N_6 ions in adjacent layers, which is somewhat longer than the 333 pm interlayer distances in the structure of h-BN. In $La_3(B_3N_6)$ ($P\bar{1}$) the B_3N_6 ions are also stacked in columns but in a staggered formation, so that only one ring edge coincides along the stacking direction (Figure 8).

In the structure of $Pr_3(B_3N_6)$, large channel like cavities are occupied by B_3N_6 ions, the exocyclic N atoms of which are fixed in square-pyramidal Pr cavities. The crystals obtained of the formula type $Ln_3(B_3N_6)$ were colorless (the calculated band gap for $La_3(B_3N_6)$ is in the order of 4 eV) or with the characteristic color of the trivalent lanthanoid ion (crystals of $Pr_3(B_3N_6)$ are green) and are marked by their mechanical hardness and chemical stability. Upon heating in air $La_3(B_3N_6)$ reacts above 700 °C to give $LaBO_3$.^[46]

In the structure of $Pr_3(B_3N_6)$ all the B–N bonds of the planar B_3N_6 ion are identical within the margins of error (average value 148 pm). Clearly distinguishable B–N bond lengths are, however, found in the nonplanar B_3N_6 ion of $La_3(B_3N_6)$. The B–N bonds determined for exocyclic bonds are between 142 and 147 pm, and those in the ring are

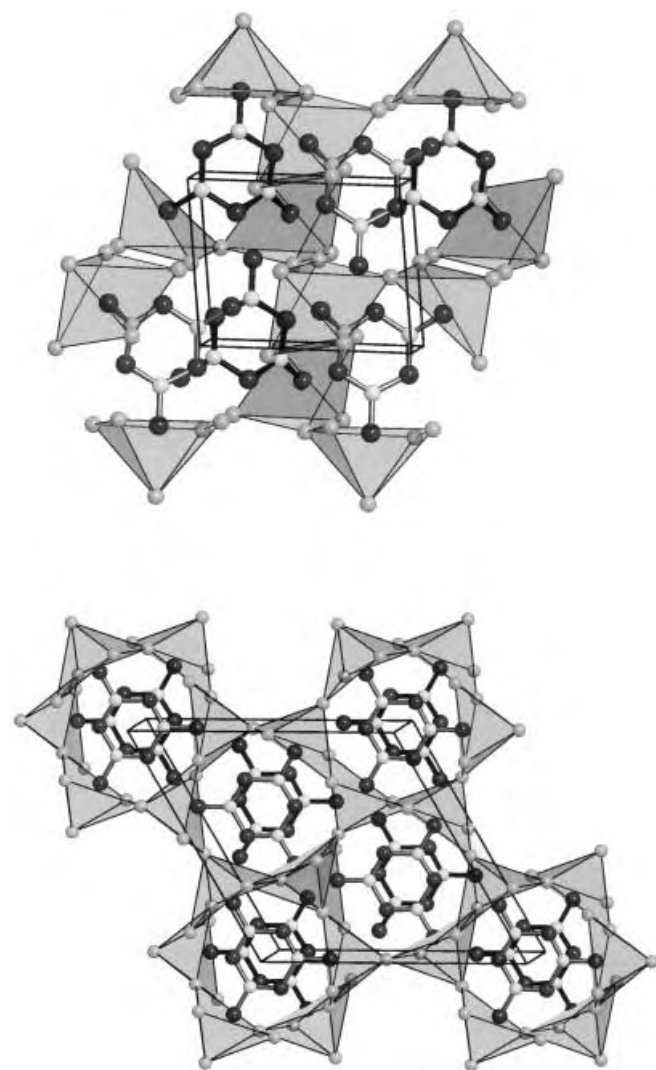


Figure 8. Comparison of the structures of $\text{La}_3(\text{B}_3\text{N}_6)$ (top) and $\text{Pr}_3(\text{B}_3\text{N}_6)$ (bottom).

between 148 and 151 pm. On account of the relatively large errors of the refined light-atom positions the slight differences in the B–N bond lengths may be subjected to a systematic evaluation only with caution. Shorter exocyclic B–N bonds of nonplanar B_3N_6 ions can be interpreted as an increasing localization of the electrons of three π combinations in the direction of the exocyclic bonds (Scheme 1, right). The trend towards shorter B–N bond lengths for exocyclic B–N bonds was also found for B_3N_6 ions in the structures of $\text{La}_5\text{B}_4\text{N}_9 = \text{La}_5(\text{B}_3\text{N}_6)(\text{BN}_3)$ and $\text{La}_6\text{B}_4\text{N}_{10} = \text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$. Here the B_3N_6 units are also not planar, but have a chair conformation in which nearly planar BN_3 arrangements at the B atoms are retained. Therefore, a planar conformation is not mandatory for the B_3N_6 unit. Because of the different electronegativity and size of B and N atoms the delocalization of electrons in π states might be limited. One reason for deviations from planarity is evidently a flexibility of the B_3N_6 units to adapt themselves into the prevailing metal matrix of the respective structures.

The B–N bonds of the BN_3 unit in $\text{La}_5(\text{B}_3\text{N}_6)(\text{BN}_3)$ and $\text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$ are, at 147–150 pm, not significantly short-

er than the mean distances in the B_3N_6 unit. In the structures of $\text{La}_5(\text{B}_3\text{N}_6)(\text{BN}_3)$ and $\text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$, the BN_3 units are stacked in columns along the c axis (Figure 9). The presence of one additional formula unit LaN (with $y=0$ and $\frac{1}{2}$) in $\text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$ results in an extension of the b axis by approximately 200 pm (Table 2).

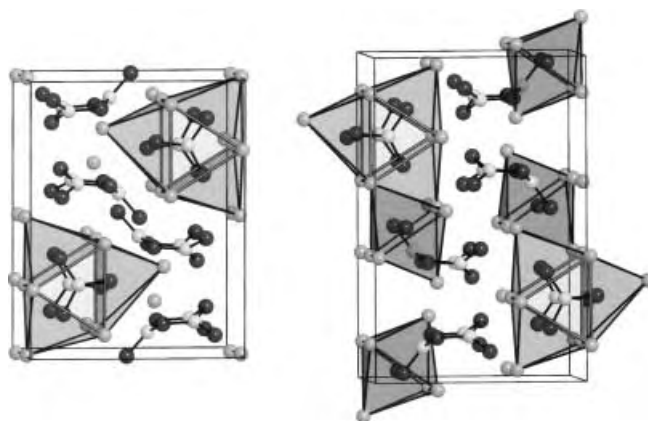


Figure 9. The structures of $\text{La}_5(\text{B}_3\text{N}_6)(\text{BN}_3)$ (space group $Pbcm$; left) and $\text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$ (space group $P2_1/c$; right) with four formula units in the unit cell. Projections along the c axis.

Table 2. Saltlike lanthanum nitridoborate compounds with B_3N_6 and BN_3 units.

Compound	Space group	Cell constants [pm, °]	Z	Cell volume [10 ⁶ pm ³]
$\text{La}_3(\text{B}_3\text{N}_6)$	$P\bar{1}$	$a = 661.3(1)$, $\alpha = 106.06(1)$ $b = 687.01(1)$, $\beta = 90.55(1)$ $c = 779.8(1)$, $\gamma = 115.63(1)$	2	303.5
$\text{La}_5(\text{B}_3\text{N}_6)(\text{BN}_3)$	$Pbcm$	$a = 988.25(5)$ $b = 1263.48(7)$ $c = 770.33(4)$	4	961.9
$\text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$	$P2_1/c$	$a = 971.89(6)$ $b = 1479.41(9)$, $\beta = 90.005(9)$ $c = 762.32(4)$	4	1096.1
$\text{La}_3(\text{BN}_3)\text{N}$	[a]	$a = 1263.4(3)$ $b = 1096.6(2)$ $c = 366.53(7)$	4	507.8
$\text{La}_6(\text{BN}_3)\text{O}_6$	$Cmcm$	$a = 366.88(3)$ $b = 2509.2(3)$ $c = 1101.1(1)$	4	1013.7

[a] Space group uncertain.

The nitride ion in $\text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$ occupies a distorted octahedral hole with four shorter (256–266 pm) and two longer (275 and 288 pm) La–N separations. For the octahedral surroundings of N^{3-} ions in the structure of LaN the La–N separations are approximately 266 pm. The BN_3 unit is surrounded by a total of nine lanthanum atoms in the formation of a tricapped trigonal-prism. In the crystal structure the prisms share their triangular faces along the c axis to form columns (Figure 10) and these are linked along the b axis over nitrogen-centered octahedra. In both structures the stacking of the BN_3 is almost eclipsitic.

Although colorless crystals are to be expected in accordance with saltlike charge assignments for $(\text{La}^{3+})_5(\text{B}_3\text{N}_6^{9-})(\text{BN}_3^{6-})$ and $(\text{La}^{3+})_6(\text{B}_3\text{N}_6^{9-})(\text{BN}_3^{6-})(\text{N}^{3-})$ black crystals were

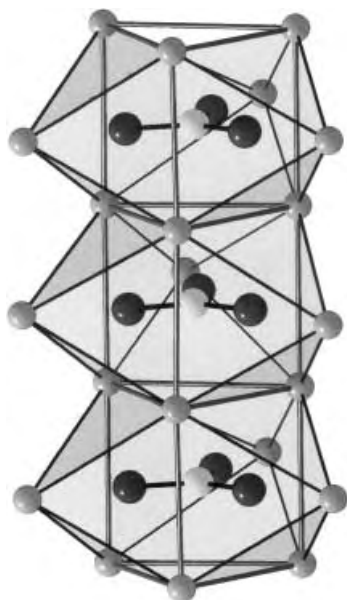


Figure 10. Column of stacked BN_3 units with tricapped trigonal formations of lanthanum atoms (gray) from the structure of $\text{La}_6(\text{B}_3\text{N}_6)(\text{BN}_3)\text{N}$.

observed as for LaN . Apart from the possibility of crystal defects, a nitride deficiency, which arises also with lanthanide nitrides, could be responsible for this observation.

The typical arrangement of trinitridoborate ions is also evident in the crystal structure of $\text{La}_3(\text{BN}_3)\text{N}^{[25]}$ (Figure 11). The BN_3 unit with B–N bonds of approximately 149 pm is located in the center of a tricapped trigonal-prism of lanthanum atoms. The BN_3 centered prisms are stacked to $[\text{La}_{6/2}(\text{BN}_3)]$ columns through shared triangular faces. Lanthanum atoms in one prism column cap N atoms of the BN_3 units in neighboring columns and at the same time form

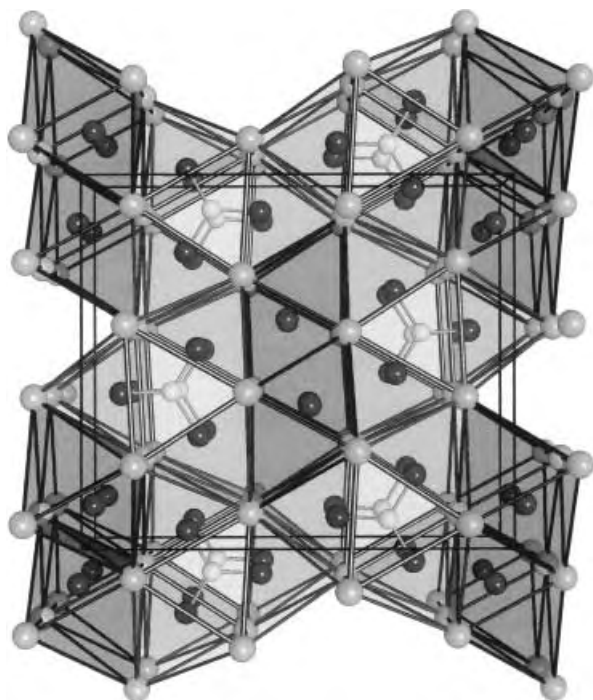


Figure 11. Projection of the crystal structure of $\text{La}_3(\text{BN}_3)\text{N}$ along the c axis.

by their arrangement octahedral cavities for the nitride ions in $\text{La}_3(\text{BN}_3)\text{N}$.

To date the compounds $\text{Ln}_{15}(\text{BN}_3)_8\text{N}^{[28, 29]}$ with $\text{Ln} = \text{La}, \text{Ce},$ and Pr are the only nitridoborates that do not follow the typical structure pattern of approximately eclipsed stacked BN_3 units. They crystallize in the same structure type as the thioborate $\text{K}_4\text{Ba}_{11}(\text{BS}_3)_8\text{S}^{[47]}$ in which K and Ba atoms occupy equivalent positions. With the charges considered for $[\text{BN}_3]^{6-}$ and N^{3-} ions the Ln elements would have to have mixed valences which is improbable for $\text{Ln} = \text{La}$. Therefore, partial substitution with oxide in accordance with $(\text{Ln}^{3+})_{15}(\text{B}^{3+})_8(\text{N}^{3-})_{19}(\text{O}^{2-})_6$ must be considered.

The transition between nitridoborates and oxoborates opens up the possibility of deliberately modifying certain characteristics of these groups of materials. Knowledge of nitridoborate nitride compounds poses the question, which anions other than nitride could be combined with the nitridoborate ions? Possible candidates are oxide and halide ions. In an attempt to synthesize nitridoborate oxides, LaOCl is used as an oxygen source. The structure of $\text{La}_6(\text{BN}_3)\text{O}_6^{[48]}$ fits nicely into the structure principles typical for nitridoborates. The trinitridoborate ions are surrounded by tricapped trigonal-prismatic arrangements $[\text{La}_6\text{La}_3(\text{BN}_3)]$ of lanthanum atoms. These are stacked over shared triangle faces to form $[\text{La}_{6/2}\text{La}_3(\text{BN}_3)]$ columns. The arrangement of these columns in the structure of $\text{La}_6(\text{BN}_3)\text{O}_6$ leaves cavities which are occupied with O^{2-} ions (coordination number = 4–6; Figure 12).

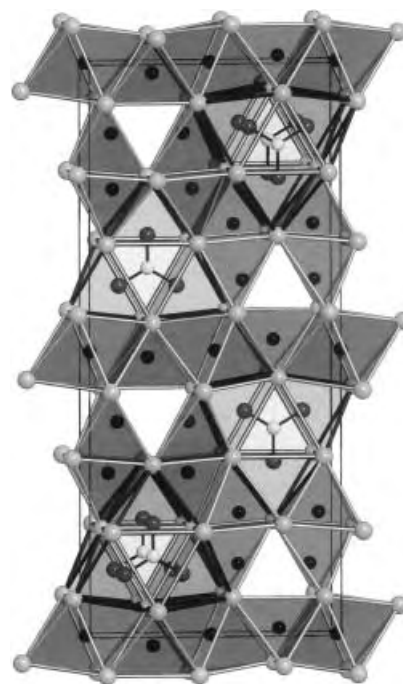


Figure 12. Projection of the crystal structure of $\text{La}_6(\text{BN}_3)\text{O}_6$ along the a axis.

6. Metal-Rich Nitridoborate Compounds and their Nitride Derivatives

A peculiarity of Ln nitridoborate compounds is that they can also form metal-rich compounds which is in contrast to, for example, the oxoborates. Metal-rich nitridoborate com-

pounds are known with B_2N_4 and BN units. As in the case for the saltlike nitridoborates, parent compounds arise also with metal-rich nitridoborates from which nitridoborate nitride compounds can be produced by formal addition of metal nitride. Among the parent compounds of metal-rich nitridoborates are $Ln_3(B_2N_4)$ and $LnNi(BN)$. Their nitride derivatives are characterized by the formulations $Ln_{3+x}(B_2N_4)N_x$ with $x = 1, 2$ and $Ln_{1+x}Ni(BN)N_x$ with $x = \frac{1}{2}$ (Table 1 and Table 3).

Table 3. Metal-rich nitridoborate compounds with B_2N_4 and BN units.

Compound	Space group	Cell constants [pm, °]	Z	Cell volume [10 ⁶ pm ³]
$La_3(B_2N_4)$	<i>Immm</i>	$a = 362.94(3), b = 641.25(6)$ $c = 1079.20(8)$	2	251.2
$La_4(B_2N_4)N$	<i>C2/m</i>	$a = 1260.4(1)$ $b = 366.15(3), \beta = 129.727(6)$ $c = 919.8(1)$	2	326.4
$La_5(B_2N_4)N_2$	<i>C2/m</i>	$a = 1255.2(1)$ $b = 367.67(4), \beta = 105.967(2)$ $c = 905.76(9)$	2	401.8
$LaNi(BN)$	<i>P4/nmm</i>	$a = 371.96(3), c = 758.23(9)$	2	104.9
$CeNi(BN)$	<i>P4/nmm</i>	$a = 358.45(4), c = 751.4(1)$	2	96.5
$PrNi(BN)$	<i>P4/nmm</i>	$a = 363.21(8), c = 761.7(2)$	2	100.5
$CaNi(BN)$	<i>P4/nmm</i>	$a = 353.38(1), c = 763.76(1)$	2	95.4
$CaPd(BN)$	<i>P4/nmm</i>	$a = 377.38(1), c = 760.95(4)$	2	108.4
$La_3Ni_2(BN)_2N$	<i>I4/mmm</i>	$a = 372.51(1), c = 2051.72(4)$	2	284.7

6.1 Compounds with the B_2N_4 Ion

Parent compounds of the type $Ln_3(B_2N_4)$ with $Ln = La, Ce, Pr, Nd$ contain the $[B_2N_4]^{8-}$ ion which is isoelectronic to the oxalate ion. Nitridoborate ions in these structures are in a characteristic metal environment. The boron atoms are integrated into planar B_2N_4 units, and the surrounding trigonal metal prisms combine in pairs to a rhombic prism. The B–B bond lengths are 176–182 pm, and the B–N bonds are at 149–150 pm somewhat longer than the corresponding distances in the h-BN (145 pm). Each of four nitrogen atoms is capped by a square-pyramidal formation of metal atoms. Thus, each N atom of the B_2N_4 unit has a distorted octahedral environment if the neighboring B atom is considered.

In the structures the $[Ln_8(B_2N_4)]$ building blocks with the rhombic-prismatic formation of their Ln atoms are stacked over shared faces to yield $[Ln_{8/2}(B_2N_4)]$ columns along the short lattice translation. All the $[Ln_{8/2}(B_2N_4)]$ columns are connected through two shared edges to form layers and arranged in such a manner that Ln atoms of one column always cap N atoms of B_2N_4 units in neighboring columns (Figure 13).

Departing from the parent compounds $Ln_3(B_2N_4)$, nitridoborate nitrides are known in which the nitride ions occupy octahedral holes. These compounds all can be summarized as $Ln_{3+x}(B_2N_4)N_x$ with $x = 0, 1, 2$ (Table 3, Figure 14). In the structures with $x = 1$ and 2, the arrangement of the $[Ln_{8/2}(B_2N_4)]$ columns alternates with one or two (*trans* edge-sharing) octahedron columns $[Ln_4Ln_2(N)]$. For the compounds $La_{3+x}(B_2N_4)N_x$ a step by step increase of the cell volume per formula unit of around $38 \times 10^6 \text{ pm}^3$ is registered

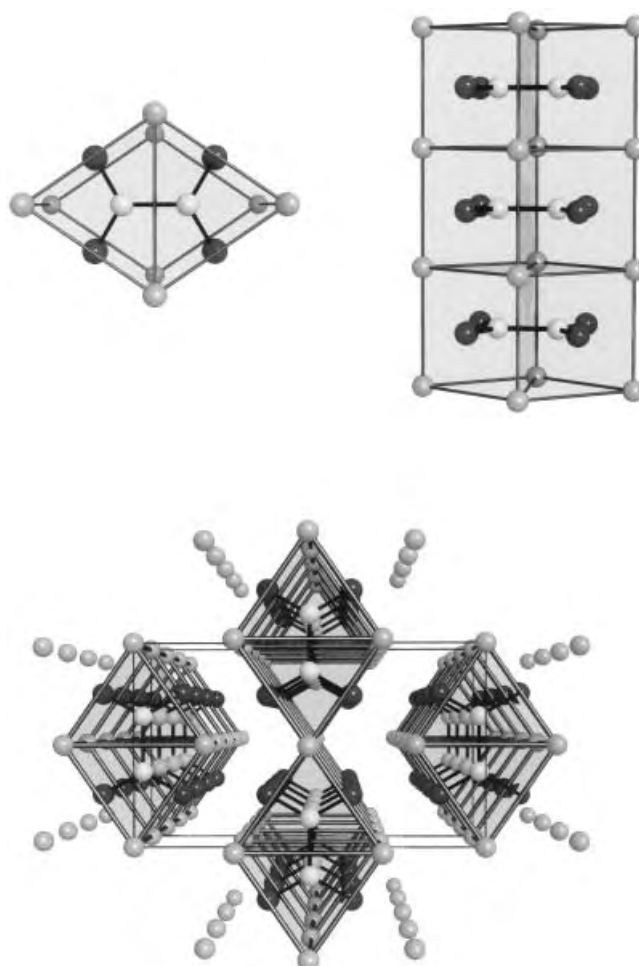


Figure 13. $[Ln_8(B_2N_4)]$ building unit, $[Ln_{8/2}(B_2N_4)]$ column, and projection of the structure of $La_3(B_2N_4)$ along the short lattice translation.

when going from $x = 0$ to 1 to 2. This increase corresponds to the cell volume of LaN (approximately $37 \times 10^6 \text{ pm}^3$).

These compounds $Ln_{3+x}(B_2N_4)N_x(e^-)$ are unique within the series of lanthanoid nitridoborates, because they possess one surplus electron per formula unit, in the metal 5d bands. The density of states (DOS) calculated for $La_3(B_2N_4)$ and the B–B overlap population resulted in B–B bonding states between the broad anionic valence band and the partially occupied conduction band from (La)5d states (Figure 15). Magnetic measurements of $La_3(B_2N_4)$ samples showed temperature-independent paramagnetic (TIP) behavior.^[34]

6.2 Compounds with the BN Ion

To date the mononitridoborate or boronitride ion is known only from quaternary compounds. A relationship which exists between graphite and h-BN could also be considered for compounds with BN and C_2 units. However, the solid-state reactions between Ca and BN (1:1) does not produce $Ca(BN)$, the analogue of CaC_2 ,^[49] but $Ca_3(BN)_2$ and CaB_6 .

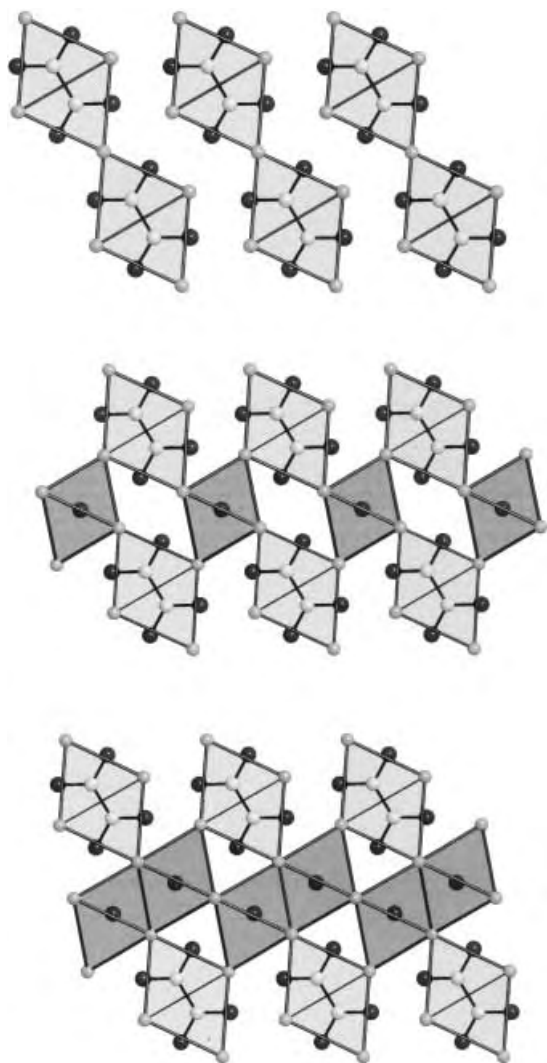


Figure 14. Comparative projections of the crystal structures of $\text{Ln}_{3+x}(\text{B}_2\text{N}_4)\text{N}_x$ with $x = 0$ (top), 1 (middle), 2 (bottom) along their short lattice translations. The constituent structure fragments $[\text{Ln}_8(\text{B}_2\text{N}_4)]$ and $[\text{Ln}_6(\text{N})]$ are highlighted.

During the years 1994/95 $\text{LaNi}(\text{BN})$ and the superconductive compound $\text{La}_3\text{Ni}_2(\text{BN})_2\text{N}$ ($T_c = 12\text{ K}$) were prepared with an electric arc from mixtures of La, LaN, Ni, and B.^[50] Neutron powder-diffraction analyses for $\text{La}_3\text{Ni}_2(\text{BN})_2\text{N}_{1-z}$ revealed a nitrogen deficiency of $z = 0.09$ and a B–N bond of 144 pm.^[51] For $\text{LaNi}(\text{BN})$ only electron-microscope data are available, which indicate an unusually long B–N bond of 202(18) pm. For the isostructural compound $\text{LuNi}(\text{BC})$ B–C bonds of 152 pm were reported.^[52] In the meantime, nitrido-borate compounds of the formula type $\text{LnM}(\text{BN})$ are known for $\text{Ln} = \text{Ca}$,^[53] La, Ce, and Pr^[54] with $\text{M} = \text{Ni}$ and Pd (Table 3). In the $\text{CaNi}(\text{BN})$ structure the B–N bond length is 138 pm. In comparison with the unknown derivative $\text{Ca}(\text{BN})$ of the CaC_2 type the $\text{LnNi}(\text{BN})$ structure (Figure 16, left) offers different chemical environments for B and N atoms. Boron atoms (of the BN units) are oriented towards the layer of nickel atoms and cap the face centers of the square-planar formations of nickel atoms from both sides, so that each nickel atom is surrounded tetrahedrally by boron atoms. This characteristic

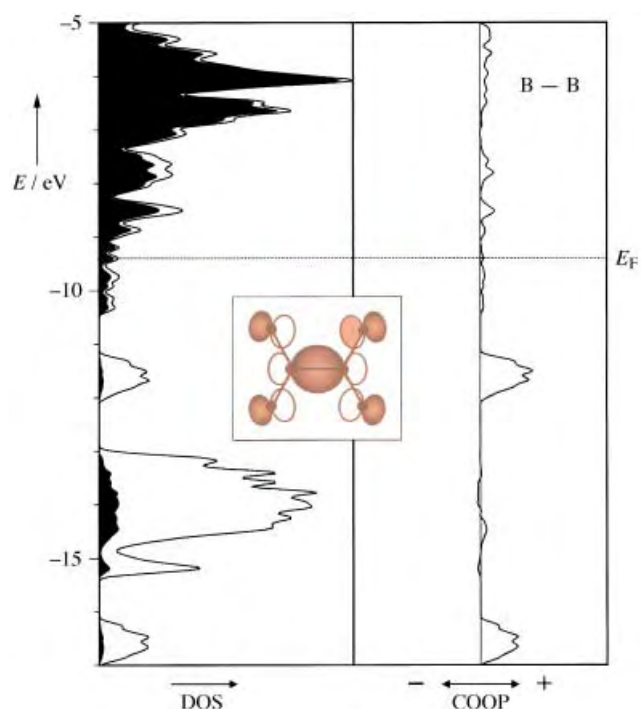


Figure 15. Calculated density of states (DOS) of $\text{La}_3(\text{B}_2\text{N}_4)$ (contribution of lanthanum states marked in black) and B–B crystal orbital overlap population (COOP). The inset shows a molecular orbital (MO) of one bonding B–B combination. The Fermi level (E_F) is marked with a dotted line.

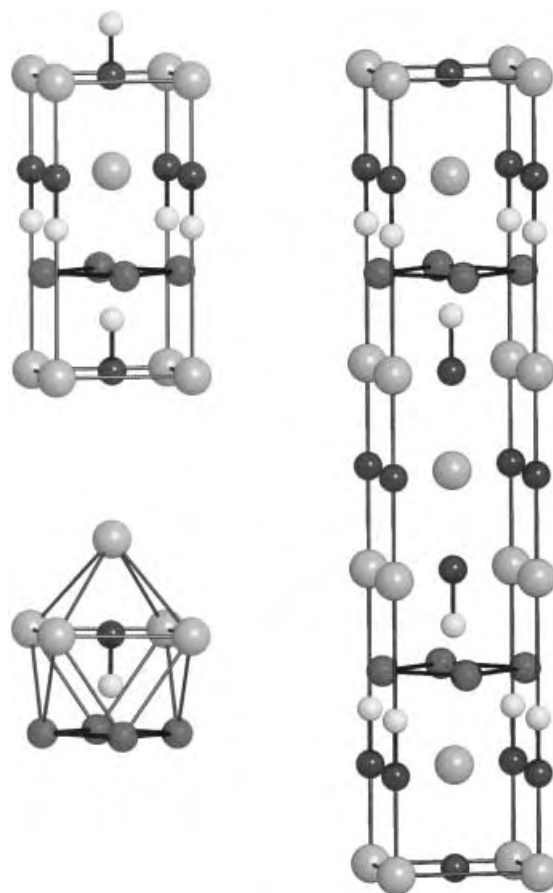


Figure 16. Coordination of the BN unit (bottom left), and structures of $\text{LaNi}(\text{BN})$ (top left), and $\text{La}_3\text{Ni}_2\text{B}_2\text{N}_3$ (right).

arrangement is observed in the compounds $\text{LnNi}(\text{BN})$, $\text{La}_3\text{Ni}_2(\text{BN})_2\text{N}$, and $\text{LnNi}_2(\text{B}_2\text{C})$ (Figure 16 and 22).

The compounds $\text{LnNi}(\text{BN})$ with $\text{Ln} = \text{La}, \text{Ce}, \text{Pr}$ have metallic properties and show temperature-independent paramagnetism (TIP) in the temperature range $20 \leq T \leq 300 \text{ K}$.^[54] For $\text{CeNi}(\text{BN})$ a magnetic ordering (Figure 17) with a weak hysteresis below 20 K is observed. $\text{PrNi}(\text{BN})$ shows additional temperature-dependent paramagnetic portions.

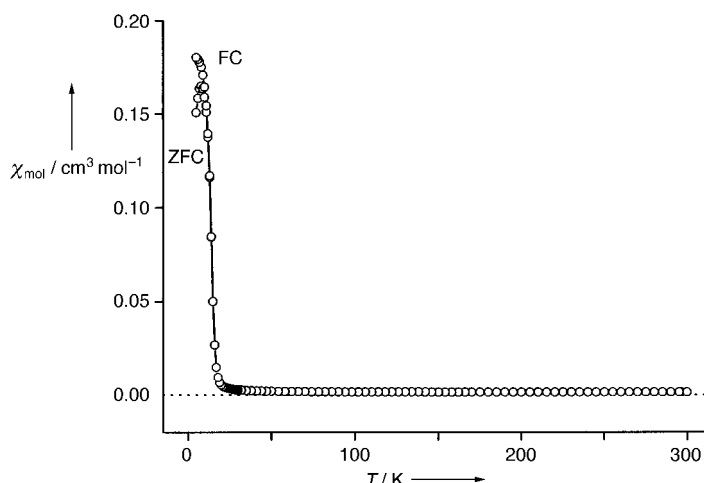


Figure 17. Magnetic ordering of $\text{CeNi}(\text{BN})$ (500 G). FC = field cooling, ZFC = zero-field cooling.

The structure of $\text{La}_3\text{Ni}_2(\text{BN})_2\text{N}$ contains additional LaN layers compared with that of $\text{LaNi}(\text{BN})$. Our attempts to reproduce the synthesis from the elements and BN resulted in impure products with transition temperatures of 12 K. Only the application of a metathesis reaction based on Li_3BN_2 and LaCl_3 resulted in X-ray-pure products^[38] on which transition temperatures of 14 K were measured (Figure 18).^[54]

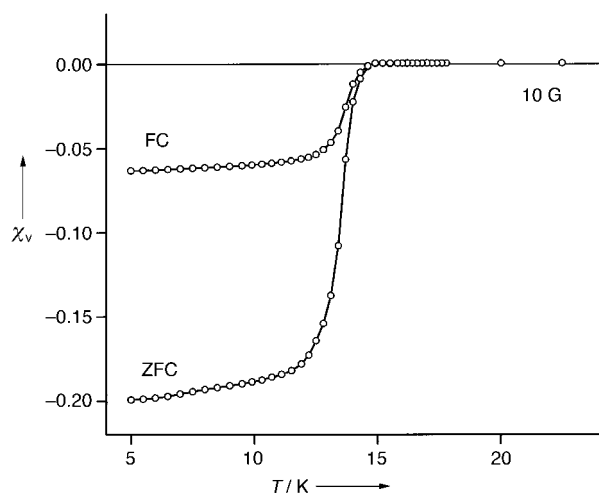


Figure 18. FC and ZFC susceptibilities of $\text{La}_3\text{Ni}_2(\text{BN})_2\text{N}$ (10 G).

Clearly there are different bond lengths and charges to be considered for BN anions in compounds $\text{CaNi}(\text{BN})$, $\text{LaNi}(\text{BN})$, and $\text{La}_3\text{Ni}_2(\text{BN})_2\text{N}$. Similar situations can be found for dicarbide compounds. The bond lengths are here

about 120 pm for $[\text{C}_2]^{2-}$ in CaC_2 , 128 pm for “ $[\text{C}_2]^{3-}$ ” in LaC_2 ,^[55] 135 pm for “ $[\text{C}_2]^{4-}$ ” in UC_2 , and 149 pm for “ $[\text{C}_2]^{6-}$ ” in $\text{Rb}[\text{Pr}_5(\text{C}_2)]\text{Cl}_{10}$.^[56] However, only the charge of C_2 in CaC_2 can be considered as being formally correct. For the electrically conductive compounds LaC_2 and UC_2 , delocalized electrons are present which can not be assigned clearly either to the metal or to the C_2 unit. The orbital combination of $(\text{C}_2)\pi^*$ and $(\text{Ln})5d$ orbitals corresponds to the HOMO in lanthanoid dicarbide compounds and contains antibonding $\text{C}-\text{C}$ as well as bonding $\text{Ln}-\text{C}$ and $\text{Ln}-\text{Ln}$ interactions. This combination expresses the increase of the $\text{C}-\text{C}$ bond lengths with rising electron numbers if successive occupations of these orbitals by zero (CaC_2), one (LaC_2), and two (UC_2) electrons take place, as well as the delocalization of electrons in lanthanoid dicarbide compounds (Figure 19).

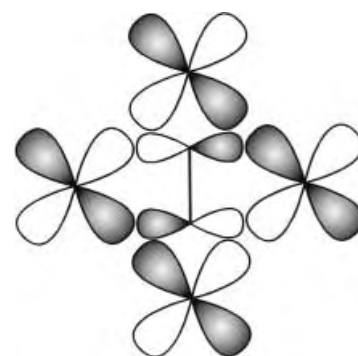


Figure 19. Interaction of one of the two π_g^* orbitals (C_2) with 5d orbitals (Ln) in LnC_2 .

6.3 The Electronic Structure of $\text{LaNi}(\text{BN})$

The formula type $\text{LnM}(\text{BN})$ is known for $\text{CaNi}(\text{BN})$, $\text{CaPd}(\text{BN})$, and $\text{LnNi}(\text{BN})$ ($\text{Ln} = \text{La}, \text{Ce}, \text{Pr}$). Only for $\text{CaNi}(\text{BN})$ is a single-crystal X-ray diffraction determination present, according to which the $\text{B}-\text{N}$ bond here is 138 pm.^[53]

The molecular orbitals of the BN unit show clear differences to those of the C_2 unit^[57] although the ordering of the respective energy levels is the same. For a $[\text{C}_2]^{2-}$ unit with 10 valence electrons and a bond length of 120 pm the electron configuration is $(2\sigma_g)^2(2\sigma_u)^2(\pi_u)^4(3\sigma_g)^2(\pi_g^*)^0$. Contained in it are one strongly bonding $2\sigma_g$ combination and two combinations of lone pairs ($2\sigma_u$ and $3\sigma_g$), of which the $3\sigma_g$ combination represents the HOMO of the $[\text{C}_2]^{2-}$ unit. The mixing of the orbitals in the $3\sigma_g$ combination of the BN unit have (because of the nondegenerate $\text{B}-\text{N}$ interaction) high coefficients located at the boron atom (Figure 20, left). Therefore, the B atom of the BN unit is predetermined to form donor bonds towards soft metal centers through this nonbonding combination—similar to C in CO . At the same time the BN unit can act as an electron acceptor through its π^* orbitals.

The unit cells of the tetragonal $\text{LnNi}(\text{BN})$ structures contain two crystallographically identical BN units. The energy bands of the BN partial structure show dispersions (between the special points $X-\Gamma$, $\Gamma-M$, $A-\Gamma$, and $Z-R$) which are a result of $\text{B}\cdots\text{B}$ interactions of neighboring BN fragments (Figure 20, middle). If all bonding and nonbonding

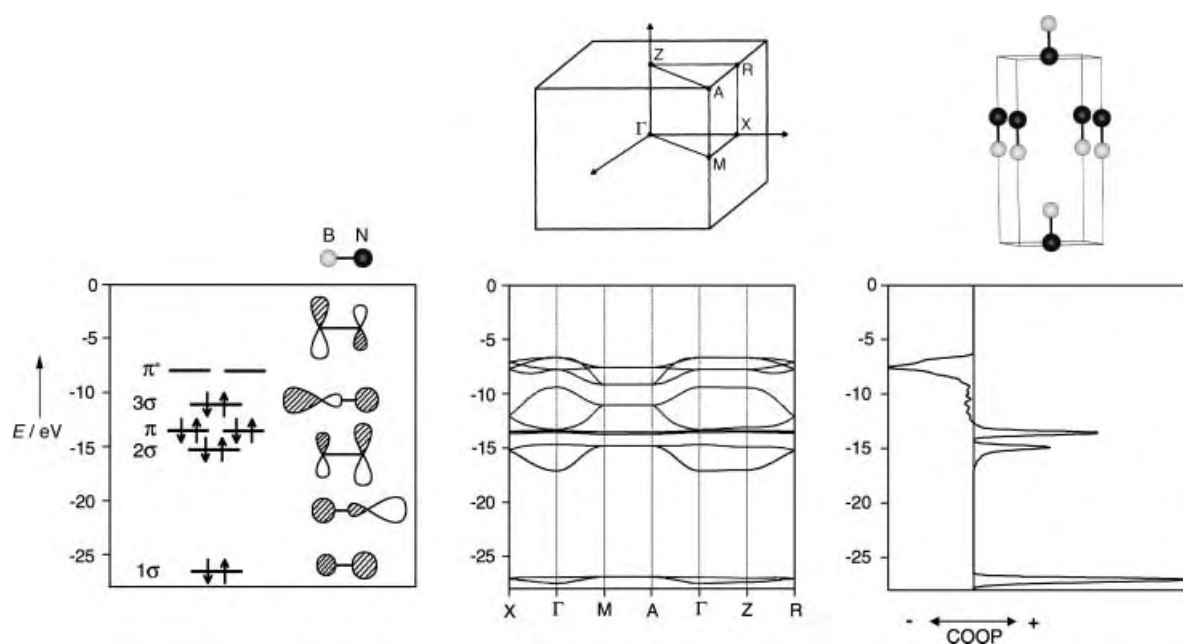


Figure 20. Molecular orbitals of the BN^{2-} unit (left), band structure with corresponding Brillouin zone (center), and B–N overlap population (COOP) of the BN partial structure of LaNi(BN) (right).

B–N states are occupied with electrons, $[\text{BN}]^{2-}$ ions can be addressed to the MO as well as to the COOP of the BN partial structure (Figure 20, right). In the projected DOS for LaNi(BN) the contributions of the (La)5d bands and the (Ni)3d bands can be traced as clear peaks at around -7 eV and -14 eV (Figure 21). Thus the (Ni)3d bands are below the Fermi energy in the range of the bonding π levels of BN. The projected B–N overlap populations allows a rough allocation of the electronic states in bonding (1σ , 2σ , π), nonbonding (3σ), and antibonding (π^*) with increasing energy. From these the 1σ , 2σ , π , and 3σ corresponding to the energy states for a $[\text{BN}]^{2-}$ unit can be considered filled. Because of the bonding and antibonding interactions with metal atoms, the π^* energy states are split into two blocks. The position of the Fermi energy for LaNi(BN) indicates that the π^* energy states are partially occupied with electrons. From this result a simple charge picture can be derived as $(\text{La}^{3+})(\text{Ni}^0)(\text{BN}^{3-})$. A similar combination between $(\text{C}_2)\pi^*$ and (Ln)5d orbitals is shown in Figure 19 for metal dicarbide compounds. With one electron

less per formula unit the antibonding π^* orbital for CaNi(BN) is only partially occupied and this should result in a shorter B–N bond. The electronic situation can be given formally as $(\text{Ca}^{2+})(\text{Ni}^0)(\text{BN}^{2-})$.

In its bonding behavior BN exhibits, through the B atom, σ -donor, but also acceptor capabilities with regard to nickel atoms. Lanthanum has stronger electron-donation properties, since the (La)5d orbitals are higher in energy and transfer charges to the BN unit. Also from this consideration it becomes clear that a charge close to zero is to be assigned to the nickel atoms in these compounds. To date the B–N vibration frequencies of the black $\text{LnM}((\text{BN}))$ substances are not known.

6.4 Comparisons of Compounds with C_2 , BN, and BCB Ions

The structure of UCoC_2 ^[58] corresponds topologically to the LnM(BN) structure. This type of structure can be generated

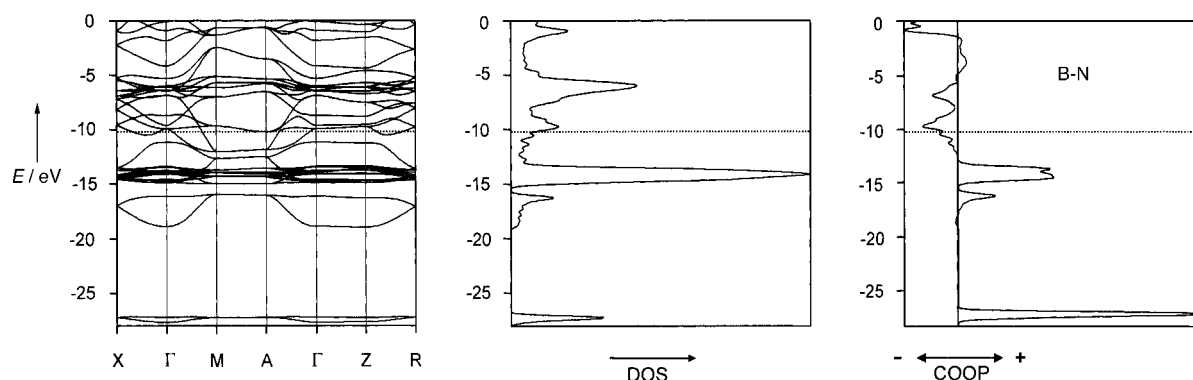


Figure 21. Band structure (left), DOS (center), and B–N overlap population (right) of LaNi(BN) . The Fermi level is marked as dotted horizontal line.

by insertion of one atom layer into the tetragonal CaC_2 structure. The UCoC_2 type can also be derived from the anti-PbFCl type, as the uranium and cobalt atoms take the positions of chlorine and fluorine and the Pb position is occupied by a C_2 unit. The C–C bond of 148 pm in UCoC_2 is in the range accepted as a C–C single bond. If a further atom layer is inserted into the UCoC_2 type, the ThCr_2Si_2 type^[59] results, in which several hundred compounds crystallize (Figure 22).

Special attention was focused on the $\text{LuNi}_2(\text{B}_2\text{C})$ ^[60] derivative of the ThCr_2Si_2 structure type in which the Si_2 unit is replaced by a triatomic B–C–B unit (Figure 22). Compounds with this structure variant exhibit superconductive characteristics with transition temperatures of up to 17 K. Triatomic linear anions with 16 valence electrons such as $[\text{NBN}]^{3-}$, $[\text{CCC}]^{4-}$, $[\text{CBN}]^{4-}$, and $[\text{CBC}]^{5-}$ are known from numerous saltlike compounds. Their bond lengths are a good reference system for metal-rich compounds containing these units. An example with a $[\text{BCB}]^{6-}$ ion has to date not been reported for saltlike compounds. This situation is not surprising, since, according to a general rule^[61] which is supported by theoretical calculations,^[62] the more electronegative atom in an $[\text{X}=\text{Y}=\text{Z}]$ trimer with 16 valence electrons has a tendency to occupy a terminal position of the triatomic unit. The superconductive compound $\text{LuNi}_2(\text{B}_2\text{C})$ ^[63] contains a linear $[\text{B}-\text{C}-\text{B}]$ ion with a B–C bond length of 147 pm. In the linear $[\text{CBC}]^{5-}$ ion of $\text{Al}_3(\text{C})(\text{BC}_2)$ ^[64] the B–C bond lengths is 144 pm, as in the compounds $\text{Ca}_9\text{Cl}_8(\text{BC}_2)_2$ ^[65] and $\text{Ca}_5\text{Cl}_3(\text{C}_2)(\text{BC}_2)$ ^[66] (145 and 144 pm) which have slightly bent $[\text{C}-\text{B}-\text{C}]$ units (162 and 164°). In such a linear trimer with 16 valence electrons the HOMO is formed by the nonbonding π_g orbitals.^[67] In conformity with the octet rule the full occupation of the nonbonding π_g orbitals would correspond to a $[\text{B}=\text{C}=\text{B}]^{6-}$ ion. Extended Hückel (EH) calculations of the electronic structure of $\text{LuNi}_2(\text{B}_2\text{C})$ were interpreted in that the π_g orbitals are only partially occupied, and lead to a formal charge description of $(\text{Ln}^{3+})(\text{Ni}^0)_2(\text{B}_2\text{C}^{3-})$.^[68, 69] The complete occupation of the (Ni)3d bands is also supported by local density approximation (LDA) calculations^[70] according

to which the (Lu)5d bands (mainly $d_{x^2-y^2}$ orbitals) dip below the Fermi level, and are thus partially occupied and therefore responsible for the mobility of charge carriers.

7. Summary

Nitridoborate compounds of the lanthanides can be produced in different ways: by direct reaction of metal and/or metal nitride together with h-BN and by solid-state metathesis reactions between LnCl_3 and Li_3BN_2 . The exothermic metathesis reaction between LnCl_3 and Li_3BN_2 occurs below 600 °C. Single crystals are formed at higher temperatures from the LiCl flux formed in the reaction. In modified metathesis reactions the N content can be controlled by using Li_3N as a nitride source. The additional use of lithium leads to the synthesis of metal-rich Ln nitridoborate compounds.

Compounds with the anionic units BN, BN_2 , B_2N_4 , B_3N_6 , and BN_3 are known with electropositive (alkaline, alkaline-earth, lanthanide) metals. The B_3N_6 unit occurs both in planar and in nonplanar conformations. Compounds of the type $\text{Ln}_3\text{B}_3\text{N}_6$ stand out for their mechanical hardness. Nitridoborate compounds of the alkaline-earth metals, perhaps also of the Ln metals, can be used for conversions of h-BN into its cubic modification.

Transition metals do not tend to form nitridoborate compounds, because electrons in B–N bonds can have a reducing effect on 3d metal ions. Therefore, Ni^{2+} in NiCl_2 is readily reduced by Li_3BN_2 at 300–400 °C to the metal.^[38] Transition metals nevertheless can occur in pseudo-ternary nitridoborate or ternary dicarbide compounds. The relationship between C_2 and BN is emphasized by structures of the UCoC_2 type and is further supported by the similarities between the carbidometallates Na_2MC_2 ($\text{M}=\text{Pd}, \text{Pt}$)^[71] and “nitridoboratometallates” $\text{CaM}(\text{BN})$ ($\text{M}=\text{Ni}, \text{Pd}$). Also the compounds Na_2MC_2 contain neutral M atoms and twofold negatively charged C_2 ions (C–C bond: 123 pm). Since the charges of BN and C_2 units cannot be assigned precisely for compounds with metallic properties, the distances in the

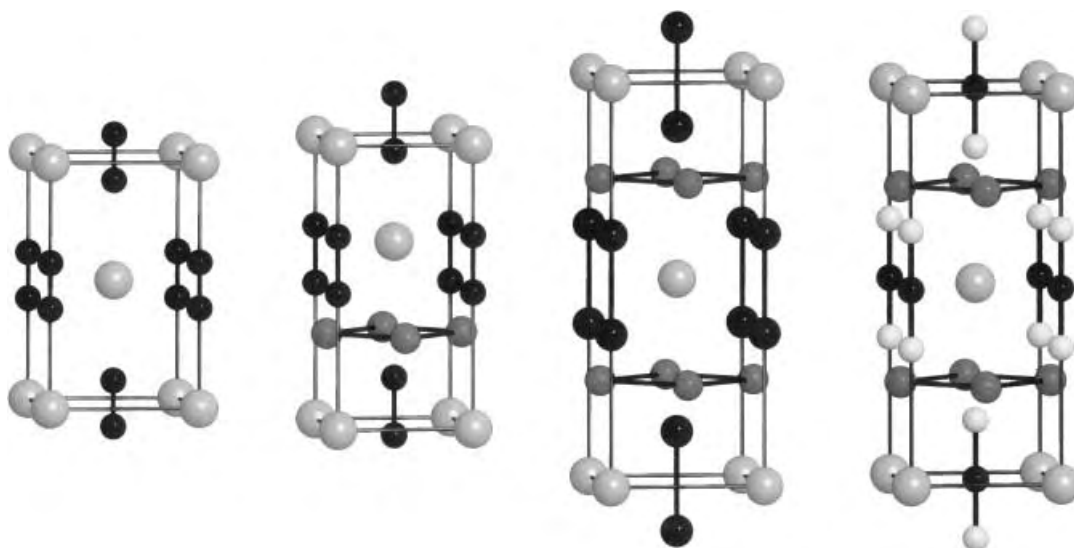


Figure 22. Comparison of the structures of CaC_2 , UCoC_2 , ThCr_2Si_2 , and $\text{LuNi}_2(\text{B}_2\text{C})$ (from left to right).

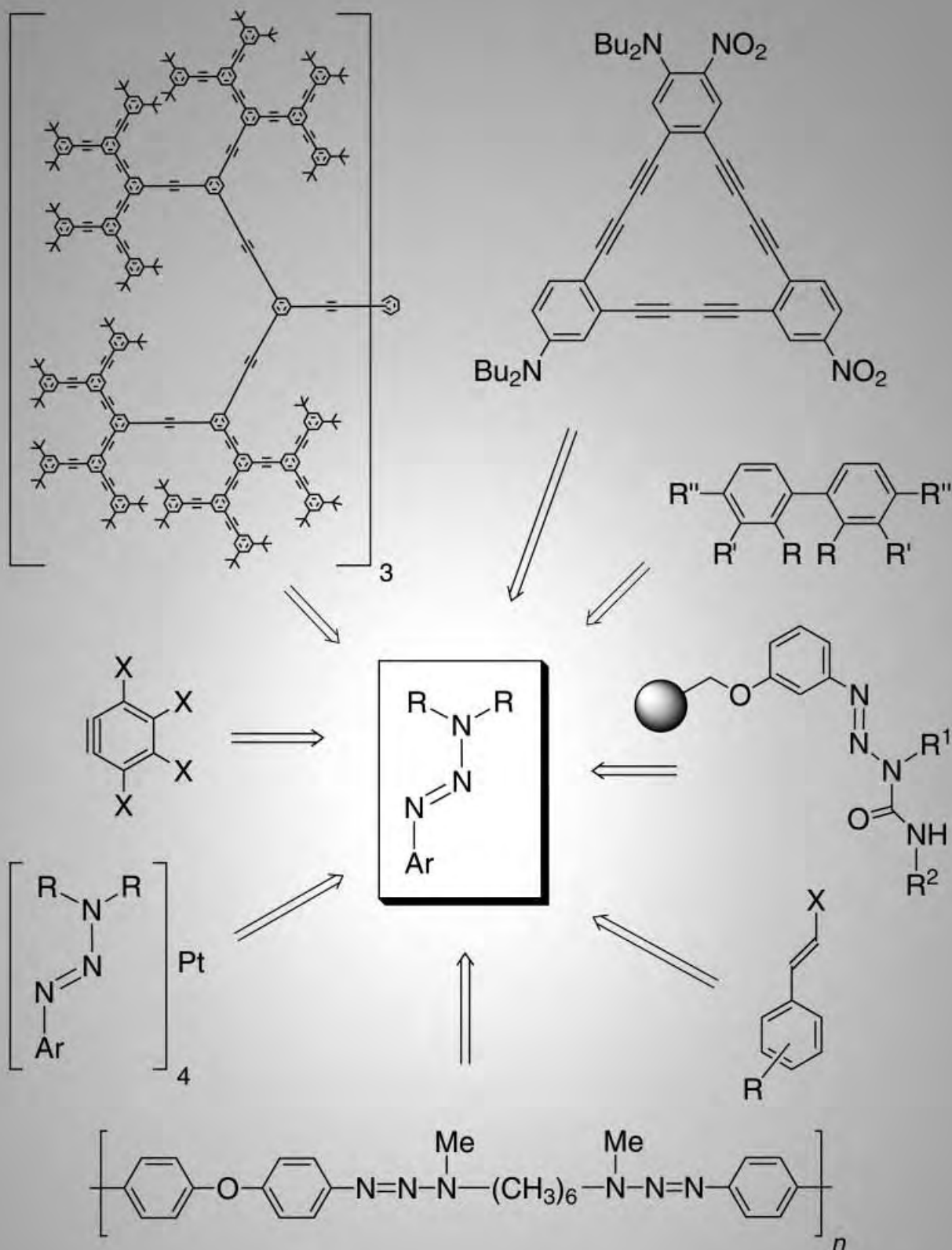
diatomic anions serve—provided they are known accurately—as a probe for their electronic condition. For the normal or superconducting properties $[\text{BN}]^{n-}$ ions serve as a charge reservoir which is increasingly emptied in the series $\text{La}_3\text{-Ni}_2(\text{BN})_2\text{N}_{1-x}$ ($x = 0.09$), $\text{LaNi}(\text{BN})$, $\text{CaNi}(\text{BN})$ if one assumes a d^{10} configuration for the nickel centers.

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Triazenes: A Versatile Tool in Organic Synthesis



Triazenes: A Versatile Tool in Organic Synthesis

David B. Kimball and Michael M. Haley*

Triazenes (RN=N–NR'R'') are a class of compounds that hold much promise in preparative chemistry as they are reactive groups which are both stable and adaptable to numerous synthetic

transformations. Useful to scientists in pharmacology, total synthesis, polymer technology, and the construction of novel ring systems, to name a few areas, triazenes also have a tendency

to surprise chemists with new reactions and increasing applicability. This review highlights some of the recent advances and diversity possible with these types of systems.

1. Introduction

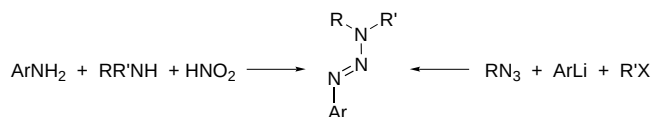
Triazenes are a very useful and diverse class of compounds. They have been studied for their anticancer potential,^[1, 2] used as protecting groups in natural product synthesis^[3] and combinatorial chemistry,^[4] incorporated into polymer^[5] and oligomer^[6] synthesis, and used to form novel heterocycles.^[7] Their biological activity derives from their ability to form diazonium salts that can alkylate DNA.^[1, 2] Triazenes can also be transformed into several different reactive groups after treatment with the appropriate reagents. In the case of aryl triazenes, iodomethane-induced decomposition yields an iodoarene, which can react with acetylenes or alkenes under mild conditions to give cross-coupled products. If acid is used, both a diazonium and an ammonium species are generated and each can be utilized depending on the desired application.^[8] Disubstituted triazenes can also form anions that are useful as ligands in organometallic chemistry.^[9]

Triazenes are easily synthesized from readily available anilines or alkyl azides (Scheme 1). Anilines are typically treated with nitrite ion under acidic conditions to form a diazonium salt, which is quenched with a primary or

secondary amine to provide the desired triazene in high yield. Dialkyl triazenes can be obtained from the reaction of an alkyl azide with the appropriate Grignard or alkyl lithium reagent. It is interesting to note that most triazene syntheses were optimized prior to the 1930s^[10] and that some of the most useful preparative routes have changed little in the 100 years since their initial discovery.

Although triazenes were extensively studied prior to 1950,^[10] their versatility in organic synthesis has been greatly expanded during the past 30 years. The ease with which triazenes can be formed and selectively decomposed to give arenes or anilines with a proton in place of the triazene group has made them useful as linkers to solid supports. In the field of poly(phenylacetylene) synthesis, triazenes are indispensable for efficient convergent and iterative methodologies. Advances in triazene synthesis and the increasing ability to study modes of activity in the body has created renewed interest in their anticancer potential.

In this review, the synthetic utility of triazenes will be detailed, with an emphasis on recent developments. The triazenes discussed are straight-chain molecules that contain three contiguous nitrogen atoms, in which N1 is double-bonded to N2, which is linked by a single bond to N3 (e.g. RN=N–NR'R''). Both formation and usage will be discussed with respect to specific applications. Exhaustive treatment of the synthesis and properties of triazenes can be found in several reviews^[8, 10–12] and is beyond the scope of this text. Instances in which triazenes are only transient intermediates, or the preparation is not practical on a preparative scale, will not be addressed.



Scheme 1. General synthetic routes to triazenes.

[*] Prof. Dr. M. M. Haley, D. B. Kimball
Department of Chemistry
University of Oregon
Eugene, OR 97403-1253 (USA)
Fax: (+1) 541-346-0487
E-mail: haley@oregon.uoregon.edu

2. Medical Applications of Triazenes

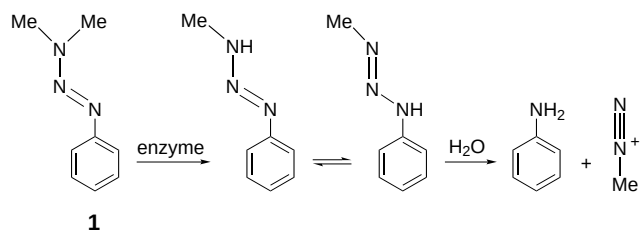
One of the most prevalent uses of triazenes is in the development of anticancer molecules. The therapeutic poten-

tial of a variety of triazenes has been extensively explored as well as their specific metabolic action.^[1, 2, 13] For aryl and alkyl triazenes, proteolytic decomposition occurs under physiological conditions to give reactive alkyl diazonium compounds capable of alkylating DNA;^[14, 15] consequently, these compounds are carcinogenic and/or mutagenic.^[12] Several triazenes, however, show low animal toxicity while retaining their potency against specific tumor cell lines.^[16, 17]

2.1. 1-Aryl-3,3-dialkyltriazenes

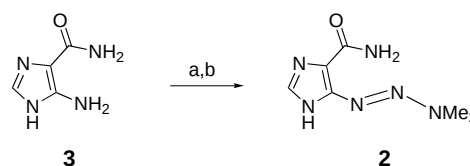
The most well-known triazene in anticancer study is 1-phenyl-3,3-dimethyltriazene (**1**).^[2, 12–15] Several groups have provided strong evidence for enzyme-catalyzed demethylation as the initial step of metabolism, followed by rearrangement of the resulting disubstituted triazene and proteolytic loss of an aniline to generate a methyl diazonium ion (Scheme 2).^[2, 13, 18–20] This species can then methylate DNA with the loss of dinitrogen.^[14, 15, 20]

Dialkylphenyl triazenes of this sort are typically synthesized from anilines and secondary amines. A typical example is the synthesis of **1** from aniline and dimethylamine.^[21] The



Scheme 2. Formation of the methyl diazonium ion from **1** under physiological conditions.

reaction conditions are surprisingly tolerant of a wide range of functional groups, including ester, halogen, and nitrile functionalities.^[22, 23] Aryl systems other than those derived from aniline have been used to make dimethylaryl triazenes for antitumor study, the most active and well-studied of which is 5-(3,3-dimethyltriazeno)imidazole-4-carboxamide (**2**, Scheme 3),^[24] also known as dacarbazine. Triazene **2** has been in clinical use for the treatment of malignant melanoma, soft-tissue sarcoma, and Hodgkin's disease since the late 1970s.^[24] Dacarbazine is synthesized from 5-aminoimidazole-4-carboxamide (**3**) using acid and nitrite, then quenching with a solution of dimethylamine in methanol. The use and study of dacarbazine is now so ubiquitous that it is commercially available.



Scheme 3. a) HCl, NaNO₂, 75 %; b) Me₂NH, MeOH, 48 %.

Aryl triazenes connected by an alkane linker, which could potentially form lethal DNA cross-links, have been reported. Peori, Vaughan, and Hooper synthesized many “bistriazenes” for this purpose (Scheme 4).^[25, 26] Aryl amines were converted into the diazonium species, then compounds of type **4** were formed from the reaction of this diazonium species with 1,3,6,8-tetraazabicyclo[4.4.1]undecane (**5**). Simpler alkyl linkers can also be used and are easily formed in good yield by coupling two equivalents of a diazonium salt with *N,N'*-dialkyl-1,2-ethylenediamine derivatives.^[27]

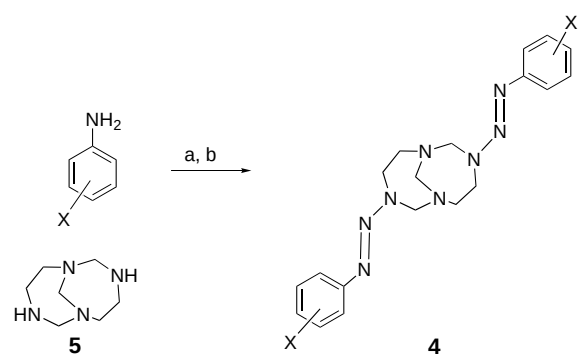
Michael M. Haley was born in 1965 in Lake Charles, LA. After growing up in Tulsa, Oklahoma, he studied cyclopropene and cycloproparene chemistry with Prof. W. E. Billups at Rice University (B.S. 1987, Ph.D. 1991). In 1991 he received a National Science Foundation Postdoctoral Fellowship to work with Prof. K. P. C. Vollhardt on [n]phenylene chemistry at the University of California, Berkeley. In 1993 he joined the faculty at the University of Oregon where he is currently an Associate Professor of Chemistry and member of the Materials Science Institute. Among his awards are a National Science Foundation CAREER Award (1995), a Camille Dreyfus Teacher-Scholar Award (1998), and an Alexander von Humboldt Research Fellowship (2000). His current research focuses on the chemistry of dehydro- and dehydrobenzoannulenes, metallabenzenes, and other novel aromatic systems.

David B. Kimball was born in Salt Lake City, Utah, in 1973. He received his B.S. in chemistry from the University of Houston in 1995, where he studied heteroaromatic ligand synthesis for use in copper and ruthenium complexes under Professor R. P. Thummel. He obtained his M.A. in chemistry from the University of Oregon, where he worked with Professor Haley, studying aromaticity in phenylacetylene-based annulenes. He completed his Ph.D. studies in June 2002, in Professor Haley's group, investigating novel triazene cyclizations to form heterocycles, and is now a postdoctoral associate at Los Alamos National Laboratory.



M. M. Haley

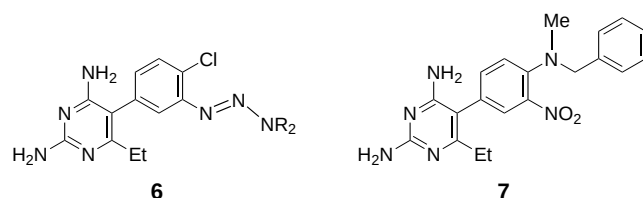
D. B. Kimball



X = *p*-NO₂, *p*-CN, *p*-COMe, *p*-CO₂Me, *p*-CO₂Et, *p*-Br, *o*-NO₂, *o*-CN

Scheme 4. a) HCl, NaNO₂; b) **5**, CH₂O.

More complex aryl systems have been used in conjunction with triazene chemistry for biological methylating purposes. Stevens et al. designed several dialkyl biaryl triazenes (**6**) based on the methylbenzoprism skeleton (**7**) for use as



inhibitors of *Pneumocystis carinii*.^[28] Triazenes of type **6** combine antitumor potential with inhibitory action against a microorganism-specific dihydrofolate reductase enzyme,^[28] which is chiefly responsible for pneumonia-related deaths in AIDS sufferers. Triazenes were prepared from the corresponding amines in the usual manner.

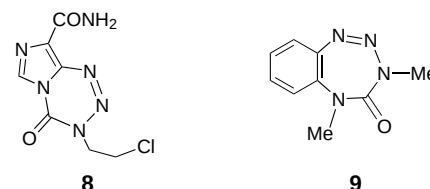
2.2. Acyl-Substituted Triazenes

Another class of triazenes which show potent antitumor activity are those bearing acyl substitution.^[29] Although many were initially designed to be more stable versions of trialkyl triazenes,^[30] the physiological fate of these compounds is now thought to be considerably more complex, possibly involving enzymatic deacylation.^[1, 31] Some acyl-substituted derivatives show structural similarity to (2-chloroethyl)nitrosourea derivatives,^[32] which are known to form lethal cross links in DNA.^[33]

The simplest examples of acyltriazenes are those that contain a 1,3-dialkyl-3-acyl structure. Compounds of this type are obtained from the reaction of an acid chloride with a triazene anion. The disubstituted anions in turn are obtained by treating an alkyl azide with the appropriate alkyl lithium or Grignard reagent. A typical preparation is that reported for 3-carbethoxy-1,3-dimethyltriazene,^[30] in which 1,3-dimethyltriazene is treated with potassium hydride, and subsequently with ethyl chloroformate, to give the desired product in 77 % yield. Michejda and co-workers showed that dialkyl acyltria-

zenes undergo hydrolytic decomposition at physiological pH levels, and most have mutagenic activity towards strains of *Salmonella typhimurium*.^[30, 34] Another acyltriazene, 1-(chloroethyl)-3-methyl-3-methylcarbamoyl)triazene, showed enhanced cytotoxicity against strains of leukemia and melanoma.^[1, 29] The synthesis of this compound also involved acylating a disubstituted triazene.

Studies with acyl-substituted triazenes have been motivated by the antineoplastic activity against malignant melanoma of the imidazo-1,2,3,5-tetrazin-4-one **8**,^[35] which can be used as a



triazene precursor. This compound can be hydrolyzed to the open-chain triazene and thus form a possible alkylating agent. Jean-Claude and Just have prepared several tetrazepinones **9** based on this cyclic N-acyl motif.^[16, 36, 37] The key feature of the synthesis involves ring formation by trapping an aryl diazonium species with an *ortho* amide. Systems such as these are among the most promising agents for clinical use.^[16, 38, 39]

2.3. Hydroxymethyl Triazenes

Derivatives of hydroxymethyltriazenes have been prepared as a result of research indicating hydroxymethyltriazenes as the immediate oxidation products of dimethyltriazenes of the type **1**.^[2, 17, 19] After reaction with cytochrome enzymes in the cell, loss of formaldehyde to generate highly reactive monomethyl triazenes is rapid in aqueous media. Rearrangement to the 1-methyl-3-aryltriazene then allows proteolytic decomposition to an aniline and a methyl diazonium ion.

The groups of Vaughan^[40, 41] and Rosa^[42, 43] have synthesized hydroxymethyl derivatives of triazenes for studies relating to the development of prodrugs. Rosa and co-workers have developed a general synthetic method for these systems, which involves loss of water in acidic solution followed by nucleophilic attack of the iminium ion by an alcohol.^[44] Use of DMF as the solvent increases yields and allows less stable alcohols to be used.^[43] In most cases, the synthesis is straightforward and high-yielding. Use of such triazine derivatives as prodrugs, however, is hampered by slow hydrolysis at pH levels near physiological conditions.^[43]

2.4. Trialkyl and Dialkyl Triazenes

Trialkyl triazenes have received moderate attention in the literature as possible antitumor agents.^[45] Although trialkyl triazenes were prepared by Dimroth^[46] almost a century ago, a general synthesis of these compounds was only accomplished

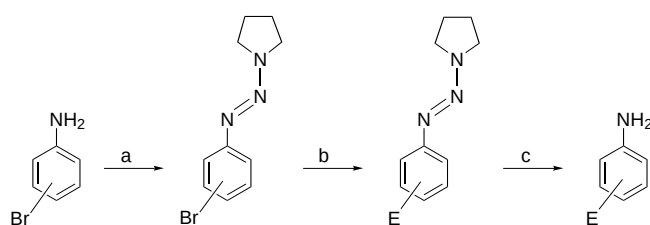
within the last 30 years.^[47] Proteolytic decomposition to the alkyl diazonium species has been demonstrated using pH-buffered solutions, however, their practical effectiveness is hampered by instability.

One exception to the instability of exclusively alkane-substituted triazenes is a series of bis(methyltriazeno)alkanes or “bistriazenes” prepared by Blumenstein and Michejda.^[48] Similar to the corresponding work of Vaughan and co-workers,^[25, 26] these systems were designed to alkylate DNA at both ends of an alkyl linker, thereby linking the strands. The compounds prepared were formally disubstituted triazenes, which possess significant antitumor activity.^[2] Unlike their dialkyl triazene analogues, however, these compounds formed stable solids, which could potentially increase their lifetimes under physiological conditions and allow them to be more effective in clinical use.

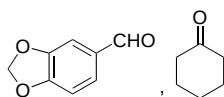
3. Triazenes Used to Protect/Generate an Amine

One of the simplest uses of triazenes is to protect or generate an amine. Although the formation of anilines from the acid-induced decomposition of aryl triazenes has been known for some time,^[10] this particular use is rare as many other protecting groups are available.^[49] Several authors, however, have shown that triazenes are indeed useful for this purpose. Triazenes, once generated, are stable to a variety of conditions^[50] and their facile and efficient conversion into the corresponding amines has been demonstrated.^[4, 51]

Triazenes are particularly useful aniline protecting groups when performing halogen-metal exchanges. Gross, Blank, and Welch used a series of triazene-protected bromoanilines for bromine–lithium exchange and subsequent reaction with electrophiles (Scheme 5).^[52] The triazene protecting group



E = CO₂, PhCOPh, PhSSPh, Me₃SiCl, D₂O, MeCOMe, Bu₃SnCl,

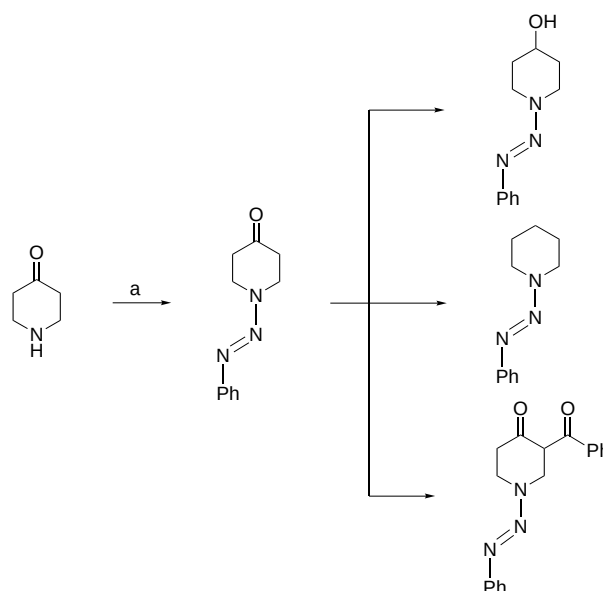


Scheme 5. a) 1. HCl, NaNO₂; 2. KOH, pyrrolidine; b) 1. *s*BuLi or *t*BuLi; 2. electrophile (E); c) Ni/Al, KOH, MeOH.

was used because of both its stability to electrophilic reagents and its compatibility with *meta*- and *para*-carbanion formation. The readily available bromoanilines were converted into the triazenes and metalated with *sec*- or *tert*-butyllithium to provide aryl carbanions that reacted smoothly with carbon, sulfur, and silicon electrophiles, or with deuterium oxide. The corresponding anilines were regenerated using nickel–alu-

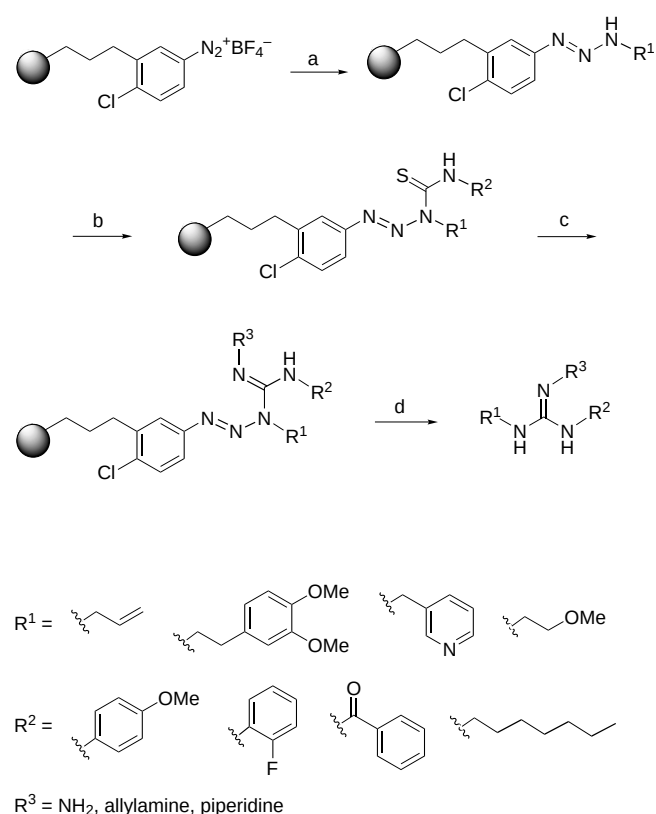
minum alloy in methanolic hydroxide solution. These fairly mild conditions provide anilines from triazenes quantitatively in almost all cases.^[51] A more recent example uses this same chemistry to generate a 17 α -(4-aminophenyl)estradiol.^[53] The key step in this synthesis was the addition of a lithiated phenyltriazene to estrone. The amine was subsequently obtained after hydrogenation in the presence of palladium.

Non-aromatic amines can also be protected efficiently as triazenes. Lazny et al. used the triazene group to protect 4-piperidone from later reactions involving hydride reduction and alcohol oxidation.^[54] After 4-piperidone reacted with phenyldiazonium salt, the resulting triazene was stable to LiAlH₄, chromium-based oxidants, NaBH₄, and other reagents to give several useful products (Scheme 6). The amines were regenerated in good yield using 50 % trifluoroacetic acid (TFA) in CH₂Cl₂ at room temperature. Other secondary amines that have been protected as triazenes for analogous purposes include piperazine derivatives,^[55] proline derivatives,^[55] 3-alkoxy-4-aryl piperidines,^[56] and nortropans.^[55]



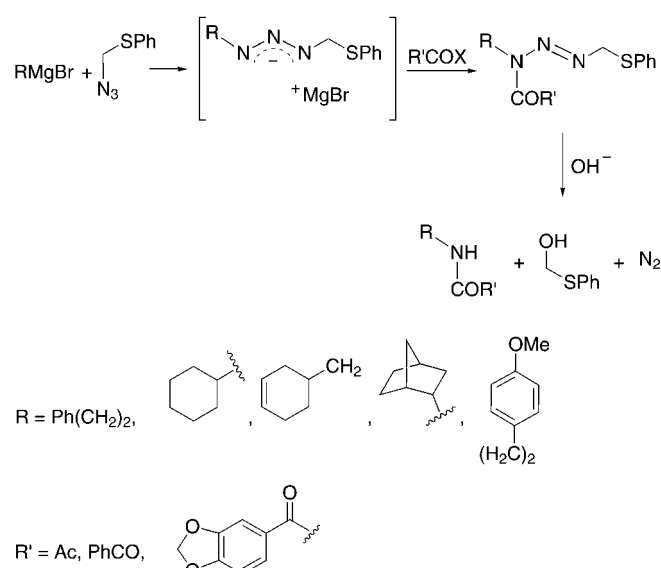
Scheme 6. a) PhN₂BF₄, Et₃N.

Bräse and co-workers have adapted triazenes to protect amines^[57, 58] and amides^[4, 59] for solid-phase organic synthesis. Using the triazene as a linker to a solid support, Bräse's group has prepared amide libraries from the reaction of polymer-bound aryl diazonium species with primary amines. The 1,3-disubstituted triazenes produced could be further alkylated or acylated in excellent yield using acid chlorides, isocyanates, or isothiocyanates (Scheme 7).^[58] Synthesis of the solid-phase triazenes began with establishing a diazonium species on a solid support, which could be accomplished by treating polymer-bound anilines with a strong Lewis acid (F₃B·OEt₂) and *t*BuONO in THF. These diazonium salt resins were remarkably stable to both isolation and thermal decomposition. Combining the diazonium species with primary or secondary amines produced triazenes that were suitable for further elaboration. Cleavage from the resins could be effected using TFA in CH₂Cl₂.



Scheme 7. a) $R^1\text{NH}_2$, THF, 12 h, $-10^\circ\text{C} \rightarrow \text{RT}$; b) NaH, DMF, $R^2\text{NCS}$, 2 h, RT; c) AgNO_3 or HgO , $R^3\text{NH}$, MeCN, 12 h, 45°C ; d) TFA, CH_2Cl_2 , 5 min, RT.

Triazenes can also be used as intermediates for the generation of useful amines. Unlike typical syntheses, however, the amine is not used to form the triazene. Instead, an alkyl or aryl anion reacts with an azide. Trost and Pearson showed that this method works well for converting alkyl or aryl bromides into amines.^[60, 61] The bromide compounds were first converted into the Grignard reagents and then treated with azidomethylphenyl sulfide (Scheme 8). The triazene



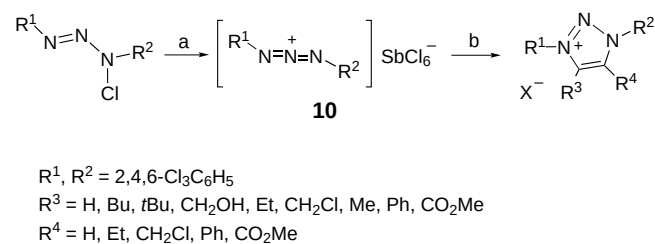
Scheme 8. Amide synthesis via acylated triazenes.

anion formed could be quenched either with a proton or an acyl source, depending on the substitution desired on the final amine. It is important to note that the less thermodynamically stable triazene is generated. The methylphenyl sulfide substituent on the azide dictates this configuration and promotes initial triazene formation. The sulfur atom also promotes decomposition to the desired amines by various nucleophiles. The authors found that aqueous formic acid would also release the amine or amide from the triazene.

4. Triazenes Used in Heterocycle Synthesis

Heterocycle synthesis is an important and complex area of organic chemistry. Interestingly, this field has been advanced as much by chance discoveries as by design. Triazene chemistry reflects this by showing a remarkable and sometimes unexpected tendency to form new heterocycles under various conditions. Although at times they are only fleeting intermediates, triazenes are often rational starting materials for heterocycles that are unattainable by other routes.

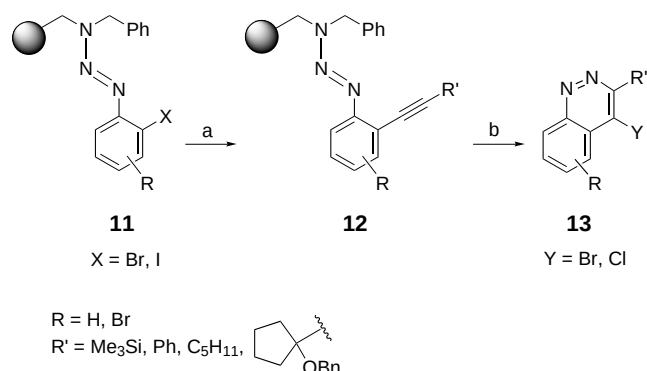
N-Chloro-substituted triazenes can react with dipolarophiles to give heterocyclic products. Jochims and co-workers have observed [3+2] cycloadditions between 1,3-diaza-2-azoniaallene ions (**10**, Scheme 9) and dipolarophiles such as



Scheme 9. a) SbCl_5 , CH_2Cl_2 , -60°C ; b) $R^3\text{C}\equiv\text{CR}^4$, CH_2Cl_2 , $-60 \rightarrow 23^\circ\text{C}$.

alkenes,^[62] 1,3-butadienes,^[63] alkynes, carbodiimides, and cyanamides.^[64] The dipolar ions were prepared from the reaction of N-chlorotriazenes with Lewis acids, typically SbCl_5 . Cycloadditions were performed at low temperatures, as a consequence of the instability of the chlorotriazenes and corresponding dipolar ions, to furnish 1,2,3-triazolium and tetrazolium salts. The triazenes themselves were synthesized from chlorine-rich anilinederivatives in the usual fashion by chlorination using *tert*-butylhypochlorite.

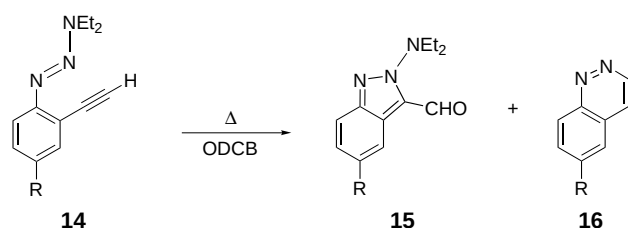
The Richter cyclization of an aromatic diazonium ion *ortho* to an acetylene functionality to give a cinnoline has been utilized extensively since its discovery in 1883.^[65] The cinnolines produced are substituted at the 4-position as a result of nucleophilic attack on the acetylene to drive the cyclization. Bräse and et al. have modified this method to include triazenes as protected diazonium species (Scheme 10).^[66] This modification also allows the triazenes to be attached to a solid support, benzylaminomethyl polystyrene, which greatly simplifies the purification of starting materials. Using anilines substituted at the *ortho* and *para* positions, formation of the diazonium ion followed by quenching with the solid-supported amine provides the aryl triazenes **11**. Iodo or bromo



Scheme 10. Synthesis of cinnolines. a) $\text{HC}\equiv\text{CR}'$, $\text{Pd}(\text{OAc})_2$, NEt_3 , DMF, 80°C , 12 h; b) HY , acetone/ H_2O , 47–95%.

substitution *ortho* to the triazene allows Sonogashira coupling^[67, 68] to give the required *ortho*-alkyne precursors (**12**). Cleavage from the resin under acidic conditions first provides the diazonium species which cyclizes to the cinnolines **13** in moderate to good yield. A significant limitation to the Richter cyclization, however, is that only 4-substituted cinnolines are produced. For cinnolines that are unsubstituted on the pyridazine ring, difficult procedures are necessary to remove these functional groups.

A new method for the generation of cinnolines as well as isoindazoles from aryl triazene moieties *ortho* to alkyne functionalities was recently developed by Haley and co-workers.^[22] Heating the 1-(2-ethynylphenyl)-3,3-diethyltriazenes **14** (Scheme 11) to 170 – 180°C in 1,2-dichlorobenzene

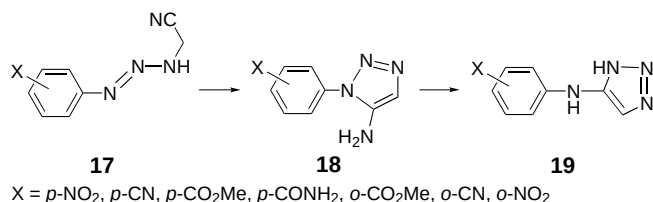


R = H, Me, *t*Bu, F, Cl, Br, C $\equiv$ CH, CO₂Me, NO₂, CN

Scheme 11. Synthesis of isoindazoles and cinnolines. ODCB = 1,2-dichlorobenzene.

gave a mixture of isoindazole **15** and cinnoline **16** products. Neutral conditions were used which allow a greater range of functional groups to be attached to the resulting cinnoline or isoindazole. High yields (>90%) of **16** were obtained by heating the starting triazenes to 190 – 200°C . Comparable yields and exclusive formation of **15** could be accomplished at much lower temperatures ($\approx 50^\circ\text{C}$) when the cyclizations were performed in the presence of CuCl .^[69]

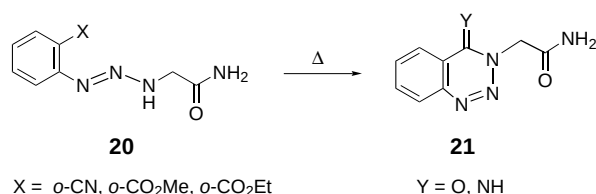
Vaughan, Hooper, and co-workers have shown that other aryl triazenes functionalized with alkyl nitriles^[70] or amides^[71] can cyclize spontaneously or at elevated temperatures to give triazoles and benzotriazoles. Triazene derivatives which contained cyanomethyl substituents (**17**, Scheme 12) were prepared by reacting an aryl diazonium species with α -aminoacetonitrile under acidic conditions.^[70] Cyclization to 5-amino-1-aryl-1,2,3-triazoles **18** and 5-(arylamino)-1,2,3-tria-



Scheme 12. Synthesis of 1,2,3-triazoles.

zoles **19** could be achieved by heating the triazenes in refluxing ethanol. Some control could be exerted over which isomer prevailed, either by heating or by treating the triazenes with alumina; however, cyclizations were limited to *para*- and a few *ortho*-substituted arenes.

Amide analogues of these triazenes with activated *ortho* substituents on the arene (**20**, Scheme 13) cyclized with slight heat or spontaneously during purification to give 1,2,3-benzotriazine derivatives **21**.^[71] Triazenes such as **20** were prepared similarly to their cyanomethyl analogues, using glycine hydrochloride in place of aminoacetonitrile. The success of the reaction, however, necessitated electron-withdrawing substituents on the aryl diazonium species. Both *ortho* methoxy- and ethoxycarbonyl as well as cyano-substituted aryl triazenes cyclized to **21**.



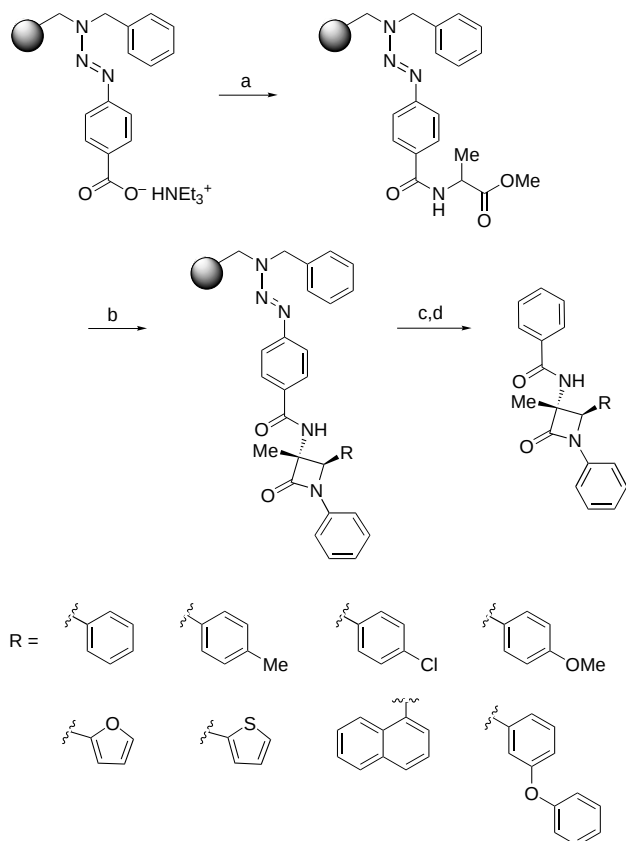
Scheme 13. Synthesis of 1,2,3-benzotriazin-4(3*H*)-ones and 1,2,3-benzotriazin-4(3*H*)-imines

5. Triazenes Used to Generate Other Functional Groups

Triazenes have been used to generate many different types of functional groups other than amines and heterocycles. The most prevalent of these is in the synthesis of reactive halides. Triazenes can be decomposed to give fluoride^[72] and iodide^[73] compounds useful for radiolabelling, and, in the case of iodoarenes, for the synthesis of phenylacetylene-based systems.^[5, 6] The latter will be detailed in the following section. Other functional groups that can be produced from triazenes include phenols,^[10] alkenes,^[74] biaryls,^[75, 76] and products resulting from aryne intermediates.^[77]

Of course, the simplest functional group that can result from the decomposition of a triazene is a hydrogen atom. Although seemingly extraneous, this reaction is useful in solid-phase synthesis when a traceless linker is needed. Bräse and co-workers have used this method to produce a variety of substituted benzenes linked to a solid support through a triazene.^[78–80] The products are cleaved from the resin under mild conditions to give the desired products in which a proton has replaced the triazene group in a traceless manner. Triazenes were synthesized by quenching a diazotized aniline

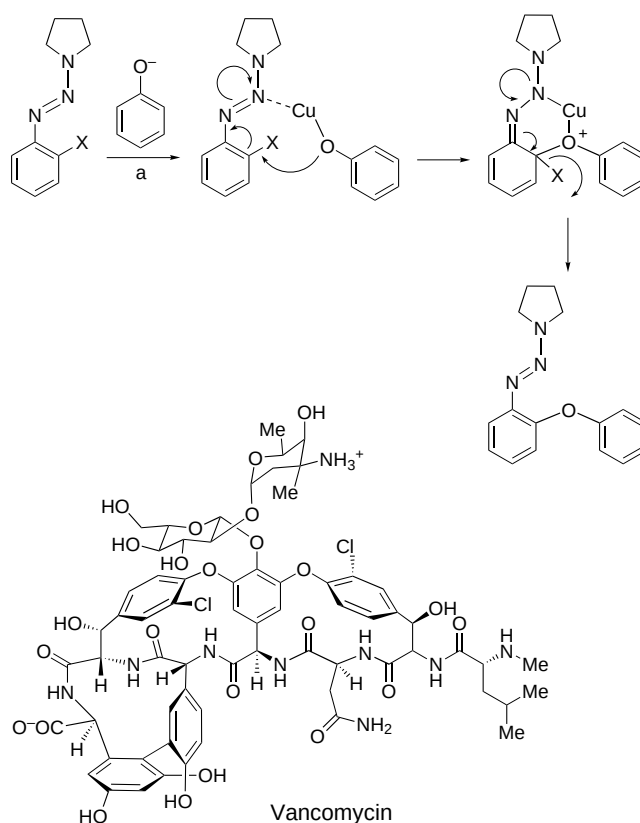
with benzylaminomethyl polystyrene resin. After appropriate reactions (Heck coupling, acylation), the triazenes were decomposed in the presence of trichlorosilane to yield the protonated arenes in good to excellent yield after simple filtration from the resin. Enders and co-workers have used this same methodology to synthesize β -lactams on a T1-triazene linker to a solid support (Scheme 14).^[81] The diazonium salt of 4-aminobenzoic acid was linked to benzylamine resin, after which amidation provided the lactam precursors. Once the β -lactam was generated, cleavage from the resin gave the desired products in moderate yield, with excellent purity.



Scheme 14. a) Alanine methyl ester, 2-chloro-1-methylpyridinium iodide, NEt_3 , CH_2Cl_2 , RT, 12 h; b) 1. LiHMDS , THF, -78°C ; 2. $\text{RCH}=\text{NPh}$, $-78^\circ\text{C} \rightarrow \text{RT}$, 23 h; 3. H_2O ; c) $\text{TFA}/\text{CH}_2\text{Cl}_2$; d) THF/DMF , 60°C , 15 min. LiHMDS = lithium bis(trimethylsilyl)amide.

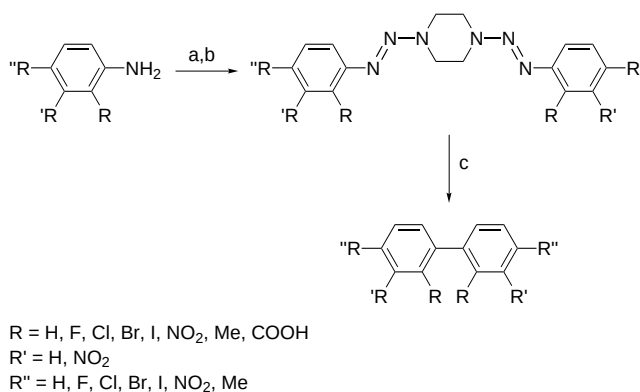
An interesting use of an aryl triazene was reported by Nicolaou in the total synthesis of vancomycin.^[82–85] The triazene functionality served a dual purpose: to protect a reactive site for later conversion into a phenol and to aid in the construction of *ortho* biaryl ether functionalities (Scheme 15). The (*ortho*-haloaryl)triazenes were treated with phenolic counterparts in the presence of base and CuBr to afford the desired ethers. Sequential reaction of the 2,6-dihalogenated aryl triazene backbone with side chains terminated in phenols installed the necessary regiochemistry for each macrocyclic ring system.

Biaryl synthesis can be accomplished through a variety of procedures. The most high yielding and selective of these use



Scheme 15. a) $\text{CuBr} \cdot \text{Me}_2\text{S}$, K_2CO_3 , pyridine, MeCN , 75°C , 3 h.

transition-metal catalysis, as is the case with Suzuki couplings.^[86] Triazenes, however, provide an alternative route to biaryls that is mild and avoids expensive catalysts. Patrick, Willaredt, and DeGonia have shown that TFA-promoted decomposition of aryl triazenes in benzene solution results in good yields of heterocoupled biaryl species.^[76] Aryl triazenes used included nitro, halo, alkyl, and alkoxy substitution. Yildirim and co-workers synthesized a similar series of homocoupled biaryl compounds starting from bistriazenes that were prepared by quenching aryl diazonium compounds with piperazine (Scheme 16).^[75] Decomposition of the triazenes and biaryl coupling occurred in the presence of acetic acid at 90°C . Biaryl yields, however, were poor, ranging from trace amounts to 31 %.



$\text{R} = \text{H, F, Cl, Br, I, NO}_2, \text{Me, COOH}$
 $\text{R}' = \text{H, NO}_2$
 $\text{R}'' = \text{H, F, Cl, Br, I, NO}_2, \text{Me}$

Scheme 16. a) NaNO_2 , HCl ; b) piperazine; c) AcOH , $85-90^\circ\text{C}$.

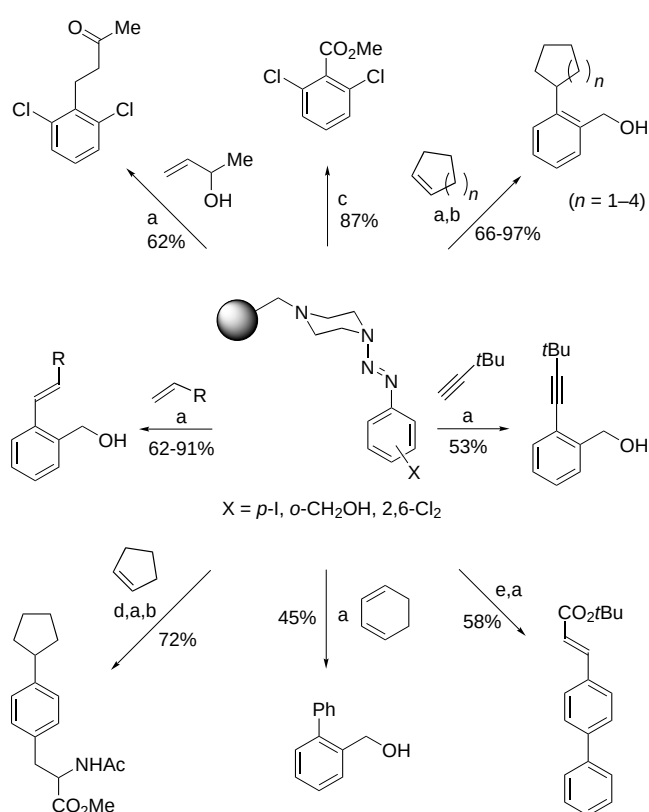
The production of phenols from aryl triazenes has been known, at least as a side reaction, almost as long as triazene synthesis itself.^[10] This use of triazenes, however, has been limited until fairly recently. Typically, the conversion of anilines into phenols is done by generating the diazonium species and quenching with hydroxide ion.^[87] The harsh conditions employed in this reaction often limit the substrates that can be employed. In the case of aryl triazenes, milder conditions can be used to generate the same phenols. Satyamurthy et al. used a sulfonic acid resin in water to decompose several triazenes to the corresponding phenols.^[88] Yields were generally high except for nitroaryl triazenes. Similar to other solid-based reactions, column chromatography or other purification methods were unnecessary. This method was easily adapted to give oxygen isotope-enriched phenols by replacing the solvent with H₂¹⁸O. Others have used similar means to generate phenols from triazenes in the arena of natural product synthesis.^[3] Mild conditions and high yields make this route particularly suitable for sensitive and/or large molecules.

Heck coupling of an alkene to a suitably functionalized arene in the presence of a palladium catalyst is a very useful tool in organic synthesis.^[89] Although haloarenes and aryl triflates are normally used for coupling to an alkene, diazonium species masked as triazenes can also be used. Sengupta and co-workers reported that aryl triazenes react with alkenes when treated with TFA or 42 % HBF₄ and catalytic Pd(OAc)₂ in refluxing methanol.^[74] The reaction time was short (45 minutes) and yields were good, with the exception of nitroarenes. Similar work has been done by de Meijere et al.^[90] Heck reactions were performed on triazenes bound to a solid support and analogous methods were used to release the reactants from the resin as diazonium salts. Coupling of arene diazonium salts after release from solid supports has been extended to include Sonogashira coupling, Suzuki coupling, and other biaryl syntheses (Scheme 17).^[91] This allows triazene-linked arenes to be used in combinatorial chemistry, as the synthesis can be automated.

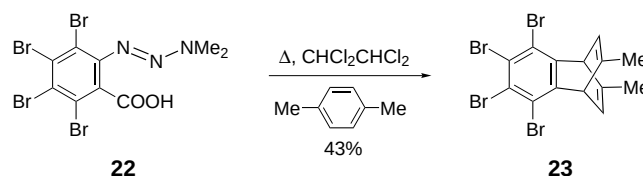
Products resulting from an aryne intermediate can be obtained from heating aryl triazenes *ortho* to carboxylate in electron-poor systems. Buxton and Heaney synthesized four tetrahalo-substituted aryltriazene-2-carboxylate systems (e.g. **22**, Scheme 18) which formed cycloadducts (e.g. **23**) when heated in the presence of arenes.^[77] Presumably the *ortho* acid first protonates the dimethylamino portion of the triazene, after which the diazonium ion is generated. Fragmentation and liberation of CO₂ and N₂ then give an aryne which can react with an arene in a [4+2] cycloaddition. In contrast to their diazonium salts, the starting triazenes are stable compounds that can be handled without special precautions and can be stored more easily.

6. Triazenes Used in Phenylacetylene-Based Systems

Phenylacetylene molecules have been synthesized for applications ranging from nonlinear optics to liquid-crystal



Scheme 17. a) Alkene, alkyne, or diene, Pd(OAc)₂ or Pd/C, TFA, MeOH, 2 h, 40 °C; b) H₂ (1 bar), 2 h, 25 °C; c) (X = 2,6-Cl₂) CO (1 bar), Pd(OAc)₂, TFA, MeOH, 2 h, 40 °C; (X = *p*-I) CH₂=C(NHAc)CO₂Me, Pd(OAc)₂, PPh₃, NEt₃, DMF, 24 h, 80 °C; e) (X = *p*-I), PhI, Pd(OAc)₂, PPh₃, NEt₃, DMF, 24 h, 80 °C; R = Ph, CO₂tBu, 2-pyridyl, butyl, hexyl.



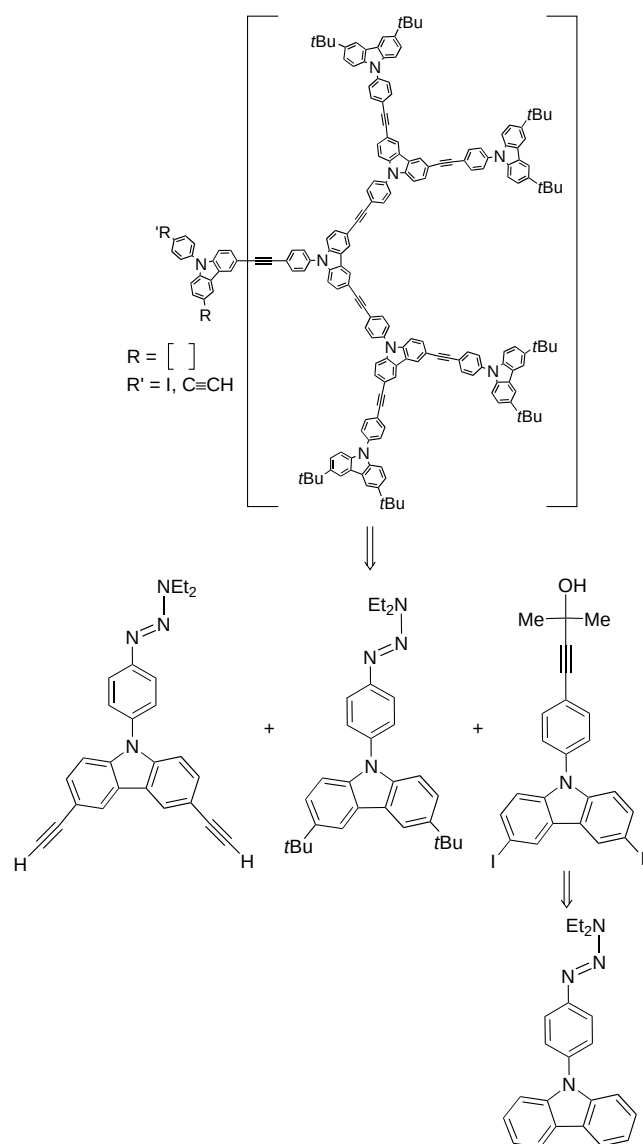
Scheme 18. Use of aryl triazenes for the formation of arynes.

technology, from chemical sensors to light-harvesting materials, and from conducting polymers to shape-persistent molecules.^[92] Phenylacetylenes are rigid, geometrically well-defined, conjugated building blocks that can be combined to give a multitude of architectures. Combined with modern cross-coupling techniques, these systems have become as widely applicable as they are readily available.

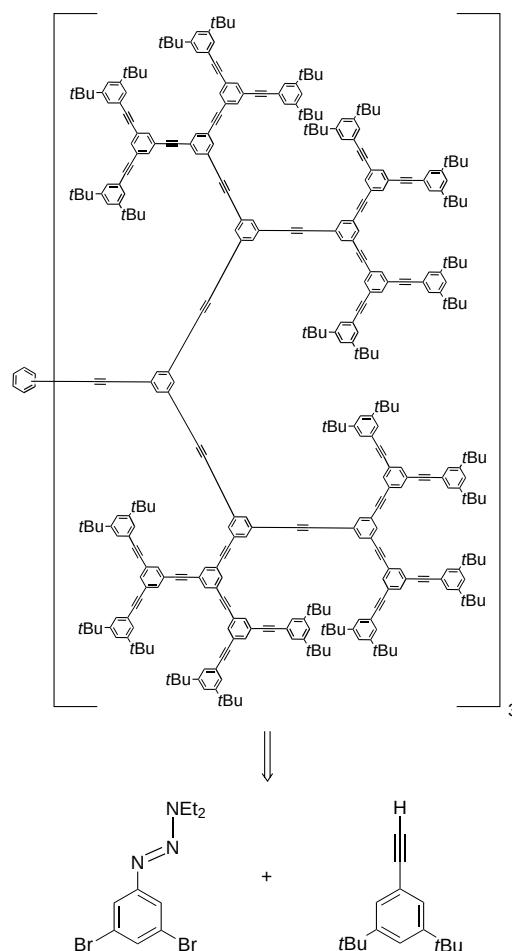
The chemistry of extended phenylacetylene-based systems relies heavily on the availability of iodoarenes. Most acetylene coupling strategies in the past two decades have been dominated by Pd-mediated reactions,^[67, 68] which link an acetylene to an iodoarene. Although other haloarenes can be used, none are more efficient or as effective as iodoarenes. Any method, therefore, which generates site-specific iodoarenes easily and in high yield would be invaluable for preparing large, shape-specific phenylacetylene systems. Such a method was found by Moore et al. when they treated aryl triazenes with iodomethane at a high temperature.^[23] The reaction conditions cause decomposition of the triazene to a diazo-

nium species and the dinitrogen component is effectively replaced with iodine. This process is site-specific and nearly quantitative for a variety of arenes. The same effect can be accomplished using trimethylsilyl halides at lower temperatures^[93] or under microwave irradiation,^[73] by treating triazenes with I₂ in 1,2-dichloroethane,^[94] or by using NaI and a cation-exchange resin.^[95] As will be seen shortly, however, iodomethane is the preferred reagent.

The Moore group has assembled a wide array of phenylacetylene macrocycles and dendrimers. The general synthetic route is based on a highly efficient strategy of triazene formation, acetylene coupling/deprotection, triazene decomposition, and further coupling. These steps can give a wide range of large, shape-specific phenylacetylene architectures rapidly and in good yield. The power of this relatively simple process is reflected both by its widespread use as well as by the large variety of possible products. Some examples from Moore and co-workers include phenylcarbazole dendrimers (Scheme 19),^[96] phenylacetylene dendrimers (Scheme 20),^[6] and phenylacetylene macromolecules



Scheme 19. Synthesis of phenylcarbazole dendrimers.

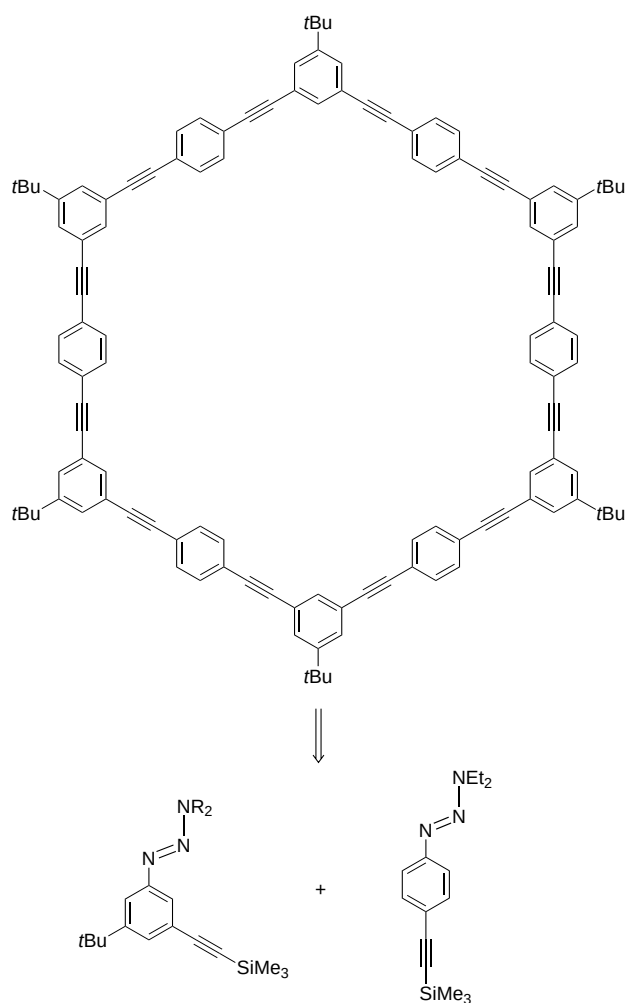


Scheme 20. Synthesis of phenylacetylene dendrimers.

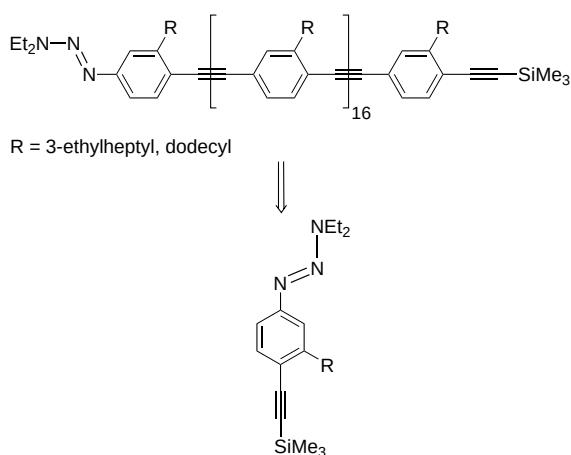
(Scheme 21).^[6] Each of these systems share a common theme; they all contain key triazene intermediates in their iterative syntheses.

Tour and co-workers have also synthesized phenylacetylene systems based on an analogous strategy.^[5, 97] Using iterative couplings and deprotections, Tour and co-workers produced long phenylacetylene rods for application as molecular wires.^[5, 97] Again, their systems usually contain key triazene intermediates which are essential for rapid and efficient synthesis of linear phenylacetylene polymers (Scheme 22). For solubility as well as simplification of purification, these systems are often linked to solid supports, which can be easily accomplished through a triazene linker.^[5, 97] This linker and other triazene intermediates decomposed on exposure to iodomethane, to generate the iodoarenes. Other groups have used this same approach to synthesize similar phenylacetylene rods for nonlinear-optical^[98] applications and liquid-crystalline^[99] applications based on the functionality of the side chain.

Aryl triazenes have been used extensively in the synthesis of dehydrobenzoannulenes. Haley and co-workers have produced annulenes with mono-,^[100] di-,^[101] and triacetylene^[102] linkages (**24–26**, respectively) between benzene rings using different triazene precursors. For these macrocycles, judicious use of aryl triazene precursors governs the eventual

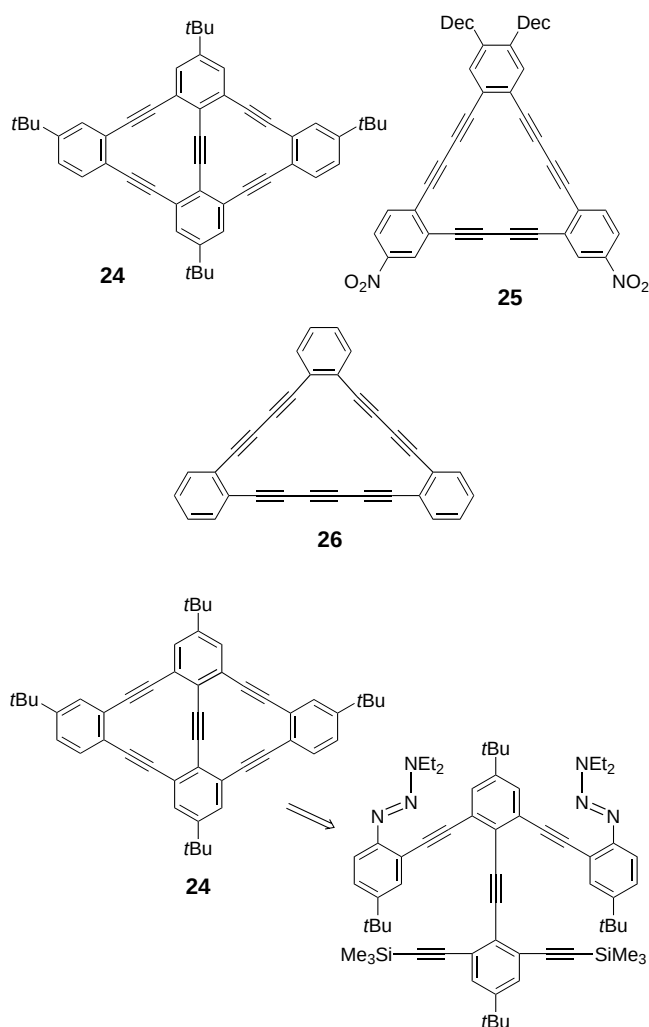


Scheme 21. Synthesis of phenylacetylene macrocycles.



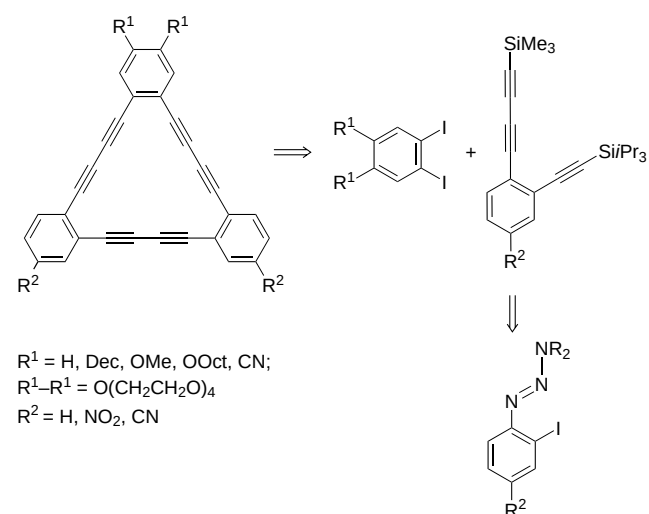
Scheme 22. Synthesis of molecular wires using triazenes.

annulene topology or substitution pattern. In monoacetylene systems, the triazene masks a reactive site that must be converted into an iodoarene and coupled intramolecularly with a nearby acetylene for cyclization to occur (Scheme 23). The ready availability of *para*-substituted aniline derivatives



Scheme 23. Triazenes in the synthesis of monoacetylene-bridged annulenes.

makes the generation of “push–pull” annulenes straightforward, as the triazene simplifies the formation of the necessary phenyltriyne building blocks (Scheme 24).^[101]

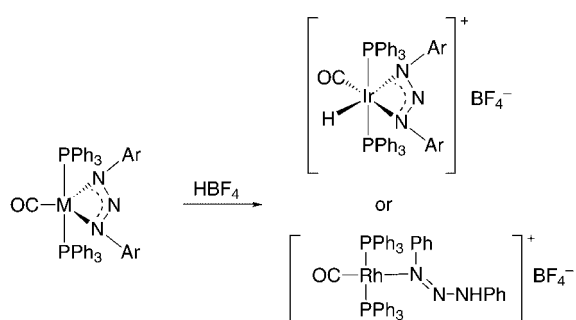


Scheme 24. Triazenes in the synthesis of diacetylene-bridged donor–acceptor annulenes.

Along these same lines, there are two recent reports of the use of aryl triazenes for later conversion into iodoarenes, both for their site-specificity and for synthetic ease. Dendritic porphyrins with phenylacetylene linkers were synthesized by Gossauer and co-workers.^[103] The *para*-substituted phenylacetylene connecting rods were prepared through successive coupling, iodomethane-induced triazene decomposition, and further coupling. Icosahedral carboranes, $C_2B_{10}H_{12}$, can also be prepared through the use of triazene precursors.^[104] These compounds result from the reaction of an acetylene with decaborane, $B_{10}H_{12}$, and are useful for a variety of high-temperature ceramic and polymer applications.^[104] Vinas and co-workers prepared methyl 5-ethynyl-3-iodobenzoate and methyl 3,5-diethynylbenzoate from a triazene precursor and treated each with decaborane to produce mono- and bis(arylcarboranes).^[104] The low yields obtained for cluster formation detract from their potential use in polymer applications.

7. Complexation Chemistry of Triazenes

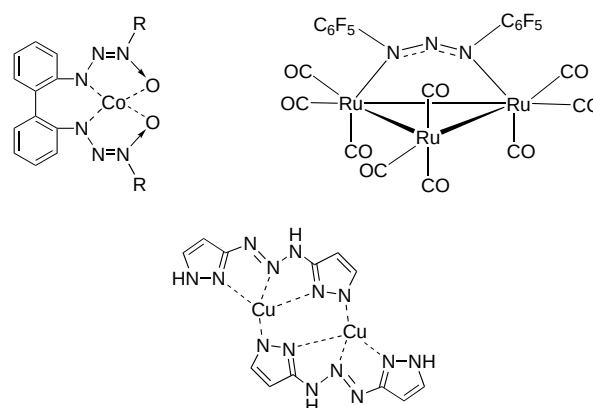
Although many triazene–metal complexes have been reported, their usefulness in organometallic synthesis has not been well explored. One notable account dealt with the interaction of disubstituted triazenes with metal perchlorates. Iley et al. observed decomposition products analogous to those from proton-catalyzed processes when alkyl aryl triazenes were treated with Fe^{2+} , Zn^{2+} , or Cu^{2+} sources.^[105] Because many triazenes used for anticancer applications suffer from instability in vivo, these findings are significant considering that these ions are all abundant in the blood stream as well as throughout the body. Another report detailed the reaction of diaryl triazene complexes of rhodium and iridium with HBF_4 (Scheme 25).^[106] It was hoped that



Scheme 25. Protonation of triazene–transition-metal complexes.

such a reaction would induce decomposition of the coordinated triazene to give an $[RN_2]^+$ ligand. This was not observed, however, and protonation of the triazene ($M = Rh$) or formation of a hydrido complex ($M = Ir$) resulted instead.

Interest in triazene–metal complexes mainly derives from their structural properties. Triazene ligands can vary in their electron-donor ability, as well as their potential to form bridging compounds or act as bidentate ligands (Scheme 26).^[9, 107] A number of metals can be bound to



Scheme 26. Different coordination modes of triazene ligands in complexes.

triazenes, including nickel,^[108] copper,^[109] platinum,^[110] cobalt,^[111, 112] ruthenium,^[9] and osmium.^[9] In fact, hydroxytriazenes have been used extensively in the spectrometric determination of metals.^[113] These triazenes can be used to detect minute amounts of metals such as nickel and cobalt even in the presence of other cations in solution.

8. Outlook

The future of triazenes in organic synthesis is very promising. New uses and reactions of triazenes are appearing in the literature more and more frequently. Of particular utility is the conversion of triazenes into iodoarenes and their use as linkers to solid supports. Indeed, instances in which extended phenylacetylene systems are synthesized without the use of triazene building blocks are rare. Their use as links to a solid support, either for traceless cleavage or as an amine/amide protecting group, is a very useful addition to combinatorial chemistry. It is very likely that triazenes will continue to expand the field of heterocycle synthesis as well.

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Can Moral Norms be Rationally Justified?

Günther Patzig*

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

1. Introduction

In Germany, the topic of whether norms can be rationally justified has gained surprising relevance and urgency in recent months. Journals and newspapers brimmed with controversy. They were full of emotionally tainted statements and arguments, often concerning bioethical and medical questions. The first problem was that of active euthanasia carried out by doctors, legalized after a long period of discussion and a kind of test run in the Netherlands; the second crucially that of our dealings with embryos and embryonic or other stem cells.

For some time the practice of “pre-implantation genetic diagnosis” was very prominent. After in vitro fertilization, parents who have reason to believe that their offspring might suffer from severe genetic defects get the chance of having the embryo tested for such genetic defects at the earliest stage of development, before it is implanted. In the worst case, they may decide against implantation. The question of whether this procedure is permissible concerns, above all, the “moral status” of the embryo. Research in the field of stem cell therapy then relates to the moral status of human cells that can, under certain circumstances, develop into a complete human being.

There is one thing about these discussions that professional moral philosophers found quite baffling: Proponents of differing views in these matters, especially those opposed to the methods mentioned above, talk and write as if morality was all on their side, as if people who hold other views say good-bye to the old consensus of Europe’s moral tradition. They frequently insinuate that those who support new technological methods such as genetic research have first and foremost great economic advantages in mind; and that in their view these advantages justify the dismantling of moral norms. When Britain decided to legalize experiments with superfluous embryos for exceptionally important research,

the German minister of justice said, very much in this vein: “England has now left the circle of cultivated nations.”

There seems to me to be a fairer and more realistic view: It is not the case that such disputes occasion the clash of guardians of moral standards on the one hand and disdainers of morality enthused, even inebriated with the idea of scientific progress on the other, but rather of proponents of two different moral outlooks. Also, the so-called “conservative” position ascribing even to the newly fertilized ovum full human dignity and the unconditional protection that our constitution accords to persons, is in fact both radical and very modern: it is not, in any way, rooted in the history of moral thought.

As with other controversial questions concerning morally right behavior, we now face the problem of having to distinguish the more correct convictions from the less correct ones amongst the diverging moral views expressed by their proponents with so much force. I shall now turn to this fundamental question.

What is a moral norm? I think the following explanation (not definition) might be acceptable: moral norms are rules of human behavior directed at making sure that human beings treat the needs, interests, and wishes of other human beings—or, in an extended version, of all sufficiently sentient beings—in all their acts and omissions in such a way that these interests etc. pertaining to those individuals affected or threatened by their behavior not be infringed upon to any unacceptable extent, but rather promoted as far as reasonable and possible. When I say “Interests etc.” I mean that, for example, the rights of others may also be seen to be factors one ought to pay attention to in one’s behavior. Some of these norms are declared legal norms by developed societies. However, many legal norms, perhaps even most of them, have no moral foundation, even though a certain compatibility with norms of justice is probably one of the most important aims of any legal system (cf. Robert Alexy’s book *Begriff und Geltung des Rechts*, 1992).

So, how can such moral norms be justified? There are, as is presumably widely known, different competing approaches, of which here I shall briefly discuss only some that seem to be particularly important: religious approaches (Section 2), value-based, that is, axiological and ontological approaches

We now face the problem of having to distinguish the more correct convictions from the less correct ones.

[*] Prof. Dr. G. Patzig
Philosophisches Seminar
Universität Göttingen
Humboldtallee 19, 37073 Göttingen (Germany)
Fax: (+49) 551-39-9607
E-mail: mpezl@gwdg.de

(Section 3), approaches within evolutionary theory (Section 4) and finally “communitarian” approaches to justifying moral standards (Section 5). I shall conclude this article by sketching my own basic method of rationally justifying moral norms to in Section 6.

However, I should first like to assess the above-mentioned approaches with a view to whether they can solve the problem of justifying moral norms.

2. Religious models of justification

All great religions—Hinduism, Judaism, Buddhism, Christianity, and Islam, in the order of their historical occurrence—contain catalogues of norms in which certain human actions are declared to be good, others bad. These rules are to be followed because they have been decreed by the Gods, by God or by some religious founder by virtue of their special authority. The Decalogue of the Old Testament and the lessons of the Sermon on the Mount of the New Testament are particularly prominent in Western culture.

As these are supposed to involve some kind of justification of moral norms, two fundamental and widely discussed difficulties immediately come to mind: First of all, it is a matter of faith whether the documents in which these norms are laid down are in fact considered to be the utterances or instructions of some superhuman authority; and secondly we must keep in mind that we always require, over and above such commandments, an independent and prior principle to tell us that it would be our moral duty to obey these commandments in all cases, even if, for example, they contradict our moral intuition.

The argument that we need a superordinate principle according to which we are morally obligated to obey the commands of God as binding even if our moral intuitions point in different directions has been developed by the philosopher Kai Nielsen in particular. Consider God’s commanding Abraham to sacrifice Isaac (Old Testament, Genesis 22), or the command of the Sermon on the Mount not to resist evil but to “turn the other cheek” to somebody who “smites thee on thy right cheek” (New Testament, Matthew 5, 39) and not to “take thought for your life” because God in his own way will care for you as he does for the “lilies of the field” and the “fowls of the air” (New Testament, Matthew 6, 25–28). These divine commands are instructions that clearly contradict the moral intuitions of many of us. Theologians must try—and indeed they do—appropriately to re-interpret passages like “Be fruitful, and multiply” (Genesis 1, 28), the command of unrestricted rule of man over all other creatures (Genesis 9, 2f.), or the sentence “Whoso sheddeth man’s blood, by man shall his blood be shed” (Genesis 9, 6) for humanity in much-changed circumstances today.

In the course of this, theologians univocally claim that the Bible announces God’s commandments in a way intelligible to contemporary readers at the time. It is therefore said to be the continuing task of biblical exegesis to adapt these historical texts in a fast-changing environment to ever new

circumstances: with regard to the threat of global overpopulation, to the responsibility for nature rather than its subjugation, to the fellowship of all living creatures on this planet, and so on. These are views that theologians now like to deduce from the Old and the New Testaments as obligations for mankind today. These views can hardly be substantiated with biblical quotations. They rather amount to adjusting what the Bible says to meet today’s needs, a move motivated by reason. This procedure is perfectly legitimate; but it also raises the following question: Why not decide directly to look for guidelines on how to behave in today’s world, without any reference to those old books? Not even religion can serve as a source of moral norms without the guidance of rational deliberation, especially when the consequences and effects of their moral commands are concerned.

Some theologians at least seem to have reached this conclusion already, for example, Hans Küng. The Dalai Lama too some time ago said that developing a secular system of ethics was a task of particular importance. He considers this necessary because half of mankind, about three thousand million people, do not feel part of any religious tradition, and their moral competence must be taken care of as well. In addition, the age of globalization renders a secular system of ethics necessary because the moral requirements of different world religions are still obviously incompatible. A secular system of ethics might thus, according to the Dalai Lama, provide a common foundation for individual religions to develop their specific ethical norms; norms which must, however, be compatible with the universal system of

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ethics. Considering the many religious conflicts in the course of world history, this thought seems very attractive to me. If there were an ethical system capable of commanding universal agreement, disputes about certain basic moral questions would be different and probably more conciliatory in character. This wraps up religious attempts to justify moral norms. The result is, I think, the following. Even if religious kinds of moral justification do not live up to our general expectations, religious allegiances and ideas must surely play a prominent, perhaps even essential role in many individuals’ willingness to abide by moral norms.

3. Value-Based Models of Justification

Let me move on to the second type of justification. This approach no longer plays a particularly prominent role in academic philosophy, but it still seems very attractive to a general public outside philosophical circles. What I mean is the following: We would have an excellent foundation of moral justifications if we could presuppose a metaphysical thesis according to which there are certain absolute values independent of our opinions, even our very existence; amongst them aesthetic and moral values. In Britain, this thesis was developed and defended under the title of “intuitionism” by George Edward Moore (1903), in Germany especially by Max Scheler (1916) and, in much greater detail, by Nicolai Hartmann (1926). Hans Jonas’ book *Das Prinzip*

Verantwortung (1979, The Imperative of Responsibility) offered an intriguing re-encounter with philosophical ideas that were highly influential in Germany in the 1920s.

According to value-based models of justifications, moral and aesthetic values are independent entities with which we get in touch intuitively or emotionally by means of a “value feeling” (Wertgefühl), and thereby encourage us to realize them. The main flaw of this appealing theory is the fact that these values are presumably introduced “ad hoc” solely for the purpose of forming the basis of justifying our moral obligations.

At this point I should like to mention a general principle in philosophical and scientific methodology that moral philosophers often ignore: a theory is the more powerful the weaker the premises on the basis of which one argues and the stronger the conclusions one is able to deduce from these premises. To put it somewhat differently: it is methodologically pointless to formulate a theory the premises of which are so strong that the result one wishes to establish can be deduced straight away. The only thing speaking in favor of the premise of positing absolute values seems to be that on this assumption formulating a “material ethic of values” would be quite easy.

The great divergence of people’s moral judgments as well as the evident cultural dependence of a so-called “value feeling” should be enough to raise serious doubts about the viability of such an ethical system. In addition, there is what John L. Mackie calls the ontological “queerness” of a class of entities which led a kind of precautionary existence even before humanity came into being. One could of course object to Mackie that “queerness” as such is hardly a reason to doubt the existence of something; for there are other kinds of things that seem queer to us, for example, black holes in astronomy, quarks in elementary particle physics, and retro-viruses in biochemistry. In these latter cases, however, there are empirical observations open, in principle, to everyone that lead to such existence claims within a framework of trusted scientific theories. That is not true in the case of values, where unproblematic every-day talk of an action being “valuable” or having “special moral value” presumably lead to a view in which over and above the action there must be something like a “value” which can be ascribed to it. It is quite natural for us to experience things, actions, artworks, character traits, and much more as “valuable”—without being conscious of the highly complex genetic preconditions of such value “perceptions”. (I do not use “genetic” in a biological sense; it rather concerns the “genesis” of such value judgments.) If, for example, watching a tennis match you are impressed by the delicacy and elegance of, say, a drop-shot, you display this kind of reaction only as a result of watching a great number of matches or actually playing tennis yourself.

A similar point can be made about values that people quite immediately seem to perceive in actions, character traits, and the like. This kind of value theory sounds plausible just because we always see or perceive something valuable in the world we live in, while at the same time we are entirely unaware of the complex genetic background of such “acts of perception”.

Neither the mere survival of the human species, as in classical Darwinism, nor the special reproductive success of the genetic pool I happen to belong to can possibly be the highest target at which my moral norms ought to be directed.

4. Sociobiological Models of Justification

Another way of explaining moral judgments and justifying some moral norms—a way moreover that is particularly influential and popular today—seems to be suggested by the sociobiological approach. Sociobiology has been a genuine competitor of philosophical models of justification for some time. Today’s sociobiological theories can indeed explain a kind of “altruism” that is both essentially reciprocal as well as (highly) selective and gradual in accordance with the degrees of relationship individuals bear to each other, especially with a view to the behavior of socially living mammals. Genes are selected by the struggle for opportunities of life and reproduction. As the same genes occur in the siblings of an individual with the same probability as in its descendants, evolution rewards the kind of behavior that serves the purpose of reproduction and care of offspring as well as the kind of behavior that even at the risk of the individual’s own destruction improves the chances of survival of siblings and other near kin. Genes directing such behavior would have an above-average chance of reproduction in a normal population. Some kinds of behavior typical of human beings—such as caring for one’s own children and helping relatives—receive a satisfactory explanation within this theory. The same may be said for “reciprocal altruism”. Mutual help is better for the survival of the genetic pool of individuals than mutual indifference or even aggressiveness. However, so-called “free riders” must be excluded, that is, individuals who accept the help of others without themselves offering any help when it is their turn. Case studies confirm that “reciprocal altruism” in conjunction with cautionary measures concerning “free riders” is wide-spread amongst socially living animals. It is a pattern of behavior characteristic even of human beings, often accompanied by indifference and even hostility towards outsiders.

How shall we interpret such sociobiological data? Have we found the true source of human morality at last, as some people think, and should we alter, in a sense adjust our historically evolved moral norms with a view to these results? Or should we rather acknowledge sociobiological data as what an empirical science tells us and then carefully weigh and decide whether we consider any morality that draws on such data to be acceptable?

The first of these two possible standpoints, that is, that there is now a scientific foundation of human morality in accordance with which we ought to re-arrange our moral views, has been argued for by the influential American biologist Edward O. Wilson, the British scientist Richard Dawkins (The Selfish Gene) and in Germany by Konrad Lorenz (who

of course still considered the preservation of the species rather than the reproduction of genes the proper end of evolution). We find the second view in the writings of, for example, the Göttingen anthropologist Christian Vogel, who died an untimely death in 1994. Like Vogel, I unambiguously favor this second approach: neither the mere survival of the human species in classical Darwinism, no matter under which

conditions, nor the special reproductive success of the genetic pool I happen to belong to can possibly be the highest target at which my moral norms ought to be directed. With a view to the threat of overpopulation there may obviously even be a moral obligation to keep reproduction within certain limits; and in the case of serious genetic risks there might be the moral question whether one should completely abstain from having offspring in order to limit the passing on of such risks and the suffering likely to result from the outbreak of certain diseases in the next generation. This would be a morally justified kind of behavior contrary to the human tendency to maximize one's reproductive success.

However, sociobiology does teach us how strong our innate tendencies towards, for example, nepotism and xenophobia in fact are. This means that we need to acknowledge such preformations and use moral standardization and education even to counter tendencies that are part of our biological make-up. For this very reason, sociobiology is a crucial resource for the justification of moral norms and especially for purposes of moral education. Sociobiology cannot itself be the foundation of moral norms, though. David Hume was the first to teach us that it is impossible logically to deduce norms from mere facts. That is precisely why even sociobiology, as an empirical science, can offer us nothing normative, nothing other than facts.

Sociobiology cannot itself be the foundation of moral norms because it is impossible logically to deduce norms from mere facts.

5. Communitarian Models of Justification

Over the last decades, the difficulty of finding moral norms that do not vary from culture to culture as well as the initially hopeless dispute about which principles to draw on in justifying universally valid norms has prompted many moral philosophers, especially in the United States, to turn their attention from "ethical theories" and their moral principles to so-called "virtue ethics". J. St. Mill and Kant are usually considered proponents of the former type of moral philosophy, whereas Aristotle and Hume are seen to be the founders of the latter.

Virtue ethics is said to have the advantage of offering justifications of a concrete and emotional, rather than rational kind. To put the question directly, without a view to the great philosophical authorities of the past: is such a "communitarian" moral theory tenable? It seems to me that this theory should rather be considered a false response to understandable fears. The effect of a principle-based universal ethical system, which levels down cultures and cultural differences, is anticipated with fear; as is the dreary monotony produced by a unitary moral code that, to make things worse, is one-sidedly based on western tradition, above all the Enlightenment. The fear of such a sterile wasteland is countered with a colorful, aesthetically much more satisfying plurality of local moral traditions. Sensitivity to concrete special cases with all their peculiar features is meant to replace sweeping rules derived from abstract principles.

An attitude of mutual tolerance is required also in the moral domain, however, there can be no toleration—in the sense of acknowledging the equal.

It is not difficult to reply to such views. It is true that the sheer variety of human "experiments of living" is as such aesthetically pleasing; but it is quite out of the question that all moral scenarios of all societies should be accorded the same moral status. Moral rules are attempts to manage problems and conflicts in society. It is thus not surprising that there should be better and worse solutions, especially since there are basic human needs that different societies satisfy differently, and more or less successfully. There are lively disputes about the most fundamental moral questions even within societies, except perhaps in strictly traditional ones.

You will hardly hold it against a German citizen that he expresses his shock and dismay about a view according to which—implicitly—the system of moral norms prevalent in Germany from 1933–1945 should be considered an equivalent, local scenario of equal moral weight and status to, say, societies of liberal democracies. The communitarian position, however, passionately defended especially in the United States, inevitably points in this direction.

Should we not, from a moral point of view, condemn an extremely unequal distribution of chances in people's working lives and their unequal share of income in some western societies, as we condemn, the subjugation of women, religious intolerance and intimidation of dissenters in other societies? Everybody will notice many moral discrepancies even in the society they grew up in. Even if human rights—as formulated by the UN in 1948 and justly defended in the face of growing opposition to this day—could be taken for granted, there would still be a many ways of realizing these principles to prevent the feared uniformity of living conditions. The plurality of values that is still to be found within single societies is a most welcome scene for experimentally conducting our search for new solutions to morally relevant social problems.

That is why an attitude of mutual tolerance is required also in the moral domain, for example, concerning the permissibility of divorce or polygamy. However, there can be no toleration—in the sense of acknowledging the equal standing of different views—of massive violations of fundamental moral principles such as human rights. To prevent an even more devastating conflict of cultures one must [often?] abstain from realizing one's views by force, however good the reasons for one's views may be.

6. Outline of a Rational Justification of Moral Norms

What shape could a rational justification of moral norms take if it is to be free from at least the gravest doubts diagnosed in the case of each of the approaches discussed so far? One must first and foremost broaden the concept of rationality, which, ever since Max Weber's study of rationality in action, has been reduced to so-called functional or means-ends rationality.

A concept of minimally rational action was defined by Carl Gustav Hempel in his classic article "Rational Action" as early as 1961. An action is rational if it is determined by an intention and if the means supposed to realize the chosen end are, according to the agent's best knowledge, suitable to further the realization of that end. Hempel does not demand that the choice of end be subject to this criterion of rationality, nor in fact that the convictions according to which the means are chosen be formed in a rational way. It would therefore be a (minimally) rational action in Hempel's sense of the word if somebody who believes that geo-radiation damages their organism, and that aluminum foil can protect their body against such radiation, lines their bed with that kind of foil. One might call this rationality of a merely "subjective" kind.

To make rationality objective, we would first have to subject our views about reality, causal relationships, and quite generally the formation of our beliefs to the standards of rationality developed first and foremost, but not exclusively, in science and in logic, especially in theories of reason and argument. Consistency—that is, logical coherence—and well-foundedness can naturally be considered the most important criteria of this kind of rationality. It is not easy to meet these standards. Implicit logical contradictions, which are difficult to detect and to delete, can creep into our beliefs. And as far as the well-foundedness of beliefs is concerned, there will be many disruptive influences that need to be taken into account: emotionally founded prejudices, perception barriers, instances of repression, social pressure, "political correctness" and many more. These mechanisms explain why obviously irrational beliefs, particularly within a framework of political ideologies, can persist even among intelligent people.

Our quest for objective rationality need not at first go beyond the choice of means to pre-given or previously adopted ends. Max Weber's usage of the term "rationality" is to a large extent responsible for the idea still prevalent in Germany that rationality is restricted to the choice of means to pre-given ends. It is an essential step on our way to broadening this type of rationality if the choice of ends itself becomes part of the agenda of rationality.

This is—at least in part—the topic of decision and games theory, founded by Oskar Morgenstern and John von Neumann in 1944. This theory has since seen a rapid development, particularly with respect to the importance its results have had for other disciplines beyond the sphere of economics. There are many rationality criteria for decisions under different conditions, such as security or risk. No rationality criterion has been found for decisions under uncertainty. Maximin, a criterion proposed by John Rawls in his epoch-making book *A Theory of Justice* in 1971—roughly: fear for the worst and try to keep the loss in utility as low as possible—is much disputed.

Here too—in the sphere of rational decision in a games-theoretical sense of the term—there have been attempts see whether the behavior of people in concrete situations actually meets the rational standards of decision theory: maximize expected utility! Characteristic deviations occurred. Many subjects preferred an instant DM 400 to a fifty-percent chance to

get DM 1000 even though, as can easily be seen, the expected utility in the latter case is DM 500. "A bird in the hand is worth two in the bush", as the proverb goes—although I have often asked myself what one would wish to do with a bird in one's hand. Many people have an irrational penchant for security as such, as amongst other things the popularity of sometimes astronomical insurance premiums for air crashes.

It is very interesting to look at the ethical conclusions drawn from decision theory, in particular the discussion of the famous "prisoners' dilemma". This dilemma, the invention of which is generally attributed to the American mathematician A. W. Tucker, can be explained as follows: two prisoners suspected (and guilty) of a robbery are separately brought before the trial judge, who tells them that if they both confess they will probably be sentenced to eight years in prison. If they both deny the crime they will, owing to a lack of evidence, be sentenced each to a year in prison for minor offenses such as unlawful possession of weapons. However, if one prisoner confesses the robbery while the other still denies the deed, the former will go free, turning queen's evidence, whereas the latter will be sentenced to ten years of imprisonment. (We can neglect the oddities of such a fictitious legal system.) Each of the prisoners knows that his comrade has been thus advised; and none of the two can get in touch with the other to make any arrangements. If they could, and trusted each other, joint denial would clearly be the best strategy because they would get away with a year in prison each. As things actually are, each of them almost inevitably suspects that if he denies the deed the other might confess in order to go free while he himself would end up in prison with a ten years sentence. Both will therefore confess, and both will receive an eight-year prison sentence, the second-worst result for both. The prisoners' dilemma is of special relevance for moral philosophy because it shows as in a focus that there are cases in which selfishly rational behavior is worse for all participants than cooperation would be.

However, the gloomy outcome of the prisoners' dilemma is somewhat brightened up by the fact that repetitions have been shown to result in a change of strategy: as has been shown by, for example, Robert Axelrod, there is reason to believe that even a society of rational egoists can agree on a kind of cooperative altruism in accordance with the maxim "You scratch my back, I'll scratch yours". For in the course of time an admittedly reciprocal kind of altruism will prove in the long run to be advantageous for all members of a group. A thought that immediately suggests itself to many is the following: such theoretical approaches might be taken to be a "rational" foundation of morality, in the sense of social cooperation, effortlessly produced by means-ends rationality. Some very prominent moral philosophers have emphatically argued for the thesis that moral behavior must be grounded in informed self-interest, especially if the norms of moral behavior are to be considered in any sense "rational". Epicurus took this line in antiquity; and in our time, Sigmund Freud, John Mackie, and Norbert Hoerster—a somewhat "mixed bag" of authors—have held the view that a rational justification of

Can a rational justification of moral norms only be achieved via the detour of long-term self-interest?

moral norms can only be achieved via the detour of long-term self-interest, Mackie and Hoerster with explicit references to games theory.

All these theories, however, suffer one basic flaw. They can only explain why we consider it right to take the interests of those individuals into account with which we cooperate, or at least could cooperate and who could, moreover, pay back in kind the reckless violation of their interests.

These theories lose all their explanatory power when moral obligations are concerned that we believe to have towards beings that cannot harm us. Severely handicapped or incurably ill people are cases in question, and especially members of future generations, as well as animals we use for our purposes and believe to have a moral obligation towards to treat them with circumspection and care. Shall we assume that rational thought is impotent in these cases?

We now enter a further and yet broader dimension of a theory of rationality. In his intriguing book *Rationality* (1988), Nicholas Rescher proposes a unitary concept of rationality that inseparably includes the elements of cognitive, practical, and “evaluative” rationality. Part of this is “evaluative” rationality, the rationality of choosing ends. Unfortunately, Rescher offers no better criterion for a rational choice of ends than the distinction between “real” and “alleged” interests of individuals, which might also be called “objective” and “subjective” interests. People pursuing their real interests act rationally, people chasing after mere alleged interests act irrationally—and respecting others is already set up as an implicit criterion of real interests. This is a bit like Erich Fromm’s distinction in *Psychoanalyse und Ethik* (1954) between (good) self-love, which allows for sacrifices in the interests of others, and (bad) self-love, that is, egoism.

However, one’s judgment of the rationality of ends in life can hardly depend on whether others believe that pursuing such an end would be in the informed self-interest of the respective agent. It is much rather the compatibility of individual ends of action and objective moral norms, and these norms are constant even compared to our “informed” or “true” interests. I share the conviction of moral philosophers in the tradition of Kantian rationalism, utilitarianism, or discursive ethics that at least some of these norms can be rationally justified. It is irrational to choose a course of action that one cannot allow anybody in a relevantly similar situation to take; it is morally illegitimate and in that sense irrational, or irrational and in that sense morally illegitimate, for example to accept environmental damage as a member of our current generation for the sake of pursuing one’s own trivial interests, damage which might be an unacceptable burden on future generations. It is impossible rationally to justify that one should oneself be allowed to do something that with good reason one would condemn in others if one were to be affected by this action. At least norms of justice, and probably some further moral norms, can thus be justified in accordance with rational criteria.

It is my firm conviction that the questions mentioned at the beginning of this article—whether active euthanasia, in

certain specified extreme cases and in accordance with the patient’s explicit wishes, or pre-implantation genetic diagnosis are morally permissible—can also be rationally solved by weighing arguments and counter-arguments.

I think we should feel a bit proud about the fact that, of our own free will, we have made the step from means-ends rationality that concerns no more than the agent’s own interest to a more comprehensive kind of

rationality that includes the interests of all creatures affected by our actions as a criterion of our choices. We have paved the way, and we shall continue to take it. It is the self-confidence of human reason which—even at a time when the principle of moral rationality is under constant threat of suffering severe set-backs—can strengthen our faith in a gradual improvement of human life.

Translation: J. Timmermann (St. Andrews)

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Nano- and Micropatterning by Organic – Inorganic Templating of Hierarchical Self-Assembled Structures

Joachim P. Spatz*

Miniaturization in electronics through improvements in established “top-down” fabrication techniques is approaching the point where fundamental issues are expected to limit the dramatic increases in computing seen over the past few decades. In aspects of biophysics, biotechnology, and diagnostics, nanostructured interfaces are regarded as valuable tools for the localization of individual ligands designed to test single events or for the construction of hierarchical intracellular micro- and nanoarchitectures by the adhesion of cells.^[1] Three essential requisites have to be accomplished for these applications: a) the location and connection of nano-sized objects with variable distances from subnanometer to submicrometer, b) pattern uniformity over large surface areas or volumes, and c) control of the pattern geometry, including the assembly of asymmetric structures.

Principally, the top-down approach addresses dimensions of 50 nm (electron-beam lithography) and larger (photolithography). Smaller dimensions down to 10 nm are feasible by electron-beam lithography, but this involves increased efforts which are economically not viable because they are restricted to small surface areas and low-throughput production. For several years wet-chemistry has provided challenging alternatives to expensive clean-room lithographic techniques. The smallest objects, that is, dots or rods of a few nanometres, are synthesized reproducibly using phases of low-molecular weight surfactants. These objects self-assemble into two- and three-dimensional structures through electrostatic, magnetic, and steric interactions as well as through capillary forces upon evaporation of solvents during film formation.^[2, 3] The problems arising are the connectivity of the nanoobjects to the macroscopic world, the limited spacings between nanoobjects, and the formation of aperiodic structures. The size range between a few nanometres and 200 nm reflects the gap between top-down approaches and structures made through the pure self-organization of low-molecular-weight species; bridging this size gap offers solutions for overcoming prob-

lems of connectivity, breaking pattern symmetry, and non-economic production aspects. Strategies to bridge this scientific and economically very important size range are addressed through self-assembly of colloidal,^[4] macromolecular,^[5] or supramolecular units,^[6] and thus rely on patterning with periodicities that relate to the molecular weight of the self-organizing molecules. This article presents examples of the latest advances in the application of the self-assembly of macromolecules and colloids, which indeed scale between 5–200 nm, overcome symmetry restriction in self-assembly and substrate choice, and allow for inorganic templating of their structure.

Jaeger and co-workers from the University of Chicago demonstrated a method for laterally patterning of metal nanocrystal monolayers onto a solid substrate.^[7] In this approach dodecanethiol-ligated gold nanocrystals were synthesized and assembled through both entropic effects and interparticle interactions onto a substrate to form a densely packed film of nanocrystals. The distance between the crystals is determined by steric interactions of the dodecane molecules. The desired pattern was written directly into the monolayer by exposing it to the electron beam of a scanning electron microscope, whereby the organic ligands were stripped from the nanocrystal cores, thus leaving the metal cores to adhere to the substrate. Presumably, this occurs through cleavage of C–H and C–C bonds. In a final washing step unexposed nanocrystals were removed by a solvent to leave the exposed areas of the monolayer firmly anchored to the substrate. Once the ligands are stripped away, the nanocrystals stick strongly to the substrate and are not removable by subsequent washing with solvents. The resolution of the technique depends on the width of the electron beam. The best resolution obtained by the authors was approximately 50 nm, but smaller values should be readily achievable with smaller spot sizes. The fact that the electron beam does not significantly disturb the spatial arrangement of the individual nanocrystals implies that the ordering is essentially controlled by the self-assembly properties of the particles prior to patterning and could be used in other self-organizing, organic–inorganic hybrid systems.

The size of the features fabricated with standard electron-beam lithography is usually much larger than the diameter of the electron beam. Secondary electrons generated by forward scattering and proximity effects increase the exposed volume,

[*] Prof. Dr. J. P. Spatz
Universität Heidelberg
Institut für Physikalische Chemie
Biophysikalische Chemie
INF 253, 69120 Heidelberg (Germany)
Fax: (+49) 6221-5449-50
E-mail: joachim.spatz@urz.uni-heidelberg.de

and the large size of the molecules in the polymeric resists limits the resolution that can be obtained. A further class of materials suitable for ultrahigh-resolution electron-beam patterning are self-assembled monolayers (SAMs), which accumulate chemical functionalities at an interface. SAMs show specific sensitivity to irradiation with electrons. Götzhäuser, Grunze, and co-workers showed that the nitro groups in SAMs of 4'-nitro-1,1'-biphenyl-4-thiol on gold are converted into amino groups by irradiation with low-energy electrons, while the underlying aromatic layer is dehydrogenated and cross-linked (Figure 1).^[8] Sequential exposures to electron beams followed by coupling of electrophilic molecules to the amino-terminated regions allowed for the formation of several chemically different units on a solid interface with molecular resolution (Figure 1).

Pure self-organization of metal nanostructures on surfaces is observed by using domains of diblock copolymers as templates with different adhesion interactions to the metal.

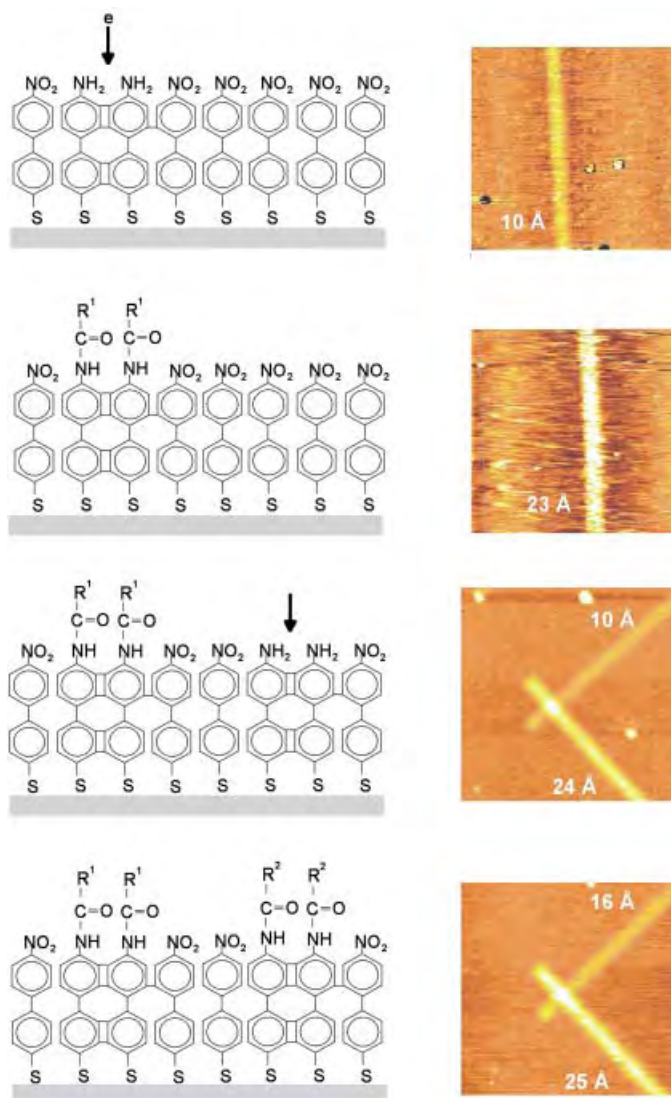


Figure 1. Electron-induced chemical lithography using self-assembled monolayers as a platform for the generation of the pattern. Scanning force microscopy images show the selective binding of acetic acid anhydride ($R^1 = \text{CH}_3$) and perfluorobutyric acid ($R^2 = \text{C}_3\text{F}_7$) onto a SAM platform.

Lopes and Jaeger applied a process where one level of self-assembly guides the next (Figure 2).^[9] In a first step, ultrathin films of an asymmetric polystyrene-*block*-poly(methylmethacrylate) (PS-*block*-PMMA) diblock copolymer form a regu-

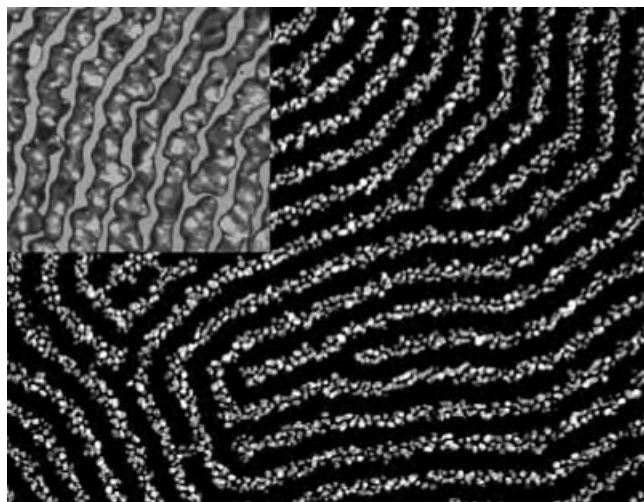


Figure 2. Hierarchically self-assembled metal-polymer structures. Both dense chains of separate nanoparticles and continuous nanowires can be achieved by varying the material parameters. The transmission electron micrograph shows gold nanoparticle chains (light) on a thin PS-*block*-PMMA copolymer film (dark background). The inset shows silver nanowires (dark gray) on the same type of template (light gray background). The center-to-center spacing between adjacent chains or wires is 50 nm, the typical Au particle diameter is 5–8 nm. The large anisotropy and very high dielectric contrast makes these structures suitable for nanogratings, interconnects, and sensor applications, thus opening up new possibilities for guided, large-scale assembly of hybrid nanomaterials and coatings.

lar scaffold of highly anisotropic, striplike domains. During a second assembly step, the diffusion of metal atoms being evaporated onto the polymer surface to aggregate selectively along the polymer scaffold is guided by differential wetting. Selective decoration of one of the two copolymer domains is already apparent for a wide range of metals and small deposited amounts (film thickness ca. 0.6 nm) immediately after metal deposition. Au and Ag prefer the PS domains, while In, Pb, Sn, and Bi prefer the PMMA domain. Selectivity of nearly 100 % is achieved by warming the system in an inert-gas atmosphere to a temperature that is above the glass temperature of the copolymer. This process leads to a coagulation inside the preferred domain that increases both the size and the separation of the nanoparticles, while the metal diffuses into the domains, perpendicular to the film plane. With the exception of Ag, depositing larger amounts of metal does not fill the domains. Rather than coalescing into continuous, elongated structures of high aspect ratio, the material ignores the template and “jumps the gap” between neighboring domains. Subsequent annealing only reduces the aspect ratio and leads to particles that are more like spheres, but does not reinstate selectivity. Metal density could be increased through repeated deposition of small amounts of metal and short annealing times. This approach produced dense nanochains with a narrow particle size distribution. A second possibility requires a very high mobility contrast

between the two copolymer domains, which allows the metal to de-wet one domain and aggregate at a high volume fraction in the other before surface tension drives the aggregate into its final, spherical shape. This is the case with Ag. It readily forms continuous nanowires along the PS domains, which follow 25-nm-wide polymer scaffolds over distances of micrometers without breaks.

Block copolymers and mixtures of homopolymers self-assemble into chemically different domains over large surface areas and on a length scale that is appropriate for many electronic and biological applications. However, for many of these applications it is necessary to have control over the orientation of the domains and also to fabricate an aperiodic pattern. T. P. Russell and co-workers from the University of Massachusetts at Amherst pioneered the application of electrical fields to orient block copolymer domains of different chemical and, hence, different dielectric properties. In addition to block copolymers, homopolymers also respond to electrical fields that are applied either between parallel electrode plates or topographically structured electrodes.^[10] This system also allows for the breaking of symmetry, as the resulting polymer pattern follows the topographical structures of the electrodes fabricated by electron-beam or photolithography. The method is based on the fact that dielectric media such as polystyrene experience a force in an electric field gradient. Strong field gradients can produce forces that overcome the surface tension in thin liquid films and induce an instability that produces a characteristic hexagonal order. The application of a laterally varying electric field causes the instability to be focused in the direction of the highest electric field. Hence, this process demonstrates how conventional lithographic techniques can be combined with self-organizing systems. The authors reported patterns with lateral dimensions of 140 nm, but the extension of the technique to pattern replication on scales smaller than 100 nm by using standard electron beam or photolithography is viable.

The orientation of diblock copolymer domains allows for the formation of ultrahigh-density nanowire arrays. A PS-*block*-PMAA polymer is composed of two materials with different dielectric constants. Thus, an external electrical field orients the polymer domains parallel to the electrical field lines. Russell, Thurn-Albrecht, and co-workers spin-coated an approximately 1- μm thick diblock copolymer film onto a conducting substrate and covered the top of the film with an aluminized kapton (a polyimide) film.^[11] The application of an electrical field across the diblock copolymer film causes alignment of cylindrical domains perfectly perpendicular to the electrodes at temperatures above the glass temperature of both polymer components. A major step forward was the use of the aligned domain structures as templates for inorganic species. Exposure of the film with ultraviolet light caused degradation of the PMAA domains and cross-links the polystyrene domains. The degraded PMMA could be removed by rinsing with acetic acid. The resulting nanoporous polystyrene film was optically transparent and contained pores of 14 nm in diameter that span the film thickness. Finally, each pore was filled simultaneously with a continuous Co or Cu nanowire by electrochemical deposition.

Periodic and nonperiodic nanostructures with micrometer spacing have been prepared through the combination of a top-down approach (electron-beam lithography) with the formation and compartmentalization of inorganic components within block copolymer micelles.^[12] Electron-beam lithography created channels with a characteristic width greater than 200 nm as a coarse prestructure. Cylindrical block copolymer micelles from organometallic polyferrocene block copolymers were positioned within these structures by means of a self-assembling polymer micelle. The cylindrical micelles are centered within the prepatterned channels and at the edges of prestructured lines as a consequence of capillary effects and steric hindering. Subsequent lifting-off of the resist allows the removal of all the cylindrical micelles with the exception of those that are in direct contact with the underlying substrate. The block copolymer is then removed by plasma etching, which strips the polymer micelle and deposited Fe/Si lines in periodic and aperiodic structures. The lines have a diameter of approximately 5 nm and a length of several micrometers (Figure 3).

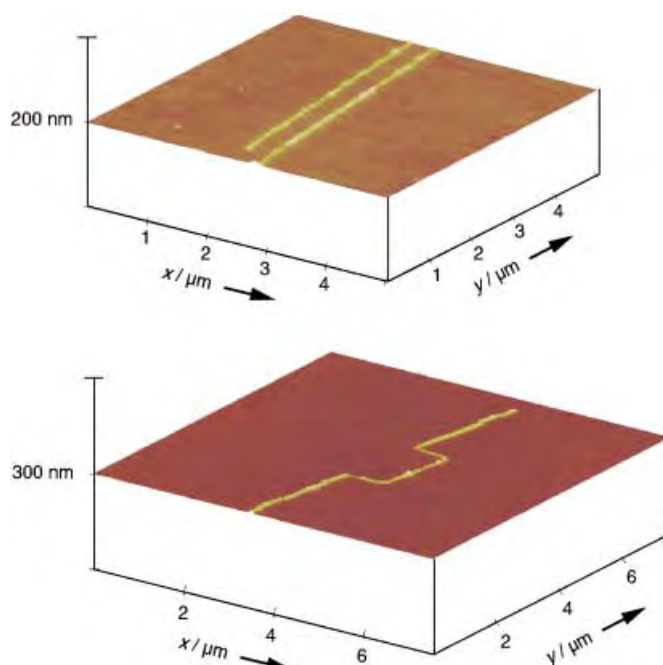


Figure 3. Deposition of Si/Fe-based lines of 5 nm in diameter and several micrometers in length from cylindrical, organometallic polyferrocene block copolymer micelles organized in a 200-nm large prestructure through capillary and steric forces.

The structure of self-organized ultrathin polymer films is usually strongly affected by the interaction of the polymer segments with the interface. Sohn et al. demonstrated that a monomeric block copolymer film which patterns a mica substrate can be transferred to any other solid substrate by separating the film from the mica substrate with water and floating the micellar film onto a new substrate.^[13]

A different length scale in self-organizing structures is addressed with charged colloids. In low ionic suspension media charged colloids arrange to liquid, glassy, or crystalline-like structures as a result of their repulsive electrostatic

interactions. The interparticle distance and degree of ordering is a function of the ionic strength and the density of the colloids in suspension. The length of a crystalline pattern can be in the range of several 100 nm. Thus, self-assembly of colloidal crystals enables the preparation of materials whose dimensions lie in the region of the wavelength of visible light, and as such are ideal for photonic crystals. However, a slight change in the ionic strength or any mechanical vibrations might destroy the colloidal structures and, hence, the optical properties. Hempelmann and co-workers demonstrated that the colloidal crystalline structure is not altered if a polyacrylamide hydrogel is polymerized around the colloids.^[14] Thus, the colloidal crystal was trapped in the highly cross-linked polymeric hydrogel. The volume between the colloids could then be filled with silver through electrochemical reactions. Accordingly, a colloidal hydrogel was polymerized onto a stainless steel electrode and Ag was electrochemically deposited into the hydrogel from an AgNO₃ solution. Finally, the resulting Ag/polymer/colloidal hybrid system was easily removed from the electrode surface (Figure 4). The material

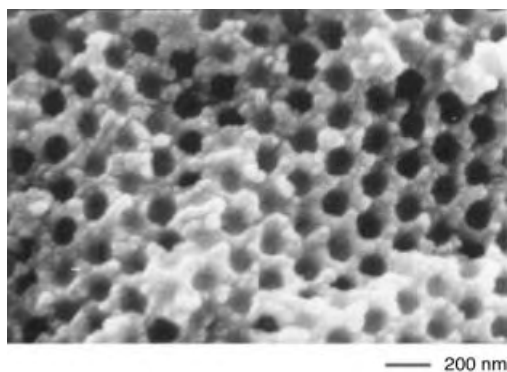


Figure 4. Scanning electron microscopy image of a mesostructured, three-dimensional Ag/polymer/colloidal hybrid material obtained through three-dimensional, inorganic templating of electrostatically organized polymer colloidal crystals.

showed a pattern periodicity of approximately 160 nm, which makes it suitable, for example, for photonic crystals or as a matrix for catalytic systems.

This Highlight can only summarize a small part of this highly active scientific field concerning the hierarchical self-organization of nano- and micro-sized objects. Colloids as well as low- and high-molecular-weight molecules self-organize

into uniform patterned structures on surfaces and in three dimensions. The pattern of the structure formed is a function of the colloidal or molecular properties and covers dimensions from the subnanometer to the submicrometer range. Even more important is the fact that the combination of conventional lithographic techniques in the submicron range with self-assembling structures in the nanometer range and electric fields result in the controlled alignment of subnanometer structures as well as enabling the breaking of the symmetry intrinsically involved in self-assembly. Thus, a combination of electron-beam or photolithography with the molecular properties mentioned makes patterning in the nanometer range feasible and accessible to a large group of scientists and industry. Most importantly, this is realized without suffering large investments into new clean-room facilities as it is mainly based on wet-chemistry in combination with existing conventional lithographic techniques. The future inclusion of inorganic templating of self-organized structures will make molecular and colloidal lithography highly competitive in the fields of electronics, nanobiotechnology, and diagnostics.

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Nanostructured Molecular Materials for Device-Quality, Highly Efficient Electrooptic Poled Polymers**

Milko E. van der Boom*

Optical telecommunications and public networking requires high-speed optical-electrical data interconversion, which in turn drives a vast need for advanced, extremely efficient device components such as waveguides, switches, emitters, and detectors.^[1] Development of functional “soft materials” in the form of robust organic thin films and their integration into prototype devices offer a great challenge, which promises new device properties, enhanced performance, and eventually lower production costs.^[2] Nonlinear optical (NLO) and electrooptical (EO) properties of poled polymers have improved considerably during the last two decades, and new developments have made them almost competitive to conventional inorganic materials such as lithium niobate (LiNbO₃).^[1–7] Trends in first and second hyperpolarizabilities (β) as a result of substituent patterns, chromophore properties, and spacer lengths between donor and acceptor units have been established for various organic compounds by Marder, Blanchard-Desce, and many others.^[2–7] Moreover, there is a reliable theoretical basis for understanding the mechanisms involved as well as predicting new molecular structures with even larger responses.^[4]

Of the diverse synthetic approaches to acentric chromophore matrices, polymer poling,^[5–7] Langmuir–Blodgett and related film-transfer techniques, and molecular self-assembly have been investigated most intensely.^[2, 8] Nevertheless, innovative design of applicable noncentrosymmetric organic materials having excellent EO responses remains challenging and highly intriguing. There are still considerable fundamental gaps in the understanding of the influence of chromophore design on material structure–function relationships. One challenge is clear: For a given high- β chromophore, which parameters can be tuned to explore and establish functional device-quality materials exhibiting optimal nonlinear and electrooptical responses?

Dalton, Jen, and Steier recently reported series of new chromophores, nanostructured functional materials (i.e., phase-separating block copolymers, dendrimers) for the formation of low-loss poled polymers, and the design of prototype devices having the desirable combination of very large EO responses and excellent thermal and temporal stability.^[6, 7] High chromophore density is a prerequisite for the formation of polar organic materials with exceptional EO properties. However, intermolecular electrostatic interactions in poled polymers significantly limit the value of the maximum possible macroscopic EO coefficient (r_{33}) for a

given chromophore with a high dipole moment.^[9] For instance, EO responses of poled polymers based on **1** (Scheme 1) are limited by the formation of dye aggregates at high chromophore densities.^[6, 7]

Decreasing or preventing aggregation of thermally robust polymer matrices (i.e., polyimides, polyquinolines)^[6e] and chromophore–chromophore interactions while maintaining a high chromophore density may largely increase macroscopic optical nonlinearity. Indeed, introduction of bulky substituents such as *n*-hexyl (**2**), *n*-butyl (**4**), or *tert*-butyldimethylsilyl (**3**, **5**) on chromophore precursors without affecting β resulted in poled polymers with significantly decreased electrostatic interactions among the chromophore building blocks. The noncentrosymmetric characteristics of these modified high- β chromophores are more effectively carried through into bulk properties, allowing realization of materials exhibiting better macroscopic second-order NLO effects and much higher r_{33} values. Sophisticated poled polymer modulators based on **1** and the electronically isolated compounds **2–5** operating at telecommunication wavelengths (1.3 and 1.55 μ m) with half-wave voltages (V_{π}) as low as 0.8 V represent a major advance.^[7] Such prototype devices are rapidly approaching or even exceeding the performance of single-crystal LiNbO₃-based devices in terms of bandwidth and operating voltage.

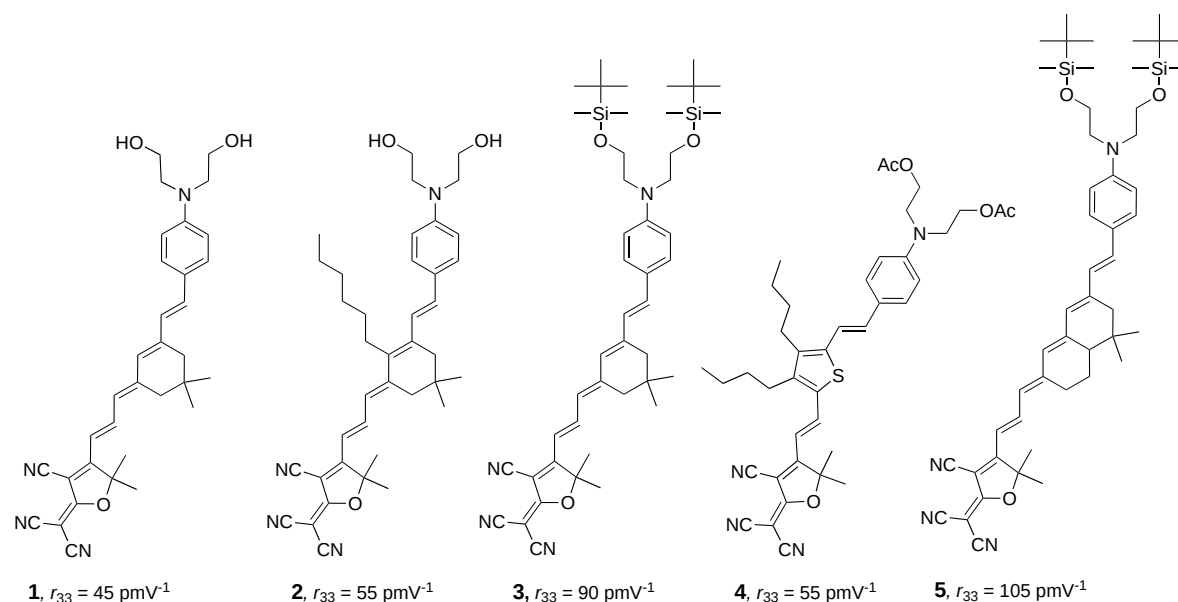
Application of poled polymers is often limited by the relatively low glass-transition temperatures (T_g) of the polymer matrices.^[2, 7] Major research efforts have been devoted to increase T_g in order to prevent thermal relaxation of the chromophore dipole moment.^[2, 5, 6] For instance, polyurethane (PU) matrices based on triethanolamine and toluene-2,4-diisocyanate have a dynamic stability till about 90 °C, which can be enhanced by 1) using more rigid cross-linkers and 2) chemically modifying PU polymers with urea and siloxane units (**6**, **7**; Scheme 2).^[6b,c]

Practical polar organic materials must meet a combination of many criteria, leading often to a trade-off between EO efficiency and material stability. There are numerous organic materials available having excellent EO values,^[2, 3] but high-quality films are extremely rare.^[2, 5–7] The temperatures at which the devices operate and which are induced in processing require materials with long-term chemical, photochemical, mechanical, and thermal stability. Electrooptic modulation is caused by voltage-induced variations in the refractive index of a functional material requiring either relatively high voltages or long electrodes. To minimize absorption losses in large device structures, C–H moieties may be replaced by C–D and/or C–F groups, which is known to enhance polymer optical transparency at telecommunication wavelengths.^[2, 7c]

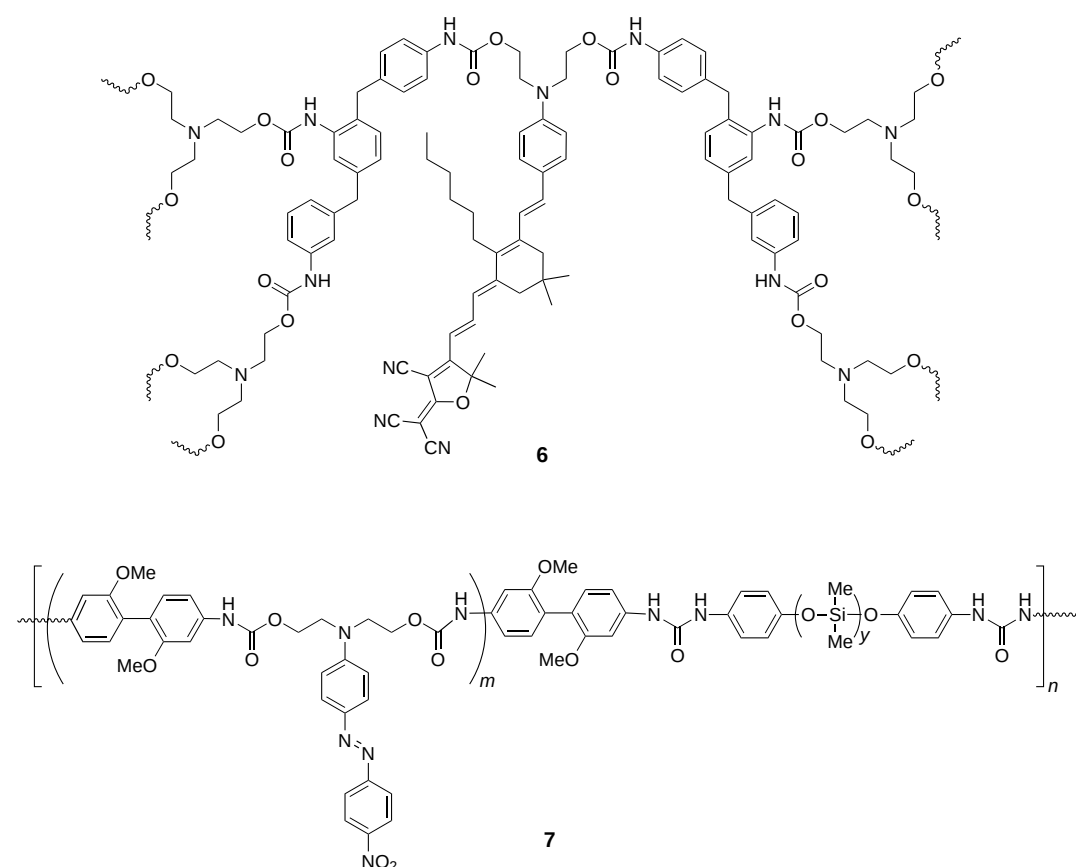
All the aforementioned crucial requirements placed on materials for device fabrication and performance are for the first time favorably combined in a recently developed dendrimer system based on the thienylstyrene chromophore (**8**;

[*] Dr. M. E. van der Boom
Weizmann Institute of Science
Department of Organic Chemistry
Rehovot, 76100 (Israel)
Fax: (+972) 8-934-4142
E-mail: milko.vanderboom@weizmann.ac.il

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Scheme 1. Chemical structures of phenyltetraene chromophore **1** and related compounds **2–5** with high dipole moments.^[6b,d, 7c]



Scheme 2. Examples of polyurethane-based films (**6** and **7**) with enhanced thermal stability.^[6b,c]

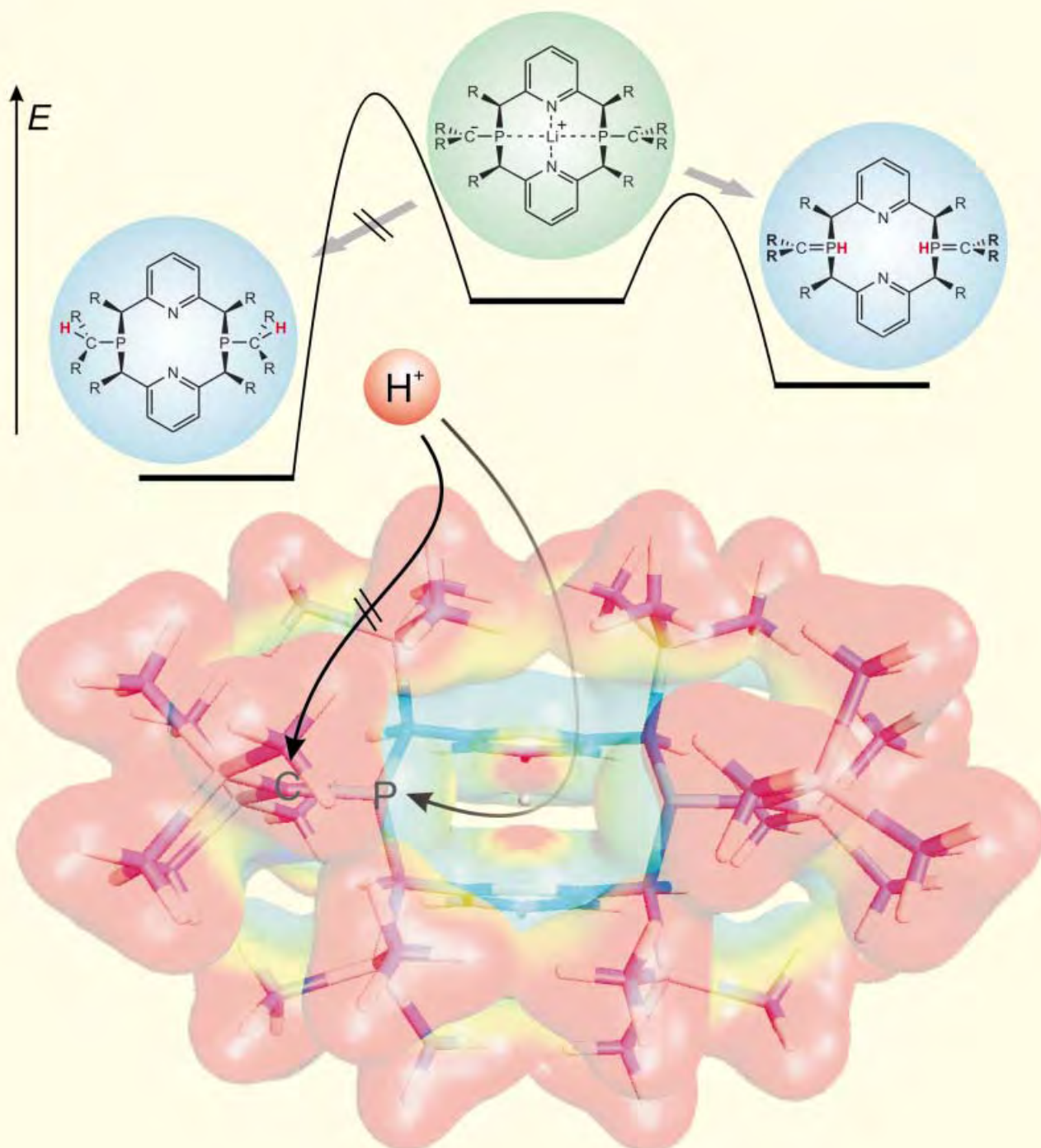
Scheme 3).^[6a] The multifunctional dendrimer **8** has trifluorovinyl ether dendrons that can be cross-linked to enhance thermal and temporal stability of the poled polymer and prevent thermal relaxation of the chromophore dipole alignment.

The high- β chromophore functionalized **8** was prepared stepwise by the Mitsunobu condensation between the carboxy

groups of the core **9** and the hydroxy groups of **10**, followed by treatment with tetracyanoethylene. Dendrimer **8** was well-characterized by a combination of gel permeation chromatography, mass spectrometry, and ^1H and ^{19}F NMR spectroscopy. Chromophore dipole alignment was achieved by applying corona poling at elevated temperatures on vac-

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Kinetically Controlled Protonation of a Phosphamethanide



The positive electrostatic potential (red) on the surface of the macrocycle inhibits the protonation of the methanide carbon atom, whereas the negatively charged tunnel (blue) through the macrocycle facilitates an approach of the proton to the phosphorus atom. This favors the formation of the thermodynamically less stable PH-phosphonium ylide instead of the phosphane. For more information see the following pages.

Kinetically Controlled Protonation of a Cyclic Phosphamethanide Complex to a PH-Phosphonium Ylide**

Sahir Ekici, Dietrich Gudat, Martin Nieger, Laszlo Nyulaszi,* and Edgar Niecke*

Dedicated to Professor Rüdiger Mews on the occasion of his 60th birthday

The parent phosphonium ylide, $\text{H}_3\text{P}=\text{CH}_2$, and the tautomeric, methylphosphane, $\text{H}_2\text{P}-\text{CH}_3$, which is energetically more stable by 56 kcal mol^{-1} , are separated by a sufficiently high isomerization barrier of 34 kcal mol^{-1} which renders the former a stable gas-phase species.^[1] In solution, PH-phosphonium ylides are generally thermodynamically less stable than the alkyl phosphane form.^[2] However, NMR studies of bis(alkoxycarbonyl)methylphosphanes suggested that even in solution the PH tautomer may be populated if an effective stabilization of the negative charge is provided.^[3] We report here on the synthesis and crystal structure of a PH-phosphonium ylide that exists as a kinetically stable species in condensed phases.^[4]

Recently, we described the coupling reaction between the lithium salt of the bifunctional carbanion **1a** ($\text{R}' = \text{Ph}$) with the bifunctional, electrophilic bis(phosphaethene)s *rac/meso*-**2a** ($\text{R} = \text{SiMe}_3$) to yield the macrocyclic complex **3a**, and its subsequent conversion into the neutral ligand **4a** (Scheme 1).^[5] The analogous reaction of the bis(phosphaethene)s *rac/meso*-**2b** ($\text{R} = \text{SiMe}_3$), which were accessible from **1b**^[6] and $\text{ClP}=\text{C}(\text{SiMe}_3)_2$,^[7] respectively, with an excess of **1b** affords the phosphamethanide complex **3b** $[\text{Li}(\text{OEt}_2)_x]$, which was, after exchange of the donor, isolated as a crystalline salt **3b** $[\text{Li}(\text{tmeda})_3]$.^[8] Quite surprisingly, protonation of **3b** with Et_3NHCl in THF yielded no bisphosphane, as in the case of **3a**, but a mixture of the PH-ylides **5b** (80 %) and **6b** (20 %). Isomer **5b** was formed exclusively when the protonation was carried out using NH_4Cl in THF/ CH_2Cl_2 (1:1) and was isolated as a crystalline product from this reaction. It was found that a mutual conversion between both isomers, or their further transformation into a bisphosphane **4b**, could be induced neither by heating to 100°C nor by means of acid or base catalysis; reaction with an excess of *n*-butyllithium proceeded under re-formation of the ate complex **3b**.

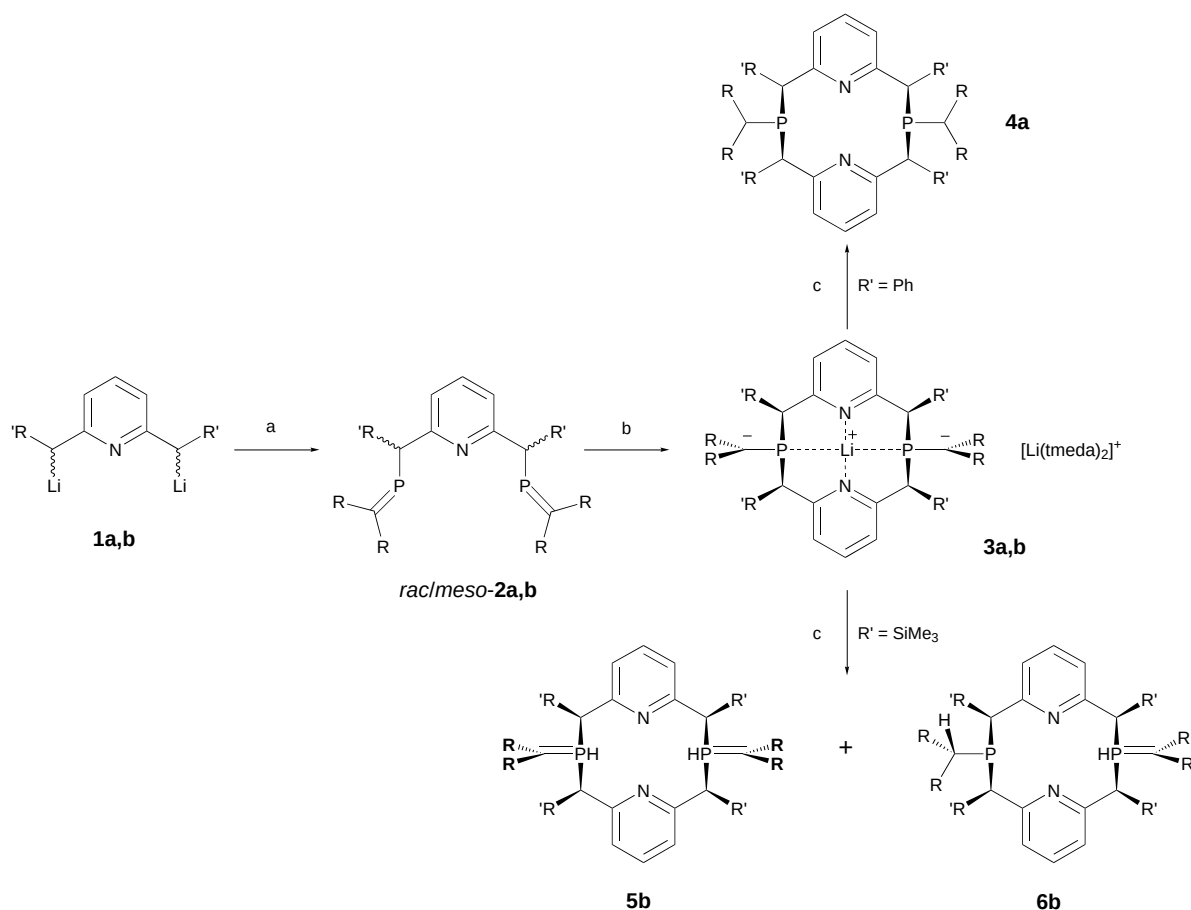
The constitution of the macrocycles **3b** and **5b** and **6b** followed from NMR investigations and was, in the case of **3b** and **5b**, confirmed by X-ray diffraction studies. The constitution of the ate complex **3b**, which features coordination of a lithium atom in the macrocycle, is substantiated by the ^{31}P and ^7Li NMR data ($\delta(^{31}\text{P}) = 14.1 \text{ ppm}$, $^1J_{\text{PLi}} = 58 \text{ Hz}$; $\delta(^7\text{Li}) = 2.5 \text{ ppm}$ (t, $^1J_{\text{PLi}} = 58 \text{ Hz}$), 0.6 (s)). The number of ^1H and ^{13}C NMR signals implies that **3b** exhibits effective C_{2v} symmetry in solution at 30°C . Interestingly, this symmetry is conserved even at -80°C , while at the same time a reduction of the $^1J_{\text{PLi}}$ coupling to 50 Hz was observed which points presumably to temperature-dependent changes in the solvation of the lithium ion. The constitution of **5b** as a PH-ylide is confirmed by the occurrence of a characteristic coupling ($^1J_{\text{PH}} = 453 \text{ Hz}$). As in the case of **3a**, the number of ^1H and ^{13}C NMR signals indicates an effective molecular C_{2v} symmetry at 30°C , with the occurrence of two chemically inequivalent exocyclic SiMe_3 groups suggesting that the $\text{C}(\text{SiMe}_3)_2$ moieties (whose carbon atoms are considered to exhibit planar geometries) do not rotate freely, but are frozen in a position similar to that in the crystal (see below). At low temperatures, a dynamic line broadening and finally a doubling of the signals of the $\text{CH}(\text{SiMe}_3)$ fragments in the macrocycle and the *meta*-CH moieties of the pyridine rings is observed. The coupling patterns and NOE measurements suggest the presence of a C_2 -symmetric molecular structure at -80°C that adopts a conformation similar to that found in the crystal. The isomer **6b** gives rise to two ^{31}P NMR signals of which only one exhibits the typical $^1J_{\text{PH}}$ coupling (457 Hz) of a PH-ylide. The ^1H NMR spectrum displays broadened signals at 30°C that decoalesce at lower temperatures. The number of signals at -80°C implies the presence of a C_1 -symmetric molecular structure that is rationalized by assuming that the rotation of the $\text{CH}(\text{SiMe}_3)_2$ group is frozen and the substituent adopts a conformation close to the one depicted in Scheme 1. This hypothesis was validated by NOE measurements and by the determination of the magnitudes and signs of the $^{12}J_{\text{PX}}$ ($\text{X} = \text{H, C, Si}$) coupling constants involving the trivalent phosphorus atom.^[9] High-temperature NMR spectra of **6b** revealed that rapid rotation of the $\text{CH}(\text{SiMe}_3)_2$ moiety on the NMR time scale is only observed above 100°C .

The molecular structure of **3b** and the resulting PH-ylide **5b** are shown in Figure 1 and Figure 2, respectively.^[10] The twelve-membered ring of **3b** displays a *syn* conformation with a boat-boat arrangement of the phosphorus atom, and is folded along the P-P axis. The coordination of the lithium by the phosphorus and nitrogen atoms can be described in terms of a strongly distorted tetrahedral, "seesaw"-like geometry (P-Li-P 171° ; N-Li-N 85°). The trigonal-planar coordination of the carbon atoms (sum of bond angles 360°) and the P-C distances ($175.3(3)$, $175.5(3) \text{ pm}$) in the phosphoniomethanide moieties match the data of similar compounds.^[11]

The protonation to give **5b** induces no substantial changes in the macrocycle conformation. The former coordination space of the lithium atom is occupied by the P-bound hydrogen atoms, each of which displays a weak hydrogen bond to one of the nitrogen atoms (PH $\cdots$ N $283(4)$, $298(4) \text{ pm}$; P-H-N $88\text{--}94(2)^\circ$). Comparable structural features have been observed for SH $\cdots$ N and PH $\cdots$ O moi-

[*] Prof. Dr. E. Niecke, Dipl.-Chem. S. Ekici, Prof. Dr. D. Gudat, Dr. M. Nieger
Anorganisch Chemisches Institut
Universität Bonn
Gerhard-Domagk-Strasse 1, 53121 Bonn (Germany)
Fax: (+49)228-73-5327
E-mail: e.niecke@uni-bonn.de
Prof. Dr. L. Nyulaszi
Department of Inorganic Chemistry
Technical University of Budapest
Gellért tér 4, 1521 Budapest (Hungary)
Fax: (+36)146-33-642
E-mail: nyulaszi@mail.bme.hu

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Scheme 1. Synthesis and reactions of **3a,b** (**1a–4a**: R = SiMe₃, R' = Ph; **1b–3b**, **5b**, **6b**: R = R' = SiMe₃); a) CIP=C(SiMe₃)₂ (2 equiv), Et₂O, –78°C; b) **1a,b** (1 equiv), Et₂O, –78→–30°C, TMEDA (2 equiv); c) Et₃NHCl or NH₄Cl, THF/CH₂Cl₂. TMEDA = tetramethylethylenediamine.

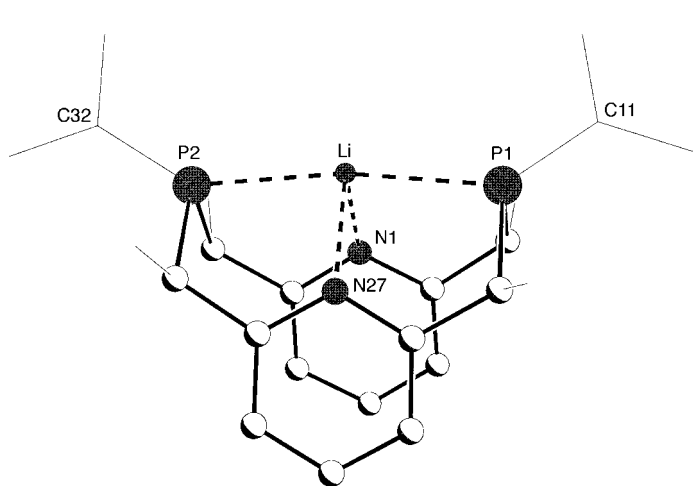


Figure 1. Molecular structure of **3b** in the crystal (without hydrogen atoms and peripheral groups). Selected bond lengths [pm] and angles [°]: Li–N1 212.1(5), Li–N27 211.5(5), Li–P1 245.8(4), Li–P2 245.7(4), P1–C11 175.5(3), P2–C32 175.3(3); N1–Li–N27 85.1(2), N1–Li–P1 85.9(2), N1–Li–P2 87.3(2), N27–Li–P1 87.0(2), N27–Li–P2 86.5(2), P1–Li–P2 171.0(2).

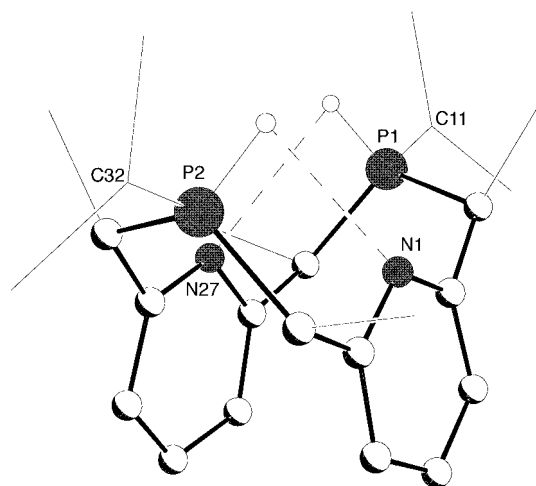


Figure 2. Molecular structure of one of the two independent molecules of **5b** in the crystal (without hydrogen atoms and peripheral groups; data for the second independent molecule in brackets). Selected bond lengths [pm] and angles [°]: P1–C11 168.2(5) [169.3(5)], P2–C32 169.7(5) [169.1(5)], H(P1)⋯N27 292(4) [283(4)], H(P2)⋯N1 296(4) [298(4)]; P1–H(P1)⋯N27 91(2) [94(2)], P2–H(P2)⋯N1 88(2) [89(2)].

eties.^[12] The trigonal-planar coordination of the carbon atoms (sum of bond angles 360°) and the P–C distances (168.2(5)–169.7(5) pm) in the ylide moieties are similar to those of other C(SiMe₃)₂-substituted phosphonium ylides (P–C 168(3) pm).^[13]

To rationalize the unexpected formation of the PH-ylides **5b** and **6b**, quantum-mechanical calculations were carried out.^[14] In view of the extreme computational expense of ab initio computations on the Me₃Si-substituted molecules studied, we first assessed the reliability of semiempirical

PM3 calculations, using a smaller model system in which all SiMe₃ groups were replaced by SiH₃ groups. The relative energies given in Table 1 reveal that, at this level of theory, the phosphane structure with C-bound hydrogen atoms is more stable than the ylide structure by some 10 kcal mol⁻¹. The application of density functional methods (B3LYP functional with different basis sets, with or without zero-point-energy

Table 1. Relative energies (in kcal mol⁻¹) of the ylide and phosphane form of model compounds.^[a]

	R ¹ , R ² = SiH ₃			R ¹ = SiMe ₃ , R ₂ = SiH ₃			R ¹ , R ² = SiMe ₃	
model ^[b]	PM3	B3	B6//B3	B6	PM3	B3//PM3	PM3	PM3
phosphane	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
transition state	56.9	66.0	66.9	66.8	52.1/55.7 ^[b]	82.5/85.7 ^[b]		
ylide	13.6	13.0	13.8	14.0	8.1	37.7	7.7	

[a] Model: PM3 = PM3, B3 = B3LYP/3-21g*, B6 = B3LYP/6-31g*. [b] The values separated by slashes refer to the energies of hydrogen shifts in the SiH₃- and SiMe₃-substituted region of the molecule, respectively.

corrections) yielded comparable results. As the replacement of SiH₃ by SiMe₃ groups has only a minor influence on the relative energies (as shown by single-point B3LYP/3-21G(*)//PM3 calculations), we consider the phosphane **4b** to be thermodynamically more stable than the ylide **5b**, and attribute the observed formation of the latter to kinetic hindrance of the competing reaction. To elucidate the origin of this effect, we have computed the electrostatic potential on the surface of a lithiated anion whose macrocyclic ligand carries two SiH₃ substituents on one side, and two SiMe₃ substituents on the other side of the ring. The representation shown in Figure 3 reveals the potential on the inner side of the macrocycle to be negative, and that on the outer side of the SiMe₃-substituted region to be positive. This potential should inhibit the approach of a proton to the reactive, negatively charged carbon atom, whereas the approach to the phosphorus atom and the formation of the PH-ylide should be readily feasible. Since the attack of a proton at the carbon atom on the SiH₃-substituted region is not obstructed, it becomes clear that the observed ylide formation is an immediate consequence of the unfavorable steric and electrostatic effects of the SiMe₃ groups, and that with smaller substituents the formation of thermodynamically more stable phosphanes is to be expected. To elucidate the possibility of a ylide/phosphane conversion by an intramolecular 1,2-H shift, we have also computed the corresponding transition states (Table 1). As the resulting energies lie more than 40 kcal mol⁻¹ above the ground state at all levels studied, an intramolecular rearrangement seems unlikely. An intermolecular hydrogen exchange should be likewise inhibited by the sterically protecting SiMe₃ groups.

Experimental Section

Synthesis of 2b: A 1.6 M solution of *n*BuLi (5.6 mL, 9 mmol) was added at -78 °C to a solution of bis(trimethylsilyl)pyridine (1.13 g, 4.5 mmol) in Et₂O (30 mL), and the mixture was stirred for 0.5 h at -78 °C and then for 5 h at room temperature. This solution was then added dropwise at -78 °C

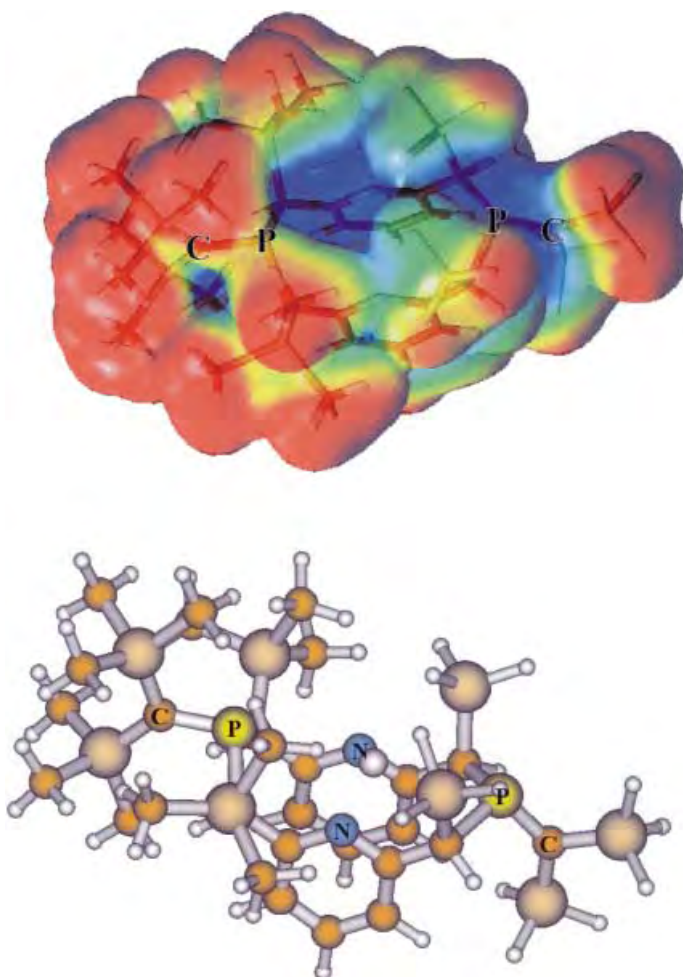


Figure 3. Representation of the electrostatic potential (with molecular structure incorporated as ball-and-stick model) on the surface of an anionic lithium complex whose macrocyclic ligand carries SiMe₃ groups on one, and SiH₃ groups on the other side of the ring.

to Cl-P=C(SiMe₃)₂ (2.02 g, 9.0 mmol) in Et₂O (30 mL). The mixture was stirred for 1 h, and after it had been warmed to room temperature, the solvents were evaporated in vacuo and the remaining residue was dispersed in *n*-hexane. Filtration and evaporation of the solvents in vacuo yielded a yellow oil consisting of a 4:1 isomer mixture of *rac*/*meso*-**2b**, which was used for subsequent reactions without further purification. MS (16 eV): *m/z* (%): 554 (3) [*M*-SiMe₃]⁺, 73 (100) [SiMe₃]⁺; ³¹P NMR (CH₂Cl₂, 25 °C): δ = 399.1, 401.2 ppm (*rac*/*meso*-**2b**).

3b: A solution of **1b** (4.5 mmol) was prepared as described above and was added dropwise at -78 °C to a solution of *rac*/*meso*-**2b** (2.83 g, 4.5 mmol) in Et₂O (30 mL). The stirred reaction mixture was warmed to -30 °C and kept at this temperature for 24 h. Addition of TMEDA (1.10 g, 9.4 mmol) and storing the mixture for two days at -30 °C produced red crystals of **3b**. Yield 4.6 g (83 %).

5b, 6b: A solution of **3b** (1.0 g, 0.9 mmol) in THF (20 mL) was added dropwise at 0 °C to a stirred suspension of Et₃NHCl (0.10 g, 1.8 mmol) in THF (30 mL). Stirring was continued for 2 h at room temperature, the solvent evaporated in vacuo, and the remaining residue was dispersed in Et₂O (30 mL), and filtered. Concentration of the filtrate to half of the original volume and storage at 0 °C for 2–3 days produced 0.72 g (91 %) of a 4:1 mixture of **5b** and **6b**. Carrying out the protonation of **3b** with NH₄Cl in CH₂Cl₂ under otherwise identical conditions afforded, after analogous work-up, pure **5b** as colorless crystals, yield: 0.67 g (85 %); MS (16 eV): *m/z* (%): 878 [*M*]⁺ (7), 628 [*M*-C₁₁H₂₅Si₂N]⁺ (5), 251 [C₁₁H₂₅Si₂N]⁺ (100).

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Self-Assembly of Trigonal-Prismatic Metallocages Encapsulating BF_4^- or CuI_3^{2-} as Anionic Guests: Structures and Mechanism of Formation**

Cheng-Yong Su, Yue-Peng Cai, Chun-Long Chen, Falk Lissner, Bei-Sheng Kang,* and Wolfgang Kaim*

The use of metal ions to promote the self-assembly of discrete, well-defined supramolecular architectures has become an important synthetic strategy during recent years, especially for encapsulating structures which possess an internal cavity capable of accommodating guest molecules.^[1] Various large polyhedral structures have been constructed and rationally classified.^[2] Among these are the M_{18}L_6 (M = metal, L = ligand) hexahedral cage,^[3] M_{12}L_8 and M_6L_8 cube-like cages,^[4] and 50-component dodecahedra^[5] with high symmetry. However, lower-symmetry hosts can ultimately be expected to show enhanced guest selectivity.^[6] Surprisingly, the simplest three-dimensional (3D) canonical cage structure with the fewest number of components (M_3L_2 or M_2L_3), the trigonal prism,^[2a] has remained rather uncommon in comparison with the various high-symmetry polyhedra.^[7] In contrast to the well studied helical structures,^[8] and despite the rapid progress in the construction of various molecular architectures with defined shapes and sizes, the mechanisms of formation for such species are often unknown.^[9] To develop synthetically viable pathways for a rational design of discrete molecular architectures, it is important to understand the dynamic behavior of such molecular architectures in solution. In the course of our work on the construction of supramolecular assemblies from tripodal ligands,^[10] we now describe the self-assembly of the M_3L_2 trigonal prismatic molecular boxes $[\text{BF}_4^- \subset \{\text{Ag}_3(\text{MsTBim})_2\}](\text{BF}_4)_2$ (**1**; MsTBim = 1,3,5-tris(benzimidazol-1-ylmethyl)-2,4,6-trimethylbenzene) and $[\{\text{CuI}_3 \subset \{\text{Cu}_3(\text{MsTBim})_2\}_2\}](\text{Cu}_2\text{I}_4)$ (**2**). The solution ^1H NMR spectroscopic study of **1** indicates that the box structure is the thermodynamically stable but kinetically labile product.

The semi-rigid ligand MsTBim,^[10e] with an arene core connecting three benzimidazolyl arms is expected to facilitate cage-structure formation instead of encapsulating one or

[*] Prof. B.-S. Kang, Dr. C.-Y. Su, Y.-P. Cai, C.-L. Chen
School of Chemistry and Chemical Engineering
Zhongshan University
Guangzhou 510275 (PR China)
Fax: (+86)20-8411-0318
E-mail: ceslhq@zsu.edu.cn
Prof. Dr. W. Kaim, Dr. F. Lissner
Institut für Anorganische Chemie
Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)
Fax: (+49)711-685-4165
E-mail: kaim@iac.uni-stuttgart.de

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more metal ions as found with other tripodal ligands.^[10a-d] Reaction of MsTBim with excess AgBF_4 or CuI in MeOH/MeCN (1/1) solution leads to rapid precipitation of solid products, the elemental analyses of which support the formulations $\text{Ag}_3(\text{MsTBim})_2(\text{BF}_4)_3$ and $(\text{CuI})_{10}(\text{MsTBim})_4$, respectively. While **1** may be readily predicted to contain an M_3L_2 cage structure, the stoichiometry of **2** is less indicative. Even in the case of the 3:2 stoichiometry the topologies may involve an M_6L_4 octahedral cage^[11] or square-pyramidal cone,^[12] an M_3L_2 trigonal or trigonal-bipyramidal cage^[7] as well as unspecified oligomers^[10b,c] or well-known (10,3) networks,^[13] depending on the size, bond angles, and rigidity of the subunits. The ^1H and ^{13}C NMR spectra of both **1** and **2** show one set of resonance signals comparable with that of the free ligand. The proton signals are shifted downfield, indicative of uniform metal complexation. Furthermore, the simple pattern of the spectrum suggests a single discrete species with a minimum symmetry of C_3 . Since larger polyhedral assemblies are disfavored under thermodynamic conditions^[9a] and the highly charged polymer structures normally result in broadening of the proton NMR signals,^[11c] a trigonal prism of D_{3h} symmetry should be favored. The largest $\Delta\delta$ value of H4 as well as the smallest $\Delta\delta$ value for H2 agrees with the formation of such a metallogage: Although both H4 and H2 hydrogen atoms are expected to lose more electron density upon coordination as a result of being adjacent to a nitrogen donor site, H2 will be shielded through the ring current once a trigonal-prismatic structure is formed.^[14]

This prediction is confirmed by X-ray crystallographic analyses of the solid-state structures. For compound **1**, three almost linearly coordinated Ag^+ ions (average N–Ag–N angle of 173.3°) join two face-to-face positioned MsTBim ligands (Figure 1) to give a five-component M_3L_2 metallogage. The six benzimidazolyl arms are nearly perpendicular to the central arene bases, thus generating a relatively regular trigonal-prism structure for the $[\text{Ag}_3(\text{MsTBim})_2]^{3+}$ ion with a height of approximately 11 Å and distance of about 6 Å between the edges. One BF_4^- ion is a guest inside the cage while two BF_4^- ions stay outside, together with one acetonitrile and one water molecule, leading to a stoichiometry of $\mathbf{1} \cdot \text{MeCN} \cdot \text{H}_2\text{O}$.

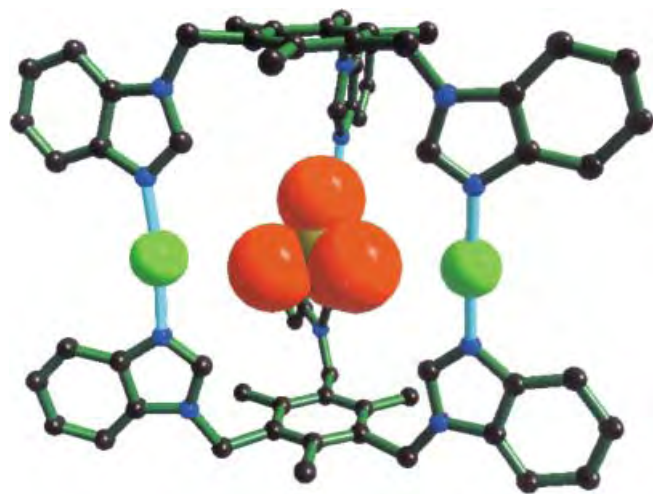


Figure 1. Representation of the $[\text{BF}_4^-][\text{Ag}_3(\text{MsTBim})_2]^{2+}$ cage in $\mathbf{1} \cdot \text{MeCN} \cdot \text{H}_2\text{O}$. Key: Ag (green); C (gray); N (blue); F (red), B (gold). The guest is shown in a space-filling mode.

A very similar metallogage is formed in the reaction with CuI. Slow solvent evaporation from the reaction mixture of MsTBim and CuI in MeOH/MeCN/DMF (1/2/2) solution resulted in small crystals the crystallographic analysis of which showed that the structure consists of two independent $[\text{CuI}_3\text{C}\{\text{Cu}_3(\text{MsTBim})_2\}]^+$ ions, one $[\text{Cu}_2\text{I}_4]^{2-}$ ion, and seven water molecules (giving the formulation $\mathbf{2} \cdot 7\text{H}_2\text{O}$). A essentially identical cage structure, $\mathbf{2} \cdot \text{C}_6\text{H}_6 \cdot 6\text{H}_2\text{O}$, can be obtained in the presence of benzene. In this latter case, the benzene molecule is located outside the cage as are the six water molecules. In both cases the cations involve the $[\text{Cu}_3(\text{MsTBim})_2]^{3+}$ trigonal-prismatic box with slightly bent N–Cu–N (average 158.7°) edges. An additional Cu^+ ion appears to be accommodated in the cage, however, this Cu^+ ion is triangularly surrounded by three iodide anions, therefore, the guest molecule really is the CuI_3^{2-} ion (Figure 2). To the best of our knowledge, such an inclusion of an anionic metal complex into a discrete cationic metallogage has not

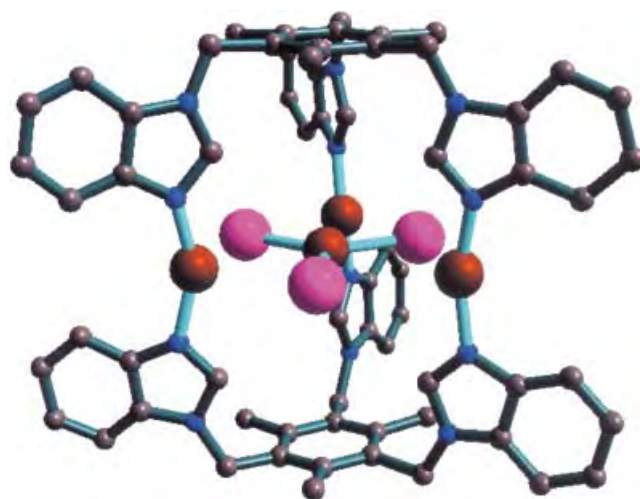


Figure 2. Representation of the $[\text{CuI}_3\text{C}\{\text{Cu}_3(\text{MsTBim})_2\}]^+$ cage in $\mathbf{2} \cdot 7\text{H}_2\text{O}$. Key: Cu (maroon); I (purple); C (gray); N (blue).

been reported before; it may be compared with Stang's host-guest molecular squares incorporating coordination of Ag^+ ions by the “ π -tweezer effect”^[15a-c] or other known ion-cryptate and ion-crown-ether encapsulating systems.^[15d-f] Outside the cage there are neutral molecules, and most importantly, an interesting $[\text{Cu}_2\text{I}_4]^{2-}$ counterion^[16] in which two Cu^+ ions are symmetrically bridged by two out of the four I^- ligands leading to the dimer shown in Figure 3.



Figure 3. Structure of the counteranion $[\text{Cu}_2\text{I}_4]^{2-}$ in $\mathbf{2} \cdot \text{C}_6\text{H}_6 \cdot 6\text{H}_2\text{O}$.

The present metallocages represent the smallest canonical 3D architecture with the shape of a trigonal prism, and are thus counterparts of an M_2L_3 trigonal box, such as $[Ag_2(pbimb)_3](CF_3SO_3)_2$ ($pbimb = 1,4\text{-bis}(\text{benzimidazol-1-ylmethyl})\text{-}2,3,5,6\text{-tetramethylbenzene}$) reported before.^[17] Therefore, two complementary strategies to construct compositionally and geometrically different but topologically identical trigonal prismatic boxes can be devised as illustrated in Figure 4. A few other M_3L_2 cages have been designed^[7] in

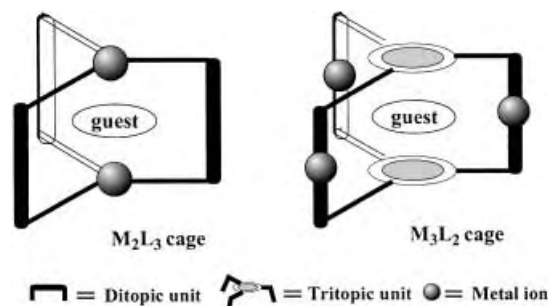


Figure 4. Schematic representation of the complementary trigonal-prismatic metal cages with different compositions but identical topologies.

which large deviations from the canonical trigonal-prismatic arrangement occur because of the square-planar or tetrahedral coordination of the metal ions used.

Considering the varied structural topologies possible even for the same metal-to-ligand ratio, the study of solution dynamics adds information beyond what may be just serendipitous solid-structure analysis. Therefore, the reaction between MsTBim and $AgBF_4$ was carried out in $[D_6]DMSO$ solution and monitored by proton NMR spectroscopy (Figure 5). When the metal salt was slowly added to the solution of the ligand (excess of MsTBim), the ^1H NMR spectrum shows one set of ligand signals shifted downfield. This is indicative of complexation, and since no signals of the “free” ligand appear, it also suggests rapid chemical exchange. Continued addition of metal salt leads to further downfield shifts until the metal-to-ligand molar ratio reaches a value of 3:2. The maximum shift is found at this stoichiometry when a spectrum identical with that of the isolated complex is obtained. Excess addition of metal salt has little influence on the proton NMR spectra which establishes quantitative self-assembly of the trigonal prismatic cage **1**. In contrast, on reverse order of addition (ligand added to metal salt), only the reverse shift of the signals (upfield) was observed without indication of any new resonance. These experiments suggest that the reaction is thermodynamically controlled and that the equilibria are rapidly achieved on the NMR time scale. Such solution dynamics is quite different from that of other known discrete molecular architectures^[3,7a,11c,18] in which the formation of oligomeric species or interconversion between several different assemblies can be detected. Although the intermediate is not clear, the rapid exchange between the labile components is prominent even after lowering the temperature to $-20^\circ C$. This behavior is a great synthetic advantage in converting all the intermediates into a single product by a “self-correction” mechanism, which leads in this particular case to a trigonal-prismatic box as the smallest possible

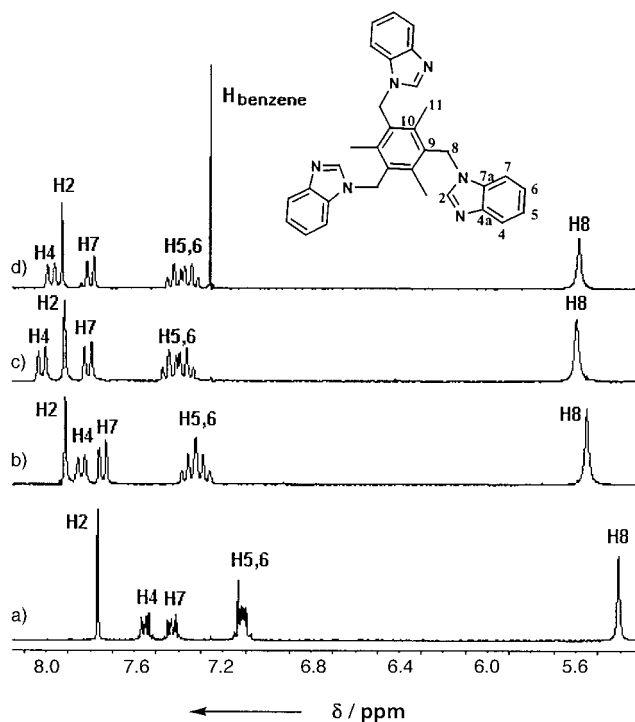


Figure 5. ^1H NMR spectra of a) the ligand MsTBim, b) the reaction mixture from an $M:L = 1:1$ ratio, c) the reaction mixture from an $M:L = 2:1$ ratio, d) $1\text{-C}_6\text{H}_6$.

discrete 3D species.^[13] In contrast, the assembly of larger polyhedra is believed to be kinetically controlled^[9a] while guest-induced^[7a,9b,18a,18c] assembly processes are found for other small metallocages.

The template effect of the guests in our case seems not specific because they can vary from the spherical BF_4^- ion to the planar Cu_3^{2-} motif. In an effort to increase the anion size while maintaining the same cage structure $AgCF_3SO_3$ was used as starting material; the $CF_3SO_3^-$ ion may not fit inside the final cage. An ^1H NMR spectrum of the complex $[Ag_3(MsTBim)_2](CF_3SO_3)_3 \cdot C_6H_6 \cdot C_6H_5CH_3$ ^[19] formed from the reaction of MsTBim with $AgCF_3SO_3$ in $MeOH/MeCN/C_6H_6/C_6H_5CH_3$ (3/2/1/1) showed almost the same signal pattern as that of **1**, indicative of formation of the same metallocage. X-ray diffraction analyses of crystals grown from this reaction mixture failed to clearly reveal the location of the anions because of the poor data quality. However, reliable structural results are available for $[Ag_3(MsTBim)_2](CF_3SO_3)(BPh_4)_2$ ^[20] which was prepared by carefully adding two molar equivalents of $NaBPh_4$ to the above reaction mixture. Since the BPh_4^- ion is too large to be accommodated inside the cage, the $CF_3SO_3^-$ ion would remain the only anionic template to induce the formation of the cage structure (if necessary). Structural analysis shows that the $CF_3SO_3^-$ ion is located *beside* the cage with the SO_3^- group facing one of the three “windows” of the cage (see Figure S1, Supporting Information). The two BPh_4^- ions occupy the other two windows with one phenyl ring each pointing inward. Therefore, the center of the cage is undoubtedly empty (Figure S2). This finding suggests that formation of such thermodynamically stable cages may not necessarily involve an anionic template effect. Further confirmation of this suggestion by

preparation of the same cage with exclusively BPh_4^- ions was prevented by the low solubility of AgBPh_4 . Recrystallization of **1** in the presence of benzene, toluene, 1,3,5-triethylbenzene, or triphenylamine, only resulted in formation of $1 \cdot \text{C}_6\text{H}_6$. ^1H NMR spectroscopic investigations showed no noticeable shift of the resonance signals of both **1** and benzene (Figure 5d), which suggests that benzene does not enter the cage, in agreement with the solid-structure analysis result of $2 \cdot \text{C}_6\text{H}_6 \cdot 6\text{H}_2\text{O}$.

It has been found that once an assembled structure is "locked" into a kinetically stable form, a lot of important properties may be available as manifested by the report of a thermally switchable molecular lock,^[18c] resolution of a chiral supramolecular assembly made from labile components,^[18b] and, more recently, postmodification of molecular rectangles resulting in enhanced structural stability.^[6] Therefore, the present thermodynamically stable but kinetically labile metal-locages may provide good models for similar studies which are currently under way.

Experimental Section

General procedure for preparation of **1** and **2**: A MeOH solution of MsTBim was added to a solution of MeCN containing excess AgBF_4 or CuI and the resulting mixture was stirred for 10 min. The solid products were collected by filtration and dried. **1**: Yield 90%. Elemental analysis calcd (%) for $\text{C}_{66}\text{H}_{60}\text{N}_{12}\text{Ag}_3\text{B}_3\text{F}_{12}$: C 49.38, H 3.77, N 10.47; found: C 49.46, H 3.79, N 10.40; ^1H NMR (250 MHz, $[\text{D}_6]\text{DMSO}$): δ = 8.12 (d, 6H, H_4), 8.02 (s, 6H, H_2), 7.91 (d, 6H, H_7), 7.54 (m, 6H, H_6), 7.46 (m, 6H, H_5), 5.69 (s, 12H, H_8), 2.36 ppm (s, 18H; Me); ^{13}C NMR (250 MHz, $[\text{D}_6]\text{DMSO}$): δ = 143.70 (C2), 141.14 (C4a), 140.72 (C7a), 133.43 (C9), 130.82 (C10), 124.80 (C4), 124.26 (C7), 119.71 (C5), 112.06 (C6), 44.32 (C8), 16.73 ppm (C11). **2**: Yield 83%. Elemental analysis calcd (%) for $\text{C}_{132}\text{H}_{120}\text{N}_{24}\text{Cu}_{10}\text{I}_{10}$: C 40.17, H 3.06, N 8.52; found: C 40.47, H 3.08, N 8.99; ^1H NMR ($[\text{D}_6]\text{DMSO}$): δ = 8.10 (s, 6H, H_2), 8.08 (d, 6H, H_4), 7.79 (d, 6H, H_7), 7.53 (m, 6H, H_6), 7.48 (m, 6H, H_5), 5.71 (s, 12H, H_8), 2.31 ppm (s, 18H; Me); ^{13}C NMR ($[\text{D}_6]\text{DMSO}$): δ = 145.88 (C2), 140.49 (C4a), 140.19 (C7a), 135.73 (C9), 130.20 (C10), 124.14 (C4), 124.01 (C7), 119.43 (C5), 112.04 (C6), 45.61 (C8), 15.82 ppm (C11).

Crystal data for **1**·MeCN· H_2O : M_r = 1664.4, tetragonal, space group $P4(2)/n$, a = 27.824(4), c = 18.108(4) Å, V = 14020(4) Å³, T = 173 K, Z = 8, 10367 unique reflections measured, final $R1$ = 0.0801 and $wR2$ = 0.1859 for 6184 observed [$I > 2\sigma(I)$] reflections. **2**· H_2O : M_r = 4083.11, triclinic, space group $P\bar{1}$, a = 16.935(3), b = 17.165(3), c = 30.625(6) Å, α = 101.72(3), β = 102.94(3), γ = 91.36(3)°, V = 8473(3) Å³, T = 293 K, Z = 2, 10822 unique reflections measured, final $R1$ = 0.0847 and $wR2$ = 0.2301 for 8007 observed reflections. **2**· C_6H_6 · H_2O : M_r = 4133.12, monoclinic, space group $P2(1)/n$, a = 19.893(6), b = 40.398(13), c = 23.814(9) Å, β = 108.19(2)°, V = 18182(11) Å³, T = 173 K, Z = 4, 16630 unique reflections measured, final $R1$ = 0.0817 and $wR2$ = 0.1726 for 5856 observed reflections. CCDC-177761 (**1**·MeCN· H_2O), CCDC-177762 (**2**· H_2O), CCDC-177763 (**2**· C_6H_6 · H_2O) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

One of BF_4^- ion in **1** and the counteranion $[\text{Cu}_2\text{I}_4]^{2-}$ in **2**· H_2O are disordered over two positions. Water molecules in all three compounds are severely disordered. Because of weak diffraction most of C and N atoms in $2 \cdot \text{C}_6\text{H}_6 \cdot 6\text{H}_2\text{O}$ were refined isotropically.

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δ = 8.09 (d, 6H, H4), 8.02 (s, 6H, H2), 7.91 (d, 6H, H7), 7.54 (m, 6H, H6), 7.46 (m, 6H, H5), 7.36 (s, 6H, C₆H₆), 7.13–7.28 (m, 5H, C₆H₅CH₃), 5.70 (s, 12H, H8), 2.34 (s, 18H; Me), 2.29 ppm (s, 3H; C₆H₅CH₃).

[20] Crystal data for [Ag₃(MSTBim)₂](CF₃SO₃)·(BPh₄)₂: M_r = 2132.35, monoclinic, space group $C2/c$, a = 25.866(5), b = 18.041(4), c = 22.125(4) Å, β = 96.90(3)°, V = 10250(4) Å³, T = 293 K, Z = 4, 8663 unique reflections measured, final $R1$ = 0.0744 and $wR2$ = 0.1981 for 5554 observed [$I > 2\sigma(I)$] reflections. CCDC-183553 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk). The CF₃SO₃[−] ion is disordered along the C_2 axis.

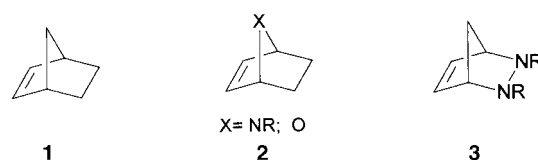
Two-Step, Stereoselective Hydrazidoarylation of 1,3-Cyclopentadiene**

Min-Liang Yao, Gunadi Adiwidjaja, and Dieter E. Kaufmann*

The first palladium-catalyzed reductive phenylation of norbornene (**1**) was published by Larock and Johnson^[1] in 1989; since then the high synthetic potential of the hydroarylation^[2] and especially its asymmetric variant^[3] with bicyclic alkenes for the one-step construction of three asymmetric centers has induced a line of follow-up papers. This situation is especially true for the hydroarylation of the 7-aza- and oxabicyclic alkenes **2** (Scheme 1)^[2b–d, 3c] as this synthetic route even in the case of the asymmetric pathway leads directly to the biologically highly active alkaloid Epibatidine^[4] and its analogues.

As we are interested in both the hydroarylation of bicyclic alkenes and, herein, in the use of these products in the stereoselective synthesis of substituted cyclopentane derivatives, we have investigated the hydroarylation followed by reductive cleavage of the easily accessible^[5] 2,3-diazabicyclo[2.2.1]heptenes **3**,^[6] in which the N–N^[7] or C–N bond^[8] represents an internal point of fracture.

Recently, we have reported the first palladium-catalyzed hydroarylation of the N,N'-diethoxycarbonyl-substituted de-

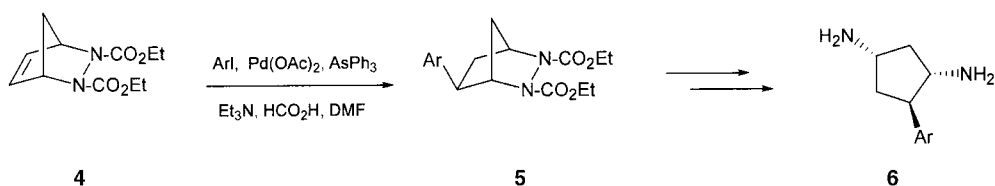


Scheme 1. (Hetero)norbornenes **1–3** as starting materials for hydroarylation reactions.

riative **4** of **3** with triethylamine as a base.^[6] The following selective N–N bond cleavage opens a highly stereoselective way to the *trans*-4-aryl-*cis*-1,3-diaminocyclopentanes **6** (Scheme 2).

Encouraged by this initial result, we turned to the hydroarylation of the sterically more hindered and more rigid, tri- or tetracyclic Diels–Alder adducts of 1,3-cyclopentadiene with the very reactive azodienophiles 4-phenyl-1,2,4-triazoline-3,5-dione (**7a**) and 2,3-phthalazine-1,4-dione (**7b**). The reaction of **7a** with iodobenzene was chosen as a model system with which to optimize the reaction conditions; selected experiments are shown in Table 1.

We started with the reaction conditions (Et₃N, DMF, 65 °C, entry 1) which were optimal in case of the hydroarylation of **4**; besides 21 % of the expected hydroarylation product **8a**, compound **9a** was formed in 9 % as the product of a C–N cleavage reaction. Formally, the formation of **9a** is the result of a 1,2-hydrazidoarylation on the primarily employed 1,3-cyclopentadiene. From the ¹H and ¹³C NMR spectroscopic data it appeared that the *trans* isomer **9a** was formed



Scheme 2. Stereoselective synthesis of threefold substituted cyclopentane derivatives.

exclusively. The structural assignment is difficult in case of five-membered ring systems; however, the stereochemistry was unambiguously supported by an X-ray analysis (Figure 1).^[9,10]

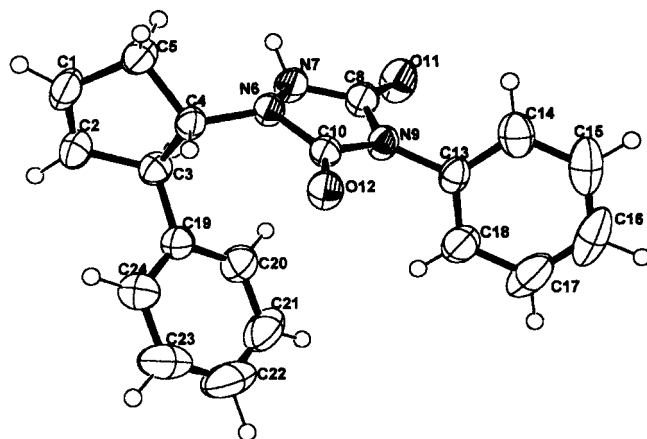


Figure 1. ORTEP plot of **9a**.

[*] Prof. Dr. D. E. Kaufmann, Dr. M.-L. Yao
Institut für Organische Chemie
Technische Universität Clausthal
Leibnizstrasse 6, 38678 Clausthal-Zellerfeld (Germany)
Fax: (+49) 5323-72-2834
E-mail: dieter.kaufmann@tu-clausthal.de
Dr. G. Adiwidjaja
Mineralogisch-Petrographisches Institut
Universität Hamburg
Grindelallee 48, 20146 Hamburg (Germany)

[**] Palladium-catalyzed reactions, part 4; part 3 ref [6]. We thank BAYER AG, Leverkusen and Fond der Chemischen Industrie (Germany) for financial support.

Table 1. Influence of base and temperature on the reaction of **7a** with PhI.

Entry	Reaction conditions ^[a]	Yield [%] ^[b] 8a	Yield [%] ^[b] 9a
1	Et ₃ N; DMF; 65 °C	21	9
2	Et ₃ N; DMF; 50 °C	22	14
3	Et ₃ N; DMF; 20 °C	31	20
4	NaOAc; DMSO; 20 °C	31	28
5	NaF; DMSO; 65 °C	18	46
6	LiCl; DMSO; 65 °C	3	25

[a] Reaction conditions: 2.5 mol % Pd(OAc)₂, 11 mol % AsPh₃, alkene **7a** (1.0 equiv), PhI (1 equiv), base (3.5 equiv), HCO₂H (3.0 equiv) in solvent (4 mL).

[b] Yields of isolated product relative to alkene **7a**.

The low yield of **8a** is because of the low stability of the starting material **7a** towards the basic triethylamine at 65 °C; the cleavage by KOH^[11] and hydrazine^[12] is known. Lowering the reaction temperature from over 50 (entry 2) to 20 °C (entry 3) led to an overall yield of more than 50 %. On the one hand, the reactivity of **7a** in comparison with **4** is clearly remarkable, allowing an addition even at room temperature, however, on the other hand there is a distinct increase in the amount of by-product **9a** produced on decreasing the reaction temperature. However, we did not succeed in raising the yield by using either a higher catalyst:ligand ratio or an excess of iodobenzene. On the other hand the use of inorganic bases proved to be successful: a heterogeneous mixture of sodium acetate and DMSO (entry 4) led to an approximately equidistribution of **8a** and **9a**. In recent years the application of alkali-metal fluorides has proved successful in palladium-catalyzed reactions.^[13] With sodium fluoride in DMSO the conversion still proceeded very sluggishly at room temperature, while at 65 °C (entry 5), under acidic conditions (formic acid),^[14] the hydroarylation was suppressed and **9a** was formed as the main product with an overall yield of 64 %. The use of lithium chloride as a base led almost exclusively to the formation of the formal hydrazidoarylation product **9a**; however the yield was dramatically reduced.

Table 2. Palladium-catalyzed reaction of (hetero)aryliodides with **7a/b**.

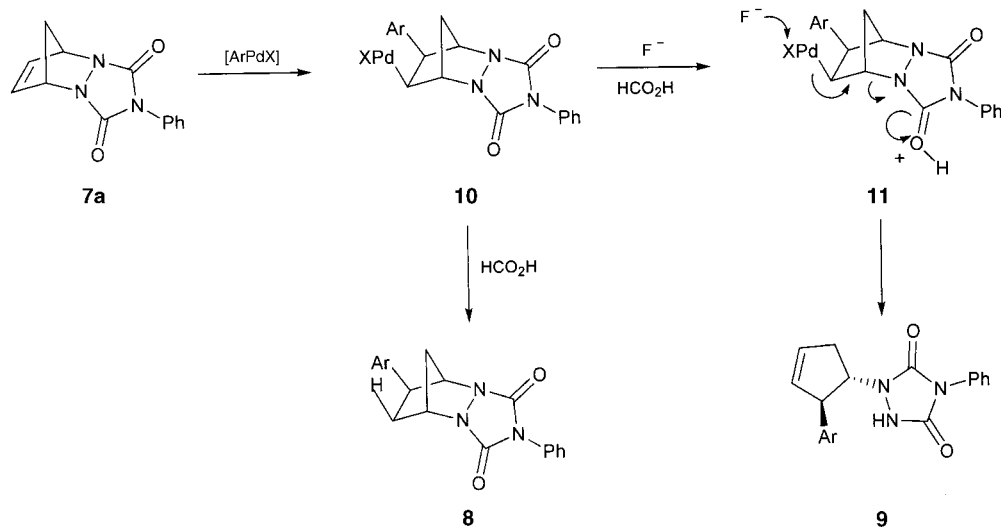
Entry ^[a]	Alkene	ArI	Yield [%] ^[b] 8a-f	Yield [%] ^[b] 9a-f
1	7a		18 (21) 8a	46 (9) 9a
2	7b		3 8d	67 9d
3	7a		5 (18) 8b	63 (5) 9b
4	7b		4 8e	64 9e
5	7a		7 (11) 8c	63 (7) 9c
6	7b		6 8f	69 9f

[a] Reaction conditions: 65 °C, 2.5 mol % Pd(OAc)₂, AsPh₃ (11 mol %), alkene (1.0 equiv), ArI (1.5 equiv), NaF (3.5 equiv), HCO₂H (3.0 equiv) in DMSO (4 mL). [b] Yields of isolated product, relative to alkene; the yields in parentheses were obtained under the reaction conditions in entry 1, Table 1.

After we had optimized the reaction conditions (Table 1, entry 5), we examined the application scope of the reaction for the polycyclic diazaalkenes **7a/b** with three aryliodides (Table 2). Apparently, the use of sodium fluoride as a base

instead of triethylamine allows the selective formation of the opening products **9a–f** in good yields.

Several reaction paths are mechanistically conceivable. The cleavage of a C–N bond in diazabicyclic compounds through acid catalysis^[15a] or heating^[15b] is known. In a two-step process from **7a**, primarily a N-cyclopentadienyl-substituted phenylurazole could be formed, the subsequent, regioselective hydroarylation of which could lead to the *trans*-configured **9a**. The reaction of **7a** with formic acid or hydrochloric acid in DMF or DMSO at 65 °C, however, did not lead to the formation of even trace amounts of an opening product. Based on this result we suggest the mechanism outlined in Scheme 3.



Scheme 3. Mechanism of the palladium-catalyzed C–N cleavage of **7a**.

At the beginning, a *syn*-addition of a $[ArPdX]$ species to the bicyclic C=C bond of **7a** occurs to give **10**. This intermediate can then be reduced to the hydroarylation product **8** either by formates or even formic acid itself. Apparently, electron-poor aromatic groups stabilize the intermediate palladium complex **10** towards reduction as effectively as the halide ions F^- and Cl^- , so that a—preferentially acid catalyzed—competitive isomerization reaction can occur (see **11**) forming **9**. This methodology opens a new, simple access to *trans*-3,4-disubstituted cyclopentene derivatives, a class of intermediates and biologically active compounds that is not easily accessible by other pathways.

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[9] Crystal structure analysis: Structure solution with direct methods and full-matrix least-squares refinement procedure (SHELX97^[10]). **9a** ($C_{19}H_{17}N_3O_2$, $M_r = 319.13$): monoclinic, space group $P2(1)/c$, $a = 17.3890(10)$, $b = 11.3510(10)$, $c = 19.9100(10)$ Å, $\beta = 156.100(10)^\circ$, $V = 1592.16(19)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.332$ Mg m⁻³, $T = 293$ K, 21904 collected, 3656 crystallographic independent and 3473 reflexes with $I > 2\sigma(I)$, $MoK\alpha$ radiation, $\lambda = 0.71073$ Å, $\theta_{\text{max}} = 27.50^\circ$, $R[I > 2\sigma(I)] = 0.0424$, $wR_2 = 0.1400$, $wR_2 = 0.1959$ (all data), 286 parameters, anisotropic thermal parameters, H-atoms isotropic. CCDC-173237 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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vacuo and the residue was purified by column chromatography (silica, petroleum ether:ethyl acetate 9:1): mixture of **8a** (18%) and **9a** (46%). **8a**: colorless crystals, mp.: 174–175 °C; ¹H NMR (400 MHz, CDCl₃, TMS): δ = 1.92–2.21 (m, 3H), 2.42–2.55 (m, 1H), 3.52–3.59 (m, 1H, HC-Ph), 4.72 (s, 1H, H_{bridgehead}), 4.80 (s, 1H, H_{bridgehead}), 7.16–7.55 ppm (m, 10H, H_{aryl}); ¹³C NMR (100 MHz, CDCl₃, TMS; Multiplicities of ¹³C NMR signals were determined by the DEPT sequence and are reported as (+) for CH or CH₃, (–) CH₂, and (o) for C): δ = 35.00 (–), 36.25 (–), 45.29 (+), 60.33 (+), 64.87 (+), 125.38 (+), 126.95 (+), 127.07 (+), 128.31 (+), 128.85 (+), 129.15 (+), 131.52 (o), 140.26 (o), 156.71 (o, C=O), 156.96 ppm (o, C=O); MS (EI): *m/z* (%) 320 (15, [M⁺ + 1]), 319 (59, [M⁺]), 214 (100), 143 (20), 142 (19), 115 (17), 104 (43), 91 (30); IR: $\tilde{\nu}_{\text{max}}$ = 3056, 3011, 1776, 1716, 1598, 1501, 1415, 735, 697 cm^{–1}. HRMS: calcd for C₁₉H₁₇N₃O₂ 319.1321; found 319.1321. **9a**: Colorless crystals, mp.: 187–189 °C. ¹H NMR (400 MHz, CDCl₃, TMS): δ = 2.49–2.63 (m, 1H), 2.77–2.92 (m, 1H), 4.03–4.07 (m, 1H, HC-Ph), 4.74–4.84 (m, 1H, HC-N), 5.73–5.83 (m, 1H, HC=), 5.90–5.96 (m, 1H, HC=), 7.17–7.49 (m, 10H, H_{aryl}), 9.07 ppm (br s, 1H, HN); ¹³C NMR (CDCl₃): δ = 35.26 (–), 54.28 (+), 64.30 (+), 125.44 (+), 127.15 (+), 127.36 (+), 128.23 (+), 128.74 (+), 129.09 (+), 129.63 (+), 131.13 (o), 132.73 (+), 141.48 (o), 152.21 (o, C=O), 154.09 ppm (o, C=O); MS (EI): *m/z* (%) 320 (16, [M⁺ + 1]), 319 (68, [M⁺]), 215 (16), 214 (100), 143 (22), 142 (21), 104 (57), 91 (26); IR: $\tilde{\nu}_{\text{max}}$ = 3160, 3059, 1772, 1687, 1595, 1493, 1378, 700, 676 cm^{–1}; HRMS: calcd for C₁₉H₁₇N₃O₂ 319.1321; found 319.1321.

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Biomimetic Model of a Plant Photosystem Consisting of a Recombinant Light-Harvesting Complex and a Terrylene Dye**

Henriette Wolf-Klein, Christopher Kohl, Klaus Müllen, and Harald Paulsen*

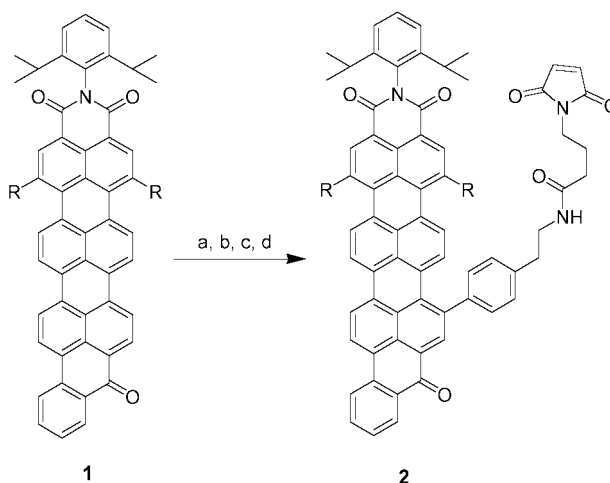
The light-harvesting chlorophyll (Chl) *a/b* antenna in higher plants contributes to photosynthesis by absorbing light energy and funneling it into the photosynthetic reaction centers where the conversion into an electrochemical potential takes place. The components of this photosynthetic antenna, the light-harvesting Chl *a/b* complexes (LHC), fulfil this task with the help of numerous protein-bound pigments, carotenoids, and Chl *a* and Chl *b*, which exchange absorbed energy rapidly and with high efficiencies.^[1] The most abundant Chl *a/b* complex is the major LHC of photosystem II, LHCIIb, which comprises roughly 50% of the total Chl in

higher plants. This complex can be reconstituted in vitro from its protein and pigment components, using either denatured thylakoid proteins^[2] or recombinant LHCIIb apoprotein, Lhcb1.^[3] Recombinant LHCIIb exhibits structural, biochemical, and spectroscopic properties very similar to those of native LHCIIb.^[3–5]

The in vitro reconstitution of recombinant LHCIIb opens up the possibility of introduce useful modifications into the structure by altering the amino acid sequence. Thus, anchors have been generated for immobilizing the complex or for site-specific fluorescence labeling.^[6] This property makes recombinant LHCIIb a promising candidate for designing hybrid biological–chemical structures that contain an ordered arrangement of fluorophores.

Herein we show that recombinant LHCIIb can be coupled to an artificial energy trap, benzoylterrylene-3,4-dicarboximide (BTI). This NIR dye collects, by efficient energy transfer, a large fraction of the light energy absorbed by the LHCIIb pigments, which makes the LHCIIb–BTI construct a simple model of a photosystem consisting of a light-harvesting pigment–protein complex and an energy trap.

To couple BTI (**1**)^[7] to cysteine side chains in the protein, a maleimido derivative of the dye was constructed (Scheme 1). Maleimido BTI (**2**) was synthesized in a four step reaction



Scheme 1. R = *tert*-butylphenol; a) Br₂, CHCl₃, RT, 16 h, 78%; b) (4-pinacolylborono)-Ph(CH₂)₂NBOC, Pd(PPh₃)₄, K₂CO₃(aq), toluene, 110 °C, 18 h, 84%; c) TFA/CH₂Cl₂, RT, 2 h, 93%; d) *N*-succinimidyl-4-maleimidobutyrate, Et₃N, CH₂Cl₂, RT, 6 h, 78%. BOC = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid.

from **1**. Bromination of **1** followed by Suzuki coupling with the BOC-protected (4-pinacolylborono)phenylethylamine afforded the corresponding BOC derivative of phenylethylamino BTI. After acidic removal of the BOC protecting group, the phenylethylamino BTI was transformed into **2** with *N*-succinimidyl-4-maleimidobutyrate.

Maleimido BTI (**2**) was attached to a single cysteine residue near the N terminus of the Lhcb1 mutant S3C. The site specificity of the labeling reaction was verified by the fact that another Lhcb1 mutant containing no cysteine at all (C79S) did not bind any BTI maleimide (not shown). Lhcb1–BTI was purified by preparative electrophoresis, in which it migrated more slowly than the nonlabeled protein. Subsequently the

[*] Prof. Dr. H. Paulsen, Dr. H. Wolf-Klein
Institut für Allgemeine Botanik
Johannes Gutenberg-Universität Mainz
Müllerweg 6, 55099 Mainz (Germany)
Fax: (+49) 6131-3923787
E-mail: paulsen@mail.uni-mainz.de

C. Kohl, Prof. Dr. K. Müllen
Max-Planck-Institut für Polymerforschung
Ackermannweg 10, 55128 Mainz (Germany)

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protein was reconstituted with pigments^[5,6] to form LHCIIb-BTI. This construct was approximately as stable towards dissociation in a detergent environment as the nonlabeled LHCIIb containing the wild-type protein and exhibited virtually 100% energy transfer from complex-bound Chl *b* to Chl *a* (not shown).

To estimate energy flow from Chl *a* to BTI, the fluorescence emission spectrum of LHCIIb-BTI was compared to that of nonlabeled LHCIIb at 297 K and 77 K (Figure 1). The

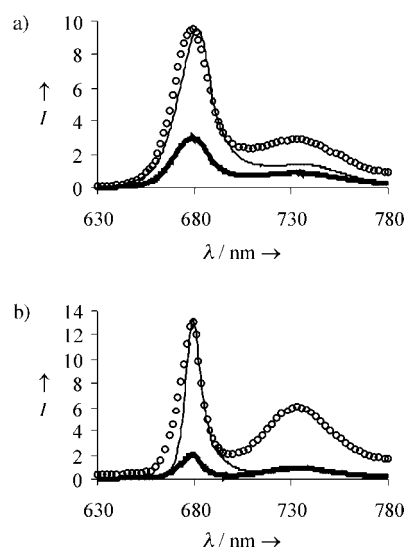


Figure 1. Fluorescence emission of LHCIIb (thin line) and LHCIIb-BTI (bold line) at 297 K (a) and 77 K (b). Purified LHCIIb and LHCIIb-BTI were brought to exactly ($\pm 1\%$) the same absorption at 410 nm. Fluorescence emission spectra were measured of these solutions using a Fluoromax-2 (Jobin Yvon, Grasbrunn, Germany) with the following instrument parameters: excitation wavelength 410 nm, excitation and emission bandwidths 3 nm, integration time 0.1 s. The spectra were corrected for fluctuations in excitation light intensity and wavelength-dependent changes in photomultiplier sensitivity. All LHCIIb samples had an optical density of <0.1 over the entire visible spectrum, to minimize fluorescence reabsorption. For measurements at 77 K, the samples were dissolved in 60% (v/v) glycerol. To visualize the BTI contribution (emission maximum at about 735 nm) to the LHCIIb-BTI emission spectrum, the latter is also shown normalized to the maximum signal of LHCIIb emission (circles).

excitation wavelength was 410 nm, near the absorption maximum of Chl *a*. The emission spectra of LHCIIb-BTI (bold lines in Figure 1) exhibit a maximum at 678 nm, near the emission maximum of Chl *a*, and a shoulder at 730 nm, near the emission maximum of BTI. The emission of Chl *a* in LHCIIb-BTI is significantly reduced compared to the emission of Chl *a* in nonlabeled LHCIIb at the same concentration (thin lines in Figure 1). From fluorescence quenching of the donor (Chl *a*), an apparent energy transfer efficiency was calculated to be $70 \pm 4\%$ at 297 K (Figure 1 a) and $85 \pm 4\%$ at 77 K (Figure 1 b). Sensitized acceptor (BTI) fluorescence was expected to be low because of the low fluorescence quantum yield of protein-bound BTI, $3 \pm 0.3\%$, measured in detergent solution at 297 K. The BTI emission band is more clearly visible in the LHCIIb-BTI fluorescence emission spectra only when these are normalized to the Chl *a* emission maximum of nonlabeled LHCIIb (circles in Figure 1).

The quenching of donor (Chl *a*) fluorescence in LHCIIb-BTI is caused by energy transfer to the acceptor (BTI), as the quenching effect ceases when donor and acceptor are separated by trypsin digestion of LHCIIb-BTI. Trypsin cleaves 35 amino acids from the N terminus of LHCIIb, leaving the pigment-binding domain of the protein intact.^[8] Upon trypsin digestion, the Chl *a* fluorescence of LHCIIb-BTI rose to the level of that of nonlabeled LHCIIb (Figure 2).

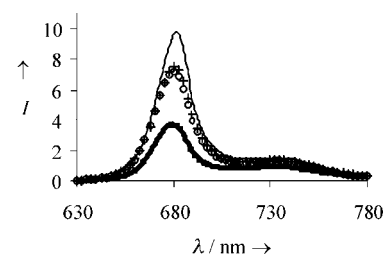


Figure 2. Fluorescence emission of LHCIIb (thin line; after trypsin digestion: crosses) and LHCIIb-BTI (bold line; after trypsin digestion: circles) before and after protein digestion with trypsin. Purified LHCIIb and LHCIIb-BTI were brought to the same Chl *a* absorption at 410 nm and trypsin digested.^[6] Emission spectra (excitation at 410 nm) were taken before and after digestion (same instrument parameters as in Figure 1).

The decrease in LHCIIb emission upon trypsin treatment is in part caused by dilution of the complex during the experiment.

The apparent energy transfer efficiencies from Chl *a* to BTI (70% and 85% at 297 K and 77 K, respectively) are quite high but may nevertheless be underestimated because of energy back-transfer from BTI to the Chls. The critical Förster distance (R_0) for the donor-acceptor pair (Chl *a*-BTI) is estimated to be 58 Å (at 297 K, assuming an orientation factor κ^2 of $\frac{2}{3}$). The R_0 value for the reversed donor-acceptor pair is estimated to be 34 Å, which is well within the possible range of distances between Chls and BTI in LHCIIb-BTI. If energy back-transfer does limit the apparent energy transfer efficiency from Chl *a* to BTI, the latter could be further increased by decreasing the fluorescence lifetime of the acceptor, for instance, by engaging the acceptor dye in a fast photochemical reaction.

A large number of biomimetic models of photosystems have been described, including self-assembling arrays of bacteriochlorophyll *c*, which mimic chlorosomes of green sulfur bacteria,^[9] and porphyrins covalently attached to other chromophores.^[10] To our knowledge, the LHCIIb-BTI construct is the first biomimetic model of a plant photosystem that contains a self-assembling recombinant light-harvesting complex of the photosynthetic apparatus in higher plants. This model mimics the efficient transfer of absorbed light energy to an acceptor but differs from a photosystem in that light energy is not converted into charge separation. Experiments to integrate this feature into our model are underway.

Experimental Section

Analytical data of **2**: green solid; m.p. $> 300^\circ\text{C}$; ^1H NMR (500 MHz NMR, $\text{C}_2\text{D}_2\text{Cl}_4$, 313 K): δ = 9.44 (d, ^3J = 7.9 Hz, 1H); 8.96 (d, ^3J = 8.6 Hz, 1H); 8.75 (d, ^3J = 7.9 Hz, 1H); 8.54 (d, ^3J = 7.9 Hz, 1H); 8.52 (d, ^3J = 7.9 Hz, 1H); 8.44 (d, ^3J = 7.9 Hz, 1H); 8.38 (s, 1H); 8.30 (d, ^3J = 8.0 Hz); 8.22 (s, 1H); 8.17 (s, 1H); 7.76 (d, ^3J = 9.2 Hz, 1H); 7.68 (tr, ^3J = 7.3 Hz, 1H); 7.53 (tr, ^3J = 7.3 Hz, 1H); 7.47–7.43 (m, 5H); 7.38–7.35 (m, 3H); 7.24–7.20 (m, 5H); 7.14 (d, ^3J =

6.8 Hz); 7.05 (d, $^3J = 9.2$ Hz, 2H); 6.62 (s, 2H); 3.53–3.49 (m, 4H); 2.87–2.86 (m, 2H); 2.64 (sept, $^3J = 8.6$ Hz, 2H); 2.13–2.10 (m, 2H); 1.90–1.87 (m, 2H); 1.32 (s, 9H); 1.29 (s, 9H); 1.08 ppm (d, $^3J = 8.6$ Hz, 12H); ^{13}C -NMR (500 MHz NMR, $\text{C}_2\text{D}_2\text{Cl}_4$, 313 K): $\delta = 185.41$ (C=O), 175.49 (C=O), 165.86 (C=O), 165.78 (C=O), 164.71 (C=O), 164.69 (C=O), 157.28, 155.35, 155.26, 150.55, 150.48, 148.06, 147.72, 142.29, 139.03, 137.79, 136.64, 136.61, 135.65, 134.77, 134.23, 133.58, 133.49, 133.44, 133.37, 133.21, 132.86, 132.41, 132.22, 132.12, 131.97, 131.53, 131.24, 131.15, 131.01, 130.59, 130.46, 130.33, 130.12, 130.04, 129.95, 129.74, 129.08, 128.29, 128.09, 126.69, 126.51, 125.51, 125.90, 125.27, 125.17, 125.12, 124.87, 124.26, 124.06, 121.85, 121.70, 117.78, 117.34, 45.10, 39.87, 37.28, 34.21, 32.08, 31.79, 31.44, 26.79, 24.66 ppm; UV/Vis (CHCl_3): λ_{max} (ϵ) = 263 (60 100), 272 (61 300), 445 (4500), 651 (47 800), 705 (89 400) nm; field desorption (FD)-MS (8 kV): m/z (%): 1289.0 (100) [M^+]; anal. calcd for $\text{C}_{87}\text{H}_{73}\text{N}_3\text{O}_8$: C 81.10, H 5.71, N 3.26; found: C 81.23, H 5.79, N 3.22

The recombinant Lhcb1 mutants used in this work were derivatives of the clone D7f.3 coding for pea wild-type Lhcb1.^[3,11] A single cysteine residue in position 79 of mutant C79S was exchanged with a serine residue, and mutant S3C carried the additional mutation of cysteine in place of serine in position 3.

BTI was covalently coupled to the N-proximal cysteine in the Lhcb1 mutant S3C. Lhcb1 (1 nmol) in buffer (25 μL ; 1 g L^{-1} sodium dodecylsulfate, 10 g L^{-1} *n*-octyl- β -D-glucopyranoside and 20 mM sodium phosphate pH 7.0) was reduced for 15 min at 37 °C with 2 mM tris(2-cyanoethyl)phosphane and then mixed with BTI maleimide (12.5 nmol), dissolved in THF (2 μL). After 2 h incubation at 37 °C, the protein was precipitated with 80 % (v/v) acetone and 10 mM acetic acid. The protein pellet was dissolved in sodium dodecylsulfate (20 μL ; 20 g L^{-1}), 100 mM Tris-HCl (Tris = tris(hydroxymethyl)aminomethane; pH 9.0), heated to 100 °C for 2 min and then centrifuged (5 min at 16 000 g) to remove insoluble material.

In LHCIIB-BTI constructs, energy transfer from Chl *a* to the dye was calculated from the quenching of donor (Chl *a*) emission in the presence of the acceptor. Samples of LHCIIB with and without bound BTI were made up to the same Chl *a* absorption at 410 nm. The dye absorption was negligible at this wavelength. Energy transfer efficiency was estimated by comparing Chl *a* fluorescence emissions with and without energy transfer to the dye:

Energy transfer [%] = $[1 - (\text{maximum Chl } a \text{ emission in LHCIIB-BTI}) / (\text{maximum Chl } a \text{ emission in LHCIIB})] \times 100$.

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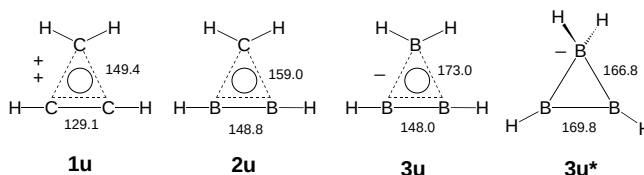
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Triboracyclopropanates: Two-Electron Double Aromatic Compounds with Very Short B–B Distances**

Carsten Präsang, Anna Młodzianowska, Yüksel Sahin, Matthias Hofmann, Gertraud Geiseler, Werner Massa, and Armin Berndt*

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

According to computations, the isoelectronic, two-electron double aromatic compounds **1u–3u**^[1–4] (Scheme 1) have one extremely short and two relatively long bonds in the ring. This results from the fact that all of the ring atoms are connected



Scheme 1. Two-electron aromatic compounds, each containing a 3c–2e π (circles) and σ bond (dashed triangle). Solid lines symbolize a 2c–2e bond. The numbers indicate the distances in pm, computed at the MP2/6-31G* level.^[1–3]

by one three-center, two-electron (3c–2e) π as well as one 3c–2e σ bond and that two ring atoms are connected by an additional 2c–2e σ bond. The planar compound **3u** is stabilized by 54.9 kcal mol^{-1} with respect to the classical structure **3u***.^[3b] We present here the syntheses and crystal structures of **3a** and **3b** (see Scheme 2), the first derivatives of the triboracyclopropanate **3u**, as well as DFT computations^[5] for model compounds **3c–f** (see Figure 2).

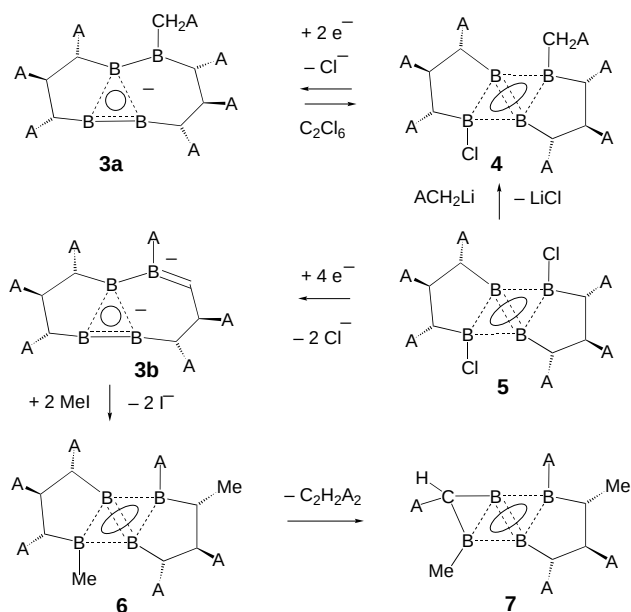
The monoanion **3a** is obtained from the reaction of two equivalents of lithium naphthalenide in THF with **4**, which forms upon treatment of **5**^[6] with $(\text{CH}_3)_3\text{SiCH}_2\text{Li}$ (Scheme 2). The dianion **3b** results when **5** is treated with lithium in Et_2O at -80°C .^[7] Compounds **3a** and **3b** react with electrophiles to tetraboranes(6). Treatment of **3a** with hexachloroethane results in the regeneration of **4**, and **3b** reacts with methyl iodide^[8] to form **6**, which spontaneously transforms into **7** in solution with elimination of 1,2-bis(trimethylsilyl)ethene. The constitutions of the new compounds are in agreement with their NMR data (Table 1), and the structures of **3a**, **3b**, and **6** have been confirmed by crystal structure analysis.^[9]

The anion **3a** forms a contact ion pair with a lithium ion, which is coordinated to the B2–B3 bond as well as to two THF

[*] Prof. Dr. A. Berndt, Dr. C. Präsang, A. Młodzianowska, Dr. Y. Sahin, G. Geiseler, Prof. Dr. W. Massa
Fachbereich Chemie, Universität Marburg
Hans-Meerwein-Straße, 35032 Marburg (Germany)
Fax: (+49) 6421/282-8917
E-mail: berndt@chemie.uni-marburg.de

Dr. M. Hofmann
Anorganisch-Chemisches Institut, Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)

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Scheme 2. Syntheses and reactions of the triboracyclopropanates **3a** and **3b**. All reactions proceed with retention of the two-electron aromaticity. A = SiMe₃.

Table 1. Selected physical and spectroscopic characteristics of **3a**, **3b**, **4**, **6**, and **7**.

3a: Yellow solid, m.p. 129 °C (decomp), yield 80 % (based on NMR spectroscopy); ¹H NMR (300 MHz, C₆D₆, 27 °C): δ = 3.49, 1.37 (each m, each 8 H, THF), 2.78, 1.98 (each pseudo t, each 1 H, C₂CHSi), 2.64, 2.10, 1.56, 1.12 (each d, each 1 H, BCHSi), 1.70, 1.22 (each d, each 1 H, BCH₂Si), 0.47, 0.43, 0.37, 0.34, 0.24 (each s, in total 63 H, SiMe₃); ¹³C NMR (75 MHz, C₆D₆, 27 °C): δ = 68.8, 25.3 (THF), 40.2, 26.9 (each d, C₂CHSi), 38.1, 36.3, 28.8, 19.7 (each brd, BCHSi), 23.7 (brpseudo t, BCH₂Si), 3.2, 2.7, 2.1, 1.2, 0.8, 0.3, −0.9 (SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 27 °C): δ = 59, 46, 27 (2 B).

3b: Yellow solid, m.p. 114 °C (decomp), yield 60 %; ¹H NMR (400 MHz, C₆D₆, 27 °C): δ = 5.35, (d, 1 H, BCHC), 3.26 (q, 8 H, Et₂O), 2.44 (dd, 1 H, C₂CHSi), 2.76, 1.61, 1.11 (each d, each 1 H, BCHSi), 1.23 (d, 1 H, C₂CHSi), 0.97 (t, 12 H, Et₂O), 0.45, 0.40, 0.26, 0.25, 0.22 (each s, in total 54 H, SiMe₃); ¹³C NMR (75 MHz, C₆D₆, 27 °C): δ = 121.9 (brd, J = 141 Hz, B = CHC), 65.6, 14.5 (Et₂O), 36.8, 26.9, 15.0 (each brd, BCHSi), 35.6, 24.6 (each d, C₂CHSi), 5.2, 2.1, 1.6, 1.0, −0.3, −2.0 (SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 27 °C): δ = 69, 59, 36 (2 B).

4: Light yellow crystals, m.p. 148 °C, yield 87 %; ¹H NMR (300 MHz, C₆D₆): δ = 2.55, 2.49, 2.33, 2.09 (each d, each 1 H, BCHSi), 1.91, 1.67 (each pseudo t, each 1 H, C₂CHSi), 1.83, 1.56 (each d, each 1 H, BCH₂Si), 0.34, 0.29, 0.28, 0.26, 0.22, 0.21 (each s, in total 63 H, SiMe₃); ¹³C NMR (75 MHz, C₆D₆, 27 °C): δ = 51.2, 46.4, 31, 30 (each brd, BCHSi), 30.1, 23.6 (each d, C₂CHSi), 25.4 (brpseudo t, BCH₂Si), 2.4, 1.9, 1.8, 1.3, 0.7, 0.0, −1.6 (SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 27 °C): δ = 68, 65, 34, 27.

6: Colorless solid, m.p. 99 °C (decomp), yield 89 %; ¹H NMR (300 MHz, C₆D₆, 27 °C): δ = 3.15 (q, 1 H, BCHMe), 2.38 (d, 1 H, MeBCHSi), 2.28 (d, 1 H, B₃BCHSi), 1.82 (dd, 1 H, C₂CHSi), 1.74 (s, 1 H, B₃BCHSi), 1.68 (s, 1 H, C₂CHSi), 1.31 (d, 3 H, BCHMe), 1.24 (s, 3 H, BMe), 0.38, 0.27, 0.25, 0.21, 0.21, 0.14 (each s, each 9 H, SiMe₃); ¹³C NMR (125 MHz, C₆D₆, 27 °C): δ = 50.9 (brd, MeBCHSi), 45.8 (brd, BCHMe), 44.2 (d, C₂CHSi), 31.4 (brd, B₃BCHSi), 29.2 (d, C₂CHSi), 27.5 (brd, B₃BCHSi), 24.0 (q, BCHMe), 17.7 (brq, BMe), 4.0, 2.8, 1.0, −0.2, −0.6, −2.4 (each q, SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 27 °C): δ = 65, 62, 43, 30.

7: Yellow oil, yield 90 % (based on NMR spectroscopy); ¹H NMR (300 MHz, C₆D₆, 27 °C): δ = 2.87 (q, 1 H, BCHMe), 1.75 (s, 1 H, C₂CHSi), 1.61 (d, 1 H, BCHSi), 1.35 (s, 3 H, MeB), 1.32, (d, 3 H, BCHMe), 1.06 (s, 1 H, B₃CHSi), 0.39, 0.30, 0.18, 0.16 (each s, each 9 H, SiMe₃); ¹³C NMR (125 MHz, C₆D₆, 27 °C): δ = 46.8 (d, C₂CHSi), 38.9 (br, BCHMe), 24.6 (br, B₃CHSi and BCHSi), 24.0 (BCHMe), 7 (br, MeB), 1.6, 1.4, 1.1, 0.1 (SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 27 °C) δ = 57, 45 (2 B), 17.

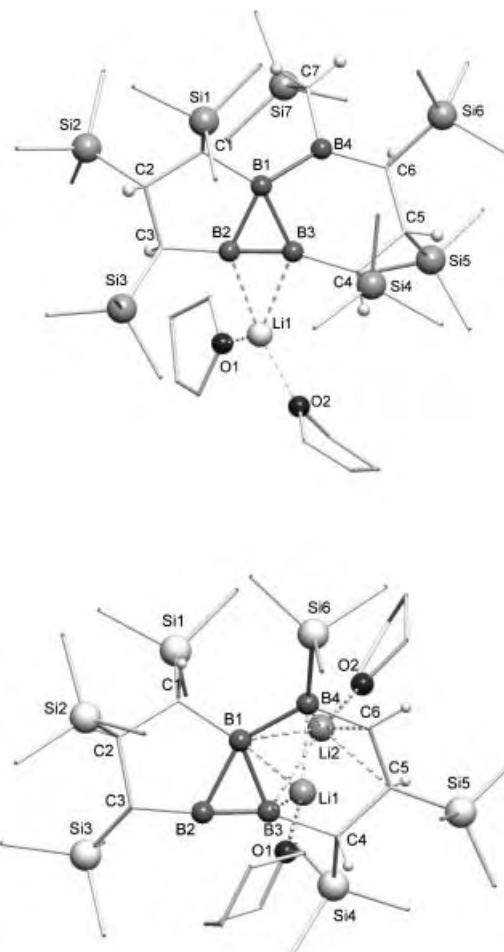


Figure 1. Structures of **3a**-Li(THF)₂ (top) and **3b**-Li(THF)-Li(THP) (bottom) in the crystal. Selected distances [pm] and angles [°] (see also Table 2): **3a**-Li(THF)₂: B2–Li1 234.9(6), B3–Li1 240.0(6); C1–B1–B4 119.7(2), C3–B2–B1 112.5(2), C4–B3–B1 130.2(2), B3–B1–B4 93.2(2). **3b**-Li(THF)-Li(THP): B1–Li1 248.0(13), B3–Li1 231.2(11), B1–Li2 245.3(12), B4–Li1 230.6(12), B3–Li2 250.1(13), B4–Li2 225.4(10); C1–B1–B4 117.1(4), C3–B2–B1 112.0(4), C4–B3–B1 130.7(2), B3–B1–B4 100.3(5).

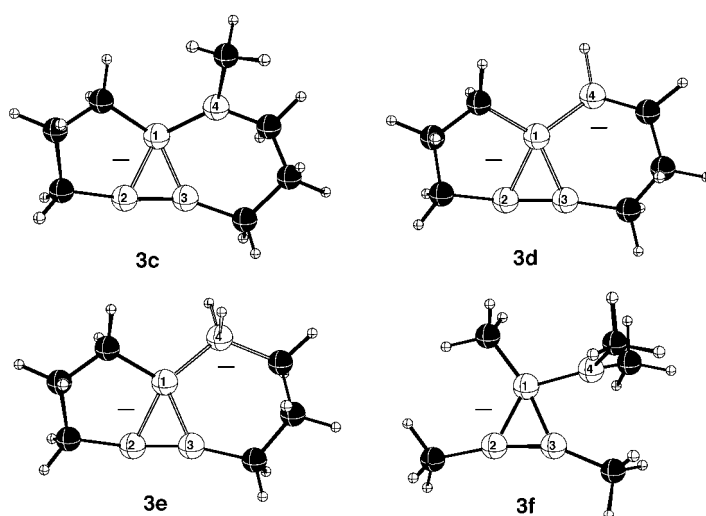


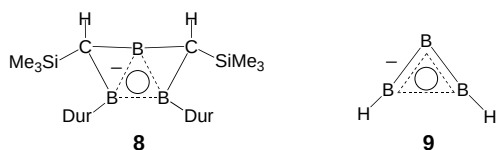
Figure 2. Structures computed at the B3LYP/6-31G* level for **3c** and **3d**, which represent models for **3a** and **3b** without silyl substituents, and related compounds **3e** and **3f**, which contain planar-tetracoordinated boron atoms.

molecules (Figure 1). In the contact ion triple **3b**·Li(THF)·Li(THP) (THP = tetrahydropyrane) the two lithium ions are located above and below the six-membered ring and in addition are coordinated by a THP or a THF molecule. The B2–B3 distances in **3a** and **3b** are 148.3 and 148.0 pm, respectively, and thus the shortest ever observed between two boron atoms.^[10] The B2–B3 and all the other B–B distances are in good agreement with those computed for **3u** and model compounds **3c** and **3d**, without silyl substituents (Figure 2, Table 2). The characteristics for three-membered, two-electron

Table 2. Selected structural data for **3a**, **3b** (experimental), **3c–3f**, and **3u** (computed at the B3LYP/6-31G* level).

	3a	3b	3c	3d	3e	3f	3u
B1–B2	173.2(4)	179.4(8)	175.8	177.1	178.1	167.6	172.9
B1–B3	172.5(4)	173.3(8)	171.8	174.2	172.8	166.6	172.9
B2–B3	148.3(4)	148.0(10)	148.7	147.3	147.2	149.9	146.8
B1–B4	172.1(4)	176.0(9)	166.1	174.1	177.9	167.4	–

tron double aromatic compounds, namely, one very short and two relatively long distances, are thus experimentally realized in **3a** and **3b**. In contrast, the well-known bishomo double aromatic compound **8**^[11] (Dur = 2,3,5,6-tetramethylphenyl) and the corresponding double aromatic compound **9**^[3a] have one long B–B bond (168.8 and 183 pm, respectively), because they lack the 2c–2e σ bond between the basal boron atoms characteristic for double aromatic compounds of the type **1–3**: Compound **9** is the dehydro form of **3u**.



The boron atom at the apex of **3u** is surrounded by its four neighbors in a planar fashion. In **3a**, **3b**, **3c**, and **3d** the plane containing the B₃ triangle forms an angle of 22, 26, 14.6, and 2.1°, respectively, with the plane C–B1–B4 at the peak of the triangle; the boron atoms B1 are therefore almost planar-tetracoordinated. Complete planarity is prevented in **3a** and **3c** by the electron deficiency of the boron atom in the six-membered ring.^[12] In the model compound **3e**, in which atom B4 is tetrahedrally coordinated, the angle between the two planes described is only 3.2°, and in **3d**, which contains a doubly bound, tricoordinated B4 atom, this angle is only 2.1°. The deviation from planarity is 24° greater in **3b** than in **3d** and results from the bulky trimethylsilyl group at B4. In the model compound **3f**, which does not contain methylene bridges, atom B1 is exactly planar-tetracoordinated. Therefore, the first triboracyclopropanates basically display the predicted structures.

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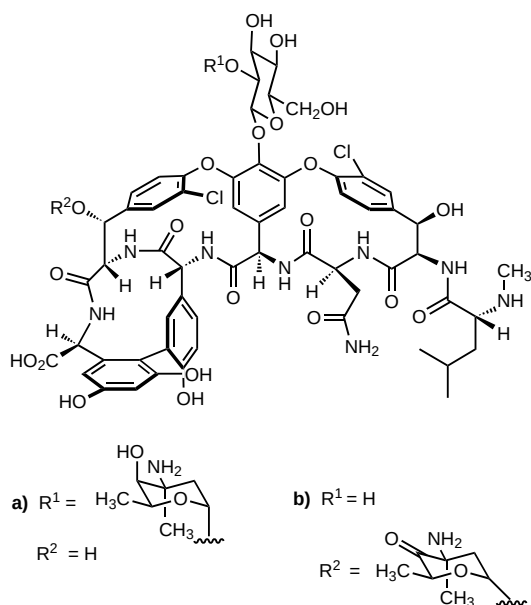
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 [7] The mechanism for the formation of **3b** from **5**, which has for the most part been clarified, will be described elsewhere.
 [8] Attempts to synthesize a monomethylation product resulted in a mixture of **6** and unchanged **3b**: Therefore, the second methylation occurs more quickly than the first one.
 [9] Crystal structure analyses: **3a**·Li(THF)₂: A yellow crystal (0.40 × 0.35 × 0.25 mm) was measured at 193 K on an IPDS area detector system (Stoe) with MoK α radiation. C₃₆H₈₇B₄LiO₂Si₇, monoclinic, space group *P2₁/n*, *Z* = 4, *a* = 1274.9(1), *b* = 1956.8(1), *c* = 2135.1(1) pm, β = 96.08(1)°, *V* = 5296.5(6) × 10^{–30} m³, ρ_{calc} = 1.002 Mg m^{–3}. Of 41 406 reflections up to θ = 25.94°, 10 047 were independent (*R*_{int} = 0.0993) and 5787 with *I* > 2 σ (*I*). The structure was solved by direct methods and refined against all *F*² data with full matrix. The hydrogen atoms of the SiMe₃ groups and the THF molecules were refined as “riding” in calculated positions, and the remaining H-atoms were refined with isotropic displacement factors. One of the two THF molecules was disordered; *wR*₂ = 0.1361 for all reflections, *R* = 0.0489 for the observed reflections. **3b**·Li(THF)·Li(THP): Under similar conditions as for **3a**·Li(THF)₂, a yellow crystal (0.25 × 0.15 × 0.05 mm) was measured. C₃₃H₇₇B₄LiO₂Si₆, orthorhombic, space group *Pca*2₁, *Z* = 4, *a* = 2021.4(1), *b* = 1226.0(1), *c* = 1979.3(2) pm, *V* = 4905.2(7) × 10^{–30} m³, ρ_{calc} = 0.991 Mg m^{–3}. Of 19 940 reflections up to θ = 25.96°, 6927 were independent (*R*_{int} = 0.0981) and 3491 with *I* > 2 σ (*I*). The structure solution and refinement were analogous to that of **3a**·Li(THF)₂. Since only very thin crystal platelets could be obtained, the accuracy of the refinement with use of a non-centrosymmetric space group is much lower than for **3a**·Li(THF)₂. Nevertheless, the hydrogen atoms H1–H6 could be freely refined; *wR*₂ = 0.1028 for all reflections, *R* = 0.0519 for the observed reflections. The structure determination of **6** is of insufficient quality owing to the very weak data set but does confirm the constitution of **6**. CCDC-183545 (**3a**·Li(THF)₂) and CCDC-183544 (**3b**·Li(THF)·Li(THP)) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
 [10] Recently, B–B distances of 152.4(3) and 151.1(3) pm were observed in derivatives of **5**.^[6]
 [11] M. Unverzagt, G. Subramanian, M. Hofmann, P. von R. Schleyer, S. Berger, K. Harms, W. Massa, A. Berndt, *Angew. Chem.* **1997**, *109*, 1567; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1469.
 [12] An NBO analysis of **3c** provides the following occupation for the p orbitals: B1 0.67, B2 0.53, B3 0.68, B4 0.26. Conjugation with B4 decreases the π bond order between B1 and B2 or between B1 and B3. This facilitates rotation of the C–B1–B4 plane with respect to the B1–B2–B3 plane, as this does not influence the 3c–2e σ bond.

Fluorobalhimycin—A New Chapter in Glycopeptide Antibiotic Research**

Stefan Weist, Bojan Bister, Oliver Puk, Daniel Bischoff, Stefan Pelzer, Graeme J. Nicholson, Wolfgang Wohlleben, Günther Jung, and Roderich D. Süssmuth*

Dedicated to Professor Anton Rieker
on the occasion of his 70th birthday

The glycopeptide antibiotic vancomycin (Scheme 1) has been used for more than 30 years against enterococcal and staphylococcal infections and meanwhile has the status of an antibiotic of last resort.^[1] The significance of vancomycin together with its unique properties have attracted many researchers to perform work on chemical, biological, and medicinal aspects.^[2] Over the past decade the increasing number of vancomycin-resistant bacterial strains has led



Scheme 1. Structures of the glycopeptide antibiotics a) vancomycin and b) balhimycin.

[*] Dr. R. D. Süssmuth, S. Weist, B. Bister, D. Bischoff, G. J. Nicholson, Prof. Dr. G. Jung
Institut für Organische Chemie
Eberhard-Karls-Universität Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49) 7071-29-5560
E-mail: roderich.suessmuth@uni-tuebingen.de
O. Puk, Dr. S. Pelzer, Prof. Dr. W. Wohlleben
Institut für Mikrobiologie/Biotechnologie
Eberhard-Karls- Universität Tübingen
Auf der Morgenstelle 28, 72076 Tübingen (Germany)

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scientists to investigate resistance mechanisms and to seek new approaches to overcome vancomycin-resistance problems.^[2,3] As a consequence, a vast number of natural and semisynthetic glycopeptide derivatives have been characterized and tested. Considerable success was obtained with the semisynthetic derivative LY333328, a potent glycopeptide, which displays antibiotic activity against both methicillin-resistant *Staphylococcus aureus* strains (MRSA) and vancomycin-resistant enterococci (VRE) and which is meanwhile being tested in clinical studies.^[4] However, these variations relate primarily to peripheral features of vancomycin and the characteristic structure of the aglycon has been left mainly unchanged because of the highly demanding chemical and biochemical accessibility of the tricyclic aglycon.

Herein we present the first in vivo modified glycopeptides with non-natural fluorine substituents. In previous contributions,^[5,6] we used the balhimycin-producing^[7] (Scheme 1) strain *Amycolatopsis mediterranei* to obtain insights into the biosynthesis through gene disruption mutants. Based on these results we focused on the two diastereomeric 3-chloro- β -hydroxytyrosine moieties (Scheme 1) as an attractive target for the introduction of structural variations, since they represent a basic element of the tricyclic aglycon structure. The presence of a chlorine substituent in each of the two β -hydroxytyrosine moieties in natural balhimycin plays a significant role for enhancing antibiotic activity.^[8] From the *A. mediterranei* wild-type strain (Figure 1, 1 a) we generated a deletion null-mutant in the *bhp* gene (Figure 1, 1 b), OP696,^[6] which is deficient in β -hydroxytyrosine biosynthesis and thus is unable to produce balhimycin (Figure 1, 3 a). In mutasynthesis experiments,^[9] we supplemented OP696 with several analogues of this amino acid. β -Hydroxytyrosine and derivatives were easily obtained as a racemic mixture of four stereoisomers in good yields by using a three-step synthesis.^[10]

Supplementing a culture of OP696 with 3-fluoro- β -hydroxytyrosine (3-Fht) resulted in antibiotic activity of the culture filtrate against the indicator strain *Bacillus subtilis* (Figure 1, 3 b). The amino acid 3-Fht did not show any antibiotic activity. Isolation from culture filtrates revealed an antibiotically active compound, and subsequent analysis with ESI-FTICR mass spectrometry revealed a mass of $[M+2H]^{2+} = 707.7439$ Da ($\Delta m = 0.3$ ppm; Figure 2) that corresponds to the molecular mass of 1413.4878 Da and to the elemental composition $C_{66}H_{73}F_2N_9O_{24}$ of a twofold fluorinated balhimycin, which we named fluorobalhimycin (Figure 1).

One- and two-dimensional NMR experiments (TOCSY, NOESY, HSQC, HMBC; Tables 1 and 2) allowed the structure to be assigned as shown in Figure 1. The presence of two fluorine substituents in fluorobalhimycin was verified independently by ¹⁹F NMR spectroscopy with $\delta(^{19}\text{F}) = -131$ and -134 ppm compared to $\delta(^{19}\text{F}) = -139$ ppm for the racemic amino acid 3-Fht. The positioning of the fluorine substituents in the biaryl ether ring systems is analogous to that of the chlorine atoms in balhimycin,^[8,11] as confirmed by the observed NOE contacts.

In further experiments we evaluated the substrate specificity of the mutant OP696. To this end, we synthesized three sets of β -hydroxytyrosines (Scheme 2). The first set comprised β -hydroxytyrosines with the phenolic hydroxy group in 2-, 3-,

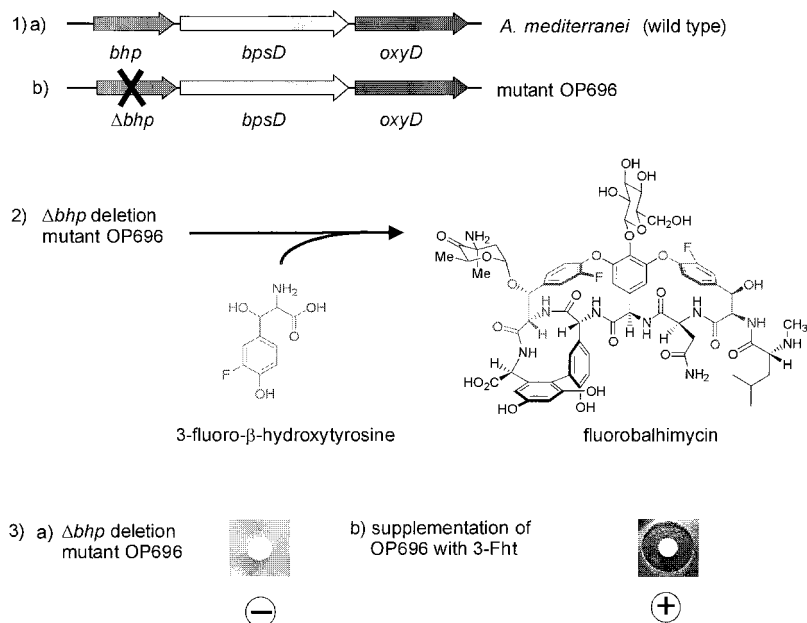


Figure 1. 1) Schematic representation of the part of the gene organization of *A. mediterranei* strains involved in β -hydroxytyrosine biosynthesis: a) wild type, b) mutant OP696; *bhp*: balhimycin perhydrolase; *bpsD*: balhimycin peptide synthetase D; *oxyD*: oxygenase D.^[8] 2) Pathway to fluorobalhimycin by supplementation of mutant OP696. 3) Bioassays of culture filtrates tested against *B. subtilis*: a) mutant OP696 (no antibiotic activity), b) mutant OP696 after supplementation with 3-fluoro- β -hydroxytyrosine (shows antibiotic activity).

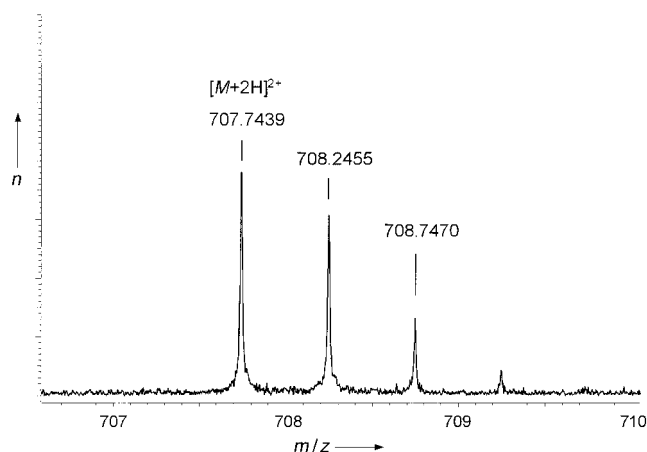


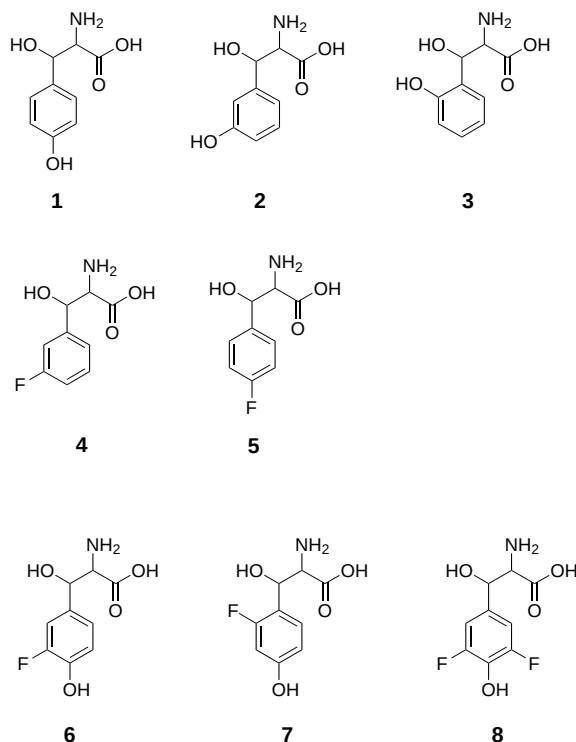
Figure 2. ESI-FTICR mass spectrum of fluorobalhimycin, $[M+2H]^{2+} = 707.7439$ Da.

and 4-position of the aromatic ring (hydroxyphenylserines **1–3**). The second and third set was composed of fluorophenylserines (**4** and **5**) and differently fluorine-substituted β -hydroxytyrosines (**6–8**) (Scheme 2). From the tested derivatives **1–3**, only feeding with β -hydroxytyrosine (**1**) resulted in antibiotic activity of the culture filtrate.^[6] Shifting of the hydroxy function into the 2- and 3-position of the aromatic ring (**2** and **3**) led to no antibiotic activity of thus supplemented culture filtrates and no corresponding metabolites could be detected by LC-ESI-MS. The same negative results as for **2** and **3** were also obtained for supplementation with fluorophenylserines **4** or **5** and D- or L-tyrosine, respectively.

Interestingly, feeding mutant OP696 with amino acids **7** or **8** led to antibiotic activity of the culture filtrates against *B. subtilis* and to detection of corresponding molecular masses of balhimycin derivatives with LC-ESI-MS (data not shown).

Our results show that the β -hydroxytyrosine motif (**1**) is essential for acceptance as a substrate in the subsequent interplay of various glycopeptide biosynthesis enzymes with peptide synthetases and oxygenases^[12] as the most directly affected ones. This cascade of interacting enzymes differentiates on the one hand between β -hydroxylated (**1–8**) and non- β -hydroxylated tyrosines (D- and L-Tyr) and between derivatives bearing (**1, 6–8**) or missing (**2–5**) the phenolic hydroxy group in the 4-position of the arene. However, substitution of aromatic hydrogen atoms with fluorine in position 3 or 2 of the arene (**6** or **7**) or even addition of a second fluorine substituent in position 5 of the arene (**8**) is tolerated.

The aim of our current studies is the structure elucidation of all detected fluorobalhimycins, and the determination of the configuration of the β -hydroxytyrosine stereoisomers that are accepted as substrates. We are further investigating the



Scheme 2. Structural formulas of synthetic β -hydroxyamino acids used for supplementation assays: β -hydroxytyrosine (**1**), (3-hydroxyphenyl)serine (**2**), (2-hydroxyphenyl)serine (**3**), (3-fluorophenyl)serine (**4**), (4-fluorophenyl)serine (**5**), 3-fluoro- β -hydroxytyrosine (**6**), 2-fluoro- β -hydroxytyrosine (**7**), 3,5-difluoro- β -hydroxytyrosine (**8**).

Table 1. ^1H and ^{13}C NMR shifts of fluorobalhimycin.^[a]

	N	α	β	Others
^1Leu	[b]	3.14 62.1	1.45/1.39 40.3	γ : 1.69; δ : 0.84/0.88, N-CH ₃ : 2.32 γ : 24.1; δ : 22.4/22.9, N-CH ₃ : 33.3
^2Fht	7.92	4.79 58.3	5.14 71.3	OH $^+$: 5.83; 2: 7.17; 1: 137.4; 2: 115.4; 3: 140.9; 4: 154.0; 5: 7.34; 6: 6.92 5: 124.3; 6: 115.3 δ : 7.36/6.96
^3Asn	[b]	4.34 51.1	2.13/2.13 37.0	δ : 7.36/6.96
$^4\text{Hpg}^{[c]}$	8.29	5.79 54.6	– –	2: 5.76; 1: 132.6; 2: 107.8; 3: 151.7; 4: [b]; 6: 5.39 5: 151.9; 6: 104.6
$^5\text{Hpg}^{[c]}$	8.83	4.59 53.7	– –	2: 7.15; OH $^+$: 9.45 1: 135.8; 2: 136.9; 3: 122.1; 4: 155.4 5: 6.70; 6: 6.76 5: 116.4; 6: 125.9
^6Fht	6.63	4.34 60.6	5.26 74.7	2: 7.63; 1: 134.7; 2: 115.6; 3: 140.7; 4: 154.2; 5: 6.67; 6: 7.32 5: 125.8; 6: 124.3
$^7\text{Dpg}^{[d]}$	8.52	4.42 56.7	– –	4: 6.39; OH ^{35} : 9.14 1: 136.3; 2: 117.9; 3: 157.4; 4: 102.5; 6: 6.22; 5: 157.2; 6: 105.9

[a] in ppm, $c = 1.2 \text{ mg mL}^{-1}$, [D₆]DMSO, 298 K. [b] assignment not determined. [c] Hpg = hydroxyphenylglycine, [d] Dpg = dihydroxyphenylglycine.

Table 2. ^1H and ^{13}C chemical shifts of the sugar residues of fluorobalhimycin.^[a]

Sugar	1'	2'	3'	4'	5'	6'	3'-Me
Glc ^[b]	5.32 102.7	3.33 74.3	3.26 76.8	3.20 70.1	3.22 77.8	3.65/3.47 61.2	– –
Ovn ^[c]	4.95 93.3	2.24/2.34 39.3	– 57.8	4.43 68.7	– 208.7	1.23 14.9	1.18 20.6

[a] In ppm, $c = 1.2 \text{ mg mL}^{-1}$, [D₆]DMSO, 298 K. [b] Glucose. [c] 4-Oxovancosamine.

scope of the *A. mediterranei* OP696 mutant to elucidate whether other substituted β -hydroxytyrosines and fluoro- β -hydroxytyrosines are accepted as substrates. Our results show that mutasynthesis can be used for creating a set of new glycopeptide antibiotics using building blocks that should be readily accessible in combination with genetically engineered mutants. This approach may also be successful in modifying other parts of the glycopeptide molecule, for example the two other aromatic amino acids 4-hydroxyphenylglycine and 3,5-dihydroxyphenylglycine. In summary, we have a tool at hand to generate novel, hitherto unknown glycopeptide antibiotics, with a perspective towards antimicrobial activity also against vancomycin-resistant organisms.

Experimental Section

The mutant OP696 of *Amycolatopsis mediterranei* DSM5908 was grown in liquid culture according to protocols described previously.^[5,6] Before inoculation with the mutant, amino acids were added to the medium in a final concentration of 0.4 g L^{-1} . Fluorobalhimycin was isolated by preparative LC-MS from 6 L of culture filtrate supplemented with 3-Fht (yield: 0.7 mg; HTP-MS System from Merck-Hitachi) and analyzed according to reported procedures.^[7,8] NMR experiments were recorded on an Avance 600 NMR spectrometer (Bruker) equipped with a 2.5 mm DUAL ^{13}C - ^1H -D Z-GRAD microsample head and on an AMX 600 NMR spectrometer (Bruker) equipped with a 5 mm Z-GRAD triple resonance probehead. ^{19}F NMR measurements ([D₆]DMSO, ^1H - ^{19}F decoupled experiment) were

performed on an Avance DRX 250 NMR spectrometer (Bruker). Mutasynthesis experiments of amino acids were repeated three times, and the culture filtrates obtained were tested against *B. subtilis*^[6] and investigated with LC-ESI-MS on an Agilent 1100 HPLC System (Hewlett-Packard) coupled with an Esquire 3000plus ESI-ion trap mass spectrometer (Bruker Daltonics). FTICR-ESI mass spectra were recorded on an APEX II FTICR Mass Spectrometer (Bruker-Franzen).

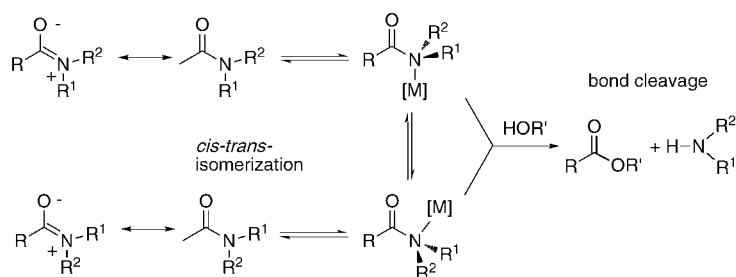
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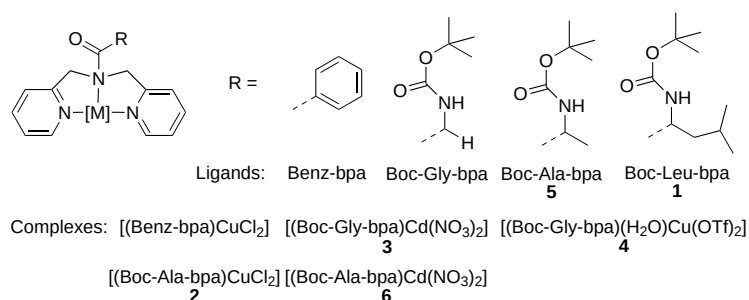
Activation of the Tertiary Carboxamide C–N Bond in Werner Complexes: A Classical Structure–Function Relationship**

Nicole Niklas, Frank W. Heinemann,
Frank Hampel, and Ralf Alsasser*

Dedicated to Professor Karl Wiegardt
on the occasion of his 60th birthday



Scheme 1. The reactivity of N-coordinated tertiary carboxamides.



Scheme 2. Ligands and complexes used.

Tertiary carboxamides, RC(O)NR_2 , are fascinating reactive building blocks in organic and biological compounds.^[1] The *cis-trans* isomerization about peptidyl-prolyl C–N bonds is a key step in many protein folding processes. Enzymes trigger this important biological switch but simple metal salts also catalyze amide isomerizations. Metal complexes have therefore attracted interest as potential synthetic peptide-folding reagents.^[2] Another biologically relevant reaction of tertiary amides, the C–N bond hydrolysis of penicillins and cephalosporins, is also accelerated by metal ions.^[3]

Coordination of a metal ion to the neutral amide nitrogen atom has been proposed to explain both *cis-trans* isomerization and C–N bond cleavage (Scheme 1).^[1,3,4] However, despite the generality and importance of their reactions very little is known about the structures of N-coordinated tertiary amides. Only two Werner complexes have been characterized to date,^[4,5] and the number of organometallic and urea derivatives is small as well.^[6]

More data are clearly necessary to explain the occurrence of *cis-trans* isomerization or solvolytic bond cleavage in Werner complexes with nitrogen-bound tertiary amides. With the structural study presented herein we are, for the first time, able to compare a family of compounds which reveal a classical structure–function relationship. Scheme 2 summarizes the relevant compounds. New are Boc-Leu-bpa (**1**), [(Boc-Ala-bpa)CuCl₂] (**2**), [(Boc-Gly-bpa)Cd(NO₃)₂] (**3**), and [(Boc-Gly-bpa)(H₂O)Cu(OTf)₂] (**4**, OTf = CF₃SO₃, Boc = *t*-butoxycarbonyl, bpa = *N,N*-bis(pyridin-2-ylmethyl)amine). We have recently reported the ligand Boc-Ala-bpa (**5**) and its Cd(NO₃)₂ complex **6**.^[5] Lectka and co-workers have published the structure of [(Benz-bpa)CuCl₂] (Benz = benzyl).^[4]

Figure 1 contains ORTEP plots of **1–4**.^[7] The structures confirm that the amide nitrogen atom is bound to the metal center in all complexes. Figure 2 illustrates that a significant distortion of the amide geometry results. A quantitative

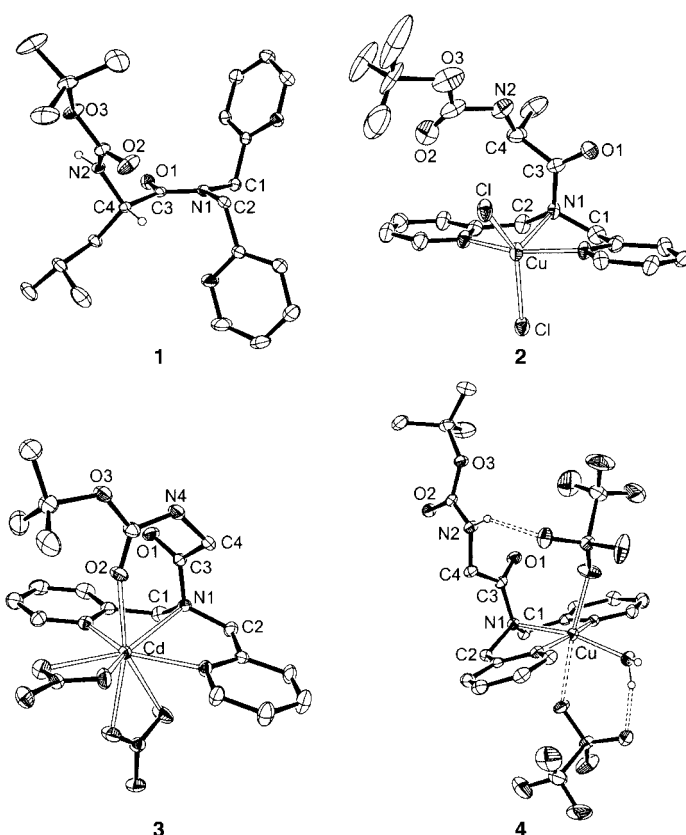


Figure 1. ORTEP plots (thermal ellipsoids set to 30% probability) of **1–4**.

[*] Dr. R. Alsasser, Dipl.-Chem. N. Niklas, Dr. F. W. Heinemann
Institut für Anorganische Chemie
Universität Erlangen-Nürnberg
Egerlandstrasse 1, 91058 Erlangen (Germany)
Fax: (+49)9131-8527387
E-mail: alsasser@chemie.uni-erlangen.de
Dr. F. Hampel
Institut für Organische Chemie
Universität Erlangen-Nürnberg
Henkestrasse 42, 91054 Erlangen (Germany)

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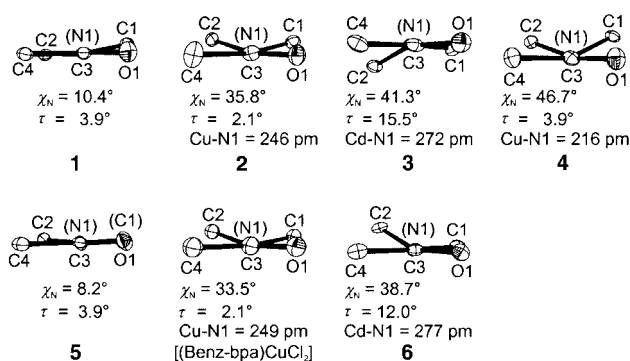


Figure 2. The tertiary amide moieties in **1–6**, and [(Benz-bpa)CuCl₂] viewed along the C3→N1 axis.

measure for the observed deplanarization is provided by the Winkler-Dunitz parameters χ_N and τ . The parameter χ_N is a measure of the pyramidalization at the N1 atom, and reflects the degree of sp³ hybridization induced by metal coordination; this value ranges from 0° in a perfectly planar amide to a maximum of 60°. The parameter τ is the twist angle between the O1–C4 and the C1–C2-axis which has a maximum of 90°. Both values are calculated from the torsion angles defined by C1, C2, C3, C4, O1, and N1.^[8] Our series shows a steady increase of χ_N from **1** to **4**. The free ligand **1** ($\chi_N = 10.4^\circ$) is practically undistorted, but coordination of CuCl₂ in **2** causes a significant distortion ($\chi_N = 35.8^\circ$) of the planar to near-pyramidal. The value of χ_N is even larger in the Cd(NO₃)₂ derivative **3** ($\chi_N = 41.3^\circ$) and reaches a maximum of 46.7° in the Cu(OTf)₂ complex **4**. The known structures of **5**, [(Benz-bpa)CuCl₂],^[4] and **6** nicely confirm this trend.

It is evident that the distortion increases with the Lewis acidity of the coordinated metal center. This is also reflected by the Cu–N bond distances which are 246 and 249 pm in the dichloro compounds and only 216 pm in the triflate complex. Thus, the activation of the tertiary amide moiety strongly depends on the coligands and on the metal ion. This variability is characteristic for Werner type complexes and does not occur in related organometallic compounds.

The differences are revealed by a plot of χ_N versus τ (Figure 3). This graph contains the data of all known

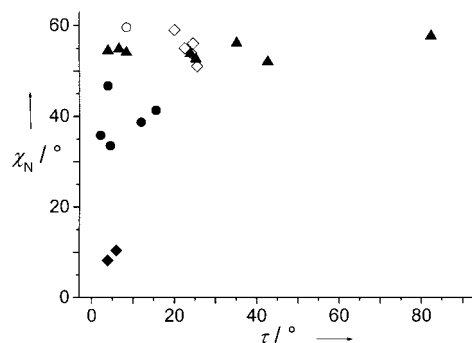


Figure 3. Plot of pyramidalizations, χ_N , versus twist angles, τ , for Werner type tertiary amide (●) and urea (○) complexes, organometallic compounds (▲), free ligands **1** and **5** (◆), and four selected organic cations RC(O)NR₃⁺ (◇).

complexes with an N-coordinated RC(O)NR₂ moiety and includes some examples of purely organic cations (C(O)NR₃⁺) for comparison.^[9] The data of the ligands **1** and **5** serve as standards for undistorted amides. It is evident from Figure 3 that the χ_N values are very similar and always close to the maximum of 60° in organometallic compounds,^[6a–g] organic cations,^[9] and in a urea complex.^[6b] The twist angles, τ , are scattered over the whole range from about 0° to about 90°. This range is a clear indication of completely sp³-hybridized nitrogen atoms and covalent M–N bonds. In marked contrast, χ_N values are smaller and more scattered in classical coordination complexes. The corresponding twist angles are small and do not differ much from those of the undistorted ligands. Thus, the M–N bonds in Werner complexes are apparently more electrostatic with distorted sp²-hybridized nitrogen atoms. Such a binding mode explains the strong dependence of χ_N on the acidity of the metal center and should allow for a fine tuning of the C–N bond activation.

This explanation is in agreement with the observed reactivity of different metal-tertiary carboxamide complexes. Lectka and co-workers reported that Cu(OTf)₂ is an efficient *cis*–*trans*-isomerization catalyst, whereas CuCl₂ shows only very low activity.^[2] We studied the effect of triflate and chloride ions on the isomerization rates of zinc complexes of **5** by temperature-dependent ¹H NMR spectroscopic measurements in acetone.^[10] At 25°C, rate constants of $k = 1400 \text{ s}^{-1}$ ($\Delta H^\ddagger = 11.4 \pm 0.3 \text{ kcal mol}^{-1}$; $\Delta S^\ddagger = -6.3 \pm 1.0 \text{ cal K}^{-1} \text{ mol}^{-1}$) for the triflate salt, and $k = 285 \text{ s}^{-1}$ ($\Delta H^\ddagger = 13.2 \pm 0.3 \text{ kcal mol}^{-1}$; $\Delta S^\ddagger = -3.0 \pm 0.9 \text{ cal K}^{-1} \text{ mol}^{-1}$) for the chloro complex have been determined. These results clearly indicate that chloride ions significantly reduce the ability of a metal center to induce *cis*–*trans* isomerization.

One would assume that C–N bond cleavage occurs only in strongly activated complexes. Thus, addition of Cu(ClO₄)₂ or Cu(OTf)₂ induces methanolysis whereas the corresponding Cd(NO₃)₂ complexes only isomerize.^[5] This result is in complete agreement with the structures of **3**, **6**, and **4**. The case of CuCl₂ is more complicated. We have observed the solvolysis of all ligands in MeOH/CH₂Cl₂ mixtures. The rates are comparable to those observed with Cu(OTf)₂. However, according to the structures of [(Benz-bpa)CuCl₂] and **2**, one would not expect bond cleavage to be feasible. The apparent contradiction is caused by an initial exchange of coordinated chloride for methanol. This exchange is evident from an induction period observed in kinetic electron paramagnetic resonance (EPR) and UV/Vis experiments. In addition, we were able to crystallize a product which contains a [(bpa)LCuCl]⁺ cation in the complex salt [(bpa)CuCl]₂–[CuCl₄].^[11] Exchange or removal of chloro ligands from [LCuCl₂] makes the metal center more Lewis acidic. Thus, the structure–reactivity relationship discussed above remains valid.

The proposed structure–function relationship may help us to a better understanding of the organic and biological chemistry of tertiary carboxamides. Interesting new insight is expected from the experiments which will be designed to test its validity for a broad range of metal ions and ligands.

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- [7] Synthesis: The ligands Boc-Gly-bpa and Boc-Leu-bpa, as well as the complexes **2**, **3**, and **4**, were prepared analogously to the procedures in reference [5]. The copper complexes were synthesized in dry CH₃CN. Cadmium complexes were prepared in methanol. All complexes were purified by recrystallization from solvent mixtures. Yields and analytical data: Boc-Gly-bpa: 62%, field-desorption (FD)-MS (CHCl₃) *m/z* (%) = 357 (100) [*M*⁺]. **1**: 54%, FD-MS (CHCl₃) *m/z* (%) = 413 [*M*⁺]. **2**: 68%; elemental analysis calcd (%) for C₂₀H₂₆Cl₂CuN₄O₃: C 47.58, H 5.19, N 11.10; found: C 47.45, H 5.32, N 10.85. **3**: 44%; elemental analysis calcd (%) for C₁₉H₂₄CdN₆O₃: C 38.49, H 4.08, N 14.18; found: C 38.90, H 4.58, N 14.15. **4**: 67%; elemental analysis calcd (%) for C₂₁H₂₆CuF₆N₄O₁₀S₂: C 34.26, H 3.56, N 7.61; found: C 34.13, H 3.54, N 7.46. X-ray crystallography: Intensity data: MoK α , λ = 0.71073 Å; Siemens P4 diffractometer (**1**, **3**, **4**; ω scans, 6° min⁻¹, *T* = 200 K); Nonius Kappa CCD area detector (**2**, *T* = 173 K). Absorption corrections: Empirical ψ scans (**1**, **3**, and **4**), or SCALE-PACK (**2**; Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307). Structure solution and refinement: direct methods and full-matrix least-squares on *F*² (**1**, **3**, **4**: SHELXTL NT 5.10, Bruker AXS, **1998**; **2**: SHELXS-97 and SHELXL-97, G. M. Sheldrick, University of Göttingen, Göttingen (Germany), **1997**). Non-H-atoms: anisotropically refined. H-atoms: localized in the density map (isotropically refined), or calculated (riding mode). Details: CCDC-182767 (**1**), CCDC-184027 (**2**), CCDC-182768 (**3**), and CCDC-182769 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). **1**: C₂₃H₃₂N₄O₃; colorless needles from CH₂Cl₂/Et₂O; monoclinic, *P*₂₁; *a* = 10.185(1), *b* = 10.174(1), *c* = 11.597(1) Å; β = 100.42(1)°; *Z* = 2; *V* = 1181.9(2) Å³; θ range = 1.79–28.5°; reflections coll./unique = 6640/6010; data/restr./param. = 6010/1/368; *R*₁ [*I* > 2 σ (*I*)] = 0.0497, *wR*₂ = 0.1253 (all data); largest diff. peak/hole = 0.300/–0.175 e Å⁻³. **2**: C₂₁H₂₉Cl₄N₄O_{3.5}; blue plates from CH₂Cl₂; 4 independent molecules + 4 CH₂Cl₂ + 2 H₂O; monoclinic, *P*₂₁; *a* = 16.960(1), *b* = 13.284(1), *c* = 26.564(1) Å; β = 101.60(1)°; *Z* = 8; *V* = 5862.4(2) Å³; θ range = 2.19–24.11°; reflections coll./unique = 18137/18137; data/restr./param. = 18137/16/1192; *R*₁ [*I* > 2 σ (*I*)] = 0.0708, *wR*₂ = 0.2029 (all data); diff. peak/hole = 1.385/–0.703 e Å⁻³. **3**: C₁₉H₂₄CdN₆O₃·2CH₂Cl₂; colorless plates from CH₂Cl₂/MeOH/Et₂O; monoclinic, *C*2/*c*; *a* = 22.364(3), *b* = 16.962(2), *c* = 17.266(2) Å; β = 110.75(1)°; *Z* = 8; *V* = 6125(1) Å³; θ range = 1.76–27.0°; reflections coll./unique = 8932/6684; data/restr./param. = 6684/9/471; *R*₁ [*I* > 2 σ (*I*)] = 0.0564, *wR*₂ = 0.1153 (all data); diff. peak/hole = 0.557/–0.668 e Å⁻³. **4**: C₂₁H₂₆CuF₆N₄O₁₀S₂·CH₂Cl₂; blue needles from CH₂Cl₂; monoclinic, *P*₂₁/*c*; *a* = 12.296(1), *b* = 15.165(3), *c* = 18.470(3) Å; β = 104.83(1)°; *Z* = 4; *V* = 3329.4(9) Å³; θ range = 1.76–27.01°; reflections coll./unique = 8915/7260; data/restr./param. = 7260/1/434; *R*₁ [*I* > 2 σ (*I*)] = 0.0519, *wR*₂ = 0.1381 (all data); diff. peak/hole = 0.486/–0.533 e Å⁻³.
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Anion- π Interactions: Do They Exist?*

David Quiñero, Carolina Garau, Carmen Rotger, Antonio Frontera,* Pablo Ballester, Antonio Costa, and Pere M. Deyà*

Noncovalent interactions play a fundamental role in many areas of modern chemistry. In particular the interactions of cations and π -electrons—cation- π interactions—are strong noncovalent binding forces of great importance in many systems.^[1,2] Crystallographic studies provide much of the information on cation- π interactions and other nonbonding interactions that have attracted considerable attention in the last years such as anti-hydrogen bonds,^[3] dihydrogen bonds,^[4] and other unconventional hydrogen bonds.^[5] These interactions have also been studied extensively by means of computational methods. Noncovalent interactions are usually characterized by Bader's theory of “atoms in molecules” (AIM),^[6] which has been used successfully to understand conventional^[7] and unconventional^[8] hydrogen bonds and cation- π interactions.^[9]

The cation- π interaction is in general dominated by electrostatic and cation-induced polarization.^[10] The nature of the electrostatic component has been rationalized, emphasizing the function of the permanent quadrupole moment of benzene (see Figure 1).^[11] The favorable interactions in the benzene-hexafluorobenzene complex have been studied, including the face-to-face stacking in its crystal structure.^[12] A detailed analysis carried out by Williams stresses the important role of the large, permanent quadrupoles of the two molecules, which are similar in magnitude but of opposite sign.^[13] The importance of the quadrupole moment for understanding intermolecular interactions of aromatic systems has been rationalized.^[14]

Theoretical studies of the possible interaction of the π -electron cloud of C_6F_6 with several small electron donor molecules have been published previously.^[15–17] In this communication we report a preliminary study of

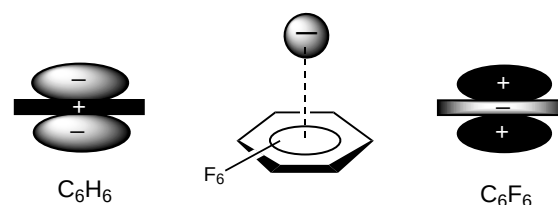


Figure 1. Representations of the quadrupole moments of benzene (left) and hexafluorobenzene (right) and the anion- π interaction (middle).

the interactions between anions and hexafluorobenzene. In these complexes the anion is positioned over the benzene ring along the C_6 axis. This study combines crystallographic and computational evidence to demonstrate that anion- π interactions exist and that they are energetically favorable. To the best of our knowledge this is the first study in which the term “anion- π interaction” is used to describe the interaction between the permanent quadrupole of C_6F_6 and anions.^[18]

Initially the geometries of all the complexes included in this study were fully optimized at the Hartree-Fock (HF) level by using the 6-31++G** basis set.^[19] The binding energies were

Table 1. Interaction energies with (E_{BSSE} , $E_{BSSE+ZPE}$ [kcal mol⁻¹]) and without (E [kcal mol⁻¹]) the basis set superposition error (BSSE) and zero-point energy correction (ZPE) and equilibrium distances (R_e [Å]) at HF/6-31++G** and MP2/6-31++G** (italics) levels of theory, and selected electron density topological properties for the complexes of hexafluorobenzene with anions.

Complex	E	E_{BSSE}	$E_{BSSE+ZPE}$	R_e	CP ^[a]	n	$10^2\rho$	$10^2\nabla^2\rho$
$C_6F_6\cdots H^-$ 1	-11.2	-11.1	-10.2	3.034	(3, -1)	6	0.578	1.135
	-17.5	-14.3	-13.4	2.706	(3, +1)	6	0.576	1.139
					(3, +3)	1	0.426	1.611
$C_6F_6\cdots F^-$ 2	-18.8	-18.1	-17.8	2.669	(3, -1)	6	1.001	4.200
					(3, +1)	6	0.996	4.226
					(3, +3)	1	0.702	4.106
$C_6F_6\cdots Cl^-$ 3	-11.0	-10.8	-10.6	3.404	(3, -1)	6	0.572	1.637
	-18.0	-13.2	-12.9	3.155	(3, +1)	6	0.571	1.637
					(3, +3)	1	0.450	1.820
$C_6F_6\cdots Br^-$ 4	-13.2	-9.3	-9.5	3.479	(3, -1)	6	0.618	1.612
	-20.7	-12.4	-11.9	3.214	(3, +1)	6	0.616	1.613
					(3, +3)	1	0.480	1.887
$C_6F_6\cdots CN^-$ 5	-11.9	-11.3	-10.9	3.020	(3, -1)	6	0.701	2.276
					(3, +1)	6	0.700	2.290
					(3, +3)	1	0.534	2.543
$C_6F_6\cdots NO_3^-$ 6	-9.7	-8.4	-8.2	3.325	(3, -1)	3	0.535	1.089
	-18.7	-12.4	-[b]	2.922	(3, +1)	3	0.324	1.477
					(3, +3)	1	0.234	1.308
$C_6F_6\cdots CO_3^{2-}$ 7	-28.4	-26.9	-26.6	3.011	(3, -1)	3	1.043	3.385
					(3, +1)	3	0.598	2.588
					(3, +3)	1	0.401	2.147

[a] The electron density (ρ) and its Laplacian ($\nabla^2\rho$) in atomic units at the critical points (CP) originating upon complexation are given, as well as the total number (n) of each CP in the complex. [b] Unfortunately, the frequency calculation of complex **6** was impossible to carry out since the program stops with an error message.

[*] Dr. A. Frontera, Prof. P. M. Deyà, Dr. D. Quiñero, C. Garau, Dr. C. Rotger, Prof. P. Ballester, Prof. A. Costa
Department of Chemistry
Universitat de les Illes Balears
07071 Palma de Mallorca (Spain)
Fax: (+34)971-173-426
E-mail: tonif@soller.uib.es

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calculated with and without correction for the basis set superposition error (BSSE) by using the Boys-Bernardi counterpoise technique^[20] and zero-point energy (ZPE) corrections. Frequency calculations at the same level confirmed that the structures are at their energy minima. Furthermore, in all cases we extended our calculations to the MP2/6-31++G** level, assuming C_{6v} symmetry for complexes **1–5** and C_{3v} symmetry for complexes **6** and **7**. Unfortunately, the frequency calculations give either one or more imaginary frequencies for all complexes. To solve this

issue, we carried out the geometry optimizations without imposing any symmetry constraints. As a result, complexes **1**, **3**, **4**, and **6** have been successfully optimized and the minimum-energy nature of the structures has been confirmed, except for complex **6** (see footnote of Table 1). For the other complexes—**2**, **5**, and **7**—the minimum-energy structures correspond to the nucleophilic attack of the anion at one of the carbon atoms. Topological analysis of the charge density $\rho(r)$ distribution and properties of critical points (CP) were determined by using the AIM method, which provides an unambiguous definition of chemical bonding,^[21] by means of the program AIMPAC^[22] using the HF/6-31++G** wave-function.

Table 1 reports the energies and equilibrium distances calculated at both HF and MP2 levels of theory corresponding to the interaction of hexafluorobenzene with a series of anions. In general, the MP2-computed binding energies are more negative than the HF ones and the equilibrium distances are shorter. For complexes **1–5** exploration of the CPs revealed the presence of six (3, −1) and six (3, +1) CPs symmetrically distributed. The bond CPs connect the anion with the carbon atoms, and the ring CPs connect the anion with the middle of the C–C bond (see Figure 2). The Laplacian of the (3, −1) CPs is positive which indicates a depletion of the electron density, as is common in closed-shell interactions.^[6] Finally, the interaction is further described by the presence of a cage CP located over the hexafluorobenzene molecule along the C_6 axis, connecting the anion with the center of the ring. Quantitative values for $\rho(r)$ and $\nabla^2\rho(r)$ at the CPs give hints on the character and strength of the interaction. The values obtained for complexes **1–7** (see Table 1) are similar to those found for cation– π interactions.^[9] The pattern of CPs that appears upon complexation is altered in the complexes **6** and **7** (NO_3^- and CO_3^{2-}). Only three bond and three ring CPs are found as a result of the geometry of the optimized complexes, in which the anion is placed parallel over the ring and the nitrogen (or carbon) atom is located

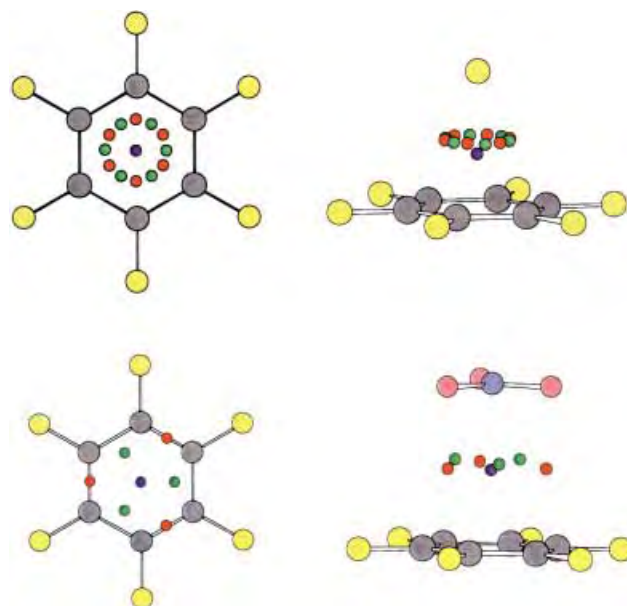


Figure 2. Representations of the location of the (3, −1) CPs (red circles), the (3, +1) CPs (green circles), and the (3, +3) CP (blue circle) originating from the interaction of hexafluorobenzene with fluoride (top) and nitrate (bottom) ions. On the left-hand side the complexes are viewed perpendicular to the benzene ring; for clarity, the anions have been omitted in these representations. On the right-hand side the complexes are viewed side-on.

along the C_6 axis (see Figure 2). In these complexes the interaction can be also viewed as a face-to-face parallel stacking interaction in which one component is electron deficient and the other is electron rich.

It is quite clear that without the results of crystallographic experiments molecular modeling would be a highly speculative activity at best. Crystal structures are so rich in information and often reveal effects that had not been noticed by the original authors. The Cambridge Structural Database (CSD) appeared to us to be a convenient and reliable storehouse for geometrical information. The utility of small-

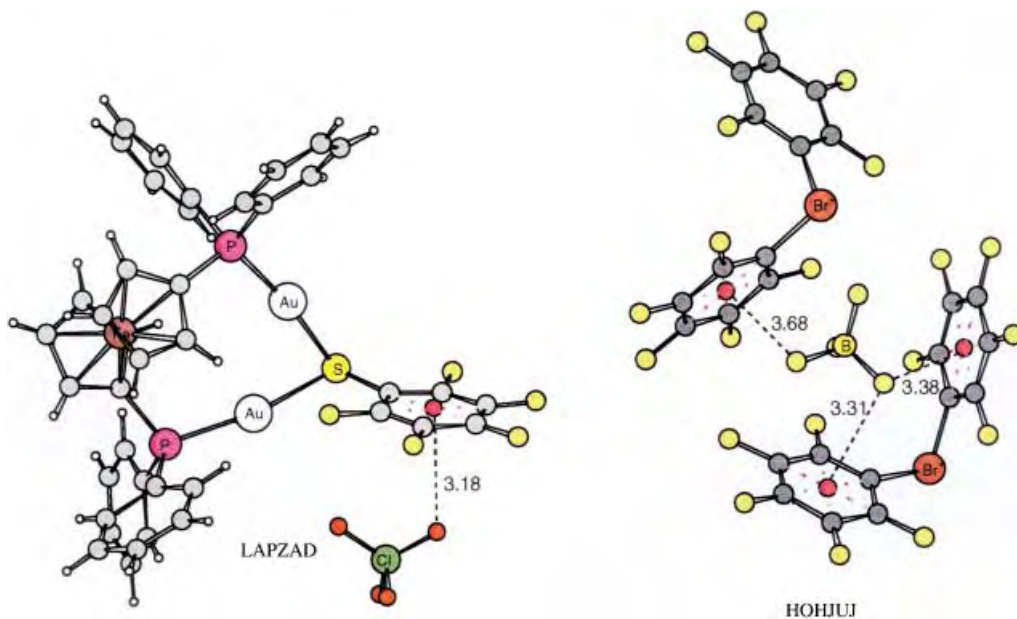


Figure 3. X-ray crystal structures of $[(\text{Ph}_2\text{PC}_5\text{H}_4)_2\text{FeAu}_2\text{SC}_6\text{F}_5][\text{ClO}_4]$ (LAPZAD)^[31] and $[(\text{C}_6\text{F}_5)_2\text{Br}][\text{BF}_4]$ (HOHJUI); distances in Å.

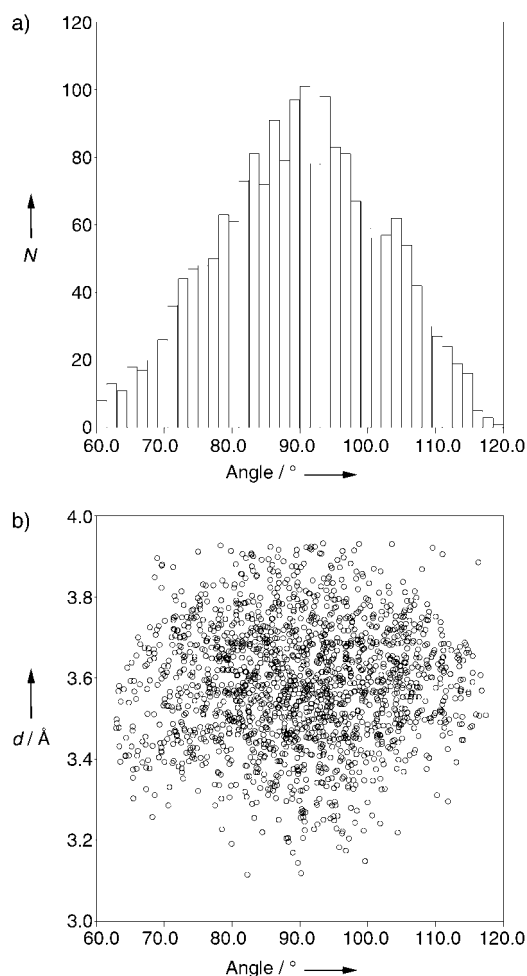


Figure 4. Plots obtained directly from analysis of the CSD database for structures in which noncovalent interactions are present between an electronegative atom (X) such as F, Cl, Br, O, S, and N and a perfluorobenzene fragment. a) Histogram showing the number of structures N obtained at an angle defined by the electronegative atom X, the ring centroid, and one carbon atom of the ring. b) Scatterplot for the structures in which the same angle and the average of all six X-C_{ring} distances are plotted. Both plots were obtained directly from the CSD database software.

molecule crystallography and the CSD in analyzing geometrical parameters and nonbonding interactions has been clearly established.^[23] In exploring the CSD we found 1944 fragments in which noncovalent π interactions are present between lone-pair electrons of electronegative atoms such as F, Cl, Br, O, S, and N and perfluorobenzene derivatives. Twenty-seven of those were π interactions between anions and pentafluorobenzene derivatives.^[24] In Figure 3 we show two selected examples and the CSD reference codes of crystal structures in which the anion- π interaction is evident. It is remarkable that the HOHJUI^[25] structure in which the tetrafluoroborate anion is surrounded by three pentafluorophenyl moieties and two fluorine atoms of the anion clearly interact with the π -electron cloud of the aromatic rings. In order to validate the crystallographic study, we provide in Figure 4 an angle histogram and an angle-distance scatterplot, in which the angle used for the histogram and the scatterplot is defined by the interacting atom (X), the ring centroid, and one carbon atom of the ring, and the distance

used for the scatterplot is the average of all six X-C_{ring} distances. The major number of hits in the search corresponds to angles close to 90° (see histogram) and the concentration of data are at angles close to perpendicular to the aromatic ring and interaction distances closer than the van der Waals contact (see scatterplot).

To analyze the physical nature of the anion- π interaction and determine whether polarization is important, we computed its contribution to the total interaction energy with the recently developed Molecular Interaction Potential with polarization (MIPp),^[26] which is a powerful tool for predicting the binding properties of aromatic compounds.^[10,27] MIPp is an improved generalization of the molecular electrostatic potential (MEP), in which three terms contribute to the interaction energy: 1) an electrostatic term identical to the MEP,^[28] 2) a classical dispersion-repulsion term, and 3) a polarization term derived from perturbational theory.^[29] Therefore, it provides a natural partitioning of the interaction energy into intuitive components.

Calculation^[30] of the MIPp of hexafluorobenzene interacting with F⁻ (see Table 2) was performed with the HF/6-311 +

Table 2. Contributions to the total interaction energy [kcal mol⁻¹] calculated with MIPp for hexafluorobenzene interacting with F⁻ at several distances [Å] from the center of the ring.

Distance	E_e	E_p	E_{vw}	E_t
1.5	-36.59	-43.84	1047.82	967.38
2.0	-22.44	-24.89	119.05	71.72
2.5	-16.39	-13.93	13.44	-16.89
3.0	-12.66	-7.96	-0.50	-20.12
3.5	-9.90	-4.74	-0.83	-15.48

G** geometries and wavefunctions. In the calculations the F⁻ ion was considered as a classical nonpolarizable particle. We explored the electrostatic (E_e), polarization (E_p), van der Waals (E_{vw}), and total (E_t) interacting energies when a fluoride ion approaches an hexafluorobenzene molecule perpendicular to the center of the aromatic ring. The results in Table 2 point out the importance of the polarization component, which is similar to the electrostatic one in the 2.0–3.0 Å range.

In summary, the results derived from crystallographic structures and theoretical calculations reported in this study reveal the existence of anion- π interactions. This new non-bonding interaction has been studied by using a topological analysis of the electron density and MIPp calculations. The interaction of anions with other benzene derivatives with positive quadrupole moments such as 1,3,5-trinitrobenzene is under study.

Note added in proof: Since submission of this manuscript, a publication has appeared that includes relevant work. It describes the interaction of π -electron deficient 1,3,5-triazine ring and several anions by ab initio calculations at the MP2 level of theory.^[32] We are grateful to the editor for bringing this to our attention.

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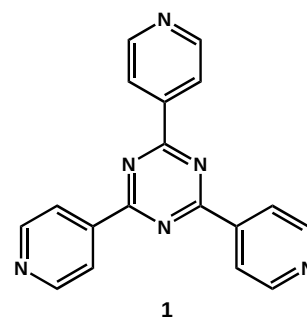
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A Springlike 3D-Coordination Network That Shrinks or Swells in a Crystal-to-Crystal Manner upon Guest Removal or Readsorption**

Kumar Biradha and Makoto Fujita*

The recent upsurge in the crystal engineering of coordination nets is caused by their several useful functional properties such as porosity, use in separation and catalysis, and magnetism.^[1] Particularly, some metal-organic 3D networks were shown to be porous: the networks and their crystalline nature are intact after the guest removal and the emptied network had the ability to reabsorb and desorb guest molecules.^[2] Here we show another class of compounds in which a 3D network contracts after guest removal and expands after a guest is readsorbed; this class of molecules can also exchange guest molecules without affecting the 3D network or its crystalline nature. Linear and rigid bifunctional ligands (1D) such as 4,4'-bipyridine form several networks with various properties.^[3] However, its 3D analogue, 2,4,6-tris(4-pyridyl)triazine (TPT, **1**), has not been explored to that extent.^[4] In solution chemistry we have already shown that panel-like ligands such as **1** self-assemble into 3D polyhedra upon reaction with



- [*] Prof. Dr. M. Fujita,† Dr. K. Biradha
Department of Applied Chemistry
Graduate School of Engineering, Nagoya University
and
CREST, Japan Science and Technology Corporation (JST)
Chikusaku, Nagoya 464-8603 (Japan)
E-mail: mfujita@appchem.t.u-tokyo.ac.jp
- [†] Present address:
The University of Tokyo Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81)3-5841-7257

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convergent metal centers.^[5] Simultaneously, in coordination polymers, Robson and co-workers showed that ligand **1** can self-assemble into 3D networks upon reaction with transition metals.^[6] We report here the unprecedented dynamic nature of a doubly interpenetrated (10,3)-b network that assembles from **1** and ZnI_2 ; that is, it shrinks when guest molecules are removed and swells when they are returned (Figure 1)

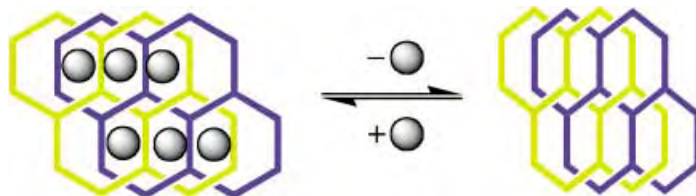


Figure 1. Schematic representation of the contraction or expansion of the 3D network on the removal or addition of guest molecules, respectively.

without destruction of the crystalline nature.^[7] Furthermore, we show that guest molecules can control the formation of doubly interpenetrated and non-interpenetrated networks of the same (10,3)-b configuration. Batten and Robson disclosed that **1** with ZnCl_2 forms a similar type of doubly interpenetrated network.^[8]

The diffusion of a solution of ZnI_2 in MeOH into a nitrobenzene/MeOH solution of **1** resulted in single crystals of the complex $[(\text{ZnI}_2)_3(\textbf{1})_2 \cdot 6 \text{C}_6\text{H}_5\text{NO}_2]_n$ (**2**). Single-crystal analysis of the complex revealed the formation of a doubly interpenetrated 3D network.^[9]

In the crystal structure of **2**, the Zn atoms adopt a tetrahedral geometry as the I atoms and pyridine moieties of TPT occupy two sites each. The shortest circuits in the 3D network contain ten molecules of **1** and ten Zn atoms (Figure 2a) and the network can be classified as having a (10,3)-b configuration, if the Zn atoms are considered to be spacers and the moieties of **1** to be three connected nodes. Along the (010) axis, the network can be regarded as a helical, hexagonal 3D network with a pitch length of 15 Å (Figure 2b).^[10] Two of these nets are interpenetrated such that continuous channels exist (Figure 2c,d). Despite this interlinking of the networks, 60% of the unit-cell volume is occupied by the nitrobenzene molecules, which are partially disordered. Interestingly, the interpenetration of the networks does not interfere in channel formation as the channels run in a direction overlapping that of the two networks (Figure 2d). The use of cyanobenzene in place of nitrobenzene also resulted in a similar complex $[(\text{ZnI}_2)_3(\textbf{1})_2 \cdot 6 \text{C}_6\text{H}_5\text{CN}]_n$ (**3**).^[11]

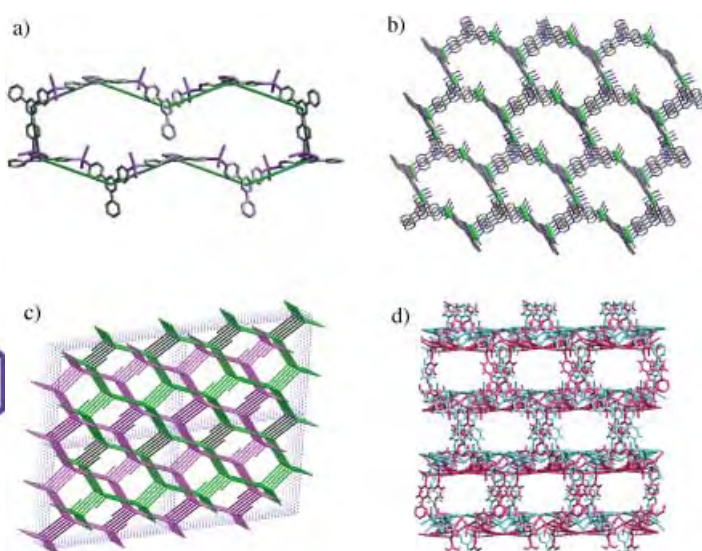


Figure 2. The crystal structure of **2**: a) the shortest circuit formed by ten molecules of **1** and ten Zn atoms (C = gray, N = blue, and Zn and I = magenta). The centers of the **1** molecules are joined by a green line; b) view of 3D network in the (010) direction (C = gray, N = blue, Zn = light green, and I = magenta); c) view of the interpenetrated networks from the (010) direction. Note that the ligands are denoted by nodes and the Zn atoms by lines; d) the formation of channels through the interpenetrated networks. In c) and d) the networks are differentiated with two different colors.

A remarkable feature of the complexes **2** and **3** is the compression of the networks, without destroying the crystalline nature, when the guest molecule is released from the crystals (Figure 1). The crystals of **2** or **3** were left at room temperature to equilibrate with the atmosphere for one day. The color of the crystals changed from colorless to light yellow. The single-crystal analysis of these crystals of **2** and **3** from which the some of the guest molecules have escaped (**2'** and **3'**, respectively) indicated large differences in unit-cell parameters from their parent crystals. The crystal-structure determinations revealed the compression of the networks with unchanged network connections. Although the crystal structures of complexes **2** and **3** are very similar, those of **2'** and **3'** are not the same because of differences in the compression of the networks.

The crystal system of **2'** is triclinic while the crystals of **2** are monoclinic.^[12] In contrast, the crystal system of **3'** is the same as that of **3** or **2**, because contraction of the network occurred only in the (100) direction.^[13] The unit-cell volumes of **2'** and

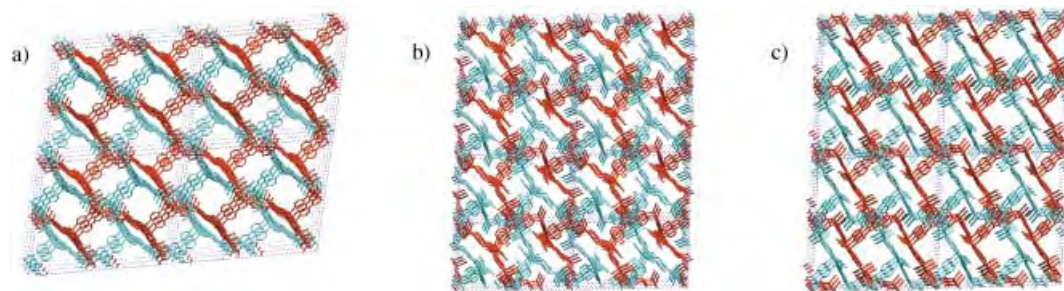


Figure 3. Illustration of interpenetrated networks before and after contraction of the crystal structure: a) **2** or **3**; b) **2'**, and c) **3'**. Notice the massive changes which occurred.

3' are reduced by 23 and 20% from those of **2** and **3**, respectively, because of the network compression (Figure 3). The intermolecular Zn–Zn distances became much shorter after compression, both in **2'** and **3'**. For example, before compression the shortest intermolecular Zn–Zn distances in **2** and **3** are 6.9 and 7.0 Å, respectively, while after compression they are 5.2 and 5.8 Å in **2'** and **3'**, respectively. Similarly, the shortest centroid–centroid distances of the ligand before compression are 8.2 Å for both **2** and **3**; after compression they are 5.1 and 7.0 Å for **2'** and **3'**, respectively. Remarkably, when the crystals of **2'** were placed in nitrobenzene for one day, the network expanded to reproduce the original crystals of **2**.^[14] The guest molecules were removed completely from **2** or **3** by heating the crystals. The diffraction of these crystals, from which the guest molecules had been fully removed, enabled the determination of the cell parameters which are the same as those for **2**.^[15] This result indicates that complete guest elimination favors the structure **2'** over **3'**. Powder diffraction studies on these transformations at room temperature indicated continuous changes in the powder patterns with time.^[16]

Interestingly, the crystals of **2** and **3** exhibited a remarkable ability to exchange nitrobenzene and cyanobenzene guest molecules for a variety of other guest molecules such as benzene, mesitylene, *cis*-stilbene, and CHCl₃. In a typical reaction, the crystals of **2** were immersed in benzene for a day and then the absorbed guest was extracted into diethyl ether after addition of HCl to the dried crystals. GC analysis of the extracted layer showed no trace of nitrobenzene but only the new guest. Importantly, the crystalline nature was not destroyed during the exchange process and hence crystals suitable for an X-ray analysis were obtained even after guest exchange.

The single crystal analysis of the crystals of **2** with the guest molecule exchanged for benzene, [(ZnI₂)₃(**1**)₂·6C₆H₆]_n (**4**) revealed that the crystal structure is virtually identical to that of **2**.^[17] Interestingly, unlike the nitrobenzene molecules, which are disordered, the benzene molecules (except one) in **4** are ordered and refined well isotropically. As a result, the crystal structure of **4** refined with a better *R* factor than the parent crystal (*R*₁ = 5.5% vs. 7.9%). The benzene molecules in **4** interact with each other through aromatic interactions to form a column of molecules that will pass through the channels of the network (Figure 4).

Our efforts to synthesize the non-interpenetrated (10,3)-b network using TPT and ZnI₂ were successful when we conducted the reaction in the presence of bromoform–MeOH. Crystals of the complex [(ZnI₂)₃(**1**)₂·2CHBr₃]_n (**5**)

grew in four days when the MeOH solution of ZnI₂ was layered onto the bromoform solution of TPT.^[18] The crystal structure of the complex **5** shows the formation of a (10,3)-b network without interpenetration. In **5**, the pitch of the helix was reduced to nearly half that in **2** or **3**. The hexagonal channels shown in Figure 2b for **2** or **3** are divided into two channels in **5** (Figure 5). The disordered bromoform molecules occupy these channels.

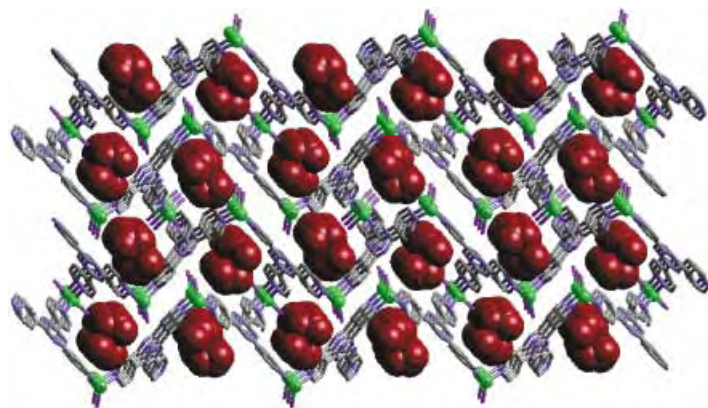


Figure 5. Illustration of 3D network in complex **5**. Bromoform molecules are shown in space-filling mode in brown (Zn = light green, I = magenta, C = gray, and N = blue).

Experimental Section

Synthesis of 2/3: Single crystals of **2/3** were prepared by layering a MeOH solution of ZnI₂ (9.6 mg in 1 mL) onto a nitrobenzene/cyanobenzene solution of **1** (6.3 mg in 4 mL). After the solution was allowed to stand for 7 days, the crystals formed were isolated in 63%/57% yield, respectively, by filtration. Similarly, the crystals of **5** were prepared by layering the MeOH solution of ZnI₂ (9.6 mg in 1 mL) onto the bromoform solution of **1** (6.3 mg in 3 mL). Single crystals suitable for X-ray studies were obtained in 15% yield in two days.

Synthesis of 2/3': The crystals of **2/3'** were prepared by leaving the crystals of **2/3** at room temperature to equilibrate with atmosphere for one day. The elemental analysis suggests the presence of a lower proportion of guest molecules than in **2/3**.

Synthesis of 4: The single crystals of **4** were obtained by immersing the crystals of **2** in benzene for a day. GC analysis of these crystals suggests the presence of benzene and the complete absence of nitrobenzene.

Elemental analysis: for **2**, found: C 36.60, H 2.28, N 10.57; calcd for [(ZnI₂)₃(**1**)₂·5.5C₆H₅NO₂]_n: C 36.68, H 2.30, N 10.85; for **2'**, found: C 33.75, H 2.12, N 10.08; calcd for [(ZnI₂)₃(**1**)₂·3.33C₆H₅NO₂]_n: C 33.94, H 2.06, N 10.78.

Elemental analysis: for **3**, found: C 42.45, H 2.50, N 11.60; calcd for [(ZnI₂)₃(**1**)₂·6C₆H₅CN]_n: C 42.56, H 2.47, N 11.45; for **3'**, found: C 38.60, H 2.25, N 11.35; calcd for [(ZnI₂)₃(**1**)₂·4C₆H₅CN]_n: C 38.54, H 2.22, N 11.23.

Crystal data collection and refinement: The data for all the structures were measured on a Bruker SMART/CCD diffractometer (MoK_α radiation λ = 0.71073 Å) at 193 K. An empirical absorption correction was applied using the SADABS program. Non-hydrogen atoms were refined anisotropically except for guest molecules and hydrogen atoms, which were fixed at calculated positions and refined using a riding model. CCDC-187829(**2**), CCDC-187830 (**2'**), CCDC-187831 (**3**), CCDC-187832 (**3'**), CCDC-187833(**4**) and CCDC-187834 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

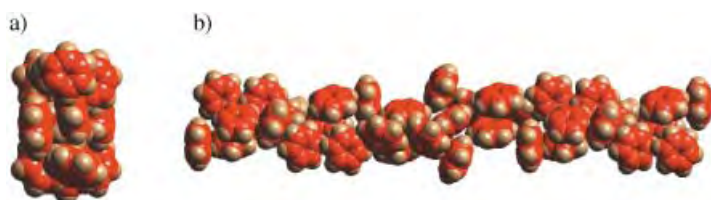


Figure 4. Space-filling representation of the column of benzene molecules exhibited in the crystal structure of **4**: a) top view and b) side view (C = red and H = light brown). Note that these columns fit into the channels shown in Figure 2d.

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- [10] Crystal data for **2**: Monoclinic, *C2/c*, *a* = 36.079(10), *b* = 14.978(4), *c* = 30.734(9) Å, β = 102.470(2)°, *V* = 16217(12) Å³, *Z* = 8, *D_c* = 1.851 g cm⁻³, 9066 reflections out of 14243 unique reflections with *I* > 2σ(*I*), 1.16 < θ < 25.00°, final *R* factors *R₁* = 0.079, *wR₂* = 0.2316.
- [11] Crystal data for **3**: Monoclinic, *C2/c*, *a* = 35.487(8), *b* = 15.080(4), *c* = 31.542(7) Å, β = 102.107(4)°, *V* = 16504(7) Å³, *Z* = 8, *D_c* = 1.772 g cm⁻³, 9884 reflections out of 14518 unique reflections with *I* > 2σ(*I*), 1.32 < θ < 25.00°, final *R* factors *R₁* = 0.0638, *wR₂* = 0.1922.
- [12] Crystal data for **2'**: Triclinic, *P1̄*, *a* = 14.297(3), *b* = 17.164(3), *c* = 27.333(5) Å, α = 89.970(5)°, β = 77.104(4)°, γ = 74.591(4)°, *V* = 6291(2) Å³, *Z* = 4, 6564 reflections out of 21852 unique reflections with *I* > 2σ(*I*), 1.16 < θ < 25.00°, final *R* factors *R₁* = 0.1194, *wR₂* = 0.2720.
- [13] Crystal data for **3'**: Monoclinic, *C2/c*, *a* = 27.482(8), *b* = 15.096(4), *c* = 31.846(7) Å, β = 94.143(6)°, *V* = 13177(6) Å³, *Z* = 8, 8052 reflections out of 11604 unique reflections with *I* > 2σ(*I*), 1.28 < θ < 25.00°, final *R* factors *R₁* = 0.0623, *wR₂* = 0.1462.
- [14] Crystals of **2'** placed in nitrobenzene: The crystals broke into small pieces, monoclinic, *C2/c*, *a* = 36.370(7), *b* = 15.090(3), *c* = 31.266(6) Å, β = 103.782(4)°, *V* = 16665(5) Å³, *Z* = 8, 5583 reflections out of 14665 unique reflections with *I* > 2σ(*I*), 1.15 < θ < 25.00°, final *R* factors *R₁* = 0.0994, *wR₂* = 0.2486.
- [15] Unit cell parameters for **2** after complete guest removal by heating on hotplate for 10 mins at 170 °C, the crystals broke into small pieces and became less transparent. The complete guest removal was confirmed by GC analysis: *a* = 14.573(19), *b* = 17.268(23), *c* = 28.044(38) Å, α = 89.685(15)°, β = 76.956(14)°, γ = 73.794(12)°. Heating the crystals of **3** to 170 °C resulted in similar cell parameters to those described above.
- [16] The powder diffraction patterns for **2** monitored at various time intervals are in the Supporting Information.
- [17] Crystal data for **4**: Monoclinic, *C2/c*, *a* = 35.316(3), *b* = 14.7247(14), *c* = 31.766(3) Å, β = 101.906(2)°, *V* = 16163(7) Å³, *Z* = 8, *D_c* = 1.686 g cm⁻³, 10419 reflections out of 14232 unique reflections with *I* > 2σ(*I*), 1.50 < θ < 25.00°, final *R* factors *R₁* = 0.0557, *wR₂* = 0.1589.
- [18] Crystal data for **5**: Orthorhombic, *Fdd2*, *a* = 35.252(5), *b* = 39.509(5), *c* = 8.153(1) Å, *V* = 11355(3) Å³, *Z* = 8, *D_c* = 2.442 g cm⁻³, 3752 reflections out of 4976 unique reflections with *I* > 2σ(*I*), 1.55 < θ < 24.99°, final *R* factors *R₁* = 0.0456, *wR₂* = 0.1038.

Crystal-to-Crystal Sliding of 2D Coordination Layers Triggered by Guest Exchange**

Kumar Biradha, Yoshito Hongo, and Makoto Fujita*

Metal–organic frameworks containing channels or voids have attracted current interest because of their functional properties, which are similar to those of zeolites and clays.^[1–4] Although the porosity is one of the most studied properties of metal–organic frameworks, there are very few studies on dynamic porous coordination networks.^[5] 2D-network materials have the potential to provide such dynamic porous materials as they can adopt changes caused by external stimuli, either within the layer or in between the layers. Here we present one such unique and novel dynamic process in the crystals of a 2D net containing square grids of dimension 20 × 20 Å.

The crystal-to-crystal sliding of the 2D nets between two packing modes A and B (Figure 1) is triggered by guest exchange, and results in considerable increase in the dimensions of channels. This crystal-to-crystal transformation was evidenced by single crystal and powder X-ray diffraction studies before and after the transformation. The single-crystal

[*] Prof. Dr. M. Fujita,[†] Dr. K. Biradha, Y. Hongo
Department of Applied Chemistry
Graduate School of Engineering, Nagoya University
and
CREST, Japan Science and Technology Corporation (JST)
Chikusaku, Nagoya 464-8603 (Japan)
E-mail: mfujita@appchem.t.u-tokyo.ac.jp

[†] Present address:
The University of Tokyo Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81)3-5841-7257

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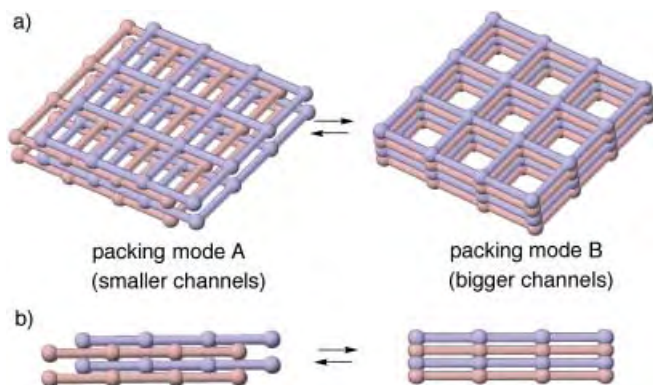


Figure 1. Schematic representation of the sliding of 2D square grids: a) top and b) side views. Channels across the layers are smaller in mode A than in mode B.

analysis of unit cell parameters at various time intervals during the transformation suggested that the first step is the exchange of guest molecules and the second step is the sliding of the layers. Furthermore, the guest-exchanged crystal with larger channel dimensions (packing mode B) is found to absorb/desorb guest molecules, while such a property is lacking in their parent crystals (packing mode A).

We have recently shown that the long ligand, 4,4'-bis(4-pyridyl)biphenyl (**1**), forms $[\text{Ni}(\text{1})_2(\text{NO}_3)_2 \cdot 4(o\text{-xylene})]$ (**2**) upon reaction with $\text{Ni}(\text{NO}_3)_2$ in the presence of *o*-xylene.^[4] Complex **2** contains 2D layers that are formed by square grids of dimension $20 \times 20 \text{ \AA}$.^[6] These layers have a short interlayer separation of $4.1 \text{ \AA}$ and can slide on each other as the binding forces between the layers are only weak aromatic and C–H $\cdots$ O interactions that are reformed after the sliding is completed.^[7]

Interestingly, the crystals of **2** show a remarkable ability to exchange the guest molecule *o*-xylene for mesitylene but not for *m*-xylene, or 1,3- or 1,2-dimethoxybenzene. In a typical reaction, the crystals of **2** were immersed in mesitylene for 6 h and then the absorbed guest was extracted into diethyl ether following addition of HCl to the dried crystals. The GC analysis of the extracted layer showed only the presence of mesitylene, which indicates the complete exchange of the *o*-xylene guest. The chemical composition of the crystals in which the *o*-xylene guest had been replaced with mesitylene was $[\text{Ni}(\text{1})_2(\text{NO}_3)_2 \cdot 1.7(\text{mesitylene})]_n$ from elemental analysis. Notably the crystalline nature was not destroyed during the process and hence crystals suitable for an X-ray analysis were obtained even after the guest exchange.

Surprisingly, the single-crystal X-ray analysis of the crystals with mesitylene as the new guest (**3**) revealed that considerable sliding of the layers on each other occurred such that the dimension of the channels was bigger than that of **2** (Figure 2). For example, the nearest distance between Ni atoms of the adjacent layers in **2** is $11.46 \text{ \AA}$ whereas it is $8.06 \text{ \AA}$ in **3**. Assuming that one of the layers is fixed, the approximate sliding distance of its neighboring layer can be calculated as $4.2 \text{ \AA}$, based on the geometry of the Ni atoms. In **2** the layers pack on each other such that they overlap in one direction and are offset in the other direction, which results in the approximate channel dimension of about $10 \times 20 \text{ \AA}$ (packing

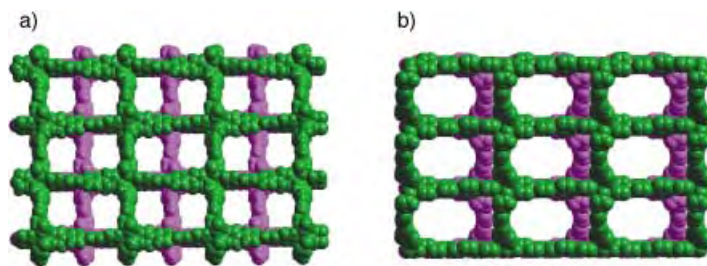


Figure 2. Packing of 2D layers in a) **2** (mode A) and b) **3** (mode B). Alternate layers colored in magenta and green. Notice the differences in channel dimensions.

mode A). Unlike **2**, the offset packing was not observed in **3** as the layers slide on each other to give channel dimensions of approximately $15 \times 20 \text{ \AA}$ (packing mode B).

In both packing motifs, edge-to-face aromatic interactions exist at the corner of the channels but not along the walls—the shortest centroid-to-centroid distances of the C_6 rings of **1** in the neighboring layers are 4.869 and $4.819 \text{ \AA}$ for A and B, respectively. There are more C–H $\cdots$ O hydrogen bonds between the nitrate ions and phenyl groups of adjacent layers in mode B (six) than mode A (three). This disparity is because in mode A only one of the C_6 rings of **1** participate in C–H $\cdots$ O hydrogen bonds whereas in mode B both of the C_6 rings participate. The entire framework of **3**, except one of the phenylene rings of **1**, had no disorder though the mesitylene molecules were highly disordered. The electron density peaks corresponding to the disordered mesitylene were distributed throughout the channels. Analysis of the structure in detail showed that the grids in **3** are somewhat contracted compared to those in **2**: $19.79 \times 19.96 \text{ \AA}$ in **3** and $19.91 \times 19.96 \text{ \AA}$ in **2** (Figure 3). Furthermore, the unit-cell volume of **3** is 7% less than that of **2**.

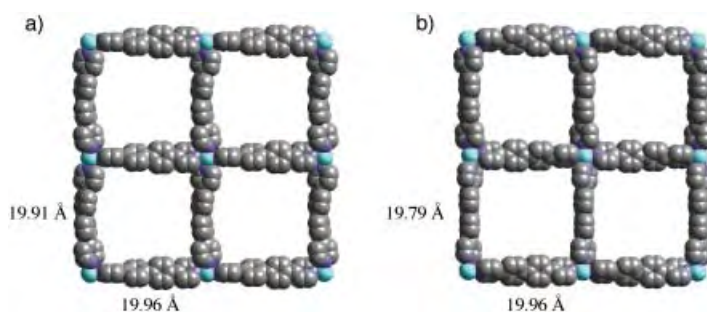


Figure 3. 2D square grid layers exhibited in a) **2** and b) **3**. The disorder in one of the C_6 rings of ligand **1** in the crystals of **3** is not shown.

The sliding of the 2D net was also monitored by X-ray powder diffraction pattern (XRPD) of the crystals. The conversion of crystal **2** into **3** by the guest exchange resulted in considerable change in the diffraction pattern. Further, the reexchange of mesitylene in **3** with *o*-xylene suggested that mode A was regenerated in a high percentage (see Supporting Information).^[8]

To establish the mechanism for guest exchange and sliding of the layers, the reaction was monitored over time by single crystal diffraction, that is, the unit-cell parameters were

determined at various time intervals, with the crystal of **2** in a glass capillary filled with mesitylene. Interestingly the results indicate no change in cell parameters (similar to **2**) up to 6 h, which is the time required for exchange of guest molecules as indicated by GC analysis. From 6 h to 9 h the crystal was not indexed but still showed diffraction. At 10 h the indexing was restarted to give cell parameters similar to those of **3**. The crystal was monitored again at 22 h and it was indexed with more reflections than at 10 h, which gave cell parameters similar to those of **3**. These results clearly indicate that the transformation indeed occurred crystal to crystal; the first step is guest exchange and the second step is the sliding of the layers.

The changes in terms of single crystal diffraction were illustrated in one of the frames recorded at various time intervals (Figure 4). Up to 3.5 h the diffraction pattern was constant but from 3.5 h the pattern changed slowly. The spots

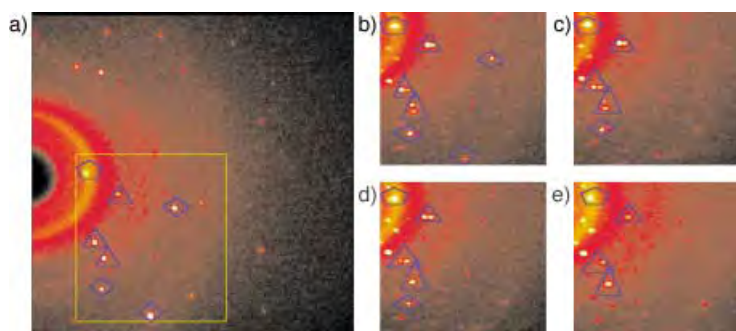


Figure 4. Diffraction patterns for transformation at various time intervals after immersion of crystal of **2** in mesitylene: a) The full frame after 15 mins. The region shown in a square box in a) after b) 4.30 h; c) 6 h; d) 8 h; e) 10 h. For comparison, the spots are marked with polygons (see text).

shown in diamonds disappeared and those shown in triangles divided into two and finally merged. The spot shown in a pentagon intensified as the time progressed and its position remained constant throughout the reaction. Some new peaks also appeared as the time progressed.

The role of mesitylene seems to be important in this transformation as a similar transformation or guest exchange was not observed when the crystals of **2** were immersed for even longer in the other guest solvents such as benzene, *m*-xylene, or 1,2- or 1,3-dimethoxybenzene. In the hope of growing crystals of **3** directly, the complexation of ligand **1** with $\text{Ni}(\text{NO}_3)_2$ was carried out in the presence of mesitylene. However this reaction resulted in fourfold, perpendicularly interpenetrated square-grid networks instead of an open framework structure.^[9]

Unlike **2**, which exhibited selectivity in guest exchange, **3** can exchange mesitylene for many liquid aromatic guest molecules without destroying or altering the crystal nature.^[10] The unit-cell parameters after the exchange of mesitylene with guests such as nitrobenzene and *o*-xylene were found to be the same as those of **3**. Guest absorption reactions were carried out on **3** after removing the mesitylene by heating it to 100 °C at 5 mmHg for 6 h. The crystals from which the

mesitylene was removed were also in packing mode B. Interestingly, the immersion of these crystals in aromatic guest solvents lead to absorption of the guests while retaining their crystalline nature; this was verified by GC, elemental analysis, and XRPD.^[11]

Experimental Section

Synthesis of 3: The crystals of **2** were immersed in mesitylene for a day and then the complete exchange of *o*-xylene for mesitylene was verified by GC analysis. The unit-cell parameters for some of these crystals were measured with single crystal diffraction and all of them were found to have similar cell parameters to those of **3**.

Elemental analysis: **2:** $[(\text{Ni}(\text{I})_2(\text{NO}_3)_2) \cdot 3.5(\text{o-xylene})]$, 0.5 equivalents of guest escaped at RT: calcd (%) C 73.85, H 5.77, N 7.18; found C 73.53, H 5.72, N 7.11; **3:** $[(\text{Ni}(\text{I})_2(\text{NO}_3)_2) \cdot 1.7(\text{mesitylene})]$: calcd (%) C 70.96, H 5.26, N 8.37; found C 70.50, H 5.25, N 8.37.

Crystal data for 2: Monoclinic, $C2/c$, $a = 27.187(3)$, $b = 19.963(2)$, $c = 12.685(4)$ Å, $\beta = 106.923(2)^\circ$, $V = 6585.9(12)$ Å³, $Z = 4$, $D_c = 1.235$ g cm⁻³, 5932 unique reflections out of 7770 with $I > 2\sigma$, $1.29 < \theta < 27.98^\circ$, final R factors $R_1 = 0.067$, $wR_2 = 0.205$. **Crystal data for 3:** Monoclinic, $P2_1/c$, $a = 13.071(3)$, $b = 19.853(4)$, $c = 12.082(3)$ Å, $\beta = 103.149(4)^\circ$, $V = 3053.1(11)$ Å³, $Z = 2$, 4527 unique reflections out of 7099 with $I > 2\sigma$, $1.90 < \theta < 27.94^\circ$, final R factors $R_1 = 0.087$, $wR_2 = 0.2219$. One of the C_6 rings of **1** was disordered; this was modeled and refined. Also the peaks corresponding to mesitylene were located and refined isotropically. The data for both **2** and **3** for were measured on a Siemens SMART/CCD diffractometer ($\text{MoK}\alpha$ radiation $\lambda = 0.71073$ Å) at 193 K. An empirical absorption correction was applied using SADABS program. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were fixed at calculated positions and refined using a riding model. CCDC-141218 (**2**), and CCDC-187955 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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- [6] The dimensions of the grid are defined as the distances between the metal atoms separated by **1**.
- [7] The interlayer separation is defined as the distance of the Ni atoms to the plane of the neighboring layer.
- [8] The diffraction pattern of **3** does not exactly match with the pattern that is calculated from its single-crystal data. This mismatch in X-ray powder diffraction patterns could be caused by incomplete conversion from mode A into mode B and hence **3** may also contain some impurity in the form of mode A packing.
- [9] Crystallographic information for interpenetrated network: This structure was solved in two space groups: $I41/a$, $a = b = 19.276(3)$; $c = 28.942(9)$ Å; $\alpha = \beta = \gamma = 90^\circ$ and $C2/c$, $a = 27.257(5)$; $b = 28.942(9)$; $c = 19.275(4)$ Å; $\beta = 134.992(4)^\circ$. The solvent molecules are highly disordered.
- [10] Styrene, nitrobenzene, and cyanobenzene were also found to exchange *o*-xylene in **2** in the same way as mesitylene.
- [11] Preliminary results on **3**, from which the mesitylene was removed, indicate that it shows sorption properties with gaseous benzene.

Amplified DNA Detection by Electrogenenerated Biochemiluminescence and by the Catalyzed Precipitation of an Insoluble Product on Electrodes in the Presence of the Doxorubicin Intercalator**

Fernando Patolsky, Eugenii Katz, and Itamar Willner*

The amplified sensing of nucleic acids on surfaces attracts research efforts directed to the development of DNA chips for gene analysis, the detection of genetic disorders, tissue matching, forensic applications, and molecular computation.^[1,2] Amplified electrochemical DNA detection was reported by the labeling of nucleic acids with a redox enzyme and amplifying the formation of the double-stranded system on the electrode surface by the activation of a secondary bioelectrocatalyzed process.^[3] A further approach involves the generation, on the electrode surface, of a redox-active replica for the analyzed DNA by using polymerase, and the application of the redox replica as a mediator for the activation of bioelectrocatalyzed transformations.^[4] A different approach for the amplified detection of DNA includes the labeling of the analyzed DNA, for example, with a biotin label, that allows the secondary association of an enzyme conjugate (e.g. avidin–alkaline phosphatase or avidin–horseradish peroxidase) that stimulates the biocatalyzed precipita-

tion of an insoluble product on the electrodes.^[5,6] Faradaic impedance spectroscopy, which probes the interfacial electron-transfer resistance at the electrode supports, or microgravimetric quartz-crystal-microbalance (QCM) measurements were used as transduction methods for the accumulation of the insoluble products on the respective surfaces, as a result of the primary DNA-recognition events. Alternative methods to amplify DNA-recognition processes include the use of particulate labels, such as liposomes,^[7] Au nanoparticles,^[8] or CdS nanoparticles^[9] as amplifying agents, and the electrochemical, microgravimetric QCM assay, and photoelectrochemical transduction of the DNA detection.

Electrogenenerated chemiluminescence is a rapidly progressing method to image biosensing events on surfaces.^[10,11] Studies pioneered by Bard and colleagues have employed Ru^{II}–polypyridine complexes that bind to a double-stranded (ds) DNA for the electroluminescent imaging of DNA on electrode surfaces.^[12] However, the partial binding of [Ru(bpy)₃]²⁺ (bpy = 2,2'-bipyridine) complexes to single-stranded DNA introduces significant background electroluminescence that prohibits the detection of low hybridization yields of DNA. The covalent labeling of nucleic acids with a Ru^{II}–trisbipyridine complex has been suggested as a possible route to resolve this difficulty.^[13] Herein we report two alternative methods for the amplified detection of DNA by using the doxorubicin intercalator as a dsDNA surface-confined label for the electrogeneration of H₂O₂. The generated H₂O₂ is then used to image the DNA by: 1) stimulated biochemiluminescence, and 2) stimulated biocatalyzed precipitation of an insoluble product on electrodes.

Figure 1 depicts the configuration of the DNA detection system. The thiolated nucleic acid **1** is assembled on an Au-electrode and the surface coverage derived from the microgravimetric (QCM) analysis^[7c] is 2×10^{-11} mol cm⁻². Then the **1**-functionalized gold surface is treated with 1-mercaptohexanol to block pinholes in the DNA-monolayer assembly associated with the electrode. The resulting monolayer-functionalized electrode is then treated with the complementary analyte-DNA **2**, to yield the dsDNA assembly on the electrode surface. The resulting system is further treated with doxorubicin (**3**), which is a specific intercalator in double-stranded CG base-pair-containing DNA sequences.^[14] The intercalator-stimulated amplified analysis of the nucleic acid **2** is outlined in Figure 2. Electrochemical reduction of the intercalated **3** leads to the electrocatalyzed reduction of O₂ to H₂O₂. The electrogenerated H₂O₂ in the presence of luminol and horseradish peroxidase (HRP) leads to the formation of 3-aminophthalate and biochemiluminescence ($\lambda = 425$ nm)^[10] which indicates the DNA hybridization process (Figure 2A). Alternatively, the electrogenerated H₂O₂ mediates in the presence of HRP the oxidation of 4-chloronaphthol (**4**) to the insoluble product **5**, which precipitates on the electrode.^[15] Precipitation of **5** on the electrode insulates the electrode surface and increases its interfacial electron-transfer resistance. The changes in the interfacial electron-transfer resistances can then be followed in the presence of an electrolyte-soluble redox probe, by using Faradaic impedance spectroscopy. The stimulated light emission, or the biocatalyzed precipitation of **5** occurs only if the dsDNA structure with the

[*] Prof. I. Willner, F. Patolsky, Dr. E. Katz
Institute of Chemistry
The Farkas Center for Light-Induced Processes
The Hebrew University of Jerusalem
Jerusalem 91904 (Israel)
Fax: (+972) 2-6527715
E-mail: willner@vms.huji.ac.il

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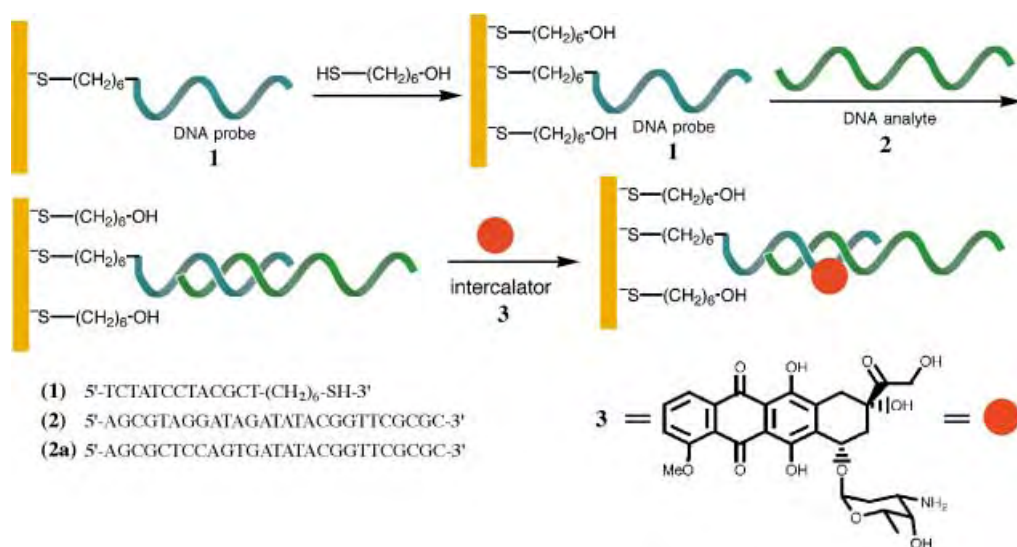


Figure 1. Assembly of the dsDNA monolayer with the intercalated doxorubicin molecules.

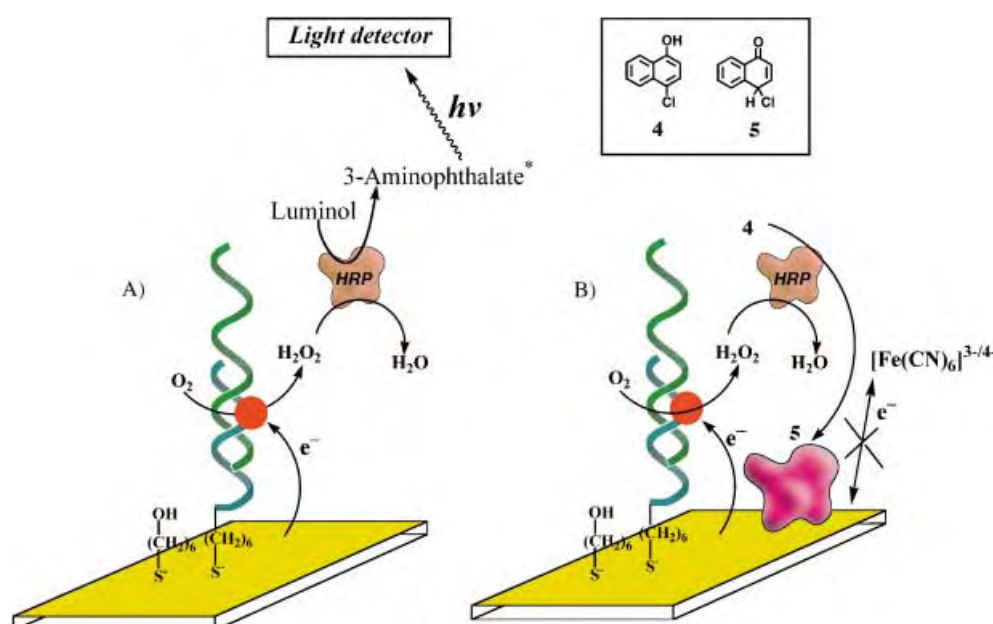


Figure 2. Amplified detection of DNA by the intercalated **3** using: A) Electrochemically generated biochemiluminescence. B) Electrochemically induced precipitation of an insoluble product on the electrode.

analyte nucleic acid **2** is formed, and provided that **3** binds to the assembly.

Figure 3 A, curve a, shows the differential pulse voltammogram of **3**, $E^0 = -0.68$ V, which is intercalated in the dsDNA assembly formed between the **1**-functionalized monolayer-electrode and **2**. Figure 3 A, inset, shows the cyclic voltammogram of the intercalated **3**. Coulometric assay of the reduction wave of **3** indicates a surface coverage of **3** of 3×10^{-11} mol cm⁻². As the surface coverage of the double-stranded structures^[16] of **1/2** is 8×10^{-12} mol cm⁻², we estimate that an average loading of a ds-DNA assembly with 3.75 units of **3** takes place. No redox response of **3** is observed when the single stranded **1**-monolayer is treated with the intercalator in a control experiment, Figure 3 A, curve b. Figure 3 B, curves a and b, show the cyclic voltammograms of the **1**- and **1/2**-monolayer-functionalized electrodes, respectively, after treat-

ment with **3** under argon. The two systems reveal almost identical responses and the redox activity of **3**, which is expected to be observed for the **1/2**-assembly accommodating the intercalator, is almost invisible at the slow potential scan rate employed in the experiment. Figure 3 B, curve c, shows the electrical response of the **1**-functionalized electrode under oxygen. A cathodic current resulting from the non-catalytic reduction of O₂ is observed. Note that the generation of a densely packed, pinhole-free, monolayer of **1**-mercaptohexanol on the electrode surface is important to introduce a barrier and a high overpotential for the direct electroreduction of O₂. Figure 3 B, curve d, depicts the cyclic voltammogram of the **1/2**-functionalized electrode after the intercalation of **3** in the ds-DNA assembly in the presence of oxygen. The cathodic current originating from the quinone-intercalator-catalyzed reduction of O₂ is enhanced and the over-

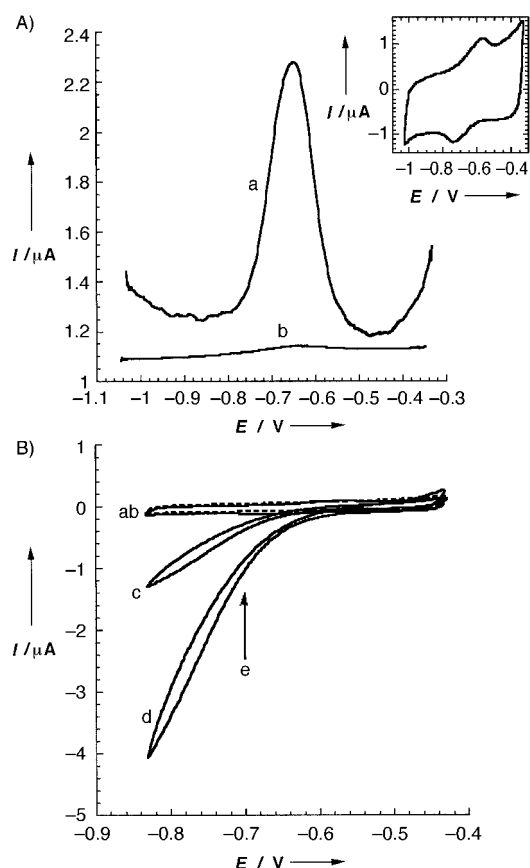


Figure 3. A) Differential pulse voltammograms of the Au-electrode functionalized with: a) the **1/2**-assembly and the intercalated **3**; b) The **1**-modified electrode treated with **3**, 5.2×10^{-5} M, and subsequently washed with phosphate buffer, pH 7.4. Potential scan rate, 20 mV s^{-1} ; pulse height, 2 mV. Inset: Cyclic voltammogram of the **1/2**- and intercalator **3**-modified electrode. Potential scan rate, 100 mV s^{-1} . The data were recorded in 0.1 M phosphate buffer, pH 7.0, under Ar. B) Cyclic voltammograms of the **1**-functionalized electrode after treatment with **3**: a) under Ar and c) in the presence of O_2 . Cyclic voltammograms of **1/2**-functionalized electrode after treatment with **3**: b) under Ar and d) in the presence of O_2 . Potential scan rate, 10 mV s^{-1} . Arrow e) shows the potential $E = -0.7 \text{ V}$ that is applied on the electrodes upon the DNA-detection according to Figure 2.

potential for the reduction of O_2 is substantially lower. These results clearly indicate that the intercalated **3** electrocatalyzes the reduction of O_2 . It is known that quinones catalyze the electrochemical reduction of O_2 to H_2O_2 .^[17] A rotating-disc-electrode experiment^[18] was performed using a Au-disc-electrode modified with the **1/2**-assembly and intercalated **3** for the reduction of O_2 , and a bare Au-ring electrode was used for the electrochemical detection of the product generated on the disc-electrode. This experiment reveals that the **3**-electrocatalyzed reduction of O_2 (at $E = -0.7 \text{ V}$) generates H_2O_2 with a yield corresponding to about 90%. It should be noted, however, that a rotating Au-disc electrode modified with **1** and treated with **3** ($5.2 \times 10^{-5} \text{ M}$) followed by rinsing, also produces H_2O_2 (detected at the Au-ring electrode) with a current yield that corresponds to about 8% (See Supporting Information). That is, in the presence of **1**-functionalized electrode and in the absence of **3**, the non-catalyzed reduction of O_2 generates mainly H_2O . These results indicate that at a constant potential of -0.7 V the **1**-functionalized electrode

will not generate substantial amounts of H_2O_2 by the direct electrochemical reduction of O_2 , but the ds-DNA assembly with intercalated **3** will effectively yield H_2O_2 at this potential. Thus, the electrically generated biochemiluminescence, or the electrically driven biocatalyzed precipitation of **5**, would occur mainly in the presence of the ds-DNA system with intercalated **3**.

Figure 4, curve a, shows the emitted light intensity by the system that includes the **1/2** double-stranded assembly with

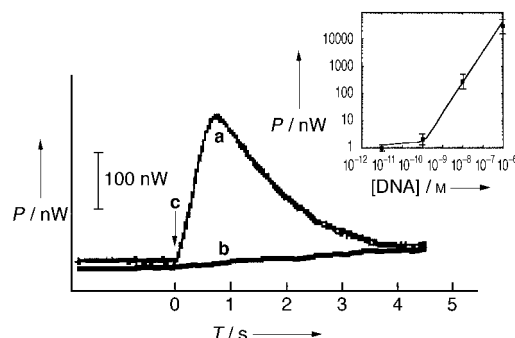


Figure 4. Emitted light intensities from the Au-electrode functionalized with: a) The **1/2**-monolayer and intercalated **3**; b) The **1/2a**-monolayer treated with **3**. The complementary DNA **2** and mutant DNA **2a** were used with a bulk concentration of $1 \times 10^{-6} \text{ M}$. The light emission was induced by the application of $E = -0.7 \text{ V}$ on the modified electrode in an electrolyte solution composed of 0.1 M phosphate buffer, pH 7.0, that includes luminol ($1 \times 10^{-6} \text{ M}$) and HRP (1 mg mL^{-1}) in the presence of O_2 . Arrow c) shows the time when the potential was applied on the electrode. Inset: Calibration plot corresponding to the emitted light intensity versus the bulk concentration of **2** analyzed according to Figure 2A. (Each of the error bars originate from four independent functionalized electrodes).

the intercalated **3** on the electrode. A peak-shaped light-emission curve was observed as a result of the rapid depletion of oxygen in the vicinity of the electrode, by its electrocatalytic reduction. Indeed, to observe reproducible light intensities upon applying a sequence of potential pulses (from 0.0 V to -0.7 V and back to 0.0 V), it is necessary to wait for 30 sec between the pulses to allow the equilibration of oxygen at the electrode surface. Figure 4, curve b, shows the intensity of the light emitted by the **1**-functionalized electrode that was interacted with the mutant (**2a**) and further treated with **3**. Only small, slowly increasing, light emission, which corresponds to the non-catalytic formation of H_2O_2 is observed, and indicates that no hybridization with the mutant occurred, and no intercalation of **3** into the monolayer took place. Further control experiments revealed that very little light emission is detected by the **1/2** double-stranded monolayer in the absence of **3**. These results clearly indicate that the main biochemiluminescence originates from the reduction of O_2 , electrocatalyzed by the intercalated **3** which yields H_2O_2 as the reactive compound for the generation of the emitted light, Figure 2A. The concentration of **1/2**, and as a result the amount of intercalated **3** and electrocatalytically generated H_2O_2 , and the intensity of emitted light, would be controlled by the bulk concentration of DNA **2**. Figure 4, inset, shows the emitted light intensities at different bulk concentrations of **2**. The detection limit of the analyte **2** by the system is around $2 \times 10^{-11} \text{ M}$.

The amplified detection of DNA according to Figure 2B, where the **3**-induced biocatalyzed precipitation of **5** is examined by using Faradaic impedance spectroscopy, is shown in Figure 5. The interfacial electron-transfer resistance

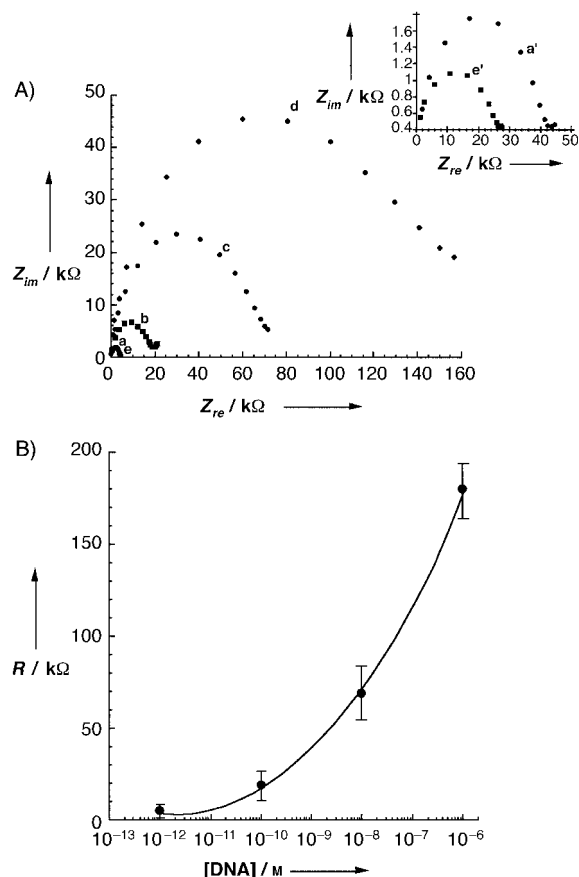


Figure 5. A) Faradaic impedance spectra (Nyquist plots) of the **1/2**-DNA assembly with the intercalator **3** after the electrochemically induced (at $E = -0.7$ V) precipitation of **5** for 2 min, upon the analysis of different bulk concentrations of **2**: a) 1×10^{-12} M, b) 1×10^{-10} M, c) 1×10^{-8} M, d) 1×10^{-6} M. Spectrum e) corresponds to the analysis of the mutant DNA (**2a**), 1×10^{-6} M. Inset: Faradaic impedance spectra recorded after 10 min of precipitation of **5** for: a') **1/2**-DNA assembly using 1×10^{-12} M of **2**, e') **1/2a**-DNA assembly using 1×10^{-6} M of **2a**. The Faradaic impedance spectra were recorded in the presence of 10 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (1:1) upon application of a bias potential of $E = 0.175$ V. B) Calibration plot of the electron transfer resistances derived from the Faradaic impedance spectra versus bulk concentration of **2**. The precipitation of **5** was performed for 2 min. (Each of the error bars originate from four independent functionalized electrodes).

of the **1**-functionalized Au-electrode corresponds to $R_{et} = 5$ k Ω (the value was derived from the respective impedance spectrum). The **1**-functionalized electrodes were hybridized with different concentrations of **2** and treated with **3**. The resulting electrodes were subjected to a potential of -0.7 V in the presence of O_2 , 4-chloronaphthol (**4**), and HRP, and the precipitation of **5** was allowed to proceed for 2 min. The interfacial electron-transfer resistances, R_{et} , at the modified electrodes that include the precipitated **5** were measured and presented in the form of a Nyquist-plot (Figure 5A). The resulting interfacial R_{et} is controlled by the bulk concentration of the analyte DNA **2**. For example, the interfacial R_{et} resulted

upon analyzing **2** at concentrations of 1×10^{-6} M and 1×10^{-10} M are 180 k Ω and 20 k Ω , Figure 5A, curves d and b, respectively. The interfacial R_{et} of the **1**-functionalized-electrodes, upon analyzing **2** at a concentration of 1×10^{-12} M or analyzing the mutant **2a**, at a concentration corresponding to 1×10^{-6} M, are very similar to the **1**-modified electrode, $R_{et} \approx 5$ k Ω , curves a and e, respectively. This result indicates that **2** cannot be sensed at a concentration of 1×10^{-12} M under these experimental conditions, and that the mutant **2a** is fully differentiated from the target DNA **2**. Enhanced sensitivities, however, may be achieved by prolonging the biocatalyzed precipitation process. Figure 5A, inset, shows the interfacial R_{et} resulting from the analysis of **2**, 1×10^{-12} M, and **2a**, 1×10^{-6} M, by stimulating the biocatalyzed precipitation of **5** for a 10 min, curves a' and e', respectively. While the precipitation of **5** on the electrodes for 2 min did not enable the sensing of **2**, 1×10^{-12} M, or its differentiation from **2a**, the biocatalyzed precipitation of **5** for 10 min enables the sensing of **2**, $R_{et} = 42$ k Ω , and its differentiation from the mutant **2a**, $R_{et} = 28$ k Ω . Control experiments reveal that the biocatalyzed precipitation of **5** occurs only if **3** is intercalated into the ds DNA, and provided that the potential of $E = -0.7$ V is applied on the electrode. These results clearly confirm that the biocatalyzed precipitation of **5** is stimulated by the electrocatalyzed reduction of O_2 to H_2O_2 by using doxorubicin (**3**), as an electrocatalyst.

In conclusion, the present study has demonstrated that the intercalation of doxorubicin (**3**), into dsDNA enables the amplified detection of DNA by the doxorubicin-electrocatalyzed reduction of O_2 to H_2O_2 . The formation of H_2O_2 is then probed by the generated biochemiluminescence in the presence of luminol/HRP, or by following the changes in the interfacial electron-transfer resistance (R_{et}) resulting from the biocatalyzed precipitation of **5**, by using Faradaic impedance spectroscopy. The detection limits of the target DNA **2** by the electrogenerated biochemiluminescence and biocatalyzed precipitation of the insoluble product are very similar, about 10^{-10} M. This detection limit is comparable to other amplification methods developed in our laboratory^[5–7] for short nucleic acids.

Experimental Section

The DNA oligonucleotides **1**, **2**, and **2a**, horseradish peroxidase, HRP, (E.C. 1.11.1.7) and all other chemicals were obtained from Aldrich and Sigma and used as supplied. The Au-coated (50 nm gold layer) glass plate (Analytical- μ System, Germany) was used as a working electrode (0.3 cm² area exposed to the solution). An auxiliary Pt electrode and a quasi-reference Ag electrode were made from wires of 0.5 mm diameter and added to the cell. The quasi-reference electrode was calibrated versus the saturated calomel electrode (SCE) and the potentials are given versus SCE. An open electrochemical cell (230 μ L) that includes the modified Au-electrode in a horizontal position and a light detector linked to a fiber optic cable enabled easy light-emission measurements upon application of the appropriate potential to the modified working electrode. The working Au-electrode was treated with a solution of thiolated DNA-primer (**1**; 5×10^{-6} M in 0.3 M phosphate buffer, pH 7.4, 12 h), the electrode was washed with the phosphate buffer, and then the **1**-functionalized Au-surface was treated with 1-mercaptohexanol (1×10^{-3} M in ethanol, 1 h). The resulting monolayer-functionalized electrode was treated with the complementary analyte DNA (**2**; various concentrations in 0.4 M phosphate buffer, pH 7.4, 3 h) to yield the ds-DNA assembly on the electrode surface. The resulting system was further treated with doxorubicin, (**3**; 5.2×10^{-5} M in 0.1 M

phosphate buffer, pH 7.4, 30 min). The electrochemical measurements were performed by using an electrochemical impedance analyzer (EG&G, model 1025) and potentiostat (EG&G, model 283) connected to a computer (EG&G Software Power Suite 1.03 and no. 270/250 for impedance and cyclic voltammetry, respectively). All the measurements were performed in 0.1 M phosphate buffer solution, pH 7.0, at room temperature. When needed, oxygen was removed from the solution by passing Ar above the cell. The Faradaic impedance measurements were performed in the frequency range of 100 mHz to 50 kHz in the presence of 10 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (1:1 mixture) as a redox probe and upon biasing the working electrode at $E = 0.175$ V. The electrochemically induced biochemiluminescence was measured with a light detector (Laserstat, Ophir) linked to an oscilloscope (Tektronix TDS 220). The light detector was connected to the electrochemical cell by an optical fiber and a potential corresponding to $E = -0.7$ V was applied on the working electrode. The background electrolyte solution was equilibrated with air and included luminol (1×10^{-6} M), and HRP (1 mg mL^{-1}). The electrochemically induced precipitation of the insoluble material (**5**) was performed upon application of a potential that corresponded to $E = -0.7$ V on the working electrode in 0.1 M phosphate buffer, pH 7.0. The electrolyte solution was equilibrated with air and included 4-chloro-1-naphthol (**4**; 1×10^{-3} M) and HRP (1 mg mL^{-1}).

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An Electrochemical Probe of DNA Stacking in an Antisense Oligonucleotide Containing a C3'-endo-Locked Sugar**

Elizabeth M. Boon, Jacqueline K. Barton,*
Pushpangadan I. Pradeepkumar, Johan Isaksson,
Catherine Petit, and Jyoti Chattopadhyaya*

The sensitivity of charge transport chemistry to base stacking^[1–5] provides the foundation for applications of DNA charge transport that probe nucleic acid structure, particularly those utilizing electrochemistry experiments on DNA films.^[6–13] In these experiments, DNA oligonucleotide duplexes modified with a thiol linker are self-assembled on a gold electrode surface. A redox-active intercalator, such as methylene blue, bound to the close-packed DNA films is electrochemically reduced and the reduced intercalator is used as a catalyst for the reduction of a species diffusing in solution outside of the DNA film (usually ferricyanide). Once re-oxidized by ferricyanide, methylene blue is available for subsequent electrochemical reduction and the catalytic cycle continues.^[9,10] The electrochemical reduction of methylene blue takes place via charge transport through the DNA base stack, and thus perturbations in base-pair stacking are repeatedly interrogated in this assay, rendering the electrocatalytic assay exquisitely sensitive to even the smallest disruptions in π stacking. Using this technique, we have detected all single base mismatches as well as several common DNA base damage products.^[10] Base-stacking perturbations are also detected within DNA/RNA hybrid duplexes.^[12] Furthermore, the electrochemical reduction of DNA intercalators bound to DNA-modified electrodes has been used to monitor DNA–protein interactions.^[13] Since this chemistry is extremely sensitive to very small changes in DNA base-pair stacking, we may exploit this assay more generally in probing

[*] Prof. J. K. Barton, E. M. Boon
Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, CA 91125 (USA)
Fax: (+1) 626-577-4976
E-mail: jkbarton@caltech.edu

Prof. J. Chattopadhyaya, P. I. Pradeepkumar, J. Isaksson, Dr. C. Petit
Department of Bioorganic Chemistry
Biomedical Center, University of Uppsala
751 23 Uppsala (Sweden)
Fax: (+46) 18554495
E-mail: jjyoti@boc.uu.se

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local perturbations in nucleic acid structure and stacking. Herein we describe the application of electrocatalysis at DNA-modified electrode surfaces to probe stacking in antisense oligonucleotides (AON) containing a 3'-endo-locked conformation. Figure 1 illustrates different duplex films that have been probed.

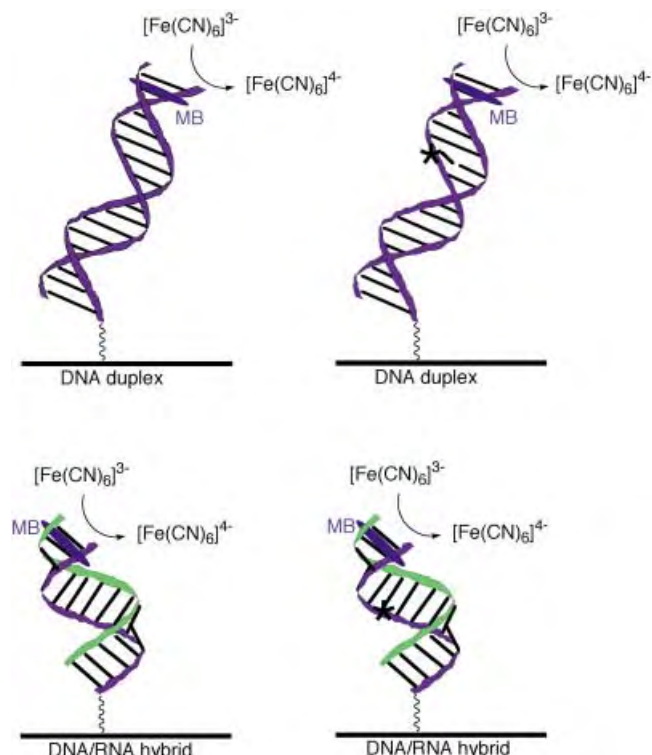
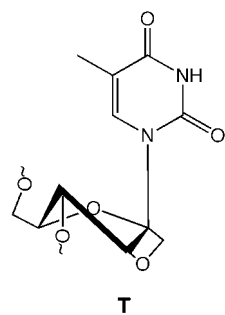


Figure 1. Schematic illustration of our electrocatalytic method to directly measure stacking in oligonucleotide duplexes. Here we probe the stacking of **T** (*) within a DNA (purple) scaffold and within a DNA(purple)/RNA(green) hybrid scaffold. Oligonucleotide duplexes are tethered to alkanethiol linkers and self-assembled onto Au electrode surfaces for use in electrochemical assays. Stacking is probed in a DNA-mediated charge transport reaction to reduce methylene blue (MB) that serves as a catalyst to reduce ferricyanide in solution. If stacking is disrupted, methylene blue is not efficiently reduced and less charge accumulates over the course of the catalytic assay.

Hybrid duplexes formed by AON containing one North-form (3'-endo) locked 1-(1',3'-O-anhydro-β-D-psicofuranosyl) thymine block **T** paired with RNA (AON/RNA heteroduplex) are completely inactive to cleavage by RNase H in four nucleotides to the 5' side of the conformationally constrained nucleotide.^[14] In fact, a single cleavage site can be engineered in a AON/RNA hybrid at the site of **T** incorporation.^[15] This protection from cleavage is proposed to result from the



formation of a local RNA/RNA fully A-form duplex conformation in the vicinity of **T** as opposed to a mixed DNA/RNA hybrid conformation. This result underscores the importance of knowledge of local conformation for antisense design and recruitment of RNase H. Furthermore, these studies lead to the suggestion that incorporation of a 3'-endo-type-locked nucleotide (typical for A-form duplexes) into a nucleic acid duplex leads to formation of a local A-form duplex which, if true, could lead to a junction in base-pair stacking.

Structural studies have also been performed on oligonucleotide duplexes containing **T** moieties.^[16] Circular dichroism (CD) spectra show that there is more distortion in a DNA/DNA duplex containing **T** than the corresponding DNA/RNA hybrid duplex. Furthermore, although a T_m drop of 6 °C/ **T** incorporation is observed, the Watson–Crick hydrogen bonding remains intact as is evident from ¹H NMR studies. This suggests that **T** is hydrogen-bonded in the duplex base stack and the T_m drop is likely the result of a change in the stacking geometry of the duplex, not loss of hydrogen bonding as with mismatches in DNA. Given the differing behavior in a DNA/DNA versus DNA/RNA duplex, it seems likely that this change in stacking geometry of the duplex is orchestrated by the sugar conformation.

These structural data coupled with the RNase H cleavage protection studies suggest that **T** may introduce a junction in the base-pair stacking of DNA. However none of these methods probe the base stacking of DNA directly. Charge transport through DNA, however, does provide a direct assay of base-pair stacking. Thus to determine whether **T** disrupts base-pair stacking within a DNA scaffold and within a DNA/RNA hybrid scaffold, we incorporated **T** into DNA-modified electrode surfaces and monitored the electrocatalytic efficiency in these films (Figure 1). Electrode surfaces modified with duplexes **1–12** (Table 1) were interrogated in electro-

Table 1. Oligonucleotides probed in this study.^[a]

	SH-5' GAAGAAAAATGAAG
1	CTTCTTTTACTTC
	SH-5' GAAGAAAAATGAAG
2	CTTCTTTTACTTC
	SH-5' GAAGAAAAATGAAG
3	CTTCTTTTACTTC
	SH-5' GAAGAAAAATGAAG
4	CTTCTTTTACTTC
	SH-5' GAAGAAAAATGAAG
5	CTTCTTTTACTTC
	SH-5' GAAGAAAAATGAAG
6	CTTCTTTTACTTC
	SH-5' GAAGAAAAATGAAG
7	CTTCTTTTACTTC
	SH-5' GAAGAAAAATGAAG
8	CTTCTTTTACTTC
	SH-5' AGTACAGTCATCGCG
9	TCATGTCAGTAGCGC
	SH-5' AGTACAGTCATCGCG
10	TCATGTCAGTAGCGC
	SH-5' AGTACAGTCATCGCG
11	tcatgtcagtagcgc ^[b]
	SH-5' AGTACAGTCATCGCG
12	tcatgtcagtagcgc

[a] SH-5' stands for SH(CH₂)₂CONH(CH₂)₆NHCO attached to the 5' OH of the DNA single strand. [b] Lowercase lettering indicates RNA.

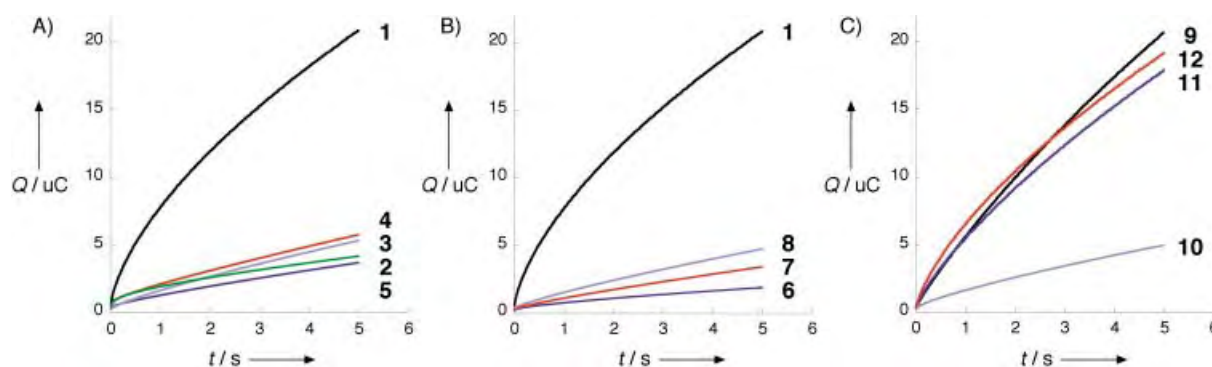


Figure 2. Electrochemical results for **T** incorporated into DNA-modified surfaces. Sequences 1–12 were self-assembled on clean gold electrode surfaces and used in electrocatalysis experiments.^[7–10] Chronocoulometric analyses took place at -350 mV with $0.5 \mu\text{M}$ methylene blue (MB) as the intercalated catalyst and 2.0 mM $[\text{Fe}(\text{CN})_6]^{3-}$ as the solution-borne substrate. A) Chronocoulometry plot (Q = charge) showing the results for **T** incorporated at a variety of positions within the duplex (sequences 1–5). Within a DNA/DNA duplex, **T** creates a stacking perturbation similar to a mismatch. B) Chronocoulometry plot showing the results for mismatches resulting in sequences 6–8, compared to the perfectly complementary native sequence 1. C) Chronocoulometry plot showing the results for **T** incorporated into DNA/DNA versus DNA/RNA modified surface, sequences 9–12. Within a DNA/DNA duplex, **T** creates a stacking perturbation (10), however, within a DNA/RNA duplex, stacking is normal (12).

catalytic chronocoulometric analyses at -350 mV (vs. SCE) with $0.5 \mu\text{M}$ methylene blue (MB) as the intercalated catalyst and 2.0 mM $[\text{Fe}(\text{CN})_6]^{3-}$ as the solution-borne substrate.^[9,10]

Figure 2A shows the results of **T** incorporation into DNA/DNA duplexes (sequences 1–5). In these DNA/DNA B-form duplexes, the current is attenuated, similarly to that in mismatch controls (Figure 2B). Thus these data suggest that incorporation of a 3'-endo constrained pentoribofuranose unit into a duplex where all other deoxyribose units are 2'-endo creates a *base stacking* perturbation.

We further explored this phenomenon by incorporating **T** into DNA/DNA homoduplexes versus DNA/RNA hybrid duplexes, as shown in Figure 2C. In the DNA/DNA homoduplexes (10) **T** again yields a diminution in integrated charge. However, upon incorporation of **T** into a DNA/RNA A-form heteroduplex (12), little diminution in integrated charge, consistent with little perturbation in stacking, is evident.

These electrochemical data are in excellent correlation with the RNase H protection studies^[14,15] and NMR results.^[16] The electrochemical data suggest that ribose conformation of a nucleotide moiety dictates its stacking in a duplex. In B-form DNA/DNA duplexes, the sugar conformation is normally 2'-endo. Thus when a nucleotide constrained to a 3'-endo-type conformation is incorporated into the duplex, the associated base assumes typical A-form stacking (and possibly transfers this conformation to four other neighboring nucleotides^[14]), which results in a stacking junction between the A- and B-form parts of the duplex. When **T** is incorporated into a hybrid duplex, where the conformation is between A- and B-form, but generally closer to A-form, this locked nucleotide is better accommodated by the neighboring nucleotides and does not lead to a stacking perturbation.

Thus, these observations suggest that the origin of the drive for helical order vis-a-vis disorder in determining the *local structure* of a nucleic acid duplex lies in the preferred nature of the sugar conformation, which can be designed, engineered, and enforced to orchestrate the helix-forming process. Importantly, these results illustrate the utility of DNA-mediated charge transport electrochemistry through DNA-

modified surfaces as a tool for directly probing DNA base pair stacking.

Experimental Section

Materials: All DNA synthesis reagents were obtained from Glen Research. Methylene blue and potassium ferricyanide were purchased from Aldrich and used as received. **T** was synthesized and incorporated into DNA by using a previously described procedure.^[17]

Preparation of DNA-modified surfaces: Thiol-modified oligonucleotides were prepared by using phosphoramidite synthesis as previously described. Thiol-terminated linkers were attached to single-stranded oligonucleotides, purified by HPLC, and hybridized to unmodified complements. These duplexes (0.1 mM) were then deposited on polycrystalline gold electrodes for 12–24 h, thoroughly rinsed with buffer, and used for electrochemical experiments.^[6–13] These surfaces were characterized by cyclic voltammetry, ellipsometry, radiolabeling of the duplexes, and atomic force microscopy. We have found that densely packed monolayers with a 45° orientation of the helical axis with respect to the gold surface are formed when no potential is applied to the electrode surface.^[7]

Electrochemical measurements: Chronocoulometry was carried out anaerobically (bubbling argon) on 0.02 cm^2 gold electrodes using a Bioanalytical Systems (BAS) Model CV-50W electrochemical analyzer. Buffer and electrolyte conditions were 5 mM sodium phosphate buffer containing 50 mM NaCl, pH 7, ambient temperature. A normal three-electrode configuration consisting of a modified gold-disk working electrode, a saturated calomel reference electrode (SCE, Fisher Scientific), and a platinum wire auxiliary electrode was used. The working compartment of the electrochemical cell was separated from the reference compartment by a modified Luggin capillary. Potentials are reported versus SCE.

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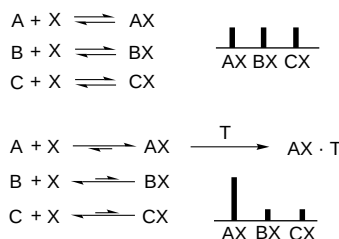
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Enzymatic Generation and In Situ Screening of a Dynamic Combinatorial Library of Sialic Acid Analogues**

Roger J. Lins, Sabine L. Flitsch,* Nicholas J. Turner,*
Ed Irving, and Stuart A. Brown

Dynamic combinatorial chemistry (DCC) is a rapidly emerging field which offers a possible alternative to the approach of traditional combinatorial chemistry (CC).^[1] Whereas CC involves the use of irreversible reactions to efficiently generate static libraries of related compounds, DCC relies upon the use of reversible reactions to generate dynamic mixtures. The binding of one member of the dynamic library to a molecular trap (such as the binding site of a protein) is expected to perturb the library in favor of the formation of that member (Scheme 1). Comparison of the "perturbed" library with that generated in the absence of the trap should indicate which members of the library are interacting with the trap, which effectively offers in situ screening of the combinatorial library.

The DCC concept has already been proven through the elegant experiments by several research groups, including those of Lehn and Sanders.^[1,2] However, significant experimental challenges remain before the method may be considered a practical complement to traditional CC. In

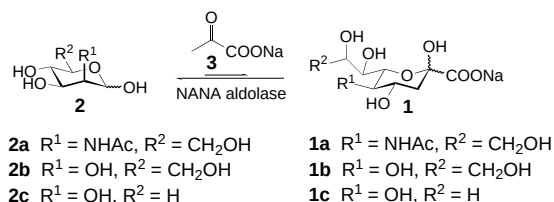


Scheme 1. The DCC concept: reversible reactions performed with a limiting amount of **X** generate a mixture of compounds **AX**, **BX**, and **CX**. The binding of **AX** to molecular trap **T** causes perturbation of the equilibria involving **A** and **X** to give overall amplification of **AX** at the expense of the other library members.

particular, the in situ screening, which is such an attractive feature of DCC, demands the use of conditions amenable both to the library-formation and -trapping stages. If the trap is envisaged as a protein or other biomolecule, the system is limited to aqueous and near-physiological conditions, with which few covalent bond forming reactions are compatible. Thus, for example, Lehn and co-workers have employed both imine and disulfide exchange reactions in DCC experiments involving biomolecular traps,^[2a] but to our knowledge no DCC experiment involving the formation of carbon-carbon bonds under physiological conditions has been performed.^[3]

We believe that enzyme-catalyzed reactions, which are characteristically reversible under physiological conditions, are ideally suited to the generation of dynamic combinatorial libraries. Many enzymes with broad specificity (required for library diversity) are already commercially available, and the application of modern techniques in directed evolution may be expected to increase their number. The products of an enzyme-catalyzed reaction are usually stable compounds; simple removal or inactivation of the enzyme stops the reaction, thus reducing the dynamic mixture to a static library which may be analyzed directly, without the need for a derivatization step to freeze the product distribution. Herein we present the first demonstration of DCC using enzyme catalysis for the generation of a dynamic library.

In considering the application of enzyme catalysis to DCC, we were encouraged by the thermodynamic resolution of a dynamic mixture of aldol products by Whitesides and co-workers through the use of a broad-specificity aldolase to effect reversible formation of carbon-carbon bonds under mild conditions.^[4] For the current investigation we chose a related enzyme, *N*-acetylneuraminic acid aldolase (NANA aldolase, EC 4.1.3.3), which catalyzes the cleavage of *N*-acetylneuraminic acid (sialic acid, **1a**) to *N*-acetylmannosamine (ManNAc, **2a**), and sodium pyruvate **3** (Scheme 2). In



Scheme 2. NANA aldolase catalyzes the cleavage of sialic acid **1a** to ManNAc **2a** and sodium pyruvate **3**; in the presence of excess sodium pyruvate, aldol products **1a-c** are generated from the respective substrates **2a-c**.

[*] Prof. S. L. Flitsch, Prof. N. J. Turner, Dr. R. J. Lins
Department of Chemistry
Edinburgh Protein Interaction Centre
The University of Edinburgh, King's Buildings
West Mains Road, Edinburgh EH9 3JJ (UK)
Fax: (+44) 131-650-4717 or (+44) 131-650-4743
E-mail: s.flitsch@ed.ac.uk
n.turner@ed.ac.uk

Dr. E. Irving, Dr. S. A. Brown
Ultrafine
Synergy House, Guildhall Close
Manchester Science Park, Manchester M15 6SY (UK)

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the presence of excess sodium pyruvate the equilibrium may be driven toward the formation of an aldol product, in which the enzyme will accept a range of reducing sugars as the electrophilic component. This stereoselective aldol reaction has been successfully employed in the efficient enzymatic syntheses of sialic acid and several related compounds.^[5] We envisaged the generation of a small dynamic library of aldol products **1a**, **1b** (ketodeoxynonulosonic acid, KDN), and **1c** (ketodeoxyoctulosonic acid, KDO) through the action of NANA aldolase on a mixture of the corresponding substrates **2a**, **2b** (D-mannose), and **2c** (D-lyxose).

Wheat germ agglutinin (WGA), a well-studied and readily available plant lectin,^[6] was chosen as the molecular trap. WGA is known to specifically bind sialic acid with modest (mM) affinity, with the diequatorial C-4 hydroxy and C-5 acetamido groups of sialic acid forming the primary recognition motif. We thus expected amplification of sialic acid to occur when the dynamic library containing sialic acid was generated in the presence of WGA.

Generation of the dynamic library proved straightforward; a mixture containing equimolar amounts of the three substrates **2a–c** and two equivalents of sodium pyruvate was incubated in the presence of NANA aldolase. Aliquots of the incubation mixture were withdrawn at intervals and analyzed by ion-exchange HPLC (Figure 1a, bottom). The three

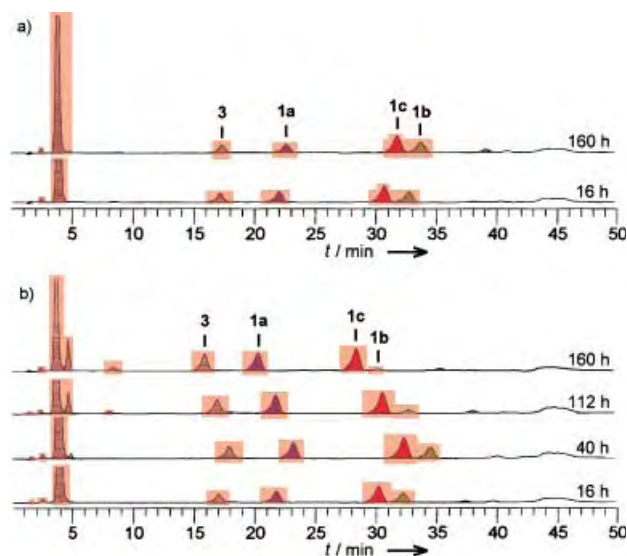


Figure 1. HPLC traces showing the change in concentration of sialic acid (**1a**, blue), KDN (**1b**, green), and KDO (**1c**, red) over time, for a) control incubation, b) incubation with WGA.

substrate sugars co-eluted with low retention times and did not give reproducible peak areas, presumably because of overlap with other variable-intensity peaks with low R_f values. The peak assigned to sodium pyruvate (**3**) was also variable in intensity; this peak was presumed to arise from the homoaldol product of sodium pyruvate, which was not expected to be stable under the elution conditions. The three aldol products gave reproducible peak areas, although absolute retention times were somewhat variable. As expected, the use of a small excess of sodium pyruvate resulted in low (15–40%) con-

version to the aldol products,^[7] and gave 2–5 mM concentrations of each. It was evident that the aldol reaction had reached equilibrium after 16 hours incubation, since the product distribution changed very little after this time.

Evidence that the enzyme does indeed catalyze both aldol formation and cleavage on the timescale employed was demonstrated by re-equilibrating a mixture of sialic acid and D-mannose in the presence of the NANA aldolase;^[8] after incubation overnight the mixture contained, in addition to the initial components, KDN and sodium pyruvate which could only arise through a retroaldol cleavage of sialic acid followed by aldol formation of KDN.

When the incubations were performed in the presence of WGA (sufficient lectin was added to provide at least one equivalent of binding sites, based on the amount of sialic acid formed in the control experiments) the product distribution was observed to change dramatically over time (Figure 1b). The system appears initially to approach a similar distribution to that observed in the control incubation, but thereafter the relative concentration of sialic acid is seen to increase, with a corresponding drop in the relative concentration of KDN. A plot of the percentage amplification in the relative concentration (as estimated from relative peak area) of each aldol product over controls is shown in Figure 2; the peak assigned

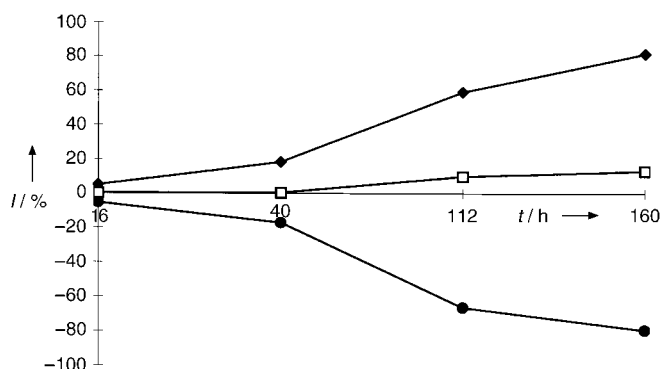


Figure 2. Time course for a three-component system showing the relative amplification of sialic acid (◆), KDO (□), and KDN (●).

to sialic acid contributed approximately 40% of the total aldol product peak area after 160 hours in the presence of WGA, but only 22% of the total aldol product peak area in the control mixture at the same time point. This difference corresponds to a relative amplification of about 80%. Conversely, the contribution of KDN to the total aldol product peak area after 160 hours was 31% in the control incubation, but only 6% in the presence of WGA; this difference corresponds to a relative suppression of 80%.

The observation that KDN and KDO were not suppressed to the same extent might be a consequence of WGA having a weak binding affinity for KDO, such that the latter species may also experience some measure of relative amplification during incubation in the presence of the lectin. In effect, the extent of relative amplification observed in the above experiment suggests a ranking order of the three components based on the relative affinities of WGA for each of them. In this case, the two-component DCC experiment involving only KDN and KDO should demonstrate some degree of ampli-

fication of KDO, while that involving only sialic acid and KDN should show amplification of sialic acid over KDN, with the extent of amplification being greater in the latter experiment. The data from these two-component experiments are shown in Figure 3, bottom; they show dramatic relative

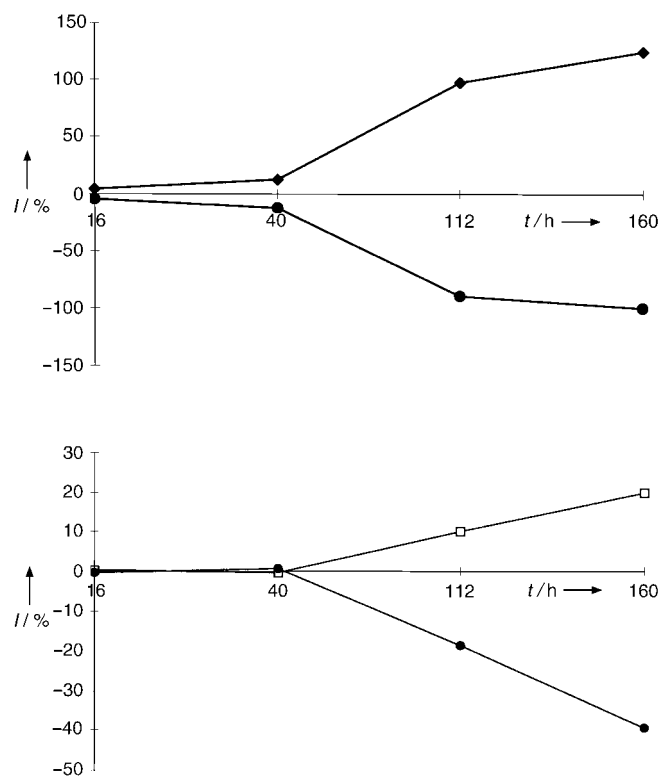


Figure 3. Time courses for two-component DCC experiments showing: top: relative amplification of sialic acid (◆) over KDN (●), bottom: relative amplification of KDO (□) over KDN (●).

amplification of sialic acid over KDN, but more modest relative amplification of KDO over KDN when sialic acid is not present. Since all three experiments showed suppression of KDN, it was necessary to exclude the possibility that this component was being affected by a selective aldolase activity associated with the lectin preparation. Thus, a mixture of sodium pyruvate, mannose, manNAc, sialic acid, and KDN, in proportions approximating their equilibrium distribution in the two component control experiment, was prepared from commercial samples and incubated in the presence of WGA (but not NANA aldolase). No change from the initial distribution was observed, which demonstrates that the changes in product distribution observed in the DCC experiments were caused by WGA acting as a thermodynamic trap, and not as a selective catalyst for KDN degradation.

In conclusion, we have successfully demonstrated, for the first time, the generation and in situ screening of a dynamic mixture of biologically significant compounds, where enzyme catalysis has been used to effect reversible formation of carbon–carbon bonds under physiological conditions. We believe this work can be extended to larger libraries through the use of broad-specificity enzymes, which represent a powerful (and hitherto overlooked) tool for the development

of dynamic combinatorial chemistry; we are currently looking to increase the size of the library, to adapt the system for the identification of novel ligands such as neuraminidase inhibitors, and to develop multienzyme systems for the generation of dynamic libraries with increased diversity.

Experimental Section

N-acetylneuramic acid aldolase (EC 4.1.3.3, 22.2 U mg⁻¹) and wheat germ agglutinin (lyophilized powder) were purchased from ICN Biomedicals. The following stock solutions were prepared in 0.05 M potassium phosphate (KPi) buffer, pH 7.5: aldolase stock (20 U mL⁻¹); wheat germ agglutinin stock (50 mg mL⁻¹); sugar stock solutions containing sodium azide (0.5 g L⁻¹); 0.1 M sodium pyruvate; and 0.05 M each of ManNAc, D-mannose, and D-lyxose (solution A), ManNAc and D-mannose (solution B), or D-mannose and D-lyxose (solution C).

Incubation mixtures A–C contained enzyme stock (10 μL), WGA stock (20 μL), and sugar stock A, B, or C (10 μL), respectively. Controls contained enzyme stock (10 μL), 0.05 M KPi buffer (20 μL), and sugar stock A, B, or C (10 μL). After centrifugation (1 min@3000 rpm), the solutions were incubated at 37°C without stirring. Aliquots (5 μL) were withdrawn at intervals, diluted to 500 μL with milli-Q water, and immediately analyzed by HPLC.

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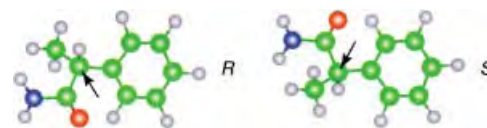
Discriminating Chiral Molecules of (*R*)-PPA and (*S*)-PPA in Aqueous Solution by ECSTM**

Qing-Min Xu, Dong Wang, Li-Jun Wan,*
Chen Wang, Chun-Li Bai,* Guo-Qiang Feng, and
Mei-Xiang Wang*

Chiral discrimination is one of the most attractive areas in chemistry because of the important applications of chiral molecules in catalysis and stereoselective synthesis. A feasible approach to chiral discrimination is the use of solid surfaces modified with chiral molecules.^[1–4] The scanning tunneling microscope (STM) is a powerful tool to reveal molecular structures on solid surfaces with atomic resolution in real space.^[5–8] Recently, STM has been successfully applied to determine the conformation and chirality of individual molecules on metal and semiconductor surfaces under ambient and ultra-high vacuum (UHV) conditions.^[9–15] Lopinski et al. determined the absolute configuration of isolated chiral centers of alkene molecules chemisorbed on Si(100) in UHV.^[10] Böhringer et al. observed the chiral packing of 1-nitronaphthalene (NN) molecules on a reconstructed Au(111) surface and found a coverage-driving chiral phase transition at low-temperature.^[11,12] Lorenzo et al. investigated the adsorption of tartaric acid molecules on a Cu(110) surface which result in formation of a chiral surface with the chiral channels by hydrogen-bonding interactions between the OH groups of the molecules.^[14,15] Ohtani et al. took advantage of the self-assembling and covalent-binding properties of 1,1'-binaphthalene-2,2'-dithiol (BNSH) molecules and fabricated a self-assembled monolayer (SAM) on Au(111); the chirality of BNSH molecules in the SAM was revealed under ambient conditions.^[13] However, most chiral molecules are in solution when chemical reactions take place. Therefore, imaging chiral molecules in solution is one of the most significant issues in discriminating chirality. This task represents a challenge to electrochemical STM (ECSTM).^[5–8] ECSTM can work in solution without the use of UHV or low temperature and allows the observation of molecules without being hindered by limitations such as solubility and evaporative properties. The application of ECSTM to chiral discrimination may result in a simple and routine analytical method.

For the first time, we have demonstrated that chiral molecules can be discriminated in aqueous solution. The discrimination was carried out by using ECSTM in the

adlayers of enantiomeric molecules ((*R*)- and (*S*)-2-phenylpropionamide (PPA; C₉H₁₁ON) on Cu(111) in 0.1M HClO₄. These compounds are used in the chemical and pharmaceutical industries. Scheme 1 shows their chemical structures



Scheme 1. Chemical structure of (*R*)- and (*S*)-2-phenylpropionamide molecules (hyperchem software).

generated by hyperchem software and optimized by an AM1 method to a root-mean-square value of less than 0.01 kcal Å⁻¹. The parameters for the molecules such as interatomic distances were estimated from the models. The chiral centers in the molecules are indicated by arrows. Cu(111) was used as a solid substrate for the molecular adsorption. Although fcc(111) is not a chiral surface, the chiral nature of the molecules makes the discrimination possible. The adsorption of (*R*)- and (*S*)-PPA molecules results in the same ordered structures with a (4 × 4) symmetry in the double-layer potential region. The structural details of the *R* and *S* molecules differ from each other because of chirality, although the applied potentials are the same. The chirality can clearly discriminated in high-resolution STM images (see below).

Both (*R*)- and (*S*)-PPA molecules form well-ordered adlayers on the Cu(111) surface in solutions. Figure 1 shows a typical STM image of (*R*)-PPA on Cu(111). It can be seen that the molecules form a highly ordered adlayer and yield a completely different pattern from Cu(111)-(1 × 1). One direction of molecular rows, indicated by arrow A, runs along the Cu(111)-[110] direction with a period of 0.96 ± 0.02 nm which corresponds to four times the Cu(111) lattice length. In direction B a period of 0.96 ± 0.02 nm (i.e. four times the Cu(111) lattice) is measured. The angle between A and B is 120° ± 2°. On the basis of intermolecular distance and orientation of molecular rows, a (4 × 4) structure for the adlayer can be determined. A unit cell is outlined in Figure 1 a.

The adlayer structure of (*S*)-PPA molecules on Cu(111) in 0.1M HClO₄ is the same as that of (*R*)-PPA molecules in a (4 × 4) symmetry array (Figure 2; a unit cell is also outlined in the image. The directions C and D are along the close-packed Cu(111) lattice and make an angle of 120 ± 2°).

The results described above show that the adlayer symmetry is independent of the chirality. To understand the electrochemical behaviors of (*R*)- and (*S*)-PPA on Cu(111) in 0.1M HClO₄ solution, a bare Cu(111) electrode was initially examined by cyclic voltammetry in 0.1M HClO₄ for comparison with published data.^[16] After the examination, the electrode was transferred into saturated 0.1M HClO₄ solutions of (*R*)- and (*S*)-PPA. The overall shape of the cyclic voltammograms of (*R*)- and (*S*)-PPA (not shown) is almost the same as that of bare Cu(111). The adsorption of the two molecules results in the formation of a featureless double-layer region which can be detected as a small electric charge in the cyclic voltammograms. This effect indicates the molecular adsorption onto Cu(111) in 0.1M HClO₄. After recording the

[*] Prof. Dr. L.-J. Wan, Prof. Dr. C.-L. Bai, Prof. Dr. M.-X. Wang,
Dr. Q.-M. Xu, D. Wang, Prof. Dr. C. Wang, G.-Q. Feng
Institute of Chemistry
The Chinese Academy of Sciences
Beijing 100080 (China)
Fax: (+86) 10-62558934
E-mail: wanlijun@infoc3.icas.ac.cn
clbai@infoc3.icas.ac.cn

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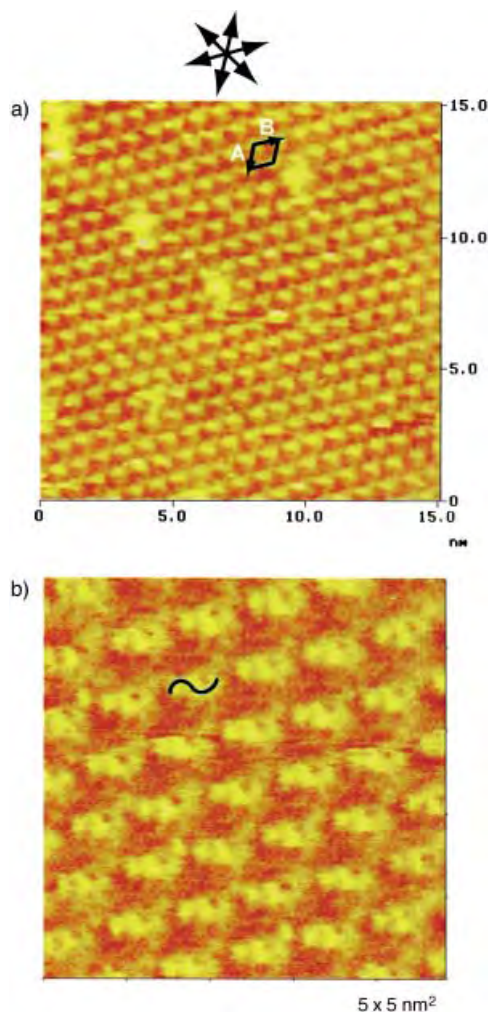


Figure 1. a) In situ STM images of (*R*)-PPA molecules on Cu(111) in 0.1M HClO₄. The image was recorded at 0 V. b) Expansion of (a), ~ indicates the shape of an (*R*)-PPA molecule.

images shown in Figure 1 and Figure 2 at 0 V, the electrode potential was stepped from -0.2 to 0.2 V in increments of 10 mV. A set of STM images of the two molecular adlayers was acquired at different potentials during the potential steps. Similar images with the same molecular features were consistently observed. The structures of both (*R*)- and (*S*)-PPA adlayers were stable in the potential region from -0.2 to 0.2 V, which indicates the same adsorption behavior of the chiral molecules at the liquid/solid interface.

However, the structural details of the two molecules can be seen by the comparison of Figure 1b and 2b. Instead of a “~” shape in Figure 1b for each (*R*)-PPA molecule, the (*S*)-PPA molecules appear in the “ω” shape shown in Figure 2b. We have tried to rotate and translate Figure 1b and 2b, but the molecular images can not be superimposed. The existence of the mirror-images indicates that the adsorbed molecules preserve their chiral nature and create 2D chiral surface on the Cu(111) surface.

The adsorbed molecules consist of a phenyl ring, methyl, and CONH₂ groups. The chiral feature of the molecules arise from the arrangement of methyl and CONH₂ groups. To reveal the internal molecular structure in the 2D chiral

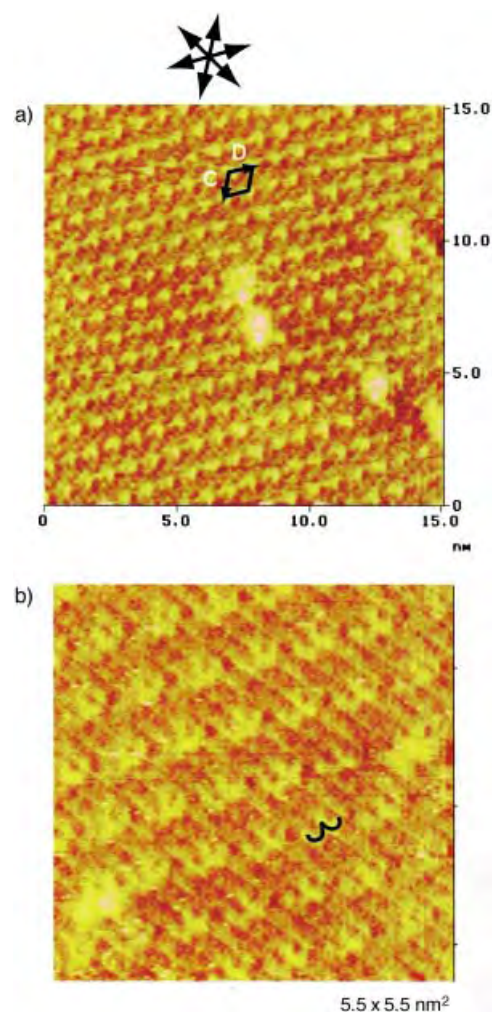


Figure 2. a) In situ STM images of (*S*)-PPA molecules on Cu(111) in 0.1M HClO₄. b) Expansion of (a) ω indicates the shape of an (*S*)-2-PPA molecule. Images acquired at 0 V by using the same imaging conditions as for Figure 1.

surfaces, higher-resolution STM images were acquired under carefully adjusted experimental conditions with minimal drift. Figure 3a shows one of the highest resolution images recorded on the (*R*)-PPA adlayer. Each molecule appears as three bright spots and a “Y” shape tail. According to the previous results, the three bright spots are attributed to a phenyl ring lying flat on a threefold hollow site of the Cu(111) lattice.^[17,18] The tail is attributed to methyl and CONH₂ groups of the chiral center. Based on the chemical structure and measured distance, M and N shown in Figure 3a correspond to the methyl and CONH₂ groups, respectively; a structural model for the (*R*)-PPA SAM is proposed in Figure 3b. In the model, the (*R*)-PPA SAM has a (4×4) structure. The phenyl rings are parallel to the Cu(111) surface and positioned in hollow sites. The amino, carbonyl and methyl groups occupy two-bridge sites.

It is intriguing to see the chirality in (*S*)-PPA adlayer. Figure 4a is one of the higher-resolution images recorded on the (*S*)-PPA adlayer. Although a great effort was made to acquire a high quality image, it was found that the image of (*S*)-PPA is not as good as that for (*R*)-PPA. This is attributed to the adsorption geometry. However, the image features for

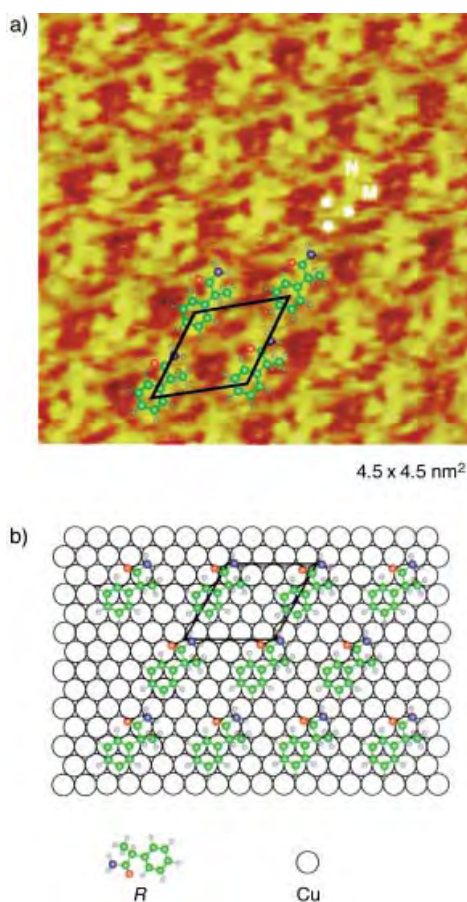


Figure 3. a) High resolution STM image of (*R*)-PPA molecules on Cu(111) in 0.1M HClO₄. b) A proposed model of (*R*)-PPA molecules with a structure of (4 × 4) symmetry.

an (*S*)-PPA molecule can still be seen in Figure 4a. The structural details are almost the same as those shown in Figure 3a, and include a three-spot phenyl ring and a “Y” shape tail. M' and N' indicate the methyl and CONH₂ groups. The molecular chirality is directly expressed in the STM image. The distances between the center of the amino group and the chiral center, and between the center of the methyl group and the chiral center, are measured to be around 0.23 nm and 0.15 nm, respectively, close to the distances in the molecule and equal to those distances in Figure 3a. A structural model for the (*S*)-PPA adlayer is illustrated in Figure 4b. Compared with the two structures of (*R*)-PPA and (*S*)-PPA in Figure 3 and 4, the chirality is clearly seen from the arrangement of the methyl and CONH₂ groups. The present results demonstrate that chirality can be discriminated by ECSTM. However, the substrate material plays an important role in molecule adsorption. Different structures could be obtained on different substrate materials and crystallographic surfaces. In electrolyte solution, protonation of the molecule will vary with solution pH value. Therefore, to generalize the observations on a substrate such as Cu(111), a systemic study of chirality on other substrates such as Au(111), Pt(*hkl*), and HOPG in various solutions is necessary. A more detailed study is now in progress.

In summary, the chirality of (*R*)-PPA and (*S*)-PPA molecules has been observed on Cu(111) in solution by using

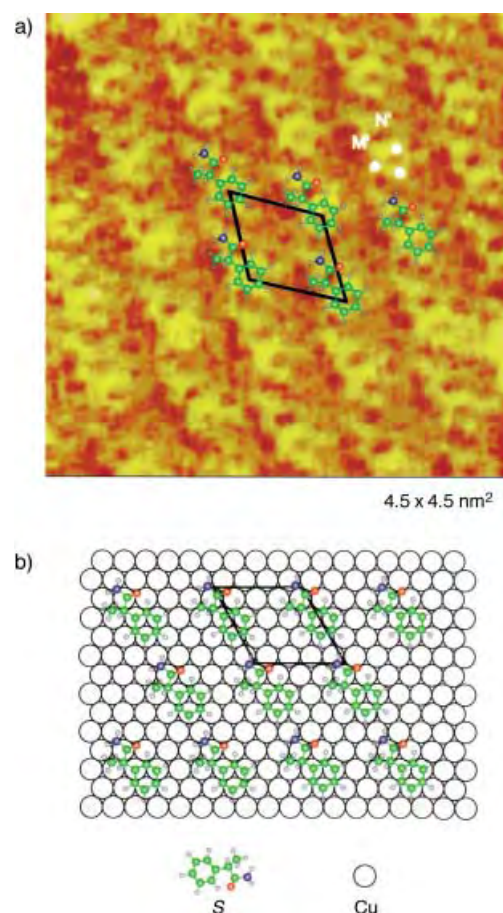


Figure 4. a) High resolution STM image of (*S*)-2-PPA molecules on Cu(111) in 0.1M HClO₄. b) A proposed model of (*S*)-PPA molecules with a structure of (4 × 4) symmetry.

ECSTM. Although the two molecules adsorb on Cu(111) in the same (4 × 4) symmetry, the molecular arrangements are different to each other. The chirality of the two molecules, which arises from the orientation of the methyl and CONH₂ groups, can be directly seen in higher-resolution STM images. The principle used here may be relevant for the development of a simple method for discriminating chiral molecules in aqueous solution.

Experimental Section

A commercial Cu(111) single-crystal disk with a diameter of 10 mm (from MaTeck) was used as a working electrode for in situ electrochemical STM observation. A well-defined single-crystal surface was prepared as described in the literature.^[16] A solution of 0.1M HClO₄ was prepared by diluting ultrapure HClO₄ (Cica-Merck, Kanto Chemicals) with ultrapure Millipore water. Solutions of 0.1 mM synthesized (*R*)- and (*S*)-2-phenylpropionamide were prepared with ultrapure Millipore water. The home-made electrochemical cell contained a reversible hydrogen electrode (RHE) in 0.1M HClO₄ and a Pt counter electrode. All electrode potentials are reported with respect to the RHE.

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Thermotropic Liquid Crystals from Planar Chiral Compounds: Optically Active Mesogenic [2.2]Paracyclophane Derivatives**

Elena L. Popova, Valeria I. Rozenberg, Zoya A. Starikova, Susanne Keuker-Baumann, Heinz-Siegfried Kitzerow, and Henning Hopf*

Chiral liquid-crystalline (LC) compounds constitute a central topic of present-day research on liquid crystals. For example, not only are the well-established applications of thermochromic materials as well as twisted nematic (TN) and supertwisted nematic (STN) displays based on chirality, but so are ferro-, ferri-, and antiferroelectric, second-harmonic

generation, polymer-stabilized cholesteric texture (PSCT) displays and certain photonic crystals. Thus, new chiral structures are continuously proposed that provide new insights and promising applications.^[1]

The way in which chirality is introduced into the mesogenic molecule is one of the crucial factors in determining the properties of the resultant LC material. The importance of the position of the stereogenic unit relative to the liquid-crystalline core is underlined by the fact that it forms the basis for a classification system for chiral LC compounds.^[2] Most chiral mesogenic compounds are classified as Type I or Type II liquid crystals. In the former case chirality is introduced through an asymmetric carbon atom located in a terminal alkyl chain, whereas in the latter it is enclosed between two liquid-crystalline core units. These LC compounds have been well-studied and widely used. In Type III liquid crystals, the chiral unit is incorporated into the rigid core itself, and is thus particularly applicable to planar and axially chiral compounds. Although properties which are important for practical application have been predicted for materials of this type (for example, shortening of helical pitch length, increase in spontaneous polarization of a chiral dopant, as well as interesting optical effects^[3]), planar, chiral liquid-crystalline compounds still remain relatively unexplored.

The molecular complexity of the structural unit necessary to generate an axis or a plane of chirality often creates serious obstacles to achieving stable mesomorphic properties. Only a few examples of planar and axially chiral mesogens have so far been reported. These include: cyclohexylideneethanone^[4] and allene derivatives,^[5] chiral biphenyls,^[6] and iron-tricarbonyl-butadiene complexes.^[7] Additionally, the first 1,3-unsymmetrically disubstituted optically active LC ferrocene derivative has recently been reported.^[8] However, in most of these cases the mesophases only had a narrow temperature interval and several of the compounds obtained appear to be chemically or photochemically unstable. Moreover, the difficulties of synthesis and optical resolution associated with these derivatives are probably the reason for the lack of systematic studies on the physical properties of planar and axially chiral compounds as well as of their practical application.

In our opinion, the ease of functionalization, ready optical resolution, and high configurational stability of paracyclophane (PC) derivatives^[9] make these bridged aromatic compounds unique candidates for chiral LC materials.

In our first attempt to investigate the ability of the PC unit to promote mesomorphism we used several racemic derivatives.^[10] As shown by these exploratory investigations, the mesogenic potential of the PC core depends on the number and position of substituents in the PC moiety: of the structures investigated, *para*-substituted PC derivatives had superior mesogenic properties with a broad interval of either nematic or smectic A (SmA) phases. Herein we describe the first family of optically active mesogenic compounds containing a PC unit. Several synthetic problems had to be solved to prepare the required chiral PC precursors.

As mentioned above, *para*-substitution of the PC moiety was shown to best induce mesomorphism,^[10] but known examples of specific *para*-PC derivatives are still scarce and a

[*] Prof. Dr. H. Hopf, Dr. E. L. Popova
Institut für Organische Chemie
Technische Universität Braunschweig
Hagenring 30, 38106 Braunschweig (Germany)
Fax: (+49)531-391-5388
E-mail: h.hopf@tu-bs.de

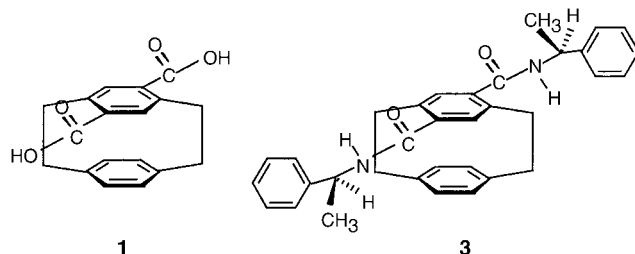
Prof. Dr. V. I. Rozenberg, Z. A. Starikova
A. N. Nesmeyanov Institute of Organoelement Compounds
Russian Academy of Sciences
Vavilova 28, 117813 Moscow (Russia)
S. Keuker-Baumann, Prof. Dr. H.-S. Kitzerow
Fachbereich Chemie
Universität Paderborn
Warburger Strasse 100, 33098 Paderborn (Germany)

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general synthetic approach to such structures is not yet available. We decided to use PC carboxylic acids, rather than the possible (and available) PC phenols or aldehydes, as the most promising starting materials to construct LC compounds. However, little is known about chiral (and optically active) PC carboxylic acids; for example, only [2.2]paracyclophane-4-carboxylic acid has been reported in an optically active form.^[11]

Optical resolution of [2.2]paracyclophane-4,7-dicarboxylic acid ((±)-**1**)^[10] was performed with (*S*)-phenylethylamine



(PEA) through formation of the diastereomeric salt (–)-**2**. The enantiomeric excess (*ee*) of (–)-**1** was determined by converting it into the corresponding amide (–)-**3** with (*S*)-PEA. As a consequence of the known stability of PC derivatives,^[9] we assume that the reactions used to prepare (–)-**3** did not alter the optical purity of diacid (–)-**1**. Therefore, the determination of the diastereomeric excess (*de*) of (–)-**3** is a measure of the *ee* value of (–)-**1**, and was accomplished by ¹H NMR spectroscopy.^[12]

Elaborate resolution techniques provided (–)-**1** with *ee* - values greater than 96% in 55% yield.^[13] Additionally, an analytical sample of diacid (–)-**1** of greater than 99% *ee* was obtained and characterized. Crystallization of the salt (–)-**2** from methanol provided crystals suitable for X-ray analysis, which revealed an *R* configuration of (–)-**1** (Figure 1).^[14]

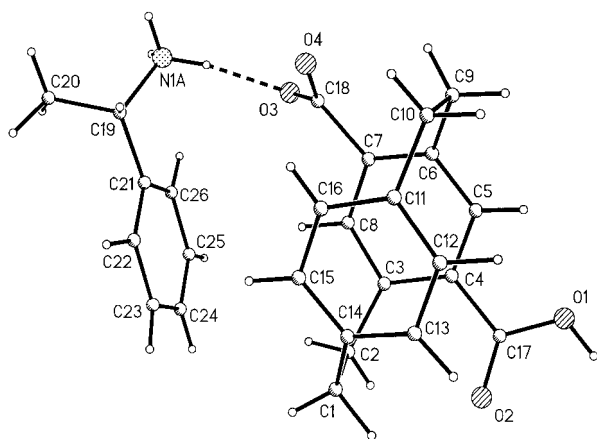


Figure 1. Structure of the diastereomeric salt derived from (*S*)- α -phenylethylamine and (*R*)-**1** as revealed by X-ray analysis.

Derivatization of diacid (*R*)-**1** to provide an elongated rigid rodlike molecular shape led to liquid-crystalline PC derivatives **4a–d** (Figure 2). Their mesomorphic behavior was studied by means of differential scanning calorimetry (DSC) and polarized optical microscopy (PLM). These studies

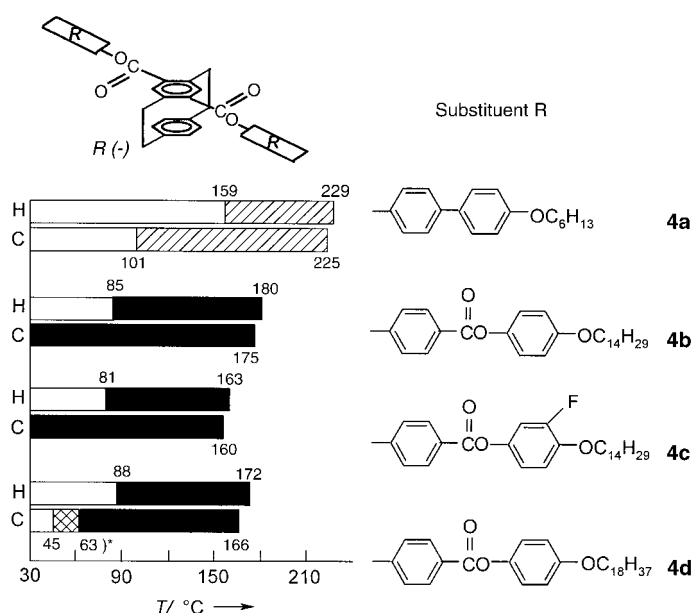


Figure 2. Phase-transition temperatures of optically active PC derivatives **4a–d**. H or C denotes a heating or cooling cycle, respectively. □: crystalline solid; ///: chiral nematic (cholesteric) phase; ■: chiral smectic A phase; ××: chiral smectic C phase. *: transition observed by means of PLM only.

revealed an excellent mesogenic potential of the PC core that is unusual and not predictable for molecules containing such bulky units (intraannular distances of the PC moiety is about 3.09 Å). The type of mesophase could be tuned by changing the nature of the substituents in the PC unit: a cholesteric phase was detected for **4a**, while compounds **4b–d** revealed enantiotropic SmA* phase behavior over a broad temperature interval. The formation of a monotropic smectic C* (SmC*) phase was also clearly detected by PLM for the longer-chain derivative **4d**: at the SmA*–SmC* transition, the dark homeotropic domains of the SmA* phase gives rise to a schlieren texture characteristic of the SmC* phase. The influence of lateral functionalization with fluorine atoms on the stability of the smectic phases was also investigated (**4c**). Relative to the unsubstituted analogue **4b**, introduction of the lateral fluorine atom insignificantly lowers the melting point and causes a 13 °C reduction of the mesophase interval, but this, however, still remains quite broad. Thus, when tailored properly (the SmC* phase gives rise to ferroelectric properties), structures of such a type can be considered as candidates for ferroelectric studies. The search of tilted smectic phases from PC-derived liquid crystals is currently underway.

The results presented in Figure 3 indicate values of the helical twisting power (HTP) obtained for compounds **4a–d** in a commercial nematic mixture, MLC 6260 (Merck, Darmstadt, Germany). These results reveal a sufficiently high twisting ability of the investigated compounds—the values obtained are comparable to that of commercially used chiral dopants such as 4-cyano-4'-(2-methylbutyl)-biphenylene (CB 15, 6.7 μm^{–1} at room temperature^[15]). As a result of the high values of the helical twisting power, mixtures of the chiral compounds with a nematic component show selective reflection (Figure 4), which indicates that the pitch of the respective mixture is not larger than a few hundred nanometers. Of

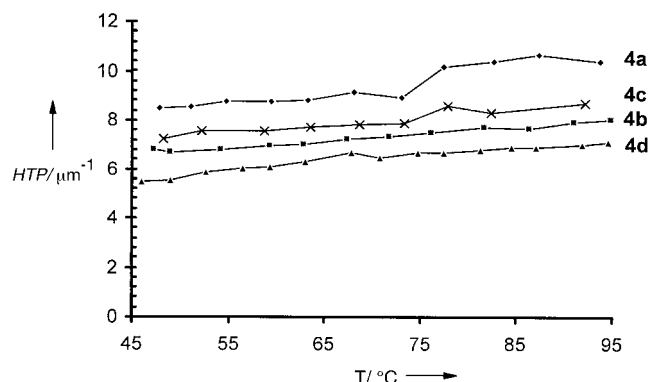


Figure 3. Helical twisting power of the investigated optically active compounds **4a–d** versus temperature. The compounds induce the formation of left-handed helices.

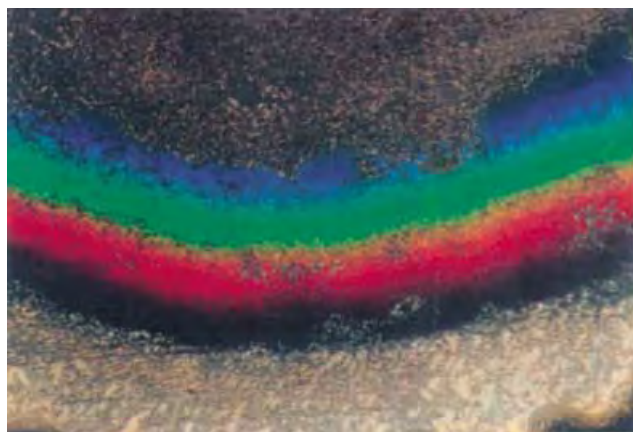


Figure 4. Selective reflection in a contact preparation between compound **4a** and the nematic mixture MLC 6260. The color of the selective reflection changes according to Bragg's law because of a gradient of the concentration, which in turn leads to a variation of the helical pitch.

course, the values of the HTP obtained are much lower than those of the highest HTP values ever observed in nematic mixtures, such as for binaphthol derivatives (up to about $100 \mu\text{m}^{-1}$)^[16] or TADDOLs ($300\text{--}400 \mu\text{m}^{-1}$).^[17]

In our opinion, the compounds presented (**4a–d**) demonstrate the principle of high twisting ability of planar chiral compounds. However, the structure could be further optimized: a PC unit which in this case protrudes from the overall linear molecule probably disrupts interaction between the chiral dopant and the nematic host; to overcome this problem PC derivatives bearing linear functionalizations on both decks of the PC unit are currently under investigation.

In conclusion, a family of mesogenic planar chiral compounds based on [2.2]paracyclophane have been introduced. Their availability and stable mesomorphic behavior permit the work presented here to be considered as a promising background for the study of the physical properties of this new type of liquid crystals, which up until now have remained mostly in the focus of theoretical predictions rather than practical investigations.

Experimental Section

Optical resolution of $(\pm)\text{-1}$:^[14] Racemic **1** (0.40 g, 1.35 mmol) was suspended in acetone (15 mL) and then the resulting suspension was

heated to reflux and treated with (*S*)-PEA (0.36 mL, 2.80 mmol). The salt begins to precipitate in a few min; afterwards acetone (17 mL) was added to the reaction mixture and the resulting suspension was refluxed for 5 h, before it was cooled and allowed to stand overnight at room temperature. The precipitate was filtered, dried (0.27 g), and then combined with the acetone/chloroform (5:1) mixture (12 mL); the resulting suspension was refluxed for 2 h and left to stand overnight at room temperature. Filtration and drying of the precipitate afforded 0.21 g of $(-)\text{-2}$. The salt was dissolved in the minimum amount of methanol and hydrolyzed with 2N HCl. The precipitate was filtered off and thoroughly washed with water to yield 0.11 g (55 %) of $(-)\text{-1}$ in $>96\%$ ee.

A sample of $(-)\text{-2}$ was additionally crystallized from an acetone/methanol mixture (1:1). Hydrolysis of the salt as described above provided $(-)\text{-1}$ of $>99\%$ ee. $[\alpha]_{\text{D}}^{20} = -269.0$ ($c = 0.25$ in methanol). Elemental analysis calcd for $\text{C}_{18}\text{H}_{16}\text{O}_4$ (296.322): C 72.96, H 5.44; found: C 72.82, H 5.41. (All spectral data are identical with those of racemic **1**).^[10]

Transition temperatures were determined with a differential scanning calorimeter Rheometric Scientific DSC SP, scanning rate 10 K min^{-1} , under nitrogen. Optical studies were conducted by using an Olympus BX 50 System Microscope equipped with a Linkam-LTS-350 variable-temperature stage. HTP was measured by means of the Cano method^[18] in a commercial nematic mixture (MLC 6260; Merck, Darmstadt, Germany).^[14] The mass fraction of the dopant was varied up to $x = 0.1$.

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- [14] Crystal structure determination of $[\text{C}_8\text{H}_{12}\text{N}]^+[\text{C}_{18}\text{H}_{15}\text{O}_4]^-$: $\text{C}_{26}\text{H}_{27}\text{NO}_4$ ($M_r = 417.49$), $0.5 \times 0.3 \times 0.2 \text{ mm}$, monoclinic, space group C2 (no. 5), at 163 K, $a = 20.503(9)$, $b = 7.028(3)$, $c = 14.943(5) \text{ Å}$, $\beta = 97.04(3)^\circ$, $V = 2137.0(15) \text{ Å}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.298 \text{ g cm}^{-3}$, $\mu = 0.087 \text{ mm}^{-1}$, $F(000) = 888$. Single-crystal X-ray diffraction experiments were carried out with a Syntex P2₁ instrument, using graphite monochromated

Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$, $\theta/2\theta$ scans, $2\theta < 56^\circ$) at 163 K. A total of 3466 reflections were measured, 2908 ($R_{\text{int}} = 0.0364$) independent reflections were used in further calculations and refinement. The structure was solved by direct methods and refined by the full-matrix least-squares method against F^2 with anisotropic (for non-hydrogen atoms) and isotropic (for H atoms) approximation. The refinement converged to $R1 = 0.0632$ (from 1914 unique reflections with $I > 2\sigma(I)$) and $wR2 = 0.1591$ (from all 2795 unique reflections), the number of the refined parameters is 388, GOF = 1.022. All calculations were performed on an IBM PC/AT using the SHELXTL software (G. M. Sheldrick, SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI, 53719, USA). CCDC-182770 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Color-Tunable Transparent Mesoporous Silica Films: Immobilization of One-Dimensional Columnar Charge-Transfer Assemblies in Aligned Silicate Nanochannels**

Akihiro Okabe, Takanori Fukushima, Katsuhiko Ariga, and Takuzo Aida*

Charge-transfer (CT) complexes in solution and in the crystalline state have attracted much attention in the fields of organic chemistry, photochemistry, solid-state physics, and so forth.^[1] For a variety of applications utilizing CT complexes, long-range structural ordering of donor/acceptor assemblies would be important. From this point of view, dislike molecules that form columnar phases are potential candidates for the formation of infinite, one-dimensional CT assemblies, which may be useful for optoelectronic applications including photoconductive materials, solar cells, and thin-film transistors.^[2] Triphenylene derivatives are representative of those molecules whose columnar phase is known to be stabilized upon complexation with suitable acceptors.^[3] Immobilization of such columnar CT assemblies in optically transparent solid

supports would be of great interest for materials science and device fabrication. Mesoporous silicates are particularly interesting^[4] because they can provide highly ordered, unidirectional channels that are optimal for the long-range structural ordering of CT assemblies. Here we report the fabrication of novel mesostructured silica films by using triphenylene-based CT complexes as templates for sol–gel synthesis. The films were highly transparent and color-tunable from blue to red depending on the nature of the intercalating electron acceptor, and showed red-shifted CT absorption bands in the aligned silica nanochannels.

Amphiphilic triphenylene derivatives **1** and **2** were found to form CT complexes with electron acceptor molecules such as 2,4,7-trinitro-9-fluorenone (TNF), 2,3,6,7,10,11-hexacyano-hexaazatriphenylene (HAT), 7,7,8,8-tetracyanoquinodimethane (TCNQ), chloranil (CA), and 1,2,4,5-tetracyanobenzene (TCNB, Figure 1). A typical procedure for the fabrication of mesostructured silica films is as follows: **1** (35.8 mg, 16.8 μmol) was added to a solution of TNF (5.28 mg, 16.8 μmol) in benzene, and the mixture was evaporated to leave a brown residue, which was then dissolved in a mixture of EtOH (1.18 g), 12N hydrochloric acid (6.18 mg), and water (81 mg). Tetrabutoxysilane (TBOS; 324 mg, 1.01 mmol) was

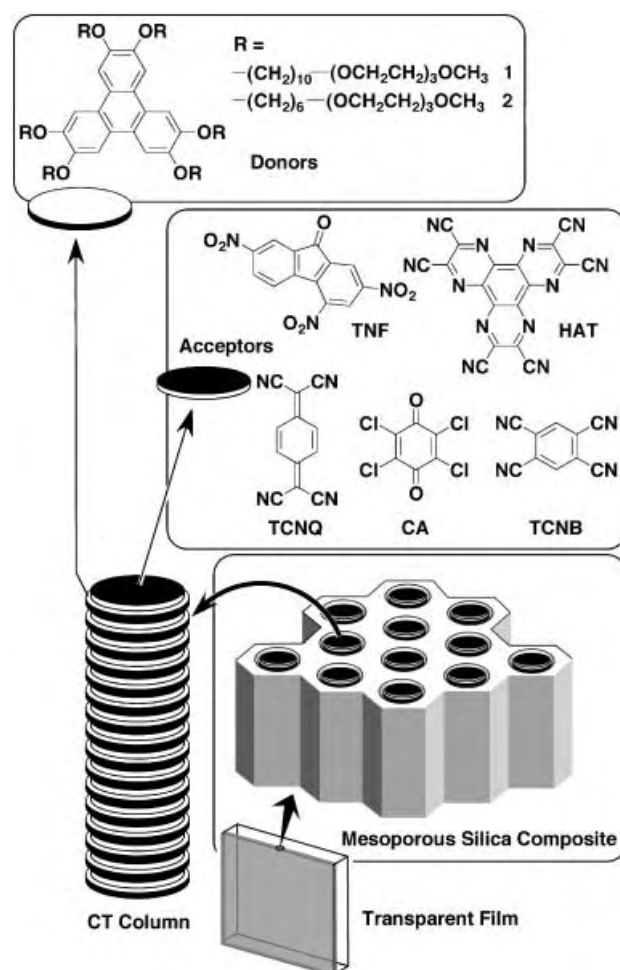


Figure 1. Formulas of donors **1**, **2**, and acceptor species, and a schematic representation of a mesoporous silica film containing one-dimensional columnar charge-transfer (CT) assemblies immobilized in a hexagonal array of nanoscopic channels.

[*] Prof. T. Aida, Dr. A. Okabe, Dr. T. Fukushima, Dr. K. Ariga
 ERATO Nanospace Project, JST
 National Museum of Emerging Science and Innovation
 2-41 Aomi, Koto-ku, Tokyo 135-0064 (Japan)
 Fax: (+81)3-5841-7310
 E-mail: aida@macro.t.u-tokyo.ac.jp

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added to this solution, and the mixture was allowed to stand for 12 h at room temperature (approximately 25°C), whereupon partial polymerization of TBOS took place. The resulting solution (a few drops) was cast on a cover glass to give a brown transparent film (see Figure 5 a(A)), which was dried in air for 24 h at room temperature and then for an additional 12 h at 100°C. The X-ray diffraction (XRD) pattern of the film was characteristic of hexagonal silicate structures, with (100) and (200) diffraction peaks, and with the *d* spacing of the former being 2.98 nm (Figure 2 a(A)).^[5] The

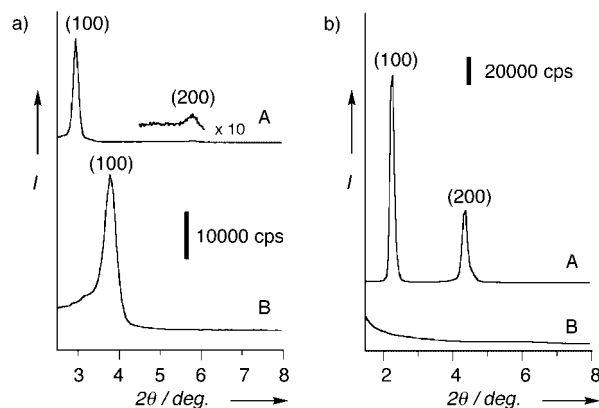


Figure 2. X-ray diffraction (XRD) patterns (A, uncalcined; B, calcined) of composite silica films prepared with an equimolar mixture of **1** and TNF, with molar ratios of TBOS and **1** of a) 60:1 and b) 20:1. Diffraction peaks (100) and (200) are at 2.98 and 1.52 nm, respectively, in Figure 2 a(A); (100) at 2.34 nm in Figure 2 a(B); (100) and (200) at 3.91 and 2.02 nm, respectively, in Figure 2 b(A).

d spacing decreased to 2.34 nm upon calcination at 450°C for 3 h (Figure 2 a(B)). The hexagonal structure was confirmed by a very clear transmission electron microscopy (TEM) image of the film (Figure 3 a). Magnified TEM images of the film (Figure 3 b and 3 c) indicate that hexagonally packed channels with a diameter of approximately 3 nm are regularly aligned, parallel to the substrate surface. The observed pore

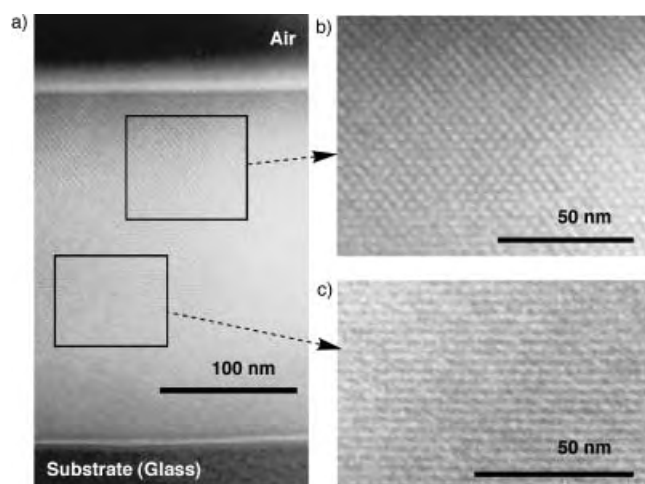


Figure 3. Transmission electron micrographs of a composite silica film (hexagonal geometry) prepared from an equimolar mixture of **1** and TNF at a TBOS/**1** molar ratio of 60:1; a) a cross-section of the whole film; b) and c) magnified for imaging the direction of the mesoporous channels with respect to the glass substrate surface. Estimated pore diameter is 2.7 nm.

diameter is comparable to the molecular dimensions of **1** with shrunken side chains, which indicates that each silicate channel contains only one CT column. Examination of the film by thermogravimetric analysis (TGA) showed that the composite silica film underwent a weight loss of 49 % at 175–600°C, which is comparable to results reported previously.^[6]

Transparent silica films with characteristic colors were successfully obtained from **1**, by a procedure similar to that described above, with all of the other acceptors listed in Figure 1, and also from **2** with TNF. Dip-coating and spin-coating, in addition to casting, were all effective for the fabrication of mesoporous composite silica films. Here, the molar ratio of TBOS to template is one of the most important factors for hexagonal structuring. A high TBOS:**1** molar ratio (for example, 60:1) resulted in a hexagonal structure, whereas silica films with a lamellar structure were obtained when the TBOS:**1** molar ratio was as low as 20:1 (Figures 2 b and 4). In

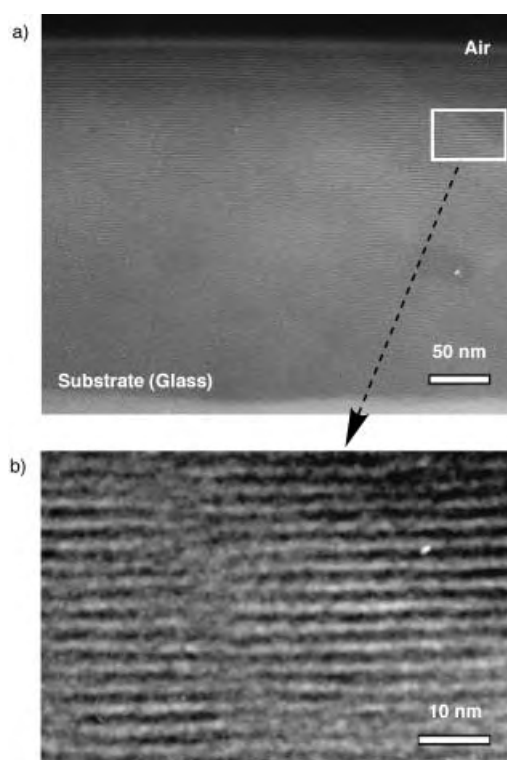


Figure 4. Transmission electron micrographs of a composite silica film (lamellar structure) prepared from an equimolar mixture of **1** and TNF at a TBOS/**1** molar ratio of 20:1; a) a cross-section of the whole film; b) magnified for imaging the direction of silica layers with respect to the glass substrate surface. The estimated thickness of the sum of the silica and the organic layers is 3.8 nm.

addition, CT interactions are crucial for the fabrication of thermally robust composite silica films. A cast silica film prepared from **1** without an acceptor displayed clear XRD peaks, which became less clear upon calcination of the film at 450°C.^[7] However, when using a CT acceptor, such as TNF, the composite silica films that were deposited maintained a clear XRD pattern, even after calcination, and at various **1**:TNF molar ratios ranging from 1:1 to 9:1. In the case where the **1**:TNF molar ratio was 9:1, it was necessary to use

tetramethoxysilane (TMOS) instead of TBOS as the silica source and MeOH instead of EtOH as the solvent for the sol-gel process.^[7] Although CT interactions contribute to the thermal stability of the composite silica films, neither **1** alone nor its CT complexes with acceptors such as TNF did not display, in the bulk phase, any liquid-crystalline textures in polarized microscopy.

The silica films were all highly transparent and exhibited a range of coloration from blue to red, characteristic of CT interactions (Figure 5a).^[8] CT absorption spectra of the silica

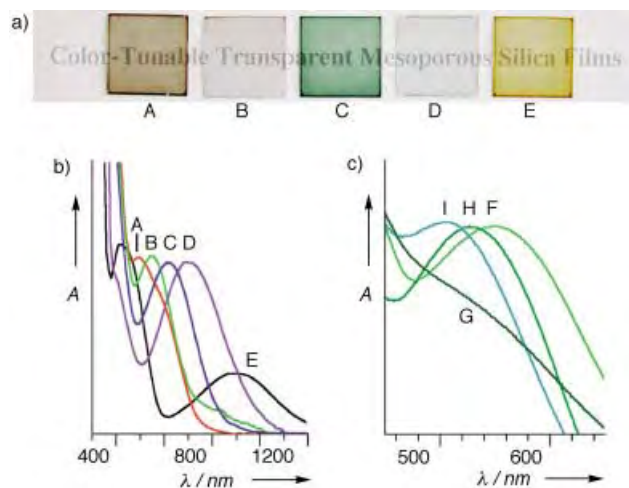


Figure 5. a) Images and b) CT absorption spectra of composite silica films prepared with equimolar mixtures of **1** and (A) TNF, (B) TCNB, (C) HAT, (D) CA, and (E) TCNQ as acceptors. c) CT absorption bands (450–650 nm) of **1**/TCNB complexes in a mesoporous silica film (F), a silica film with a lamellar structure (G), bulk phase (a cast film) without silica (H), and an acetonitrile solution (I).

films prepared with equimolar mixtures of **1** and TNF (A), TCNB (B), HAT (C), CA (D), and TCNQ (E) showed absorption maxima at 490, 548, 615, 700, and 890 nm (with another absorption at 410 nm), respectively (Figure 5b), which are red-shifted from those observed for the reference CT complexes without silica (Figure 5c). For example, the CT absorption band of the composite silica film prepared from an equimolar mixture of **1** and TCNB (Figure 5c(F); 548 nm) was red-shifted by 43 and 22 nm from those of the CT complexes in acetonitrile (2.0 mM, Figure 5c(I); 505 nm) and from the bulk phase (a cast film on a cover glass, Figure 5c(H); 526 nm), respectively. The spectral profile of the composite silica film prepared **1** and TCNB (1:1) remained unchanged when immersed for 12 h in acetonitrile and even in a solution of HAT in acetonitrile; HAT is a stronger electron acceptor than TCNB.^[9] These observations suggest that the structure of the composite silica films are defect-free, in which the included CT complex is highly stabilized within nanoscopic channels and isolated from outer environments. The red shifts of the absorption maxima for the silica-immobilized CT complexes (for example, Figure 5c(F)) may be as a result of an enhanced, long-range structural ordering of densely packed donor/acceptor assemblies within the nanoscopic silicate channels. In relation to this, a silica film with a lamellar structure, prepared from **1** and TCNB (1:1 molar ratio) and used as a reference material, showed a very broad

CT band (Figure 5c(G)), which was apparently blue-shifted from that of the composite silica film with a hexagonal geometry (Figure 5c(F)). Furthermore, the composite lamellar film, when immersed in acetonitrile, was immediately decolorized because of the release of the included CT complex.

In conclusion, we have demonstrated the first example of the immobilization of one-dimensional columnar charge-transfer (CT) assemblies in mesoporous silica films consisting of a hexagonal array of nanoscopic channels. The films are highly transparent and color-tunable by the appropriate choice of the intercalating acceptor, and therefore have potential for a variety of optical applications. The silica wall segregates the individual CT columns, which display neither solvatochromism nor guest-exchange activity, and exhibit red-shifted absorption bands, possibly as a consequence of a long-range structural ordering. Furthermore, the donor/acceptor molar ratio, which is related to photoconductive properties, can be varied over a wide range from 1:1 to 9:1. The present work may be the basis for new research on nanoscopic composite materials. In particular, the fabrication of anisotropic composite silica films with mesoscopic channels aligned vertically to the film surface is worthy of further investigation.

Experimental Section

HAT was synthesized according to a literature method,^[10] while other acceptors were obtained from commercial sources. Donor molecules **1** and **2** were synthesized as follows: A mixture of 2,3,6,7,10,11-hexahydroxytriphenylene (80.0 mg, 0.247 mmol), 1-bromo-10-(2-(2-methoxyethoxy)ethoxy)decane (970 mg, 2.53 mmol),^[4] and potassium carbonate (600 mg, 4.35 mmol) in dry DMF (8 mL) was heated at 90°C under Ar. After 66 h, the reaction mixture was poured into water, the organic layer separated, and extracted with CH₂Cl₂. The combined extract was evaporated to dryness, and the residue was purified by chromatography on silica gel with CH₂Cl₂/MeOH as eluent to give **1** as a pale-yellow oil (464 mg, 88 %); ¹H NMR (500 MHz, CDCl₃): δ = 7.83 (s, 6H), 4.22 (t, *J* = 6.8 Hz, 12H), 3.67–3.53 (m, 72H), 3.44 (t, *J* = 6.8 Hz, 12H), 3.37 (s, 18H), 1.97–1.89 (m, 12H), 1.61–1.52 (m, 24H), 1.45–1.27 ppm (m, 60H); ¹³C NMR (125 MHz, CDCl₃): δ = 148.83, 123.49, 107.34, 71.88, 71.46, 70.57, 70.53, 70.46, 70.00, 69.70, 58.96, 29.68, 29.64, 29.62, 29.55, 26.22, 26.14 ppm; MALDI-TOF-MS: 2138.48 ([*M*+H]⁺ calcd for C₁₂₀H₂₁₇O₃₀: 2138.55). **2** (1.39 g, 86 %) was obtained as a pale-yellow oil by a procedure similar to that for the preparation of **1**. ¹H NMR (500 MHz, CDCl₃): δ = 7.82 (s, 6H), 4.22 (t, *J* = 6.8 Hz, 12H), 3.67–3.52 (m, 72H), 3.49 (t, *J* = 6.8 Hz, 12H), 3.37 (s, 18H), 1.98–1.90 (m, 12H), 1.70–1.56 (m, 24H), 1.52–1.44 ppm (m, 12H); ¹³C NMR (125 MHz, CDCl₃): δ = 148.83, 123.53, 107.35, 71.89, 71.35, 70.58, 70.55, 70.47, 70.08, 69.58, 58.99, 29.70, 29.52, 26.09, 26.06 ppm; MALDI-TOF-MS: 1802.10 ([*M*+H]⁺ calcd for C₉₆H₁₆₉O₃₀: 1802.17). Composite silica films with hexagonally aligned mesoporous channels were prepared in a manner described in the previous section. Composite silica films containing **1**/TNF (1:1) and **1**/TCNB (1:1) with a lamellar structure were prepared according to a method described below: Typically, an equimolar mixture of **1** (15.0 mg, 7.0 μmol) and TNF (2.2 mg, 7.0 μmol) was dissolved in EtOH (1.48 g) containing 12N hydrochloric acid (7.77 mg). Tetrabutoxysilane (TBOS, 45 mg, 140 μmol) was added to this solution, and the mixture was allowed to stand for 12 h at room temperature (approximately 25°C) for partial polymerization of TBOS. A viscous solution was obtained, which was cast, dip-coated, or spin-coated onto a cover glass, and dried in air for 24 h at room temperature and then an additional 12 h at 100°C. Electronic absorption spectra and XRD patterns were recorded on a JASCO V-570 spectrophotometer and a Rigaku RINT2500PC small- and wide-angle X-ray diffractometer, respectively. The TEM images were obtained on a JEOL JEM-2010 transmission electron microscope at Mitsui Chemical Analysis and Consulting Service Inc. TGA profiles were recorded on a Shimadzu TGA 50 thermogravimetric analyzer. Calcination

of composite silica films was carried out by initially heating for 12 h at 100 °C, followed by heating for 3 h at 450 °C in a Yamato F0810 muffle furnace.

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Characterization of a Planar Cyclic Form of Water Hexamer in an Organic Supramolecular Complex: An Unusual Self-Assembly of Bimesityl-3,3'-Dicarboxylic Acid**

J. Narasimha Moorthy,* R. Natarajan, and P. Venugopalan*

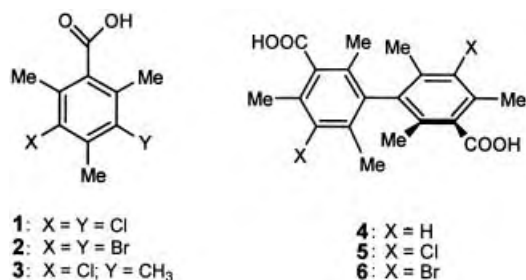
Dedicated to Professor Waldemar Adam on the occasion of his 65th birthday

There is an upsurge of interest in contemporary theoretical and experimental research to unravel the structural details of water clusters.^[1–8] The clusters are believed to be the perfect means for characterizing the structural changes and bonding mechanisms in passing from isolated molecules to a macroscopic collection, namely, bulk water, whose anomalous properties still remain mysteries.^[1,2,9] A variety of modern theoretical and experimental methods have been employed to characterize the clusters. Both experiment and theory strongly suggest that the water trimer, tetramer, and pentamer have cyclic and quasiplanar minimum-energy structures. The larger clusters are expected to have 3D geometries, with the hexamer behaving as the transition from 2D to 3D structures.^[1,2] The X-ray structural characterization of a decamer^[10] and an octamer water cluster (cubic^[11] and cyclic^[12] forms) have been reported recently. Theoretical calculations for the hexamer have revealed the existence of several energy minima corresponding to “ring”, “book”, “bag”, “cage”, and “prism” topologies within 0.7 kcal mol^{−1}.^[13–15] The lowest energy conformer is the “cage” followed by the “book” and “prism” structures, which are less than 0.1 and 0.2 kcal mol^{−1} higher in energy, respectively.^[13–15] The “ring” and “bag” structures have been shown to be 0.5 and 0.7 kcal mol^{−1} higher in energy than the “cage”. To date, “chair”^[16,17] and “boat”^[18] cyclic hexamers included in host lattices have been characterized by X-ray crystallographic analysis. While Saykally and co-workers characterized the cage form of the hexamer,^[15] Nauta and Miller reported the detection of a “quasiplanar” hexamer in a helium droplet.^[19] Herein, we report the first X-ray structural characterization of the high-energy cyclic form of the water hexamer trapped in an organic supramolecular complex with the bimesityl dicarboxylic acid **4**. The planar ring constitutes the basic structural motif of the high-pressure Ice II modification,^[20] and is also one of the prominent morphologies found in the computer simulation of liquid water.^[21]

[*] Dr. J. N. Moorthy, R. Natarajan
Department of Chemistry
Indian Institute of Technology
Kanpur 208 016 (India)
Fax: (+91) 512-597436
E-mail: moorthy@iitk.ac.in
Dr. P. Venugopalan
Chemistry Department
Panjab University
Chandigarh 160 014 (India)

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Our recent study has shown that sterically encumbered mesitoic acids (**1–3**) adopt neither a centrosymmetric dimer motif nor a catemer motif in their crystal structures, but self-assemble into helical organizations when substituted in *meta*-



positions with chloro or bromo substituents.^[22] The helical self-assembly was found to be mediated by a composite of the X...X and C–H...X interactions. This discovery prompted us to explore the possibility of propagation of helical assemblies in two dimensions with halogen-substituted dicarboxylic acids such as **5** and **6**. Thus, we synthesized bimesityl dicarboxylic acids **4–6** to examine the molecular packing in **5** and **6**, and to establish the influence of halogen atoms by a comparison with the crystal packing of the acid **4**. Our numerous attempts at crystallizing the acids **5** and **6** were unsuccessful, which suggests that these acids do not exploit the stronger (O–H...O) and weaker (X...X and C–H...X) interactions jointly to stabilize the crystal lattice. Remarkably, the dicarboxylic acid **4** crystallized readily in MeOH–CH₂Cl₂ mixture by incorporating water (1 equiv) in its crystal lattice (trigonal, *R*3̄; Figure 1).^[23] As expected, the two aromatic rings of the

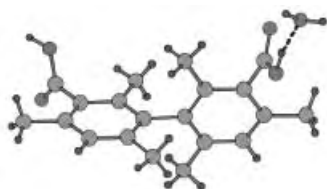


Figure 1. The molecular structure of acid **4** with one of its carboxy groups linked to the water molecule through an O–H...O hydrogen bond.

bimesityl moiety are almost orthogonal, with an angle of 82.4° between the two planes. The symmetry operation about the *c* axis generates a hexameric cluster of water (Figure 2). Figure 3 shows the overall association of water molecules with themselves and with the carboxy groups of the diacid molecules **4**. The space-group symmetry imposes a perfect planarity on the oxygen atoms of the water cluster. One of the two hydrogen atoms of each water molecule is involved in hydrogen bonding with an oxygen atom of the symmetry-related molecule, while its own oxygen atom is simultaneously hydrogen-bonded to another molecule of water, to complete the ring (see the hydrogen bond HB1 in Figure 3). The second hydrogen atom of the water molecule forms a hydrogen bond to the carboxy oxygen atom of the host diacid **4** (HB2). Furthermore, each of the cluster water molecules participates in hydrogen bonding with the carboxylic proton of the diacid **4** by engaging one of its lone pair of electrons (HB3). Overall,

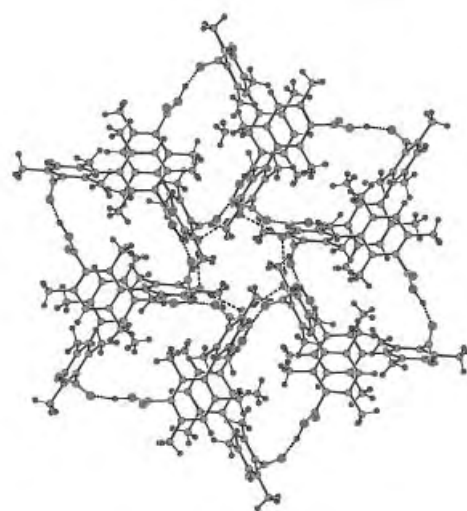


Figure 2. The crystal packing (projection down *c* axis) of **4**·H₂O complex. The hydrogen bonds (O–H...O) between the host and water molecules and between the two host molecules themselves are shown with broken lines.



Parameter	HB1	HB2	HB3
$d_{\text{O–H}}/\text{\AA}$	0.92	0.92	0.95
$d_{\text{O–O}}/\text{\AA}$	2.167	1.905	1.664
$\theta_{\text{O–H–O}}/^\circ$	136.59	169.55	168.73
$d_{\text{O–O}}/\text{\AA}$	2.905	2.816	2.606

Figure 3. The water hexamer together with the acid molecules (only –COOH are shown for clarity) linked through O–H...O hydrogen bonds (projection down *c* axis). The bonding parameters for the hydrogen bonds are given.

the six water molecules are bound to the host lattice through 12 O–H...O hydrogen bonds and the water molecules of the cluster typically assume a tetrahedral geometry. The hydrogen bonding parameters for all of the O–H...O bonds suggest that the interaction in all the cases is moderate^[7] and that the hydrogen bond between the water oxygen atom and the carboxylic hydrogen atom (HB3, Figure 3) is stronger than the other two, that is, HB1 and HB2. Regarding the interactions between the host acids, the second carboxylic hydrogen atom of the acid **4** forms a hydrogen bond with the carboxy oxygen atom of the symmetry-related molecule, which in turn forms another hydrogen bond (with its second carboxylic hydrogen atom) with the carboxy oxygen atom of the original acid (Figure 4). The protons of the carboxy group form hydrogen bonds with water molecules, while their carbonyl oxygen atoms accept hydrogen bonds from the water hydrogen atoms, to complete the crystal packing

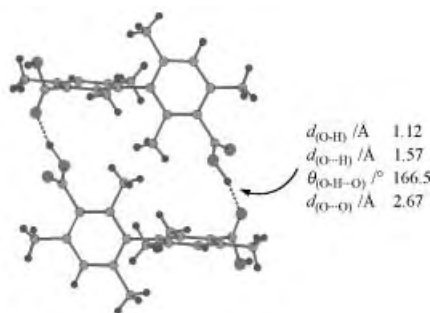


Figure 4. The unusual dimeric association of the acids through O–H...O hydrogen bonds.

(Figure 2). Thus, it appears that the water cluster acts as a template around which the acid molecules pack and vice versa.

To characterize the vibrational stretching frequency associated with the O–H bond of the water cluster, the FTIR spectrum of the complex was recorded (Figure 5). The broad band centered about 3400 cm^{-1} in Figure 5 is readily attributed to the O–H stretching frequency of the water cluster. It should

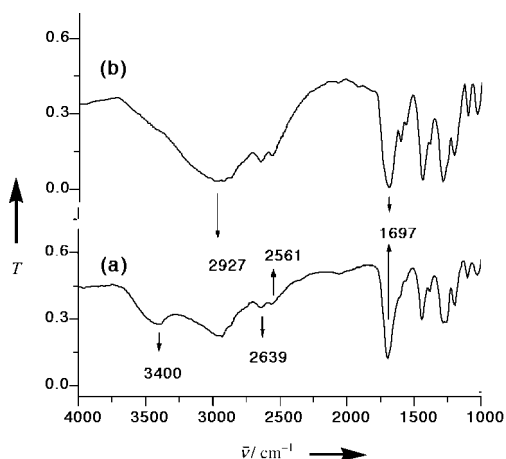


Figure 5. The FTIR spectra of acid **4**·H₂O complex before (a) and after (b) heating under vacuum at 100°C .

be noted that the carboxylic OH group gives rise to a broad band with some structure in the region around about $2600\text{--}3200\text{ cm}^{-1}$, which slightly obscures the C–H stretching vibrations. The IR spectrum of the same crystals when heated at about 100°C under vacuum (0.1 mm) for 2 h is also shown in Figure 5. The broad band corresponding to the water hexamer disappears, which suggests that the associated water molecules escape from the crystal lattice. Deliberate re-exposure of these crystals to water vapor for 2 days, monitored by FT-IR spectroscopy, did not lead to reversible absorption into the lattice. Powder X-ray diffractograms of the crystals before and after expulsion of water at about 100°C under vacuum (Figure 6) reveal only marginal differences in the diffraction patterns and intensities, which suggests that the integrity of the host lattice is robust to the exclusion of water. The crystal packing is reminiscent of polymer imprinting in that it is generated utilizing the water cluster as a template and it carries the imprint of the water hexamer after exclusion of the template (water cluster) on heating under vacuum.

As mentioned at the outset, tremendous effort has gone into establishing the structural details of water clusters. For a

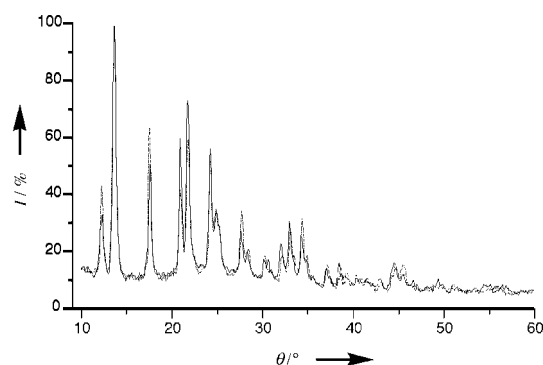


Figure 6. The X-ray diffraction patterns of **4**·H₂O complex before (solid line) and after heating under vacuum at 100°C for 2 h (broken line).

hexamer, the highest level ab initio calculations have revealed the cage structure as the minimum energy form.^[15] Indeed, this structure has been confirmed by Saykally and co-workers from their pioneering work utilizing Far-Infrared (FIR) Vibration–Rotation Tunneling (VRT) spectroscopy.^[15] From a comparison of the experimentally observed infrared O–H stretches of water clusters formed in a helium droplet with those of the clusters formed in free jet expansion, and extensive theoretical calculations, Nauta and Miller have characterized the high-energy ring form of the water hexamer in a helium droplet.^[19] Accordingly, the absorption caused by the O–H stretch occurs at about 3325 cm^{-1} . Similarly, the O–H stretches of the hexamers in the Ice I and II phases were reported to occur at about 3220 cm^{-1} .^[24] In comparison, the same absorption for the hexamer in the present supramolecular complex occurs at about 3400 cm^{-1} (Figure 5). Thus, the observed differences in the absorptions arising from the O–H stretch should be explained by the differences in the matrices in which the clusters are formed. In a similar vein, a comparison of the structural parameters of the planar hexamer with those found in the Ice I and II forms is quite instructive; the average O...O distances reported for the Ice I and II phases are 2.75 and 2.77–2.84 Å, respectively.^[9] This distance for the water cluster reported herein is 2.905 Å, which is remarkable given that the planar hexamer is implicated in bulk water. Notably, the bulk water has a short-range order in the O...O X-ray diffraction radial-distribution curve at 2.85 Å (for the gas phase it is 0.1 Å longer).^[9]

The packing of the acid molecules **4** does not conform to any of the known association patterns of carboxylic acids. A recent Cambridge Structural Database analysis has shown that the dimer motif is found in 90% of the crystal structures reported for the acids, while the catemer motif is found in 4%; the dimer motif expanded by one or two solvent water molecules is found in the remaining 6%.^[25] Given the importance of the centrosymmetric dimer motif of the carboxylic group in supramolecular network design and synthesis,^[26,27] the observed departure of the packing of **4** from any of the known motifs emphasizes the need to understand the factors that enforce a paradigm shift in the association. Obviously, the observed packing must be a result of compact packing that maximizes the crystal lattice stabilization, which appears to be best achieved in the present instance by incorporation of the water as a guest molecule in the crystal lattice. In the absence of any readily perceivable

influences, we believe that the crystal packing, contrary to that expected based on centrosymmetric dimer motifs, is most likely manifest in compounds, whose structures are 1) characterized by steric hindrance about the carboxy group and 2) endowed with certain interacting groups that are non-linearly built into the molecules (at the *meta* position). We are continuing to investigate the self-assembly of aromatic carboxylic acids of varying structures and a variety of interactions.

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crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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NMR Reporter Screening for the Detection of High-Affinity Ligands

Wolfgang Jahnke,* Philipp Floersheim, Christian Ostermeier, Xiaolu Zhang, Rene Hemmig, Konstanze Hurth, and Doncho P. Uzunov

The ability to detect protein–ligand interactions in a robust and sensitive manner (“NMR screening”) is one of the prime assets of biomolecular NMR spectroscopy in drug discovery.^[1–6] It is being used for validation of hits identified in other biological assays, or for the discovery of high-affinity ligands for a given target. NMR screening can be performed by observation of either target resonance signals or ligand resonance signals. Observation of target resonance signals requires large amounts of isotopically labeled protein, very-soluble protein, and has an upper limit for protein size. Since many therapeutically interesting targets do not fall into this class, observation of ligand resonances is the more generally applicable method. A variety of NMR techniques are available to perform these studies. None of them requires isotopically labeled protein, and some of them require only very small amounts of protein.^[7–9] A general drawback of all ligand-observation methods, however, is their inability to detect high-affinity ligands—these are false negative and appear to be non-binding. The cause of this significant drawback lies in that for ligand-observation methods, only unbound ligand is observed because of the high excess of ligand over protein. In the case of weak or medium binding affinity (K_D typically less than $1 \mu\text{M}$), the dissociation rate is generally so large that a significant exchange between bound and free ligand occurs during the time scale of the experiment, typically a few hundred milliseconds. This exchange process transfers ligand properties from the bound state (e.g. fast relaxation, large negative NOEs) to the free ligand, so that information about binding has been conveyed to the unbound ligand. In strongly bound ligands (sub-micromolar K_D), the

[*] Dr. W. Jahnke, Dr. P. Floersheim, Dr. C. Ostermeier, Dr. X. Zhang, R. Hemmig, Dr. K. Hurth, Dr. D. P. Uzunov
Novartis Pharma AG
P.O. Box, 4002 Basel (Switzerland)
Fax: (+41) 61-324-2686
E-mail: wolfgang.jahnke@pharma.novartis.com

slow dissociation rate prevents the information of binding to be conveyed to the unbound ligand, so that these strongly bound ligands appear false negative.

Herein we present a novel technique, called NMR reporter screening, which enables the detection of high-affinity ligands by observation of ligand resonance signals. The method has a number of additional advantages: It only detects ligands if they bind to the protein active site while not detecting unspecific binding. Only small amounts of protein in natural isotopic abundance are needed, the experimental time for data collection is so short that it is not throughput-limiting, and data acquisition and analysis can be easily automated.

NMR reporter screening changes the principles of NMR screening: Not the binding of test compounds to the protein target is directly observed, but the ability of a test compound to displace a known ligand, which binds to the protein with medium affinity and which is routinely added as a “reporter ligand” to the mixture of protein and test compounds. Figure 1 shows the principle of the experiment: In the presence of target protein but in the absence of test compounds (Figure 1b), the reporter ligand is bound to the target protein with moderate affinity, and its relaxation rate is increased as a result of fast relaxation in the bound state, and because of intermediate exchange broadening. This leads to moderate or severe line broadening of the reporter ligand resonances. The same situation prevails if test compounds are added that do not bind to the protein target, bind more weakly than the reporter ligand, or bind non-specifically at a different non-competitive binding site: The reporter ligand is still bound to

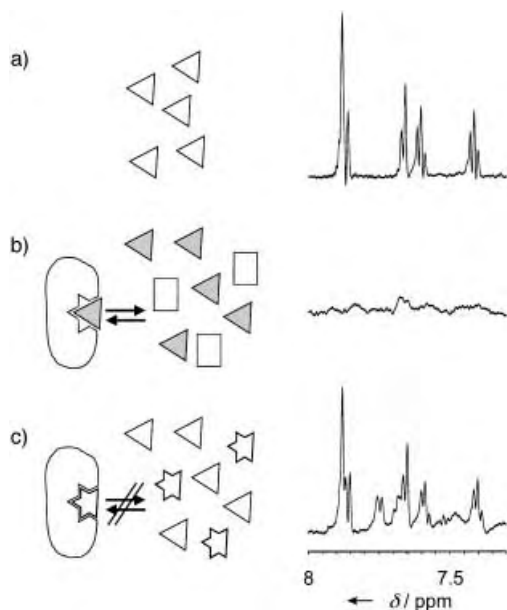


Figure 1. Principle of NMR reporter screening. NMR reporter screening detects the resonance signals of a reporter ligand (triangles) in the presence of target protein and test compounds by simple 1D proton spectra. a) Without protein target, the reporter ligand has sharp signals typical for a small molecule. b) Broad signals of the reporter ligand indicate that the reporter ligand is bound to the target, and that no test compound has comparable binding affinity. c) Sharp signals of the reporter ligand indicate unbound reporter ligand: At least one of the compounds binds more tightly to the protein target and thus displaces the reporter ligand. In the sketch, compounds with increased relaxation (broad lines) are shaded gray, compounds with sharp lines are white. 4 μ M spin-labeled 3 α -HSD and 100 μ M reporter ligand were used for (b) and (c).

the target, which can easily be seen by its broadened resonances. However, if test compounds are added that bind to the active site more strongly than the reporter ligand (Figure 1c), the reporter ligand is displaced from the binding site, so that it becomes unbound. Unbound reporter ligand can be readily distinguished from bound receptor ligand by its sharp resonance signals as seen in a simple 1D proton spectrum, or by other NMR observables such as STD^[7] or waterLOGSY^[8] signal intensity.

The reporter screening technique is illustrated with the example of human 3 α -HSD type III, a hydroxysteroid dehydrogenase that is involved in the biosynthesis and degradation of allopregnanolone (5 α -pregnan-3 α -ol-20-one), a potent positive endogenous allosteric modulator of GABA_A-receptor function. Considering the wide neuropsychopharmacological profile of allopregnanolone and other 3 α -reduced neuroactive steroids, 3 α -HSD type III is a potential target for the treatment of mental disorders such as depression, anxiety, and schizophrenia.^[10–12] NMR screening has been applied to identify a small fragment, 2-acetylbenzofuran (**1**), which binds to the active site of 3 α -HSD as indicated by the NMR data and by its ability to inhibit the enzymatic activity of the protein. A molecular model of the complex between 3 α -HSD and **1** is shown in Figure 2. Compound **1** fits favorably into the binding pocket of 3 α -HSD, yet there is space for additional groups to make favorable interactions. The resonance signals of compound **1** experience severe line broadening in the presence of 3 α -HSD as a result of increased relaxation in the bound state and intermediate exchange broadening (Figure 1b). Compound **1** is therefore an ideal reporter ligand since a simple pulse-acquire proton spectrum reveals whether the reporter ligand is bound or unbound. To identify more potent inhibitors of 3 α -HSD, 713 candidate ligands from the Novartis compound database were docked to a model of the X-ray structure of 3 α -HSD by using the docking program GOLD^[13] followed by TAFF^[14]/X-PLOR^[15] minimization. 30 of the top-ranking compounds were selected by visual inspection for NMR reporter screening. These test compounds were added to a solution of 3 α -HSD to which **1** was

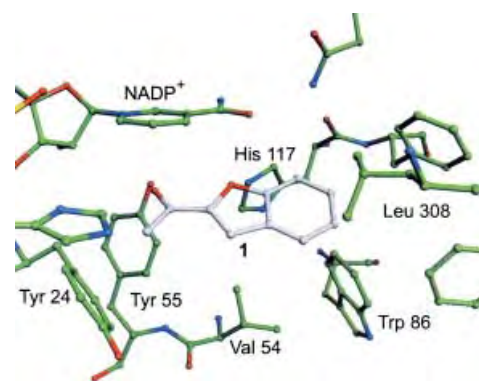


Figure 2. High-scoring model of the complex between human 3 α -HSD and **1** obtained by the docking program GOLD, based on an in-house apo crystal structure of human 3 α -HSD type III at 2.0 Å resolution.^[21] The carbonyl group of **1** (gray skeleton, O atoms in red) is placed below the pyridinium ring of the cofactor NADP⁺ and the carbonyl and ether O atom of **1** are hydrogen bonded to the hydroxyl group of Tyr55 and the NE2 atom of His 117, respectively. The main non-polar contacts of **1** are with Tyr24, Tyr55, Trp86, and Leu308; O red, N blue, C green.

added as reporter ligand. Screening of these compounds as five mixtures of six compounds took only 30 min experimental time, and identified three potent inhibitors that were able to displace the reporter ligand **1**.

To quantify the displacement of reporter ligand (R) from protein (P) by test compound (C), the ternary system in Equation (1) was considered and the resulting cubic poly-



nomial equation describing the concentration of PR was numerically solved.

In Figure 3, the percentage of bound reporter ligand, as measured by NMR spectroscopy, is plotted versus the added concentration of test compound, for three different test

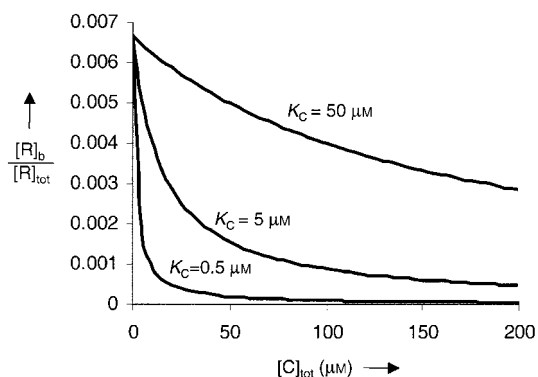


Figure 3. Ratio of bound reporter ligand, $[R]_b$ to $[R]_{tot}$, as a function of total test compound concentration, $[C]_{tot}$, for three different dissociation constants of C between $K_C = 0.5 \mu\text{M}$ and $K_C = 50 \mu\text{M}$. The curves have been computed with $[P]_{tot} = 1 \mu\text{M}$ (total protein concentration), $[R]_{tot} = 100 \mu\text{M}$ (total reporter ligand concentration), $K_R = 50 \mu\text{M}$ (dissociation constant of reporter ligand).

compound affinities. To displace 50% of the reporter ligand under typical conditions (1 μM protein concentration, 100 μM reporter ligand concentration, 50 μM reporter ligand affinity), the calculations show that for test compound affinities of 50 μM , 5 μM , and 0.5 μM , test compound concentrations of 150 μM , 15.5 μM , and 2 μM , respectively, are required. Displacement of 50% reporter ligand can be observed by reporter screening, so that these numbers indicate the detection limit of the method. If the percentage of bound reporter ligand is calibrated by NMR spectroscopic parameters, such as relaxation time, line width, or STD signal, the NMR parameter at a given test-compound concentration can be used to calculate the dissociation constant, K_C , of this test compound. Dissociation constants can thus be determined in a one-point measurement, based on the known dissociation constant of the reporter ligand.^[16,17]

The sensitivity of NMR reporter screening in terms of protein consumption depends on the relaxation rate enhancement of the reporter ligand in the bound state. This enhancement will generally be largest for ligands that bind in the 1–20 μM K_D range, where relaxation enhancement from intermediate exchange processes can contribute significantly to the overall relaxation rate. The recently introduced SLAPSTIC method^[9] can be ideally applied to NMR reporter screening since it drastically increases relaxation in the bound state even in the absence of exchange broadening. In fact, all our NMR

experiments on 3 α -HSD used spin-labeled 3 α -HSD which was readily prepared by the reaction of the lysine side chains with 1-oxyl-2,2,5,5-tetramethylpyrroline-3-carboxylate *N*-hydroxysuccinimide ester (Toronto Research Chemicals, Inc.). The preparation of spin-labeled 3 α -HSD required only 4 hours of work time and overnight reaction time. Mass spectrometric analysis indicated that on average, 15 out of the 26 lysine side chains were modified. Control experiments were carried out also with non-spin-labeled 3 α -HSD. Spin labeling reduced the protein amounts required for NMR reporter screening by about a factor of 15 for 3 α -HSD. With reporter ligand **1**, spin-labeled 3 α -HSD concentrations of 4 μM yield drastic effects (see Figure 1b), while the effects with 200 nM spin-labeled 3 α -HSD are still sufficiently strong if T1 ρ -edited spectra^[18,19] are recorded.

If mixtures consisting of a large number of compounds are to be screened in the presence of reporter ligand, resonance overlap of the test compounds with the reporter ligand can make data analysis difficult. In this case, it may be advisable to introduce an isotope label into the reporter ligand, and to record isotope-edited 1D proton spectra, which do not suffer from signal overlap with the (unlabeled) test compounds. Reporter ligand **1** with a ^{13}C -acetyl methyl group was prepared in two steps from coumarilic acid by Grignard addition of $^{13}\text{CH}_3\text{MgI}$ to the corresponding Weinreb amide. Figure 4 shows examples of homonuclear spectra using unlabeled **1** and isotope-edited spectra using ^{13}C -labeled **1**. While the spectra with unlabeled **1** are hardly interpretable because of severe signal overlap, analysis is much easier with isotope-edited spectra using ^{13}C -**1**.

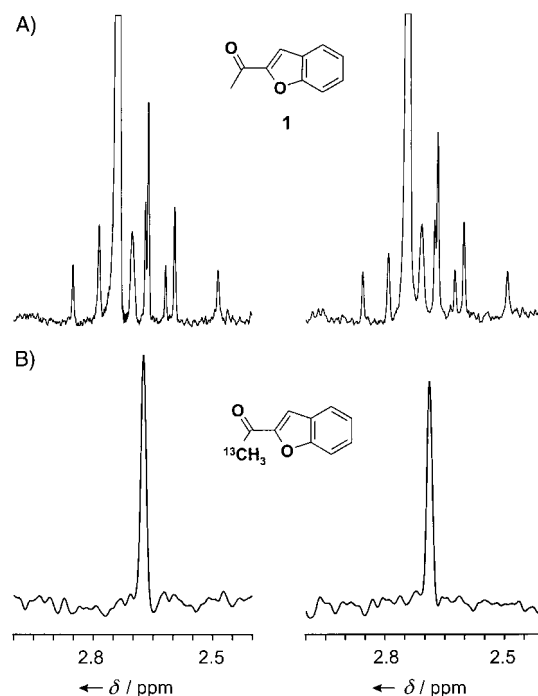


Figure 4. Signal overlap of the reporter ligand with test compounds can be circumvented by isotopic labeling of the reporter ligand. While the test compound signals obscure the relevant signal from T1 ρ spectra^[18,19] of the unlabeled reporter ligand (A), ^{13}C -edited T1 ρ proton spectra of ^{13}C -labeled reporter ligand are devoid of overlap problems (B); 200 nM of spin-labeled 3 α -HSD were used. The T1 ρ periods were 10 ms (left) and 100 ms (right). All experiments were carried out at 296 K on a Bruker DRX600 instrument.

Competition assays have been widely used for high-throughput screening in a variety of assay formats, but their use in NMR spectroscopy has so far been limited to investigating specificity of binding, and to measure dissociation constants of known ligands.^[16,17,20] NMR reporter screening eliminates the major shortcoming of all current ligand-observation methods of not being able to detect high-affinity ligands with slow dissociation rates. Moreover, it also solves the problem of non-specific binding: Only ligands binding to the active site displace the reporter ligand and appear positive in the reporter screening assay, provided that the reporter ligand binds at the desired binding site. While test compounds need to be fairly soluble (50–500 μM) for current NMR screening methods, NMR reporter screening works even for poorly soluble ligands, if their affinities are high enough, since the test compounds are not actually observed. Finally, NMR reporter screening is very fast since it requires only the acquisition of a simple pulse-acquire spectrum, which typically takes only a few minutes. The throughput of samples is then effectively dominated by the need for sample exchange, temperature equilibration, and magnet shimming, rather than by the duration of the NMR experiment itself. Optionally, the target protein can be spin-labeled to enhance the effect and reduce protein consumption by a factor of 10, and/or the reporter ligand can be isotopically labeled to facilitate spectral interpretation. The reporter ligand does not need to be so-called drug-like. It can be found by NMR screening, or could even be a peptidic ligand. We expect that NMR reporter screening will be of widespread use in NMR-supported drug design.

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Molecular Encapsulation of Anions in a Neutral Receptor**

Osamu Hayashida, Alexander Shivanyuk, and Julius Rebek, Jr.*

We describe here molecular assemblies that allow the direct observation of individual anions in contact with one or two solvent molecules. The system involves reversible encapsulation of ionic guests in uncharged, synthetic host structures. The anions and solvent are held in confined spaces and extended times amenable to NMR spectroscopy in solution at ambient temperatures. Anions and cations can be even further separated by placement in different capsules.

Recognition of anions by synthetic receptors usually involves charge–charge interactions, hydrogen bonds, or coordination contacts with metals, all carefully arranged in space.^[1–5] Reversible encapsulation complexes, in which various anionic guests are surrounded by positively charged hosts, are well-characterized in solution and in the solid state.^[6–12] Anions alone are not known to be sequestered in, or even recognized by neutral, reversibly formed capsules but, on occasion, they can be encapsulated as ion pairs.^[13–15] We report here the unexpected affinity of neutral cylindrical capsule **1**₂^[16] (the dimeric form of **1**, Figure 1) for anions in CDCl_3 . The anions are bound reversibly along with one or two solvent molecules. The polar seam of hydrogen-bonded imide groups of **1**₂ is undoubtedly involved in the recognition process, but even anions not known for hydrogen bonding are readily encapsulated.

The ¹H NMR spectrum of cavitand **1** in CDCl_3 (Figure 2a) shows the characteristic pattern of the vase^[17] conformation but the N–H chemical shift at $\delta = 9.85$ ppm indicates hydrogen bonding typical of a dimeric, capsular structure **1**₂. Neutral guests such as *trans*-stilbene and benzanilide are readily encapsulated by **1**₂ in $[\text{D}_{12}]$ mesitylene (a solvent too large to fit in the capsule) but not in CDCl_3 . These guests, at the millimolar concentrations of NMR experiments, cannot compete for the cavity with the solvent at concentrations of about 12 molar. Remarkably, anions can displace the resident solvent. Addition of tetrabutylammonium *p*-toluenesulfonate ($\text{Bu}_4\text{N}^+\text{TsO}^-$) to a solution of **1**₂ in CDCl_3 gave a complex of reduced symmetry, featuring two NH signals and aromatic signals of the resorcinol rings. The resonance signal of the methyl protons of the encapsulated TsO^- ion appeared at $\delta = -2.86$ ppm ($\Delta\delta = -5.1$ ppm), which positions them near the resorcinarene rings of **1**₂ (Figure 2b). Integration confirmed the stoichiometry of the complex, indicating that the new signals correspond to a complex of **1**₂ with encapsulated

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[*] Prof. J. Rebek, Jr., Dr. O. Hayashida, Dr. A. Shivanyuk
The Skaggs Institute for Chemical Biology and
Department of Chemistry
The Scripps Research Institute, MB-26
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2876
E-mail: jrebek@scripps.edu

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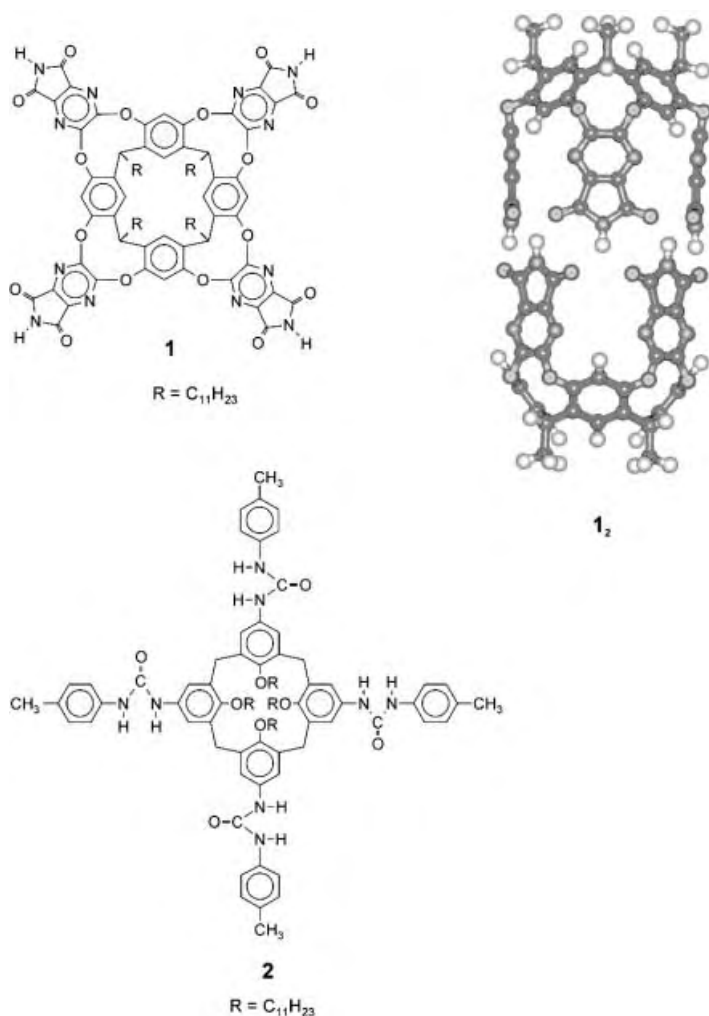


Figure 1. Line formulas of calix[4]arene **1** and calix[4]arene **2**, and ball-and-stick model presentation of cylindrical capsule **1**₂.

tosylate. No induced shifts were detected for the protons of Bu₄N⁺. The exchange rate between the new complex and the original CDCl₃-filled capsule **1**₂ is slow on the ¹H NMR time scale at ambient temperatures and 600 MHz.

Encapsulation complexes of Bu₄N⁺ tetrafluoroborate (BF₄⁻), hexafluorophosphate (PF₆⁻), and perfluorobutylsulfonate (C₄F₉SO₃⁻) also form readily, and the direct observation of these encapsulated ions by ¹⁹F NMR spectroscopy confirmed their structures. The induced shifts for BF₄⁻ and PF₆⁻ were $\delta = -2.43$ and $\delta = -3.37$ ppm, respectively (Figure 2d). These modest upfield shifts, along with the symmetry of the proton NMR spectra, place the ions at the center of the capsule. In the case of C₄F₉SO₃⁻, shifts of up to $\delta = -6.38$ ppm were observed for the fluorine atoms, and the ¹H NMR spectrum of this complex showed a pattern similar to that of the tosylate complex, indicating the same mode of binding. All of the anions could be released from their complexes in CDCl₃ by the addition of 10% of CD₃OD.

Anions differing in geometry, size, and hydrogen-bonding ability were also encapsulated (Table 1), although the evidence for these complexes is indirect. For example, addition of Bu₄N⁺Cl⁻ gives rise to new ¹H NMR signals for the imide-NH protons and the protons in the 2-position of the resorcinol

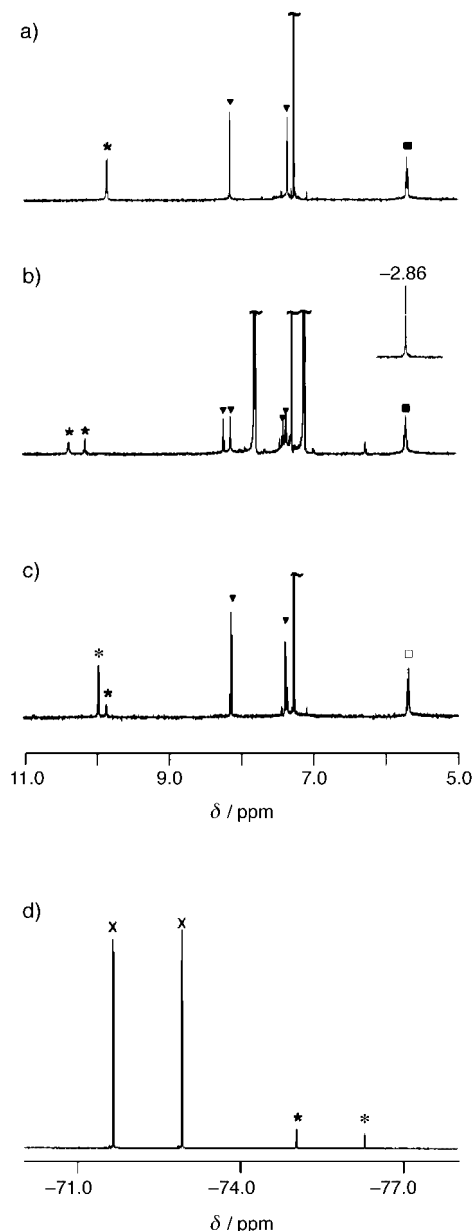


Figure 2. NMR spectra of the complexes in CDCl₃ at 295 K with [**1**₂] = 1.0 mM. ¹H NMR spectra at 600 MHz: a) of **1**₂ alone, $\blacktriangledown$ = Ar-H; $\star$ = NH protons; b) of **1**₂ with 40 equivalents of Bu₄N⁺ TsO⁻; $\blacksquare$ = Ar₂CHR; c) **1**₂ with three equivalents of Bu₄N⁺ PF₆⁻ (the minor set of signals corresponds to the original CDCl₃-filled capsule). d) ¹⁹F spectrum at 564.5 MHz of **1**₂ with three equivalents Bu₄N⁺ PF₆⁻, x = free PF₆⁻, $\star$ = encapsulated PF₆⁻.

rings. The signals of the complex grew upon further addition of the salt as the original set diminished and at [Bu₄N⁺Cl⁻]/[**1**₂] = 20, no original capsule could be detected. A Job plot revealed that two molecules of **1** complex one anion (data not shown). Since complexation has the strongest influence on the NH signals of **1**₂, the encapsulated chloride ion is likely positioned near the middle of the cavity near the belt of hydrogen bonds, while the remaining space is filled with CDCl₃ molecules (as in Figure 3, middle).

Anion binding by **1**₂ (Table 1) does not appear to depend on the polarity, hydrogen-bonding ability, geometry or the size of the anion. Rather, we propose that encapsulation is driven by solvophobic effects: the anions are better accommodated by

Table 1. Binding constants (K_a) of anion encapsulation complexes, corresponding ΔG^0 values, downfield chemical shifts observed ($\Delta\delta$) for the NH protons of the anion-filled capsule versus the solvent-filled capsule, van der Waals volumes (V), and packing coefficients (PC).

Anion ^[a]	K_a ^[b]	ΔG_{95}^0 ^[c] [kJ mol ⁻¹]	$\Delta\delta$ [ppm]	V ^[d] [Å ³]	PC ^[e]
Cl ⁻	640	-16	0.49	25	0.41
Br ⁻	140	-12	0.31	31	0.42
SCN ⁻	170	-12.6	0.51	43	0.45
ClO ₄ ⁻	270	-13.7	0.19	46	0.46
ReO ₄ ⁻	3400	-20	0.23	49	0.48
BF ₄ ⁻	90	-11.0	0.13	42	0.45
PF ₆ ⁻	4200	-20.5	0.12	58	0.48
IO ₄ ⁻	4600	-20.7	0.12	62	0.49
NO ₃ ⁻	260	-13.6	0.49	34	0.43
TsO ⁻	178	-12.7	0.51, 0.29	115	0.45 ^[f]
<i>n</i> -C ₄ F ₉ SO ₃ ⁻	152	-12.3	0.15, 0.0	144	0.52 ^[f]

[a] Data for B_u4N⁺ salts. [b] $K_a = [1_2X^-]/[1_2][X^-]$. [c] $\Delta G^0 = -RT \ln K_a$. [d] Based on crystallographic data. [e] Calculated for coencapsulation with two CHCl₃ molecules. [f] Calculated for coencapsulation with one CHCl₃ molecule.

the capsule than by the bulk solution. The association constant for the strongly hydrogen-bonding chloride ion is only 2.5 times larger than that of the non-hydrogen-bonding perchlorate ion (Table 1), while the constant for the perchlorate ion is twice as large as that of the bromide ion. Iodide and Br₃⁻ interacted too weakly with the capsule for accurate determination of binding constants by NMR spectroscopy. The strongest binding was observed for periodate, perhenate, and hexafluorophosphate anions; the latter is not considered capable of conventional hydrogen bonding. Accordingly, the interactions of the anions and the NH groups of the capsule may better be described as ion–dipole interactions than as hydrogen bonds.

The role of solvent in the capsule was further explored by NMR experiments. Molecular modeling indicates that the cavity of **1**₂ ($V = 420 \text{ Å}^3$) can accommodate three CHCl₃ molecules ($V = 220 \text{ Å}^3$), with a packing coefficient of 0.51—a value close to the optimal for encapsulation of neutral guests (Figure 3, right).^[18] The three CHCl₃ molecules were directly observed by ¹H NMR spectroscopy in a 2:1 mixture of CHCl₃ and [D₁₂]mesitylene. With the anionic guests, the chemical

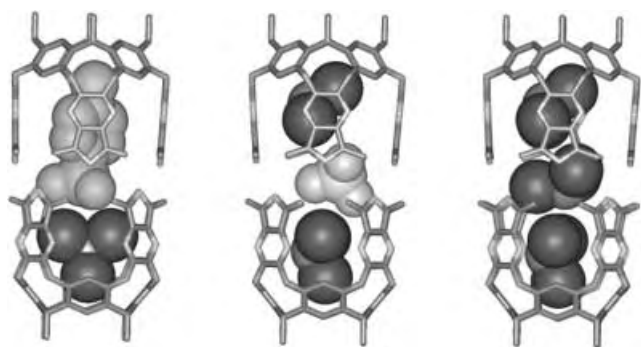


Figure 3. Models of anion encapsulation in **1**₂. Structures were optimized using MM⁺ and AMBER force fields. Left: A large anion (tosylate) and one CHCl₃; middle: a small anion (BF₄⁻) and two CHCl₃ molecules; right: the resting state in CHCl₃ with three solvent guests. Only the first carbon atoms of the peripheral alkyl groups are shown and hydrogen atoms are omitted for viewing clarity.

shifts of coencapsulated CHCl₃ depend on the nature of the anion. For example, in the cases of PF₆⁻, TsO⁻, IO₄⁻, and C₄F₉SO₃⁻, the resonance signals of the coencapsulated CHCl₃ appeared as sharp singlets at $\delta = 5.22, 5.34, 5.41$, and 5.73 ppm , respectively. Two CHCl₃ molecules are present with IO₄⁻ and PF₆⁻, while only one is coencapsulated with TsO⁻ or C₄F₉SO₃⁻. The variations in chemical shift speak for specific interactions between encapsulated anion and CHCl₃.

The newfound affinity of **1**₂ for anions and the well-known affinity of capsules **2**₂ for cations^[19] led to the unprecedented arrangement shown in Figure 4: a two-capsule-separated pair. It forms spontaneously when **1** and **2** are mixed with Et₄N⁺ PF₆⁻ in CDCl₃ in a 1:2:0.25 molar ratio. The Et₄N⁺ ion in the calixarene dimer showed the characteristics

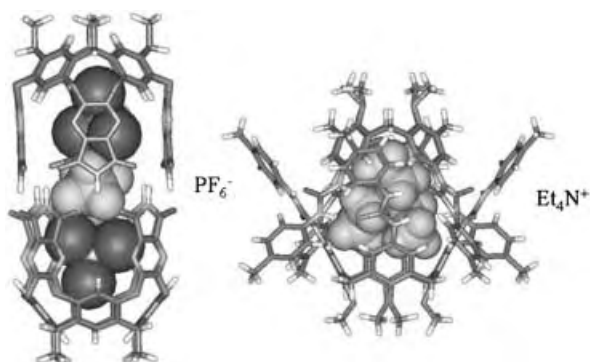


Figure 4. A capsular ion pair: **1**₂·PF₆⁻ and **2**₂·Et₄N⁺. The peripheral alkyl groups are replaced by methyl groups for viewing clarity.

described by Böhmer et al.^[20] in its NMR spectrum, and the PF₆⁻ in the resorcinarene was indistinguishable from its complex described above. No signals of the free salt could be detected in either the ¹H or ¹⁹F NMR spectra. Accordingly, the capsules maintain mechanical barriers between the anion and cation that keep them at least 10 Å apart in a medium of low polarity. The cost of this separation is defrayed by cation– π interactions in one capsule and whatever forces drive the anion into the other. The wide separation contrasts with the contact ion pairs observed with Bu₄N⁺ BH₄⁻ in this solvent,^[21] or other ion pairs in even more competitive media.^[22]

In solution encounters between ions and individual solvent molecules occur so rapidly that the fastest of spectroscopic methods are required for their observation. Within the capsule the time scale is dilated and convenient for conventional NMR spectroscopy. The lipophilic outer surface of these encapsulation complexes also suggests that **1**₂ could be useful to extract anions from aqueous solutions or carry them across membranes. The further possibility of coencapsulating

certain anions with electrophilic molecules augurs well for the facilitation of some S_N2 reactions.

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Unusual Uranyl Tellurites Containing $[\text{Te}_2\text{O}_6]^{4-}$ Ions and Three-Dimensional Networks**

Philip M. Almond, Michael L. McKee, and Thomas E. Albrecht-Schmitt*

Solid-state chemistry of the actinides is the subject of significant investigation because of its relevance to nuclear waste disposal and power generation,^[1] mineralogy,^[2] and catalysis.^[3] One system that is poorly understood is that of the uranyl tellurites, which are currently known only from three minerals, $\text{UO}_2(\text{Te}_3\text{O}_7)$,^[4] $\text{PbUO}_2(\text{TeO}_3)_2$,^[5] and $\text{UO}_2(\text{TeO}_3)$,^[6] and the synthetic phase $\text{Pb}_2\text{UO}_2(\text{TeO}_3)_3$.^[7] In spite of their low representation, these compounds differ substantially in their dimensionality,^[2] the coordination environments of the U^{VI} center, and in the Te^{IV} oxoanions present.

The ubiquitous presence of a stereochemically active lone pair of electrons on the Te^{IV} centers certainly plays a substantial role in the crystalline architecture of this family of compounds. However, the general tendency is for oxoanions containing nonbonding electrons to either not affect the overall dimensionality of U^{VI} compounds, or to reduce it from two-dimensional to one-dimensional, as demonstrated by uranyl iodates^[8,9] and selenites.^[10] In uranyl tellurites this trend is not observed. The ability of Te^{IV} to bind four or five O atoms in its inner sphere, as found in the ternary phases, BaTe_3O_8 ,^[11] BaTe_4O_9 ,^[11] TeSeO_4 ,^[12] $\text{UO}_2(\text{TeO}_3)$,^[6] and $\text{UO}_2(\text{Te}_3\text{O}_7)$,^[4] does not offer a satisfying explanation for the atypical behavior of uranyl tellurites because $\text{Pb}_2\text{UO}_2(\text{TeO}_3)_3$ contains only TeO_3^{2-} ions, and yet it still adopts a three-dimensional architecture.^[7]

To address the unusual bonding in the uranyl tellurite system we are systematically preparing a series of compounds by hydrothermal methods that differ primarily in their counteranions. For example, the reaction of TiCl_4 with $\text{UO}_2(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}$ and Na_2TeO_3 at 180°C in aqueous media for three days produces $\text{Ti}_2[\text{UO}_2(\text{TeO}_3)_2]$ (**1**), whereas, in the absence of TiCl_4 , $\text{Na}_8[(\text{UO}_2)_6(\text{TeO}_3)_{10}]$ (**2**) is isolated instead.

The simplicity of the formula of **1** is quite misleading because its structure is far from predictable. The uranyl tellurite architecture in this compound is constructed from uranyl moieties that are bound by five O atoms to create UO_7 pentagonal bipyramids. These polyhedra edge-share to form dimers. The dimers are joined by bridging TeO_3^{2-} ions to yield one-dimensional chains. The chains are in turn linked by $[\text{Te}_2\text{O}_6]^{4-}$ ions that are bischelating/bridging, producing two-dimensional ${}^2[\text{UO}_2(\text{TeO}_3)_2]^{2-}$ sheets that are separated by Ti^+ ions. Part of a ${}^2[\text{UO}_2(\text{TeO}_3)_2]^{2-}$ sheet is illustrated in Figure 1. Bond valence sum calculations are consistent with U^{VI} and

[*] Prof. T. E. Albrecht-Schmitt, P. M. Almond, Prof. M. L. McKee
179 Chemistry Building
Department of Chemistry
Auburn University, Auburn, AL 36849 (USA)
Fax: (+1) 334 844 6959
E-mail: albreth@auburn.edu

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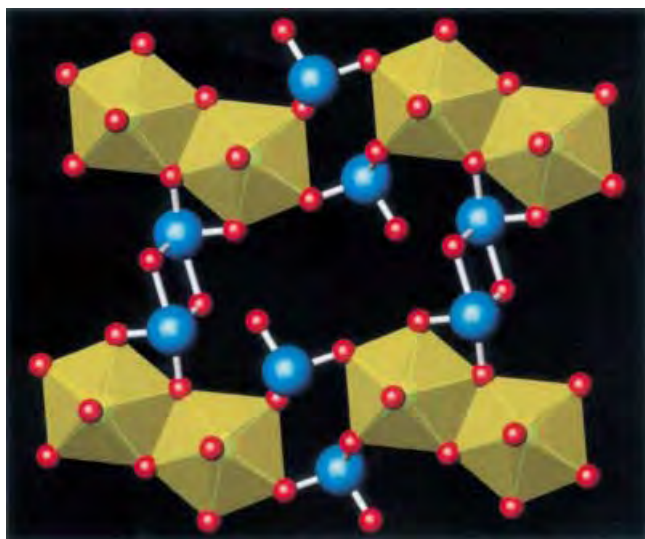


Figure 1. Section of the two-dimensional $[\text{UO}_2(\text{TeO}_3)_2]^{2-}$ sheets in **1**.

provide a value of 5.90,^[13] and the UV/Vis diffuse reflectance spectrum shows characteristic uranyl absorptions near 420 nm.

At first glance the $[\text{Te}_2\text{O}_6]^{4-}$ ion (Figure 2) appears merely to be two TeO_3^{2-} ions forming short interactions with one another, as is common in solids containing the isoelectronic

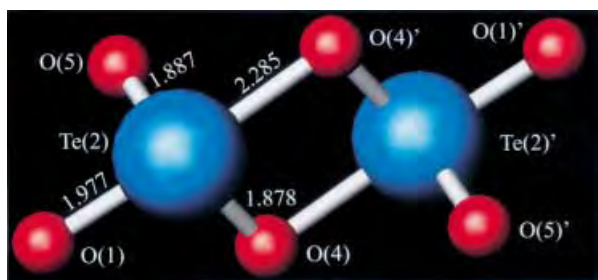


Figure 2. The $[\text{Te}_2\text{O}_6]^{4-}$ ion found in **1**.

iodate, IO_3^- ion.^[8,9] However, it is important to note that the interactions between iodate anions do not result in a perturbation of the geometry around the I^{V} centers. In contrast, the bonding around the Te^{IV} centers in the $[\text{Te}_2\text{O}_6]^{4-}$ ions consists of two short Te–O bonds of 1.878(6) and 1.887(7) Å, one intermediate bond of 1.977(6) Å, and one long bond of 2.285(7) Å. Therefore, the interactions between the two tellurite anions has resulted in a significant change in the bonding around the Te^{IV} centers. The geometry around each tellurium atom is intermediate between that expected

for square-pyramidal TeO_4^{4-} and trigonal-pyramidal TeO_3^{2-} ions. This type of $\text{TeO}_3^{2-} \cdots \text{TeO}_3^{2-}$ interaction has been described as a TeO_{3+1} polyhedron where the additional long Te–O bond represents the fourth vertices.^[11,14] If the long Te–O bonds between tellurite anions are removed, the resultant $[\text{UO}_2(\text{TeO}_3)_2]^{2-}$ chains are very similar to those found in $\text{Sr}[\text{UO}_2(\text{SeO}_3)_2] \cdot 2\text{H}_2\text{O}$ where there are no close Se $\cdots$ O interactions between selenite anions.^[15]

In order for the $[\text{Te}_2\text{O}_6]^{4-}$ ion to form from two TeO_3^{2-} ions, significant repulsive coulombic forces must be overcome. The ligation of the $[\text{Te}_2\text{O}_6]^{4-}$ ion to two highly electron-withdrawing U^{VI} centers is the likely source of stabilization in this system. To test this theory, we modeled the $[\text{Te}_2\text{O}_6]^{4-}$ ion as the neutral $[\text{AlTe}_2\text{O}_6\text{Al}]$ unit using B3LYP density functional methods^[16] with the 6-31G(d) basis set for Al and O and an effective core potential for Te.^[17] All calculations were made with the Gaussian program.^[18]

In the absence of metal centers for binding the tellurite anions, the $[\text{Te}_2\text{O}_6]^{4-}$ anionic dimer is not stable and simply separates into two TeO_3^{2-} ions as the structure is minimized. However, when Al^{2+} ions are placed at opposite edges, the $[\text{Te}_2\text{O}_6]^{4-}$ ion becomes a stable minimum, and the Te–O bond lengths and O–Te–O bond angles determined from this calculation, are in reasonable agreement with those measured from the crystal structure. The calculated distances and angles are given in Table 1. Based upon these calculations it does indeed appear that the metal centers stabilize the formation of the $[\text{Te}_2\text{O}_6]^{4-}$ ion. In contrast, if the same calculation is carried out with SeO_3^{2-} , a stable dimer does not form.

The structure of **2** is substantially different from that of **1** even though they share some of the same structural features. Here the UO_7 pentagonal bipyramids are observed again. However, the Te^{IV} oxoanions consist solely of C_{3v} TeO_3^{2-} ions. The Te–O bond lengths show little variation with distances ranging from 1.848(5) to 1.891(5) Å. These anions bridge UO_7 units to create a three-dimensional network structure that is chiral. Part of the network is shown in Figure 3 with the Na^+ ions omitted. The Na^+ ions reside in small twisting interconnected cavities and channels. Three-dimensional network structures are not common with U^{VI} and typically require cross-linking of uranium oxide layers by additional building units,^[19] or the orthogonal orientation of uranyl polyhedra with respect to one another.^[20,21]

The chiral nature of **2** is likely a consequence of the presence of stereochemically active lone pairs of electrons on the Te^{IV} centers. While anions of this type often promote the formation of noncentrosymmetric structures due to the alignment of the lone pairs of electrons,^[22] this property is not typically observed in uranyl structures, because the

Table 1. Selected bond lengths [Å] and angles [°] for the $[\text{Te}_2\text{O}_6]^{4-}$ ion in **1**. Calculated bond lengths and angles from DFT calculations are given in parentheses.

Bond lengths [Å]			
Te(2)–O(1)	1.977(6) (2.036)	Te(2)–O(4)'	2.285(7) (2.138)
Te(2)–O(4)	1.878(6) (1.903)	Te(2)–O(5)	1.887(7) (1.959)
Bond angles [°]			
O(1)–Te2–O(4)	92.6(3) (89.8)	O(4)–Te2–O(4)'	78.1(3) (76.6)
O(1)–Te2–O(4)'	160.6(3) (160.3)	O(4)–Te2–O(5)	97.4(3) (100.6)
O(1)–Te2–O(5)	82.9(3) (79.3)	O(4)–Te2–O(5)	81.5(3) (89.4)

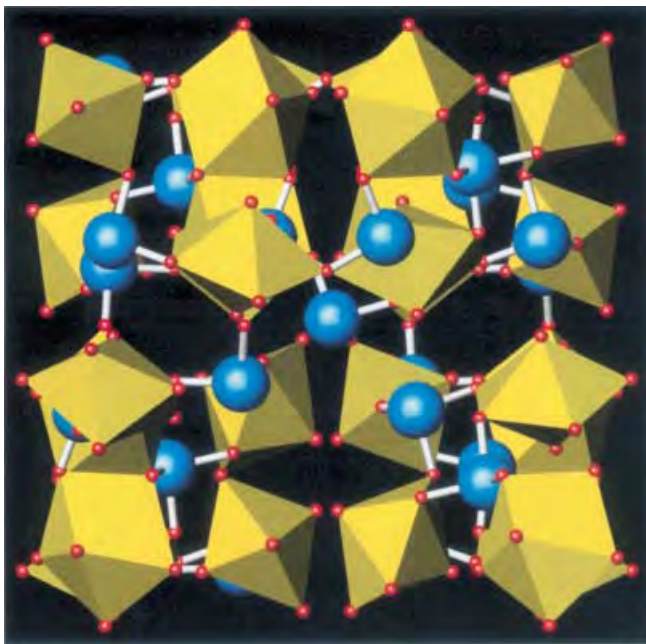


Figure 3. Part of the three-dimensional network structure of **2**. Na^+ ions have been omitted for clarity.

uranium atoms in UO_6 tetragonal bipyramids or UO_8 hexagonal bipyramids often reside on centers of inversion or higher symmetry. While UO_7 pentagonal bipyramids cannot be placed on inversion centers without disorder, they are often related to one another through such centers. A consequence of the chirality of **2** is that it should display second-harmonic generation (SHG) properties. This attribute was confirmed by irradiating a sample with a 1064 nm laser; the compound revealed a distinct green emission (532 nm) consistent with second-harmonic generation with a response of approximately $5 \times$ that of $\alpha\text{-SiO}_2$.

In conclusion, we have demonstrated that the A- UO_2^{2+} -Te-O system is quite unlike that found with other uranyl compounds that contain oxoanions with nonbonding electrons. The stabilization of acceptor orbitals on the Te^{IV} centers by uranyl cations offers a partial explanation of the unusual bonding observed thus far. Further studies are needed to explain why uranyl tellurites containing only TeO_3^{2-} ions are often three-dimensional.

Experimental Section

1: Na_2TeO_3 (320 mg, 1.45 mmol), $\text{UO}_2(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}$ (180 mg, 0.424 mmol), TiCl_4 (130 mg, 0.542 mmol), and distilled and Millipore filtered water (1.5 mL) were loaded in a 23-mL PTFE-lined autoclave. The autoclave was heated at 180°C for three days, and slow cooled at 9 K h^{-1} to 22°C . The product consisted of orange tablets of **1**. Yield for **1**: 75 mg (17 % based on U). EDX analysis provided a $\text{Ti}:\text{U}:\text{Te}$ ratio of 2:1:2.

2: Na_2TeO_3 (500 mg, 2.26 mmol), $\text{UO}_2(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}$ (180 mg, 0.424 mmol), CsCl (150 mg, 0.891 mmol), and distilled and Millipore filtered water (1.5 mL) were loaded in a 23-mL PTFE-lined autoclave. All other conditions were the same as for **1**. The product consisted of bright yellow dodecahedral crystals of **2**. Yield for **2**: 190 mg (76 % based on U). EDX analysis provided a $\text{Na}:\text{U}:\text{Te}$ ratio of 8:6:10.

X-ray structural analyses: $\text{Ti}_2[\text{UO}_2(\text{TeO}_3)_2]$ (**1**): orange tablet, crystal dimensions $0.102 \times 0.125 \times 0.150$ mm, triclinic, $P\bar{1}$, $Z = 2$, $a = 7.4054(9)$, $b = 7.9268(9)$, $c = 8.994(1)$ Å, $\alpha = 94.122(2)$, $\beta = 107.438(2)$, $\gamma = 107.180(2)^\circ$, $V = 471.08(9)$ Å³ ($T = 193$ K), $\mu = 573.50\text{ cm}^{-1}$, $R_1 = 0.0319$, $wR2 = 0.0811$.^[23]

$\text{Na}_8[(\text{UO}_2)_6(\text{TeO}_3)_{10}]$ (**2**): yellow dodecahedron, crystal dimensions $0.116 \times 0.124 \times 0.140$ mm, cubic, $I2_3$, $Z = 4$, $a = 16.8969(5)$, $V = 4824.2(2)$ Å³ ($T = 193$ K), $\mu = 261.76\text{ cm}^{-1}$, $R_1 = 0.0178$, $wR2 = 0.0505$.^[23] Bruker APEX CCD diffractometer: $\theta_{\text{max}} = 56.60^\circ$ (**1**) and 56.48° (**2**), $\text{MoK}\alpha$, $\lambda = 0.71073$ Å, $0.3^\circ \omega$ scans, 4745 (**1**) and 24374 (**2**) reflections measured, 2301 (**1**) and 2013 (**2**) independent reflections all of which were included in the refinement. The data was corrected for Lorentz polarization effects and for absorption (analytical and SADABS), solutions were solved by direct methods, anisotropic refinement of F^2 by full-matrix least-squares, 119 (**1**) and 108 (**2**) parameters. Further details on the crystal structure investigation(s) 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 numbers CSD-412560 and CSD-412561.

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A C_{2v} -Symmetric Barbaralane**

Markus Reiher* and Barbara Kirchner*

Barbaralane **1** (see Figure 1) is one of the fluxional molecules that undergo a degenerate Cope rearrangement. It was proposed by W. von E. Doering that the activation barrier of the Cope rearrangement is lower in **1** than in 3,4-homotropilidene^[1] as barbaralane is already fixed in the appropriate boat conformation by a bridge between the two corner atoms C1 and C5. If this activation barrier were lowered even further, one might arrive at a symmetrical and therefore homoaromatic, biradical, or biradicaloid ground state. The objective is to transform the double-minimum system **1** into one with a single minimum by increasing the symmetry, that is, by changing from a C_s - to a more symmetric (C_{2v}) ground-state structure. Much effort was made to find a symmetrical ground-state structure by studying various derivatives experimentally and theoretically (e.g., semiempirical MO calculations^[2,3]). The most valuable overview was given by Quast et al.^[4] Additional reviews can be found in refs. [1,5,6] and references cited therein. These investigations yielded the following results: At the C2 and the C6 positions only electron-withdrawing groups that are π acceptors lower the barrier. Aryl groups at these positions are most effective. The same π -acceptor substituent causes only slight changes at the C3 and C7 positions.

From the possible derivatives of **1** we chose to replace the 2,4,6,8-positions of barbaralane by heteroatoms (Figure 1). The use of nitrogen or oxygen has been suggested.^[4] A derivative of 2,4,6,8-tetraazabarbaralane (**2a**) was studied before; it does not give a symmetrical ground state (**2b** or **2c**), but the activation barrier of the Cope rearrangement is

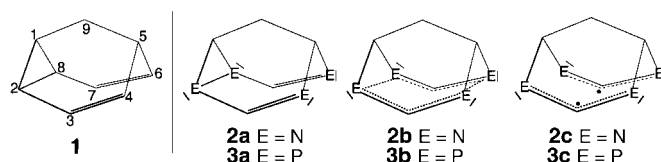


Figure 1. Barbaralane **1** and some possible heterobarbaralanes **2**.

lowered relative to that of the carbon analogue.^[7] This is in accordance with the observation of Schnieders et al., who found lowering of the Cope barrier in a 2,6-diazasemibullvalene derivative^[8] relative to the carbon analogue. A logical consequence from these studies is replacement of carbon by phosphorus atoms, which can be achieved by replacing a CH moiety with a P atom as they are valence isoelectronic. Phosphorus produces smaller bond angles than carbon, and this can affect the stability of cyclic compounds.^[9] Hence, we proposed to study the novel compound 2,4,6,8-tetraphosphabarbaralane (**3**), and we also re-examined parent barbaralane (**1**) and 2,4,6,8-tetraazabarbaralane (**2a**).

Figure 2 shows the three molecules with selected bond lengths, as obtained from DFT geometry optimizations (see Methods of Calculation). The most striking feature is that **3**

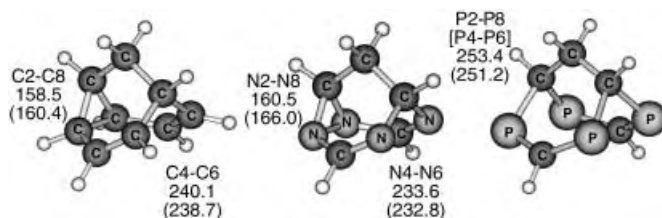


Figure 2. B3LYP/TZVPP optimized structures of barbaralane (left), tetraazabarbaralane (middle), and tetraphosphabarbaralane (right). Distances are given in picometers (BP86/TZVPP values in parentheses).

clearly has C_{2v} symmetry. Frequency analysis of this geometrical arrangement indeed confirmed a minimum structure.

The overall agreement between the B3LYP and BP86 (in parentheses) bond lengths is very good: deviations are less than 2 pm (with the exception of the N2–N8 bond length, for which the BP86 value deviates by 5.5 pm from the B3LYP value). Therefore, in the following discussion we concentrate on B3LYP/TZVPP data. Closer inspection reveals that the C1–C9–C5 substructure (1,5-bridge) is almost identical in all the barbaralanes (e.g., the C9–C5 distances vary between 154.7 and 152.1 pm). Deviations are within 2.6 pm and are due to bond shortening in the heterobarbaralanes compared to the parent barbaralane. The two bonds building this bridge are of almost identical length in **1** and **2a**, and completely identical in **3**. Whereas all nitrogen–carbon distances are contracted by about 5 pm compared to the equivalent C–C distances in parent barbaralane, the N2–N8 distance is longer and the N4–N6 distance is shorter than the equivalent C–C distance, and this results in a molecule more symmetrical than the parent barbaralane.

In **3** we found for every interatomic distance involving phosphorus a bond elongation by more than 25 pm compared to the parent barbaralane **1**. Since the P2[4]–P8[6] distances (253.4 pm) are larger than the typical σ bond lengths in P_6 ^[10]

[*] Dr. M. Reiher
 Lehrstuhl für Theoretische Chemie
 Universität Erlangen-Nürnberg
 Egerlandstraße 3, 91058 Erlangen (Germany)
 Fax: (+49)91318527736
 E-mail: markus.reiher@chemie.uni-erlangen.de

Dr. B. Kirchner
 Physikalisch-Chemisches Institut
 Universität Zürich
 Winterthurerstrasse 190, 8057 Zürich (Switzerland)
 Fax: (+41)635 6838
 E-mail: kirchner@pci.unizh.ch

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(236 and 222 pm) and P_4 (222 pm)^[11] (all distances from B3LYP/TZVP calculations), we assume we are not dealing with such a bond type. This is confirmed by consideration of the HOMOs and the electron localization function (ELF; see below). Note that for some substituted semibullvalenes it was previously observed that shortening of the 1,5-bridge is accompanied by opening of the cyclopropane ring,^[4] as can be seen in tetraphosphabarbaralane in Figure 2. Thus, the symmetrical phosphabarbaralane is achieved by two geometrical changes: 1) the C1-C9-C5 bridge is shortened, and 2) the angle at C1 is enlarged, that is, the C2-C8 bond is elongated.

Unrestricted B3LYP/TZVP calculations on **3** showed that the energy of the lowest lying triplet state (biradical) was more than 100 kJ mol⁻¹ higher than that of the lowest lying singlet state. While this singlet state (as obtained in a restricted Kohn–Sham formalism) has no biradicaloid nature, we examined a possible lower lying biradicaloid singlet structure by calculating an unrestricted singlet with the triplet wavefunction as the starting approximation. This led to the same energy and structure as in the restricted calculation, and hence the best description of **3** is homoaromatic (**3b**). To test whether the single-determinant Kohn–Sham and coupled-cluster schemes describe **3b** adequately, CAS(12,12) calculations on **3b** were performed. They revealed a squared weight of 0.84 for the configuration state function with the same occupation as the Kohn–Sham determinant, which indicates the absence of a multideterminant case here. Furthermore, the CASSCF calculations confirm that the ground-state multiplicity of **3b** is singlet. According to the CASSCF results the triplet state is more than 200 kJ mol⁻¹ higher in energy. Tetraphosphabarbaralane is thus homoaromatic, and Lewis structure **3b** is the best representation of the bonding situation.

By considering the HOMOs of the three barbaralanes, additional insight can be gained (Figure 3). Note that the HOMOs for each structure are plotted from different angles to give an optimal view.

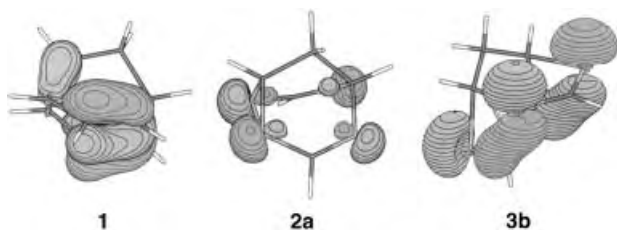


Figure 3. HOMOs of **1**, **2a**, and **3b**. The cyclopropane ring in **1** and **2a** is on the left-hand side.

The HOMO of **1** has two localized π orbitals at positions 3,4 and 6,7 as well as two sp^3 - p σ -type orbitals at the cyclopropyl moiety. The frontier orbitals of **1** are mainly built from p atomic orbitals, while the frontier orbital region of **2a** and **3b** contains MOs of the lone pairs. The HOMO of **3b** deviates from that of **2a**, as **3b** shows a p_z - p_z -like interaction without involvement of σ bonding (i.e., homoaromaticity). Tetraazabarbaralane **2a** and tetraphosphabarbaralane **3b** have in common that there is no contribution to the HOMO from the

atomic orbitals in positions 3 and 7. The ELF shown in Figure 4 facilitates further comprehension of the bonding situation.

In contrast to **1** and **2a** the phosphabarbaralane **3b** shows extensive basins that indicate extended lone pairs (double-headed arrow in Figure 4). The ELF isosurface can be

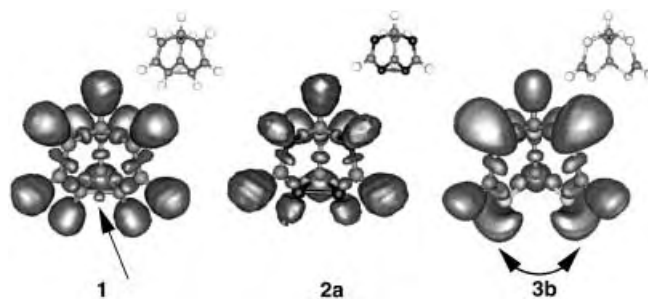


Figure 4. Isosurfaces for ELF = 0.85 of barbaralane (left), tetraazabarbaralane (middle), and tetraphosphabarbaralane (right).

increased up to a value of 0.99 for **3b** before it disappears at these lone pairs, whereas the lone pairs in **2a** already disappear at a value of 0.96. Both observations indicate highly localized lone pairs in the case of **3b** and hence a repulsive interaction between the P–P pairs which causes the long P–P distances. Further inspection reveals a bubblelike region of ELF on the C2–C8 bond in **1** (arrow in Figure 4). Such a bubble can only be obtained in the tetraazabarbaralane **2a** if the isosurface value is lowered to ELF = 0.72, and for the phosphorus compound **3b** no such bubble is observed. This indicates σ -type bonding at the 2,8-positions in **1** and in **2a**, but no such bonding in **3b**. Whereas the double bonds (dumbbell ELF) can be clearly distinguished from the single bonds (spherical ELF) in **1** and **2a**, **3b** has oval-like regions at all four bonds (positions 2-3, 3-4, 6-7, and 7-8), and this again indicates homoaromaticity.

To estimate the stability of the C_{2v} -symmetric barbaralane **3b**, we calculated the activation barrier for the Cope rearrangement of all three molecules together with the barrier of the experimentally known tetraazabarbaralane derivative **4a** (Figure 5). This molecule was used^[7] to estimate an experimental value for the Cope barrier of the parent system **2a** by increment analysis, because the synthesis of **2a** might not be an easy task. For instance, instead of the sought-

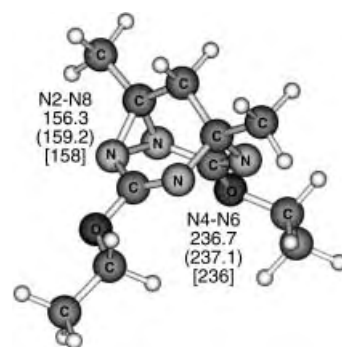


Figure 5. Minimum structure of **4a**. Distances are given for B3LYP/TZVP and BP86/TZVP (in parentheses) and compare very well with experimental data (in brackets).^[13]

for tetraazasemibullvalene, 1,3,5,7-tetrazocines^[12] were obtained.

For the C_s -symmetric barbaralanes **1** and **2a** a transition state was obtained on enforcement of C_{2v} symmetry. In the case of **4a** a transition state was found by increasing the N2–N8 distance stepwise in several constrained optimization procedures. For **3b** the “inverse barrier” can only be estimated from a C_s -distorted structure: We looked at the P–P distance of 1,2,3,4,5,6,7,8-octaphosphabarbaralane (P_8CH_2), which has a C_s minimum structure (B3LYP/TZVP), and forced one P–P distance of **3b** to become, in a stepwise fashion, closer to the corresponding P–P bond length of the optimized C_s -symmetric P_8CH_2 . Here, we also applied several constraint optimization procedures. The results of our calculations are given in Tables 1 and 2. Whereas in Table 1 only electronic energy differences ΔE are listed, Table 2 lists the electronic energy differences with corrections for zero-point energy ($\Delta D^\ddagger$) and enthalpies $\Delta H^\ddagger$ at 298.15 K. Table 1 demonstrates how well the DFT methods perform in comparison to more accurate quantum chemical methods, while Table 2 serves for comparison with experimental data.

Table 1. Barrier heights $\Delta E = E_{C_s}^{\text{el}} - E_{C_s}^{\text{el}}$ [kJ mol^{−1}], obtained with different methods and basis sets. The C_s -symmetric structures were always taken as the zero-energy reference levels.

Compound	B3LYP		BP86/RI		MP2/RI		CCSD		CCSD(T)
	TZVP	TZVPP	TZVP	TZVPP	TZVP	TZVPP	SVP	TZVP	
1	28.5	28.6	19.7	20.0	17.7	13.5	64.0	56.9	48.6
2	14.0	14.2	3.8	4.5	−8.8	−11.6	43.1	45.7	16.6
3	−5.8	−5.9	−6.7	−5.7	−10.2	−14.1	−2.6	−2.8	−[a]
4	53.4	–	32.7	–	–	–	–	–	–

[a] See Methods of Calculation.

The DFT data in Table 1 indicate no strong dependency on the basis-set size. The BP86 functional systematically underestimates the B3LYP barriers by about 10 kJ mol^{−1} but gives similar trends. Note that this systematic deviation does not occur for **3**, because the B3LYP C_s -symmetric structure was used for the corresponding BP86 single-point calculations. The MP2 calculation finds not only a C_{2v} -symmetric tetraphosphabarbaralane, but also a C_{2v} -symmetric tetraazabar-

baralane **2**. This MP2 result for **2** neither meets the predictions of all other methods nor the experimental findings for **4a**. The fact that the CCSD and CCSD(T) data (where available) are in reasonable agreement with the B3LYP data is very satisfying. It is unlikely that this agreement results from an error cancellation due to the smaller basis set used for the CCSD(T) calculations, because the CCSD calculations show that the barriers differ comparatively little with increasing basis-set size (i.e., from the SVP to the TZVP basis set). On the other hand, the correction caused by the perturbatively included triplets is much larger (cf. CCSD/SVP and CCSD(T)/SVP). This systematic investigation gives us the confidence to be able to describe all structures sufficiently accurately with DFT/B3LYP.

Table 2 compares our DFT data with experimental results. Whereas the B3LYP data for parent barbaralane **1** compare very well with experimental results, the agreement for the tetraazabarbaralane **2** is rather poor. This is not surprising, since several approximations were made to obtain the “experimental” value. To obtain this barrier we took an estimate of the increment from ref. [7], made for $\Delta G^\ddagger$, and added it to the experimental value of $\Delta H^\ddagger$ from ref. [4].

However, for estimating the increment Moskau et al.^[7] already made the following assumptions: 1) a methoxy is comparable to an ethoxy group, 2) methyl groups in positions 1 and 5 are negligible, 3) the situation in the semibullvalene is compared to the case of barbaralane, and 4) substitution at positions 3 and 7 is equivalent to substitution at positions 2 and 6. Alto-

gether the change in energy is in the correct direction, but it could be larger by a factor of two (see the extensive data collection in ref. [4]).

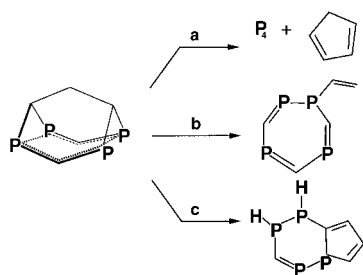
To circumvent the ambiguities of increment analysis in deriving experimental barriers we directly calculated the barrier of **4a**, which Moskau et al.^[7] measured in NMR experiments. We restricted ourselves to DFT calculations with the TZVP basis set, which have proven to be sufficiently accurate. The B3LYP/TZVP value for $\Delta H^\ddagger$ (44.3 kJ mol^{−1}) is in good agreement with the experimental value (41.6 kJ mol^{−1}). Again the BP86/TZVP barrier is more than 10 kJ mol^{−1} lower, which is consistent with our findings for **1** and **2**.

Another way to examine the stability of the symmetrical tetraphosphabarbaralane **3b** is to consider its decomposition reactions. Decomposition to P_4 and cyclopentadiene (Scheme 1, path a) is assumed to be the thermodynamic sink. We found that these two molecules are only about 150 kJ mol^{−1} more stable than 2,4,6,8-tetraphosphabarbaralane (see Table 3). However, this is not a good estimate for molecules that possibly serve as starting materials for the synthesis of **3b** or which result from rearrangement of **3b**. Therefore, we also calculated the decomposition to give a retro-Diels–Alder product (i.e., a tetraphospho derivative of 7-vinyl-1,3,5-cycloheptatriene, path b), and the formation of a dihydroindene derivative (path c).

Table 2. Barrier heights $\Delta D^\ddagger = D_{0,C_{2v}} - D_{0,C_s}$ (0 K) and $\Delta H^\ddagger = H_{C_{2v}}^{298} - H_{C_s}^{298}$ [kJ mol^{−1}] (298.15 K). The C_s -symmetric structures were always taken as the zero-energy reference levels.

Compound	B3LYP		BP86/RI		exp.	
	TZVP	TZVPP	TZVP	TZVPP	$\Delta D^\ddagger$	$\Delta H^\ddagger$
1	27.5	29.2	24.4	26.7	16.4	18.5
2	11.7	13.6	13.1	14.8	3.7	4.7
3	−5.8	−5.8	−5.1	−4.8	−8.5	−8.6
4	44.3	44.3	–	–	23.3	27.8

[a] This value was obtained by adding an increment for the $\Delta G^\ddagger$ value of parent barbaralane to its $\Delta H^\ddagger$ value. The increment was estimated by the authors of ref. [7] to obtain a value for the barrier of structure **2a** from that of **4a**.



Scheme 1. Possible decomposition reactions of tetraphosphabarbaralane.

Table 3. Energies [kJ mol⁻¹] for the model decomposition reactions a–c in Scheme 1, calculated with B3LYP/TZVPP. ΔE denotes the electronic energy difference, ΔD_0 also includes the zero-point vibrational energies, and ΔH at 298.15 K is the enthalpy calculated within the harmonic force-field approximation.

reaction	ΔE	ΔD_0	ΔH
a	-146.2	-148.4	-159.5
b	120.9	107.6	112.9
c	10.1	-5.5	-3.4

The reaction energies and enthalpies for the decomposition reactions a, b, and c are given in Table 3. While the cycloheptatriene derivative in reaction b is more than 100 kJ mol⁻¹ less stable than **3b**, the dihydroindene compound in reaction c is of similar stability to **3b**. Because the activation barrier for decomposition reaction c may be high due to the extensive rearrangement of the molecular σ -bonded skeleton, we assume that tetraphosphabarbaralane is a feasible synthetic target.

Apart from X-ray structure analysis, vibrational spectroscopy could be an important experimental tool for identification of **3b**. From the calculated IR line spectrum of **3b**, compared with that of **1** in Figure 6, four characteristic intensive normal modes can be identified at 582, 825, 976, and 1264 cm⁻¹. These may serve as diagnostic bands in an experimental spectrum.

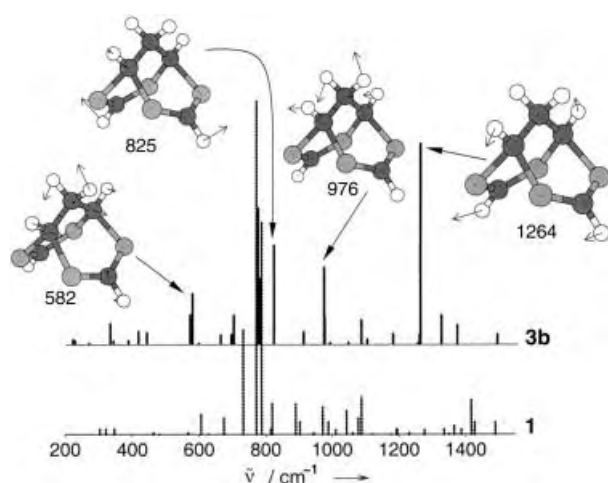


Figure 6. Characteristic normal vibrations of C_{2v} -symmetric tetraphosphabarbaralane (top) and barbaralane (bottom). Wavenumbers are given in cm⁻¹ (B3LYP/TZVPP). Each normal mode is indicated by small arrows on the atoms of the molecule.

In ref. [5] the authors write “There remains the dearth of neutral homoaromatics.” and further: “Quast reports observing vibronically excited homoaromatic semibullvalene and barbaralanes under ordinary condition. Even more exciting is his evidence for homoaromatic semibullvalenes and barbaralanes being of lower energy than the corresponding localized forms in highly dipolar solvents. Surely ground-state homoaromatic semibullvalenes and barbaralanes cannot be far away.”

Tetraphosphabarbaralane is such a symmetrical barbaralane. Our study demonstrates that barbaralanes become the more symmetrical the heavier the heteroatoms in positions 2,4,6,8 are. In the case of phosphorus, we found a fully symmetrical ground state, that is, we have presented the first example of a neutral C_{2v} -symmetric ground-state barbaralane at zero temperature. We tested **3b** against decomposition and could show it is even stable from a purely thermodynamic viewpoint. Now we would like to let the experimentalists take their turn and see whether 2,4,6,8-tetraphosphabarbaralane is stable under laboratory conditions.

Methods of Calculation

We employed DFT with the functional BP86^[16,17] and the hybrid functional B3LYP^[18,19], second-order Møller–Plesset (MP2) perturbation theory, the coupled-cluster models CCSD and CCSD(T), and multiconfiguration SCF calculations with CAS(12,12) to gain a consistent picture independent of the method, although systematic investigations of organophosphorus compounds were already undertaken by Nguyen et al. The main conclusion of their broad study was that “the B3LYP method, when employed with a large basis set, yields energetic results comparable to the CCSD(T) results”.^[20] In addition, several studies could show the excellent agreement of the B3LYP with the CCSD(T) method for the Cope rearrangement of many different molecules, including bullvalenes; see ref. [21] and references therein. The CCSD(T) calculations are needed to support the other methods, as such calculations lack exact exchange (DFT/BP86), non-dynamical correlation (DFT/BP86, DFT/B3LYP), and dynamical correlation (CASSCF). As the CASSCF calculations are able to confirm whether the electronic structure of a molecule is dominated by a single configuration but otherwise are less accurate than CCSD and CCSD(T), they were used for this purpose only. The all-electron DFT calculations and MP2 calculations were carried out with the programs provided by the Turbomole 5.1 suite.^[22] For the MP2^[23] and the BP86^[24,25] calculations the resolution-of-identity (RI) technique was applied. Ahlrichs’s TZVPP basis set (i.e., TZV kernel^[26] + polarization functions from Dunning’s cc-pVTZ, as implemented in Turbomole) was used for DFT and MP2 calculations. To demonstrate the basis-set dependence, we also report TZVP results.

The CCSD(T) and CASSCF calculations were performed with the program Dalton^[27] on the B3LYP optimized structures. Since the TZVPP basis set is too large to sustain such correlation methods we employed Ahlrichs’s SVP and TZVP basis sets.^[26,28] Furthermore, tetraphosphabarbaralane is beyond the scope of current standard CCSD(T) calculations, as it is known^[29] that at least triple-zeta basis sets must be used. This situation is complicated further by the fact that a frozen-core approximation can hardly be applied, because test calculations have revealed that at most the energetically lowest lying four molecular orbitals can be frozen.

All frequency analyses were performed within the harmonic approximation with the SNF program package^[30,31] as numerical first derivatives of analytical gradients of the total electronic energy obtained from Turbomole. The electron localization function (ELF), which we utilize for understanding electronic structure, is a measure of the spherically averaged Fermi hole around a reference electron.^[32] It is mapped onto an interval $0 < \text{ELF} < 1$. $\text{ELF} \approx 1$ indicates areas of a localized exchange potential, where electrons are highly localized.

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A Highly Reactive Uranium Complex Supported by the Calix[4]tetrapyrrole Tetraanion Affording Dinitrogen Cleavage, Solvent Deoxygenation, and Polysilanol Depolymerization**

Ilia Korobkov, Sandro Gambarotta,* and Glenn P. A. Yap

Pyrrole-based polyanions are versatile ligands for *f* block metals which have been proved capable of assembling large cluster structures and of substantially increasing the reactivity of their low-valent derivatives. This is especially evident in the chemistry of divalent samarium, where the utilization of tetra- and dipyrrolyl anions leads to a larger extent of dinitrogen reduction through interaction with four metal centers.^[1,2] However, a complete breakage of the N–N bond, as observed in transition-metal chemistry,^[3] has not been observed in lanthanide chemistry, despite the possibility of assembling high-nuclearity low-valent clusters.^[4]

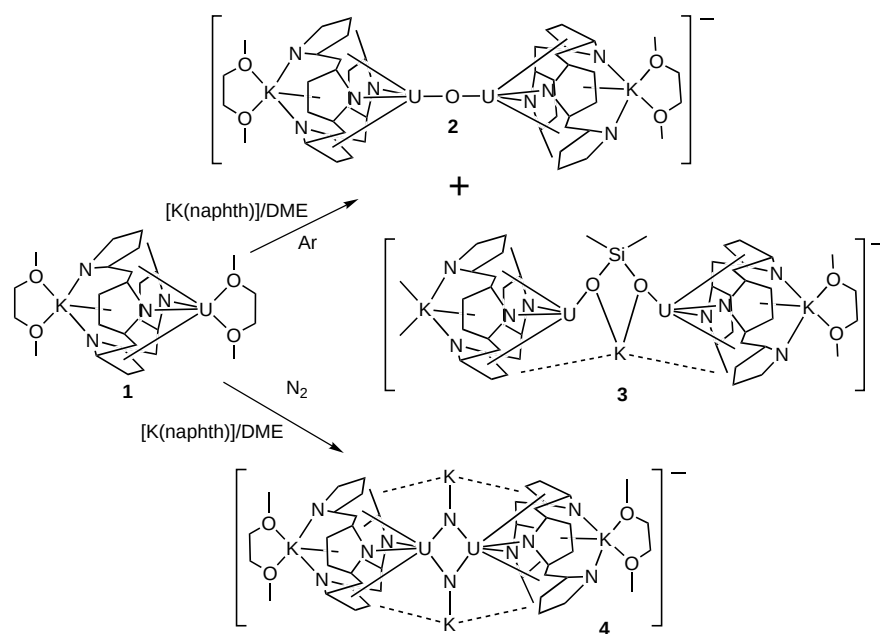
Trivalent and lower valence uranium complexes might be promising substrates for N₂-activation purposes. For example, trisamide derivatives have recently provided the first two examples of dinitrogen fixation in actinide chemistry,^[5] while the only existing complex of a formally divalent uranium amide displays a rare μ, π coordination of toluene.^[6] These studies suggest that a high level of reactivity may be expected for low-valent uranium compounds with N-donor-based ligands. In addition, the possibility of uranium exhibiting several oxidation states and of affording multielectron reductions makes its low-valent derivatives particularly desirable. Accordingly, a preliminary study has shown that a trivalent uranium tetrapyrrolyl complex may perform different types of solvent fragmentation, C–H bond oxidative addition, and ligand isomerization.^[7]

Herein, we describe the results of our attempts to prepare a highly reduced uranium complex, which results in a surprising variety of processes including dinitrogen cleavage, solvent deoxygenation, and polysilanol depolymerization.

The starting complex [(Et₈-calix[4]tetrapyrrole)U(dme)][K(dme)] (**1**, DME = 1,2-dimethoxyethane) was synthesized by using the procedure previously reported for the preparation of the cyclohexyl congener^[7] by the direct reaction of [UI₃(dme)₂] with the tetrapotassium salt of the Et₈-calix[4]-tetrapyrrole ligand (Scheme 1). The crystalline compound, isolated upon cooling the solution in DME, was characterized by X-ray crystallography (see Supporting Information) and standard analytical techniques.

[*] Prof. S. Gambarotta, Dr. I. Korobkov, Dr. G. P. A. Yap
Department of Chemistry
University of Ottawa
Ottawa, ON, K1N 6N5 (Canada)
Fax: (+1) 613-5672-5170
E-mail: sgambaro@science.uottawa.ca.

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Scheme 1. Synthesis of **2-4**.

The reduction of the trivalent **1** with [K(naphthalenide)] carried out under Ar and in DME afforded a mixture of two different crystalline compounds. Manual separation of the crystalline mass under a microscope allowed the structural determination of the two species. In spite of the employment of a strong reducing agent, the first complex was a mixed-valence, dinuclear anionic U^{III}/U^{IV} μ -oxo derivative $[[K(dme)(calix[4]tetrapyrrole)U]_2(\mu-O)][K(dme)_4]$ (**2**, Figure 1). Given the reproducibility of the reaction, the high

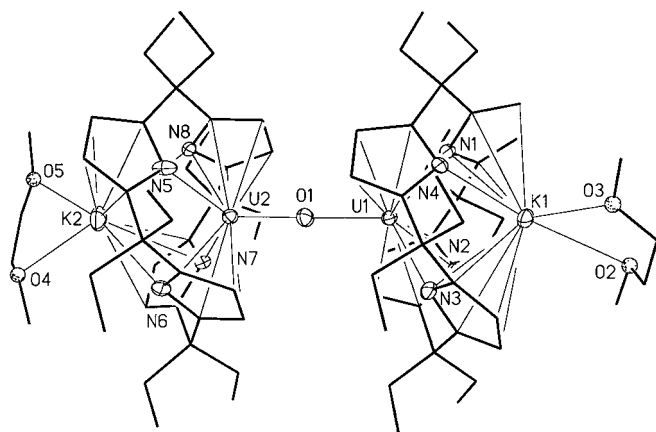


Figure 1. Thermal ellipsoid plot of the anionic moiety of **2**; bond lengths [Å] and angles [°]: U1-O1 2.226(10), U2-O1 2.017(10), U1-N1 2.539(12), U1-N2 2.748(11), U1-N3 2.542(12), U1-N4 2.757(10), K1-N1 3.072(11), K1-N3 3.200(12); U1-O1-U2 179.0(6).

yield and the stability of [K(naphthalenide)] solutions in DME, the formation of **2** is likely to be the result of a DME deoxygenation reaction performed by a transient intermediate. Furthermore, the presence of both methane and ethylene was clearly detected in the gas chromatogram of the reaction

mixture, thus substantiating the proposal of DME fragmentation. The cleavage of DME, although rare, is not particularly surprising given the variety of THF fragmentation patterns displayed by tri- and tetravalent uranium complexes of a closely related ligand system.^[7]

The second product was even more unexpected. The crystal structure shows that the complex is the trivalent $[[[K(dme)(calix[4]tetrapyrrole)U](\mu-Me_2SiO_2)(\mu-K)\{U-(calix[4]tetrapyrrole)K\}[K(dme)_4]]_n]$ (**3**, Figure 2). This species is an infinite anionic polymer counterbalanced by discrete $[K(dme)_4]$ cations. The polymer asymmetric unit consists of a dinuclear anion formed by two different $[(calix[4]tetrapyrrole)UK]$ moieties bridged by Me_2SiO_2 and one potassium atom. In the first moiety the potassium atom is solvated by one

DME molecule, while in the second moiety the potassium atom is connected to the pyrrolyl ring of another dinuclear unit, thus assembling the polymeric structure.

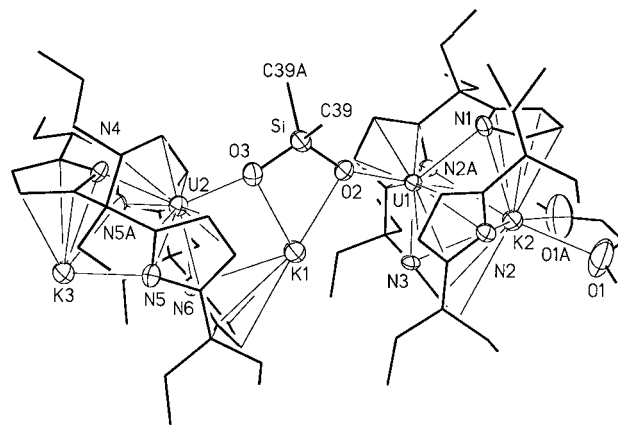


Figure 2. Thermal ellipsoid plot of the anionic moiety of **3**; bond lengths [Å] and angles [°]: U1-N1 2.555(19), U1-N2 2.724(12), U1-N3 2.541(16), U1-O2 2.178(15), U2-O3 2.20(15), K1-O2 2.727(15), K1-O3 2.819(16), O2-Si 1.627(15), O3-Si 1.586(17), K1-N6 3.047(18), K3-N4 3.060(18), K2-N2 3.05(14), K2-N3 3.258(18); O2-Si-O3 109.0(9), O2-K1-O3 56.2(5), U1-O2-Si 157.6(9), U2-O3-Si 16.5(10).

The trivalent state of **3** suggests that the complex was generated by the attack of a transient, highly reactive polysilanol species (silicon grease) which had contaminated the reaction flask. It is noteworthy that solutions of [K(naphthalenide)] in DME do not react with silicon grease over a long time period. As expected, reactions carried out without exposure to polysilanols yielded analytically pure **2** as the only detectable reaction product. This result was reproduced in six separate experiments.

Identical reactions carried out under dinitrogen afforded the unprecedented dinuclear, anionic μ -nitrido U^V/U^{IV} mixed-valent complex, $[[K(dme)(calix[4]tetrapyrrole)U]_2(\mu-NK)_2][K(dme)_4]$ (**4**) contaminated with small quantities of **2**. Experiments carried out in Schlenk tubes, rather than in a N_2 -filled dry-box, also gave **4** contaminated by a small amount of **2** as well as a variable amount of **3**. Analytically pure samples of **4** were conveniently obtained upon recrystallization of the crude crystalline mass from DME/hexane mixtures (61% yield). Complex **4** is a symmetry-generated anionic dimer (Figure 3) consisting of two crystallographically iden-

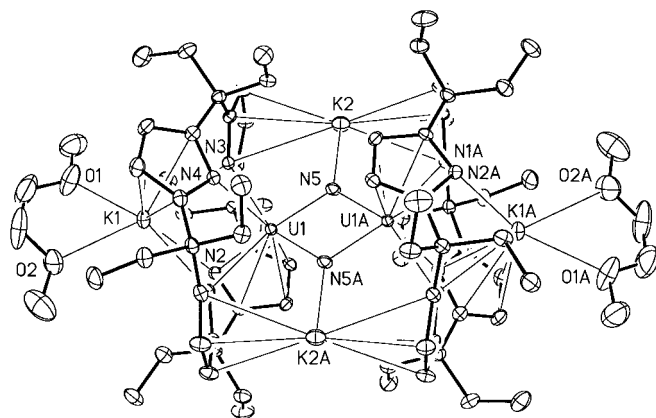


Figure 3. Thermal ellipsoid plot of the anionic moiety of **4**; bond lengths [Å] and angles [°]: U1–N5 2.076(6), U1–N5A 2.099(5), U1–N1 2.665(5), U1–N2 2.899(6), U1–N3 2.697(5), U1–N4 2.612(5), U1–U2 3.3549(6), K2–N5 2.554(6); U1–N5–U1A 106.9(2), U1–N5–K2 124.8(3), N5–U1–N5A 73.1(2).

tical $[[[(calix[4]tetrapyrrole)U][K(dme)]]]$ moieties bridged by two K–N units. One potassium cation, solvated by four DME molecules and without bonding contacts with the anionic moiety, completes the asymmetric unit of the structure.

The fact that the structure is centrosymmetric might suggest the presence of a Class 1 mixed-valence uranium complex. On the other hand, it is possible that a Class 2 mixed-valence dimer, with two distinct U^{IV} and U^V metal centers, could exist with the two metals disordered over both positions, thus averaging the bond distances and angles. However, the presence of a pentavalent uranium center was conclusively proved from the near-IR spectrum, which clearly displays the characteristic absorption at 1247 nm,^[8] and thus supports the idea that **4** might possess two chemically distinct metal centers. As expected for a uranium dimer with a short intermetallic contact,^[9] the magnetic properties were uninformative. The complex is paramagnetic and displays a magnetic moment at room temperature that is lower than expected ($3.41 \mu_B$ per dimeric unit). The value of the magnetic moment drops with temperature to $1.91 \mu_B$ at 2.5 K, with a flex at around 10 K that possibly indicates the presence of substantial antiferromagnetic coupling or superexchange.

A reaction carried out under $^{15}N_2$ gave the isotopically enriched derivative. Unfortunately, the paramagnetism of **4** destroyed both the ^{15}N and ^{14}N NMR spectra. However, the two crystalline compounds (with identical cell parameters) provided two strikingly different ESR spectra in solution at

100 K. While the unlabeled complex displayed a broad, single-line spectrum, the isotopically labeled derivative displayed a hyperfine structure consisting of 14 lines (see Supporting Information). These results in combination with the fact that **4** can only be reproducibly formed under an N_2 atmosphere (10 experiments) provide, together with the successful anisotropic refinement, satisfactory analytical data, and the near-IR spectrum, strong supporting evidence for identifying the bridging atoms as nitrides.

Experimental Section

1: A solution of $[U_3(dme)_2]$ (3.1 g, 3.9 mmol) in DME (30 mL) was combined with a solution of $[(Et_5-calix[4]tetrapyrrole)K_4(dme)_2]$ (3.4 g, 3.9 mmol) in the same solvent (30 mL). The resulting dark-green mixture was stirred for 4 h. Insoluble colorless material was removed from the solution by centrifugation and the resulting mother liquor was concentrated to about 15 mL. After the solution had stood for 24 h at room temperature, dark-green prisms of **1** were formed (3.1 g, 3.2 mmol, 82%). Elemental analysis calcd (%) for $C_{44}H_{68}N_4O_4UK$: C 53.16, H 6.89, N 5.64; found: C 53.01, H 6.78, N 5.53; IR (Nujol mull): $\tilde{\nu}$ = 1604(m), 1494(m), 1322(s), 1269(s), 1243(s), 1210(w), 1192(m), 1152(m), 1128(s), 1110(s), 1092(m), 1064(s), 1042(s), 1022(s), 976(m), 924(s), 886(s), 865(s), 772(s), 747(s), 730(s), 694(m), 618(m) cm^{-1} . μ_{eff} = $2.80 \mu_B$.

2: The following experiment was carried out in an Ar atmosphere in Schlenk glassware and with the joints lubricated with teflon grease (Krytox, DuPont). A solution of potassium naphthalenide was prepared from metallic K (0.06 g, 1.4 mmol) and naphthalene (0.18 g, 1.4 mmol) in DME (20 mL). The resulting dark-green solution was combined with a solution of **1** (1.4 g, 1.4 mmol) in DME (20 mL). The color of the reaction mixture changed instantly from dark-green to dark red-brown on stirring, which was continued for 4 h. The solution was concentrated to about 10 mL and layered with hexane (50 mL). After 3 days, dark red-brown prisms of **2** were formed (1.2 g, 0.5 mmol, 76%). Elemental analysis calcd (%) for $C_{96}H_{156}N_8O_{13}U_2K_3$: C 51.85, H 7.07, N 5.04; found: C 51.77, H 6.98, N 4.96; IR (Nujol mull): $\tilde{\nu}$ = 1323(m), 1261(s), 1192(w), 1157(w), 1089(s), 1022(s), 980(m), 925(m), 887(m), 853(m), 799(s), 764(m), 739(m), 650(s) cm^{-1} . μ_{eff} = $3.81 \mu_B$.

3: The procedure was the same as for **2** but employing high-vacuum grease (Dow Corning). A dark-green solution of **1** (2.4 g, 2.5 mmol) in DME (20 mL) was mixed with a solution of potassium naphthalenide prepared from metallic K (0.10 g, 2.5 mmol) and naphthalene (0.3 g, 2.5 mmol) in DME (20 mL). After stirring for 4 h, the solution was concentrated to a volume of about 15 mL and layered with hexane (60 mL). After 2 days a mixture of dark red-brown crystals of **2** and dark-red prisms of **3** were formed (total yield 2.1 g). The manual separation of **3** for analytical purposes proved unfeasible in this case and no analytical characterization, other than X-ray structure determination, was possible. However, crystals of **2** could be manually separated under a microscope and identified by IR and by comparison of the crystallographic cell parameters.

4: The experiment was either carried out following a procedure identical to **2** but under an N_2 atmosphere or in a dry-box. In a typical dry-box experiment, a solution of potassium naphthalenide was prepared from metallic K (0.023 g, 0.59 mmol) and naphthalene (0.076 g, 0.59 mmol) in DME (7 mL). The solution was mixed with a solution of **1** (0.55 g, 0.55 mmol) in DME (10 mL). The reaction mixture immediately changed from dark-green to dark brown-red. Stirring was continued for 4 h at room temperature. The solution was then concentrated to a volume of about 4 mL and layered with hexane (10 mL). After 2 days, dark-orange crystals of **4** contaminated by a small amount of **2** were separated. Recrystallization of the crystalline mass from DME/hexane (4 mL/20 mL) yielded analytically pure dark-orange crystals of **4** (0.387 g, 0.17 mmol, 61%). Elemental analysis calcd (%) for $C_{96}H_{156}N_{10}O_{12}U_2K_5$: C 49.83, H 6.80, N 6.05; found: C 49.78, H 6.77, N 6.01; IR (Nujol mull): $\tilde{\nu}$ = 1321(m), 1269(m), 1245(s), 1207(w), 1189(m), 1128(m, br), 1086(s, br), 1042(m), 978(m), 921(m), 887(m), 851(s), 785(s), 739(s, br), 680(s), 673(s), 635(s) cm^{-1} .

Crystal data. **1:** $C_{88}H_{136}N_8O_8K_2U_2$, M_r = 1988.30, orthorhombic, space group $Pbca$, a = 13.226(3), b = 21.313(7), c = 31.827(11) Å, V = 8972(5) Å³, Z = 8, ρ_{calcd} = 1.472 Mg m⁻³, μ = 3.755 mm⁻¹, $F(000)$ = 4024, 26017 reflections col-

lected, 9658 independent reflections, $GOF = 1.049$, $R = 0.0526$, $wR^2 = 0.1196$. **2**: $C_{96}H_{156}N_8O_{13}K_3U_2$, $M_r = 2223.65$, triclinic, space group $P\bar{1}$, $a = 17.325(1)$, $b = 18.258(1)$, $c = 19.616(2)$ Å, $\alpha = 108.527(2)$, $\beta = 90.998(2)$, $\gamma = 105.658(2)^\circ$, $V = 5628.9(8)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.312$ Mg m⁻³, $\mu = 3.039$ mm⁻¹, $F(000) = 2266$, 44317 reflections collected, 16076 independent reflections, $GOF = 1.021$, $R = 0.0723$, $wR^2 = 0.1947$. **3**: $C_{94}H_{102}N_8O_{12}K_4SiU_2$, $M_r = 2196.34$, monoclinic, space group $P2_1/m$, $a = 16.322(1)$, $b = 17.691(2)$, $c = 19.772(2)$ Å, $\beta = 98.956(2)^\circ$, $V = 5643.4(9)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.293$ Mg m⁻³, $\mu = 3.076$ mm⁻¹, $F(000) = 2184$, 44186 reflections collected, 6134 independent reflections, $GOF = 1.058$, $R = 0.0529$, $wR^2 = 0.1737$. **4**: $C_{96}H_{156}N_{10}O_{12}K_3U_2$, $M_r = 2313.87$, monoclinic, space group $P2_1/n$, $a = 13.111(1)$, $b = 22.953(3)$, $c = 17.976(2)$ Å, $\beta = 91.634(2)^\circ$, $V = 5407(1)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.421$ Mg m⁻³, $\mu = 3.241$ mm⁻¹, $F(000) = 2354$, 12592 reflections collected, 6924 independent reflections, $GOF = 1.002$, $R = 0.0383$, $wR^2 = 0.0908$. CCDC-177345, -177346, -177347, -177348 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

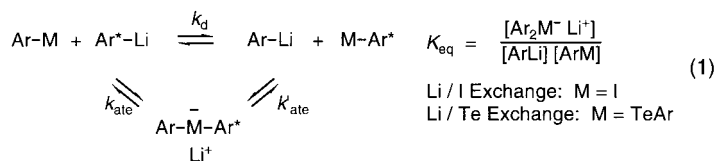
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Are Ate Complexes True Intermediates in Lithium–Metalloid Exchange? Subtle Effects of Ion-Pair Structure in Lithium–Tellurium and Lithium–Selenium Exchange Reactions**

Hans J. Reich,* Martin J. Bevan,
Birgir Ö. Gudmundsson, and Craig L. Puckett

The lithium–metalloid exchange reaction is widely used to prepare synthetically valuable organolithium reagents. The full synthetic potential of one of the most important of these reactions, the Li/I exchange, was not realized (e.g., in the synthesis of alkyllithium reagents) until mechanistic studies showed that it was a well-behaved polar process without a significant radical component.^[1a,b,2] Ate complexes, first proposed by Wittig and Schöllkopf,^[3] are presumptive intermediates in these reactions [Eq. (1)]. Ate complexes of



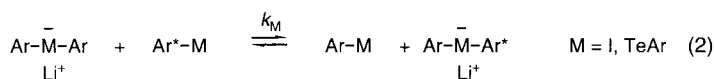
iodine,^[1a,b,4] tellurium,^[1b,5] selenium,^[1c,5] tin,^[1d,6] and silicon^[7] having only alkyl and aryl ligands have been characterized in solution and in the solid state, and probed by high-level calculations.^[8] Their presence, however, is not proof that they are intermediates in the exchange. No direct evidence has been reported for any Li/M exchange which shows that all of the exchange proceeds along path k_{ate} , and none by the direct exchange path k_{d} , which bypasses the ate complex [Eq. (1)]. To perform such an experiment with dynamic NMR (DNMR) spectroscopy, the three reactants (monomeric ArLi, ArM, and Ar₂MLi) in the triangular equilibrium of Equation (1) must be present in detectable concentrations under conditions for which the rates k_{d} , k_{ate} , and k'_{ate} can each be measured.

A number of Li/I and Li/Te exchanges we investigated failed to provide a clear answer. Exchanges of PhI and Ph₂Te with PhLi could not be analyzed because no solvent of appropriate polarity was found such that all species were detectable. In THF both monomer and dimer were observable, but the equilibrium constant K_{eq} [Eq. (1)] for the ate complex was so high that insufficient PhLi and/or PhI/Ph₂Te (whichever was stoichiometrically limiting) was present.^[1b] In less polar, mixed solvents, the concentration of PhLi monomer was too low for proper line-shape analysis^[1e,9] (the dimer of PhLi is not active in the exchange process^[1b]). A problem which prevents kinetic analysis of Li/I exchanges is the fast reaction between ArI and the ate complex, in which the latter

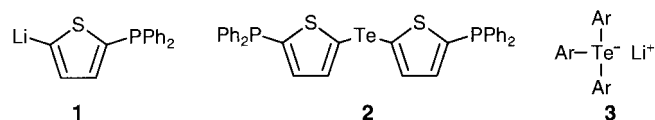
[*] Prof. Dr. H. J. Reich, M. J. Bevan, Dr. B. Ö. Gudmundsson, Dr. C. L. Puckett
Department of Chemistry
University of Wisconsin
1101 University Ave., Madison, WI 53706 (USA)
Fax: (+1) 608-265-4534
E-mail: reich@chem.wisc.edu

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acts as an anion donor [k_M , Eq. (2)], which causes the ArI and Ar₂I-Li⁺ signals to coalesce at temperatures down to -130 °C.^[1a]



We now report that a high-quality test of this mechanism can be performed on the exchange of 5-(diphenylphosphanyl)-2-lithiothiophene (**1**) with the telluride **2**, provided that the



somewhat unusual solvent mixture 1,3-dioxolane/2-methyltetrahydrofuran (4/1) is used.^[10] In this solvent the lithium reagent is completely monomeric, and the equilibrium constant K_{eq} [Eq. (1)] is ideal in the temperature range in which rates can be measured. A major advantage is the availability of ³¹P NMR spectroscopy for the DNMR analysis, which provides excellent signal-to-noise ratio and dispersion of signals.

The low-temperature ³¹P NMR spectrum of roughly equimolar ArLi and Ar₂Te showed well-resolved ArLi and Ar₂Te signals, as well as the characteristic 2:1 ratio of signals for apical and equatorial groups in the T-shaped ate complex **3** (Figure 1).^[1b,5] On warming, all four signals coalesced to a single peak at about -40 °C.

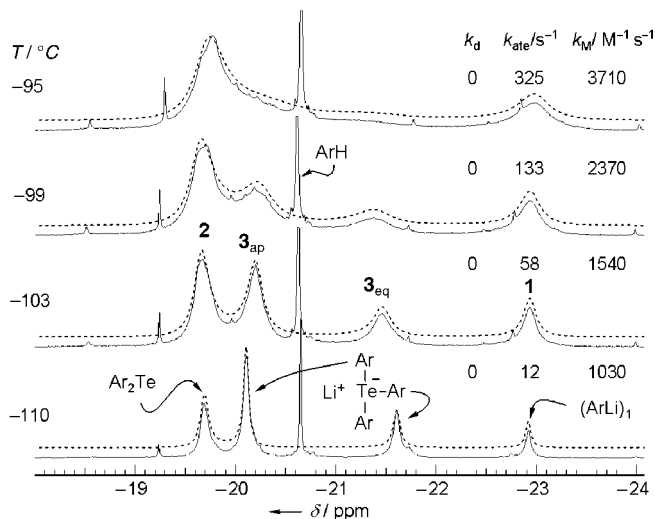
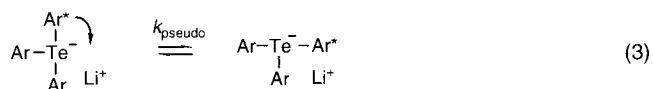


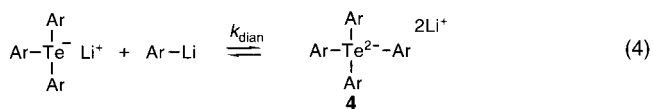
Figure 1. Variable-temperature 145.8 MHz ³¹P NMR study of the exchange of **1** (0.033 M) and **2** (0.039 M) with **3** in 1,3-dioxolane/2-methyltetrahydrofuran (4/1) solution (Ar = 5-diphenylphosphanyl-2-thienyl). Temperatures were measured with the (Me₃Si)₃CH ¹³C chemical-shift thermometer.^[11] The thermodynamics and kinetics of Equation (1) at -99 °C are: for k_{ate} , $\Delta G^\ddagger = 8.3$ kcal mol⁻¹, $\Delta H^\ddagger = 11.5$ kcal mol⁻¹, $\Delta S^\ddagger = 18$ cal K⁻¹ mol⁻¹; for K_{eq} , $\Delta H^0 = -6.5$ kcal mol⁻¹, $\Delta S^0 = -30.2$ cal K⁻¹ mol⁻¹.

Analysis of these spectra is potentially complicated by several exchange processes: 1) The ate-complex mechanism, which averages all of the signals [k_{ate} in Eq. (1)]; 2) the ate complex as an aryl-anion donor^[1a] [k_M in Eq. (2)], which

would average the signals of **2** and **3**; 3) pseudorotation of **3**,^[1f] which would average the signals of the ate complex **3** [Eq. (3)]; 4) reversible formation of a square-planar inter-



mediate **4**, which would average the signals of **1** and **3** [k_{dian} in Eq. (4)];^[11] and 5) direct exchange between telluride and lithium reagent, which would average the signals of **1** and **2** [k_d in Eq. (1)].

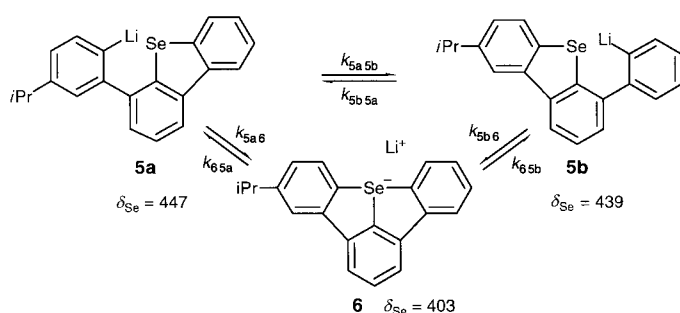


Experiments on solutions containing hexamethylphosphoramide (HMPA), in which the formation constant of the ate complex is very high,^[12] allowed us to address interference from processes 3 and 4. In the presence of excess ArLi and 8 equiv of HMPA, the ³¹P NMR signals of the ate complex remained sharp, and the signal of ArLi broadened only slightly up to -50 °C. Thus, neither the normal Li/Te exchange (process 1) or the pseudorotation (process 3), nor exchange via **4** (process 4) proceed at a significant rate, even at temperatures more than 40 K higher than those used in the experiment of Figure 1. Solutions containing HMPA also allowed process 2, mutual exchange between the ate complex and telluride signals, to be detected and quantified (e.g., at -95 °C with 10 equiv of HMPA and excess telluride: $k_M = 2900$ s⁻¹ M⁻¹, $\Delta G_{-95}^\ddagger = 7.4$ kcal mol⁻¹, $\Delta H^\ddagger = 6.6$ kcal mol⁻¹, $\Delta S^\ddagger = -4.6$ cal K⁻¹ mol⁻¹).^[13]

Accurate simulations for the spectra in Figure 1 were achieved^[14] in using only process 1 (k_{ate}) and a small (20–35 %) contribution to the total rate from process 2 (k_M), which manifests itself as a line broadening of the ArLi signal, slightly smaller than expected, when only k_{ate} is allowed.^[1b] No contribution from non-ate-complex exchange by process 5 (k_d) was detected. Hence, the ate complex is a kinetic intermediate in this Li/Te exchange, and there is no significant exchange between ArLi and Ar₂Te by any mechanism other than via the ate complex.

While characterizing a selenium ate complex^[1c] we found that **5** also met the requirements for testing the ate-complex mechanism for an Li/Se exchange. Here ⁷⁷Se NMR spectroscopy could be used to detect the interconversion of **5a**, **5b**, and **6**. In dimethyl ether/diethyl ether the intramolecular Li/Se exchange was fast on the NMR timescale down to -100 °C (Figure 2a). At lower temperatures the ⁷⁷Se NMR signals of lithium reagents **5a** and **5b** decoalesced in a 1:3 ratio.

The addition of 12 % THF to this sample caused the appearance of a new signal at $\delta = 403$ ppm (Figure 2b) which we assigned to the ate complex **6**.^[15] At -149 °C k_{ate} (k_{65}) is slow on the NMR timescale, but no decoalescence of the two lithium reagents can be detected. Thus, Li/Se exchange (**5a** ⇌ **5b**) is still fast under conditions for which exchange with the ate complex **6** is slow on the NMR timescale (we



	A (ate-apical)	B (ate-eq)	C (ArLi)	D (Ar ₂ Te)	
A	$i2\pi(\nu_A)$ $-1/T-\Sigma k_{AX}$	k_{AB}	k_{AC}	k_{AD}	$E = \begin{bmatrix} k_{AB} = \frac{k_{\text{pseudo}}}{2} + \frac{k_{\text{dian}}[1]}{4} \\ k_{AC} = \frac{k_{\text{ate}}}{2} + \frac{k_{\text{dian}}[1]}{4} \\ k_{AD} = \frac{k_{\text{ate}} + k_M[2]}{2} \\ k_{BC} = \frac{k_{\text{dian}}[1]}{4} \\ k_{BD} = k_{\text{ate}} + k_M[2] \\ k_{CD} = k_d[2] \end{bmatrix}$
B	k_{BA}	$i2\pi(\nu_B)$ $-1/T-\Sigma k_{BX}$	k_{BC}	k_{BD}	
C	k_{CA}	k_{CB}	$i2\pi(\nu_C)$ $-1/T-\Sigma k_{CX}$	k_{CD}	
D	k_{DA}	k_{DB}	k_{DC}	$i2\pi(\nu_D)$ $-1/T-\Sigma k_{DX}$	

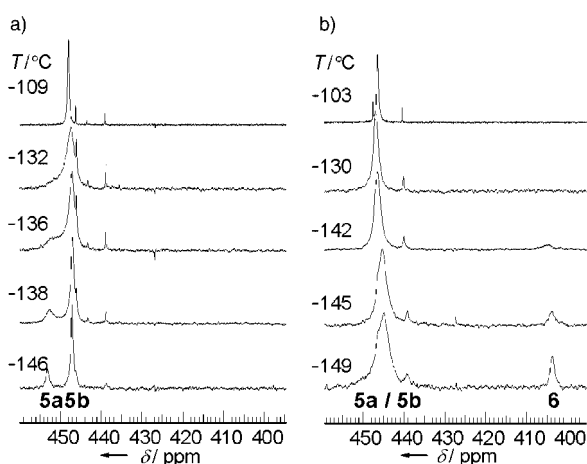


Figure 2. Variable-temperature 68.68 MHz ^{77}Se NMR spectra of **5a/5b/6**. a) In $\text{Me}_2\text{O}/\text{Et}_2\text{O}$ (54/46). b) With addition of THF ($\text{Me}_2\text{O}/\text{Et}_2\text{O}/\text{THF}$ 48/40/12). Line-shape simulation of the spectra on the left gave $\Delta G_{-136^\circ\text{C}}^\ddagger = 6.2 \text{ kcal mol}^{-1}$, $\Delta H^\ddagger = 6.4 \pm 0.6 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -0.7 \pm 4 \text{ cal K}^{-1} \text{ mol}^{-1}$ for k_{5b5a} . The small impurity signals at $\delta = 439$ and $\delta = 447$ ppm are due to compounds formed by protonation of **5a** and **5b**.

assume that addition of 12% THF will appreciably affect neither the ^{77}Se chemical shifts of **5a** and **5b** nor their ratio).

The dynamics can be quantified by performing three-spin DNMR simulations,^[1b] as shown in Figure 3.^[14] Simulation 1 fits the spectrum of the sample containing no THF and no detectable ate complex. If we attempt to fit the spectrum in the solution containing 12% THF (bottom spectrum in Figure 3) and allow exchange only via the ate complex ($k_{5a5b} = k_d = 0$), then the lithium reagent isomers **5a** and **5b** are predicted to be well below coalescence when the signal of the ate complex has the correct line shape (Figure 3, simulation 2). Increasing the rate of exchange broadens this signal (simulation 3). Only when a substantial rate of direct exchange between the two lithium reagents is included can a successful simulation be performed (simulation 4, $k_{5a5b} \geq 45k_{5a6}$). There is thus an alternate pathway for exchange of

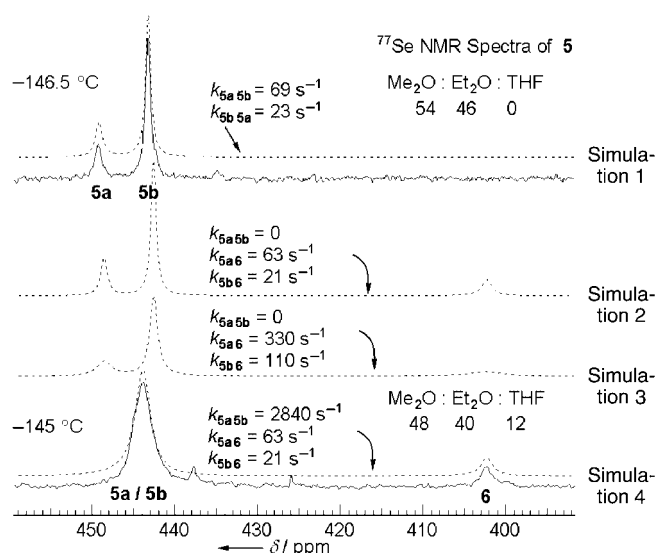
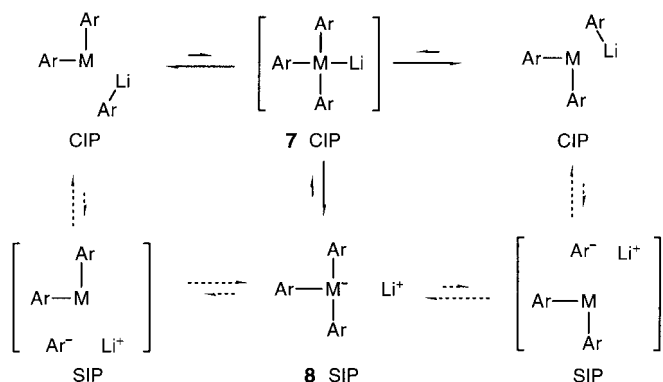


Figure 3. ^{77}Se NMR spectra of solutions of **5/6** with simulations (dotted lines).^[1b]

5a and **5b** [k_d in Eq. (1)] which is at least 45 times as fast as that involving **6**.

How can we explain the different behavior of systems **1/2/3** and **5/6**? We considered single-electron transfer (SET) mechanisms, but the absence of decomposition in solutions in which tens of millions of Li/Te, Li/Se, or Li/I exchanges have occurred argues strongly against radical intermediates. A more satisfactory explanation is as follows: Since organometalloid ate complexes in THF and more polar solvents are separated ion pairs (SIPs),^[1b,e] and ArLi reagents are strong contact ion pairs (CIPs),^[1e,i] a mechanism for ArLi/ArM exchange which involves the observable ate complex requires ion-pair separation of either ArLi or the ate complex (vertical arrows in Scheme 1). We propose that the Li/Se exchange of **5a/5b** proceeds along the top row of Scheme 1 much faster than dissociation of the CIP ate complex **7** to the more stable



Scheme 1. CIP and SIP intermediates in the Li/M exchange ($M = \text{Te, Se}$). Species in brackets are not observable for either the **1/2/3** or **5a/5b/6** systems.

SIP ate complex **8**. The observable ate complex **8** (**= 6**) is then just a parasitic equilibrium on the actual exchange pathway, which has more the character of an $\text{S}_\text{N}2$ substitution. The Li/Te exchange of **1** probably involves the same pathway as for **5**,

except that the rates to and from CIP **7** are slow enough that dissociation of **7** to **8** is faster than the exchange process (**5a**/**5b** exchange is faster than the dissociation of **3** by about a factor of 10^3).

In summary, DNMR studies have shown that the Li/Te exchange of the lithiothiophene **1** with the telluride **2** proceeds exclusively through the ate complex **3**. The very fast intramolecular Li/Se exchange of **5a** and **5b**, on the other hand, does not proceed appreciably through the observable SIP ate complex **6**. We propose that here the SIP/CIP interconversion is slower than the Li/Se exchange rate, and this allows the intramolecular substitution to bypass the SIP of **6**.

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- [13] The exchange of Ar_2Te with Ar_2TeLi in 1,3-dioxolane/2-methyltetrahydrofuran/HMPA solution was shown to be first order in $[Ar_2Te]$ by DNMR experiments with variable telluride concentrations, as expected for process 2. Under conditions for which the formation

constant of the ate complex is large, such as in the presence of several equivalents of HMPA,^[1g] the exchange between Ar_2Te and the ate complex by process 1 would be zero order in $[Ar_2Te]$.

- [14] The exchange matrix for the simulations in Figure 1 and Figure 3 and the relationship between the NMR rate constants (k_{AB} , k_{AC} , etc.) and the physical rate constants of Equations (1)–(4) (k_{ate} is first order; k_{pseudo} , k_{dian} , k_M , and k_d are second order) are given below (in the simulations of Figure 1, k_{pseudo} , k_{dian} , and k_d were set to zero).
- [15] The appearance of the signal assigned to **6** was fully reversible and strongly temperature dependent (in 1/1/1 ether/dimethyl ether/THF at $-60^\circ C$: > 80% **5**; at $-143^\circ C$: ca. 60% **6**). Conversion to **6** ($\delta_{Se} = 403$ ppm) was quantitative if excess HMPA was added ($\delta_{Se} = 409$ ppm), an effect also seen for the parent system (without the isopropyl substituent)^[1c] and for other Te, I, and Sn ate complexes.^[1a,d,g] The signals of the two apical C atoms of **6** were characteristically shifted downfield ($\delta = 181.9$, 187.2 ppm), as was also seen for numerous other ate complexes.^[1b] Quenching of the HMPA solution of **6** with bromotrimethylstannane cleanly gave the stannylated precursors (2:1 mixture), that is, no structural changes had occurred.

Generation of Polyunsaturated Cumulene Chains by Unprecedented Insertions of the Ynamine $MeC\equiv CNet_2$ in Ruthenium(II) Allenylidene Complexes**

Salvador Conejero, Josefina Díez, Maria Pilar Gamasa, Jose Gimeno,* and Santiago García-Granda

Allenylidene (propadienylidene) complexes $[ML_n]C\equiv C=CR^1R^2$, which belong to the series of unsaturated carbenes $[ML_n]C(C\equiv C)=CR^1R^2$ ($i > 0$) have received increasing interest during the last few years.^[1] These derivatives have a great potential to promote novel carbon–carbon and carbon–heteroatom coupling reactions, because of the electrophilic (C_α and C_γ) and nucleophilic (C_β) character of the carbon nuclei of the allenylidene chain. While simple nucleophilic and electrophilic additions are well-studied, cycloaddition processes are scarce, in particular those involving $C\equiv C$ dipolar substrates.^[2] In 1998 Fischer and co-workers reported the synthesis of cyclobutenylidene and alkenylallenylidene Group 6 metal complexes which are formed as a mixture by the cycloaddition of ynamines to both the $C_\alpha=C_\beta$ and $C_\beta=C_\gamma$ bonds of an

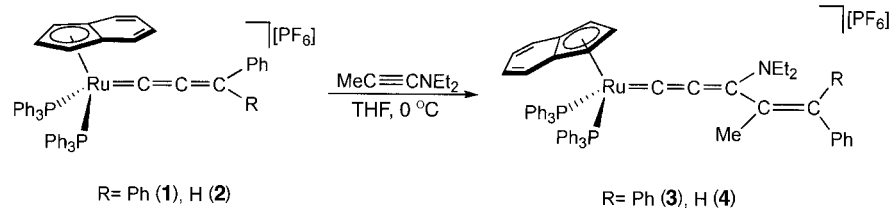
[*] Prof. Dr. J. Gimeno, Dr. S. Conejero, Dr. J. Díez, Dr. M. P. Gamasa
Departamento de Química Orgánica e Inorgánica/I.U.Q.O.E.M.,
Facultad de Química
Universidad de Oviedo-C.S.I.C., 33071 Oviedo (Spain)
Fax: (+34) 98-5103-446
E-mail: jgh@sauron.quimica.uniovi.es
Dr. S. García-Granda
Departamento de Química Física y Analítica
Facultad de Química, Universidad de Oviedo
33071 Oviedo (Spain)

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allenylidene chain, respectively.^[2a] During our investigations into the reactivity of indenyl–allenylidene complexes $[\text{Ru}(\text{C}=\text{C}=\text{C}\text{R}^1\text{R}^2)(\eta^5\text{-C}_9\text{H}_7)(\text{PPh}_3)_2][\text{PF}_6]$ we have shown that the addition of nucleophiles to the unsaturated chain takes place regioselectively at the C_γ . C_α atom of the cumulene moiety is sterically protected by the bulky phosphane and the indenyl group.^[3] This regioselectivity prompted us to study cycloaddition reactions as a synthetic approach to highly unsaturated allenylallenylidene derivatives. Herein we report that not only does this process occur selectively, but it is also a synthetic methodology of unprecedented polyalkenyl allenylidene chains $\text{C}=\text{C}=\text{C}(\text{R})-(\text{CH}=\text{CMe})_n-\text{C}(\text{Me})=\text{CPh}_2$ ($n=1,2$; $\text{R}=\text{H}, \text{NEt}_2$) which notably, is high yielding, sequential, and stereoselective.

Allenylidene indenylruthenium(II) complexes **1** or **2**^[4] react immediately with an excess of the ynamine $\text{MeC}\equiv\text{CNEt}_2$ ^[5] in THF at 0 °C, yielding the alkenyl(amino)allenylidene complexes **3** and **4** regio- and stereoselectively^[6] as orange crystalline air-stable solids in nearly quantitative yield (Scheme 1).^[7] The most distinctive features of the spectro-



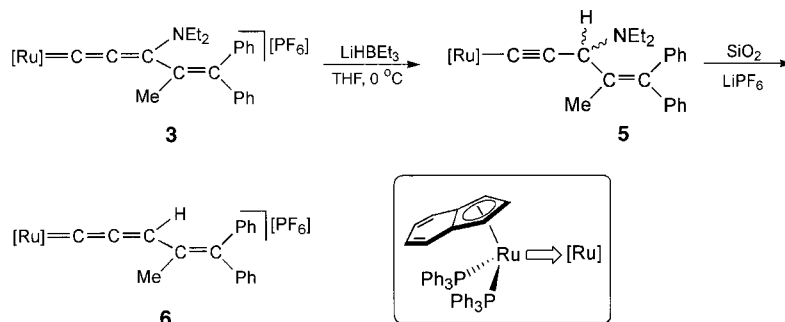
Scheme 1.

scopic data are the characteristic $\nu(\text{C}=\text{C}=\text{C})$ absorption band at 1989 cm^{-1} and the three downfield signals for the allenylidene carbon nuclei in the $^{13}\text{C}\{^1\text{H}\}$ NMR spectra which appear in the range $\delta=199.39\text{--}206.68$ (C_α), $155.26\text{--}156.79$ (C_β), and $121.72\text{--}122.76$ ppm (C_γ).

Conclusive 2D NMR (NOESY) experiments for complex **4** showed that the hydrogen and methyl substituents are in a *trans* arrangement. The formation of **3** and **4** probably proceeds through an initial addition of the ynamine at the C_γ atom of the cumulene moiety, which leads to the formation of a cationic alkynyl intermediate complex. Further ring closure, which involves the C_β atom, gives the $[2+2]$ vinylidene cycloadduct. A subsequent cycloreversion reaction yields the alkenyl(amino)allenylidenes **3** and **4**. An analogous mechanism was also proposed in the cycloaddition of ynamines with Group 6 allenylidene complexes.^[2a]

It is interesting that alkenyl(amino)allenylidenes, in contrast to the allenylidene precursors **1** and **2**, are not prone to further insertions despite the presence of an excess of the ynamine. This is probably because of the alkynyl character of the organic chain in **3**.^[8] To facilitate further insertion reactions, we set up the transformation of the amino

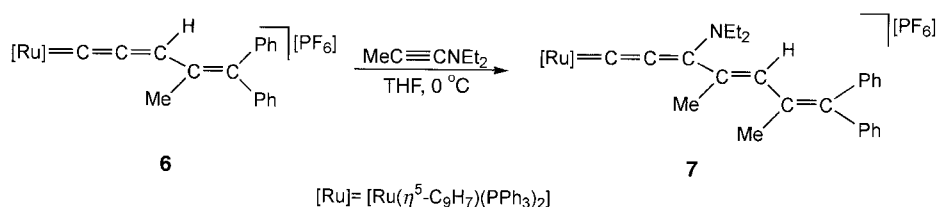
allenylidene **3** into the corresponding secondary derivative **6**, which was obtained in two steps via the unstable alkynyl derivative **5**,^[6] from the treatment of **3** with a slight excess of LiHBEt_3 in THF, followed by purification on a short silica



Scheme 2.

column (Scheme 2). Complex **6**^[6] is isolated as a violet microcrystalline powder (86%). Characterization of **6** is supported by the spectroscopic data which can be compared to those of the parent allenylidene complex **2** ($\nu(\text{C}=\text{C}=\text{C})=1932\text{ cm}^{-1}$; $\text{Ru}=\text{C}=\text{C}=\text{C}$ carbon resonances at $\delta=295.05$ (C_α), 208.84 (C_β), and 150.61 ppm (C_γ)).

Complex **6** reacts with 2 equivalents of ynamine $\text{MeC}\equiv\text{CNEt}_2$, in a way analogous to the above-described allenylidene complex **2**, affording the butadienyl(amino)allenylidene complex **7**,^[6] isolated (80%) as an air-stable orange solid (Scheme 3). IR and NMR spectroscopic data for **7** indicate the presence of the cumulene moiety and the insertion of the ynamine. It is remarkable that the



Scheme 3.

insertion proceeds in a regio- and stereoselective manner, because only one isomer is obtained. The structure of **7** has been unambiguously confirmed by X-ray diffraction (Figure 1).^[9] The main feature of the molecular structure is the *s-trans*, *s-trans* stereochemistry of the butadienyl–allenylidene chain arrangement in which the metal–cumulene moiety is *trans* to the terminal diphenyl–alkenyl group fragment. The plane including the butadienyl fragment C4–C5–C6–C7 is almost perpendicular ($99.2(3)^\circ$) to that defined by C2–C3–N1, which is probably the appropriate orientation to minimize the repulsive interactions between the diethylamino group and the substituents at the C–C double bonds.^[10]

These sequential processes constitute an efficient synthetic methodology for building up a butadienyl–allenylidene chain. We have succeeded in preparing a higher unsaturated chain by following an identical synthetic procedure. Thus, the

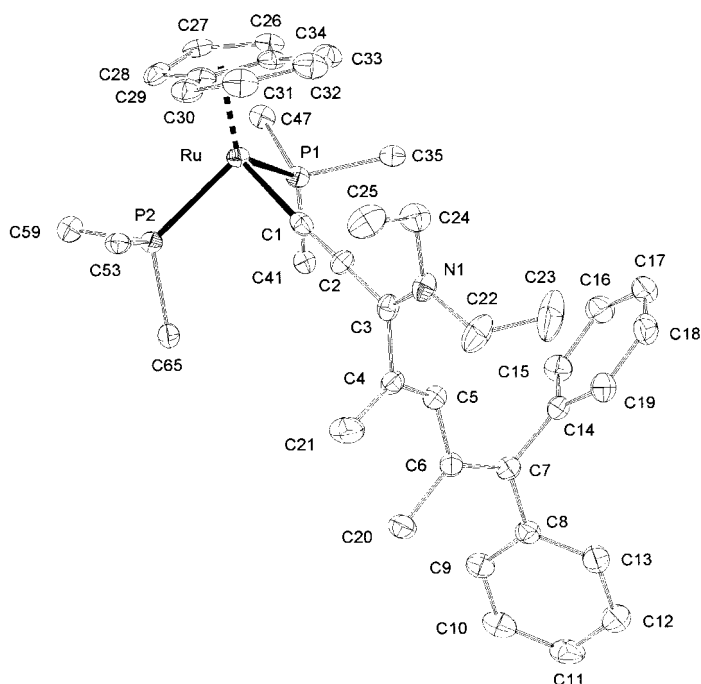


Figure 1. Molecular structure for the cation of complex **7** (ORTEP plot). Selected bond lengths [Å] and angles [°]: Ru-P1 2.299(9), Ru-P2 2.305(9), Ru-C1 1.946(4), C1-C2 1.229(5), C2-C3 1.390(5), C3-C4 1.500(5), C4-C5 1.340(6), C5-C6 1.510(5), C6-C7 1.355(5), C3-N1 1.319(5); Ru-C1-C2 174.6(3), C1-C2-C3 177.8(4), C2-C3-N1 122.1(3), C4-C3-N1 119.0(3), C2-C3-C4 118.4(2).

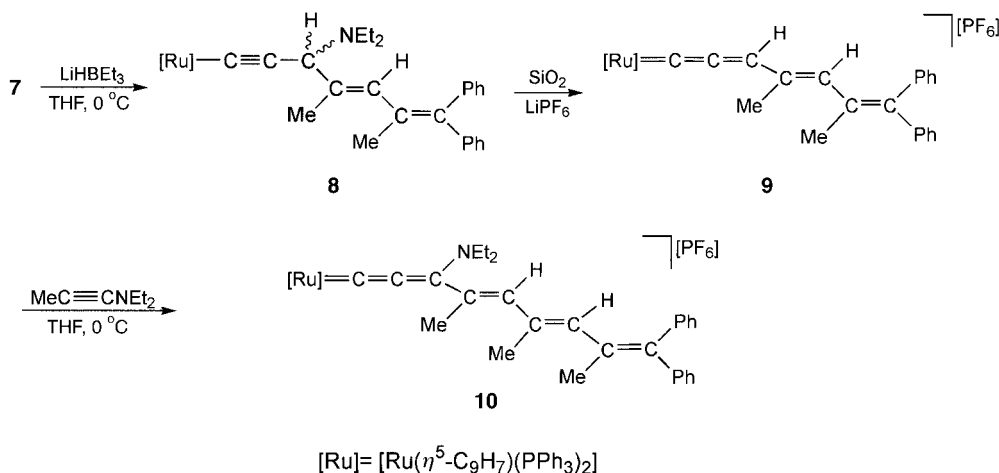
reaction of **7** with one equivalent of LiHBEt_3 in THF, followed by treatment of the resulting alkynyl complex **8** solution (characterized by $^{31}\text{P}\{^1\text{H}\}$, ^1H , and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy) with silica, yields the desired secondary butadienyl-allenylidene complex **9**, which is isolated as a violet solid in 83 % yield after workup (see Scheme 4). Complex **9** also reacts with $\text{MeC}\equiv\text{CNEt}_2$ in THF at 0 °C yielding the hexatrienyl(amino)allenylidene complex **10** regio- and stereoselectively^[6] as an orange solid (45 %; Scheme 4). Complexes **9** and **10** have been fully characterized by elemental analysis, and IR and NMR spectroscopy. In particular, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum and NOESY experiments for **10** are

comparable to those of **7**, and support the *all-trans* stereochemistry of the substituents in the conjugated $\text{C}=\text{C}$ chain.

These stereoselective sequential insertions of ynamines into allenylidene moieties have disclosed an unprecedented synthetic approach of polyunsaturated cumulene chains.

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Scheme 4.

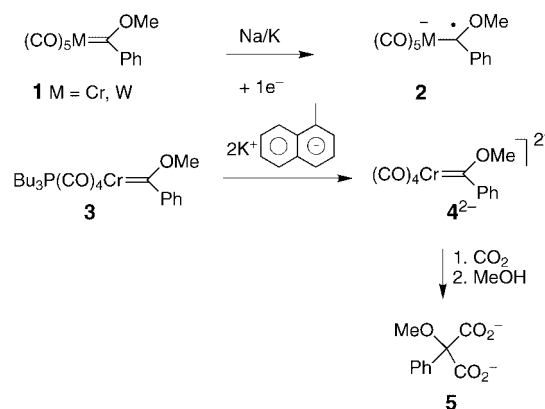
- 3 H; CH_2CH_3), 1.21 (t, $^3J(\text{H,H}) = 6.8$ Hz, 3 H; CH_2CH_3), 1.51 (s, 3 H; $=\text{CCH}_3$), 1.86 (s, 3 H; $=\text{CCH}_3$), 3.08 (q, $^3J(\text{H,H}) = 6.8$ Hz, 2 H; CH_2CH_3), 3.76 (q, $^3J(\text{H,H}) = 6.8$ Hz, 2 H; CH_2CH_3), 5.88 ppm (s, 1 H; $=\text{CH}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.47 MHz, CDCl_3 , 18°C): $\delta = 12.90$ (s; CH_2CH_3), 13.78 (s; CH_2CH_3), 17.33 (s; $=\text{CCH}_3$), 20.60 (s; $=\text{CCH}_3$), 45.91 (s; CH_2CH_3), 47.02 (s; CH_2CH_3), 121.07 (s; C_β), 126.98–143.33 (m; C_{arom} , $=\text{CCH}_3$, $=\text{CPh}_2$), 132.41 (s; $=\text{CH}$), 156.21 (s; C_γN), 202.21 ppm (t, $^2J(\text{C,P}) = 21.2$ Hz; Ru = C_α). **10**: Yield: 0.14 g, 45 %, IR (KBr): $\tilde{\nu} = 1990$ ($\text{C}=\text{C}$) cm^{-1} ; $^{31}\text{P}\{^1\text{H}\}$ NMR (121.44 MHz, CDCl_3 , 18°C): $\delta = 49.59$ ppm (s); ^1H NMR (300 MHz, CDCl_3 , 18°C): $\delta = 1.26$ (t, $^3J(\text{H,H}) = 7.4$ Hz, 3 H; CH_2CH_3), 1.31 (t, $^3J(\text{H,H}) = 7.4$ Hz, 3 H; CH_2CH_3), 1.49, 1.65 (s, 3 H; $=\text{CCH}_3$), 1.88 (s, 3 H; $=\text{CCH}_3$), 3.54 (q, $^3J(\text{H,H}) = 7.4$ Hz, 2 H; CH_2CH_3), 3.88 (q, $^3J(\text{H,H}) = 7.4$ Hz, 2 H; CH_2CH_3), 5.50 (s, 1 H; $=\text{CH}$), 5.97 ppm (s, 1 H; $=\text{CH}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.47 MHz, CDCl_3 , 18°C): $\delta = 13.02$ and 13.76 (s; CH_2CH_3), 16.78 (s; $=\text{CCH}_3$), 18.22 (s; $=\text{CCH}_3$), 21.09 (s; $=\text{CCH}_3$), 46.40 (s; CH_2CH_3), 47.55 (s; CH_2CH_3), 121.14 (s; C_β), 126.60–143.18 (m; Ph, $=\text{CCH}_3$, $=\text{CPh}_2$, $=\text{CH}$), 157.11 (s; C_γN), 202.61 ppm (t, $^2J(\text{C,P}) = 21.5$ Hz; Ru = C_α).
- [7] Other vinyl allenylidene complexes are known: D. Péron, A. Romero, P. H. Dixneuf, *Organometallics* **1995**, *14*, 3319; D. Touchard, N. Pirio, L. Toupet, M. Fétouhi, L. Ouahab, P. H. Dixneuf, *Organometallics* **1995**, *14*, 5263.
- [8] $^{13}\text{C}\{^1\text{H}\}$ NMR (Ru C_α) $\delta = 199.39$ (**3**) versus 295.05 ppm (**6**) and $\tilde{\nu}(\text{C}=\text{C})$ 1989 (**3**) versus 1932 cm^{-1} (**6**).
- [9] Data for the X-ray structure analysis for **7**: Crystal from MeOH/ CH_2Cl_2 /pentane, $\text{C}_{70}\text{H}_{64}\text{F}_6\text{NP}_3\text{Ru}$ ($M_r = 1227.20$); crystal size $0.37 \times 0.27 \times 0.20$ mm³; orthorhombic, space group $P2_12_12_1$ $a = 14.41810(10)$, $b = 14.57510(10)$, $c = 28.23070(10)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $Z = 4$, $V = 5932.55(6)$ Å³, $\rho = 1.374$ g cm⁻³; $T = 200(2)$ K; $2\theta_{\text{max}} = 68.2^\circ$; 95891 reflections measured, 10850 unique ($R_{\text{int}} = 0.000$), and 9859 observed ($I > 2\sigma(I)$); Nonius KAPPA-CCD diffractometer, $\text{CuK}\alpha$ radiation ($\lambda = 1.54184$ Å), graphite monochromator; multiscan absorption corrections (Ψ scan, min. transmission 79.67 %). The structure was solved by DIRDIF and refined with the full-matrix, least-squares method; $R_1 = 0.00397$, $wR_2 = 0.0999$ (for 9859 reflections with $I > 2\sigma(I)$), $R_1 = 0.0437$, $wR_2 = 0.1035$ (for all data); residual electron density $+0.678/-0.759$ e Å⁻³. CCDC-179713 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
- [10] Interatomic distances and angles of the cumulene moiety, as well as those of the rest of the unsaturated chain, are usual for this type of carbon–carbon connectivity (see ref. [1]).

C₈K-Promoted Self-Condensation and Self-Condensation-Cycloisomerization Reactions of α,β -Unsaturated Fischer Carbene Complexes**

Miguel A. Sierra,* Pedro Ramírez-López, Mar Gómez-Gallego, Tore Lejon, and María José Mancheño

Dedicated to Professor William M. Horspool

The chemistry of stabilized Group 6 metal carbene complexes (Fischer carbenes) has reached a high level of maturity and carbenes have become very valuable building blocks in organic synthesis.^[1] In spite of this, the reactivity of highly reduced Fischer carbene complexes has been somewhat neglected. The one-electron reduction of the Group 6 alkox-aryl carbene complexes **1** by Na/K alloy was originally reported by Casey.^[2] In this case, radical anion species **2** stable in diluted THF/hexamethyl phosphoramide (HMPA) solutions were detected by ESR spectroscopy. Further, Cooper and Lee^[3] reported the reaction of $[\text{Bu}_3\text{P}(\text{CO})_4\text{CrC}(\text{OMe})\text{Ph}]$ (**3**), with potassium 1-methylnaphthalenide to yield the highly reduced carbene complex **4**²⁻ (Scheme 1). This species **4**²⁻ shows the expected umpolung at the carbene carbon atom (which becomes a nucleophile as a result of the increased



Scheme 1.

[*] Prof. Dr. M. A. Sierra, P. Ramírez-López, Prof. Dr. M. Gómez-Gallego, Dr. M. J. Mancheño
Departamento de Química Orgánica
Facultad de Química
Universidad Complutense, 28040 Madrid (Spain)
Fax: (+34) 91-394-4103
E-mail: sierraor@quim.ucm.es
Prof. Dr. T. Lejon
On sabbatical leave, permanent address:
Department of Chemistry
University of Tromsø
9037 Tromsø (Norway)

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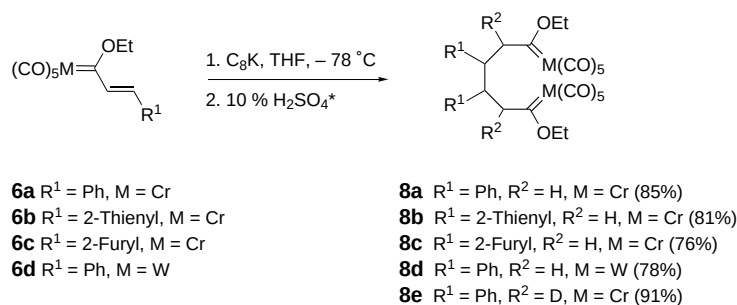
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

metal back donation) and reacts with CO₂ as electrophile to yield malonic acid derivative **5** (Scheme 1). Recently, Iwasawa and Fuchibe^[4] used SmI₂ to effect the one-electron reduction of alkoxyaryl chromium(o) and tungsten(o)carbene complexes. The anion radical species generated from these complexes give reactions such as carbene-ligand dimerization, carbonyl insertion, and insertion into α,β -unsaturated esters.

In spite of the plethora of versatile processes involving α,β -unsaturated Group 6 carbene complexes,^[5] the behavior of this class of compounds towards simple reducing agents has only recently been reported by us,^[6] and others.^[7] These processes are considerably more complex than the expected hydride addition reaction and they involve the metal center in many cases.^[6] In this context, α,β -unsaturated chromium(o) or tungsten(o)carbene complexes are ideal substrates to effect one-electron reactions, since the hypothetical radical anions formed would be multidentate intermediates which may react in diverse ways. Therefore, we decided to study the reactivity of complexes **6** and **7** towards potassium graphite (C₈K). This reducing agent is easily prepared by heating metallic potassium and graphite at 150–160 °C for a short time under argon and it is recognized as an exceptional heterogeneous reducing reagent.^[8] Nevertheless, its use in organometallic chemistry has been somewhat neglected and, to our knowledge, it has not been used in metal-carbene chemistry. The exception is the preparation of [Cr(CO)₅]²⁻ from [Cr(CO)₆] in the Hegedus synthesis of aminochromiumcarbene complexes.^[9]

First, we checked the reaction between complex **6a** and C₈K in THF at –78 °C. After quenching with water, a new chromium-containing product was isolated in very low yields. Several experiments were then carried out varying both the temperature and the reaction times without significant improvement in the yields. The spectroscopic data of the new compound were fully consistent with an equimolecular mixture of diastereomeric complexes **8a** (see Scheme 2). We thought at this point that, perhaps, the quenching agent was not electrophilic enough to effectively protonate the expected intermediate dianions (see below), allowing for the decomposition of these materials during workup and hence for the low yields obtained. Based on these premises, the reaction between complex **6a** and C₈K was effected at –78 °C in THF and quenched with 10 % H₂SO₄ at this temperature. Under these conditions an 85 % yield of the inseparable (65:35) diastereomeric mixture of compounds **8a** was obtained by adsorption of the crude on neutral Al₂O₃, followed by filtration of the resulting material through a short path of silica gel with CH₂Cl₂. Having optimized the reaction conditions, the procedure was applied to α,β -unsaturated carbene complexes **6b** and **6c**. Dimers **8b** and **8c** were obtained in both cases as a (60:40) diastereomeric mixture in yields over 75 %. Tungsten carbene complex **6d** also reacted efficiently with C₈K, yielding tungsten(o) biscarbene complex **8d** in 78 % yield (Scheme 2). It is remarkable that complexes **6** exclusively dimerize in a tail-to-tail fashion.

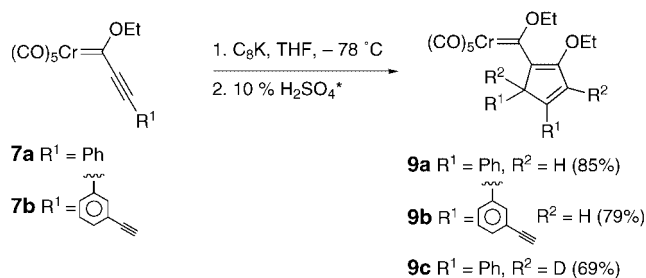
Alkynyl chromium(o)carbene complex **7a** was also employed and again a new carbene complex was obtained. However, and in contrast with the results obtained for the



*D₂SO₄/D₂O (10 %) in the deuteration experiment

Scheme 2.

alkenyl carbene complexes **6**, this new complex was not a biscarbene but a monocarbene derivative, albeit it incorporated two units of the starting complex. The structure of this product could not be unambiguously established by means of a combination of 1D and 2D NMR spectroscopic techniques. Therefore, a single crystal of this compound was submitted to X-ray diffraction analysis and its structure was unambiguously established as the cyclopentadienylchromium(o)carbene **9a**.^[10] Complex **7b**, bearing an additional triple bond, formed cyclopentadienylchromium(o)carbene **9b** in 79 % yield (Scheme 3). It has been reported that mixtures of dimeriza-



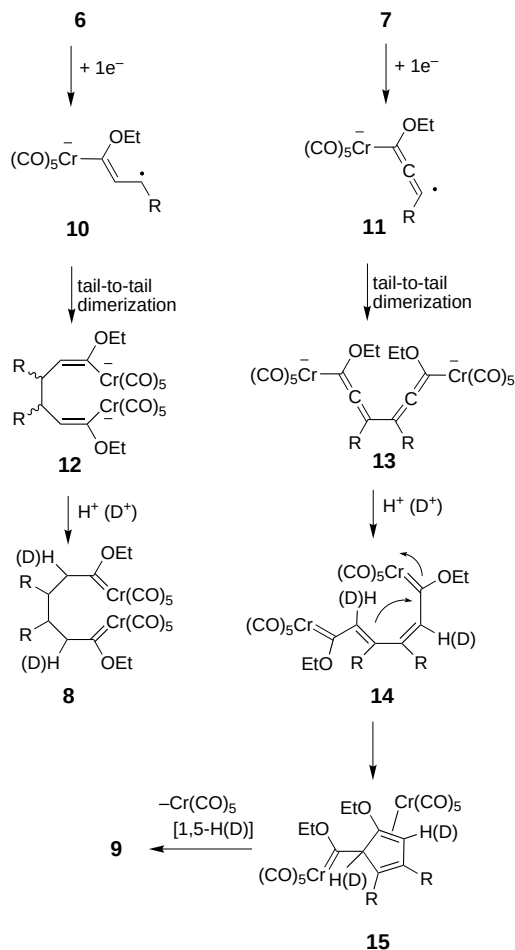
*D₂SO₄/D₂O (10 %) in the deuteration experiment

Scheme 3.

tion products are mainly obtained with C₈K and α,β -unsaturated esters.^[11]

To shed light into the mechanism of these processes, the reactions of complexes **6a** and **7a** were repeated as above but using D₂SO₄ (10 % in D₂O) as the quenching agent. Dideuterated complexes **8e** and **9c** were obtained in these cases in 91 % and 69 % yields, respectively (Scheme 2 and 3). The deuteration positions were unambiguously determined by ¹H and ¹³C NMR spectroscopy.^[12] From the results of these deuteration experiments we could propose that the first step of these reactions is the single-electron addition to the starting α,β -unsaturated complexes to form the radical anions **10** and **11** (see Scheme 4). The next step is the dimerization of these intermediates to form biscarbene anions **12** and **13**, respectively. The reaction pathways diverge at this point. Thus, biscarbene anion **12** would survive until acid quenching, and protonation (deuteration) at both α positions accounts for the observed products **8**.^[13] The situation with bisallenyl-intermediate **13** is different. Once the quenching agent is added, protonated (deuterated) 1,8-dichroma-1,3,5,7-tetraene com-

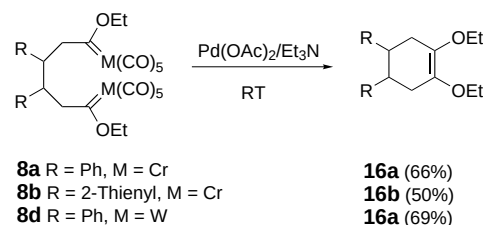
plexes **14** are formed. These intermediates undergo a fast cyclization reaction to produce new complexes **15**, that lose one chromium moiety to yield the final products **9** after a 1,5-H (D) shift. Within this proposal, the deuterated positions may be defined in the conversion of **13** into **14** and therefore they are fully compatible with the experimental results (Scheme 4).^[14,15]



Scheme 4.

The efficient entry into symmetrical biscarbene complexes **8** developed above offered an opportunity to combine these results with our recently developed palladium chemistry.^[16] In fact, the Pd-induced dimerization of complexes **8** yields the dimethoxycyclohexenes **16** in 50–70 % yields (Scheme 5).^[17] Therefore, the sequential C₈K intermolecular dimerization of α,β -unsaturated carbene complexes, followed by Pd-catalyzed intramolecular dimerization of the resulting biscarbene complexes, is a new two-step entry to six-membered rings.

In conclusion, the reaction of α,β -unsaturated chromium(o) or tungsten(o)carbene complexes and C₈K occurs through one-electron transfer, from the interstitial potassium to the organochromium complex, to generate intermediate radical anions. These intermediates undergo a tail-to-tail dimerization to form biscarbene anions, which upon protonation with a strong acid produce complexes **8** or 1,8-dichroma-1,3,5,7-tetraene complexes **14** which convert in situ into cyclopentadienylchromium(o)carbenes **9**.^[18] This mechanistic proposal is



Scheme 5.

supported by deuteration experiments. Complexes **8** may in turn be transformed into functionalized cyclohexenes by Pd-catalyzed ring closure.

Experimental Section

General Procedure for the reaction of complexes 6 and 7 with potassium-graphite (C₈K) laminate. In a two-neck round-bottom flask equipped with reflux condenser and magnetic stirring bar, graphite (17.6 equiv) was heated (while stirred) under argon, for 15 min at 150–160 °C. Potassium (2.2 equiv) was added under argon, and the mixture was kept at 160 °C with careful stirring until the laminate had formed (10–15 min). The material was highly pyrophoric, necessitating cautious handling in thoroughly dried solvents. The distinctive bronze color of the mixture indicates that C₈K is formed, this is then suspended in anhydrous THF and cooled to –78 °C. To this suspension was added by syringe, a solution of the corresponding complex^[19] (1.0 equiv) in THF at –78 °C over a period of 10 min. This solution was allowed to stir until the starting material was consumed (checked by TLC). The reaction was quenched with H₂SO₄ (10 %) at –78 °C and then was warmed to 25 °C for 30 min. The crude was adsorbed on neutral Al₂O₃, and the solvent carefully removed under reduced pressure. The resulting dry powder was filtered through a short pad of SiO₂ with CH₂Cl₂ as eluent, to obtain the corresponding complex as the only reaction product. For the deuterium experiments the same procedure was followed using D₂SO₄/D₂O (10 %) as quencher.

8a: 85 % (65:35 mixture of diastereoisomers). Major isomer: ¹H NMR (300 MHz, COCl₂): δ = 1.23 (t, *J* = 7.1 Hz, 6H), 3.27–3.31 (m, 2H), 3.58 (dd, *J*₁ = 16.2 Hz, *J*₂ = 3.5 Hz, 2H), 3.95 (dd, *J*₁ = 16.2 Hz, *J*₂ = 9.6 Hz, 2H), 4.75 (q, *J* = 7.1 Hz, 4H), 6.74–7.03 ppm (m, 10H); ¹³C NMR (75.43 MHz, COCl₂): δ = 357.9, 222.7, 216.0, 141.4, 128.5, 127.8, 127.0, 78.0, 67.4, 48.3, 14.5; IR (film): $\tilde{\nu}$ = 2060, 1942 cm^{–1}. Minor isomer (from an enriched mixture): ¹H NMR: δ = 1.32 (t, *J* = 7.1 Hz, 6H), 2.93 (dd, *J*₁ = 16.4 Hz, *J*₂ = 2.7 Hz, 2H), 3.16–3.21 (m, 2H), 3.76–3.92 (m, 2H), 4.67–4.80 (m, 4H), 7.11–7.28 ppm (m, 10H); ¹³C NMR: δ = 356.7, 222.6, 216.1, 140.5, 128.3, 127.7, 126.3, 77.8, 66.1, 47.8, 14.3 ppm.

9a: Yield 85 %; ¹H NMR: δ = 1.24 (t, *J* = 7.0 Hz, 3H), 1.62 (t, *J* = 7.1 Hz, 3H), 4.40–4.54 (m, 3H), 4.74 (dq, *J*₁ = 10.4 Hz, *J*₂ = 7.1 Hz, 1H), 4.97 (s, 1H), 6.90 (s, 1H), 6.97–7.40 ppm (m, 10H). ¹³C NMR: δ = 304.9, 225.0, 217.9, 174.8, 160.9, 138.9, 138.5, 133.0, 129.6, 128.6, 128.2, 127.8, 127.4, 126.4, 120.1, 74.0, 68.4, 54.8, 15.3, 14.7 ppm; IR (film): $\tilde{\nu}$ = 2048, 1978, 1931 cm^{–1}.

General procedure for the reaction of complexes 8 with Pd(OAc)₂/Et₃N: A mixture of the corresponding complex (1.0 equiv) and Pd(OAc)₂ (0.1 equiv) in anhydrous THF at room temperature, was placed in a flame-dried airless flask containing a magnetic stirring bar, degassed by evacuation/back fill with argon (3 ×). Then, Et₃N (1.1 equiv) was added by syringe at room temperature and the mixture was stirred at this temperature until complete disappearance of the starting material (checked by TLC). Finally, the reaction was concentrated under vacuum, diluted with AcOEt and filtered through Celite. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel.

16a: 66 % (65:35 mixture of diastereoisomers) ¹H NMR (for the mixture of diastereoisomers): δ = 1.20 (t, *J* = 7.0 Hz, 3.9H), 1.25 (t, *J* = 7.0 Hz, 2.1H), 2.31–2.50 (m, 4H), 3.06–3.09 (m, 0.7H), 3.24 (t, *J* = 4.7 Hz, 1.3H), 3.79 (q, *J* = 7.0 Hz, 2.6H), 3.90 (q, *J* = 7.0 Hz, 1.4H), 6.72–7.13 ppm (m, 10H); ¹³C NMR: δ = 144.0, 142.1, 137.2, 136.7, 128.6, 128.5, 127.9, 127.8, 126.4, 126.1, 65.2, 65.1, 46.4, 44.7, 35.9, 30.2, 16.0, 15.9 ppm; IR (film): $\tilde{\nu}$ = 1655,

1215 cm⁻¹. Compound **16a** was unstable and correct analytical data could not be obtained.

Further experimental details can be found in the Supporting Information.

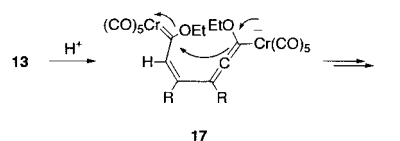
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Probing Fast Facilitated Ion Transfer across an Externally Polarized Liquid–Liquid Interface by Scanning Electrochemical Microscopy**

Peng Sun, Zhiquan Zhang, Zhao Gao, and Yuanhua Shao*

Ion transfer reactions at a liquid–liquid interface or an interface between two immiscible electrolyte solutions are essential for many biological and chemical processes, such as transmembrane signaling, drug delivery, and phase-transfer catalysis.^[1–3] Over the last three decades, the thermodynamics and kinetics of such processes have been extensively studied using electrochemical methods. Several groups have tried to measure the rate constant using transient techniques,^[4] but met with limited success. This is mainly because the ion transfer is often very fast and therefore the transfer rate is difficult to measure.^[4]

Recently we obtained the rate constant of potassium ion transfer from water to 1,2-dichloroethane facilitated by dibenzo[18]crown-6 (DB18C6) using nanopipet voltammetry.

[*] Prof. Y. Shao, P. Sun, Z. Zhang, Z. Gao
State Key Laboratory of Electroanalytical Chemistry
Changchun Institute of Applied Chemistry
of the Chinese Academy of Sciences
Changchun 130022 (China)
Fax: (+86) 431-568-5653
E-mail: yshao@ns.ciac.jl.cn

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try.^[5] This type of pipet provides a very high mass transfer rate and efficiently reduces an uncompensated drop in iR . Scanning electrochemical microscopy (SECM) is a powerful tool in the investigation of fast heterogeneous kinetics at liquid–solid and liquid–liquid interfaces, microfabrication, and imaging of local electrochemical reactivity.^[6] The use of a micropipet as the tip of the SECM instrument has shown promise for the imaging of various substrates, especially biological specimens.^[7–9]

Up to now, SECM studies on the kinetics of electron transfer across a liquid–liquid interface have been carried out at a nonpolarized liquid–liquid interface, where a common ion is employed in both phases to control the drop in potential across the interface.^[6–9] One limitation of this approach is that the adjustable potential differences are rather narrow (± 120 mV). However, most of the thermodynamic and kinetic data on charge transfer reactions have been obtained by using convenient electrochemical techniques to polarize and control the potential difference externally at such polarized liquid–liquid interfaces. The adjustable potential difference is limited by the potential window and is usually about 300 to 600 mV. We have recently applied SECM to study electron transfer reactions at a polarized liquid–liquid interface, based on a novel three-electrode setup that we developed.^[10,11]

To the best of our knowledge, SECM studies on the kinetics of facilitated ion transfer across an externally polarized interface have not been described in the literature. Here we report the kinetic measurements of K^+ transfer across the water–1,2-dichloroethane (W–DCE) interface facilitated by DB18C6 through the use of SECM with a nanopipet as the tip. As shown in Figure 1, an Ag/AgCl electrode is covered with a

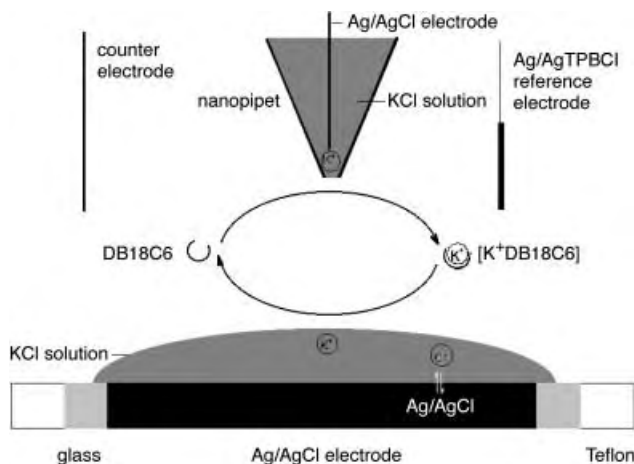


Figure 1. Schematic diagram of the application of SECM to probe facilitated ion transfer at an externally polarized liquid–liquid interface. TPBCL = tetrakis(4-chlorophenyl)borate.

droplet of aqueous KCl solution and immersed in the DCE phase. The Ag/AgCl electrode serves both as a counter and a reference electrode, and its potential remains constant as long as the concentration of KCl in the droplet is not changed.^[10] The W–DCE interface formed can be polarized externally by a three-electrode setup (the experimental setup shown in the lower part of Figure 1, where the SECM tip is not involved).

This assembly can be employed to study simple, facilitated ion and electron transfer reactions. The Ag/AgCl electrode is covered fully with 2 μ L of a 0.1 M KCl solution and immersed into 0.4 mL of a DCE solution; a phase volume ratio ($r = V_O/V_W$; V_O = volume of organic phase, V_W = volume of aqueous phase) of about 200 was used in all experiments. The area of this interface is about 0.009 cm², and well-defined voltammograms have been obtained for the three cases studied (Figure 2). Although the droplets are small and the size of

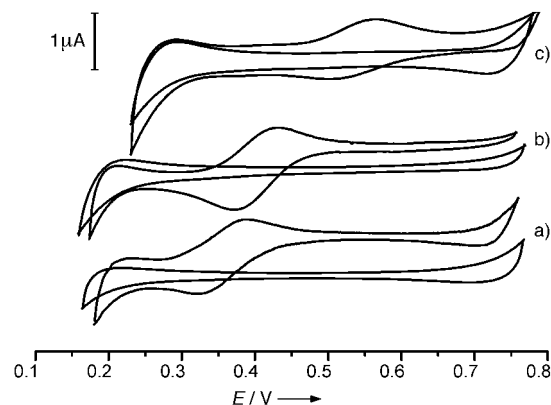


Figure 2. Cyclic voltammograms obtained for charge transfer reactions by use of a three-electrode setup. The potential E is given versus Ag/Ag(TPBCl). a) Potential window and facilitated K^+ transfer reaction. The cell consists of Ag/Ag(TPBCl)/10 mM TBA(TPBCl) + 0.25 mM DB18C6//100 mM KCl/AgCl/Ag; b) Potential window and electron transfer reaction. The cell consists of Ag/Ag(TPBCl)/10 mM TBA(TPBCl) + 0.2 mM TCNQ//1 M LiCl + 10 mM $K_3[Fe(CN)_6]$ + 400 mM $K_4[Fe(CN)_6]$ /AgCl/Ag; c) Potential window and TEA⁺ transfer reaction. The cell consists of Ag/Ag(TPBCl)/10 mM TBA(TPBCl)//100 mM LiCl + 0.4 mM TEACl/AgCl/Ag. TCNQ = 7,7,8,8-tetracyano-*p*-quinodimethane, TEA = tetraethylammonium.

the W–DCE interface formed is in the mm range, all of voltammograms are peak-shaped, indicating that the charge transfer reactions are controlled by a semi-infinite diffusion field. These results clearly indicate that this three-electrode setup works well as it simplifies the instrumentation used for studying charge transfer across liquid–liquid interfaces.

A nano-sized liquid–liquid interface can be formed at the nanorifice of the pipet between the bulk organic phase and the aqueous solution inside the nanopipet. The outer wall of the nanopipet was silanized prior to use.^[8c] A nearly perfect steady-state voltammogram can be obtained at the same potential as shown in Figure 2a.^[12] For the kinetic analysis, one needs to know the radius of the pipet a as well as the value of R_g ($R_g = r_g/a$, where r_g is the radius of the glass insulator plus the radius of the pipet). The latter can be estimated from SEM and is equal to 1.3. The radius of the pipet can be obtained either by SEM or by theoretical simulation. In our case, a value of 240 nm was determined from the SEM image of the pipet (Figure 3).

For comparison, we carried out the theoretical simulation as well, following the approach described in reference [8b]. The principle of this approach is to apply a theoretical equation with a certain value for R_g and calculate the radius of the pipet from an experimental cyclic voltammogram. We simulated the case of a nanopipet with $R_g = 1.3$ and obtained



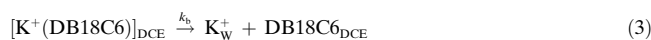
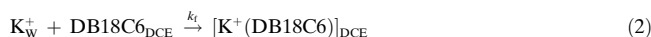
Figure 3. An SEM image of the pipet used in the experiments. Scale bar = 1 μm .

the steady-state limiting current (I), which can be represented by Equation (1), where n is the number of charge transferred,

$$I = 4.82 n F a D c^0 \quad (1)$$

F is the Faraday constant, a is the radius of the pipet, D is the diffusion coefficient, and c^0 is the bulk concentration of the ionophore. The concentration of K^+ in the aqueous phase is much higher than that of DB18C6 in the DCE phase, and the tip current is limited by diffusion of DB18C6 to the interface.^[8a] Assuming that the diffusion coefficient of DB18C6 in the DCE phase is $5.2 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$,^[5] the effective radius of the nanopipet is found to be 238 nm, which is in good agreement with the value obtained by SEM.

The reactions in the system studied can be described by Equations (2) and (3). Reaction (2) takes place at the tip and



reaction (3) at the substrate. We chose this interfacial transfer reaction as a model system mainly because its mechanism is well established and attributed to transfer by interfacial complexation/transfer by interfacial dissociation (TIC/TID). In a typical SECM experiment, the tip is usually placed in a solution containing the oxidized (or reduced) form of a redox mediator, and this mediator is reduced (or oxidized) at the tip. If the tip is positioned close to an electrically conductive substrate, the species produced on the tip can diffuse to the substrate surface and in turn be re-oxidized (or re-reduced). This recycling produces an enhancement in the tip current (i_T) depending upon the distance d between the tip and the substrate; this is called positive feedback. For an insulating substrate, there is no recycling process and the substrate blocks the diffusion of the oxidized species to the tip. Thus i_T decreases at smaller d ; this is called negative feedback. The overall rate constant of mediator regeneration at the substrate can be evaluated from the tip current–distance curve (i_T – d), which is also referred to as an approach curve.

In our experiment, the recycling process is not the result of an electrochemically active mediator, but it is maintained by the TIC/TID mechanism. The tip is held at a potential E_T where the reaction in Equation (2) is diffusion-controlled.

Meanwhile, the potential difference E_S at the larger W–DCE interface (substrate) is externally controlled by a bipotentiostat to observe the effect of a polarized substrate on the transfer process at the tip (see Figure 1). The point of $d = 0$ can be precisely determined when the tip touches the substrate interface, which causes a sharp increase (or decrease) in the tip current.

Under our experimental conditions, the rate constant of the total interfacial reaction may be expressed by Equation (4),

$$k_\text{f} = k^\circ \exp[\alpha n f (E_\text{S} - E_\text{S}^0)] \quad (4)$$

where k° is the standard rate constant, α is the transfer coefficient, n is the number of charge transferred, E_S^0 is the formal potential, and $f = RT/nF$. When the value of $E_\text{S} - E_\text{S}^0$ becomes larger, k_f becomes smaller, and it becomes easier to obtain the kinetic parameter. Therefore the rate constant of this recycling can be adjusted by controlling the potential of this interface. When E_S is smaller than the half-wave potential $E_{1/2}$, the substrate functions approximately like a conducting substrate. The recycling shown in Figure 1 can be maintained.

From the experimental approach curves shown in Figure 4, we can determine the rate constants k_f by using the best fit of the experimental results with the theoretical values. The value

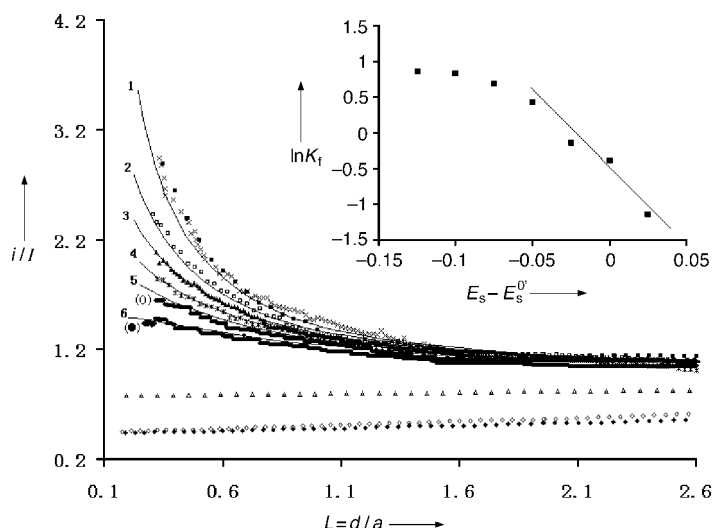


Figure 4. Experimental approach curves of a pipet with a 238 nm radius fitted with the theoretical values. The tip potential is 0.45 V, the substrate potential is 0.20 (■), 0.225 (×), 0.25 (□), 0.275 (▲), 0.30 (*), 0.325 (○), 0.35 (●), 0.375 (△), 0.40 (◇), and 0.425 V (◆). Curve 1 shows the theoretical curve for a diffusion-controlled process, and curves 2–6 are theoretical curves for kinetically controlled processes. Inset: the dependence of the heterogeneous rate constants on different values for E_S^0 .

of E_S^0 is evaluated from $E_{1/2}$ of the nernstian voltammograms,^[10a] and is equal to 0.325 V for Figure 2a. The values of k_f are in the range of 0.3–1.9 $\text{cm}^2 \text{ s}^{-1}$. The plot of $\ln k_\text{f}$ vs. E_S^0 is depicted in the inset of Figure 4. The values of k° and α can be evaluated from the intercept of the extrapolation and the slope of the plot, and are equal to $0.7 \pm 0.3 \text{ cm}^2 \text{ s}^{-1}$ and 0.56 ± 0.08 , respectively. These results are in good agreement with the values obtained by nanopipet voltammetry.^[5]

Let us now consider two limiting cases associated with the application of high negative and positive potentials. If more negative potentials are applied, the approach curves will overlap with the diffusion-controlled curves. In addition, the contribution of the transfer of supporting electrolyte will be significant. In such cases, the rate constants will be difficult to evaluate. When E_s is larger than $E_{1/2}$, most of the DB18C6 molecules in the DCE phase near the substrate exist as complexes with K^+ , and the concentration of free DB18C6 is close to zero. The recycling shown in Figure 1 cannot be maintained, and hence the substrate functions approximately like an insulating substrate. On the other hand, when the applied potentials at the substrate are larger than 0.35 V the experimental approach curves obtained deviate significantly from the theoretical ones. This is probably due to the fact that the substrate surface is positive under those conditions, preventing K^+ from diffusing to it. Consequently, the recycling is not maintained. The reaction shown in the Equation (3) can also be involved competitively, and thus the theoretical equations developed for fitting the experimental approach curves may be inadequate in this case.

Experimental Section

1,2-Dichloroethane (DCE, A.R.), potassium chloride (A.R.), and trimethylchlorosilane (A.R.) were obtained from Shanghai Chemical Co., China. Dibenzo[18]crown-6 (DB18C6, 98 %) was purchased from Aldrich. Tetrabutylammonium tetrakis(4-chlorophenyl)borate (TBA-TPBCl) was synthesized according to published procedures,^[4d] and used as the supporting electrolyte in the organic phase. Millipore water was employed for the preparation of aqueous solutions.

A Model P-2000 laser puller (Sutter Instrument Co., USA) was used to prepare the pipet with an orifice radius in the range of 0.2–4 μm from borosilicate capillaries (1 mm outer diameter, 0.58 mm inner diameter). The outer walls of the pipets were silanized according to a described procedure.^[8c] A 0.1 M KCl solution was filled from the back using a 10- μL syringe. Silver wire (0.125 mm in diameter) coated with AgCl was inserted into the pipet as the reference electrode. The pipet was checked using an Olympus BX-60 optical microscope (BX-60, Olympus) prior to each measurement to ensure there was no bubble trapped inside. The R_g value of the pipets employed is about 1.3; this can be achieved by developing a suitable program and checked by a JXA-840 SEM (JEOL).

For experiments using the three-electrode setup with an Ag/AgCl electrode covered with an aqueous phase, silver wire (2 mm diameter) was first sealed in a glass tube (3 mm outer diameter, 2 mm inner diameter) and then mounted in Teflon. Precautions must be taken to prevent leakage from these electrodes. After the silver surface was polished, it was coated with a layer of AgCl by electrolysis. Since glass and silver are hydrophilic, whereas Teflon is hydrophobic, a stable aqueous droplet can form on the Ag/AgCl surface. The glass insulator can also prevent the organic bulk phase from coming into contact with the Ag/AgCl surface. The schematic representation of the three-electrode system is similar to that in ref. [10b]. Cyclic voltammograms were recorded using a bipotentiostat (CHI900, CH Instruments, USA).

The larger liquid–liquid interface as the substrate of SECM was formed between an Ag/AgCl electrode covered with 2 μL of a 0.1 M KCl solution and 0.4 mL of a DCE solution containing 0.01 M TBA-TPBCl and 0.25 mM DB18C6. A Ag/AgTPBCl wire (0.125 mm diameter) and a Pt wire (0.5 mm diameter) were used as the reference and counter electrodes, respectively. The interfacial potential differences at the substrate and the tip were controlled separately by the CHI900 bipotentiostat, and measured versus the Ag/AgTPBCl reference electrode in the DCE solution. The approach curve was obtained by moving the tip toward the substrate interface and by recording the tip current as a function of d .

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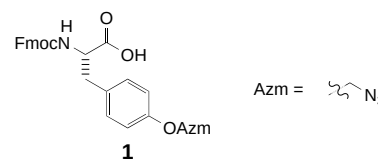
A Strategy for the Synthesis of Sulfated Peptides**

Travis Young and Laura L. Kiessling*

The sulfation of tyrosine residues is a posttranslational modification that occurs in all eukaryotes.^[1] This ubiquitous modification has been identified on many secretory proteins with diverse biological activities. Tyrosine *O*-sulfate (Tyr(SO₃H)) residues often are important for facilitating specific protein–protein interactions.^[2] However, there is little information on the molecular basis for the importance of tyrosine sulfation.^[3] Characterization of the molecular interactions of Tyr(SO₃H) has been hampered by lack of access to the necessary quantities of sulfated proteins and peptides. We report a method for the efficient production of sulfated peptides using a new protecting-group strategy.

Although several strategies for the synthesis of sulfated peptides have been reported,^[4] a general, efficient approach is still being sought. The primary obstacle in the synthesis of sulfated peptides is the predilection of sulfotyrosine to undergo desulfation under acidic conditions. Sulfotyrosine-containing peptides generally decompose rapidly in the presence of trifluoroacetic acid, the standard reagent used for side-chain deprotection and cleavage from the solid supports employed in Fmoc-based (Fmoc = (9H-fluoren-9-ylmethoxy)carbonyl) solid-phase peptide synthesis (Fmoc-SPPS). The sulfate group counterion has been shown recently to have a dramatic influence on the stability of sulfated peptides toward acidic treatment.^[5] Alternatively, acid-sensitive substrates can be released from the 2-chlorotriyl- (2-Clt-) derivatized resin without significant decomposition.^[6] Indeed, sulfated peptides may be liberated from this support without significant accompanying desulfation.^[7] Thus, the most attractive published method for sulfated peptide synthesis involves stepwise incorporation of FmocTyr(SO₃Na)OH into the growing peptide.^[8] Unfortunately, couplings using this salt and subsequent reactions to elongate the resulting peptide can be sluggish.^[9] Moreover, our attempts to synthesize peptides containing multiple sulfotyrosine residues were plagued by poor resin swelling and the need for extended coupling times.

Given the lack of general methods for the synthesis of sulfated peptides, we set out to develop a new approach. For the greatest flexibility, we employed a postsynthetic sulfation strategy. We envisioned that selective unmasking and sulfation of the desired tyrosine residues could be conducted on the solid support. Incorporation of orthogonally protected

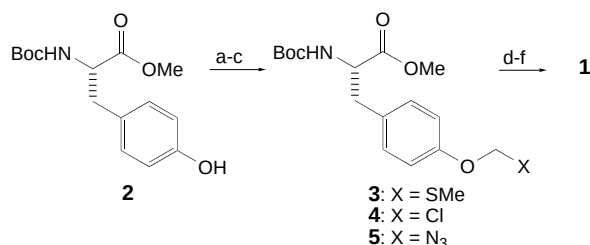


Scheme 1. Target tyrosine building block for the synthesis of sulfated peptides.

tyrosine derivatives at the peptide-assembly stage would allow the synthesis of multiply sulfated peptides with various sulfation patterns. Additionally, a solid-phase sulfation step would avoid the complicated purification of partially protected, sulfated peptide intermediates and, in the case of polysulfated peptides, mixtures with different sulfation patterns. Excess reagents could also be used to drive the sulfation reaction to completion. With this strategy, both sulfated and unmodified peptides could be produced from the same peptide synthesis. To implement this approach, we required a protecting group for the tyrosine phenol that is stable to the conditions used in Fmoc-SPPS, yet can be unmasked selectively and quantitatively under mild conditions. Strongly acidic or basic conditions for protecting-group removal must therefore be avoided. We also wished to circumvent the laborious process of cleavage and characterization of intermediates to confirm the success of the deprotection reaction. We therefore sought to design a protecting group that could be removed under mild conditions and that possesses a characteristic spectroscopic signal by which to monitor the deprotection step.

We identified Loubinoux's little-used azidomethyl (Azm) phenol protecting group as an excellent candidate for tyrosine protection.^[10] The mild conditions required for azide reduction were expected to release the phenol group without cleavage of the Clt-ester bond or modification of oxidation-sensitive amino acid residues such as cysteine and methionine.^[11] We therefore pursued the synthesis of Fmoc-Tyr(OAzm)OH (Scheme 1).

The synthesis of target **1** proceeds from BocTyrOMe (**2**, Boc = *tert*-butoxycarbonyl). Attempted alkylation of **2** with dibromomethane or bromochloromethane affords only the dimeric tyrosine methylene acetal, even when high concentrations of the electrophile are employed. Alkylation with an alternate, bifunctional methylene equivalent, chloromethyl methylsulfide, proceeds in good yield (Scheme 2). Initial



Scheme 2. Scheme for the synthesis of **1**. Conditions: a) KO^t-Bu, NaI, CH₃SCH₂Cl, DMF, 82%; b) NCS, TMSCl, CH₂Cl₂; c) NaN₃, DMF, H₂O, 87% (over 2 steps); d) TMSOTf, CH₂Cl₂; e) FmocOSu, Et₃N, THF, 84% (over 2 steps); f) LiOH-H₂O, THF-H₂O, 0 °C, 88%. DMF = *N,N*-dimethylformamide, OSu = *N*-hydroxysuccinimide.

[*] L. L. Kiessling, T. Young

Departments of Chemistry and Biochemistry, University of Wisconsin, Madison, Wisconsin 53706 (USA)
E-mail: kiessling@chem.wisc.edu

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

screening of precedented^[12] methods for the selective activation of the O,S-acetal **3** failed to yield satisfactory results.^[13] For example, treatment of **3** with *N*-chlorosuccinimide (NCS) in CH₂Cl₂ afforded only 48 % yield of the desired compound, **4**.

Our unsuccessful attempts to transform the O,S-acetal prompted a search for more reactive electrophilic activators. We reasoned that Lewis acid activation of NCS would increase the consumption of starting material without compromising the stability of the product. Indeed, activation of the O,S-acetal with NCS in the presence of *tert*-butyldimethylsilyl chloride (TMSCl) provides the chloride **4** in good yield (Scheme 2).

The labile intermediate **4** can be purified by flash chromatography on deactivated silica gel, but not without some hydrolysis. A simple aqueous workup, however, provided **4** with little decomposition. The transformation of this material to the azide **5** proceeds in high yield (87 % for 2 steps).

The azidomethyl group is not impervious to acidic conditions, a feature that complicates the synthesis of **1**, as we were unable to remove the Boc carbamate selectively using protic acids. We therefore employed TMSOTf to remove the Boc group,^[14] and protected the resulting amino group by reaction with Fmoc-*N*-hydroxysuccinimide ester.^[15] Selective saponification of the methyl ester, the precursor to **1**, provides the target compound without loss of the Fmoc group^[16] in excellent yield. The structure of the protected tyrosine derivative **1** was unequivocally established by X-ray crystallographic analysis.^[17] The enantiopurity of this compound was confirmed by the synthesis of diastereomeric dipeptides.^[18]

With FmocTyr(Azm)OH (**1**) in hand, we set out to demonstrate its use in sulfated peptide synthesis (Figure 1). Our approach involves standard Fmoc-based solid-phase peptide synthesis, followed by unmasking the desired phenols by removal of the Azm group using homogeneous conditions for azide reduction.^[19] Complete removal of the Azm moiety is confirmed by inspection of the IR absorption spectrum for the strong, distinct band arising from the azide. The free phenolic hydroxy groups are then sulfated by the action of DMF·SO₃ in a pyridine/DMF mixture.^[20] We opted for benzyl side-chain

protecting groups for other tyrosine residues: serine, threonine, aspartic acid, and glutamic acid residues; this necessitated a two-step cleavage/deprotection procedure. Cleavage from the acid-labile 2-Clt resin under conditions compatible with the labile sulfate esters is followed by routine hydrogenolysis of the benzyl groups.

To test our new method, we synthesized a sequence derived from PSGL-1, a sulfated glycoprotein. PSGL-1 is the relevant ligand for P-selectin.^[21] Significantly, a sulfated and glycosylated epitope at the N-terminus of PSGL-1 is crucial for binding.^[22] We synthesized peptides related to this epitope.^[23] Access to such compounds could facilitate dissection of the contributions caused by the distinct posttranslational modifications.^[24] We synthesized a sequence; the corresponding residues 5–12 of mature PSGL-1 that contains all three putative sulfated tyrosine residues. To demonstrate the flexibility of our strategy, we targeted the fully sulfated octapeptide and a monosulfated octapeptide (Figure 2).

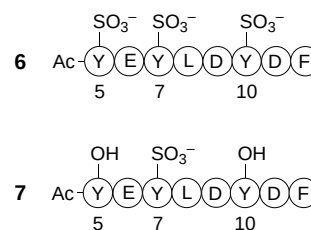


Figure 2. Sulfated octapeptide targets **6** and **7**.

Synthesis of the precursor to the trisulfated sequence **6** by automated continuous-flow Fmoc-based chemistry proceeds smoothly. Gratifyingly, amide-bond formation with our building block proceeds with a similar efficiency as with other amino acids; no special reagents or conditions are required. After the postsynthetic operations of Azm removal, sulfation, resin cleavage, and benzyl-group hydrogenolysis, the desired peptide **6** was isolated in 27 % yield after HPLC purification. Importantly, we observed no desulfated peptide in either the MALDI-TOF mass spectrum (prior to HPLC) or during HPLC purification. Synthesis of the monosulfated peptide **7** proceeds somewhat less efficiently, yielding several apparent deletion peptide products as well as the desired product. However, after HPLC purification, we isolated the target peptide in 5 % overall yield based on resin loading. Again, we were unable to detect the corresponding desulfated peptide. These achievements validate our strategy for the synthesis of sulfated peptides.

Protein tyrosine sulfation has been pushed to the forefront of research by its role in important physiological protein–protein recognition events. The ubiquity and emerging significance of this posttranslational modification provides an imperative for the development of efficient synthetic approaches to sulfated peptides. We anticipate the strategy outlined here will aid the study of tyrosine sulfation by making sulfated peptide ligands and their analogues readily available.

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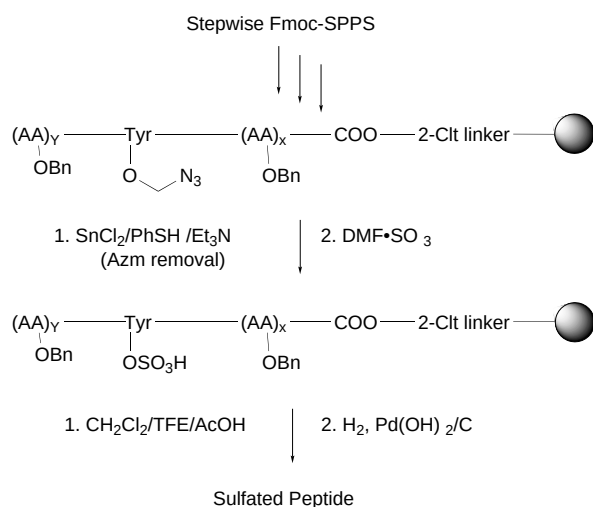


Figure 1. Overview of sulfated peptide synthesis.

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- [17] See the Supporting Information for the structure. Crystal data for $C_{26}H_{24}N_4O_5$: Crystal size = $0.09 \times 0.02 \times 0.02$ mm³, orthorhombic, $P2_12_12_1$, $a = 5.0195(5)$, $b = 19.2028(12)$, $c = 24.566(2)$ Å, $V = 2367.9(3)$ Å³, $D_{\text{calc}} = 1.325$ mg m⁻³, $2\theta_{\text{max}} = 41.06^\circ$, $\text{AgK}\alpha$ radiation ($\lambda = 0.5594$ Å), ω scans, $T = 173(1)$ K, 26122 independent and 2803 unique reflections. The data were corrected for Lorentz and polarization effects, the empirical absorption correction was performed with SADABS as described in R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, 51, 33–38, $\mu = 0.058$ mm⁻¹, $T_{\text{max}}/T_{\text{min}} = 0.9988/0.9948$. The structure was solved and refined with the program package SHELXTL (version 5.1) program library (G. Sheldrick, Bruker Analytical X-Ray Systems, Madison, WI). All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure-factor calculation at idealized positions. The final least-squares refinement of 317 parameters against 2803 data resulted in residual factors R (based on F^2 for $I \geq 2\sigma$) and wR (based on F^2 for all data) of 0.0667 and 0.2167, respectively. The final difference Fourier map was featureless. CCDC-188441 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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Nanotubes of Group 4 Metal Disulfides**

Manashi Nath and C. N. R. Rao*

Since the discovery of the carbon nanotubes, there has been active interest in exploring whether other layered materials, especially metal disulfides such as MoS₂ and WS₂, form nanotubes and related structures. Tenne et al.^[1,2] succeeded in preparing nanotubes of MoS₂ and WS₂ by first heating the metal oxide in a stream of forming gas (95 % N₂ + 5 % H₂) followed by reaction with H₂S at elevated temperatures (700–1000 °C). Thermal decomposition of the ammonium thiometallate (NH₄)₂MS₄ (M = Mo or W) in a H₂ atmosphere has been employed recently to obtain the disulfide nanotubes.^[3] Metal trisulfides are formed as intermediates in the formation of the disulfide nanotubes in both of the above methods. Accordingly, MoS₂ and WS₂ nanotubes could be prepared directly from the decomposition of MoS₃ and WS₃ in a hydrogen atmosphere.^[3] NbS₂ nanotubes have also been prepared by the thermal decomposition of NbS₃ in a hydrogen atmosphere at 1000 °C.^[4] These results suggested that it may indeed be possible to prepare nanotubes of other layered disulfides by the thermal decomposition of appropriate trisulfide precursors. Since the disulfides of Group 4 metals, such as Ti, Zr, and Hf, possess layered hexagonal structures,^[5,6] we considered it feasible to prepare the nanotubes of these materials starting from their trisulfides. Herein we

[*] Prof. Dr. C. N. R. Rao, M. Nath
CSIR Centre For Excellence In Chemistry and
Chemistry and Physics of Materials Unit
Jawaharlal Nehru Centre for Advanced Scientific Research
Jakkur P.O., Bangalore 560 064 (India)
E-mail: cnrrao@jncasr.ac.in
and
Solid State And Structural Chemistry Unit
Indian Institute of Science
Bangalore 560 012 (India)
Fax: (+91) 80-846-2760

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report the first successful synthesis and characterization of these nanotubes of the Group 4 metal disulfides.

Thermal decomposition of HfS_3 at 900°C in an atmosphere of $\text{Ar}(95\%) + \text{H}_2(5\%)$ gave a good yield of nanostructures as evident from the scanning electron microscope (SEM) image (Figure 1a). Analysis by energy-dispersive X-ray spectroscopy (EDX) showed the $\text{Hf}:\text{S}$ ratio to be 1:2. The

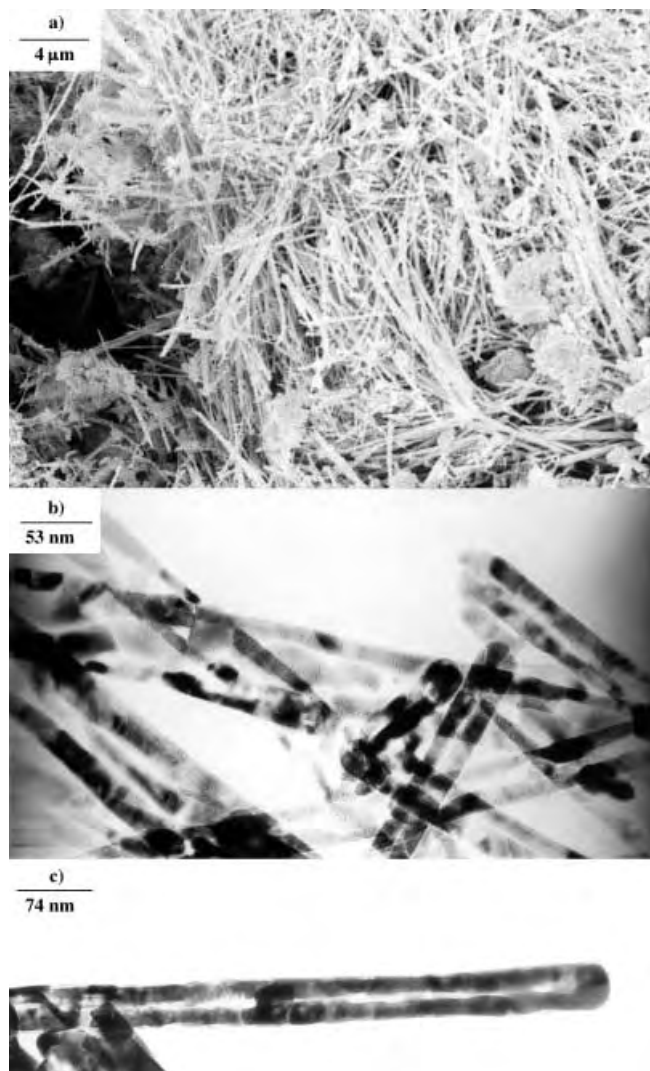


Figure 1. a) SEM image showing a large collection of HfS_2 nanostructures, some being more than a micron long; b) and c) low-resolution TEM images of the HfS_2 nanotubes with closed caps.

powder X-ray diffraction (XRD) pattern of the product confirmed it to be 1T- HfS_2 , with the lattice parameters $a = 3.635$ and $c = 5.851 \text{ \AA}$ (JCPDS card No. 28-0444). There is a slight expansion (ca. 1 %) in the c -axis of the nanostructures. The expansion is much smaller than that observed in the MoS_2 and WS_2 nanotubes (ca. 3 %),^[1b] possibly because the mean c -axis compressibility of HfS_2 is higher than that of MoS_2 .^[7] The nanostructures are typically more than a micron long, with a large proportion of them being nanotubes. A low magnification transmission electron microscope (TEM) image of the nanotubes is shown in Figure 1b. A TEM image of a nanotube with a length greater than 500 nm is shown in Figure 1c. The

outer diameter of the nanotubes is in the range of 55–60 nm, while the inner core diameter is around 17–30 nm. The diameter of some of the nanotubes varies along the length. Thus, the nanotube in Figure 1c has an outer diameter of 40 nm and an inner diameter in the range of 7–13 nm. These nanotubes have non-uniform walls and generally have non-spherical tips, with some being rectangular.

The TEM image of a HfS_2 nanotube with a rectangular tip is shown in Figure 2a. At the outer corners of the tip there are ripplelike undulations which can arise from the strain

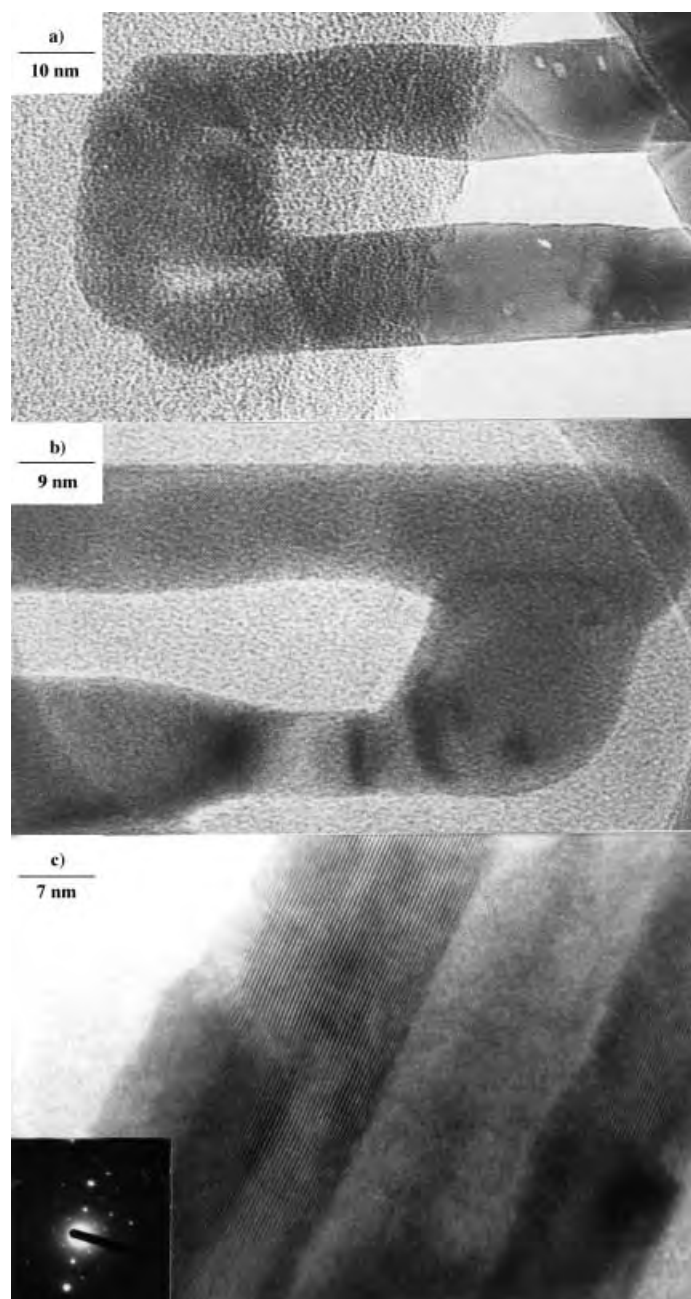


Figure 2. a) Low-resolution TEM image of HfS_2 nanotubes; b) TEM image of a HfS_2 nanotube with layer fringes at an angle to the tube axis; c) high-resolution TEM image of a HfS_2 nanotube showing layer fringes with a separation of $5.8 \text{ \AA}$. The tube axis is perpendicular to the c direction. The inset in (c) shows the ED pattern exhibiting a hexagonal arrangement of layers.

involved in bending the layers. Layer fringes are visible along the tube walls on close inspection. Terminated layers occur both in the outer and inner edges of the wall, which causes non-uniformity in the wall thickness. Such rectangular tips have been observed in the nanotubes of MoS_2 , WS_2 , and $\text{Mo}_{1-x}\text{W}_x\text{S}_2$ nanotubes.^[8,9] The image of the nanotube in Figure 2b shows an unusual rectangular tip, and the layer fringes along the tube walls show a layer separation of approximately 5.8 Å (the separation between (001) planes in bulk HfS_2 is 5.84 Å). The layers are, however, not parallel to the tube axis as expected, and instead make an angle of about 40° with the tube axis; in other words, the tube axis is at an angle of 40° to the c direction.

Figure 2c shows a high-resolution image of a HfS_2 nanotube with the tube axis perpendicular to the c -direction. The layer separation here is approximately 5.8 Å. We observe several terminated layers at the outer edges of the tube walls, possibly as a result of the absence of growing material at the edges. A considerable number of defects and edge dislocations seem to be present along the length of the tube wall. The inset in Figure 2c shows an electron diffraction (ED) pattern characteristic of the hexagonal arrangement of the $d(101)$ layers. The ED pattern also contains Bragg spots corresponding to the $d(002)$ plane (2.923 Å). Overall, the ED pattern indicates the tube axis to be perpendicular to the c -direction.

The growth of the HfS_2 nanotubes appears to start from the HfS_3 particles. The first disulfide layers formed initially entrap the trisulfide particles and inhibit the formation of larger aggregates. HfS_3 then decomposes to form the HfS_2 layers, which grow outward from the precursor particle to form tubules. As a consequence of such growths, defects and edge dislocations occur near the tube tip and walls, which are the active points for tube growth.

We have recorded the electronic absorption and emission spectra of the HfS_2 nanotubes. HfS_2 is an indirect band-gap semiconductor with an indirect band gap energy of about 2 eV.^[10] The reflectance spectrum of bulk HfS_2 shows a band with a maximum at 550 nm and a sharper band at 250 nm. The nanotubes show a small blue-shift of the longer wavelength band. The photoluminescence spectrum of the nanotubes shows a peak at 676 nm, while the bulk sample has a band at 687 nm (Figure 3a). This feature is likely to arise from sub-band-gap emission or from gap states.

The Raman spectrum of the HfS_2 nanotubes has a band arising from the A_{1g} mode, which corresponds to the S atom vibration along the c -axis perpendicular to the basal plane, and another arising from the E_g mode as a consequence of the movement of the S and Hf atoms in the basal plane.^[11] The Raman bands of the nanotube correspond exactly to the bands obtained for the bulk HfS_2 powder, but the A_{1g} band shows some broadening. The full-width at half maximum (FWHM) of the A_{1g} band is 11 cm^{-1} in the nanotubes compared to 8 cm^{-1} for the bulk sample. Such a broadening of the Raman band has been noted in MoS_2 and WS_2 nanotubes.^[12] The broadening of the Raman band in the nanotubes can be explained by the spatial correlation or the phonon confinement model, which predicts a broadening of the Raman signal as the crystallite decreases.^[13] The decrease in the crystallite size relaxes the $\Delta q=0$ selection rule, thus

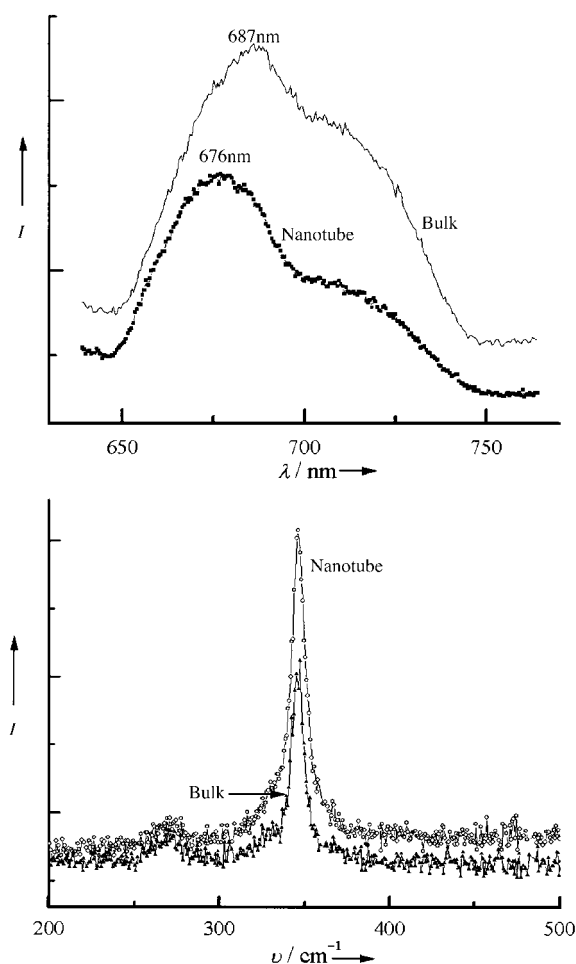


Figure 3. a) Photoluminescence spectra of nanotubes and a bulk sample of HfS_2 ; b) Raman spectra of the nanotubes and a bulk sample of HfS_2 .

allowing transitions with $q \neq 0$, which in effect cause a broadening of the signal.

We have been able to obtain nanotubes of ZrS_2 by the thermal decomposition of ZrS_3 , under conditions similar to those mentioned earlier for HfS_2 . The powder XRD pattern of the decomposed product showed it to possess the hexagonal structure with $a = 3.660$ and $c = 5.825$ Å (JCPDS card No. 11-0679). EDX analysis confirmed the composition. The low-resolution TEM image (Figure 4a) shows a ZrS_2 nanotube with a closed rectangular tip. The outer diameter of the tube is approximately 125 nm, while the inner core diameter is about 60 nm. Besides nanotubes, nanorods and onions are also seen in the images. The nanotube in Figure 4b, also with a rectangular tip, contains undulations at the outer edge, just as in HfS_2 nanotubes, with the inner wall showing non-uniformity resulting from the discontinuous growth of the ZrS_2 layers. Figure 4c shows nanotubes with diameters of about 140 nm and possessing fairly linear uniform walls. The inset of Figure 4c shows an ED pattern with the characteristic hexagonal arrangement of the (101) layers and containing Bragg spots corresponding to $d(002)$.

We were able to prepare TiS_2 nanotubes by the thermal decomposition of TiS_3 in a $\text{H}_2 + \text{He}$ atmosphere at 800 °C. These nanotubes were more beam sensitive, but we could, however, obtain low-resolution TEM images.

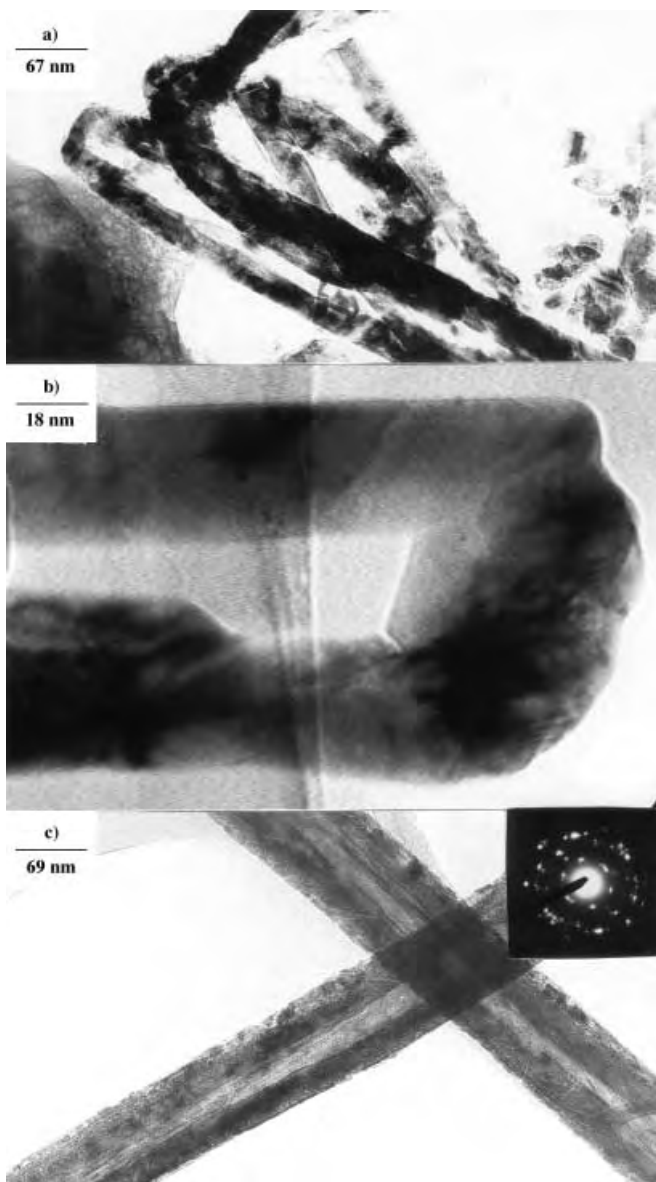


Figure 4. Low-resolution TEM images of the ZrS_2 nanotubes. The tubes in images (b) and (c) show rectangular tips. The inset in (c) shows a typical ED pattern.

In conclusion, nanotubes of the disulfides of the three Group 4 metals, Hf, Zr, and Ti have been successfully prepared by the decomposition of the corresponding trisulfides in a reducing atmosphere.

Experimental Section

The trisulfides were synthesized in a sealed-tube reaction by the direct combination of the elements.^[5,6] In a typical synthesis Hf and S powders were mixed in a stoichiometric ratio and the mixture sealed in a quartz ampoule under vacuum. The ampoule was placed in a furnace, which was raised slowly to 560 °C and maintained at that temperature for 36 h. HfS_3 formed as a bright orange solid.

The trisulfides were decomposed in a stream of Ar and H_2 around 900 °C to obtain the disulfide nanotubes. The HfS_3 powder was placed in the central zone of a horizontal furnace, the temperature of which was slowly raised to 900 °C (heating rate of 10 °C min⁻¹), and a steady flow of a mixture of Ar (285 standard cubic centimeters (sccm)) and H_2 (15 sccm) was maintained. The decomposition was carried out for 40 min, after which the temperature

of the furnace was reduced. A dark brown powder containing HfS_2 nanostructures were obtained.

Powder X-ray diffraction patterns were obtained using a Seifert diffractometer. SEM images and EDX analysis was carried out using a Leica S440I instrument equipped with ISIS Link software. TEM images were obtained by using a JEOL JEM-3010 transmission electron microscope operating at 300 kV. The HfS_2 and ZrS_2 nanotubes were quite beam-stable, unlike the TiS_2 nanotubes. Photoluminescence studies were performed with a Perkin Elmer LS 55 luminescence spectrometer. Raman measurements were performed with a solid-state Nd-YAG laser and an excitation of 532 nm.

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A Straightforward NMR-Spectroscopy-Based Method for Rapid Library Screening**

Aloysius H. Siriwardena,* Fang Tian,
Schroder Noble, and James H. Prestegard

A variety of NMR-based methods have been devised to facilitate the screening of compound mixtures for components that bind protein drug targets.^[1–6] The majority of these approaches have been developed in recent years, hand in hand with methods for generating libraries of compounds by combinatorial chemistry.^[7] The ability to screen such libraries rapidly and simply to identify potential leads is an important

[*] Prof. Dr. A. H. Siriwardena, Dr. F. Tian, S. Noble,
Prof. Dr. J. H. Prestegard
The Complex Carbohydrate Research Center
University of Georgia
220, Riverbend Road, Athens, GA 30602—4712 (USA)
Fax: (+1) 706-542-4412
E-mail: siriward@ccrc.uga.edu

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requirement of the drug discovery process, hence the considerable activity seen in developing such methods. Although NMR-based screening methods are less sensitive than other alternatives, they are less prone to give artifacts and can be considered comparatively robust. In one class of NMR-based approach, the binding of a molecule to the target macromolecule is monitored by observing changes in the characteristic ^{15}N , ^{13}C , or ^1H NMR spectroscopy protein chemical shifts upon ligand-binding.^[2,8] In the other class of NMR-based screening methods, low molecular-weight molecules are detected *directly*, by making use of differential relaxation, diffusion, transferred NOEs, or saturation transfer effects of free and bound molecules.^[9–16] Direct methods require that the molecule to be detected be in fast chemical exchange between bound and free states, as only then can the easily detected signals display average properties that reflect the bound state. Generally speaking, in the bound state, a small ligand will behave as a macromolecule and exhibit the attendant broad peaks, negative NOEs, and small diffusion coefficients, whereas in the free state molecules will continue to manifest their characteristic narrow linewidths, small and positive NOEs, and large diffusion coefficients. Despite numerous examples of successful applications, methods based on transferred NOEs, relaxation, or diffusion techniques have a shortcoming in that they cannot be used for monitoring high-affinity ligands, which will undergo only slow chemical exchange.

We present herein a 1D ^1H NMR screening method that exploits the well-known phenomenon of competitive binding.^[17] A known *low-affinity* ligand for a targeted receptor—a “probe”—is included as a component in the mixture of compounds to be screened. In the event that a molecule in the library under scrutiny happens to be a ligand, it competes with the “probe” for binding sites on the target receptor. There ensues a change in the NMR parameters which, at equilibrium, reflects the binding affinity of any new ligand.^[18] Here the approach is experimentally demonstrated by using the plant lectin, concanavalin A (Con A),^[19] as a model receptor and a handful of designed libraries, consisting of commercially available compounds—essentially mono— and disaccharides. Con A is a ≈ 120 kD homotetrameric carbohydrate-binding protein (lectin) that has been the subject of extensive structural and binding studies.^[20,21] Interactions of lectins with their respective saccharide ligands is increasingly identified as crucial in a wide variety of biologically important processes.^[20] The possibility that oligosaccharides or mimetics thereof might have promise as drugs has motivated the synthesis of oligosaccharide libraries intended to uncover tight-binding ligands of this particular class of protein.^[21]

That the method is fundamentally sound was established by a series of straightforward experiments. Thus, Con A (0.1 mM) was mixed with α -D-(+)-methylglucopyranoside (**1**;

0.05 mM) and D-(+)-galactose (**4**; 0.1 mM) in D_2O and a 500 MHz 1D ^1H NMR spectrum of the solution recorded (Figure 1a). As **4** does not bind to Con A, signals from this sugar can conveniently serve as an internal reference to aid in monitoring changes in spectral intensity or linewidth. Based on the reported binding constant data for Con A (Table 1), approximately 25% of **1** in this sample is expected to be bound. The resonance signals corresponding to **1** remain

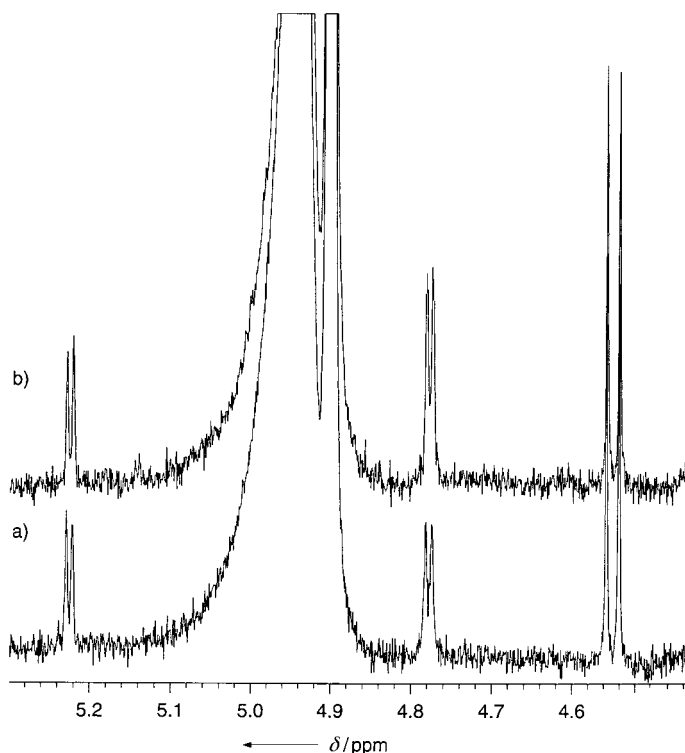


Figure 1. Portion of 1D proton spectra acquired of Con A (0.1 mM) in D_2O : a) in the presence of 0.05 mM compound **1** and 0.1 mM compound **4**, b) upon addition of a 20 mM solution of compound **3** to the mixture. The final concentration of compound **3** is 0.12 mM. The signal at $\delta = 4.78$ ppm is from H-1 of compound **1**. Signals at $\delta = 4.55$ and 5.22 ppm are from H-1 of α and β -anomers, respectively, of compound **4**. Spectra were acquired at 10°C with spectral width 6000 Hz, 1.5 s acquisition time, 1.5 s recycle delay, and 360 scans.

Table 1. Components of the library and their binding constants^[a] to concanavalin A.

	Compound	$K_D \times 10^{-4}$
Active compounds ^[b]		
1	methyl- α -D-glucopyranoside	3.2
2	methyl- α -D-mannopyranoside	0.91
3	methyl 3,6-di-O-(α -D-mannopyranosyl)- α -D-mannopyranoside (trimannoside)	0.03
Inactive compounds ^[b]		
4	D-(+)-galactose	
5	L-(+)-fucose	
6	6-deoxy-L-mannose (rhamnose)	
7	L-threonine	
8	6-O- α -D-galactopyranosyl-D-glucose (melibiose)	
9	4-O- β -D-galactopyranosyl-D-glucose (lactose)	
10	L-histidine	

[a] Data taken from ref. [20a]. [b] Con A and all compounds are commercially available

sharp (Figure 1a) and are derived from the fraction of this molecule that remains free in solution (slow exchange), as resonance signals of the bound fraction would be too broad to be observable. The change in intensity of the proton signal at $\delta = 4.78$ ppm (H-1 of the probe) is proportional to the amount unbound **1**. Addition of a large molar excess of trimannoside **3** to the sample results in an increase in the relative intensity of signals corresponding to **1** in the ^1H NMR spectrum (Figure 1b). Ligand **3** binds considerably more tightly to Con A than does **1** (Table 1) which results in a greater proportion of bound **1** displaced into the bulk solution. The observed increase in the integrated intensity of the anomeric proton of probe **1** upon addition of **3** is $\approx 30\%$, and is consistent with the increase expected from reported binding constant values (Table 1).

The scope of this method for identifying potential ligands from a pool of unknowns is demonstrated by using three designed compound libraries. The libraries are each composed of five compounds, all present in concentrations of 0.1 mM. Library I is composed of components **5–10** (none of which are ligands of Con A). Library II is identical to library I, except that compound **10** is replaced by compound **2** (a known ligand of Con A). Library III is also essentially identical to library I, except that in Library III, compound **10** is exchanged for compound **3** (also known to bind Con A). To each of these libraries is added a cocktail comprising Con A (0.1 mM), compound **1** (0.1 mM)—the “probe”—and compound **4** (0.2 mM)—the reference. The 500 MHz 1D ^1H NMR spectrum of each mixture was recorded and are shown, in part, in Figure 2. It is immediately apparent that variation in the probe signal intensities correctly reflect the presence, *or not*, of active compounds in the designed libraries. Moreover, the observed difference in signal intensity of the “probe” in the spectra of libraries II (Figure 2d) and III (Figure 2c) suggests that the ligand identified in library III is of a higher affinity than that present in library II. When only one active compound is present in a given mixture (true for the libraries under consideration here), a lower limit of K_D (dissociation constant) for that compound can be estimated from the relative changes in “probe” signal, provided that the binding constant of the latter is known. Further, classical titration experiments allow binding strengths of any “hit” to be assessed semi-quantitatively.^[17b] The K_D values of the active compounds in libraries II and III, estimated in this way (data not shown), are in agreement with values obtained by independent methods (listed in Table 1).

The method described here is operationally very simple, requiring only that one 1D ^1H NMR spectrum be recorded per library under scrutiny. No isotope labeling is required, either of the probe or the target protein nor is the protein required to be pure. The only prerequisite is that at least one molecule be available capable of binding weakly to this macromolecule, and thus, of serving as the all-important probe. All the active ligands, including those displaying either very fast or very slow exchange behavior, are equally susceptible to detection. Moreover, the method is opaque to non-specific association of compounds to the target protein, which includes any binding to secondary sites, minimizing potential sources of false positives. Furthermore, the ratio of protein to probe may

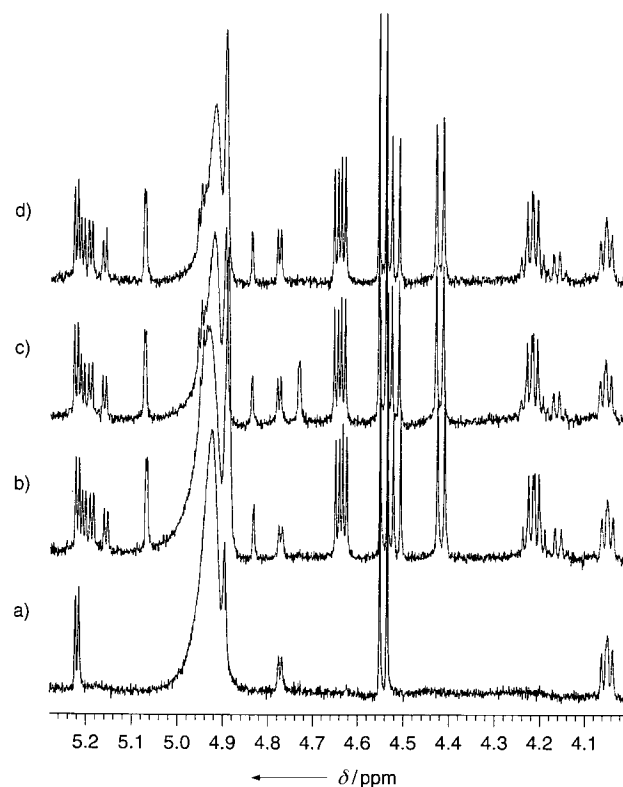


Figure 2. Portions of 1D proton spectra acquired on compound mixtures: a) stock solution, Con A (0.1 mM) with compound **1** (0.05 mM), and compound **4** (0.2 mM), b) compounds **5–10** (0.1 mM) with stock solution, c) compound **2** (0.1 mM) and compound **5–9** with stock solution (Library II), d) Compound **3** (0.1 mM) and compound **5–9** with stock solution (Library III). The signal at $\delta = 4.78$ ppm is from H-1 of compound **1**—the probe molecule. Spectra were acquired at 10°C with spectral width 6000 Hz, 1.5 s acquisition time, 1.5 s recycle delay and 240 scans. Water suppression is achieved by presaturation.

be tuned so as to limit selection of ligands to those of a chosen binding strength or greater. For example, the binding constant of compound **2** is only about three times greater than that of the probe (compound **1**), but was nevertheless identified in Library II. The sensitivity of this approach compares well with other NMR-based screening methods. In the model experiments described here, $100\ \mu\text{M}$ Con A was used per sample, with constituents of the libraries each present in concentrations of $100\ \mu\text{M}$. Under these conditions each screen took less than 15 minutes to perform using a 500 MHz NMR spectrometer. However, a significant reduction in amounts of required ligand would result if ligands displaying K_D values in the nM range were being screened. Resonance intensity has been exploited in this study to monitor the percentage of free probe, but other parameters—including line broadening or transferred NOEs (in the case of a probe in rapid exchange)—might also be taken advantage of to achieve this end.^[18] No structural information can be gleaned and in the event of an active molecule being detected, its identity would have to be elucidated with recourse to more sophisticated NMR spectroscopic techniques. If resonances derived from the probe were to overlap with others arising from the library, editing techniques such as the diffusion-filter method would be expected to allow selective monitoring of the probe signals. Alternatively, use of an isotopically labeled probe would

effectively render “invisible” signals other than those of the probe and, if the label could be easily incorporated, lead to a further simplification of the screening method.

The approach demonstrated here provides a general and rapid means for detecting active molecules, especially when these are constituents of a combinatorially generated library. The method could conceivably be automated, and thereby transformed into a routine, high-throughput technique of even greater potential in the process of drug discovery.^[22]

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Highly Enantioselective Rh-Catalyzed Intramolecular Alder–Ene Reactions for the Syntheses of Chiral Tetrahydrofurans**

Aiwen Lei, Minsheng He, Shulin Wu, and Xumu Zhang*

Dedicated to Professor Robert H. Grubbs on the occasion of his 60th birthday

Alder–ene reactions are a powerful way to construct carbon–carbon bonds. The intramolecular version of these reactions can provide efficient routes to produce a variety of heterocyclic and carbocyclic compounds.^[1] Since the thermal Alder–ene reaction requires high temperature, it has found limited applications in organic syntheses. In contrast, transition-metal-catalyzed Alder–ene reactions can be performed under mild conditions and therefore are widely applied to organic syntheses.^[2] However, the enantioselective processes of metal-catalyzed Alder–ene reactions are relatively unexplored and the development of highly efficient catalysts still remains a great challenge.^[3] Recently, we have developed Rh-catalyzed intramolecular Alder–ene reactions of enynes using a $[\{\text{Rh}(\text{diphos})\text{Cl}\}_2]$ precursor.^[4] Enantioselectivities between 65–98 % *ee* were obtained by using 1,2-bis(phospholano)benzene (Duphos), (2*R*,2'*R*)-bis(diphenylphosphanyl)-(1*R*,1'*R*)-dicyclopentane (BICP), or the related (2*R*,2'*R*)-bis(diphenylphosphinite)-(1*R*,1'*R*)-dicyclopentane (BICPO) as chiral ligands.^[4a] Herein, we report a significant improvement of the catalytic system for these reactions. The new catalysts are prepared in situ by simply mixing a commercially available metal precursor and a ligand. Over 99 % *ee* has been achieved for a number of substrates.

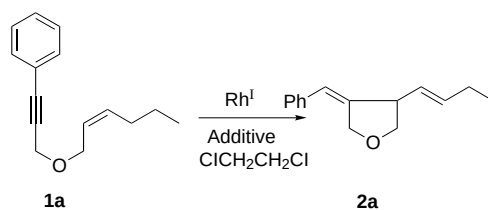
To achieve high enantioselectivities for Rh-catalyzed Alder–ene reactions, we have screened a number of chiral phosphane ligands. The enyne **1a** was chosen as a standard substrate to optimize the reaction conditions and the results are given in Table 1. In the absence of phosphane ligand, $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ was an ineffective catalytic precursor at either room temperature or 65 °C (Table 1, entries 1 and 2). However, $[\{\text{Rh}(\text{nbd})\text{Cl}\}_2]$ (nbd = norbornadiene) can be used as a catalyst precursor at 65 °C (Table 1, entry 6). Using the *C_n*-Tunaphos ligands developed by our group,^[5] high efficiency was observed. When *rac*-C₄-Tunaphos was used as the ligand in the presence of $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ and AgSbF₆, high conversion (100 %) and a high yield (98 %) were obtained at room temperature within 20 min (Table 1, entry 9). Control experiments indicated that there were big differences between this new catalytic system and the earlier protocol developed by us using $[\{\text{Rh}(\text{diphosphane})\text{Cl}\}_2]$ as catalytic precursor. We previously reported that $[\{\text{Rh}(\text{BINAP})\text{Cl}\}_2]$ (BINAP = 2,2'-

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[*] Prof. Dr. X. Zhang, Dr. A. Lei, M. He, Dr. S. Wu
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: xumu@chem.psu.edu

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Table 1. Rh-catalyzed Alder–ene reaction of **1a**.^[a]



Entry	Rh ^I	T	Additive	Conversion [%] ^[b]
1	[[Rh(cod)Cl] ₂]	RT	AgSbF ₆	< 5
2	[[Rh(cod)Cl] ₂]	65 °C	AgSbF ₆	< 5
3	[Rh(cod) ₂]SbF ₆	RT	none	< 5
4	[Rh(cod) ₂]SbF ₆	65 °C	none	< 5
5	[Rh(nbd)Cl] ₂	RT	AgSbF ₆	< 5
6	[Rh(nbd)Cl] ₂	65 °C	AgSbF ₆	100(65)
7	[Rh(nbd) ₂]SbF ₆	RT	none	< 5
8	[Rh(nbd) ₂]SbF ₆	65 °C	none	100(60)
9	[[Rh(cod)Cl] ₂]/ <i>rac</i> -C ₄ -Tunaphos	RT	AgSbF ₆	100(98)
10	[[Rh(cod)Cl] ₂]/ <i>rac</i> -BINAP	RT	AgSbF ₆	100(99)
11	[[Rh(cod)Cl] ₂]/PPh ₃	RT	AgSbF ₆	< 5
12	[RhCl(PPh ₃) ₃]	RT	AgSbF ₆	< 5
13	[[Rh(cod)Cl] ₂]/dppb	RT	AgSbF ₆	< 5
14	[[Rh(cod)Cl] ₂]/dppbO	RT	AgSbF ₆	< 5
15	[[Rh(cod)Cl] ₂]/ <i>rac</i> -BICPO	RT	AgSbF ₆	< 5

[a] All reactions were performed using 10 mol % Rh^I in 0.2 mmol scale. dppb = 1,4-bis(diphenylphosphanyl)butane, dppbO = 1,4-bis(diphenylphosphinito)butane. [b] Conversion was detected by GC, and isolated yield was reported in parentheses.

bis(diphenylphosphanyl)-1,1'-binaphthyl) was inactive towards the Alder–ene reaction. In contrast to our earlier report, *rac*-BINAP was found to be an efficient ligand in this new catalytic system for Rh-catalyzed Alder–ene reactions; 100 % conversion and 99 % yield were obtained within 5 min at room temperature by simply mixing [[Rh(cod)Cl]₂] and *rac*-BINAP (Table 1, entry 10).^[6] Further changes in catalysts and ligands showed that some systems did not work (Table 1, entries 11–15).^[7]

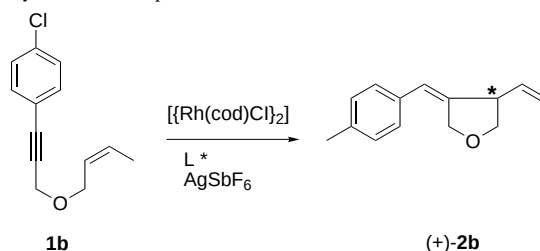
Encouraged by these results, we focused our studies on the asymmetric Rh-catalyzed Alder–ene reaction. All C_n-Tunaphos^[5] (*n* = 1–6) were effective ligands, and highly enantioselective products (> 99 % *ee*) were obtained (Table 2, entries 1–6). It is noteworthy that extremely high enantioselectivities were achieved when (*S*)-C₃-, (*S*)-C₄-Tunaphos, and (*S*)-BINAP were used as ligands (Table 2, entries 3, 4, and 8).

With the optimized conditions in hand, we screened the reaction with a variety of enyne substrates (Table 3). Using enantiomerically pure BINAP as the ligand, high enantioselectivities were achieved with most tested substrates (Table 3, entries 1–6). Reactions of an enyne bearing an aryl terminal group were completed within 20 min at room temperature; high yields and over 99 % *ee* were achieved. Enyne substrates with an alkyl group were more reactive than enyne substrates with an aryl terminus (Table 3, entries 8 and 9); these reactions were completed less than 5 min.

To broaden the substrate scope, we introduced ketone (Table 4, entries 1, and 2), ester (Table 4, entry 3), alcohol [Eq. (1)], and ether groups [Eq. (2); MOM = methoxymethyl] at the alkyne carbon terminus. As expected, high yields and enantioselectivities were obtained.

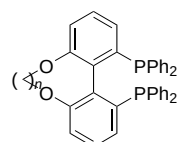
The vinyl propargyl ether **18** was obtained in high yield (91 %) and enantioselectivity (99.3 % *ee*) from the cycloiso-

Table 2. Highly enantioselective Alder–ene reactions of enyne **1b** catalyzed by rhodium complex.^[a]

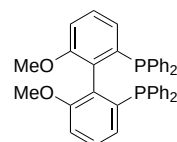


Entry	L*	Conversion ^[b]	<i>ee</i> [%] ^[c]
1	3	100	99.2
2	4	80	99.3
3	5	100	> 99.9
4	6	100	> 99.9
5	7	100	99.2
6	8	100	99.3
7	9	100	98.3
8	10	100	> 99.9

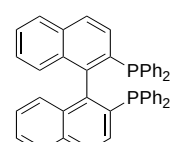
[a] All reactions were performed using 10 mol % Rh^I and 12 mol % BINAP in 0.2 mmol scale. [b] Conversion was detected by GC. [c] Determined by GC with chiral select 1000.



n = 1 (*S*)-C₁-Tunaphos **3**
n = 2 (*S*)-C₂-Tunaphos **4**
n = 3 (*S*)-C₃-Tunaphos **5**
n = 4 (*S*)-C₄-Tunaphos **6**
n = 5 (*S*)-C₅-Tunaphos **7**
n = 6 (*S*)-C₆-Tunaphos **8**

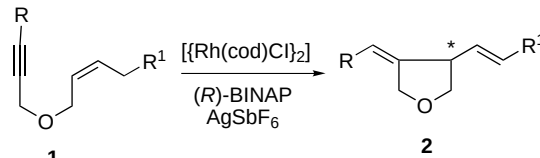


(*S*)-**9**



(*S*)-**10**

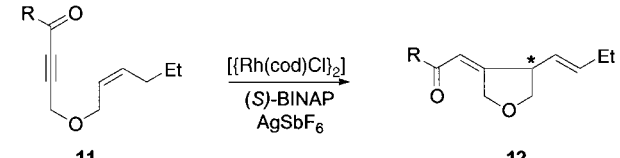
Table 3. Highly enantioselective Alder–ene reactions of enynes **1** catalyzed by a rhodium complex using BINAP as ligand.^[a]



Entry	1	R	R ¹	2	Yield [%] ^[b]	ee [%] ^[c]
1	1a	Ph	Et	(–)- 2a	96	> 99.5
2	1b	Ph	H	(–)- 2b	96	> 99.5
3	1c	C ₆ H ₄ (<i>o</i> -Cl)	H	(–)- 2c	95	99.0
4	1d	C ₆ H ₄ (<i>m</i> -Cl)	H	(–)- 2d	92	99.5
5	1e	C ₆ H ₄ (<i>p</i> -Cl)	H	(–)- 2e	95	> 99.9
6	1f	C ₆ H ₄ (<i>p</i> -Me)	H	(–)- 2f	94	99.9
7	1g	C ₆ H ₄ (<i>p</i> -CF ₃)	H	(–)- 2g	93	99.1
8	1h	Me	Me	(–)- 2h	82	> 99.9
9	1i	<i>n</i> Bu	H	(–)- 2i	89	> 99.9

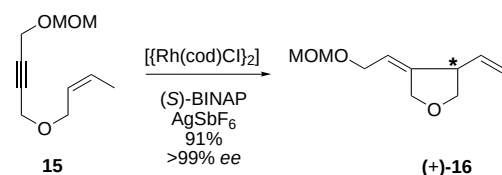
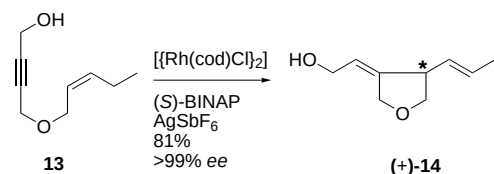
[a] All reactions were performed using 10 mol % Rh^I and 12 mol % BINAP in 0.2 mmol scale. [b] Yield of isolated product. [c] Determined by GC and HPLC.

Table 4. Highly enantioselective Alder–ene reactions of functional enyne **11** catalyzed by rhodium in the presence of BINAP.^[a]

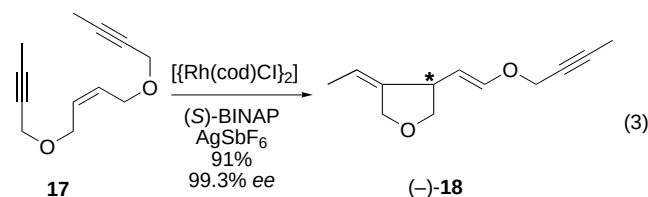


Entry	11	R	12	Yield [%] ^[b]	ee [%] ^[c]
1	11a	Me	(+)- 12a	86	99.5
2	11b	Ph	(+)- 12b	99	> 99.9
3	11c	EtO	(+)- 12c	82	> 99.9

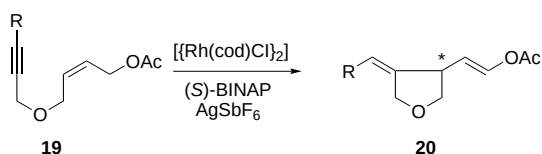
[a] All reactions were performed using 10 mol % Rh^I and 12 mol % BINAP in 0.2 mmol scale. [b] Yield of isolated product. [c] Determined by GC with chiral select 1000.



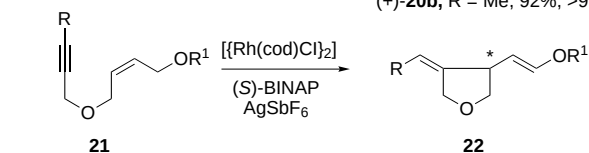
merization of yne–ene–yne **17** [Eq. (3)]. Since vinyl ethers and vinyl acetates are important functionalities in organic syntheses, we incorporated these groups by designing an array



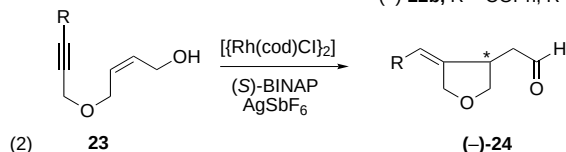
In conclusion, we have developed a highly efficient Rh-catalyzed Alder–ene reaction for preparing a variety of chiral



(+)-**20a**, R = Ph, 96%, 99.7 % ee
(+)-**20b**, R = Me, 92%, >99.9 % ee



(+)-**22a**, R = Ph, R¹ = Me, 92%, >99 % ee
(–)-**22b**, R = COPh, R¹ = Et, 93%, >99 % ee



(R)-BINAP (+)-**24a**, R = Ph, 98%, 99 % ee
(S)-BINAP (–)-**24b**, R = Me, 94%, 99.1 % ee

Scheme 1. Highly enantioselective Alder–ene reactions of enynes substituted at the allylic terminus.

tetrahydrofurans using an air-stable [(Rh(cod)Cl)₂] precursor with commercially available BINAP or the C_n-Tunaphos ligands. Functionalized tetrahydrofurans were obtained in high yields and over 99 % ee for all the substrates we tested. Syntheses of other functionalized carbocycles and heterocycles such as lactams and pyrrolidines are in progress and will be reported in due course.

Experimental Section

The procedure for the asymmetric alder–ene reaction of **1b** catalyzed by rhodium (**2b**):^[4] In a dried Schlenk tube, $[\text{Rh}(\text{cod})\text{Cl}]_2$ (4.9 mg, 0.01 mmol) and (*S*)-BINAP (13.8 mg, 0.022 mmol) were dissolved in freshly distilled 1,2-dichloroethane (2 mL), then freshly prepared **1b** (37.2 mg, 0.2 mmol) was added to the solution at room temperature under nitrogen. After the mixture had been stirred for 1 min, AgSbF_6 (0.04 mmol) was added, and the reaction was complete within 5 min. The reaction mixture was directly subjected to column chromatography. Compound **2b** (35.8 mg, 96% yield, >99.9% ee) was obtained. The ee value was determined by GC with chiral select 1000 at 150 °C. $[\alpha]_D^{25} = 23.85$ ($c = 0.5$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.33\text{--}7.29$ (m, 2H), 7.22–7.18 (m, 1H), 7.12–7.10 (m, 2H), 6.24 (s, 1H), 5.70–5.65 (m, 1H), 5.2–5.16 (m, 2H), 4.77 (d, $J = 14.0$ Hz, 1H), 4.64 (d, $J = 14.0$ Hz, 1H), 4.15 (t, $J = 7.7$ Hz, 1H), 3.60–3.48 ppm (m, 2H); ^{13}C NMR (90 MHz, CDCl_3): $\delta = 144.1$, 137.6, 137.1, 128.9, 128.3, 127.1, 122.5, 118.1, 72.8, 70.7, 51.1 ppm.

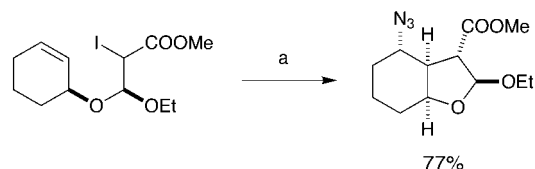
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- [6] Using $[\text{Rh}(\text{BINAP})\text{Cl}]_2$ as catalyst precursor and AgSbF_6 as additive, the reaction of **1a** yielded **2a** in less than 5% conversion within 20 min at room temperature. This was consistent with the low reactivity observed in ref. [4b].
- [7] Compared with our earlier system, $[\text{Rh}(\text{dppb})\text{Cl}]_2$ and $[\text{Rh}(\text{dppbo})\text{Cl}]_2$ were effective catalytic precursors for the Alder–ene reaction.^[4] This clearly indicates the differences between our previous catalyst and the new catalytic system.

Radical Carboazidation of Alkenes: An Efficient Tool for the Preparation of Pyrrolidinone Derivatives**

Philippe Renaud,* Cyril Ollivier, and Philippe Panchaud

The use of free radical reactions in multistep synthesis has steadily increased over the last years, mainly because of their compatibility with a large number of functional groups and their high potential for performing sequential transformations.^[1] Recently, we developed a novel method that allows the efficient formation of carbon–nitrogen bonds by reaction of radicals with sulfonyl azides.^[2,3] Since sulfonyl azides possess an electrophilic character, this azidation process is particularly efficient with nucleophilic radicals and does not occur with ambiphilic or electrophilic radicals. For instance, the cyclization depicted in Scheme 1 can be performed by



Scheme 1. Radical cyclization–azidation process. a) PhSO_2N_3 (3 equiv), $(\text{Bu}_3\text{Sn})_2$ (1.5 equiv), $t\text{BuON}=\text{NO}t\text{Bu}$ (3 mol %), benzene.

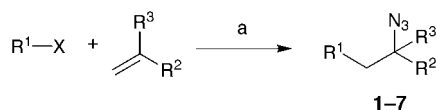
mixing all the reagents at once under relatively concentrated conditions (0.5 M substrate) without the formation of even traces of noncyclized products.

This observation let us speculate that the reaction could also be accomplished in intermolecular processes. Here we report our first results on the intermolecular addition of radicals to unactivated alkenes followed by azidation. This reaction sequence represents a formal carboazidation of alkenes, and it is the key process for an efficient three-component synthesis of pyrrolidinone, pyrrolizidinone, and indolizidinone derivatives.

In a first series of experiments, we tested the feasibility of the reaction starting from terminal alkenes and different radical precursors that are known to be efficient in radical atom or group transfer reactions (Scheme 2, see also Table 1).^[4] A one-pot procedure similar to that used for intramolecular reactions gave promising results: The radical precursors are treated with phenylsulfonyl azide (3 equiv),

[*] Prof. P. Renaud, P. Panchaud
University of Berne
Department of Chemistry and Biochemistry
Freiestrasse 3, 3000 Berne 9 (Switzerland)
Fax: (+41) 31-631-3426
E-mail: philippe.renaud@ioc.unibe.ch
C. Ollivier
University of Fribourg
Department of Chemistry
1700 Fribourg (Switzerland)

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Scheme 2. Reaction of terminal alkenes with various radical precursors. a) PhSO_2N_3 (3 equiv), $(\text{Bu}_3\text{Sn})_2$ (1.5 equiv), $t\text{BuON}=\text{NO}t\text{Bu}$ (3–21 mol %), benzene.

Table 1. Radical carboazidation of terminal alkenes according to Scheme 2.^[a]

Entry	X	R ¹	R ² , R ³	Product	Yield [%]
1	I	EtOOCCH_2	C_6H_{13} , H	1	79
2	I	EtOOCCH_2	$(\text{CH}_2)_5$	2	89
3	I	EtOOCCH_2	$(\text{CH}_2)_3\text{OTBDMS}$, H	3	77
4	Br	EtOOCCH_2	C_6H_{13} , H	1	66
5	SC(S)OEt	EtOOCCH_2	C_6H_{13} , H	1	70
6	SC(S)OEt	EtOOCCH_2	CH_2SiMe_3 , H	4	80
7	I	$(\text{EtOOC})(\text{Me})\text{CH}$	C_6H_{13} , H	5	75 ^[b]
8	Br	$(\text{COOEt})_2\text{CH}$	C_6H_{13} , H	6	46 ^[c]
9	SePh	$(\text{COOEt})_2\text{CH}$	C_6H_{13} , H	6	50 ^[d]
10	SC(S)OEt	$(\text{COOEt})_2\text{CH}$	C_6H_{13} , H	6	76
11	Br	Cl_3C	$(\text{CH}_2)_5$	7	40 ^[e]

[a] See the Experimental Section for the reaction conditions. [b] 1:1 Mixture of diastereomers. [c] 26 % of Br transfer. [d] 34 % of PhSe transfer. [e] 36 % of Br transfer. TBDMS = *tert*-butyldimethylsilyl.

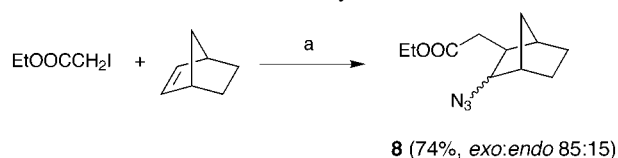
terminal olefins (2 equiv), hexabutyldistannane (1.5 equiv), and di-*tert*-butylhyponitrite (DTBHN, 3–21 mol %) as initiator in refluxing benzene.^[5] Slow addition of the benzenesulfonyl azide is not necessary because this electrophilic reagent does not react with the initial ambiphilic or electrophilic radicals, such as enolate radicals and the trichloromethyl radical.

Reactions of 1-octene, methylenecyclohexane, and silylated 5-pentene-1-ol with ethyl iodoacetate give the expected azides **1**, **2**, and **3** in good yields (Table 1, entries 1–3). Reactions of ethyl bromoacetate and ethyl 2-ethoxythiocarbonylsulfanylmalonate with 1-octene (entries 4, 5) furnish the azide **1** in 66 and 70 % yield, respectively.^[6] Reaction of the same dithiocarbonate with allyltrimethylsilane delivers the addition–azidation product **4** in 80 % yield (entry 6). As expected, other enolate radicals react with similar efficiency, as demonstrated by the reaction of ethyl 2-iodopropionate with 1-octene, affording **5** in 75 % yield (entry 7). The reaction of the malonyl radical, generated from either diethyl bromomalonate or diethyl phenylselenomalonate, with 1-octene gives the carboazidation product **6** in only 46 or 50 % yield, respectively (entries 8, 9). The products of bromine atom and phenylseleno group transfer were identified as the major side products. Interestingly, when the malonyl radical is generated from diethyl ethoxythiocarbonylsulfanylmalonate, the carboazidation product **6** is obtained in higher yield (76 %, entry 10). Finally, the use of bromotrichloromethane, a reagent known to be very efficient for bromine atom transfer reactions, was investigated. Reaction with methylenecyclohexane furnishes the azide **7** in 40 % yield (entry 11). In this last example, the only identified side product was again the product of bromine atom transfer.

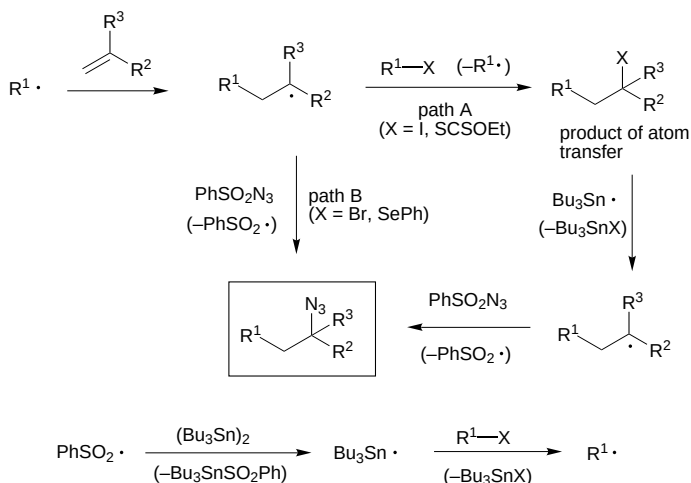
By analogy to iodine atom transfer, we were expecting that the radical addition–azidation process would be limited to terminal alkenes. Indeed, Curran and co-workers showed that

olefins substituted at both carbon atoms give low yields in atom transfer processes with iodoacetate derivatives.^[7] We tested the reaction with dimethyl cyclohex-4-ene-1,2-dicarboxylate, and observed only traces of the desired azide.^[8] Interestingly, norbornene, a more reactive 1,2-disubstituted alkene, reacts cleanly with ethyl iodoacetate to afford the azide **8** in 74 % yield as a 85:15 *exo:endo* mixture of isomers (Scheme 3).

From a mechanistic point of view, the reaction is expected to occur in a stepwise manner involving carbon–carbon bond formation by an atom or group transfer reaction followed by an azidation process (Scheme 4, path A). This mechanism is supported by the detection of the intermediate product of iodine or dithiocarbonate transfer. However, in the case of diethyl bromomalonate, diethyl phenylselenomalonate, and bromotrichloromethane, the products of bromine and phenylselenanyl transfer are not efficiently converted into azides.^[2,9]



Scheme 3. Reaction of norbornene with ethyl iodoacetate. a) PhSO_2N_3 (3 equiv), $(\text{Bu}_3\text{Sn})_2$ (1.5 equiv), $t\text{BuON}=\text{NO}t\text{Bu}$ (6 mol %), benzene.

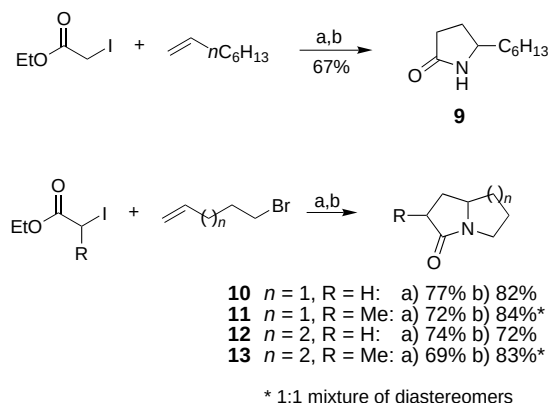


Scheme 4. Proposed mechanism for the radical carboazidation process.

Therefore, the observed azides are presumably issued from a direct mechanism of radical addition–azidation (path B). The rate of azidation of the intermediate radical competes with the rate of bromine atom and phenylseleno group transfer.^[10,11] Path A contributes only marginally to the formation of the azide due to the inefficient azidation of the intermediate alkylbromide and selenide.

The radical carboazidation of alkenes with 2-iodoesters can be coupled with the reduction of azides to afford 3-amino

esters that spontaneously cyclize to pyrrolidinones (Scheme 5). For example, 5-hexylpyrrolidinone (**9**) is prepared in 67% overall yield from 1-octene and ethyl iodoacetate. The intermediate 3-azidoester is reduced with indium in



Scheme 5. Two-step preparation of mono- and bicyclic lactams from terminal alkenes. a) PhSO_2N_3 (3 equiv), $(\text{Bu}_3\text{Sn})_2$ (1.5 equiv), $t\text{BuON}=\text{NO}t\text{Bu}$ (3–21 mol%), refluxing benzene. b) 1. Indium 1 equiv), NH_4Cl (1 equiv), refluxing EtOH. 2. Et_3N (5 equiv), refluxing EtOH.

ethanol.^[12] Spontaneous cyclization to **9** is observed, but it is slow. The lactamization process can be promoted by adding triethylamine and by heating the crude reaction mixture under reflux. Starting from 5-bromopent-1-ene and 6-bromohex-1-ene, the reduction of the azide initiates a double cyclization leading to pyrrolizidinones **10** and **11** as well as indolizidinones **12** and **13** (Scheme 5). It is interesting to note that, even in the presence of primary bromides, the carboazidation process with iodoesters proceeds in good yields.

In conclusion, a one-pot intermolecular radical addition–azidation procedure has been developed. Remarkably, this reaction is efficient with nonactivated terminal alkenes and takes advantage of the radical atom or group transfer processes. In order to illustrate the utility of the reaction, the preparation of pyrrolidinones, pyrrolizidinones, and indolizidinones starting from phenylsulfonyl azide, terminal alkenes, and 2-iodoesters was developed. This reaction is expected to be of great importance for the total synthesis of alkaloids. Such applications are currently underway in our laboratory and will be reported in due course.

Experimental Section

Carboazidation reaction: DTBHN (5 mg, 0.03 mmol) was added every 2 h to a solution of ethyl 2-iodoacetate (214 mg, 1.0 mmol), benzenesulfonyl azide (550 mg, 3.0 mmol), olefin (2.0 mmol), and Bu_6Sn_2 (0.76 mL, 1.5 mmol) in dry benzene (2.0 mL) at reflux under N_2 . The reaction was monitored by thin-layer chromatography. Upon completion of the reaction (4–12 h), the solvent was removed under reduced pressure and the crude product was filtered through silica gel. Elution with hexane allowed the removal of unchanged Bu_6Sn_2 , and then elution with hexane/ Et_2O gave a crude product that was purified by flash chromatography (hexane/ Et_2O). **Reductive lactamization:** Indium powder (230 mg, 2.0 mmol) and NH_4Cl (107 mg, 2.0 mmol) were added to a solution of the azide (2.0 mmol) in dry ethanol (6.0 mL). The reaction mixture was stirred under reflux for 2 h. Then Et_3N (1.4 mL, 10.0 mmol) was added, and the reaction mixture was stirred under reflux for 4 h. The cooled reaction mixture was diluted with EtOAc (10 mL), stirred for 10 min, and filtered through a short pad of

celite. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$).

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Functionalization of Elemental Phosphorus with $[\text{Zr}(\eta^5\text{-C}_5\text{Me}_5)(\eta^5\text{-C}_5\text{H}_4\text{tBu})\text{H}_2]_2^{**}$

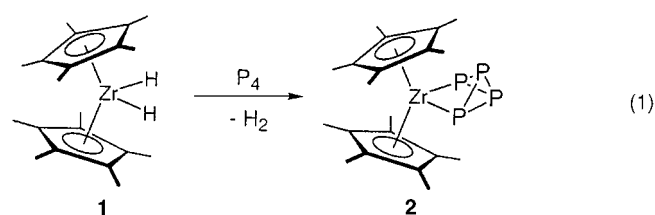
Paul J. Chirik,* Jaime A. Pool, and Emil Lobkovsky

Organophosphorus compounds are indispensable in synthetic chemistry because of their utility as reagents^[1] and as ligands for innumerable catalytic processes.^[2] Despite these applications, construction of P–H and P–C bonds directly from allotropes of elemental phosphorus remains a significant challenge.^[3] Although dinitrogen is converted to ammonia on a several billion ton scale annually by the Haber–Bosch reaction,^[4] no comparable process for elemental phosphorus functionalization has been developed.^[5] Instead, organophosphorus compounds are prepared by using a multistep procedure involving the chlorination of white phosphorus (P_4) to PCl_3 , followed by alkylation with Grignard reagents or reduction with LiAlH_4 to assemble the P–C or P–H linkage, respectively.^[6]

Insertion of P_4 into a metal–carbon or metal–hydrogen bond offers a direct, efficient, and potentially catalytic methodology for the synthesis of phosphanes. However, reports describing the reaction of P_4 with transition metal hydrides have been limited to only a few cases. Green et al.^[7] have described the synthesis of $[\text{Cp}_2\text{Mo}(\eta^2\text{-P}_2\text{H}_2)]$ by reaction of P_4 with $[\text{Cp}_2\text{MoH}_2]$ at 90°C , whereas Stephan et al.^[8] have used a similar protocol for the preparation of $[\text{Cp}_2\text{TaH}(\eta^2\text{-P}_2\text{H}_2)]$ from $[\text{Cp}_2\text{TaH}_3]$ and P_4 at 85°C . More recent reports by Peruzzini and co-workers^[9] have described the stoichiometric hydrogenation of P_4 at elevated temperatures with trihydridorhodium and -iridium complexes. Early transition metal hydrides, by virtue of their polarized metal–hydrogen bond, have been shown to be effective in delivering hydride (H^-) to numerous organic^[10] and inorganic^[11] substrates and are excellent candidates for functionalizing P_4 under mild conditions. Herein, we report the hydrogenation of P_4 to the unusual $[\text{P}_4\text{H}_2]^{4-}$ moiety promoted by $[\text{Zr}(\eta^5\text{-C}_5\text{Me}_5)(\eta^5\text{-C}_5\text{H}_4\text{tBu})\text{H}_2]_2$. Preliminary data suggests that the reaction proceeds through a cooperative reductive elimination/insertion sequence involving two zirconium centers.

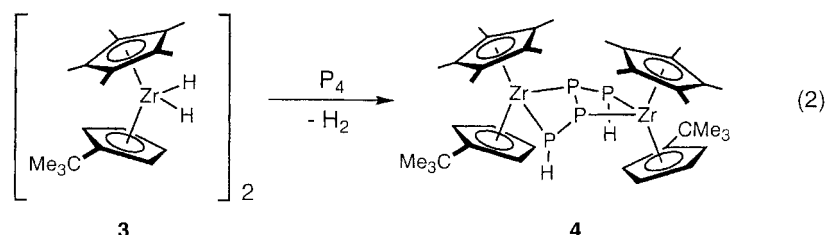
Attempts to hydrozirconate elemental phosphorus by addition of P_4 to $[\text{Cp}_2^*\text{Zr}(\text{H})\text{Cl}]$ ^[12] ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$), produced no reaction over the course of several days at 25°C . Replacing $[\text{Cp}_2^*\text{Zr}(\text{H})\text{Cl}]$ with the more reactive $[\text{Cp}_2^*\text{ZrH}_2]$ (**1**),^[13] resulted in a facile reaction with P_4 at -35°C , affording a deep red solid. Analysis of the product by ^1H and ^{31}P NMR spectroscopy revealed that P_4 did not undergo the desired insertion into the Zr–H bond but rather induced reductive

elimination of H_2 to afford $[\text{Cp}_2^*\text{Zr}(\eta^2\text{-P}_4)]$ (**2**), as previously described by Scherer et al. [Eq. (1)].^[14] Addition of σ -



donating ligands that are also effective in stabilizing low-valent zirconium have been shown to induce reductive elimination of alkane from $[\text{Cp}_2\text{Zr}(\text{R})\text{H}]$ complexes.^[15] In the present case, P_4 appears to fall into this ligand class since reductive elimination rather than insertion is observed from the putative $[\text{Cp}_2^*\text{ZrH}_2(\text{P}_4)]$ intermediate.

Based on these results, we postulated that addition of one equivalent of P_4 to two equivalents of **1** may afford one equivalent of a zirconium–phosphorus complex that may be susceptible to hydrogenation by the remaining equivalent of dihydride. Although employing this strategy with **1** led to a mixture of products, including **2**, addition of one equivalent of P_4 (0.5 per Zr center) to a solution of $[\{\text{Cp}^*(\eta^5\text{-C}_5\text{H}_4\text{tBu})\text{ZrH}_2\}_2]$ (**3**) in toluene at -35°C resulted in immediate effervescence and formation of a red solution. Removing the toluene in vacuo and recrystallization of the resulting red solid from diethyl ether afforded $[\{\text{Cp}^*(\eta^5\text{-C}_5\text{H}_4\text{tBu})\text{Zr}(\mu_2\eta^2, \eta^2\text{-P}_4\text{H}_2)\}_2]$ (**4**) in 90% yield [Eq. (2)].



Interestingly, addition of P_4 to $[\text{Cp}^*(\eta^5\text{-C}_5\text{H}_4\text{tBu})\text{Zr}(\text{CH}_2\text{CHMe}_2)(\text{H})]$ produced **4**, along with one equivalent of isobutane, arising from reductive elimination, and one equivalent of isobutene, generated from β -hydrogen elimination.

Brick red **4** is readily soluble in aromatic hydrocarbon and ethereal solvents but insoluble in aliphatic hydrocarbons such as pentane and hexane. Although extremely air- and moisture-sensitive, solutions of **4** in $[\text{D}_6]$ benzene may be heated to 100°C for several hours in an inert atmosphere without noticeable decomposition. Compound **4** was characterized through a combination of multinuclear NMR and IR spectroscopies, elemental analysis, and X-ray diffraction. In $[\text{D}_6]$ benzene, the ^1H NMR spectrum of **4** displays the expected ancillary ligand resonance signals as well as a complex multiplet centered at $\delta = 3.31$ ppm consistent with an AA'BB'XX' spin system attributable to the P–H resonance signals. Diagnostic symmetric and asymmetric P–H stretches of medium intensity are observed at 2360 and 2342 cm^{-1} in the diethyl ether solution IR spectrum of **4**. The ^{31}P NMR spectrum of **4** in $[\text{D}_6]$ benzene displays two resonance signals

[*] Prof. P. J. Chirik, J. A. Pool, Dr. E. Lobkovsky
Department of Chemistry and Chemical Biology
Baker Laboratory, Cornell University, Ithaca, NY 14853 (USA)
Fax: (+1) 607-255-4137
E-mail: pc92@cornell.edu

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centered at $\delta = 11.61$ ppm and -46.25 ppm with an AA'BB' splitting pattern^[16] consistent with observed spectral data for P_4H_6 .^[17] The resonance signal at $\delta = 11.61$ ppm was assigned to the terminal, hydrogenated phosphorus based on the observation of additional splitting in the proton-coupled ^{31}P NMR spectrum. The peak centered at $\delta = -46.25$ ppm does not change upon proton coupling.

X-ray structural analysis on a single crystal of **4**^[18] (Figure 1) reveals a dinuclear zirconium complex with a puckered, bicyclic Zr_2P_4 core. Somewhat surprisingly, the sterically

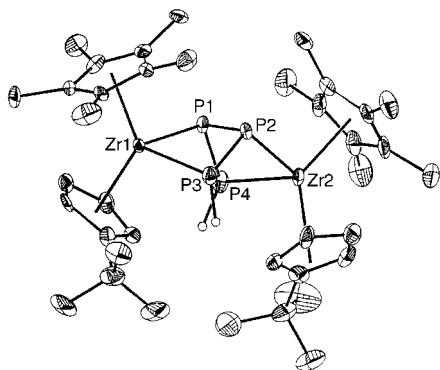


Figure 1. Molecular structure of **4** (thermal ellipsoids at 50% probability level, hydrogen atoms of the cyclopentadienyl ligands omitted for clarity).

demanding Cp^* ligands are arranged in a *cis*-like fashion, although the pyramidalization of the P_4H_2 unit serves to minimize unfavorable steric interactions between the Cp^* rings. The X-ray data was of sufficient quality to locate and refine both of the hydrogen atoms attached to phosphorus. No excess electron density around the internal phosphorus atoms was observed in the difference maps, consistent with the spectroscopic data. Each of the P–P distances and angles (Table 1) are in accord with the values typically observed in hydrogenated polyphosphorus chains.^[19]

In light of the spectroscopic and structural data obtained for **4**, the phosphorus core is best viewed as a $[P_4H_2]^{4-}$ fragment resulting in two formally 16-electron Zr^{IV} centers, and may be considered as a hydrogenated analogue of the P_4^{4-} ligand in $[Cp^*Co(CO)]_2(\mu_2, \eta^2, \eta^2-P_4)$ reported by Scherer and co-workers.^[20] Isolation of the $[P_4H_2]^{4-}$ moiety is noteworthy

Table 1. Selected bond lengths and angles for **4**.

Bond lengths [Å]	Bond angles [°]
P1–P2 2.2587(18)	Zr1–P1–P4 119.17(7)
P1–P4 2.221(2)	P2–P1–Zr1 73.24(5)
P2–P3 2.2091(19)	P2–P1–P4 113.74(4)
P1–P3 3.7470(19) ^[a]	P1–P2–P3 114.00(7)
P2–P4 3.751(2) ^[a]	P1–P2–Zr2 73.69(5)
Zr1–P1 2.6646(14)	Zr2–P2–P3 118.79(7)
Zr1–P3 2.6044(14)	P2–P3–Zr1 75.23(5)
Zr2–P2 2.6602(15)	P2–P3–H(P3) 105(2)
Zr2–P4 2.6146(14)	Zr1–P3–H(P3) 102(2)
P3–H(P3) 1.32(5)	P1–P4–Zr2 75.20(5)
P4–H(P4) 1.32(6)	P1–P4–H(P4) 117(3)
	Zr2–P4–H(P4) 106(2)
	P1–Zr1–P3 90.65(4)
	P4–Zr2–P2 90.04(3)

[a] Non-bonded distances.

since the corresponding neutral tetraphosphorus dihydride P_4H_2 has only been observed by mass spectrometry, and the parent phosphane P_4H_6 exists as a mixture of constitutional isomers.^[21] In summary, we have demonstrated the facile reactivity of white phosphorus with zirconium dihydride complexes and used a combination of reductive elimination and insertion processes to prepare the first example of the polyphosphane ion $[P_4H_2]^{4-}$ directly from white phosphorus.

Experimental Section

4: A 100-mL flask was charged with **3** (0.400 g, 1.14 mmol) and toluene (ca. 50 mL) and chilled in the dry box freezer to -35°C . To the clear yellow solution, solid P_4 (73 mg, 0.568 mmol) was added in three portions. Upon addition, a red reaction mixture was immediately formed. The resulting solution was stirred for 5 min and the toluene was removed in vacuo leaving a red solid. Recrystallization from diethyl ether afforded **4** (0.518 g, 0.511 mmol, 90%) as analytically pure red crystals. ^1H NMR (22°C , 400 MHz, $[D_6]benzene$): $\delta = 1.84$ (s, 30 H; C_5Me_5), 1.33 (s, 18 H; *t*Bu), 3.31 (m, 2 H; P–H), 5.19 (m, 2 H; Cp), 5.31 (m, 2 H; Cp), 5.39 (m, 2 H; Cp), 6.97 ppm (m, 2 H; Cp); ^{13}C NMR (22°C , 100.5 MHz $[D_6]benzene$): $\delta = 13.17$ (C_5Me_5), 33.54 (CM_5), 117.61 (C_5Me_5), 92.68, 94.55, 104.81, 108.03 (Cp) 121.67 ppm (CM_5); ^{31}P NMR ($[D_6]benzene$): $\delta = 11.61$ (PH), -46.35 ppm (P); elemental analysis (%) calcd for $C_{38}H_{58}P_4Zr_2$: C 55.58 H 7.12; found: C 55.21 H 6.89.

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0.6305. CCDC-185204 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

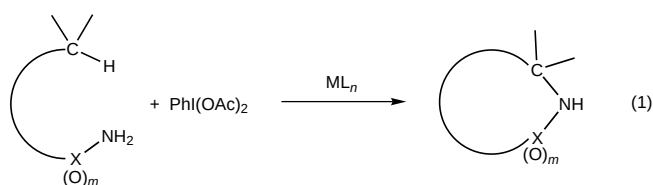
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Highly Diastereo- and Enantioselective Intramolecular Amidation of Saturated C–H Bonds Catalyzed by Ruthenium Porphyrins**

Jiang-Lin Liang, Shi-Xue Yuan, Jie-Sheng Huang, Wing-Yiu Yu, and Chi-Ming Che*

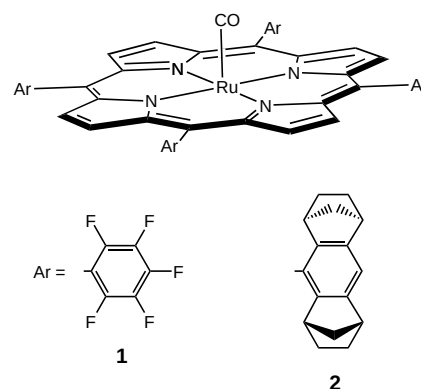
Metal-complex-catalyzed amidation of saturated C–H bonds^[1–7] is increasingly attractive as a C–N bond-formation methodology. The nitrogen sources in most of these amidation reactions are iminoiodanes $\text{PhI}=\text{NR}$, which are prepared from $\text{PhI}(\text{OAc})_2$ and RNH_2 and are currently accessible for rather limited types of R groups (usually $\text{R} = \text{ArSO}_2$). In very few cases can the $\text{PhI}=\text{NR}$ amidation procedure be applied to intramolecular amidation.^[1b,3c,5] About two years ago,^[4d] we found that $\text{PhI}(\text{OAc})_2$ and RNH_2 ($\text{R} = p\text{-MeC}_6\text{H}_4\text{SO}_2$, $p\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2$) could be used directly as the nitrogen source in intermolecular amidation processes. More interestingly, the “ $\text{PhI}(\text{OAc})_2 + \text{RNH}_2$ ” amidation protocol is extendable to “ $\text{PhI}(\text{OAc})_2 + \text{MeSO}_2\text{NH}_2$ ”^[4d,e,g] and “ $\text{PhI}(\text{OAc})_2 + \text{CF}_3\text{-CONH}_2$ ”^[4d] or PhCONH_2 ^[4e], in which cases the respective iminoiodanes are explosive or unknown. We envisioned that such a “ $\text{PhI}(\text{OAc})_2 + \text{RNH}_2$ ” amidation procedure might be applicable to a wide variety of RNH_2 compounds and could be more readily extended to intramolecular amidation, as shown in Equation (1).

Recent work by Du Bois and co-workers^[7] excellently demonstrated that reactions of a series of carbamates ($-\text{OCONH}_2$)^[7a] and sulfamate esters ($-\text{OSO}_2\text{NH}_2$)^[7b] with

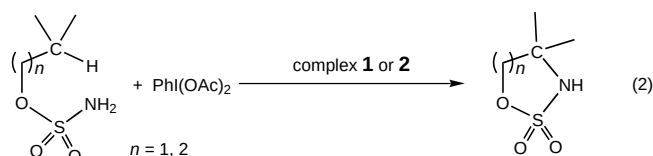


$\text{PhI}(\text{OAc})_2$, catalyzed by dirhodium complexes, afford oxazolidinones and cyclic sulfamides, respectively, with high regioselectivity and good to excellent diastereoselectivity. These reactions occur by the direct intramolecular amidation of saturated C–H bonds. Du Bois and co-workers found that these intramolecular amidation reactions are stereospecific, allowing synthesis of enantiomerically pure amidation products from enantiomerically pure carbamates or sulfamate esters.^[7] However, it remains a challenge to realize asymmetric intramolecular amidation of saturated C–H bonds from prochiral RNH_2 substrates.

Herein, we report the first metalporphyrin-catalyzed intramolecular amidation reactions of saturated C–H bonds that employ a “ $\text{PhI}(\text{OAc})_2 + \text{RNH}_2$ ” procedure. The catalysts used are mainly the electron-deficient ruthenium porphyrin $[\text{Ru}(\text{tpfpp})(\text{CO})]$ ^[8] (**1**, $\text{H}_2\text{tpfpp} = \text{meso-tetra(pentafluoro-}$



phenyl)porphyrin) and the chiral ruthenium porphyrin $[\text{Ru}(\text{por}^*)(\text{CO})]$ ^[9] (**2**, $\text{H}_2\text{por}^* = 5,10,15,20\text{-tetrakis}[(1S,4R,5R,8S)\text{-}1,2,3,4,5,6,7,8\text{-octahydro-1,4:5,8-dimethanoanthracene-9-yl}]\text{-porphyrin}$ ^[10]). In the presence of these catalysts, reactions of sulfamate esters with $\text{PhI}(\text{OAc})_2$ afforded cyclic sulfamides with high regioselectivity and virtually complete diastereoselectivity [Equation (2)]. Remarkably, the intramolecular



amidation of prochiral sulfamate esters catalyzed by **2** produced optically active cyclic sulfamides in up to 87% *ee*.^[11] This value contrasts with the highest *ee* value of

[*] Prof. Dr. C.-M. Che, J.-L. Liang, S.-X. Yuan, Dr. J.-S. Huang, Dr. W.-Y. Yu
 Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis
 The University of Hong Kong, Pokfulam Road (Hong Kong)
 Fax: (+852) 2857-1586
 E-mail: cmche@hku.hk

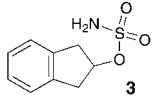
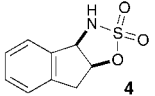
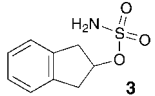
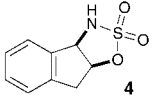
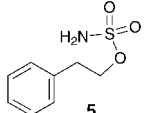
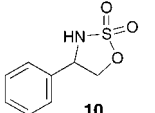
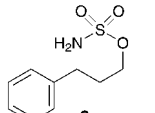
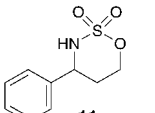
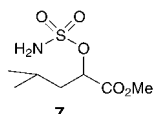
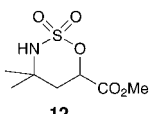
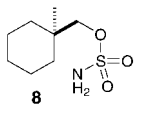
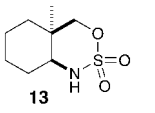
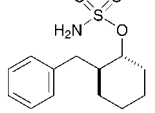
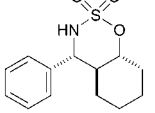
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58% in the intermolecular amidation of saturated C–H bonds catalyzed by the same ruthenium porphyrin.^[4c,g] Prior to this work, only in a single case did metal-complex-catalyzed intramolecular amidation of saturated C–H bonds proceed in asymmetric manner; this procedure employs the $\text{PhI}=\text{NR}$ protocol and a chiral dirhodium catalyst and affords a cyclic sulfonamide in 10% *ee*.^[3c]

The intramolecular amidation catalyzed by **1** was initially explored with sulfamate indan-2-yl ester (**3**, see Table 1) as the substrate. Treatment of **3** with 2 equiv of $\text{PhI}(\text{OAc})_2$ in dichloromethane at 40 °C, in the presence of 1.5 mol % of **1**, afforded the corresponding cyclic sulfamidate **4** in 52% yield

Table 1. Intramolecular amidation of sulfamate esters catalyzed by $[\text{Ru}(\text{tpfp})(\text{CO})]$ (**1**).^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1 ^[c]			52
2			61
3			56
4			77
5			76
6			88
7			88

[a] Reaction conditions: CH_2Cl_2 , 40 °C, 2 h; **1**:substrate: $\text{PhI}(\text{OAc})_2$: Al_2O_3 0.015:1:2:2.5. [b] Yield of isolated product, based on starting substrate. [c] In the absence of Al_2O_3 .

within 2 h (entry 1, Table 1). Addition of inorganic bases such as MgO and ZnO (2.5 equiv) to the amidation system increased the yield of **4** to 58%. However, organic bases (such as pyridine) and more strongly basic inorganic additives (such as K_2CO_3 and NaOH) exhibited deleterious effects. The best additive we found is Al_2O_3 , which enabled us to isolate **4** in a 61% yield (entry 2, Table 1), similar to the 60% yield obtained by employing dirhodium catalyst.^[7b] Examination of solvent effects revealed that dichloromethane is superior to 1,2-dichloroethane, acetonitrile, and benzene. For example, when the reaction was conducted in the latter three solvents

with MgO as an additive, the yield of **4** dropped to 28, 8.3, and 45%, respectively.

Note that the reaction of **3** with $\text{PhI}(\text{OAc})_2$ to form **4** can also be catalyzed by other achiral metalloporphyrins such as $[\text{M}(\text{tp})\text{Cl}]$ ($\text{M} = \text{Fe}, \text{Mn}$; $\text{H}_2\text{tp} = \text{meso-tetraphenylporphyrin}$) and $[\text{Ru}(\text{tp})(\text{CO})]$. However, the yields of the cyclic sulfamidate obtained by employing these metalloporphyrin catalysts (15–25%, reaction conditions: dichloromethane, 40 °C, MgO, 2.0 mol % catalyst) were substantially lower than those obtained by employing catalyst **1**. Non-porphyrin ruthenium complexes such as $[\text{Ru}(\text{Me}_3\text{tacn})(\text{CF}_3\text{CO}_2)_3 \cdot \text{H}_2\text{O}]$ ($\text{Me}_3\text{tacn} = N,N',N''\text{-trimethyl-1,4,7-triazacyclononane}$), *trans*- $[\text{Ru}(\text{pybox-ip})\text{Cl}_2(\text{CH}_2=\text{CH}_2)]$ (pybox-*ip* = bis(2-oxazolin-2-yl) pyridine), and $[\text{Ru}(\text{Br}_4\text{salen})(\text{PPh}_3)_2]$ ($\text{H}_2\text{Br}_4\text{salen} = 1,2\text{-bis(3,5-dibromo-2-hydroxybenzylideneamino)cyclohexane}$) were ineffective or poor catalysts for this intramolecular amidation reaction, affording **4** in < 16% yields under similar conditions.

We then treated sulfamate esters **5–9** (see Table 1) with $\text{PhI}(\text{OAc})_2$ in dichloromethane at 40 °C, in the presence of catalyst **1** (1.5 mol %) and Al_2O_3 , with the same substrate: $\text{PhI}(\text{OAc})_2$: Al_2O_3 molar ratio as for **3**. These reactions afforded cyclic sulfamidates **10–14** in 56–88% yields (entries 3–7 in Table 1). The regioselectivity of the **1**-catalyzed intramolecular amidation of **3** and **5–9** is comparable to that of the dirhodium-catalyzed analogues.^[7b] For substrates **3** and **5**, only their β -C–H bonds were amidated, producing five-membered cyclic sulfamidates **4** and **10** (entries 1–3 in Table 1). For the other substrates, the amidation occurred at the secondary or tertiary γ -C–H bonds to form six-membered cyclic sulfamidates **11–14** (entries 4–7 in Table 1), although these substrates, except **8**, also contain β -C–H bonds. The yields of the six-membered cyclic sulfamidates **11–14** were substantially higher than those of the five-membered sulfamidates **4** and **10**.

Complex **1** is the most robust catalyst ever reported for the intramolecular amidation of saturated C–H bonds. The intramolecular amidation of **3** and **5–9** catalyzed by 1.5 mol % of **1** features up to 59 catalytic turnovers. By lowering the loading of **1** to 0.1 mol %, over 300 catalytic turnovers were obtained for the intramolecular amidation of **8** to form **13**. In contrast, previously reported intramolecular amidations of saturated C–H bonds all feature < 50 catalytic turnovers.^[1b,3c,5,7]

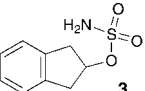
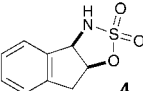
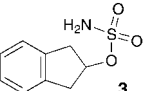
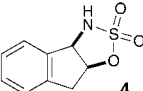
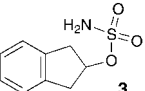
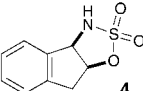
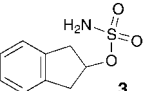
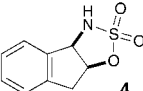
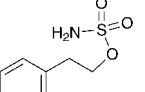
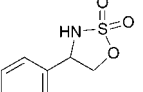
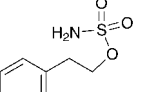
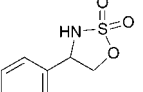
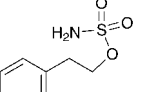
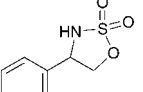
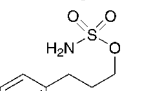
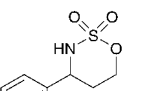
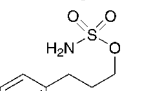
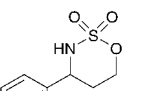
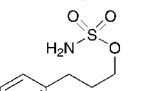
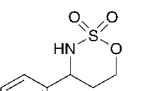
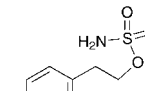
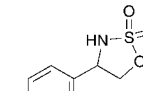
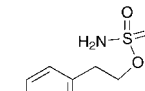
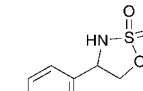
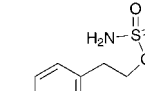
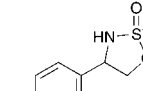
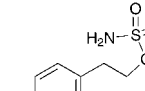
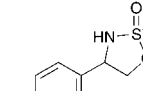
Strikingly, although the intramolecular amidation of **3**, **8**, and **9** might form **4**, **13**, and **14**, respectively, as a mixture of two diastereomers, only the indicated *cis* diastereomers of **4** and **13** and the diastereomer of **14** (entry 7, Table 1) were isolated by employing catalyst **1**^[12] (the other diastereomers of **4**, **13**, and **14** were not detected by ¹H NMR spectroscopy in the unpurified reaction mixtures). This result differs from the amidation of **8** catalyzed by a dirhodium complex,^[7b] which afforded **13** as a mixture of *cis* and *trans* diastereomers in 8:1 ratio.

Excellent diastereoselectivity was also observed in the intramolecular amidation of **3** catalyzed by **2**. Treatment of **3** with $\text{PhI}(\text{OAc})_2$ in dichloromethane at 40 °C, in the presence of Al_2O_3 and 10 mol % of **2** with a substrate: $\text{PhI}(\text{OAc})_2$: Al_2O_3 molar ratio of 1:1.4:2.5, afforded the *cis* diastereomer of **4** in 57% yield (entry 1, Table 2). The chiral auxiliaries in **2**

induced significant enantioselectivity in the intramolecular amidation process, with the optically active compound **4** obtained in 71 % *ee* (entry 1, Table 2).

Surprisingly, when the amidation of **3** catalyzed by **2** was carried out in benzene at 80 °C, the enantioselectivity observed for **4** was considerably higher (81 % *ee*, entry 2, Table 2).^[13] Lowering the reaction temperature to 5 °C further

Table 2. Asymmetric intramolecular amidation of sulfamate esters catalyzed by [Ru(por*)(CO)] (**2**).^[a]

Entry	Substrate	Product	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1 ^[d]			57	71
2			53	81
3 ^[e]			39	82
4 ^[f]			39	77
5 ^[d]			53	69
6			43	82
7 ^[e]			35	87
8 ^[d]			77	46
9			63	79
10 ^[e]			48	84
11			40	80
12 ^[e]			20	83
13			46	78
14 ^[e]			31	86

[a] Reaction conditions: C₆H₆, 80 °C, 2 h; **2**:substrate:PhI(OAc)₂:Al₂O₃ 0.1:1:1.4:2.5. [b] Yield of isolated product, based on starting substrate. [c] Determined by HPLC using a chiral OD column. [d] In CH₂Cl₂ at 40 °C. [e] Reaction temperature: 5 °C. [f] In toluene at 0 °C.

increased the *ee* value to 82 % (entry 3, Table 2); but the *ee* value decreased to 77 % when the reaction was conducted in toluene at 0 °C (entry 4, Table 2). The absolute configuration of the predominant enantiomer of **4** is (1*R*, 2*S*) in all cases, as determined by X-ray crystallographic studies.^[14]

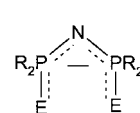
We also performed the **2**-catalyzed amidation of **5** and **6** under conditions similar to those for **3** (entries 5–10 in Table 2); in these cases, substantially higher *ee* values were again attained in benzene than in dichloromethane, although the yields of the cyclic sulfamidates were lower in the former solvent. The amidation of **5** in benzene at 5 °C gave the highest enantiocontrol, giving optically active **10** in 87 % *ee* (entry 7, Table 2). To examine the effect of *para* substituents on the asymmetric amidation of **5**, we prepared sulfamate esters **15** and **16** (see Table 2). The enantioselectivity observed in benzene for the two substrates (entries 11–14 in Table 2) was slightly lower than that for **5**.

Attempts were made to identify the intermediates in the foregoing intramolecular amidation of sulfamate esters catalyzed by ruthenium porphyrins. Treatment of **3** with PhI(OAc)₂ afforded a light-yellow solid,^[15] which we tentatively assigned as the iminoiodane PhI=NSO₂(O-indan-2-yl) (**19**) by ¹H NMR spectroscopy.^[16] Interestingly, reaction of **19** with **2** (molar ratio: 2.5:1) in dichloromethane at 40 °C for 2 h produced the *cis* diastereomer of **4** in 57 % yield and 85 % *ee*. These values are comparable with those observed in the corresponding catalytic reaction (entry 1, Table 2).^[17] In view of this observation, together with the facile formation of bis(tosylimido)ruthenium(vi) porphyrins [Ru(por)(NSO₂-*p*-C₆H₄Me)₂] from [Ru(por)(CO)] and PhI=NSO₂-*p*-C₆H₄Me,^[4b,c,g] we propose that the bis(imido) species [Ru(por)(NSO₂(OR))₂] (por = tpfp or por*) could be involved in the intramolecular amidation of sulfamate esters with PhI(OAc)₂, catalyzed by **1** or **2**. Efforts are underway to detect and isolate these intriguing species.

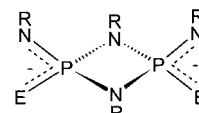
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- [12] The structures of racemic **4**, **13**, and **14** have been determined by X-ray crystallography. CCDC-184691 (**4**), CCDC-184693 (**13**), and CCDC-184694 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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- [14] CCDC-184692 ((1*R*,2*S*)-**4**) contains the supplementary crystallographic data for this paper.^[12] The single crystal used for the structure determination was obtained from an optically active sample of **4** with 82% *ee*. The small absolute structure parameter of 0.15(12) derived from the structure determination confirms the chirality of the crystal.
- [15] Following the procedures reported by Dauban and Dodd for preparation of iminoiodane $\text{PhI}=\text{NSO}_2(\text{CH}_2)_2\text{SiMe}_3$ from $\text{PhI}(\text{OAc})_2$ and $\text{Me}_3\text{Si}(\text{CH}_2)_2\text{SO}_2\text{NH}_2$ (P. Dauban, R. H. Dodd, *J. Org. Chem.* **1999**, *64*, 5304).
- [16] ¹H NMR (CDCl_3 , 400 MHz) of **19**: δ = 7.89 (d, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.16 (m, 4H), 5.19 (m, 1H), 3.06 (m, 4H). The rather high instability of **19** renders it difficult to characterize this compound fully.
- [17] The lower *ee* value in the catalytic reaction than in the reaction between **2** and **19** may arise from a lower loading of **2** in the former case. We once observed that reducing the loading of **2** from 10 to 2 mol% in the amidation of **6** in CH_2Cl_2 , under otherwise the same conditions, led to a decrease in the *ee* value of **11** from 46 to 39%. Notice that some other metal-catalyzed asymmetric reactions also show significant dependence of enantioselectivity on catalyst loading (see for example: H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063).

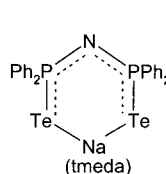


1 (E = O, S, Se)

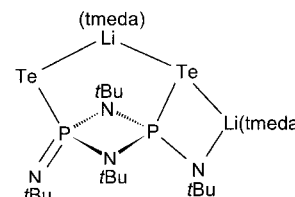


2 (E = S, Se)

Despite this intense activity, the tellurium analogues of **1** and **2** are unknown. Anionic tellurophosphinic amides of the type $[\text{tBu}_2\text{P}(\text{Te})\text{NR}]^-$ (R = *i*Pr, Cy) can be prepared by lithiation of $[\text{tBu}_2\text{P}(\text{Te})\text{NHR}]$ with *Li*nBu, and chelate complexes of this anion with Group 12 metals have been investigated as single-source precursors of binary metal tellurides.^[8] Although ditellurides of the type $[\text{R}(\text{Te})\text{P}(\mu\text{-N}t\text{Bu})_2\text{P}(\text{Te})\text{R}]$ (R = Me, *t*Bu) have been reported,^[9] our attempts to oxidize $t\text{BuN}(\text{H})\text{P}(\mu\text{-N}t\text{Bu})_2\text{PN}(\text{H})t\text{Bu}$ with an excess of elemental tellurium in boiling toluene produced only the monotelluride $[\text{tBuNH}(\text{Te})\text{P}(\mu\text{-N}t\text{Bu})_2\text{PN}(\text{H})t\text{Bu}]$ in about 5% yield.^[10] Endeavors to generate $(\text{TePPH}_2)_2\text{NH}$ in a similar manner have also been unsuccessful. Consequently, we adopted a different approach to the synthesis of the anionic ligands **1** (E = Te) and **2** (E = Te), which involves metalation of the neutral imido or amido precursor prior to the reaction with tellurium.^[11] Herein, we report the synthesis and X-ray structures of $[\{\text{Na}(\text{tmeda})\}[\{\text{TePPH}_2\}_2\text{N}]]_2$ (**3**) and $[\text{Li}(\text{tmeda})_2[\text{Te}(\text{N}t\text{Bu})\text{P}(\mu\text{-N}t\text{Bu})_2\text{P}(\text{N}t\text{Bu})\text{Te}]]$ (**4**), (tmeda = tetramethylethylenediamine), which contain the first examples of **1** (E = Te) and **2** (E = Te), respectively.



3



4

A New Approach to Metalated Imido and Amido Tellurophosphoranes**

Glen G. Briand, Tristram Chivers,* and Masood Parvez

Monoanionic ligands of the type $[\text{R}_2\text{P}(\text{E})\text{NP}(\text{E})\text{R}_2]^-$ **1** have been investigated extensively as ligands for both main group elements^[1] and transition metals.^[2] This widespread interest stems from their potential uses as lanthanide shift reagents,^[2] industrial catalysts,^[3] luminescent materials,^[4] or in metal extraction processes.^[5] Recently we^[6] and Stahl et al.^[7] reported the first ambidentate dianionic ligands $[\text{RN}(\text{E})\text{P}(\mu\text{-NR})_2\text{P}(\text{E})\text{NR}]^{2-}$ **2**, which adopt a variety of bonding modes, that is *N,E*, *N,N'*, or *E,E'*, with metal centers.

[*] Prof. T. Chivers, Dr. G. G. Briand, Dr. M. Parvez
Department of Chemistry
University of Calgary
Calgary, AB T2N 1N4 (Canada)
Fax: (+1) 403-289-9488
E-mail: chivers@ucalgary.ca

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The reaction of $\text{Na}[\text{Ph}_2\text{PNPPh}_2]$ with tellurium powder in hot toluene in the presence of TMEDA produced **3** as moisture-sensitive, yellow crystals in 33% yield. The molecular structure of **3** (Figure 1) was determined by X-ray diffraction^[12] on crystals obtained from hexane. The ditelluroimido-diphosphinate ligand **1** (R = Ph, E = Te) is *Te,Te'* chelated to sodium and forms a centrosymmetric dimer through Na–Te interactions. This is the first example of *Te,Te'* chelation to an alkali metal. The coordination sphere of the Na^+ ions is completed by one *N,N'* chelating tmeda ligand. A similar structure has been reported for the sodium salt of a monothioimido-diphosphinate $[\{\text{Na}(\text{thf})_2\}[\{\text{OPPh}_2\}(\text{SPPH}_2)\text{-N}]]_2$.^[13] The central Na_2Te_2 ring in **3** is almost square-planar (bond angles at Na1 and Te1 are 87.51(5) and 92.49(5)°, respectively) with Na–Te distances of 3.143(2) and 3.181(2) Å, which are close to the value of 3.16 Å predicted from the ionic radii^[14] and much shorter than the weak Na–Te interactions (3.494(3) Å) in the telluroate $[\text{Na}(\text{tmeda})_2][\text{Te}(2,4,6\text{-Me}_3\text{C}_6\text{H}_2)]$.^[15] The P–Te bond lengths of 2.383(1) and 2.403(1) Å are only slightly longer than the values of about 2.37 Å determined for $t\text{Bu}_3\text{P}=\text{Te}$ ^[16] and amino-substituted tellurophosphoranes.^[9c,17] The shorter P–

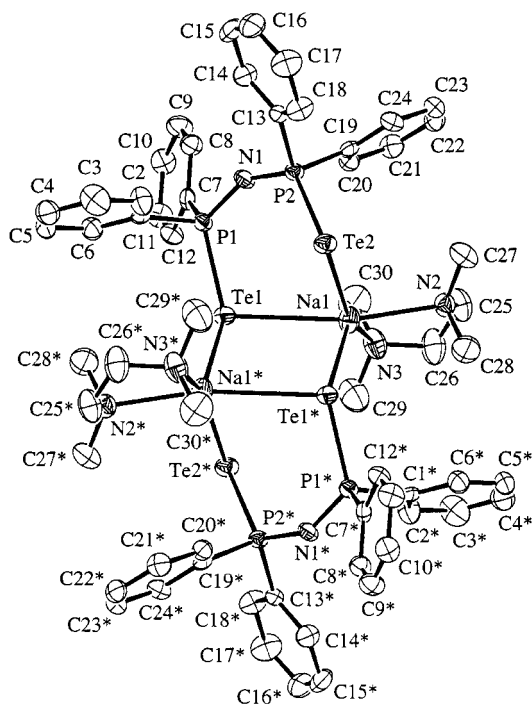


Figure 1. X-ray crystal structure of **3**. Selected bond lengths [Å] and angles [°]: P1–N1 1.591(4), P2–N1 1.589(4), P1–Te1 2.4029(13), P2–Te2 2.3827(13), Na1–Te1 3.143(2), Na1–Te2 3.259(2), Na1–Te1* 3.181(2); P1–N1–P2 143.3(3), N1–P1–Te1 122.18(15), N1–P2–Te2 120.88(15), P1–Te1–Na1 104.20(5), P2–Te2–Na1 93.10(5), Te1–Na1–Te2 84.69(5), Te1–Na1–Te1* 87.51(5), Na1–Te1–Na1* 92.49 (5). Symmetry transformations used to generate equivalent atoms: * $-x, -y, -z + 2$.

Te bond is associated with the two-coordinate tellurium center, which also participates in the longer Te–Na bond (3.259(2) Å) in the six-membered $\text{NP}_2\text{Te}_2\text{Na}$ ring. The ^{31}P NMR and ^{125}Te NMR spectrum of **3** in $[\text{D}_8]\text{THF}$ at 235 K reveal single environments for both the phosphorus and tellurium atoms. This observation may be attributed to a fast exchange process involving the Na and Te sites or to dissociation into a monomer in which the Na^+ ion is solvated by THF. The coupling constant $^1J_{(\text{P-Te})} = 1619 \text{ Hz}$ is, as expected, significantly smaller than the values of 1663–2095 Hz reported for neutral tellurophosphoranes.^[18]

The treatment of $[\text{Li}(\text{thf})]_2[\text{tBuNP}(\mu\text{-NtBu})_2\text{PNtBu}]$ with tellurium powder in toluene at 80 °C in the presence of TMEDA produces **4** as yellow, moisture-sensitive crystals in 19% yield. The molecular structure of **4** (Figure 2) was determined on single crystals obtained from hexane.^[19] The structure reveals a unique bonding mode for ligands of the type **2** in which one Li^+ ion is coordinated in a Te, Te' fashion, while the second Li^+ ion is N, Te chelated by the dianion. By contrast, the sulfur analogue, **4** (E = S), exhibits bis- N, S chelation to two Li^+ centers.^[6b] The X-ray structures of $\text{Li}[\text{tBu}_2\text{P}(\text{Te})\text{NR}]$ (R = *i*Pr, Cy) were not determined, but chelate complexes of the anion with transition metals are N, Te bonded.^[8] The P–Te bond length involving the two-coordinate Te center in **4** is 0.027 Å longer than that involving the three-coordinate Te atom, presumably because the former is associated with the shorter exocyclic P–N bond (1.534(2) versus 1.574(2) Å). The mean value of $d(\text{P}–\text{Te})$ in **4** is, as expected, significantly longer by about 0.07 Å than the value

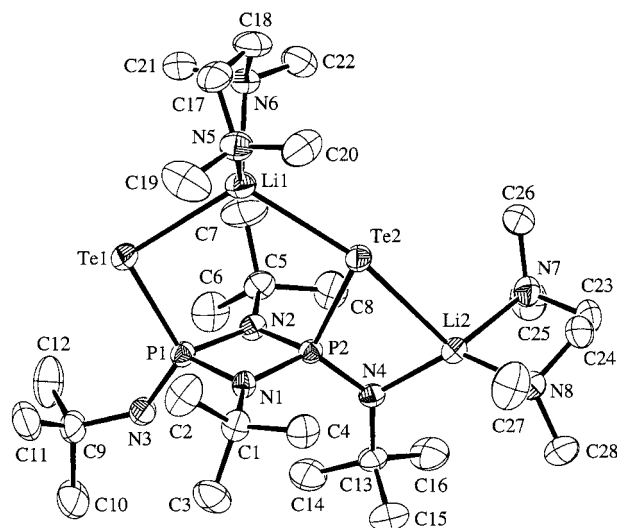


Figure 2. X-ray crystal structure of **4**. Selected bond lengths [Å] and angles [°]: Li1–Te1 2.842(5), Li1–Te2 2.791(5), Li2–Te2 2.865(5), Li2–N4 1.973(5), P1–Te1 2.4515(8), P2–Te2 2.4243(7), P1–N3 1.534(2), P2–N4 1.574(2); Te1–Li1–Te2 113.35(17), N4–Li2–Te2 80.93 (18), N3–P1–Te1 119.94(11), N4–P2–Te2 104.89(9), P2–Te2–Li2 65.59 (10), P2–Te2–Li1 96.51(10), Li1–Te2–Li2 160.06(14), P1–Te1–Li1 97.15(11).

of 2.370(1) Å found for the monotelluride $[\text{tBuNH}(\text{Te})\text{P}(\mu\text{-NtBu})_2\text{PN}(\text{H})\text{tBu}]$.^[10] The NMR data for **4** in $[\text{D}_8]\text{toluene}$ demonstrate that the novel, asymmetric coordination of the two Li^+ ions to the dianion **2** observed in the solid state is maintained in solution at 235 K. Thus, the ^7Li NMR spectrum of **4** in $[\text{D}_8]\text{toluene}$ exhibits two well-separated resonance signals at $\delta = 0.70$ and 3.88 ppm, while the ^{31}P NMR spectrum shows two singlets (with ^{125}Te satellites) at $\delta = -113.7$ and -75.3 ppm . Consistently, the ^{125}Te NMR spectrum displays two doublets at $\delta = -289$ and -87 ppm . The smaller values of $^1J_{(\text{P-Te})}$, 1309 and 1467 Hz, are consistent with the longer P–Te bond lengths in **4** compared to those in **3**.

In summary, the discovery of a new approach to the previously inaccessible ditelluroimidodiphosphinate anion **1** (E = Te) and the ditellurodiimidocyclodiphosph(v)azane dianion **2** (E = Te) paves the way for extensive investigations of the coordination chemistry of these tellurium-centered ligands. Semiempirical PM3 calculations indicate that the success of this method can be attributed to an increase in the nucleophilicity of the phosphorus(III) centers in $(\text{PPh}_2)_2\text{NH}$ and $\text{tBuN}(\text{H})\text{P}(\mu\text{-NtBu})_2\text{PN}(\text{H})\text{tBu}$ upon metalation. Details of this study, as well as additional examples of the successful application of this approach to the synthesis of novel $\text{N}(\text{v})\text{Te}$ anions, will be discussed in a full account of this work.

Experimental Section

All manipulations were carried out under anaerobic and anhydrous conditions. NMR spectra were obtained on $[\text{D}_8]\text{THF}$ (**3**) or $[\text{D}_8]\text{toluene}$ (**4**) solutions at 235 K using a Bruker DRX 400 MHz spectrometer.

3·0.25 C_6H_{14} : A mixture of $\text{Na}[\text{Ph}_2\text{PNPPH}_2]$ ^[20] (0.100 g, 0.245 mmol), tellurium powder (0.063 g, 0.49 mmol), and TMEDA (0.114 g, 0.982 mmol) in toluene (5 mL) was heated to 80 °C for 3 h. After cooling to 23 °C, the mixture was centrifuged and decanted to remove unreacted tellurium. Yellow crystals of **3**·(C_6H_{14})_{0.25} (0.065 g, 33%) were obtained after one day at 23 °C. Elemental analysis calcd for $\text{C}_{31.5}\text{H}_{39.5}\text{N}_3\text{NaP}_2\text{Te}_2$: C 47.27, H 4.97, N

5.25; found: C 48.42, H 5.35, N 5.32; $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = 9.5$ ppm (s, $^1J_{\text{P(Te)}} = 1632$ Hz); ^{125}Te NMR: $\delta = -403.6$ ppm (d, $^1J_{\text{P(Te)}} = 1619$ Hz).

4: A mixture of $[\text{Li}(\text{thf})_2][\text{tBuNP}(\mu\text{-NbBu})_2\text{NbBu}]^{[21]}$ (0.200 g, 0.396 mmol), tellurium powder (0.101 g, 0.79 mmol), and TMEDA (0.368 g, 3.17 mmol) in toluene (5 mL) was heated at 80°C for 3 h. The mixture was centrifuged and the supernatant was decanted from unreacted tellurium. After removal of solvent under vacuum, the product was redissolved in *n*-hexane (ca. 1 mL). Yellow crystals of **4** (0.062 g, 19%) were deposited after one day at 23°C . Elemental analysis calcd for $\text{C}_{28}\text{H}_{68}\text{Li}_2\text{N}_8\text{P}_2\text{Te}_2$: C 39.66, H 8.08, N 13.22; found: C 38.06, H 8.23, N 12.25; ^1H NMR ($[\text{D}_8]\text{toluene}$, 235 K): $\delta = 1.62$ (s, 9H; NbBu), 1.97 (s, 9H; NbBu), 2.18 (s, 18H; $\mu\text{-NbBu}$), 2.20 (s, 12H; NMe₂), 2.30 ppm (s(br), 8H; NCH₃); $^{31}\text{P}\{^1\text{H}\}$ NMR: $\delta = -113.7$ (s, $^1J_{\text{P(Te)}} = 1467$ Hz), -75.3 ppm (s, $^1J_{\text{P(Te)}} = 1309$ Hz); ^7Li NMR: $\delta = 0.70$ (s), 3.88 ppm (s); ^{125}Te NMR: $\delta = -289$ (d, $^1J_{\text{Te,P}} = 1352$ Hz), -87 ppm (d, $^1J_{\text{Te,P}} = 1486$ Hz). The values of $^1J_{\text{Te,P}}$ obtained from the ^{31}P NMR spectrum are more reliable than those obtained from the ^{125}Te NMR spectrum owing to the broad line widths ($\Delta\nu_{1/2} \sim 225$ Hz) in the latter spectrum.

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Metallabenzenes and Valence Isomers. Synthesis and Characterization of a Platinabenzene**

Volker Jacob, Timothy J. R. Weakley, and Michael M. Haley*

Dedicated to Professor Gottfried Huttner on the occasion of his 65th birthday

In our group we have developed a convenient method for the preparation of iridabenzenes starting from the C₅ synthetic equivalent Z-3-(2-iodovinyl)-1,2-diphenylcyclopropane (**1**).^[1] Using this precursor, iridabenzene synthesis can also be carried out in a stepwise manner via an iridabenzvalene intermediate, which could be characterized and converted into the corresponding iridabenzene by thermal treatment.^[2] In addition to varying the coordination pattern at the iridium center and the substituents on the vinylcyclopropene precursor,^[3] we are currently trying to show this concept to be generally applicable for the synthesis of metallabenzenes and

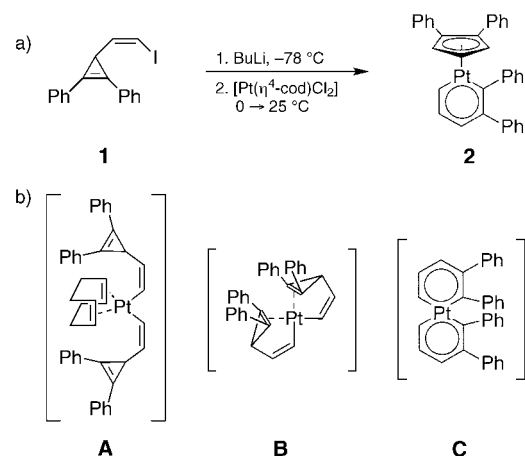
[*] Prof. Dr. M. M. Haley, Dr. V. Jacob, Dr. T. J. R. Weakley
Department of Chemistry
University of Oregon
Eugene, OR 97403-1253 (USA)
Fax: (+1) 541-346-0487
E-mail: haley@oregon.uoregon.edu

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their valence isomers containing metals other than iridium and osmium, which is the limiting factor of previous metal-labenzene syntheses. We report herein our initial studies using platinum complexes, which resulted in the formation and characterization of the first platinabenzene **2**.

Platinum chemistry is an attractive field of study, as a vast array of Pt compounds displaying a variety of metal–carbon bonding modes can be found in the literature.^[4] Complexes in which the coordination sphere around the Pt center is made up exclusively of hydrocarbon ligands are amply known for the three principal oxidation states of Pt^{0,II,IV}. The ligands therein are bonded to the Pt center in σ and/or π fashion. Especially for Pt^{II} complexes, ligand sets with almost every imaginable mixture of these donors are realized.^[5,6]

Exchange of chloride ligands in [Pt(η^4 -1,5-cod)Cl₂] (1,5-cod = 1,5-cyclooctadiene) by use of organolithium reagents is a well-known and commonly used method for the synthesis of Pt- σ -alkyl compounds.^[6] By treating [Pt(cod)Cl₂] with two equivalents of **1** (Scheme 1a), which was converted into a



Scheme 1. a) The formation of the first platinabenzene **2**; b) possible intermediates **A–C** in the formation of **2**.

nucleophilic agent by lithium–iodine exchange,^[1,2] we hoped to obtain a [Pt(η^4 -1,5-cod){-CH=CH-(cyclo-C₃HPh₂)₂}] complex (**A**; Scheme 1b) with two σ -bonded vinylcyclopropene ligands. Intramolecular displacement of the 1,5-cyclooctadiene ligand by the cyclopropene double bonds would give **B**. Subsequent ring-opening of the strained cyclopropenes would ideally lead to **C** or to other closely related platina-aromatics (i.e. **2**).

Upon addition of the vinyl lithiate, the colorless ethereal [Pt(cod)Cl₂] suspension immediately turned into a dark brown slurry containing an appreciable amount of light brown precipitate. Investigation of the crude reaction solution by ¹H NMR spectroscopy showed neither signals attributable to coordinated 1,5-cod as expected for **A**, nor for chelating vinylcyclopropene ligands coordinated in σ -alkenyl and π -fashions (i.e. **B**). The NMR spectrum was dominated by a broad shapeless absorption at $\delta \approx 6.7$ –7.3, which indicates degradation of the carbon skeleton of **1**. Pt-promoted decomposition^[7] of cyclopropene **1**, presumably through opening of the cyclopropene ring followed by oligomerization

or polymerization, appears to be the main process. In the downfield region of the spectrum, however, two signal groups at approximately $\delta = 12.8$ and 8.2 ppm were observed. The compound responsible for these resonances is (cyclopentadienyl)platinabenzene (**2**), which was isolated as a red solid after column chromatography.

¹H NMR spectra of orange-red C₆D₆ solutions of **2** show characteristically downfield-shifted signals. The multiplet at $\delta = 12.76$ ppm is clearly assignable to the metallaaromatic proton in the *ortho* position to Pt, because of its splitting pattern and the value for ²J_{PtH} = 65 Hz.^[8] The *para*-proton signal is well visible at $\delta = 8.20$ ppm, while the *meta*-proton gives rise to a pseudotriplet at $\delta = 7.42$ ppm (³J_{PtH} = 150 Hz). Irida- and osmabenzenes exhibit signals with similar chemical shifts (*o*-H: $\delta = 9.0$ –14.0; *m*-H: $\delta = 6.6$ –8.0; *p*-H: $\delta = 7.0$ –8.6).^[9] The protons of the η^5 -coordinated^[5,10,11] 1,2-diphenylcyclopentadienyl ligand^[12] of **2** appear as a doublet and triplet at $\delta = 5.36$ and 5.09 ppm, respectively.

In the ¹³C NMR spectrum of **2**, the two signals at $\delta = 195$ and 204 ppm are attributable to the metallaaromatic carbon atoms directly bonded to the Pt; these δ values are again comparable to ¹³C NMR δ values in irida- and osmabenzenes.^[9] Pt–C couplings of ¹J_{PtC} $\approx$ 1330 and 1400 Hz are in the range of values reported for Pt^{II}–carbene and σ -alkenyl complexes.^[8,13,14] Signals for the carbon atoms of the 1,2-diphenylcyclopentadienyl ligand are found at $\delta = 96$, 98, and 115 ppm.

The structure of **2** was confirmed by X-ray crystallography (Figure 1).^[15] Selected bond lengths and angles are given in Table 1. Red blocks of **2**, which were obtained by cooling a saturated hexanes/EtOAc solution to 0 °C, crystallize in the triclinic space group $\bar{P}1$ without inclusion of solvent molecules. The Pt^{II} center is part of a six-ring metallacycle, formed by cyclopropene–vinylalkylidene rearrangement^[7,16] of the

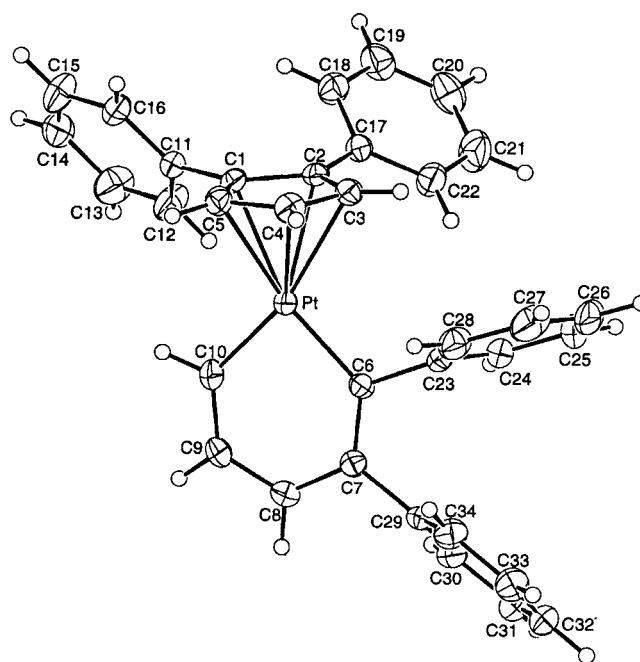


Figure 1. Molecular structure of platinabenzene **2**; ellipsoids drawn at the 30% probability level.

Table 1. Selected bond lengths [Å] and angles [°] in **2**.

Pt-C1	2.327(3)	C1-C2	1.439(5)
Pt-C2	2.342(3)	C2-C3	1.425(5)
Pt-C3	2.299(4)	C3-C4	1.399(6)
Pt-C4	2.270(4)	C4-C5	1.415(5)
Pt-C5	2.289(4)	C5-C1	1.414(5)
Pt-C6	1.959(3)	Pt-C10	1.929(4)
C6-C7	1.387(5)	C8-C9	1.381(6)
C7-C8	1.395(5)	C9-C10	1.364(6)
C6-Pt-C10	89.3(2)	C7-C8-C9	124.8(4)
Pt-C6-C7	129.2(3)	Pt-C10-C9	130.0(3)
C6-C7-C8	122.6(3)	C8-C9-C10	124.1(4)

strained precursor. Hughes and co-workers have reported the synthesis of a platinacyclohexadiene by a similar vinylcyclopropene rearrangement.^[14] In contrast to the puckered six-membered ring in that compound, the metallacycle in **2** is strictly planar (deviations from mean plane ≤ 0.02 Å, sum of angles = 720°). The two Pt–C bond distances in this ring are approximately equal (1.929, 1.959 Å), comparable to Pt–C bond lengths in Pt^{II}–carbene complexes.^[8] The C–C bonds in the aromatic ring are nonalternating and range between C–C single and double bonds (average 1.382 Å). The three C–C–C angles are about 124° , while C–Pt–C is close to 90° , and the Pt–C–C angles are around 130° . As with the NMR spectroscopic data, these structural observations are in good agreement with the values for reported metallabenzene structures^[9] and together corroborate the aromatic character of this ring. Pt–C_{ipso} distances around 2.30 ± 0.05 Å confirm η^5 -coordination of the 1,2-diphenylcyclopentadienyl ligand in the solid state.^[11,17] Interestingly, this ligand must also be derived from rearrangement of the vinylcyclopropene starting material, probably through a platinabenzene intermediate such as **C** (see Scheme 1b), which isomerizes into the η^5 -cyclopentadienyl ligand by extrusion of the metal fragment.^[9] Such a conversion involving an iridabenzene rearranging cleanly to an iridium(I) cyclopentadienyl complex has recently been observed.^[3]

Metallacycle **2** is the first example of a platinabenzene. The formation of **2**, which contains two different rearrangement products of the vinylcyclopropene precursor, as a stable compound in this complicated reaction can be rationalized by mutual stabilization of the η^5 -bonded cyclopentadienyl ligand and the platinabenzene moiety. The synthesis and characterization of this compound show that the existence of isolable metallabenzenes, which are not stabilized by η^6 -coordination to a second transition-metal fragment, is no longer confined to the classical cases of osmium and iridium.^[18] Experiments to extend our methodology to additional metals are underway.

Experimental Section

Cyclopropene **1** (688 mg, 2.0 mmol) was dissolved in dry Et₂O (20 mL) under Ar and cooled to -78°C . Butyllithium (0.8 mL, 2.5 M in hexanes, 2.0 mmol) was added dropwise and the resulting yellow solution was stirred at -78°C for 15 min. This solution was added dropwise to a stirred, ice-cooled suspension of [Pt(cod)Cl₂] (374 mg, 1.0 mmol) in Et₂O (5 mL). The resulting dark brown suspension was allowed to warm to room temperature and stirred for 12 h before filtration. The filtrate was evaporated to give a dark brown solid which was chromatographed twice on silica (25 × 1.5 cm) using hexanes/EtOAc (30:1) as the eluent. After evaporation, the red band afforded **2** (45 mg, 7%) as a red solid. M.p. 168°C (decomp.); ¹H NMR (500 MHz, C₆D₆, 25°C): δ = 5.09 (t, ³J(H,H) = 2.7 Hz, 1H; CpH), 5.36 (d,

³J(H,H) = 2.7 Hz, 2H; CpH), 6.74 (br t, ³J(H,H) = 7.5 Hz, 1H; C₆H₅), 6.85–6.94 (m, 3H; C₆H₅), 6.94–6.98 (m, 6H; C₆H₅), 6.99 (t, ³J(H,H) = 7.7 Hz, 2H; C₆H₅), 7.07 (d, ³J(H,H) = 7.3 Hz, 2H; C₆H₅), 7.13 (d, ³J(H,H) = 7.3 Hz, 2H; C₆H₅), 7.25–7.30 (m, 4H; C₆H₅), 7.42 (t, ³J(H,H) = 7.7 Hz, ³J(Pt,H) = 150 Hz, 1H; CH_{meta}), 8.20 (dd, ³J(H,H) = 8.1 Hz, ⁴J(H,H) = 1.7 Hz, 1H; CH_{para}), 12.76 ppm (dd, ³J(H,H) = 7.7 Hz, ⁴J(H,H) = 1.7 Hz, ²J(Pt,H) = 65 Hz, 1H; CH_{ortho}); ¹³C NMR (125 MHz, C₆D₆, 25°C): δ = 96.09 (s; CH_{Cp}), 97.83 (s; CH_{Cp}), 114.97 (s; CPh_{Cp}), 124.51, 125.00, 125.46, 125.72, 126.19, 128.51, 130.54, 130.92, 132.22 (all s; C₆H₅ and CH_{meta}), 135.73 (s; C_{ipso}), 140.99 (s, ³J(Pt,C) ≈ 150 Hz; CH_{para}), 144.17 (s; C_{ipso}), 161.74 (s; CPh_{meta}), 194.96 (s, ¹J(Pt,C) = 1330 Hz; CH_{ortho}), 204.01 ppm (s, ¹J(Pt,C) = 1400 Hz; CPh_{ortho}) (2 signals obscured by solvent peaks); ¹⁹⁵Pt{¹H} (107 MHz, C₆D₆, 25°C): δ = –5059 ppm (s);^[19] UV/Vis (CH₂Cl₂, λ_{max} , ϵ , M^{–1}cm^{–1}): 258 (120 000), 443 nm (43 000); elemental analysis calcd (%) for C₃₄H₂₆Pt: C 64.86, H 4.16; found: C 64.95, H 4.29.

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phenyl H atoms riding) with teXsan (v. 1.7 for SGI workstations), 340 refined parameters, $R(F) = 0.022$ [$I \geq \sigma(I)$], $wR(F^2) = 0.051$, residual electron density: 1.29/−1.31 e Å^{−3}. Data was obtained on an Enraf-Nonius CAD-4 diffractometer. CCDC-185114 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

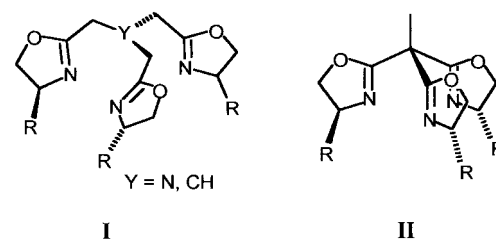
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A Modular Approach to C₁ and C₃ Chiral N-Tripodal Ligands for Asymmetric Catalysis**

Stéphane Bellemin-Laponnaz and Lutz H. Gade*

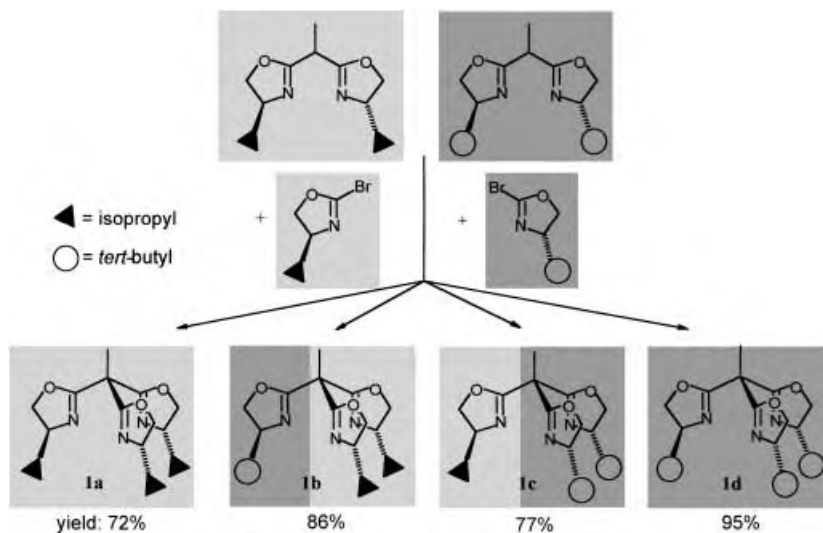
In memoriam John Osborn

In the development of nitrogen ligand based homogeneous catalysis,^[1] oxazoline derivatives have emerged as a paradigmatic class of ligands in asymmetric catalysis.^[2,3] Most attention has been centered on mono- or bisoxazoline ligands many of which proved to be highly efficient in a large variety of stereoselective transformations.^[4] In contrast, the combination of three oxazolines to form ligands of podand topology, possessing C₁ or C₃ symmetry, has received much less attention. There are several reports of trisoxazoline ligands,^[5,6] the most notable example being the N(CH₂-ox)₃ and CH(CH₂-ox)₃ (ox = 2-oxazolynyl) systems (**I**) developed by Katsuki's group, the copper complexes of which have been employed in asymmetric allylic oxidations.^[7] The way these conformationally very flexible trisoxazolines coordinate to the metal centers in the active catalysts remains an



open question. However, the access to 1,1,1-tris(oxazolynyl)-methane or -ethane ligands (**II**), which provide a geometry of the metal binding site that is most adapted to tripodal coordination of the metal center and would lead to a relatively rigid and well-defined coordination geometry, proved to be elusive for a long time.^[8]

Attempts to synthesize these tripodal ligands by sequential formation of the three oxazoline rings failed due to decarboxylation and related decomposition of the precursors during the formation of the third oxazoline ring. Very recently, we discovered that 1,1,1-tris(oxazolynyl)ethane derivatives may be synthesized by coupling lithiated bisoxazolines with 2-bromooxazolines and reported the achiral 1,1,1-tris[2-(4,4-dimethyl)oxazolynyl]ethane (“trisox-Me₂”, **II**).^[9] This strategy, which is formally based on a [1+2] condensation scheme of a metalated bisoxazoline^[10] with a 2-bromooxazoline^[11] has now been used for the synthesis of the first *chiral* tripods and it establishes 2-bromooxazolines as potentially powerful tools in ligand design (Scheme 1).



Scheme 1. Modular assembly of the trisoxazoline ligands **1a–1d** by reaction of the metalated bisoxazolines with 2-bromooxazoline derivatives.

[*] Prof. L. H. Gade, Dr. S. Bellemin-Laponnaz
Laboratoire de Chimie Organométallique et de Catalyse
UMR 7513, Institut Le Bel, Université Louis Pasteur
67070 Strasbourg (France)
Fax: (+33)390-241531
E-mail: gade@chimie.u-strasbg.fr

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Our synthetic method allows the high-yield access to symmetrically substituted derivatives, such as 1,1,1-tris[2-((S)-4-isopropyl)oxazolynyl]ethane (**1a**) or 1,1,1-tris[2-((S)-4-tert-butyl)oxazolynyl]ethane (**1d**). Additionally, the synthesis of tripods with mixed substitution patterns, such as **1b** and **1c**, is achieved in excellent yields. This opens up the possibility to approach the synthesis of such polydentate oxazolines in a *modular* way, as displayed in Scheme 1 for the isopropyl/tert-butyl couple. From the point of view of ligand design these

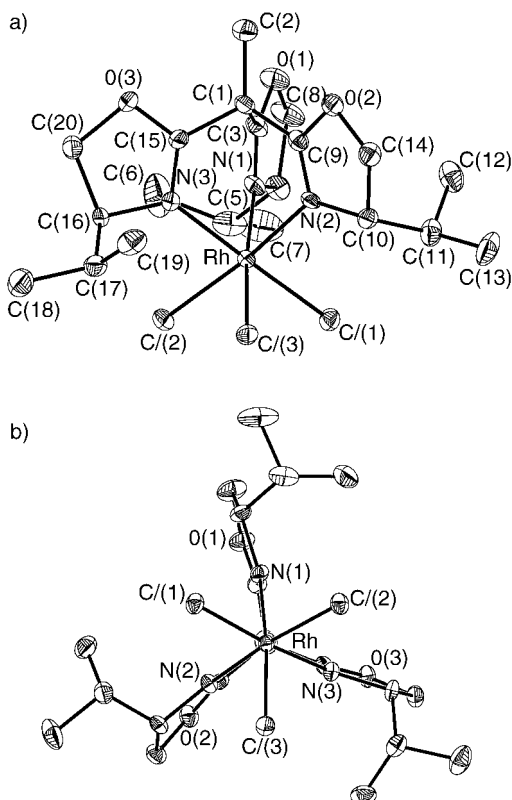


Figure 1. a) Molecular structure of the rhodium complex **2**. Principal bond lengths [Å] and angles [°]: Rh-Cl(1) 2.337(2), Rh-Cl(2) 2.328(2), Rh-Cl(3) 2.315(1), Rh-N(1) 2.066(5), Rh-N(2) 2.063(4), Rh-N(3) 2.066(5), Cl(1)-Rh-Cl(2) 90.32(6), Cl(1)-Rh-Cl(3) 89.35(6), Cl(2)-Rh-Cl(3) 90.45(6), N(1)-Rh-N(2) 85.0(2), N(1)-Rh-N(3) 85.5(2), N(2)-Rh-N(3) 85.4(2). b) View along the virtual threefold molecular axis of **2**.

podands are adapted to non-square-planar coordination geometries in transition metals, including the late elements such as the ubiquitous Cu^I/Cu^{II} couple in asymmetric catalysis.

To assess the binding capability of the new trisoxazoline tripods as facially coordinating tridentate ligands, we first chose a transition metal that is less substitutionally labile than copper. Reaction of **1a** with one molar equivalent of [RhCl₃(H₂O)₃] cleanly gave the trisoxazolinerhodium complex [RhCl₃{trisox-(*S*)-*i*Pr}] (**2**), for which the NMR spectroscopic data obtained in solution indicated the expected threefold symmetric structure. An X-ray diffraction study of **2** was carried out to establish the details of the molecular structure. The view along the threefold molecular axis of the rhodium complex (Figure 1) established the *C*₃ chirality of the system also in the solid state. The bond lengths and angles within the [2.2.2]bicyclooctane-related ligand cage are within the typical range and confirm the suitability of the ligands **1a–1d** for facial coordination.

As a first test in copper(I)-based asymmetric catalysis, ligands **1a–1d** were employed in the asymmetric cyclopropanation of styrene with ethyl and *tert*-butyl diazoacetate (Table 1).^[12] The strong preference for the *trans* diastereomer (80–90 %) is similar to results previously obtained with bisoxazoline derivatives.^[2a–c,13,14] The stereoselectivity varied with the combination of substituents at the oxazoline ligands and is maximized for the nonsymmetrical ligand **1c**: 85 % *ee* for the *cis* diastereomer in the reaction with *tert*-butyl diazoacetate and 86 % *ee* for the *trans* diastereomer in the reaction with ethyl diazoacetate. It is notable that in the former conversion the *cis* products are generated with high enantioselectivity, while the trend is reversed for the conversion with ethyl diazoacetate.

As is evident from this first study, the possibility of introducing and combining different substituents at the oxazoline rings within the same tripodal ligand system allows a straightforward access to a large variety of such systems. Moreover, the combination of chiral and achiral units or of oxazoline ligands of opposite absolute configuration within the same ligand system is feasible by this strategy and will provide the foundation for the application of this class of ligands in parallel screening experiments for the optimization of homogeneous catalysts.

Experimental Section

General procedure for the synthesis of the trisoxazolines (given for **1d**): *t*BuLi (1.26 mL, 1.7 M in hexanes, 2.14 mmol) was added dropwise to a solution of 2,2-bis[4-(*S*)-*tert*-butyl-1,3-oxazolinyl]ethane (0.5 g, 1.78 mmol) in anhydrous THF (30 mL) at –78 °C over 10 min. The resulting yellow solution was stirred for an additional 30 min prior to the addition of 1.4 equivalents of 4-(*S*)-*tert*-butyl-2-bromooxazoline. The solution was then stirred at room temperature for one hour, concentrated to about 25 mL and, finally, the Schlenk tube was sealed. The stirred solution was heated at 80 °C for five days. The resulting orange solution was evaporated to dryness; the residue was redissolved with dichloromethane (100 mL) and washed with water (10 mL). The organic extract was dried over Na₂SO₄ and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (EtOAc/MeOH, 50/1) gave the desired product **1d** (0.70 g, 0.69 mmol; 95 % yield). Compounds **1a–1c** were synthesized accordingly. Yields: **1a** 72 %, **1b** 86 %, **1c** 77 %; see Table 2 for spectroscopic data.

Table 1. Copper(I)-catalyzed asymmetric cyclopropanation of styrene with *tert*-butyl and ethyl diazoacetate using the novel oxazoline tripod ligands.

L*	R = <i>t</i> Bu			R = Et		
	<i>cis:trans</i>	% <i>ee cis</i>	% <i>ee trans</i>	<i>cis:trans</i>	% <i>ee cis</i>	% <i>ee trans</i>
1a	22:78	70	65	29:71	64	67
1b	22:78	72	66	29:71	72	78
1c	23:77	85	81	31:69	81	86
1d	19:81	73	70	31:69	68	70

[a] Styrene (1.0 mmol), diazoacetate (1.2 mmol), [CuOTf]₂ (0.005 mmol) and ligand (0.012 mmol). A solution of diazoacetate in CH₂Cl₂ (1.0 mL) was added with a syringe over a period of 8 h to the mixture of styrene and the catalyst in the appropriate solvent (2.0 mL). The resulting solution was stirred for 16 h. The product was purified by flash chromatography. Yields of isolated product are 70–80 % (*cis* + *trans*); *ee* values were determined by chiral GC.

Table 2. Selected spectroscopic data.^[a]

1a: ¹H NMR: δ = 4.26 (m, 3H), 4.09–3.97 (m, 6H), 1.82 (s, 3H), 1.85–1.74 (m, 3H), 0.91 (d, J = 6.8 Hz, 9H); 0.86 ppm (d, J = 6.8 Hz, 9H); ¹³C NMR: δ = 164.6 (C=N), 71.8 (CHiPr), 70.6 (CH₂), 44.7 (C_{quat}), 32.3 (CH(CH₃)₂), 21.3 (CH₃), 18.6 (CH(CH₃)(CH₃)), 17.8 ppm (CH(CH₃)(CH₃)); MS (EI): m/z (%): 363.2 (1) [M]⁺, 348.2 (7.6) [M –CH₃]⁺, 320.2 (100) [M –CH(CH₃)₂]⁺; [α]_D²⁵ = –88.9° (c = 0.4, CHCl₃).

1b: ¹H NMR: δ = 4.28–3.95 (m, 8H), 3.91 (dd, J = 7.3 Hz, J = 10.2 Hz, 1H), 1.81 (s, 3H), 1.85–1.74 (m, 2H), 0.89 (m, 12H), 0.87 ppm (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃): δ = 164.6, 164.5, 164.4 (C=N), 75.4 (CHiBu), 71.7 (2 CHiPr), 70.5 (2 CH₂), 69.4 (CH₂), 44.7 (C_{quat}), 33.9 (C(CH₃)₃), 32.3 (2 CH(CH₃)₂), 25.7 (C(CH₃)₃), 21.2 (CH₃), 18.5 (2 CH(CH₃)(CH₃)), 17.8 ppm (2 CH(CH₃)(CH₃)); MS (EI): m/z (%): 376.3 (1) [M –H]⁺, 362.3 (8.5) [M –CH₃]⁺, 334.2 (35) [M –CH(CH₃)₂]⁺, 320.1 (100) [M –C(CH₃)₃]⁺; [α]_D²⁵ = –71.0° (c = 0.4, CHCl₃).

1c: ¹H NMR: δ = 4.27–3.96 (m, 7H), 3.90 (dd, J = 7.3 Hz, J = 10.1 Hz, 2H), 1.82 (s, 3H), 1.85–1.74 (m, 1H), 0.89 (m, 6H), 0.87 ppm (s, 18H); ¹³C NMR: δ = 164.6, 164.4, 164.3 (C=N), 75.4 (2 CHiBu), 71.7 (CHiPr), 70.4 (CH₂), 69.3 (2 CH₂), 44.8 (C_{quat}), 33.9 (2 C(CH₃)₃), 32.2 (CH(CH₃)₂), 25.8 (2 C(CH₃)₃), 21.0 (CH₃), 18.5 (CH(CH₃)(CH₃)), 17.8 ppm (CH(CH₃)(CH₃)); MS (EI): m/z (%): 390.3 (0.5) [M –H]⁺, 376.2 (7.5) [M –CH₃]⁺, 348.2 (2) [M –CH(CH₃)₂]⁺, 334.2 (100) [M –C(CH₃)₃]⁺; [α]_D²⁵ = –82.8° (c = 0.4, CHCl₃).

1d: ¹H NMR: δ = 4.27–4.16 (m, 6H), 3.95 (dd, J = 7.4 Hz, J = 10.1 Hz, 3H), 1.84 (s, 3H), 0.91 ppm (s, 27H); ¹³C NMR: δ = 164.7 (C=N), 75.8 (CHiBu), 69.7 (CH₂), 45.2 (C_{quat}), 34.3 (C(CH₃)₃), 26.2 (C(CH₃)₃), 21.3 ppm (CH₃); MS (EI): m/z (%): 405.2 (0.4) [M]⁺, 390.3 (8.5) [M –CH₃]⁺, 348.1 (100) [M –C(CH₃)₃]⁺; [α]_D²⁵ = –81.0° (c = 0.5, CHCl₃).

2: ¹H NMR: δ = 5.06 (m, 3H), 4.75–4.61 (m, 6H), 3.26 (m, 3H), 1.80 (s, 3H), 0.84 (d, J = 7.3 Hz, 9H), 0.65 ppm (d, J = 6.6 Hz, 9H); ¹³C NMR: δ = 166.0 (C=N), 73.7 (CHiPr), 68.7 (CH₂), 44.5 (C_{quat}), 27.4 (CH(CH₃)₂), 18.6 (CH(CH₃)(CH₃)), 14.3 (CH(CH₃)(CH₃)), 11.1 ppm (CH₃); MS (FAB): m/z (%): 536.0 ([M –Cl]⁺, calculated for the most abundant isotopomer: 536.1 amu).

[a] NMR spectra recorded at 300.17 MHz (¹H) and 75.48 MHz (¹³C) in CDCl₃. Correct elemental analyses obtained for all compounds.

2: A mixture of the ligand **1a** (116 mg, 0.32 mmol) and [RhCl₃(H₂O)₃] (82 mg, 0.31 mmol) in ethanol (5 mL) was stirred under nitrogen at 50 °C for one hour and then at room temperature for 12 h. The solvent was removed in vacuo and the resulting orange solid was dissolved in chloroform. Filtration over celite, followed by addition of diethyl ether gave orange crystals. Yield: 150 mg, 0.26 mmol; 84 % (see Table 2 for spectroscopic data). X-ray structure analysis of **2**: C₂₀H₃₃Cl₃N₃O₃Rh·2 CHCl₃, orange, crystal dimensions 0.20 × 0.16 × 0.14 mm, M_r = 811.52, orthorhombic, space group $P2_12_12_1$, a = 30.2795(1), b = 11.9730(1), c = 9.6101(3) Å, V = 3484.0(1) Å³, Z = 4, ρ_{calcd} = 1.55 g cm^{–3}, μ = 1.208 mm^{–1}, $F(000)$ = 1640, number of data measured: 7998 ($2.5 < \theta < 27.48^\circ$) at 173 K, number of data with $I > 3\sigma(I)$: 3479, number of variables: 343, R = 0.039, R_w = 0.057, GOF = 1.069, largest peak in final difference: 0.881 e Å^{–3}. The crystal data were collected on a Nonius Kappa CCD diffractometer at –100 °C and transferred to a DEC Alpha workstation; for all subsequent calculations the Nonius OpenMoleN package was used.^[15] The structures were solved by using direct methods; absorption corrections were used as part of the scaling procedure of the data reductions. After refinement of the heavy atoms, difference Fourier maps revealed the maxima of residual electron density close to the positions expected for the hydrogen atoms; they were introduced as fixed contributors in the structure factor calculations with fixed coordinates (C–H: 0.95 Å) and isotropic temperature factors ($B(\text{H}) = 1.3 B_{\text{eq}}(\text{C})$ Å²) but not refined. Full-matrix least-square refinements on F^2 . A final difference map revealed no significant maxima of electron density. The scattering factor coefficients and the anomalous dispersion coefficients were taken from ref. [16].

CCDC-185098 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/

conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+ 44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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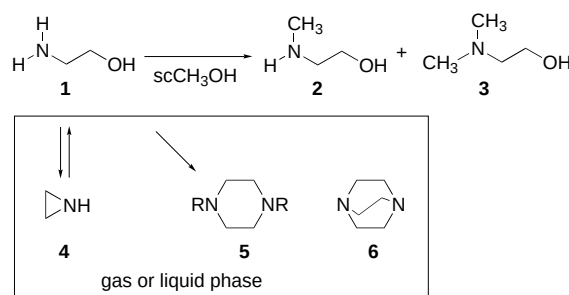
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Enhanced Product Selectivity in Continuous N-Methylation of Amino Alcohols over Solid Acid–Base Catalysts with Supercritical Methanol

Tomoharu Oku and Takao Ikariya*

Supercritical fluids (SCFs) used as reaction media for homogeneous molecular catalysis or as compressed carriers for heterogeneous catalysis^[1–4] have great potential for the manipulation of catalytic reactions. We have demonstrated that the pressure-tunable, unique properties of SCFs can remarkably enhance the reactivities and selectivities of molecular catalysts.^[1] Besides these benefits for homogenous catalysis, when heterogeneously catalyzed reactions are performed over solid catalysts under supercritical conditions, the pressure-tunable, liquidlike solubility and gaslike diffusivity of the SCFs can significantly enhance the selectivity of the reactions if the unique properties of SCFs favor one of the reactions. Rapid deactivation of the catalyst resulting from coke formation on the surface can also be suppressed. Furthermore, applications of SCFs as a reactant and carrier medium can influence the outcome of the reaction owing to an increase in the concentration of the reactant on the catalyst surface. In fact, Baiker et al. reported that the selectivity of the amination of alkanediols or alkanolamines to give diamines conducted with scNH_3 over a Co–Fe catalyst increased remarkably when the pressure of the scNH_3 was changed.^[3] Thus, heterogeneous catalysis in SCF media has received considerable attention as researchers have tried to manipulate the catalyst performance in terms of the selectivity.^[3,4] However, fine-tuning the product selectivity of supercritical-phase reactions over solid catalysts has remained largely unexplored. Here we report the successful chemo-selective alkylation of functionalized amines such as 2-aminoethanol (**1**) over solid acid or acid–base bifunctional catalysts with supercritical methanol (scCH_3OH , $P_c = 8.1$ MPa, $T_c = 239.5^\circ\text{C}$). A significant increase in the selectivity of N-alkylation was achieved by using scCH_3OH as a reactant and carrier medium for continuous-flow reactions.

For the reaction of **1** with CH_3OH to provide industrially useful chemicals,^[5] the product distribution is highly influenced by the reaction phase as well as by the catalyst (Scheme 1). For example, the vapor-phase reaction of **1** over conventional solid acid catalysts such as H- β zeolites^[6] provides predominantly the products of intermolecular dehydration, piperazine (**5**) and triethylenediamine (**6**), in addition to N-methylated products, N-methylaminoethanol (**2**) and N,N-dimethylaminoethanol (**3**). Alkaline earth metal–silicon



Scheme 1. The reaction of **1** with methanol.

or alkali metal–phosphorus–silicon oxides in the gas phase selectively afford the product of intramolecular dehydration, ethyleneimine (**4**), at higher temperatures instead of **5** and **6**.^[7] Therefore, in general, the N-alkylation of **1** with methanol under such severe conditions proceeds in a nonselective manner and leads to various side reactions, cyclization, oligomerization, and decomposition through C–N bond cleavage.

We screened various solid acid catalysts for the reaction of **1** with scCH_3OH by using a continuous-flow fixed-bed tubular reactor at 250 – 300°C and a pressure range of 0.1 to 15 MPa (contact time of amine to catalyst, $W/F = 55$ – 111 g-cat h/mol-amine, amine/ CH_3OH molar ratio = $1/10.8$). The catalysts tested—H-mordenite,^[8] H- β zeolite,^[6] amorphous silica-alumina,^[9] γ -alumina,^[10] and the Cs–P–Si mixed oxide—effected N-methylation under supercritical conditions to give predominantly N-methylation products **2** and **3** in good to excellent yields. Compounds **4**, **5**, and **6** were also obtained as minor products as listed in Table 1. A visual inspection of the inside of a 10-mL high-pressure vessel equipped with sapphire windows confirmed that the reactants and expected products are all dissolved into scCH_3OH to make a single supercritical phase under the reaction conditions examined here. Obviously, application of supercritical conditions improves the conversion of amine as well as the selectivity for N-methylated products in comparison to gas-phase reactions which give only low conversion.^[11]

Among the most efficient catalysts in scCH_3OH are combined ternary mixed-oxide catalysts, M–P–Si (M = alkali metal), which have both very weak acidic and basic sites. The product selectivity is delicately influenced by the alkali metal components in these catalysts and by the reaction conditions. A Cs–P–Si mixed-oxide catalyst effected the efficient N-methylation of **1** at 300°C and under otherwise the same conditions as described in Table 1 to give the desired products **2** and **3** in 67% yield (71% conversion and 94% cumulated selectivity). When the reaction was performed with a W/F value of 133 g/mol^{–1} and an amine/ CH_3OH ratio of $1/20$ under otherwise identical conditions, the yield of the desired products increased to 81% (86% conversion and 94% selectivity). An increase in the temperature from 300 to 400°C caused a serious drop in the selectivity to 25%, although the conversion of **1** increased, as shown in Figure 1. At the higher reaction temperature of 400°C , the supercritical-phase reaction gave a complicated mixture of **4**, methoxyethylamine, and some other degradation compounds. In contrast to the scCH_3OH phase, the gas-phase reaction

[*] Prof. T. Ikariya
Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2637
E-mail: tikariya@o.cc.titech.ac.jp
T. Oku
Joint Research Center for Supercritical Fluids
Japan Chemical Innovation Institute (JCII)

Table 1. Reaction of **1** with methanol over various solid catalysts in both gas and supercritical phases.^[a]

Entry	Catalyst	$T/^{\circ}\text{C}/P/\text{MPa}$	$W/F/\text{g h mol}^{-1}$	Conv. [%]	Yield [%]		Selectivity [%]		
					2	3	2 + 3	4	5 + 6
1	H-mordenite	300/0.1	111	0	0	0	0	0	0
2	H-mordenite	300/15	111	26	12	4	61	0	0
3	H- β zeolite	250/0.1	55	18	2	1	17	0	46
4	H- β zeolite	250/15	55	32	12	8	63	0	0
5	$\text{SiO}_2\text{-Al}_2\text{O}_3$	300/0.1	66	34	7	2	26	0	0
6	$\text{SiO}_2\text{-Al}_2\text{O}_3$	300/8.2	66	77	15	10	32	0	10
7	$\text{SiO}_2\text{-Al}_2\text{O}_3$	300/15	66	81	15	13	35	0	8
8	$\gamma\text{-Al}_2\text{O}_3$	300/0.1	79	21	12	3	71	tr	9
9	$\gamma\text{-Al}_2\text{O}_3$	300/8.2	79	48	24	9	69	0	3
10	$\gamma\text{-Al}_2\text{O}_3$	300/15	79	48	26	10	75	0	1
11	Na-P-Si oxide	270/8.2	55	100	1	36	37	0	16
12	K-P-Si oxide	300/8.2	55	74	35	12	64	0	0
13	Cs-P-Si oxide	300/0.1	55	12	6	1	58	37	4
14	Cs-P-Si oxide	300/8.2	55	71	51	16	94	0	1
15	Cs-P-Si oxide	300/8.2	133	79	48	24	91	0	0
16	Cs-P-Si oxide	300/8.2 ^[b]	133	86	48	33	94	0	0

[a] Conditions: The reaction was conducted in a fixed-bed, tubular reactor with an amine/ CH_3OH molar ratio of 1/10.8 and $W/F=55\text{--}133\text{ g h mol}^{-1}$. The product ratio was determined by GC after the reaction conditions had been at steady state for 6 h. [b] Amine/ $\text{CH}_3\text{OH}=1/20$.

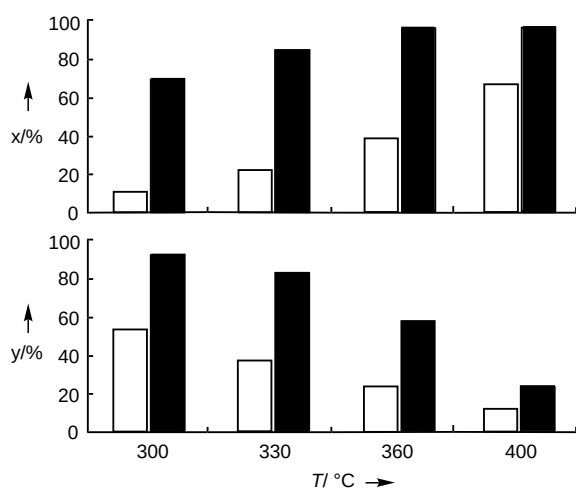


Figure 1. The effect of temperature on the conversion of **1** (x) and selectivity for N-methylated products (y) in the gas phase (white bars) and the supercritical phase, $P=8.2\text{ MPa}$, (black bars) in the methylation of **1** over the Cs-P-Si catalyst. Conditions: $W/F=25\text{ g h mol}^{-1}$, $\text{CH}_3\text{OH}/\text{amine}=10.8/1$.

under otherwise identical conditions at 300°C exhibited unsatisfactory productivity, 12 % conversion, and 58 % selectivity. The reaction at the higher reaction temperature of 400°C afforded **4** with 72 % selectivity as the major product. Thus, the use of scCH_3OH as a carrier medium and reactant improved the productivity of N-methylation significantly over that of the gas-phase reaction. The change in the selectivities might be attributed to the milder reaction conditions possible with scCH_3OH , as well as the increased concentration of CH_3OH on the catalyst surface.

The scope and limitation of this N-methylation over the Cs-P-Si mixed-oxide catalyst in scCH_3OH was investigated at 300°C and 8.2 MPa with an amine/ CH_3OH molar ratio of 1/20. N-Methylation of various functionalized amines proceeded smoothly to provide the corresponding N-methylated products with a high selectivity (Table 2). Noticeably, the structures of the amino alcohols influenced the outcome of

Table 2. N-Methylation of various amines over the Cs-P-Si catalyst in scCH_3OH .^[a]

Entry	Amine	Conv. [%]	Sel. 2 + 3 [%]	Sel. 4 + 5 + 6 [%]
1	$\text{HO}(\text{CH}_2)_2\text{NH}_2$	90	94	1
2	$\text{HO}(\text{CH}_2)_3\text{NH}_2$	81	93	1
3	$\text{HO}(\text{CH}_2)_4\text{NH}_2$	87	12	87
4	$\text{HO}(\text{CH}_2)_5\text{NH}_2$	51	80	20
5	$\text{HO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{NH}_2$	71	87	13
7	$\text{HO}(\text{CH}_2)_2\text{NHC}_2\text{H}_5$	76	88	0.1
8	$\text{HO}(\text{CH}_2)_2\text{NHC}_2\text{H}_5$	45	82	0.5
9	$\text{HO}(\text{CH}_2)_2\text{NHCH}(\text{CH}_3)_2$	24	78	1
10	$n\text{-C}_4\text{H}_9\text{NH}_2$	18	94	–
11	$\text{C}_6\text{H}_5\text{NH}_2$	15	94	–
12	2-pyrrolidone	16	88	–
13	$\text{C}_2\text{H}_5\text{O}(\text{CH}_2)_2\text{NH}_2$	11	98	–

[a] Conditions: The reaction was conducted over the Cs-P-Si catalyst at 300°C in a fixed-bed tubular reactor with an amine/ CH_3OH molar ratio of 1/20 and $W/F=140\text{ g h mol}^{-1}$.

the reaction. The reactivity decreases in the order of 2-aminoethanol > 3-aminopropanol > 5-aminopentanol, although 4-aminobutanol gave predominantly the cyclization product, pyrrolidine, in 87 % selectivity, possibly because of thermodynamic reasons. Diglycolamine with a structural similarity to 5-aminopentanol provided N-methylated products along with morpholine as a byproduct. Unlike bifunctionalized amines, simple amines including *n*-butylamine, aniline, and 2-pyrrolidone were far less reactive regardless of their structures; the conversion of the amines ranged from 10 to 20 % with high selectivity for N-methylation. The hydroxy group on the other terminus in the functionalized amines is a crucial structural factor in achieving high reactivity, possibly because of the anchoring effect of the hydroxy group on the catalyst surface. In fact, ethoxyethylamine bearing no hydroxy group was far less reactive than **1**.

Although the mechanism of the reaction on the catalyst surface is not clear yet, valuable information was provided by the N-methylation of *N*-alkylaminoethanols with scCH_3OH under conditions similar to those described in Table 2. The

reaction gave only *N,N*-alkylmethylaminoethanols without formation of any disproportionation products under these conditions. Substituents on the nitrogen atom of *N*-alkylaminoethanols affect the reactivity with scCH_3OH mainly because of steric and electronic factors; the reactivity decreased in the substituent order of $\text{H} > \text{CH}_3 > \text{C}_2\text{H}_5 > \text{CH}(\text{CH}_3)_2$. Furthermore, the lack of formation of *O*-methylated products in the reaction of **1** with CH_3OH under supercritical conditions may exclude the possibility of the intramolecular dehydration producing ethyleneimine **4**, which is a main product in the gas-phase reaction over the Cs-P-Si mixed-oxide catalysts. These experimental results as well as those previously reported^[7] suggest that the reaction proceeds by means of selective adsorption of **1** through the hydroxy group on the acid–base pair site of the catalyst to lead to the β -aminoethyl silyl ester or the β -aminoethyl phosphate species.^[7] CH_3OH should form its methylester on the neighboring acidic sites in a similar manner. After *N*-methylation on the amino group with methyl moieties through deprotonation of the amino groups by the basic sites, these *N*-methylated adsorbates may be effectively desorbed with the aid of scCH_3OH . In contrast to the reactivity of the Cs-P-Si mixed-oxide catalyst, which has both acidic and basic sites on the surface, β -zeolite or amorphous silica-alumina catalysts with relatively strong acid sites exerted unsatisfactory selectivity, while the γ -alumina catalyst, which has both strong acid and base sites, exhibited comparatively good reactivity and selectivity.

In summary, we have described the first examples of the selective *N*-methylation of bifunctional amines over the solid acid–base bifunctional catalyst in scCH_3OH as well as enhanced product selectivity on changing the pressure of CH_3OH . The use of scCH_3OH , which acts as a methylating agent and a reaction medium, as well as adjustment of the catalyst components results in the fine-tuning of the reaction conditions and particularly the reaction temperature for chemoselective methylation of the functionalized amines. Further investigations of the detailed mechanism of the methylation of the amines, the origin of the enhancement of the selectivity in scCH_3OH , and the effect of the cogenerated water on the reactivity^[12] are now in progress.

Experimental Section

The Cs-P-Si mixed-oxide catalyst was prepared by the following procedure: Silica beads of 10 to 20 mesh size (CARIAC Q-30, Fuji Silysia Chemical Co. LTD.) were impregnated with an aqueous solution of cesium nitrate and ammonium dihydrogenphosphate. The crude mixture was then dried at 120 °C and calcined at 500 °C for 2 h in air. The Cs/P/Si atomic ratio in the catalyst was 1/0.8/5 and the specific surface area was $7 \text{ m}^2 \text{ g}^{-1}$. The acid and base strength measured by the Hammett indicator method was weaker than $H_0 = +6.3$ and $H_- = +8.3$, respectively. Chemisorption of NH_3 and CO_2 at room temperature from the vapor phase did not occur in temperature-programmed desorption (TPD) analysis.

The *N*-methylation reaction of **1** in the gas or supercritical phase was carried out isothermally in a continuous up-flow tubular reactor (SUS316 tubular reactor with a Swagelok VCR joint, 1/2 inch $\times$ 10 mm $\times$ 135 mm). The reactor was loaded with catalyst particles and placed in an oven. A mixture of amine and methanol was introduced into the reactor through the preheating coil with an HPLC pump (PU1580, JASCO Co.). The pressure in the reaction system was controlled by the automatic back-pressure regulator (880-81, JASCO Co.) at 0.1 to 15 MPa. Standard reaction conditions were used (5.0 mL catalyst, 300 °C, 8.2 MPa, methanol/amine

molar ratio = 10.8/1 or 20/1 and the LHSV (mL-liquid/mL-cat h), which is the space velocity as normal liquid flow rate of the mixed solution of reactants, is 5 h^{-1}).

The reaction products were identified by GC-MS analysis (Agilent 5973N-6890N, Agilent Technologies). The selectivity and chemical yield of the products were determined by GC analysis (GC-17A, Shimadzu Co.; FID detector and DB-1 capillary column, J&W)). Conversion of amines X_a , yield Y_n , and selectivity S_n of each of the methylated products **2**, **3**, and **n** were defined as:

$$X_a = (F_{a(\text{ini})} - F_a) / F_{a(\text{ini})} \times 100 (\%) \quad (1)$$

$$Y_n = F_n / F_{a(\text{ini})} \times 100 (\%) \quad (2)$$

$$S_n = Y_n / X_a \times 100 (\%) \quad (3)$$

$F_{a(\text{ini})}$ and F_a represent molar flow rates of reactant amine at the reactor inlet and outlet, respectively, and F_n represents that of methylated product **n** at the reactor outlet.

During the reaction, no degradation products of methanol such as dimethylether, carbon monoxide, and methane were detected. Methanol was only consumed as a reactant in the *N*-methylation reaction.

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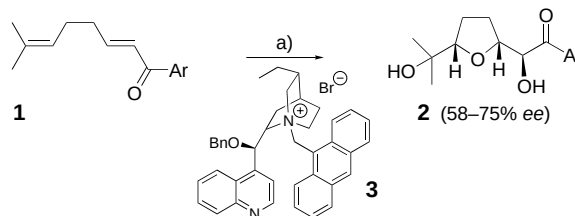
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- [8] H-Mordenite (HSZ640HOA, protonated form, Tosoh Co.; Si/Al atomic ratio of 9/1) was used after it had been pelletized to 0.3–0.8 mm.
- [9] Amorphous silica-alumina (N632L, Nikki Chemical Co.; SiO₂/Al₂O₃ molar ratio of 11/1, specific surface area 400 m² g⁻¹) was used after it had been pelletized to 0.3–0.8 mm.
- [10] γ -Alumina (N612N, Nikki Chemical Co.; specific surface area 200 m² g⁻¹) was used after it had been pelletized to 0.3–0.8 mm.
- [11] After 6 h reaction time under supercritical conditions the H-mordenite catalyst was still white and very active. In contrast, reaction in the gas phase resulted in immediate blackening and deactivation of the catalyst due to coking.
- [12] Effect of water: Water generated from methylation of **1** may possibly inhibit the reaction by competitive adsorption with the reactants on the catalyst surface. In fact, we found that the adsorption equilibrium constants (*K*) of CH₃OH and water are much larger than that of **1** by a simulation in the reaction kinetics by Langmuir–Hinshelwood mechanism, $K_{\text{CH}_3\text{OH}}/K_1 = 100$, $K_{\text{water}}/K_1 = 3000$. An increase in the portion of scCH₃OH by changing the molar ratio of CH₃OH to **1** at the same amine contact time (*W/F*) improved the reaction conversion and the space–time yields, which suggests that desorption of the generated water from the catalyst surface could be promoted by scCH₃OH.

An Asymmetric Phase-Transfer Dihydroxylation Reaction**

Riaz A. Bhunnoo, Yulai Hu, Dramane I. Lainé, and Richard C. D. Brown*

The asymmetric dihydroxylation of olefins using osmium tetroxide is a powerful process that has found widespread application in organic synthesis.^[1] Systems developed to date realize enantioinduction through the use of chiral ligands on

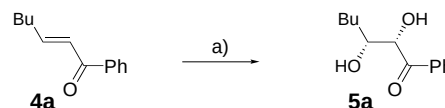
the osmium center,^[2] or chiral auxiliaries present in the substrate.^[3,4] Here we report a conceptually different approach to asymmetric dihydroxylation using permanganate in the presence of a chiral phase-transfer reagent.^[5,6] Recently, we reported the asymmetric oxidative cyclization of 1,5-dienes **1** by permanganate using a chiral phase-transfer catalyst (Scheme 1).^[5] Whereas the permanganate promoted



Scheme 1. Asymmetric oxidative cyclization of 1,5-dienes **1**. a) KMnO₄ (powder) (1.6 equiv), AcOH (6.5 equiv), **3** (0.1 equiv)/CH₂Cl₂, –30°C.

oxidative cyclization reaction of 1,5-dienes and the formation of α -ketols from olefins occur under slightly acidic conditions, permanganate oxidations conducted under basic conditions favor dihydroxylation.^[7] Therefore, permanganate oxidations using chiral phase-transfer agents in alkaline media should provide a new approach to asymmetric dihydroxylation.

Enones had been shown to undergo permanganate oxidative cyclization reactions to afford tetrahydrofuran diols **2** with good levels of enantioselectivity (Scheme 1),^[5,8] and were therefore chosen as substrates for initial dihydroxylation studies (Scheme 2). Oxidation of **4a** under liquid–liquid achiral phase-transfer conditions gave racemic diol **5a** as the major isolated product in reasonable yield (entry 1, Table 1). The majority of the remaining mass balance was accounted



Scheme 2. Phase-transfer promoted dihydroxylation of enone **4a**. For conditions and yields see Table 1.

Table 1. Phase-transfer (PT) promoted dihydroxylation of enone **4a** (see Scheme 2).^[a]

Entry	Method ^[b]	PT [equiv]	Time [min]	Yield of 5a [%] ^[c] [BRSM [%]]	ee ^[d] [%]
1	A	Adogen 464 (1.0)	45	55	N/A
2	A	3 (1.0)	45	41 [45]	47
3	B	3 (1.0)	30	41 [96]	63
4	B	3 (1.0)	60	51 [87]	62
5	B	3 (1.0)	180	27 [40]	62
6	B	3 (0.2)	420	33 [64]	63
7 ^[e]	B	3 (3.0)	60	30 [42]	61

[a] Reactions were conducted on a 0.37 mmol scale. [b] Method A: KMnO₄ (s) (0.37 mmol), CH₂Cl₂ (16 mL), pH 9 buffer (8 mL), 0°C. Method B: KMnO₄ (s) (1.5 equiv), CH₂Cl₂, –60°C. [c] Yields represent analytically pure isolated material. BRSM indicates the isolated yield based on recovered enone. [d] Enantiomeric excess was determined by HPLC using a CHIRALCEL OD-H column, hexane/iPrOH (80:20) eluent. *R*_t = 5.28 min (major), *R*_t = 6.24 min (minor). [e] Reaction carried out with three equivalents of KMnO₄.

[*] Dr. R. C. D. Brown, R. A. Bhunnoo, Dr. Y. Hu
Department of Chemistry
University of Southampton
Highfield, Southampton SO17 1BJ (UK)
Fax: (+44)23-80596805
E-mail: rcb1@soton.ac.uk

Dr. D. I. Lainé
GlaxoSmithKline
Medicines Research Centre
Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY (UK)

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for by benzoic acid, resulting from oxidative cleavage of **4a**. The same reaction using the chiral phase-transfer reagent **3** gave optically enriched diol **5a** with an encouraging level of enantioselectivity (47% *ee*) (entry 2, Table 1). Further improvement of the enantioselectivity (61–63% *ee*) was seen with the same substrate at lower temperature in solid-liquid phase-transfer reactions (entries 4–6, Table 1). The results show a relatively fast and clean dihydroxylation of the substrate after 30 and 60 min (yields based on recovered enone 96% and 87%, entries 3 and 4, Table 1). Prolonged reaction times led to lower yields, as did excess KMnO_4 and phase-transfer reagent (entries 5 and 7). It was observed that the cinchonidine-derived phase-transfer agent **3** was destroyed under the oxidation conditions, explaining its lack of catalytic activity. This finding is in contrast to the results obtained for the oxidative cyclization reaction where as little as 1–5 mol% of the quaternary ammonium salt has been employed.^[5]

A variety of other alkenes were subjected to the dihydroxylation conditions (Table 2; Scheme 3), with all the *para*-substituted arylenones **4b–h** affording diols with *ee* values superior (up to 80% *ee*) to the simple phenyl derivative **4a**. The absolute stereochemistry of the major enantiomer was determined from the X-ray crystal structure of the bromo derivative **5b**, crystallized to enantiomeric purity from hexane.^[9]

Preliminary efforts to extend the methodology to other types of olefins were less rewarding; a simple terminal olefin,

4-phenyl-1-butene, gave the corresponding diol without detectable *ee* and stilbene and chalcone gave over oxidation products. However, dihydroxylation of styrene did show a modest level of enantioselectivity, providing the (*S*)-diol with 17% *ee*.^[10] The diminished enantioselectivity for dihydroxylation of other olefin classes was not unexpected on the basis of the mechanistic rationale previously presented, where a strong interaction with the chiral quaternary ammonium salt is required in the transition state.^[5,6f]

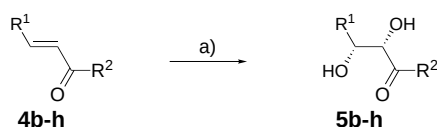
In conclusion, a new approach to asymmetric dihydroxylation of enones has been demonstrated. The initial enantioselectivities obtained are good, although relatively large quantities of the chiral quaternary ammonium salt are required. Efforts to apply other, more oxidatively robust phase-transfer agents and other metal–oxo species in the dihydroxylation reaction are currently underway in our laboratory.

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Table 2. Asymmetric phase-transfer promoted dihydroxylation of enones **4b–h** (see Scheme 3).^[a]

Entry	R ¹	R ²	Time [min]	Yield [%] ^[b] [BRSM [%]]	<i>ee</i> ^[d] [%]
1	<i>n</i> Bu	(<i>p</i> -Br) C_6H_4	60	52 [59]	77
2	<i>n</i> Bu	(<i>p</i> -Cl) C_6H_4	60	32 [64]	77
3 ^[c]	<i>n</i> Bu	(<i>p</i> -F) C_6H_4	180	25	67
4	<i>n</i> Bu	(<i>p</i> -OMe) C_6H_4	90	34 [61]	80
5	<i>n</i> Bu	(<i>p</i> -Me) C_6H_4	60	40 [93]	75
6	Et	Ph	60	19 [37]	65
7 ^[e]	<i>i</i> Pr	Ph	60	28 [59]	67

[a] Reactions were conducted on a 0.26–0.37 mmol scale using one equivalent of **3** and 1.5 equivalents of KMnO_4 at -60°C except for entry 3. [b] Yields represent analytically pure isolated material. BRSM is the yield calculated based on recovered starting material. [c] Reaction mixture warmed to -25°C . [d] Enantiomeric excess was determined by HPLC using CHIRALCEL OD-H or OB-H columns, hexane/*i*PrOH eluent. [e] Enantiomeric excesses of compounds **4c** and **4d** were determined by conversion to the corresponding cyclic carbonates, which were resolved on a CHIRALCEL OD-H column (hexane/*i*PrOH, 90:10).^[11]



4b/5b $\text{R}^1 = n\text{Bu}$, $\text{R}^2 = p\text{-BrC}_6\text{H}_4$; **4c/5c** $\text{R}^1 = n\text{Bu}$, $\text{R}^2 = p\text{-ClC}_6\text{H}_4$;
4d/5d $\text{R}^1 = n\text{Bu}$, $\text{R}^2 = p\text{-FC}_6\text{H}_4$; **4e/5e** $\text{R}^1 = n\text{Bu}$, $\text{R}^2 = p\text{-MeOC}_6\text{H}_4$;
4f/5f $\text{R}^1 = n\text{Bu}$, $\text{R}^2 = p\text{-MeC}_6\text{H}_4$; **4g/5g** $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Ph}$;
4h/5h $\text{R}^1 = i\text{Pr}$, $\text{R}^2 = \text{Ph}$.

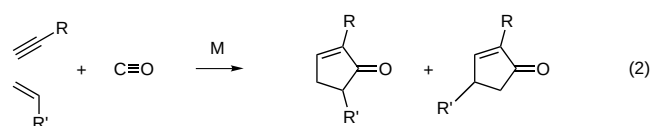
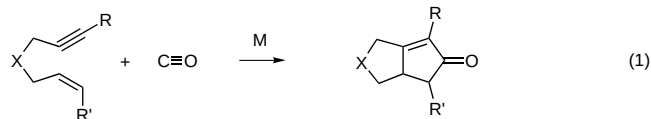
Scheme 3. Asymmetric phase-transfer promoted dihydroxylation of enones **4b–h**. a) KMnO_4 (powder) (1.2–1.5 equiv), **3** (1.0 equiv)/ CH_2Cl_2 , -60°C .

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A Pyridylsilyl Group Expands the Scope of Catalytic Intermolecular Pauson–Khand Reactions**

Kenichiro Itami,* Koichi Mitsudo, and Jun-ichi Yoshida*

The [2+2+1] cycloaddition of alkyne, alkene, and carbon monoxide mediated or catalyzed by a transition metal M, which is known as the Pauson–Khand reaction (PKR),^[1] has received particular attention in organic synthesis, since it allows the construction of biologically interesting five-membered carbocycles in a convergent manner. Although tremendous progress has been seen for the catalytic *intramolecular* PKR [Eq. (1)] and many reactions have been reported,^[1] the

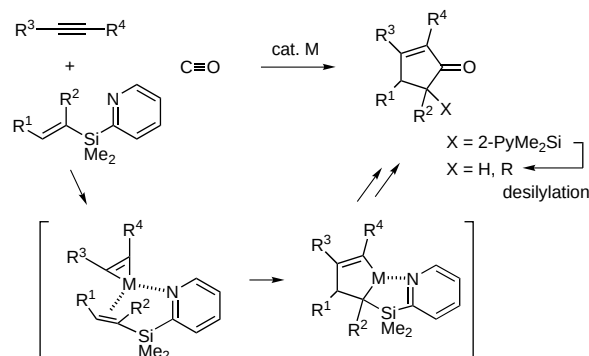


development of an efficient and general procedure for a catalytic *intermolecular* PKR [Eq. (2)] lags far behind.^[1,2] In particular, the limitations imposed on the alkene counterpart are serious: 1) No catalytic intermolecular PKR has been reported yet for simple alkenes (the reactions are restricted to ethylene gas and strained alkenes),^[2] and 2) in a stoichiometric PKR, simple alkenes exhibit low reactivity and regioselectivity.^[1,3] This may be due to the low coordinating ability of alkenes in comparison with alkynes and carbon monoxide.

Although such problems might be overcome by incorporating a coordinating heteroatom tethered to the alkenes,^[4,5] the removal of such a directing group after the PKR is strongly desirable from a synthetic point of view. Therefore, the utilization of a removable directing group^[6] is expected to enhance the synthetic potential of the catalytic intermolecular PKR by eliminating the problems associated with reactivity and regioselectivity issues of the alkene.

Our recent demonstration that the dimethyl(2-pyridyl)silyl (2-PyMe₂Si) group serves as an excellent, removable directing group in a number of metal-catalyzed reactions^[7,8] led us to investigate the possibility of alkenyldimethyl(2-pyridyl)silane

as a substrate for a catalytic intermolecular PKR. The oxidative cyclization of alkyne, alkene, and metal can be regarded as a carbometalation of an (alkyne)metal complex across an alkene.^[9] Therefore, we expected the facile and regioselective formation of a metallacyclopentene intermediate owing to the coordination effect of the pyridyl group on silicon (Scheme 1). We have already established the high



Scheme 1. The catalytic intermolecular Pauson–Khand reaction directed by a pyridylsilyl group.

reactivity of alkenyldimethyl(2-pyridyl)silanes in several carbometalation processes.^[7b,f,10] Moreover, the resultant 2-PyMe₂Si-substituted cyclopentenone should be easily converted into the Si-free derivative by using various desilylation methods that we developed.^[11]

We first screened for a catalyst for the intermolecular PKR using dimethyl(2-pyridyl)(vinyl)silane (**1a**). Among various metal complexes (Ti, Fe, Co, Mo, Ru, Rh, Pd, Ir, and Pt), [Ru₃(CO)₁₂] was found to catalyze this process.^[12,13] The reaction of **1a** (1.0 equiv), phenylacetylene (**2a**, 1.5 equiv), and carbon monoxide (1 atm) at 100°C in toluene in the presence of [Ru₃(CO)₁₂] (5 mol %) gave the desilylated cyclopentenone **3aa**, which was isolated in 55 % yield with virtually complete regioselectivity (Table 1, entry 1).^[14] The trend in regioselectivity (the Ph group is in the position α to the carbonyl group) is in line with that observed in the stoichiometric PKR.^[1] The realization of a catalytic intermolecular PKR without the need for a high pressure of carbon monoxide is particularly noteworthy. Under the identical conditions, no reaction occurred when dimethylphenyl(vinyl)silane was used in place of **1a**, which clearly implicates the strong directing effect of the pyridyl group. This is not only an example of the successful utilization of vinylsilane as an alkene counterpart in a catalytic intermolecular PKR,^[15] but also a demonstration that **1a** could serve as a nongaseous ethylene equivalent in this reaction.^[16]

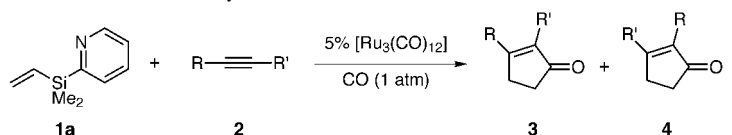
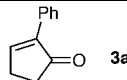
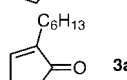
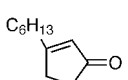
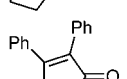
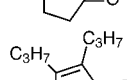
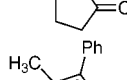
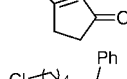
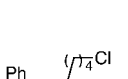
When the alkyl-substituted alkyne **2b** was employed, a substantial decline in regioselectivity was observed (Table 1, entry 2). Symmetrical internal alkynes also participate in the catalytic intermolecular PKR with reasonable efficiency. When 1-phenylpropyne (**2e**) was used, cyclopentenone **3ae** was obtained with virtually complete regioselectivity (entry 5). However, when the chloro-substituted alkyne **2f** was allowed to react, there was a substantial decline in the regioselectivity (entry 6). Since **2e** and **2f** are sterically and

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

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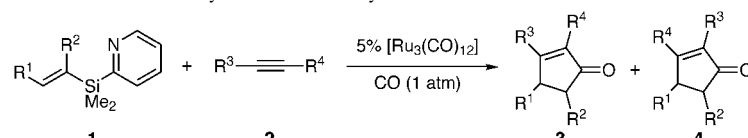
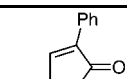
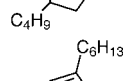
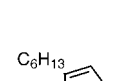
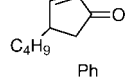
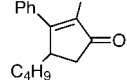
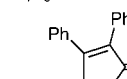
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Table 1. Catalytic intermolecular PKR of **1a** and various alkynes **2**.^[a]

			
Entry	2	Products	Yield [%] (3/4)
1	2a (R = H, R' = Ph)	 3aa	55 (100/0) ^[b,c]
2	2b (R = H, R' = C ₆ H ₁₃)	 3ab  4ab	91 (59/41) ^[b]
3	2c (R = R' = Ph)	 3ac	88 ^[d]
4	2d (R = R' = C ₃ H ₇)	 3ad	59 ^[d]
5	2e (R = CH ₃ , R' = Ph)	 3ae	75 (100/0) ^[b,c]
6	2f (R = (CH ₂) ₄ Cl, R' = Ph)	 3af  4af	67 (87/13) ^[d]

[a] Reaction conditions: **1a** (0.50 mmol), **2** (0.75 mmol), [Ru₃(CO)₁₂] (0.025 mmol), CO (1 atm), solvent (1.5 mL). [b] Reaction at 100 °C in toluene. [c] Compound **4** was not detected by NMR spectroscopy and GC analysis. [d] Reaction at 120 °C in xylenes.

Table 2. Catalytic intermolecular PKR of substituted vinylsilanes **1** and alkynes **2**.^[a]

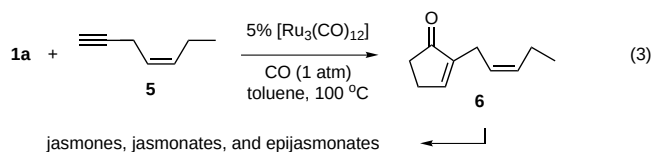
			
1	2	Products	Yield [%] (3/4)
1b (R ¹ = C ₄ H ₉ , R ² = H)	2a (R ³ = H, R ⁴ = Ph)	 3ba	41 (100/0) ^[b,c]
1b (R ¹ = C ₄ H ₉ , R ² = H)	2b (R ³ = H, R ⁴ = C ₆ H ₁₃)	 3bb  4bb	55 (89/11) ^[d]
1b (R ¹ = C ₄ H ₉ , R ² = H)	2c (R ³ = R ⁴ = Ph)	 3bc	44 ^[b]
1c (R ¹ = (CH ₂) ₄ OMe, R ² = H)	2c (R ³ = R ⁴ = Ph)	 3cc	48 ^[b]
1d (R ¹ = H, R ² = CH ₃)	2b (R ³ = H, R ⁴ = C ₆ H ₁₃)	 3db  4db	40 (62/38) ^[e]

[a] Reaction conditions: **1** (0.50 mmol), **2** (0.75 mmol), [Ru₃(CO)₁₂] (0.025 mmol), CO (1 atm), solvent (1.5 mL). [b] Reaction at 140 °C in xylenes. [c] Compound **4** was not detected by NMR spectroscopy and GC analysis. [d] Reaction at 100 °C in toluene. [e] Reaction at 120 °C in xylenes.

electronically similar, the observed differences in regioselectivity may be due to the directing effect of chloride, which has been occasionally observed in Ru and other metal complexes.^[17]

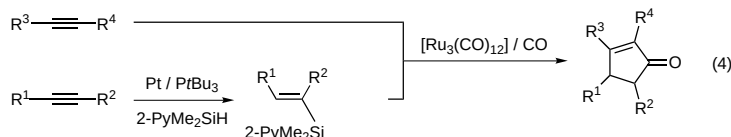
We next turned our attention to the synthesis of more highly substituted cyclopentenones by employing substituted vinylsilanes (Table 2). The advantage of our system is that the use of α - or β -substituted vinylsilanes (**1b–d**)^[18] results in the regioselective production of substituted cyclopentenones with the substituent at the 5- or 4-position, respectively. In all cases, virtually complete regioselectivity with regard to the alkene subunit was observed. Thus, these substituted vinylsilanes not only serve as surrogates for terminal alkenes that cannot be applied in the previously reported catalytic PKR, but also enable the complete regioselective incorporation of the alkene subunit into the cyclopentenone skeleton. Although converting the 2-PyMe₂Si group into functional groups other than a hydrogen atom is not feasible at this stage, the present observations clearly demonstrate the power and usefulness of using the 2-PyMe₂Si group as a removable directing group in the catalytic intermolecular PKR.

Our catalytic intermolecular PKR should be a straightforward approach toward the synthesis of natural and nonnatural cyclopentanoid products. For example, cyclopentenone **6**, which has emerged as an excellent precursor for the synthesis of jasmones,^[19] methyl jasmonate,^[19] and methyl epijasmonate,^[19] can be prepared in a single chemical operation from **1a** and enyne **5** [Eq. (3); 60 % yield, 63 % regioselectivity].^[20]



Moreover, the synthesis of rosaprostol,^[21] tetrahydrodicranone B,^[21] equilenins,^[22] or, more importantly, prostaglandins^[23] should be also possible starting from a suitably substituted 2-cyclopentenone that can, in principle, be prepared by our catalytic intermolecular PKR methodology.

In conclusion, we have developed an efficient procedure for the catalytic, intermolecular, and regioselective PKR of unstrained alkenes by utilizing a 2-PyMe₂Si group as a removable directing group. Multisubstituted 2-cyclopentenones can now be analyzed retrosynthetically, as in Equation (4). The advantages of our strategy are that 1) it allows a



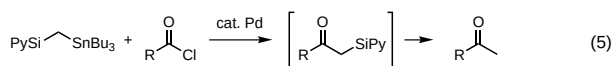
formal catalytic intermolecular PKR using simple alkenes, which was previously difficult to achieve; 2) it allows a complete regioselective incorporation of a substituent at the 4- or 5-position of the 2-cyclopentenone skeleton simply by choosing the position of the substituent in the starting alkenylsilane; 3) the position of the C=C bond can be

strategically altered by simply changing the alkyne subunit to be hydrosilylated prior to the intermolecular PKR;^[18] and 4) all the substituents arise from substituents on alkyne subunits which can be easily altered. Thus, this new strategy offers a general approach to a diverse range of cyclopentenoid structures and should find further applications in organic synthesis.

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DNA-Mediated Electron Transfer across Synthetic T:A·T Triplex Structures**

Frederick D. Lewis,* Yansheng Wu, Ryan T. Hayes, and Michael R. Wasielewski*

Oligonucleotides which contain three sequences capable of triplex formation, and which are connected with appropriate linkers, can fold into intramolecular triplex structures.^[1] Both natural and synthetic linkers have been used to assemble intramolecular T:A·T triplexes in which poly(T:A) forms a normal Watson–Crick duplex and the third strand (polyT) is parallel to the polyA sequence and associated by Hoogsteen hydrogen bonding (Figure 1a,b).^[2–4] The conformation of intermolecular poly(T:A·T) triplexes is similar to that of duplex B-DNA with a π -stacking distance of 3.3 Å and a helical pitch of 28°. We report here the preparation of the donor–acceptor intramolecular triplex DNA structures **1–5** which possess a stilbenedicarboxamide derivative (**Sa**) as an electron-acceptor linker and a stilbenediether derivative (**Sd**) as an electron-donor linker (Figure 1c,d). The two chromophores undergo intramolecular, photoinduced electron transfer across the π -stacked triplets by single-step tunneling (for **1–4**) and multistep hopping (for **5**) pathways.

The conjugates **1–5** were prepared by conventional phosphoramidite methods as previously described for the preparation of **Sa**- and **Sd**-linked hairpins.^[5,6] The 3'-3' linkages between the Watson–Crick T:A hairpin sequence and the Hoogsteen-bound polyT were formed by 5' solid-phase oligonucleotide synthesis. The absorption spectra of conjugates **1–5** consist of a broad, long wavelength band with a maximum at 340 nm that is attributed to the overlapping absorptions of the **Sa** and **Sd** chromophores and a band at 260 nm attributed to absorption of these chromophores and the nucleobases.^[7] The thermal dissociation profiles are independent of concentration and display melting transitions at between 60–71 °C, which are attributed to melting of the **Sd**-capped **Sa**-linked Watson–Crick duplex, and premelting behavior at lower temperatures, which is attributed to melting of the Hoogsteen base pairs.^[8]

The fluorescence spectra of the conjugates **1–5** are similar to those of **Sa**-linked hairpins such as **6**.^[5] The **Sa**-linked poly(T:A) hairpins are strongly fluorescent, whereas the **Sd**-linked hairpins are very weakly fluorescent, as a consequence of quenching of the singlet form of **Sd** by neighboring thymine.^[6] The fluorescence intensity of **1–5** is strongest when

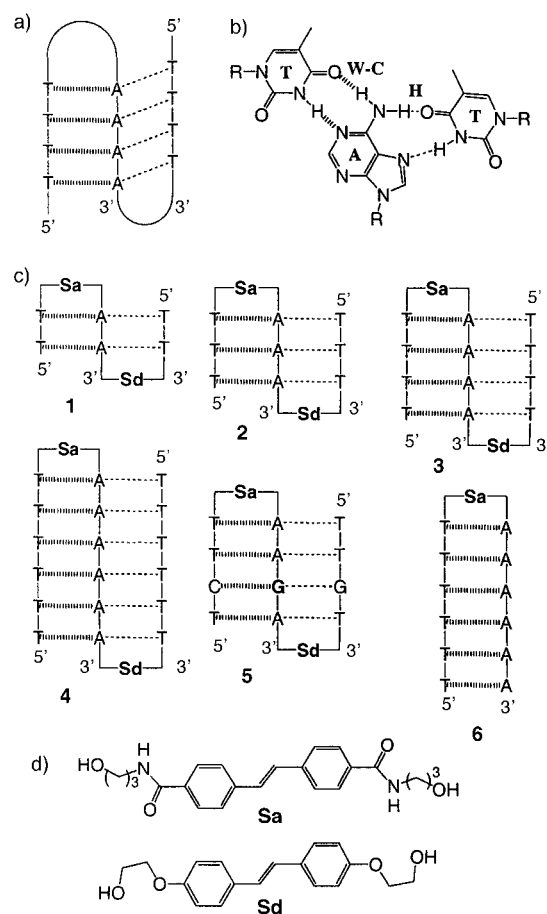


Figure 1. a) Structure of an intramolecular antiparallel DNA triplex with Watson–Crick (W–C |||||) and Hoogsteen (H ----) hydrogen bonding; b) structure of the T:A·T canonical triplet; c) structure of intramolecular triplexes **1–5** and hairpin **6**; d) structures of the **Sa** and **Sd** linkers.

excited in the red edge of the 340 nm absorption band, where **Sa** absorbs more strongly than **Sd**. The value of Φ_f for conjugates **1–4** decreases as the number of T:A·T steps separating the **Sa** and **Sd** chromophores decreases (Table 1),^[7] in accord with an electron-transfer mechanism for fluorescence quenching of **Sa** by **Sd**. The free energy of the photochemical electron transfer process can be estimated using Weller's equation [$\Delta G_{et} = -(E_s + E_{rdn}) + E_{ox}$], using the **Sa** singlet excitation energy ($E_s = 3.35$ V) and ground-state reduction potential $E_{rdn} = -1.91$ V (vs. SCE in DMF solution) and the **Sd** oxidation potential ($E_{ox} = 0.92$ V).^[5,6] The resulting value of $\Delta G_{et} = -0.52$ eV shows that this reaction is more exergonic than quenching of **Sa** by G ($\Delta G_{et} = -0.20$ eV).

Normalized time-resolved transient absorption spectra of conjugate **1** are shown in Figure 2. The spectrum observed 5 ps after excitation at 360 nm (absorbed predominantly by **Sa**) is assigned to **Sa*** (575 nm maximum and 625 nm shoulder). At longer delay times the shoulder at 625 nm disappears and maxima are observed at 525 and 575 nm, assigned to **Sd**⁺ and **Sa**[−], respectively.^[5] The 575 nm decays of **1–5** display fast (ps to ns) and slow (ns to μ s) components, which are assigned to decay of **Sa*** and **Sa**[−], respectively (Table 1). The 525 nm decay of **1** displays both rising and falling components with time constants similar to those for the two 575 nm components and assigned to the formation and

[*] Prof. F. D. Lewis, Prof. M. R. Wasielewski, Dr. Y. Wu, R. T. Hayes
Department of Chemistry
Northwestern University
Evanston, IL 60208-3113 (USA)
Fax: (+1) 847-467-2184
E-mail: lewis@chem.northwestern.edu
wasielew@chem.northwestern.edu

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Table 1. Fluorescence quantum yields and transient decay times for conjugates 1–6.^[a]

Conjugate	$\Phi_f^{[b]}$	τ_{ss} , ps ([%]) ^[c,d]	$k_{cs} \times 10^{-9}$ [s ⁻¹] ^[e]	τ_{575} [ns] ([%]) ^[d,f]	τ_{525} [ns] ^[g]	$k_{cr} \times 10^{-7}$ [s ⁻¹] ^[h]
1	0.06	75 (30)	13	8.4 (70)	8.2 ^[i]	12
2	0.18	280 (49)	3.1	127 (51)	145	7.4
3	0.32	540 (55)	1.3	5800 (45)	8200	0.14
4	0.31	1800 (100)	0.5	[j]	[j]	
5	0.08	141 (37)	6.6	800 (25)		0.15 ^k
6	0.38	2000 (100)		6700 (38)		

[a] Data for approximately 10^{-6} M solutions in standard buffer (0.1 M NaCl, 10 mM sodium phosphate, pH 7.2). [b] Fluorescence quantum yields determined by comparison to quinine sulfate. Limits of error for multiple detection $\pm 10\%$. [c] Decay of the singlet state determined at 575 nm, estimated error $\pm 10\%$ of the reported value. [d] Amplitudes for 575 nm decay in parentheses. [e] Rate constant for charge separation, $k_{cs} = \tau_{obs}^{-1} - \tau_6^{-1}$. [f] Decay component assigned to charge recombination of $Sa^{\bullet-}$. [g] Decay component assigned to charge recombination of $Sd^{\bullet+}$. [h] Rate constant for charge recombination, $k_{cr} = \tau_{obs}^{-1}$. Average of 575 and 525 nm values where available. [i] Rising component with $\tau = 94$ ps also resolved. [j] No long-lived transient resolved. [k] Estimated from the long-lived 575 nm decay component.

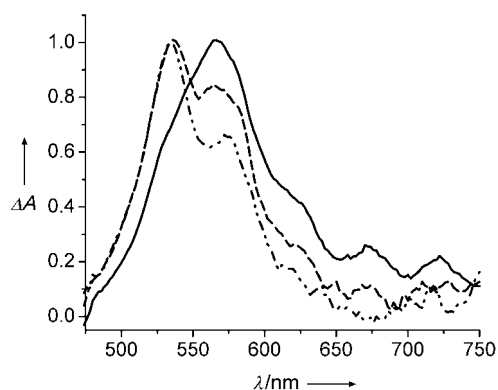
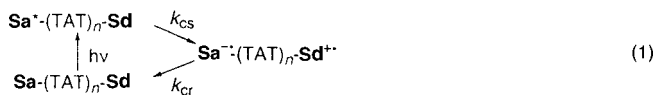


Figure 2. Normalized transient absorption spectra for conjugate 1 obtained at delay times of 5 ps (—), 100 ps (---), and 1 ns (···) following excitation at 360 nm with a 0.13 ps laser pulse.

decay of $Sd^{\bullet+}$,^[6] respectively. The formation and decay of $Sa^{\bullet-}$ and $Sd^{\bullet+}$ is attributed to charge separation and charge recombination (k_{cr} and k_{cs} , respectively) through single-step electron tunneling across a bridge consisting of T:A·T triplet steps [Eq. (1)].



Plots of $\ln(k_{cr})$ and $\ln(k_{cs})$ versus the donor–acceptor distance (R_{DA}) for conjugates 1–4 are shown in Figure 3, along with data for quenching of Sa by G in Sa -linked hairpin molecules containing a single C:G base pair.^[5] The slopes of these plots provide values of β [$k_{cs} = A \exp(-R_{DA}\beta)$], where R_{DA} is the distance between the donor and acceptor. The value of β obtained for triplex charge separation is smaller than that for duplex hairpin charge separation ($\beta = 0.39$ vs. 0.64 Å^{-1}), whereas the values of β for charge recombination are similar for the triplex and duplex ($\beta = 1.0$ vs. 0.94 Å^{-1}).^[9] The magnitude of β is determined by the energy gap between

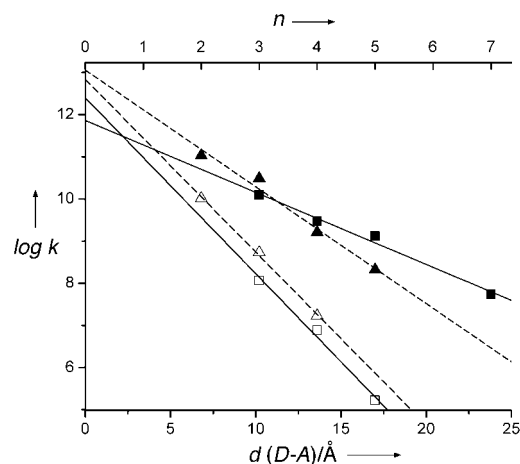


Figure 3. Distance dependence (n is the number of base triplets separating the donor and acceptor) of the rate constants obtained from transient absorption data for charge separation (filled symbols) and charge recombination (open symbols) from triplex (squares) and hairpin (triangles) conjugates.

the donor and bridge states (ΔE eV) and the time after mixing elements (t_{mn}) between bridge states ($\beta = (2R_0) \ln |\Delta E/t_{mn}|$).^[10,11] The shorter distance between steps in triplex versus duplex DNA (3.3 vs. 3.4 Å) should result in increased mixing. In addition, increased hydrogen bonding in the triplex versus duplex should lower the oxidation potential of adenine in the bridging T:A·T triples.^[12] Both factors could contribute to the decrease in β for triplex versus duplex charge separation. However, a decrease in the energy of the charge-separated state for $Sa^{\bullet-}/Sd^{\bullet+}$ versus $Sa^{\bullet-}/G^{\bullet+}$ may compensate for increased mixing in the triplex, resulting in similar values of β for charge recombination in the triplex and duplex systems.

Conjugate 5 possesses a C:G·G triplet positioned between the Sd and Sa linkers. The value of k_{cs} obtained for 5 from the 575 nm ps decay is larger than that for 3, in accord with primary electron transfer from G to $Sa^{\bullet+}$. The curve of decay of the radical ions is best fit by a biexponential function with decay times of 0.8 and $6.7 \mu s$, which is attributed to charge recombination of the primary $Sa^{\bullet-}/G^{\bullet+}$ radical ion pair and of the $Sa^{\bullet-}/Sd^{\bullet+}$ secondary radical-ion pair formed by exergonic hole transport from $G^{\bullet+}$ to Sd .^[13–15] The long decay time for 5 is similar to that for an Sa -linked hairpin with an Sa -AAGAZA (Z = deazaguanine) hole-hopping sequence. The oxidation potentials of Sd and Z are similar and thus both systems will have similar values of ΔG_{cr} .

In summary, we have, for the first time, characterized both the radical anion and radical cation products of photoinduced electron transfer mediated by DNA. Long-range single-step electron transfer is rapid for triplex than duplex DNA, plausibly because of the shorter π -stacking distance and lower energy of the T:A·T versus T:A bridging states. The value of $\beta = 0.39 \text{ Å}^{-1}$ for charge separation is the smallest value yet determined from the direct measurement of distance-dependent dynamics. In the case of conjugate 5, formation of a long-lived charge-separated state occurs by a hole-transport mechanism in which G and Sd serve as the primary and secondary hole acceptors, respectively. Introduction of multiple hopping sites should facilitate efficient charge transfer between Sa and Sd linkers across long triplex sequences.

Supporting Information available: Ultraviolet absorption and fluorescence spectra of the conjugates and representative transient absorption spectra and transient decays.

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Electrocatalytic O₂ Reduction by Synthetic Analogues of the Heme/Cu Site of Cytochrome Oxidase Incorporated in a Lipid Film**

James P. Collman* and Roman Boulatov

Over 95 % of dioxygen consumed by an aerobe is used in respiration,^[1] whereby O₂ is reduced by four electrons (4e) to two molecules of H₂O. In most aerobes the reduction occurs at a heterodimetallic Fe/Cu site (Figure 1A) of membrane-bound heme/Cu terminal oxidases (cytochrome c or ubiquinol

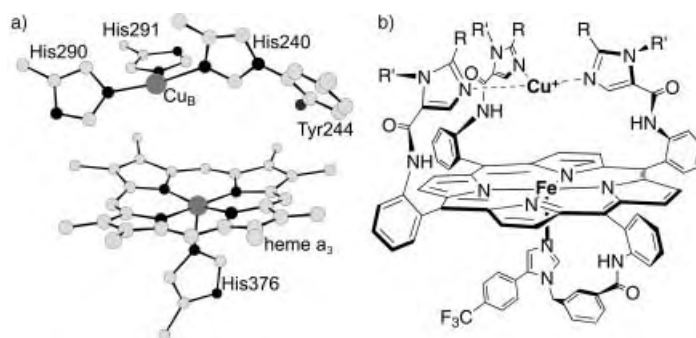
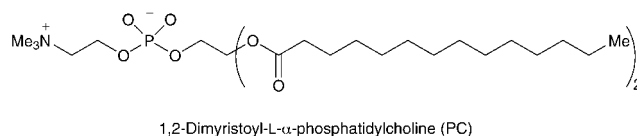


Figure 1. A) The heme/Cu site of bovine cytochrome oxidase;^[5] the C atoms are light gray and the N and O atoms are black. B) The catalysts in the reduced form without probable exogenous ligands^[6] (the NH series: R = Pr, R' = H; the NMe series: R = H, R' = CH₃).

oxidases).^[2,3] Coupling of this exergonic reaction to proton translocation against the electrochemical transmembrane gradient^[2,4] maintains the proton-motive force that drives ATP synthesis.

The O₂-reducing heme/Cu site has long been a target for biomimetic chemists.^[7] A number of synthetic Fe porphyrins with various degrees of structural similarity to the heme/Cu site when adsorbed on a graphite electrode catalyze the electrochemical 4e reduction of O₂, although rarely at physiological potentials (namely those of cytochrome c and ubiquinol). Electrocatalytic O₂ reduction is the only known method to probe the reactivity of synthetic heme/Cu analogues under catalytic and biologically relevant conditions. This technique is conceptually similar, and in some respects superior, to spectrophotometric and polarographic assays traditionally used to quantify the activity of cytochrome oxidase.^[8] Previously, biomimetic O₂ reduction have been probed only by electrode-adsorbed heme/Cu mimics. However, studies of adsorbed heme/Cu analogues, while experimentally simple, limits the potential of such systems to unravel the structure/function relationship within this enzymatic site, and thus to contribute to understanding the enzyme. Firstly, cytochrome oxidase reduces O₂ under diffusion-limited electron delivery, whereas the electron-transfer rate to an electrode-adsorbed catalyst usually far exceeds the catalytic turnover frequency (TOF). Secondly, the high concentration of redox sites in films of adsorbed catalysts creates an environment which both differs notably from that of a protein matrix and depends strongly on the overall redox state of the film.^[6b]

Herein we report on electrocatalytic O₂ reduction by a series of synthetic heme/Cu analogues (Figure 1B) incorporated into a matrix of 1,2-dimyristoyl-L- α -phosphatidylcholine (PC), which is a major constituent of mitochondrial mem-



1,2-Dimyristoyl-L- α -phosphatidylcholine (PC)

branes. Among the known synthetic porphyrins, those employed in the present study most faithfully mimic the heme/Cu site.^[6] High dilution of the redox centers by, and relatively

[*] Prof. J. P. Collman, R. Boulatov
Department of Chemistry
Stanford University
Stanford CA 94305 (USA)
Fax: (+1) 650-7250259
E-mail: jpc@stanford.edu

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facile diffusion of the catalysts in, PC films eliminates complications associated with the use of adsorbed catalysts and permits biomimetic reduction of O_2 under more biological conditions of diffusion-limited electron flux to isolated catalytic sites.

Among several matrixes screened only PC was found suitable.^[9,10] In all the experiments performed the amount of PC at the electrode surface was identical (375 nmol cm^{-2}), with a catalyst loading between 3 and 0.7 mol %.

The electrochemical behavior of the catalysts in the PC matrix under anaerobic conditions was studied by cyclic voltammetry. Diffusion-limited charging of the catalyst/PC film is evident from the downward curvature of the peak current (i_p) versus scan rate (v) graph (Figure 2A)^[11] at $v > 5 \text{ mV s}^{-1}$. The constant peak separation ($\Delta E_p \sim 70 \text{ mV}$)^[9] at scan rates faster than 100 mV s^{-1} indicates facile heterogeneous electron transfer between the catalyst and the electrode. As expected in thin-layer voltammetry,^[12] the ΔE_p value approaches 0 V at slow scan rates.^[9] This observation suggests that the redox state of the catalyst in a PC matrix does not significantly affect the film's morphology and/or ionic composition, an effect that accounts for the scan-rate-independent non-zero peak separation of an adsorbed catalyst (Figure 2B).^[13]

Reduction of O_2 by catalyst/PC films was studied by rotating ring-disk voltammetry^[12] (RRDV) in pH 7 buffered aqueous electrolytes saturated with air. The catalyst/PC film was deposited on an edge-plane graphite disk, whose potential was scanned. The Pt ring electrode was set at a sufficiently oxidizing potential so that any H_2O_2 released by the catalytic film would be oxidized and generate a ring current (Figure 3). Catalysis starts at about 250 mV, which is comparable to the Fe^{III}/Fe^{II} potential observed under anaerobic conditions (Figure 2B). Application of a more reducing potential than -100 mV increases the catalytic currents. This result indicates that the overall rate of O_2 reduction in this regime is limited by a redox-based process, which becomes more facile at lower potentials. At E_{disk} values less than -100 mV the current reaches a plateau, thus revealing a change of the turnover-determining step (TDS) to a nonredox process. The zero ring current (the lower trace) throughout the potential range demonstrates that the FeCu/PC film does not release detectable amounts of H_2O_2 into the electrolyte (the fraction of the 4e pathway exceeds 99 %).

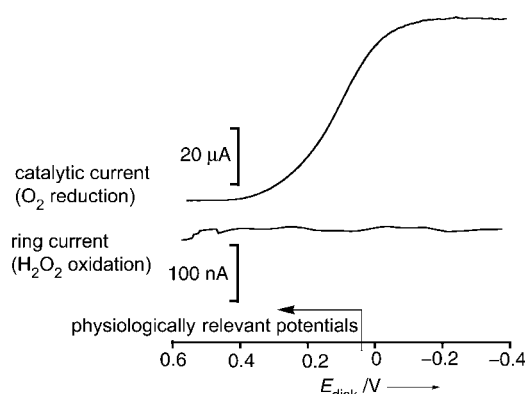


Figure 3. A linear sweep voltammogram of the FeCu catalyst (3 % mol)/PC film in an air-saturated electrolyte at the electrode rotation frequency (ω) of 200 rpm. The ring collection efficiency 15 %.^[9] Note the different scale for the ring and disk (catalytic) currents. Physiological potentials are determined by the midpoint potentials of the physiological reductants of terminal oxidases, cytochrome c (ca. 200 mV) and ubiquinol (ca. 50 mV).

The catalytic currents i_{cat} at physiological potentials are independent of O_2 flux, which was modulated by changing the electrode rotation frequency ω (Figure 4) or the bulk O_2

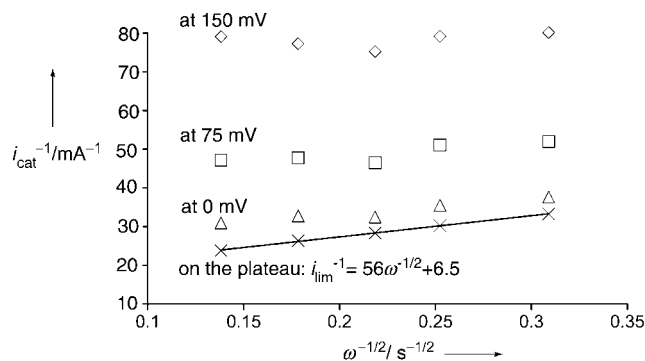


Figure 4. Dependence of the catalytic currents i_{cat} on O_2 flux (controlled by the electrode rotation frequency ω) as a function of the applied potential.^[9] The solid line is a linear least-squares fit to the equation shown.

concentration. Such independence is a commonly used criterion for a charge-transfer-limited catalytic rate.^[14] Consistent with this assertion is the fact that the i_{cat} values in this regime ($\leq 100 \mu\text{A cm}^{-2}$) are comparable to the independently measured rate of charge propagation through the film under a similar potential gradient (for example, $70 \mu\text{A cm}^{-2}$ at 150 mV).^[9] Hence, at potentials above about 75 mV the reduction of O_2 by our biomimetic assembly proceeds under diffusion-limited electron flux.

The linear dependence of the inverse limiting (plateau) currents i_{lim}^{-1} on $\omega^{-1/2}$ indicates that TOF is no longer charge-transfer limited at potentials below -100 mV . As a result, the slope of the i_{lim}^{-1} versus $\omega^{-1/2}$ graph provides a means of assessing the redox stoichiometry of the catalysis. This slope is similar to that measured for O_2 reduction on Pt, and is half the slope for O_2 reduction on graphite.^[9] This observation confirms the RRDV measurements (Figure 3) that show the catalyst/PC film does not release significant amounts of partially reduced oxygen species. Since the maximum TOF of the catalyst/PC system (the inverse intercept of the i_{lim}^{-1}

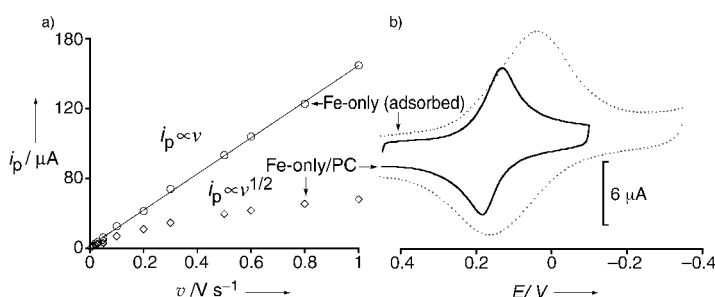


Figure 2. The electrochemical behavior under N_2 of the Fe-only catalyst in a PC film (0.7 % mol) and the same amount of the catalyst adsorbed on graphite (2.5 nmol cm^{-2}): A) peak current i_p versus scan rate v ; B) cyclic voltammograms ($v = 50 \text{ mV s}^{-1}$; all potentials are versus the normal hydrogen electrode, NHE).

versus $\omega^{-1/2}$ graph, ca. 0.7 mA cm^{-2}) is comparable to the rate of substrate transfer within the PC film (ca. 0.8 mA cm^{-2}),^[9] the latter process is the plausible TDS at the plateau.^[14] In contrast, the TOF of an electrode-adsorbed catalyst is limited by the rate of the catalytic cycle, not charge or substrate transfer, at all potentials.^[6b]

As expected for catalysis under limited electron availability, the PC-dispersed catalyst degrades more than 100 times faster than the electrode-adsorbed analogue during O_2 reduction at 100 mV. Intra- or intermolecular oxidation of the organic ligand is likely in a PC matrix when other reductants (Fe^{II} , Cu^{I} , or the electrode) are inaccessible to complete the O_2 reduction cycle. Indeed, the very low stability of the Cu-free, NMeFe-only catalyst in the PC matrix appears to account for the lack of a well-defined catalytic wave in this system.^[9] This result contrasts with only minor differences in the catalytic properties of the FeCu and Fe-only complexes adsorbed on the electrode.^[6b]

In summary we presented a biomimetic system that reproduces a key aspect of terminal oxidases reactivity. The synthetic heme/Cu analogue dispersed in a PC matrix catalyzes O_2 reduction: 1) at physiological potentials, 2) under diffusion-limited electron flux, and 3) without releasing partially reduced oxygen by-products into the bulk medium. In contrast to electrode-adsorbed systems,^[6b] notable differences in the catalytic behavior of the FeCu and Cu-free analogues in a PC matrix illustrate the benefit engendered by an additional readily accessible reductant (Cu^{I}) within the catalyst molecule. This system mimics the proposed role of Cu_B as an electron reservoir at the catalytic site. The use of a PC matrix should allow meaningful studies of the catalytic properties, under steady-state turnover, of heme/Cu analogues containing a phenol moiety. In cytochrome oxidase, a tyrosine residue (Tyr244 in Figure 1 A) is involved in catalysis when the availability of electrons is limited^[15] (for example, O_2 reduction by a mixed-valence enzyme). Whereas such conditions are inaccessible for an electrode-adsorbed functional analogue, they are realized for a PC-dispersed complex.

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Taking Nanocasting One Step Further: Replicating CMK-3 as a Silica Material



An-Hui Lu, Wolfgang Schmidt, Akira Taguchi, Bernd Spliethoff, Bernd Tesche, and Ferdi Schüth*

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

The replication of nanoscale structures by a direct templating process has been used in recent years in several creative ways for the synthesis of carbon replicas of zeolites^[1] or ordered mesoporous carbons, such as CMK-1^[2] or SNU-1.^[3] Such processes rely on the fact that an ordered pore system, provided by the zeolite or ordered mesoporous silica, can be filled with a carbon precursor which is pyrolyzed and the silica leached with NaOH or HF solution. However, the technique is difficult to apply to the synthesis of framework compositions other than carbon, since the leaching of the silica typically also affects the material which is filled into the silica pore system. This problem could possibly be circumvented by not using the silica as the mold, but to instead go one step further and use the mesoporous ordered carbons as templates, which could then easily be removed by combustion or other techniques, as suggested recently.^[4] On the macroscale, that is, for the production of photonic crystals, similar approaches are well known, where latex spheres are used as templates which can be removed by calcinations.^[5] Also carbon black has been used as a “template”, for instance to synthesize mesoporous zeolite single crystals, in which the pores, however, are disordered.^[6]

In a first attempt to show the feasibility of using ordered mesoporous carbon to synthesize ordered mesoporous oxides, we decided to template mesostructured silica by using an ordered mesoporous carbon. Although this brings one only back to the starting point, that is, a mesoporous silica, it

[*] Prof. Dr. F. Schüth, Dr. A.-H. Lu, Dr. W. Schmidt, Dr. A. Taguchi, B. Spliethoff, Dr. B. Tesche
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1
45470 Mülheim (Germany)
Fax: (+49) 208-3062995
E-mail: schueth@mpi-muelheim.mpg.de

demonstrates the principle possibility to use ordered porous carbons to template ordered inorganic materials. The usefulness of such a templating procedure to create nanoparticles has been shown in the synthesis of various high surface-area oxides by impregnating activated carbons with highly concentrated metal nitrate solutions and subsequent combustion of the carbon.^[7] Silica was chosen because tetraethoxysilane (TEOS) has 1) a relatively high ratio between the central atom and the hydrolyzable groups, which allows high filling of the pore system of the carbon and 2) a moderate susceptibility to hydrolysis, which avoids a too rapid and vigorous reaction. However, it is expected that under properly chosen conditions with adapted precursors many other inorganic frameworks can be templated with carbon.

We chose to employ CMK-3,^[8] the replica of SBA-15, as the mold, because the relatively large pore size of this carbon should make its pore system very accessible. SBA-15 appears on first sight only to be a hexagonal array of cylindrical pores in a silica matrix. However, the cylindrical mesopores are connected by micropores in the walls, which result in a 3D pore system.^[9] Only thus is it possible to obtain the carbon negative of SBA-15 as a stable structure. SBA-15 was synthesized with Pluronic 123 according to published procedures.^[10] Figure 1a shows a small-angle X-ray diffraction (XRD) pattern of a calcined aluminum-containing SBA-15

with a specific surface area of $760 \text{ m}^2 \text{ g}^{-1}$. The lattice parameter is $a = 10.7 \text{ nm}$, the pore size, determined by nitrogen adsorption and Barrett, Joyner, Halenda (BJH) analysis from the adsorption branch of the isotherm, is 6.9 nm , from which the wall thickness of the SBA-15 is calculated to approximately 3.8 nm . The pores of the material were impregnated with a carbon precursor by adsorption of furfuryl alcohol, according to Shin et al.^[8] Carbonization of the carbon precursor in the pores at 850°C under nitrogen atmosphere and subsequent removal of the silica with hydrofluoric acid led to the formation of CMK-3, the XRD pattern of which is shown in Figure 1b. The lattice parameter of that CMK-3 is $a = 10.5 \text{ nm}$. The pore size derived from nitrogen sorption and BJH analysis of the adsorption branch corresponds to 3.8 nm , well in agreement with published data on such materials and the wall thickness of the SBA-15 precursor. To check the completion of the silica removal, the carbon was combusted and the amount of ash determined. The ash content of the sample was less than $0.5 \text{ wt}\%$, thus demonstrating almost complete removal of the silica, which is important to check the success of the next step.

The pore system of CMK-3 was then filled with TEOS and hydrolysis of the TEOS in the pore system initiated by treatment with an HCl solution of pH 1. The sample was left to stand for 10 min, and then placed in a box furnace which was first kept at 40°C and then 80°C for 3 h each, to remove the products, such as water and ethanol which result from the hydrolysis of the TEOS and subsequent condensation from the system. This procedure was repeated several times to achieve full loading. Depending on the pore volume of the starting CMK-3, an SiO_2 content of about 60–70 wt % could be achieved in the final material. In some cases, the amount of silica was too high for the pore volume of the CMK-3 material by about 10 %, assuming a silica density of 2.2 g cm^{-3} , which indicates the presence of some externally deposited silica. The detailed procedure is described in the Experimental Section. After the last thermal treatment, the sample was transferred to a horizontal tube furnace with a quartz tube and heated under flowing nitrogen at a heating rate of $0.5^\circ\text{C min}^{-1}$ to 250°C , and then with 1°C min^{-1} to 700°C where it was kept for 4 h, to complete the silanol condensation as far as possible. The carbon was removed in a box furnace within 5 h at a temperature of 550°C . Alternatively, the carbon was removed in a fluidized bed reactor in flowing air at a temperature of 550°C to avoid temperature hot spots which could damage the structure of the forming silica. This procedure results in enhanced adsorbed volume and a better defined capillary condensation step in the isotherm.

Figure 1c shows the diffraction pattern of the white material (designed as NCS-1 for nanocasted silica No. 1) recovered after calcination. There is a low-angle-feature centered at an angle of $1.07^\circ 2\theta$ ((100) reflection), with a relatively weak intensity. In addition, intensity is observed at higher angles with reflections at about 1.85° and $2.10^\circ 2\theta$, which correspond to the (110) and (200) reflections of the usual hexagonal mesostructure. The relative intensity of the (100) reflection compared to the (110) and (200) reflections is lower than for the normal mesostructured materials, but the typical hexagonal pattern is clearly discernable. The success-

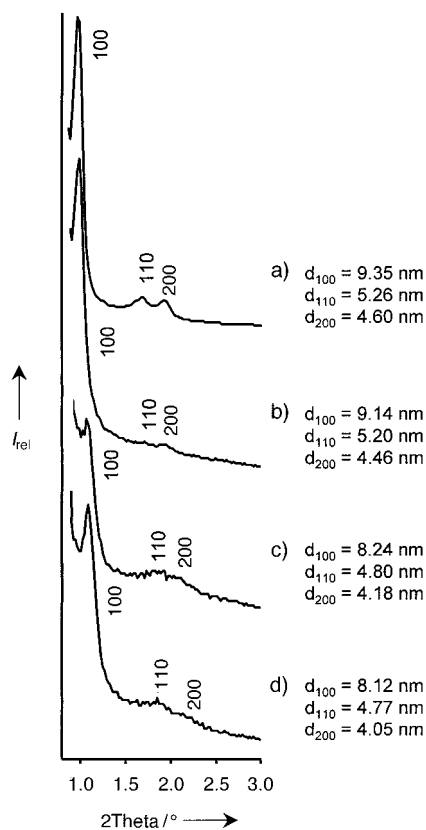


Figure 1. XRD-patterns of a) Al-SBA-15 ($S_{\text{BET}} = 676 \text{ m}^2 \text{ g}^{-1}$, $D_{\text{BJH}} = 6.9 \text{ nm}$), b) CMK-3 ($S_{\text{BET}} = 764 \text{ m}^2 \text{ g}^{-1}$, $D_{\text{BJH}} = 3.8 \text{ nm}$) synthesized from the SBA-15 in (a), c) NCS-1 ($S_{\text{BET}} = 272 \text{ m}^2 \text{ g}^{-1}$, $D_{\text{BJH}} = 7.2 \text{ nm}$) replicated from the CMK-3 in (a), and d) NCS-1 ($S_{\text{BET}} = 557 \text{ m}^2 \text{ g}^{-1}$, $D_{\text{BJH}} = 4.9 \text{ nm}$) replicated from another CMK-3 ($S_{\text{BET}} = 1043 \text{ m}^2 \text{ g}^{-1}$, $D_{\text{BJH}} = 3.7 \text{ nm}$) obtained from a Al-SBA-15 ($S_{\text{BET}} = 680 \text{ m}^2 \text{ g}^{-1}$, $D_{\text{BJH}} = 5.8 \text{ nm}$) with smaller pore size (S_{BET} : BET surface area, D_{BJH} : pore diameter according to BJH).

ful casting of an ordered silica from the carbon is even more clearly demonstrated, if the sorption isotherm (Figure 2) and the TEM (Figure 3) are analyzed. The adsorption step in the isotherm is rather steep, which suggests a narrow pore-size distribution.

If an SBA-15 with smaller pore size (5.8 nm) is used, also the lattice parameter and the pore size of the resulting NCS-1 is changed (Figure 1 d and Figure 2 c). The pore size calculated from the adsorption branch of Figure 2 c is 4.9 nm, the lattice parameter corresponds to 9.4 nm. In addition, the better

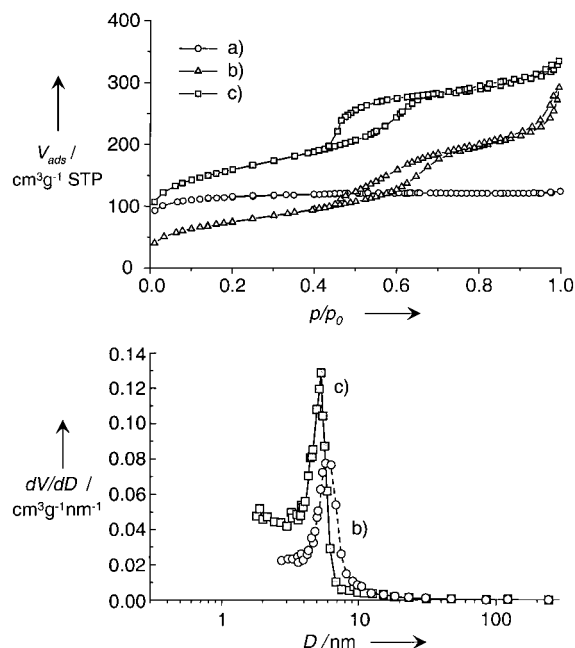


Figure 2. Nitrogen adsorption isotherms (top) and pore-size distributions (bottom) of a) a composite of silica and CMK-3 after treatment in nitrogen at 700 °C, b) NCS-1, the diffraction pattern of which is given in Figure 1 c, c) NCS-1, the diffraction pattern of which is given in Figure 1 d. STP = Standard temperature and pressure.

developed steps in the isotherm demonstrate that fluidized-bed calcination, which was used for the sample represented by Figure 1 d and Figure 2 c, is beneficial with respect to sample quality. Most convincing with respect to the ordered pore system are the TEMs of all the obtained materials. All sections of the samples look like the one displayed in Figure 3 a and Figure 3 b, which clearly shows channels similar to the ones present in SBA-15 viewed sideways as well as the hexagonal pattern if the sample is viewed along the six-fold axis; also quite indicative are the noodle-shaped particles which are often observed for SBA-15 and CMK-3. The repetition unit (8–9 nm) observed in the TEM corresponds well to the repeat distance calculated from the XRD experiments.

The results clearly show, that the structure of CMK-3 is transferred to the silica replica. The hexagonal order of the channels is visible in the TEM in many sections, the sorption isotherm also corresponds to a highly ordered pore system. The X-ray diffraction pattern is not as well developed as for the starting SBA-15. However, a complete filling of the CMK-3 pore system with silica can not be expected. Even if impregnation with TEOS is repeated several times, the last

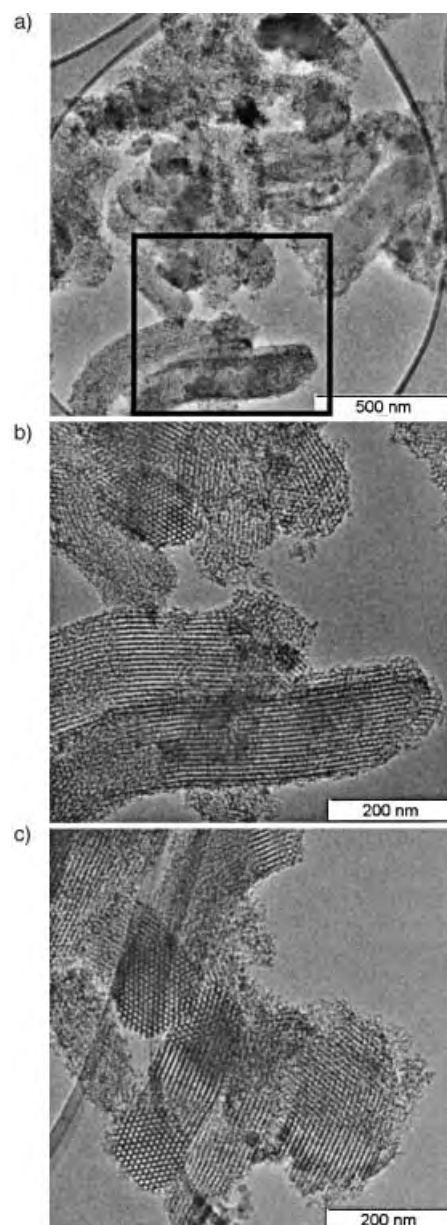


Figure 3. Typical TEM images of a) NCS-1, b) magnification of the section marked with a box in (a), and c) section showing the well-defined hexagonal ordering of the pores.

TEOS introduced is still decomposed, and part of the material in the pores leaves the pore system. Thus, additional micropores are created in the silica part which are detected in the sorption isotherm of the $\text{SiO}_2/\text{CMK-3}$ composite heat treated at 700 °C in nitrogen, which is given for comparison in Figure 2 a. The distribution of matter in the unit cell will thus be rather different compared to SBA-15, which can lead to strong deviations of the relative intensities of the low-angle reflections.^[11] This explains the variation of the XRD patterns of the materials.

We have shown that it is in principle possible to take nanocasting one step further and use the nanocasted carbon CMK-3 as a matrix for the production of an ordered mesoporous silica. It should be possible to extend this approach to other carbon templates, such as CMK-1 or SBU-1, or to other inorganic framework compositions. The

carbon has been removed by an oxidation process in the example presented here, which would suggest, that only stable oxides or oxidation-resistant compositions could be obtained following this pathway. However, carbon can also be removed by other reactions, such as high-temperature hydrogenation, which should allow the synthesis of compounds which are not stable against oxidation.

Experimental Section

Materials: The following materials, tetraethylorthosilicate (TEOS, 98%, Aldrich), furfuryl alcohol (98%, Fluka), trimethylbenzene (THB, 98%, Aldrich), and hydrochloric acid 37%, were used as received without further purification.

Synthesis of SBA-15: The synthesis of the SBA-15 was performed following published procedures^[10] by first heating the reaction mixture at 40 °C for 4 h, followed by aging at 80 °C for 24 h. The filtered samples were calcined at 550 °C for 5 h with a heating rate of 1 °C min⁻¹ to the final temperature. To improve the carburization, the SBA-15 (12 g) was stirred for 12 h in a solution of AlCl₃ (2 g) in ethanol, collected by filtration, and washed with ethanol.

Synthesis of CMK-3: CMK-3 was synthesized by the incipient wetness technique to introduce furfuryl alcohol into the pores of SBA-15 following two different procedures: 1) furfuryl alcohol was introduced as received in the channels of SBA-15, followed by carbonization of the infiltrated furfuryl alcohol with a heating rate of 1 °C min⁻¹ from 80–150 °C, where the sample was kept at 150 °C for 3 h, then the temperature was increased from 150 °C to 300 °C at a rate of 1 °C min⁻¹, and, finally, the temperature was increased to 850 °C with a rate of 5 °C min⁻¹ and maintained at this temperature for 4 h. 2) furfuryl alcohol, diluted with ethanol or TMB was introduced into SBA-15 and then carbonized following the procedure outlined in 1).

Synthesis of NCS-1: Under vigorous agitation CMK-3 (0.15 g) was impregnated drop by drop with TEOS (0.15 mL), then one drop of HCl solution (pH 1) was added under vigorous agitation. After 10 min, the sample was put into a box oven at 40 °C for 3 h and then at 80 °C for 3 h. Subsequently, the sample was removed, cooled, and the impregnation was repeated until the desired amount of TEOS (typically corresponding to a silica loading of 60%) was introduced. The sample was then heated to 700 °C in flowing nitrogen as described in the text, then calcined in a box furnace at 550 °C for 5 h in air with the heating rate of 1 °C min⁻¹ to the final temperature. After that treatment, a white powder was obtained in a yield of typically 1.5–2 g SiO₂ g⁻¹ CMK-3, depending on the pore volume of the CMK-3 starting material.

Characterization: Low-angle X-ray diffraction patterns were recorded with a Stoe STADIP diffractometer in the Bragg–Brentano (reflection) geometry. The step width was 0.02° 2θ at an acquisition time of 8 s per step. Nitrogen adsorption isotherms were measured with an ASAP 2010 adsorption analyzer (Micromeritics) at liquid nitrogen temperature. Prior to the measurements, all samples were degassed at a temperature of 250 °C for at least 3 h. Pore sizes and pore-size-distribution curves were calculated from the adsorption branch, since calculation from the desorption branch might be influenced by network percolation effects and the instability of the meniscus at $p/p_0 = 0.42$.

TEM images were obtained with a HF2000 electron microscope from Hitachi equipped with a cold field emission gun. The acceleration voltage was 200 kV. Samples were prepared dry on a lacey carbon grid.

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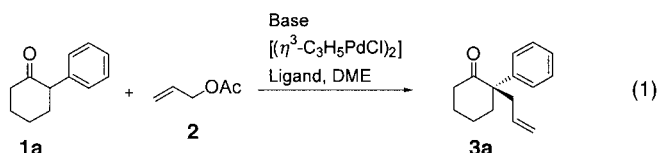
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Palladium-Catalyzed Asymmetric Allylic Alkylation of α -Aryl Ketones**

Barry M. Trost,* Gretchen M. Schroeder, and Jesper Kristensen

The generation of quaternary chiral centers through catalytic asymmetric alkylation of ketone enolates has been the subject of investigation in recent years.^[1] The palladium-catalyzed asymmetric allylic alkylation (AAA) of prochiral nucleophiles represents one such strategy for the creation of quaternary chiral centers.^[2] Given the success of stabilized nucleophiles such as β -ketoesters in palladium-catalyzed AAA^[3,4] we inquired whether simple ketone enolates, perhaps the most important class of nucleophiles, would function. Previously, we reported the AAA of α' -blocked α -alkylcycloalkanones.^[3a] Herein we report the palladium-catalyzed AAA of a series of α' -unblocked enolates: aryl ketone enolates.

Initial studies examined the reaction of 2-phenylcyclohexanone (**1a**) with allyl acetate (**2**) using the conditions developed in our previous work with α' -blocked α -alkylcycloalkanones: 2 equivalents of LDA, 1 equivalent of trimethyltin chloride, 2.5% [$(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2$], and 5% **L**_{ST} in DME as solvent [Eq. (1)]. Unfortunately, under these standard



[*] Prof. B. M. Trost, G. M. Schroeder, J. Kristensen
Department of Chemistry
Stanford University
Stanford, CA 94305-5080
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu

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

conditions, the allylated product **3a** was generated with a very poor *ee* value. We therefore sought to re-optimize the palladium-catalyzed AAA for this class of nucleophile by first varying the counterion of the enolate in the absence of any additional additive such as trimethyltin chloride (Table 1). The potassium enolate gave the best *ee* value with the standard ligand **L_{ST}** (Table 1, entry 3 versus entries 1 and 2). Since the largest counterion gave the best *ee* value, we

Table 1. Selected optimization studies of the AAA of 2-phenylcyclohexanone.^[a]

Entry	Base (1.1 equiv)	Ligand	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	LDA	L_{ST}	96	28
2	NaH	L_{ST}	75	28
3	KH	L_{ST}	46	42
4	LDA	L_N	46	32
5	NaH	L_N	93	84
6	KH	L_N	55	53

[a] All reactions were performed using DME as solvent (0.18 M), 2.5 equiv $[(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2]$, and 5% ligand at room temperature. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

thought that perhaps the *ee* value could be further improved by enhancing the steric interactions between the nucleophile and the ligand through the use of a more sterically demanding ligand such as naphthyl-derived ligand **L_N**. With this ligand, the lithium enolate still appeared to be too small (entry 4), the potassium enolate was perhaps a bit too large (entry 6), and the sodium enolate gave the best fit of the approaching nucleophile with its counterion into the chiral pocket to give ketone **3** in 93% yield and 84% *ee*. To summarize, the use of 1.1 equivalents of sodium 1,1,1,3,3,3-hexamethyldisilazone (NaHMDS) as base, 1,2-dimethoxyethane (DME) as solvent, 2.5% $[(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2]$ as the palladium source, and 5% **L_N** as the chiral ligand became the standard conditions for alkylating α -aryl ketones.

Next, the scope of the reaction was examined. The reaction was found to be general in terms of the ring size and the aryl substituent on the nucleophile. As shown in Table 2, six- (entry 1), seven- (entry 2), and eight-membered (entry 3) cycloalkanones all gave products with good *ee* values. A variety of aryl groups were tolerated. For example, the sterically bulky naphthylcyclohexanone **1d**^[5] (entry 4) and biphenylcyclohexanone **1e**^[6] (entry 5) gave their respective allylated products in 89% *ee*. Importantly, electron-rich and electron-poor aromatic substrates both functioned well. Thus, methoxy-substituted ($\sigma_p = -0.27$) aryl ketone **1f**^[7] and fluoride-substituted ($\sigma_p = +0.06$) aryl ketone **1g**^[8] gave the allylated products in 84% and 90% *ee*, respectively. Interestingly, the methoxy-bearing naphthalene ring ketone **1h** (entry 8) gave the best *ee* value.

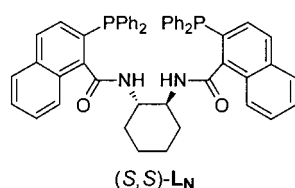
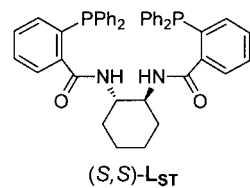
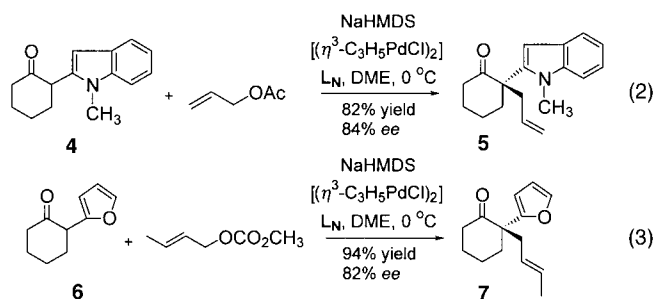


Table 2. Examples of the Pd-catalyzed AAA of aryl ketones.^[a]

Entry	<i>n</i>	Ar	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	1	a (phenyl)	90	88
2	2	b (phenyl)	90	83
3	3	c (phenyl)	89	84
4	1	d (naphthyl)	82	89
5	1	e (biphenyl)	95	89
6	1	f (4-methoxyphenyl)	92	84
7	1	g (4-fluorophenyl)	77	90
8	1	h (1-methoxy-2-naphthyl)	84	92

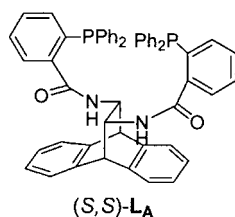
[a] All reactions were performed using DME as solvent (0.18 M), 1.1 equivalents of NaHMDS as base, 2.5% $[(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2]$, and 5% **L_N** at 0 °C.

Two heterocycles have also been alkylated as shown in Equations (2) and (3). Furan **6** shows that the reaction is not



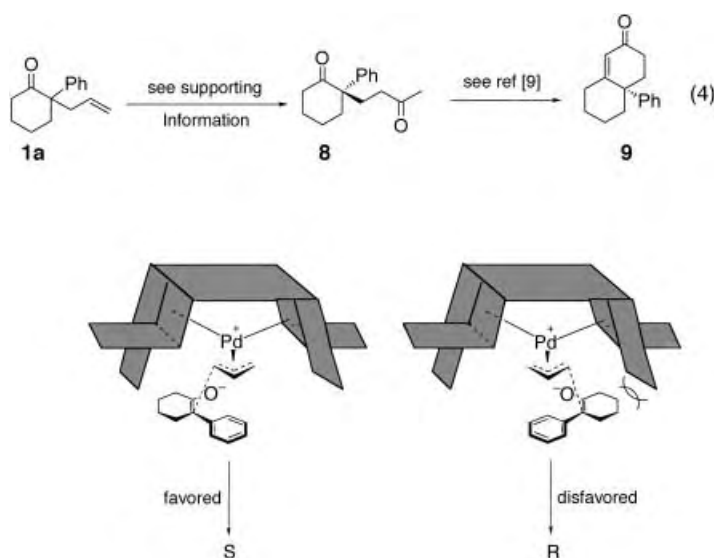
limited to allyl acetate as an electrophile. Other electrophiles can function equally well.

The absolute configuration has been determined in the case of 2-phenylcyclohexanone by comparison of the optical rotation of diketone **8** to that reported in the literature [Eq. (4)].^[9] Thus, the (*S,S*)-naphthyl ligand gives the stereochemistry illustrated and is consistent with the mnemonic developed in our group (Scheme 1). The absolute configuration of the other examples were assigned by analogy.



Diketone **8** has itself been cyclized to give enone **9**. Thus, this methodology can give access to enantio-enriched polycycles in which the ring junction is substituted with an aryl group.

The impact of the orientation of the aryl group with respect to the



Scheme 1. Rationale for chiral recognition.

enolate was explored by using the conformationally rigid β -tetralone. Unfortunately, the conditions developed for 2-phenylcyclohexanone gave poor *ee* values (20%) with 1-methyl-2-tetralone (**10**). Therefore we investigated new conditions for this class of nucleophile (Table 3). The *ee* value obtained using the standard ligand **L_{ST}** (entries 1–4) was found to vary dramatically with the base: with LDA, the *ee* value was –33%, whereas with cesium carbonate the *ee* value was 45%, a total change of 78%. Such a remarkable effect clearly indicates the importance of the structure of the ion pair which constitutes the nucleophile rather than the simple enolate. The same trend was observed with naphthyl-derived ligand **L_N** (entries 4–5). The ligand was then varied, and gratifyingly, the anthracene-derived ligand **L_A**, which has a larger bite angle than **L_{ST}** and **L_N** and can therefore better embrace the substrate, was found to give ketone **11**^[10] in 93% yield and 90% *ee*.

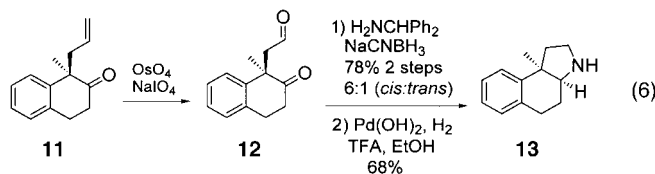
The absolute configuration of allylated tetralone **11** was established by the synthesis of the known pyrrolidine-fused tetralin **13**, a family of molecules that has attracted attention

Table 3. Pd-catalyzed AAA of 1-methyl-2-tetralone (**10**).^[a]

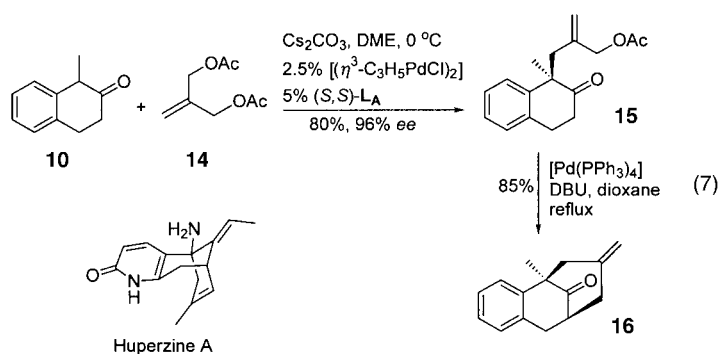
Entry	Base (1.1 equiv)	Ligand	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	LDA	L_{ST}	90	–33
2	NaHMDS	L_{ST}	79	–23
3	KHMDS	L_{ST}	83	15
4	Cs ₂ CO ₃	L_{ST}	91	45
5	LDA	L_N	93	–1
6	Cs ₂ CO ₃	L_N	91	41
7	Cs ₂ CO ₃	L_A	93	90

[a] All reactions were performed using DME as solvent (0.18 M), 1.1 equivalents of base, 2.5% [(η^3 -C₃H₅PdCl)₂], and 5% *S,S* ligand at 0°C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. A negative sign indicates the absolute stereochemistry to be opposite to that depicted in **11**.

due to their serotonin and dopamine agonist activity.^[11,12] To this end, the terminal olefin of tetralone **11** was oxidatively cleaved to give unstable keto aldehyde **12**. Aldehyde **12** was reductively aminated with benzhydrylamine and then the tertiary amine was deprotected by hydrogenation with Pearlman's catalyst to give aminotetralin **13**. Thus, (*S,S*)-anthracene ligand **L_A** gives the stereochemistry shown in Equation (6)



and allows for a concise, enantioselective synthesis of aminotetralin **13**. Performing the alkylation with the allyl bisacetate **14** gave **15** in good yield. Sequential cyclization using an



achiral Pd catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided tricycle **16**, whose *ee* value was established to be an excellent 96%. Thus, this method may provide an asymmetric synthesis of huperzine A,^[15] an alkaloid with potent activity as an inhibitor of acetylcholinesterase.

To conclude, a variety of aryl ketones can be alkylated asymmetrically in a catalytic manner to generate quaternary chiral centers. These results confirm the broad compatibility of ketone enolates with the palladium-catalyzed AAA.^[13] A strong correlation between the size of the enolate cation and the size of the chiral pocket is observed. The ease of access to the aryl ketones by the Buchwald–Hartwig Pd-catalyzed arylation^[13] as well as by more classical routes and the utility of the allyl and substituted allyl groups for further elaboration impart great synthetic potential to this method. The alkylation of β -tetralone gives enantioenriched products that are versatile building blocks for the synthesis of diterpenes, steroids, and quassinoids.^[14] The utility of these products is illustrated in the synthesis of aminotetralin **13** and a model system for huperzine A,^[15] an alkaloid with potent activity as an inhibitor of acetylcholinesterase.^[15] As a consequence of the success of ketone enolates in the palladium-catalyzed AAA, the investigation of even less stabilized nucleophiles is currently underway in our laboratories.

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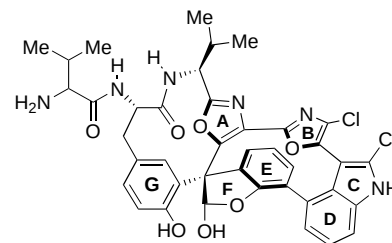
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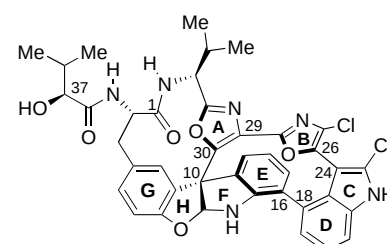
Total Synthesis of Diazonamide A**

K. C. Nicolaou,* Marco Bella, David Y.-K. Chen, Xianhai Huang, Taotao Ling, and Scott A. Snyder

In 1991, Fenical and co-workers reported structure **1** for diazonamide A, a marine natural product which had been isolated from the colonial ascidian *diazona angulata*.^[1] A



1: original structure of diazonamide A



2: revised structure of diazonamide A

decade later, Harran and his group synthesized the proposed structure **1** only to prove that it was in error, and advanced structure **2** for diazonamide A instead.^[2] In the intervening time, numerous efforts directed at the total synthesis of **1** had been reported;^[3–13] no research activities related to the newly proposed structure **2** have yet been disclosed. The appeal of diazonamide A (**2**) stems both from its biological activity (cytotoxicity against several tumor cell lines with IC₅₀ values < 15 ng mL⁻¹) and its highly strained and unprecedented

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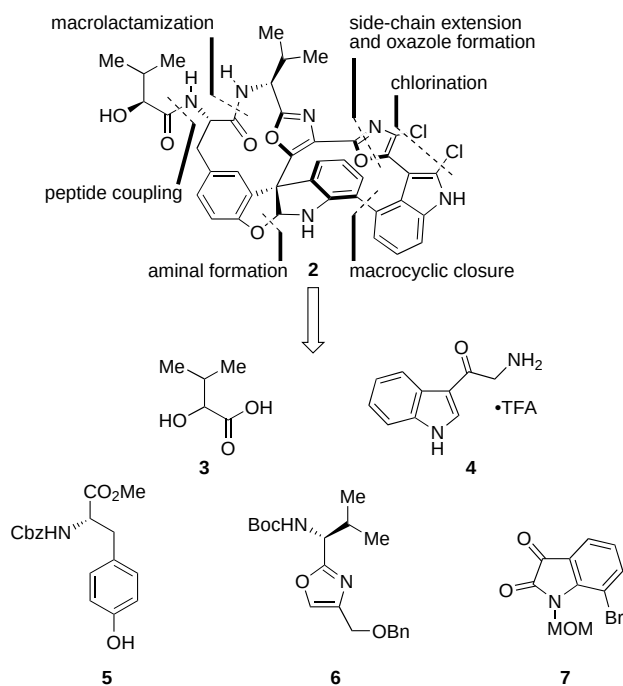
[*] Prof. Dr. K. C. Nicolaou, Dr. M. Bella, Dr. D. Y.-K. Chen, Dr. X. Huang, Dr. T. Ling, S. A. Snyder
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

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structure. Because of its scarcity from natural sources and its potential as a lead for the development of new chemotherapeutic agents, **2** presents a unique opportunity for chemical synthesis. In this communication, we report a total synthesis of diazonamide A (**2**) which required the development of new synthetic technologies and strategies and which provides a solution to this formidable molecular puzzle.

The revised structure of diazonamide A (**2**) represented a greater synthetic challenge than the one posed by the originally proposed structure (**1**) in that it contains an additional ring (ring H) and a nitrogen atom instead of the oxygen substituent in ring F which leads to a structurally unique aminal moiety. In addition to the rigidity associated with this EFGH tetracyclic system, its quaternary center (C10) preeminently stood as the central cornerstone of any synthetic strategy. The two 12-membered rings of the structure were also expected to pose considerable recalcitrance to formation owing to their severely constrained environments. In all, structure **2**, with its ten exquisitely arrayed rings and unique elements of stereochemistry, amounted to a rare challenge to modern synthetic chemistry.

Scheme 1 presents the blueprint of our strategy towards this target molecule in retrosynthetic format. Thus, excision of the



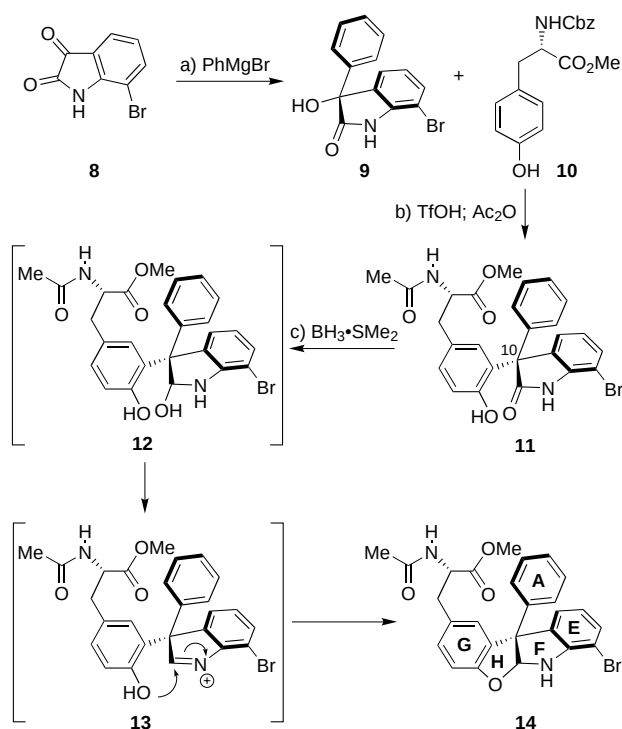
Scheme 1. General retrosynthetic analysis of diazonamide A (**2**). Cbz = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, MOM = methoxy methyl, TFA = trifluoroacetic acid.

side chain and the chlorine atoms, and rupture of the macrolactam, aminal, oxazole, and bis-aryl ring systems as shown, led to fragments **3–7**. In the synthetic direction, the challenge was thus reduced to the following milestone events: a) construction of the required building blocks; b) assembly of the quaternary center with its substituents; c) formation of the 12-membered macrolactam ring system; d) introduction of the indole–oxazole domain; e) closure of the 12-membered

polycyclic framework and chlorination; f) fusion of the aminal bicyclic network; and g) attachment of the isovaleric acid side chain (the operations to be executed in that order). The proposed late introduction of the side chain would allow for expedient construction of analogues, including the synthesis of the natural product's epimer at C37 for purposes of structural and biological comparison.

While all of the defined building blocks (**3–7**) were readily generated from commercially available starting materials according to literature procedures, the construction of the quaternary center (C10) with its peripheral structural motifs required considerable process development. To this end, the model study depicted in Scheme 2 was designed and executed. Thus, 7-bromoisatin (**8**)^[14] was treated with excess PhMgBr to afford tertiary alcohol **9** in 96% yield. Upon mixing compound **9** with tyrosine derivative **10** in the presence of TfOH, and following acetylation of the resultant primary amine (as TfOH cleaved the Cbz group), phenolic lactam **11** emerged in 84% yield as a mixture of diastereomers (ca. 1:1).^[15] Exposure of **11** to excess BH₃·SMe₂ resulted in the formation of the bicyclic aminal system **14** (40% overall yield, unoptimized) containing some of diazonamide A's most challenging structural features, presumably via intermediates **12** and **13** as suggested in Scheme 2.

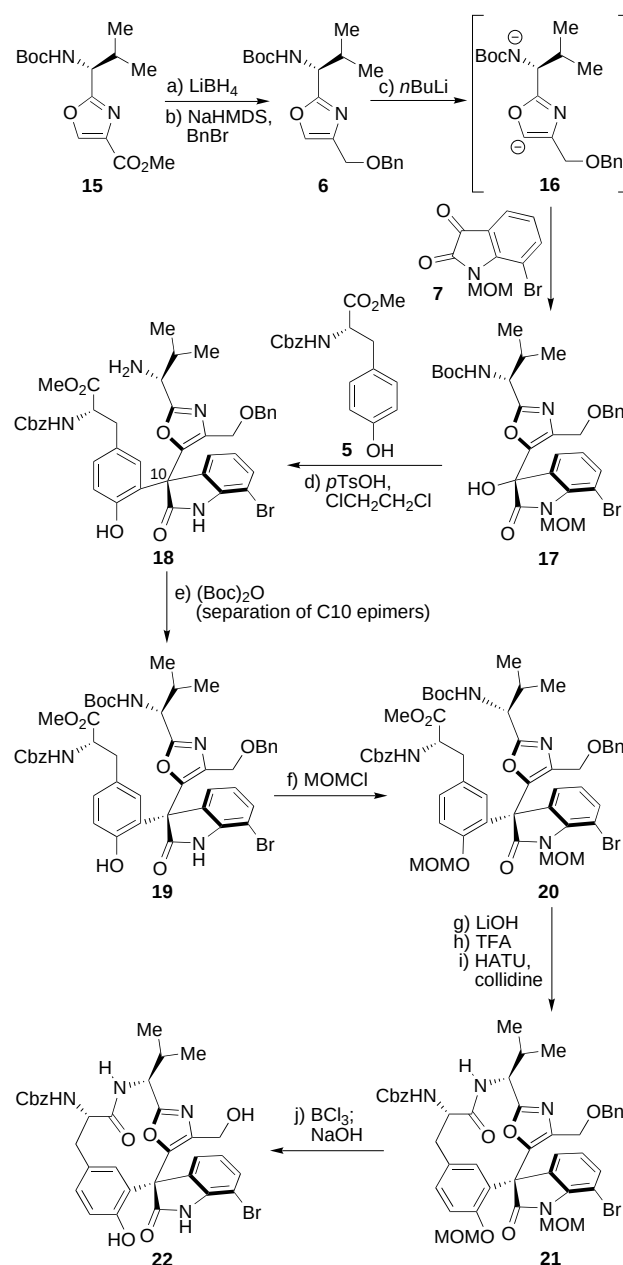
Prompted by this encouraging set of preliminary results, we then proceeded to apply the developed chemistry to the target molecule **2** as shown in Scheme 3. Having failed to successfully utilize the known oxazole ester derivative **15**^[16] in the intended coupling reaction, we resorted to its reduction



Scheme 2. Model studies exploring the generation of the C10 quaternary center: a) PhMgBr (3.0 equiv), THF, 0°C, 96%; b) **10** (1.1 equiv), TfOH (10 equiv), CH₂Cl₂, 0°C, 20 min; then Ac₂O (10 equiv), CH₂Cl₂, 25°C, 5 min, 84%; c) BH₃·SMe₂ (3.0 equiv), THF, 25°C, 4 h, 40%. TfOH = trifluoromethanesulfonic acid. Note: compounds **11–14** are mixtures of C10 epimers (ca. 1:1).

(LiBH₄) and selective protection (60% overall yield)^[17] to afford benzyl ether **6** as an alternative substrate for this process. Reaction of **6** with 2.0 equiv of *n*BuLi in THF at −78°C resulted in the formation of dianion **16** which was treated with 1.1 equiv of isatin derivative **7**^[18] at −78°C to afford, upon standard workup, tertiary alcohol **17** in 73% yield. The crucial step of establishing the quaternary center assembly with its structural entourage was then accomplished by refluxing **17** with tyrosine derivative **5** (4.0 equiv) in 1,2-dichloroethane in the presence of *p*TsOH to furnish compound **18**, which had lost both the MOM and the Boc protective groups, in 33% yield. It is important to note that the triflic acid conditions utilized successfully in the model study (Scheme 2) failed in this instance; only decomposition products were obtained, which most likely arose from the oxazole moiety. Reprotection of the primary amine in **18** with (Boc)₂O led to two C10 epimers whose chromatographic properties allowed their convenient separation to yield pure **19** and its epimer (not shown). Since the configuration of the quaternary center in these intermediates could not be determined at this stage, both epimers were separately carried forward to the corresponding macrolactams (**22** and its C10 epimer) whose spectroscopic data were suggestive of their structures (see below). The following step involved protection of the phenolic hydroxy group and the oxindole amide nitrogen atom, an objective which was accomplished by exposing **19** to excess MOMCl and K₂CO₃ to afford compound **20** (94% yield). This precursor (**20**) was then transformed to the coveted macrolactam **21** by first liberating the carboxylic acid (LiOH) and the amino groups (TFA), in that order, and then cyclizing the resultant amino acid through the action of HATU and collidine in DMF/CH₂Cl₂ in 36% overall yield. This challenging formation of the 12-membered ring required high-dilution conditions to minimize formation of dimers and higher oligomers. It should also be noted that MOM protection of the precursor considerably improved the yield of this ring closure as compared to that obtained with unprotected material (i.e., **19**). Furthermore, of the two C10 epimers, only one cyclized smoothly whereas the other led to preferential dimerization even under extremely high dilution conditions. The next step in the sequence required removal of the benzyl group in the presence of the Cbz and the aryl bromine moieties, a challenging task that was accomplished by the use of BCl₃ in CH₂Cl₂ at −78°C followed by treatment with NaOH. In this reaction, the two MOM groups in **21** were concomitantly cleaved to yield compound **22** in 61% overall yield.^[19] At this stage, the ¹H NMR spectroscopic data of the more accessible macrolactam epimer (see Table 1) were reminiscent of those of diazonamide A (**2**). Therefore, we assumed the structure of this epimer to be that of **22** (that is to say, the one corresponding to the targeted natural product).

Having chosen epimer **22** as the most likely candidate to yield diazonamide A (**2**), its further elaboration proceeded as shown in Scheme 4. Thus, selective protection of the phenolic hydroxy group of **22** (Boc₂O), followed by sequential oxidation first with IBX and then with NaClO₂, furnished the expected carboxylic acid whose coupling with indole ammonium salt **4** in the presence of EDC and HOBt led to **23** (41% overall yield from **22**). This keto amide was then converted to



Scheme 3. Synthesis of advanced macrolactam **22**: a) LiBH₄ (2.0 M in THF, 3.0 equiv), EtOH (10 equiv), Et₂O/THF (2:1), 0→25°C, 3 h, 83%; b) NaHMDS (1.0 M in THF, 2.0 equiv), THF, −78°C, 10 min, then TBAI (0.1 equiv), BnBr (10 equiv), −78→25°C, 24 h, 72%; c) *n*BuLi (2.0 equiv), THF, −78°C, 20 min, then **7** (1.1 equiv), 10 min, 73%; d) **5** (4.0 equiv), *p*TsOH (4.0 equiv), ClCH₂CH₂Cl, 83°C, 15 min, 33%; e) (Boc)₂O (1.1 equiv), aq. NaHCO₃/dioxane (1:2), 25°C, 2 h, 65%; f) MOMCl (30 equiv), K₂CO₃ (40 equiv), acetone, 0→25°C, 2 h, 94%; g) LiOH (20 equiv), MeOH/THF/H₂O (2:10:1), reflux, 10 min, 98%; h) TFA, 10 min, 98%; i) HATU (2.2 equiv), collidine (6.6 equiv), DMF/CH₂Cl₂ (1:2, 3.0 × 10^{−4} M), 25°C, 12 h, 36%; j) BCl₃ (1.0 M in hexanes, 20 equiv), CH₂Cl₂, −78°C, 2 h; then THF, sat. aq. NaHCO₃, 10% aq. NaOH, 25°C, 30 min, 61%. NaHMDS = sodium salt of 1,1,1,3,3,3-hexamethyldisilazane, TBAI = tetra-*n*-butylammonium iodide, *p*TsOH = *p*-toluenesulfonic acid, HATU = 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

the corresponding oxazole system through a Gabriel–Robinson cyclodehydration effected by a unique set of conditions (POCl₃/pyridine)^[20] which set the stage for the critical

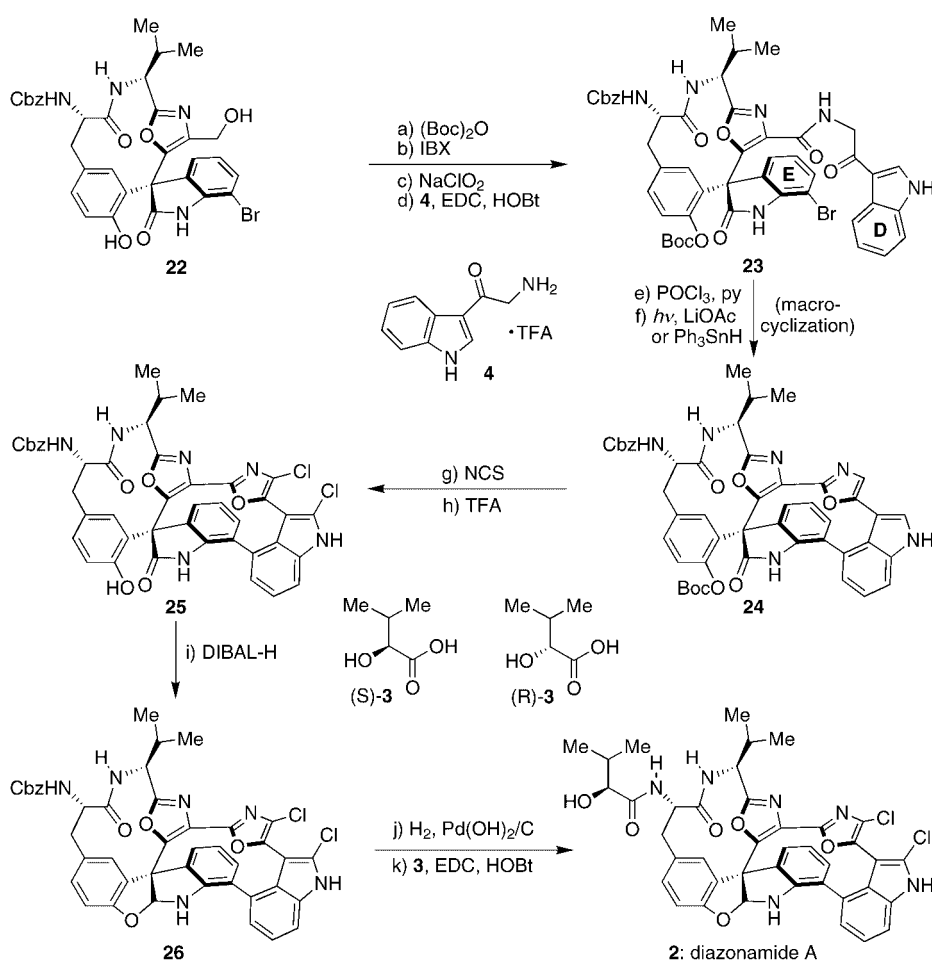
Table 1. Selected data for compounds **22** and **26**.

22: R_f = 0.41 (silica gel, ethyl acetate); IR (film): $\tilde{\nu}_{\max}$ = 3392, 1715, 1649, 1614, 1508, 1455, 1390, 1261, 1220, 1126, 1090, 1020, 750, 597 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN): δ = 8.66 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.37 (m, 4H), 7.34 (m, 1H), 7.27 (br d, 1H), 7.22 (s, 1H), 7.07 (d, J = 7.4 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.90 (t, J = 7.9 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.23 (s, 1H), 6.04 (br d, 1H), 5.07 (AB, J = 12.3 Hz, $\tilde{\nu}_{\text{AB}}$ = 21.9 Hz, 2H), 4.45 (t, J = 7.4 Hz, 1H), 4.11 (t, J = 9.2 Hz, 1H), 3.63 (qd, J = 9.2, 5.7 Hz, 2H), 3.06 (t, J = 12.7 Hz, 1H), 2.77 (brs, 1H), 2.62 (d, J = 12.7 Hz, 1H), 2.04 (m, 1H), 1.01 (d, J = 7.4 Hz, 3H), 0.91 ppm (d, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN): δ = 175.5, 173.4, 164.6, 155.9, 153.0, 144.7, 142.4, 139.0, 138.0, 133.6, 133.0, 130.6, 130.0, 129.3, 128.8, 128.7, 128.6, 127.7, 125.4, 124.2, 116.2, 102.9, 67.0, 57.6, 57.0, 55.8, 38.4, 30.7, 19.6, 19.3 ppm; HR-MS (matrix-assisted laser desorption/ionization, MALDI) for $\text{C}_{33}\text{H}_{31}\text{BrN}_4\text{O}_7\text{Na}^+$ [$M+\text{Na}^+$]: calcd: 697.1268, found: 697.1266

cyclization event required to form the second 12-membered ring of diazonamide A. Most gratifyingly, radical cyclization of this precursor with $\text{Ph}_3\text{SnH}/\text{AIBN}$ induced the desired ring closure to **24**, albeit in low yield (ca. 10%). The efficiency of this ring closure was improved to 30% by resorting to a Witkop-type reaction^[21a] based on a literature procedure,^[2a] a process that was proven effective in previous instances of macrocycle construction.^[21b,c] Significantly, and in contrast to the Ph_3SnH -induced reaction (in which the majority of the substrate was reductively debrominated), the bulk of the remaining material from this process remained unchanged which allowed for productive recycling of recovered starting material. As such, this observation lends further support that this particular macrocyclization reaction proceeds through a mechanism based on intramolecular photo-induced electron transfer from the D-ring indole chromophore to the adjacent benzenoid E-ring,^[2a] rather than some exclusively radical-based event in which case the halogen in the starting material would most likely be expelled.

With the establishment of both macrocyclic scaffolds of diazonamide A through the successful generation of **24**, completion of the synthesis required only a few finishing touches (see Scheme 4). First, the two, still missing, chlorine

residues were installed at their proper positions by electrophilic aromatic substitution (NCS, 53% yield). Second, the resulting product was exposed to TFA to effect removal of the Boc group and furnish phenolic intermediate **25** (98% yield). Chemoselective reduction of the five-membered ring lactam of **25** with DIBAL-H initiated ring closure with participation of the adjacent phenolic hydroxy group to afford the desired cyclic aminal **26** in 55% overall yield. Finally, hydrogenolysis of the Cbz group with H_2 and Pearlman's catalyst followed by installation of the remaining peptide side chain with isovaleric acid ((*S*)-**3**) in the presence of EDC/HOBt furnished structure **2** in 82% overall yield. The ^1H NMR signals of synthetic **2** in [D_4]MeOH matched those reported for natural diazonamide A precisely, while those of the C37 epimer obtained by employing (*R*)-**3** in the final step were slightly, but diagnostically, different.^[22] Based on this data, we confirm structure **2** for diazonamide A.



Scheme 4. Final stages and completion of the total synthesis of diazonamide A (**2**): a) $(\text{Boc})_2\text{O}$ (30 equiv), sat. aq. $\text{NaHCO}_3/\text{dioxane}$ (1:2), 25°C , 24 h, 91% based on recovered starting material; b) IBX (3.0 equiv), DMSO, 25°C , 2 h; c) NaClO_2 (5.0 equiv), NaH_2PO_4 (5.0 equiv), resorcinol (5.0 equiv), DMSO/ H_2O (10:1), $0 \rightarrow 25^\circ\text{C}$, 2 h, 69% over two steps; d) **4** (3.0 equiv), EDC (5.0 equiv), HOBt (5.0 equiv), NaHCO_3 (15 equiv), DMF, 25°C , 12 h, 65%; e) $\text{POCl}_3/\text{pyridine}$ (1:4), 25°C , 2 h, 52%; f) $h\nu$ (200 nm), epichlorohydrin (3.0 equiv), LiOAc (2.0 equiv), MeCN/ H_2O (3:1), 25°C , 15 min, 30% — or Ph_3SnH (2.0 equiv), AIBN (0.1 equiv), C_6H_6 , 80°C , 3 h, 10%; g) NCS (4.0 equiv), CCl_4/THF (1:1), 60°C , 2 h, 53%; h) TFA, 25°C , 10 min, 98%; i) DIBAL-H (1.0 M in toluene, 100 equiv, added portionwise), THF, $-78 \rightarrow 25^\circ\text{C}$, 3 h, 56%; j) H_2 (2.0 atm), $\text{Pd}(\text{OH})_2/\text{C}$ (20 wt %, catalytic), EtOH, 25°C , 2 h; k) (*S*)-**3** (5.0 equiv), EDC (5.0 equiv), HOBt (5.0 equiv), NaHCO_3 (15 equiv), DMF, 25°C , 12 h, 82% over two steps. IBX = 1-hydroxy-1,2-benziodoxol-3(1H)-one, py = pyridine, AIBN = 2,2'-azobisisobutyronitrile, NCS = *N*-chlorosuccinimide, DIBAL-H = diisobutylaluminum hydride.

In conclusion, a path has now been chartered for the total synthesis of the long-sought diazonamide **A** which confirmed its structure as **2**, and through which this valuable, but scarce, natural substance is now rendered available for biological investigations.^[23] Further synthetic work is expected to facilitate chemical biology studies and establish a clear structure–activity profile for this highly unusual molecular architecture.

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- [17] The use of NaHDMS was crucial in obtaining the desired benzylated product (**16**) in high yield. Other bases such as NaH or LiHMDS/HMPA led to significant amounts of bis-benzylated material by enabling engagement of the Boc-protected amine.
- [18] MOM-protected 7-bromoisatin (**7**) was prepared from 7-bromoisatin (**8**) by treatment with LiHDMS and MOMCl. This protection was required to allow the use of stoichiometric amounts of the more precious oxazole species in the coupling reaction.
- [19] In the conversion of **20** to **21**, partial cleavage of the phenolic MOM group was observed. The resulting material, however, was also serviceable for the subsequent steps leading to **22**.
- [20] To the best of our knowledge, this particular reagent combination to generate an oxazole has not been reported previously, though simple dehydration with neat POCl₃ is known: R. L. Dow, *J. Org. Chem.* **1990**, *55*, 386–388. In our hands, this protocol provides a powerful method for oxazole construction in instances where more conventional dehydration procedures fail.
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- [22] Especially revealing was the C37 proton signal (400 MHz, [D₄]MeOH) which, in the case of **2**, coincided precisely with the reported value for the natural product ($\delta = 3.88$ ppm), whereas in the case of its C37 epimer the signal for this proton appeared at $\delta = 3.92$ ppm. We should note that we were unable to obtain a sample of natural diazonamide **A** for direct comparison.
- [23] Synthetic diazonamide **A** (**2**) exhibited potent cytotoxic activity at single digit nM concentrations against various human cancer cell lines of distinct origin, including ovarian carcinoma 1A9, lung carcinoma A549, prostate carcinoma PC-3, breast carcinoma MCS-7, and the taxol-resistant 1A9/PTX10 cell line. Its C37 epimer, although less active, also exhibited significant activity against the same cell lines. We thank Dr. Paraskevi Giannakakou and Aurora O'Brate of the Winship Cancer Institute, Emory University School of Medicine, for these biological assays.