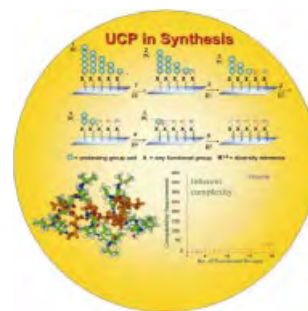


COVER PICTURE

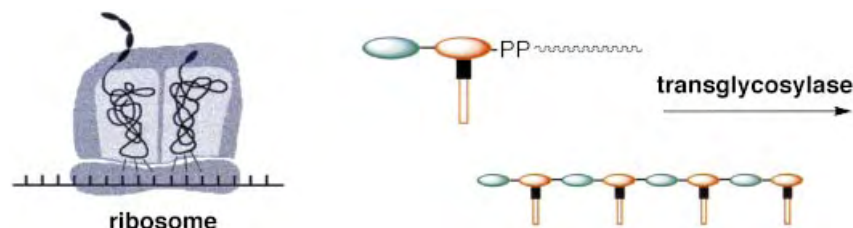
The cover picture shows a new concept in protecting-group chemistry termed unichemo protection (UCP). This strategy only requires a single chemical process for all deprotection reactions. The UCP protecting groups are derived from a repetitive unit that permits their controlled and efficient step-wise removal. Functional-site selectivity is achieved by varying the degree of oligomerization at each site, and, after each deprotection cycle, only the newly liberated functional site is available for derivatization. The UCP strategy does not impose a restriction on the possible number of selectively protected sites in a molecule. The low-energy conformer of the pentalysine scaffold assembled with *N*-sec-butylglycyl protecting-group units is shown bottom left. By using the UCP approach the five protecting groups were sequentially removed and the exposed amino acid groups functionalized with five different organic acids. UCP facilitates an orthogonal process that is not dependent on a range of finely tuned and differently compatible processes. Moreover, since UCP is based on uniform deprotection reactions, the requirement of reaction compatibility with other parts of a molecule only increases linearly with the degree of polyfunctionalization (graph, bottom right). That is, after the initial requirement of parent-molecule stability is satisfied, only the sequential requirements towards each newly introduced group is an issue. In contrast, a quadratic increase in complexity with respect to the number of protected functional groups, even in the simplest cases, accompanies existing orthogonal protection strategies. More about the UCP strategy is reported by L. P. Miranda and M. Meldal on p. 3655 ff.



REVIEWS

Contents

The most important targets of antibiotics include the translation of RNA in bacterial ribosomes and the biosynthesis of the bacterial cell wall (see picture). As a result of the recent interest in antibiotic resistance, carbohydrate mimics have been considered as new inhibitors of these processes. Carbohydrate receptors as well as carbohydrate-modified enzymes have emerged as new targets.



Angew. Chem. 2001, 113, 3616–3641

T. K. Ritter, C.-H. Wong* .. 3508–3533

Carbohydrate-Based Antibiotics: A New Approach to Tackling the Problem of Resistance

Keywords: antibiotics • carbohydrates • enzyme inhibitors • peptidoglycans • RNA

What do the bent alkaline earth dihalides, the (distorted) trigonal-prismatic hexamethyltungsten or -molybdenum, and the “inverse Bent’s rule” structure of $[\text{TiCl}_2(\text{CH}_3)_2]$ have in common? They all belong to the growing class of complexes with a formal d^0 electronic configuration of the metal center which defy the traditional structure models. This article provides a comprehensive review of both experimental and computational studies of such “non-VSEPR” d^0 systems. The bonding features that control the unusual structures are discussed in a unified framework, and the possible relevance for important catalytic or biological processes, as well as materials properties, is highlighted.

Angew. Chem. **2001**, *113*, 3642–3677

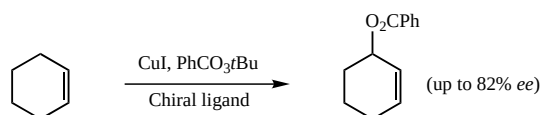
M. Kaupp* 3534–3565

“Non-VSEPR” Structures and Bonding in d^0 Systems

Keywords: bond theory • d^0 complexes • density functional calculations • transition metals • VSEPR model

MINIREVIEW

Chiral ligands such as oxazolines and prolines are important in the copper-catalyzed oxidative conversion of prostereogenic alkenes into enantiomerically pure allylic esters (see scheme). This contribution highlights some of the recent developments in this area using an asymmetric Kharasch–Sosnovsky reaction.



Angew. Chem. **2001**, *113*, 3679–3683

J. Eames,* M. Watkinson* . 3567–3571

Catalytic Allylic Oxidation of Alkenes Using an Asymmetric Kharasch–Sosnovsky Reaction

Keywords: alkenes • asymmetric catalysis • copper • enantioselectivity • oxidation

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.com>

Experimental Detection of Tetraoxygen

F. Cacace,* G. de Petris,
A. Troiani

[12.12]Paracyclophanedodecaynes C_{36}H_8 and C_{36}Cl_8 : The Smallest Paracyclopynes and Their Transformation into the Carbon Cluster Ion C_{36}^-

Y. Tobe,* R. Furukawa,
M. Sonoda, T. Wakabayashi

Fluorescence Quenching via Sequential Hydrogen, Electron, and Proton Transfer in the Proximity of a Conical Intersection

A. Sinicropi, R. Pogni*,
R. Basosi, M. A. Robb,
G. Gramlich, W. M. Nau,*
M. Olivucci*

Side-Wall Functionalization of Carbon Nanotubes

M. Holzinger, O. Vostrowsky,
A. Hirsch,* F. Hennrich,
M. Kappes, R. Weiss, F. Jellen

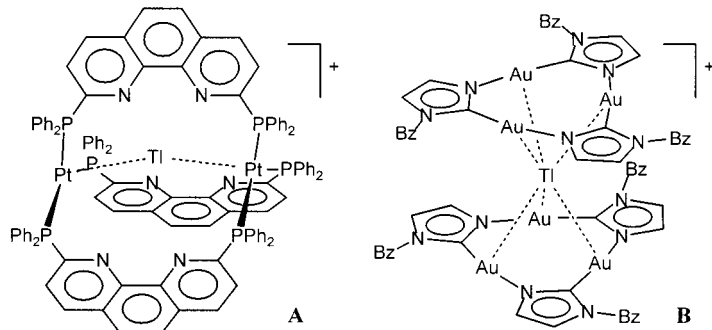
Origin of Ferromagnetism in Cyano-Bridged Compounds Containing d^1 Octacyanometallates

L. F. Chibotaru,* V. S. Mironov,
A. Ceulemans

Lewis Acid/Base-Stabilized Phosphanalane and -gallane

U. Vogel, A. Y. Timshkin,
M. Scheer*

The assembly of a new class of metallocryptands **A** and “metallo sandwiches” **B**, as well as studies on the bonding of Tl^+ with d^{10} -configured Group 10 and 11 complexes in solution and in the solid state have established relatively strong “metallophilic” interactions between d^{10} metal centers and thallium(I). These materials have interesting luminescence properties which differ markedly from those of the individual components. The stability of the d^{10} - s^2 aggregates contrasts with the weak attraction between s^2 -metal centers proposed in the solid state for many thallium(I) compounds and which is frequently superceded by competing intra- and intermolecular interactions. Bz = benzyl.



Angew. Chem. **2001**, *113*, 3685–3688

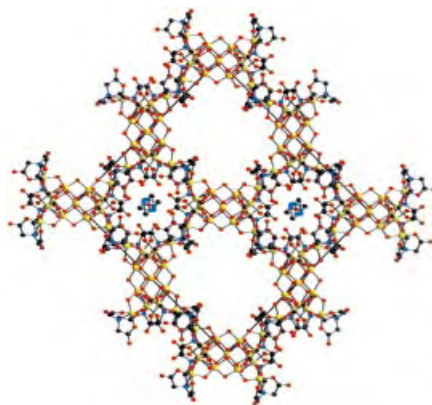
L. H. Gade* 3573–3575

Encapsulated, Sandwiched, or Sticking Out: Closed-Shell Interactions of d^{10} Metal Centers with Thallium(I)

Keywords: cryptands • metal–metal interactions • thallium

COMMUNICATIONS

Separate areas of differing polarity in the structure of an inorganic cluster compound are favored by the introduction of organic ligands on the periphery of the aggregate. This has been demonstrated by the synthesis of compounds containing the title anion (see picture for an example).



Angew. Chem. **2001**, *113*, 3690–3693

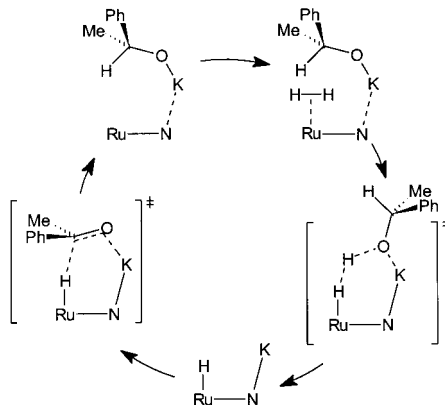
W. Schmitt, E. Baissa, A. Mandel, C. E. Anson, A. K. Powell* . 3578–3581

$[Al_{15}(\mu_3-O)_4(\mu_3-OH)_6(\mu-OH)_{14}-(hpda)_4]^{3-}$ —A New Al_{15} Aggregate Which Forms a Supramolecular Zeotype

Keywords: aluminum • cluster compounds • zeolite analogues



Alkali metal cations are indispensable cocatalysts for the high activity of Ru^{II} complexes with phosphane and amine ligands in the catalytic hydrogenation of ketones. The proposed mechanism (see scheme) is based on structural evidence as well as on the hydrogen-cleaving activity of other Ru^{II} complexes.



Angew. Chem. **2001**, *113*, 3693–3697

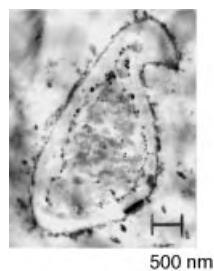
R. Hartmann, P. Chen* 3581–3585

Noyori's Hydrogenation Catalyst Needs a Lewis Acid Cocatalyst for High Activity

Keywords: asymmetric catalysis • homogeneous catalysis • hydrogenation • Lewis acids • ruthenium



Fungi make piles of gold! A green-chemistry route, based on the bioreduction of AuCl_4^- ions by the fungus *Verticillium* sp., for the formation of gold nanoparticles is demonstrated. The TEM micrograph shows a single *Verticillium* cell after reaction with gold ions and entrapment of gold nanoparticles on the cell wall and cytoplasmic membrane.



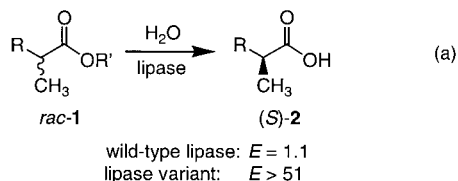
P. Mukherjee, A. Ahmad, D. Mandal, S. Senapati, S. R. Sainkar, M. I. Khan, R. Ramani, R. Parischa, P. V. Ajayakumar, M. Alam, M. Sastry,* R. Kumar* 3585–3588

Bioreduction of AuCl_4^- Ions by the Fungus, *Verticillium* sp. and Surface Trapping of the Gold Nanoparticles Formed

Keywords: bioinorganic chemistry • biosynthesis • gold • green chemistry • nanostructures

Angew. Chem. 2001, 113, 3697–3701

Recombinant methods work exceedingly well in the directed evolution of an enantioselective enzyme. For the kinetic resolution of the ester *rac*-1 by a lipase [Eq. (a)] three steps were applied: 1) Generation of mutants by the error-prone polymerase chain reaction (epPCR), 2) identification of “hot spots” in the enzyme by epPCR and simplified combinatorial multiple-cassette mutagenesis (CMCM), and 3) extension of the process of CMCM to cover a defined region of protein sequence space. From less than 40 000 enzyme variants generated, one was found which catalyzes the reaction with almost 50-times higher enantioselectivity than the wild-type enzyme.



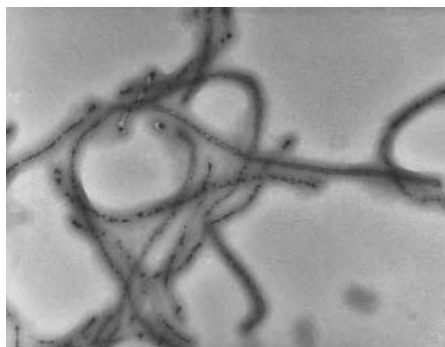
M. T. Reetz,* S. Wilensek, D. Zha, K.-E. Jaeger 3589–3591

Directed Evolution of an Enantioselective Enzyme through Combinatorial Multiple-Cassette Mutagenesis

Keywords: asymmetric catalysis • combinatorial chemistry • directed evolution • enzyme catalysis • lipases

Angew. Chem. 2001, 113, 3701–3703

Impregnating the cores of triblock-copolymer nanotubes with Fe_2O_3 renders them superparamagnetic. The resultant polymer/ Fe_2O_3 hybrid nanofibers (see TEM image) have interesting properties in magnetic fields. The nanofibers align themselves in the magnetic-field direction, and mixtures of the nanofibers and nanotubes undergo phase separation.



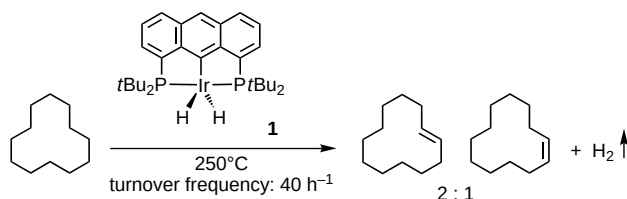
X. Yan, G. Liu,* F. Liu, B. Z. Tang, H. Peng, A. B. Pakhomov, C. Y. Wong 3593–3596

Superparamagnetic Triblock Copolymer/ Fe_2O_3 Hybrid Nanofibers

Keywords: copolymerization • magnetic properties • nanostructures • self-assembly • thin films

Angew. Chem. 2001, 113, 3705–3708

Thermostability is “conditio sine qua non” (a necessity) if organometallic compounds are used in the homogeneous catalysis of endothermic processes such as the dehydrogenation of alkanes to alkenes and hydrogen (see scheme). This thermostability and other requirements for such a catalyst are fulfilled by the anthrathos iridium(III)dihydride complex **1**.



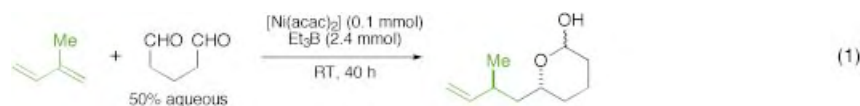
M. W. Haenel,* S. Oevers, K. Angermund, W. C. Kaska,* H.-J. Fan, M. B. Hall* 3596–3600

Thermally Stable Homogeneous Catalysts for Alkane Dehydrogenation

Keywords: C–H activation • dehydrogenation • density functional calculations • homogeneous catalysis • iridium • molecular modeling

Angew. Chem. 2001, 113, 3708–3712

Bishomoallyl alcohols are obtained with excellent 1,2- and 1,3-asymmetric induction from reactions of unsymmetrical dienes with glutaraldehyde (50 % aqueous) or cyclic hemiacetals at room temperature [see for example, Eq. (1)]. These homoallylations of aldehydes in the presence of water are promoted by the catalytic system $[\text{Ni}(\text{acac})_2]/\text{Et}_3\text{B}$ (acac = acetylacetonate).



Angew. Chem. **2001**, *113*, 3712–3714

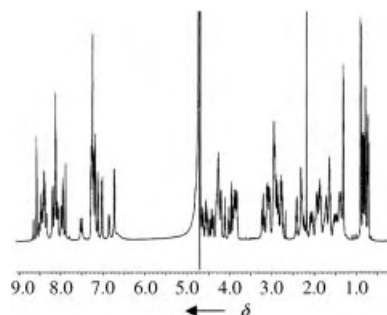
M. Kimura, A. Ezoe, S. Tanaka,
Y. Tamaru * 3600–3602

Nickel-Catalyzed Homoallylation of
Aldehydes in the Presence of Water and
Alcohols

Keywords: aldehydes • allylation •
boron • dienes • nickel



Unlabeled samples of the β -amyloid peptide(1–28) fibrils typical of Alzheimer's disease could be used to obtain well-resolved one- and two-dimensional ^1H NMR spectra (see picture). The technique applied was high-resolution magic-angle spinning on a 600 MHz NMR spectrometer. The results are in agreement with a parallel, in-register arrangement of the β -amyloid peptide in the fibril.



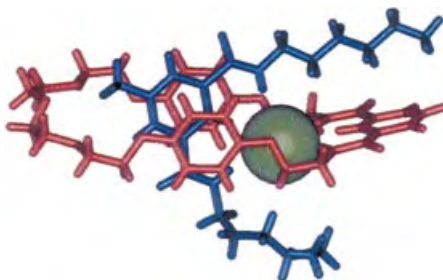
Angew. Chem. **2001**, *113*, 3715–3717

E. Mikros,* D. Benaki, E. Humpfer,
M. Spraul, S. Loukas,
C. I. Stassinopoulou,
M. Pelecanou * 3603–3605

High-Resolution NMR Spectroscopy of
the β -Amyloid(1–28) Fibril Typical for
Alzheimer's Disease

Keywords: amyloid fibrils •
NMR spectroscopy • structure
elucidation

First- and second-sphere coordination of a chloride anion templates the formation of a [2]pseudorotaxane (see picture) in which a pyridinium diamide threads through the annulus of a macrocyclic isophthalamide wheel. The formation of the pseudorotaxane depends on the nature of the anion involved: the use of a larger anion destabilizes the entire recognition motif.



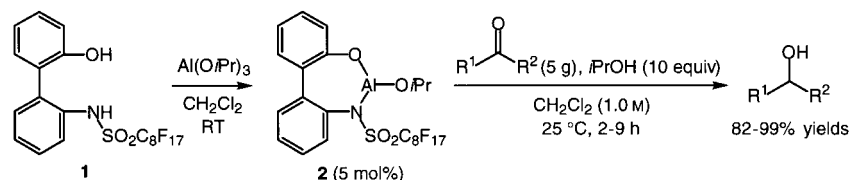
Angew. Chem. **2001**, *113*, 3718–3721

J. A. Wisner, P. D. Beer,*
M. G. B. Drew 3606–3609

A Demonstration of Anion Templatation
and Selectivity in Pseudorotaxane
Formation

Keywords: amides • anions • rotaxanes •
self-assembly • supramolecular chemistry

Simple mixing of $\text{Al}(\text{O}i\text{Pr})_3$ with the requisite ligand **1** in CH_2Cl_2 at room temperature smoothly generates the new, powerful aluminum catalyst **2**, which efficiently catalyzes Meerwein–Ponndorf–Verley (MPV) reduction of various carbonyl substrates under mild conditions (see scheme). Scale-up experiments highlight the potential of the new MPV reduction procedure for practical use.



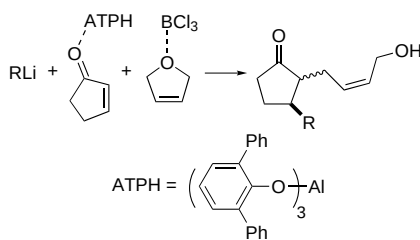
Angew. Chem. **2001**, *113*, 3722–3724

T. Ooi, H. Ichikawa,
K. Maruoka * 3610–3612

Practical Approach to the Meerwein–
Ponndorf–Verley Reduction of Carbonyl
Substrates with New Aluminum Catalysts

Keywords: aluminum •
homogeneous catalysis • ketones •
reduction

A one-pot three-component coupling involving organolithium reagents, ATPH·cyclopentenone complex, and dihydrofuran·BCl₃ complex (see scheme) gives moderate to good yields of the products with selective formation of either the 2,3-*cis* or 2,3-*trans* isomer, depending on the nature of the lithium reagent.



S. Saito, S. Yamazaki,
H. Yamamoto * 3613–3617

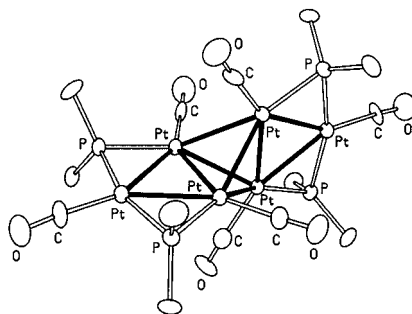
Novel Three-Component Coupling Using Aluminum Tris(2,6-diphenylphenoxide) (ATPH): The Same Synthetic Strategy Leads to *trans*- and *cis*-Jasmonates

Keywords: allylation •
diastereoselectivity • enones •
Michael addition •
multicomponent reactions

Angew. Chem. **2001**, *113*, 3725–3729



The unusual cluster [Pt₆(CO)₆(μ-PtBu₂)₄](CF₃SO₃)₂ (**1**) has a tetrahedral Pt₄ core, two opposite edges of which are bridged by two other platinum atoms (see picture). Complex **1** is remarkably stable and can be regioselectively functionalized at the two apical sites. Its reaction with NaBH₄ affords the first platinum formyl complex: [Pt₆(CO)₄(CHO)₂-(μ-PtBu₂)₄].



P. Leoni,* F. Marchetti, L. Marchetti,
M. Pasquali, S. Quaglierini .. 3617–3618

The First Platinum Formyl, a Member of a Series of Hexanuclear Clusters Exhibiting a Rare Structure

Keywords: carbonyl complexes •
cluster compounds • formyl complexes •
platinum • P ligands

Angew. Chem. **2001**, *113*, 3729–3730

More helix than peptide? The helical polypeptides have distinctive circular dichroism (CD) spectra, as shown in the graphic. The recent experimental observation of a peptide with an intense CD spectrum, which suggests a helical content of greater than 100% is therefore highly anomalous. We present calculations from first principles which could explain this unusual observation.



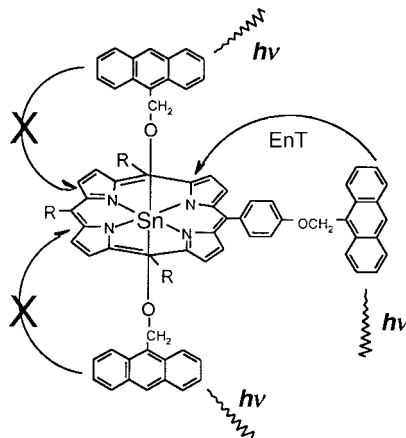
Z. Dang, J. D. Hirst * 3619–3621

Short Hydrogen Bonds, Circular
Dichroism, and Over-Estimates of
Peptide Helicity

Keywords: ab initio calculations •
circular dichroism • helical structures •
hydrogen bonds • peptides

Angew. Chem. **2001**, *113*, 3731–3733

“Equatorial” energy transfer: Orientation control of intramolecular energy transfer (EnT) is found in the donor–acceptor system shown, light absorbed by the “peripheral” anthracene is efficiently transferred to the porphyrin, but that by the “axial” anthracene subunits is not.



L. Giribabu, A. Ashok Kumar,
V. Neeraja, B. G. Maiya * ... 3621–3624

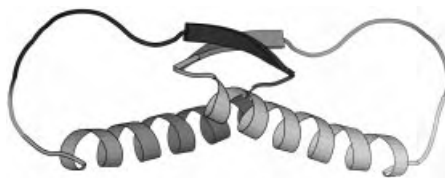
Orientation Dependence of Energy
Transfer in an Anthracene–Porphyrin
Donor–Acceptor System

Keywords: anthracene •
donor–acceptor systems •
energy transfer • fluorescence •
porphyrinoids

Angew. Chem. **2001**, *113*, 3733–3736



In contrast to DNA, proteins with topologically linked backbone structures have not yet been observed in Nature. We have chemically synthesized a p53 protein catenane (see schematic representation) consisting of interlocking cyclic polypeptides to demonstrate that such structures are synthetically attainable and can significantly stabilize the folded conformation of a protein.



Angew. Chem. **2001**, *113*, 3737–3739

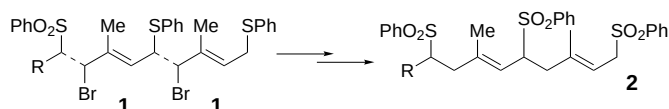
L. Z. Yan, P. E. Dawson* ... 3625–3627

Design and Synthesis of a Protein Catenane

Keywords: catenanes • chemoselectivity • protein design • protein engineering • solid-phase synthesis



Successive elongation by a C₅ unit is possible when an allylic sulfone is coupled with 4-bromo-3-methyl-2-butenyl phenyl sulfide (**1**). The thiosulfone compound formed was then oxidized to the corresponding disulfone, which, upon coupling with another equivalent of **1** and oxidation, produced the trisulfone **2**, again elongated by a C₅ unit (see scheme). This process, which can be repeated again, is the basis for a highly efficient synthesis of carotenoids.



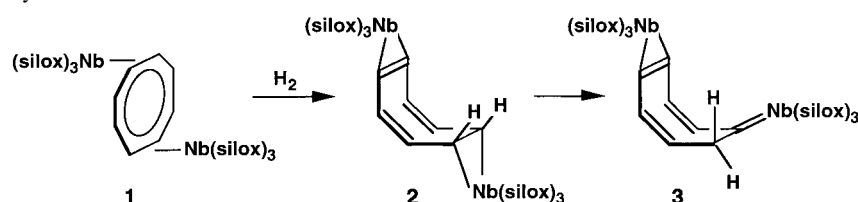
Angew. Chem. **2001**, *113*, 3739–3741

M. Ji, H. Choi, M. Park, M. Kee, Y. C. Jeong, S. Koo* ... 3627–3629

A Highly Efficient Chain-Extension Process in the Systematic Syntheses of Carotenoid Natural Products

Keywords: alkenes • carotenoids • sulfones • synthetic methods • total synthesis

The resonance energy of COT²⁻ in [(silox)₃Nb]₂(η -1,2; η -5,6-C₈H₈)] (**1**) is indirectly responsible for its dehydrogenation to **2**, but this olefin complex is thermodynamically less stable than the alkyldiene **3**. silox = *t*Bu₃SiO, COT = cyclooctatetraene.



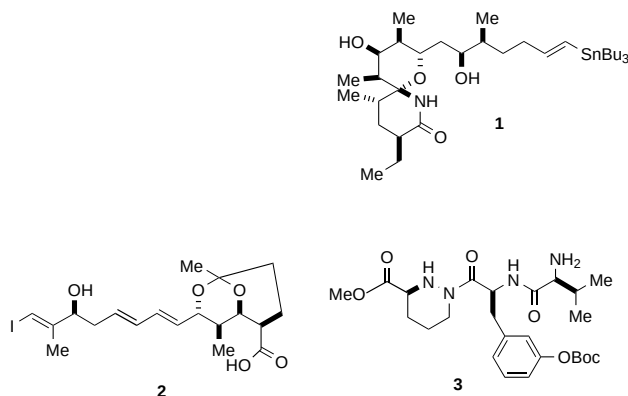
Angew. Chem. **2001**, *113*, 3741–3744

A. S. Veige, P. T. Wolczanski*, E. B. Lobkovsky ... 3629–3632

Dehydrogenation of [(silox)₃Nb]₂(η -1,2; η -5,6-C₈H₈)] (silox = *t*Bu₃SiO) to [(silox)₃Nb]₂(η -1,2; η -5,6-C₈H₆)] and Its Subsequent Alkene-to-Alkyldiene Rearrangement

Keywords: alkyldiene ligands • cyclooctatetraene • dehydrogenation • niobium • rearrangements

Crafting of the building blocks **1**–**3** allows the convergent conjoining of **2**–**3** in advance of macrolactonization. The subsequent linkup of the eastern sector with **1** by Stille coupling enabled the convenient stereocontrolled assembly of the immunosuppressive agent (–)-sanglifehrin A (Boc = *tert*-butoxycarbonyl).



Angew. Chem. **2001**, *113*, 3744–3748

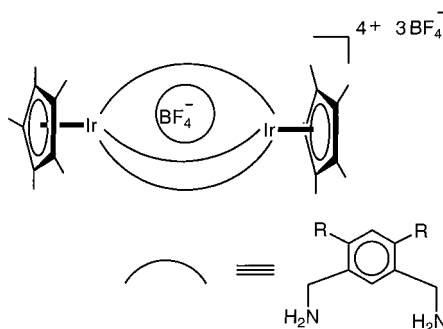
M. Duan, L. A. Paquette* ... 3632–3636

Enantioselective Total Synthesis of the Cyclophilin-Binding Immunosuppressive Agent Sanglifehrin A

Keywords: cyclizations • immunochemistry • macrolactonization • Stille coupling • total synthesis

Iridium and rhodium coordination chemistry

has been used to self-assemble metallocryptands: Treatment of two equivalents of $[(Cp^*M(solv)_3)[BF_4]_2]$ ($Cp^* = C_5(CH_3)_5$; $M = Rh, Ir$; $solv = acetone$) with three equivalents of the bidentate ligand 1,3-bis(aminomethyl)-2,5-dimethoxy-4,6-dimethylbenzene (**L**) afforded the first irido- and rhodocryptands $[(Cp^*M)_2L_3][BF_4]_4$ in high yields (70–85%). The use of less congested ligands increased the accessibility of the cavity of the metallocryptands and enabled the encapsulation of tetrafluoroborate ions (see scheme).



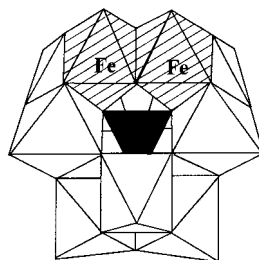
H. Amouri,* M. N. Rager, F. Cagnol, J. Vaissermann 3636–3638

Rational Design and X-ray Molecular Structure of the First Irido-Cryptand and Encapsulation of a Tetrafluoroborate Anion

Keywords: host–guest systems • iridium • rhodium • self-assembly • supramolecular chemistry

Angew. Chem. **2001**, *113*, 3748–3750

The diiron-substituted silicotungstate γ - $SiW_{10}[Fe^{3+}(OH_2)_2]_2O_{38}^{6-}$ (schematically shown) is an effective catalyst for the oxygenation of alkenes in homogeneous reaction media with 1 atm of molecular oxygen. For example, a selectivity for cyclooctene oxide of 98% and a turnover number of 10000 were achieved in the epoxidation of cyclooctene. The catalyst is stable under the reaction conditions, and its ability to use molecular oxygen raises the prospect of using it in industrial epoxidation processes.



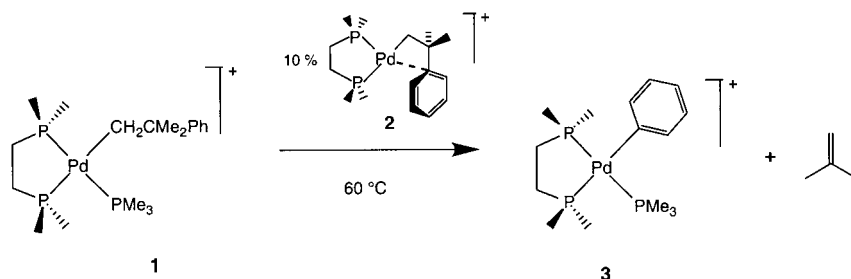
Y. Nishiyama, Y. Nakagawa, N. Mizuno* 3639–3641

High Turnover Numbers for the Catalytic Selective Epoxidation of Alkenes with 1 atm of Molecular Oxygen

Keywords: epoxidation • homogeneous catalysis • oxygenation • polyoxometalates

Angew. Chem. **2001**, *113*, 3751–3753

 **The extrusion of isobutene** from the neophyl derivative **1** is catalyzed by the cationic palladium π -arene complex **2** in a process that involves the cleavage of the β C–C bond of the latter (see scheme). The inverse reactivity, that is olefin insertion, is observed when the reaction proceeds in the presence of ethylene.



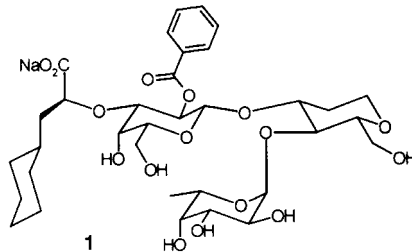
J. Cámpora,* E. Gutiérrez-Puebla, J. A. López, A. Monge, P. Palma,* D. del Río, E. Carmona* ... 3641–3644

Cleavage of the $C_{alkyl}-C_{aryl}$ Bond of $[Pd-CH_2CMe_2Ph]$ Complexes

Keywords: arene ligands • C–C activation • insertions • metallocycles • palladium

Angew. Chem. **2001**, *113*, 3753–3756

A mix of accident, serendipity, and rational design led to compound **1**, the most potent E-selectin inhibitor known to date. It was assembled in ten linear steps in an overall yield of > 25%. In a static assay it was 100-fold more potent than sialyl Lewis^x. In an even more relevant flow assay that mimics the dynamic in vivo conditions, **1** showed an IC_{50} of 1–2 μM , whereas sialyl Lewis^x did not inhibit at concentrations up to 1000 μM .



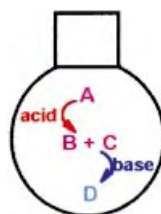
G. Thoma,* R. Banteli, W. Jahnke, J. L. Magnani, J. T. Patton ... 3644–3647

A Readily Available, Highly Potent ESelectin Antagonist

Keywords: carbohydrates • inhibitors • medicinal chemistry • selectins • sialic acids

Angew. Chem. **2001**, *113*, 3756–3759

Here is a solution to a classical problem: How to put, in one pot, both an acid and a base without their mutual destruction? The sol–gel materials method offers an approach: acids or bases are entrapped within these materials, and then organic reaction sequences, which require these opposing reagents, are carried out simultaneously or consecutively in the same pot (see scheme).



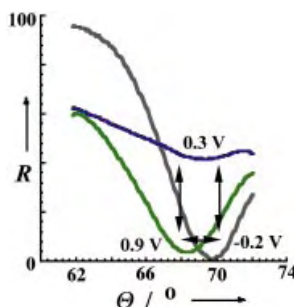
F. Gelman, J. Blum,*
D. Avnir* 3647–3649

Acids and Bases in One Pot while
Avoiding Their Mutual Destruction

Keywords: Brønsted acids •
Brønsted bases •
heterogeneous catalysis •
immobilization •
multicomponent reactions •
sol–gel processes

Angew. Chem. **2001**, *113*, 3759–3761

A prussian-blue thin film assembled on an Au electrode yields an optoelectronic three-state switching system for the photonic transduction of electrical signals, and a sensing device for the electrocatalyzed oxidation of NADH, using surface plasmon resonance (SPR) spectroscopy. The SPR spectra measured for the modified Au surface are shown for different potentials and the generation of the different redox states of the prussian-blue film: -0.2 V = fully reduced, 0.3 V = semi-oxidized, 0.9 V = fully oxidized.



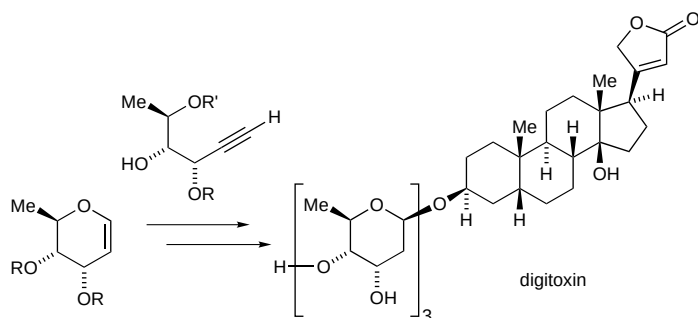
O. A. Raitman, E. Katz, I. Willner,*
V. I. Chegel, G. V. Popova ... 3649–3652

Photonic Transduction of a Three-State
Electronic Memory and of
Electrochemical Sensing of NADH by
Using Surface Plasmon Resonance
Spectroscopy

Keywords: electrochemistry •
molecular switches • optoelectronics •
prussian blue • sensors •
surface plasmon resonance

Angew. Chem. **2001**, *113*, 3761–3764

Tungsten-catalyzed alkynol cycloisomerization and iterative acid-catalyzed stereoselective glycosylations form the basis of a revolutionary new strategy for oligosaccharide synthesis. The method has been successfully applied to a highly convergent synthesis of *Digitalis* 2-deoxyglycosides (see scheme).



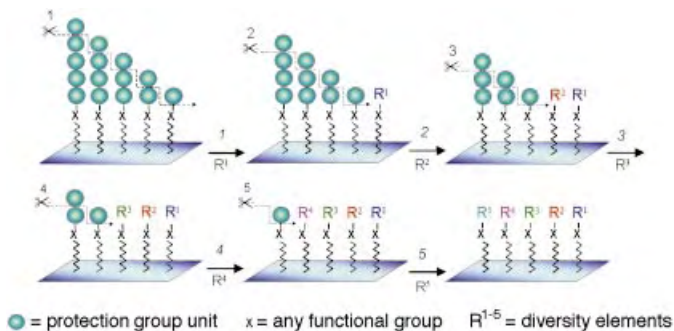
F. E. McDonald,*
K. S. Reddy 3653–3655

Convergent Synthesis of Digitoxin:
Stereoselective Synthesis and
Glycosylation of the Digoxin
Trisaccharide Glycal

Keywords: cycloisomerization •
glycosylation • homogeneous catalysis •
oligosaccharides • tungsten

Angew. Chem. **2001**, *113*, 3765–3767

Modular cleavage of oligomer protecting groups is at the heart of the unichemo-protection (UCP) strategy (see scheme) that simplifies synthesis and facilitates construction of polyfunctional molecules.



L. P. Miranda, M. Meldal* . 3655–3657

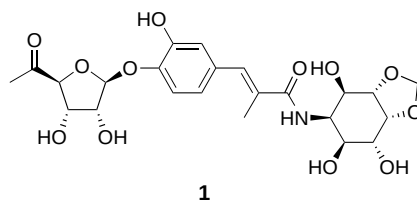
Unichemo Protection: A Concept for
Chemical Synthesis

Keywords: combinatorial chemistry •
protecting groups •
solid-phase synthesis • synthetic methods

Angew. Chem. **2001**, *113*, 3767–3769



The power of Pd-catalyzed asymmetric allylic alkylation (AAA) reactions is clearly demonstrated by the efficient synthesis of the complex title compound **1**, an analogue of hygromycin A. The modular nature of the synthetic route is ideally suited to provide access to further analogues.



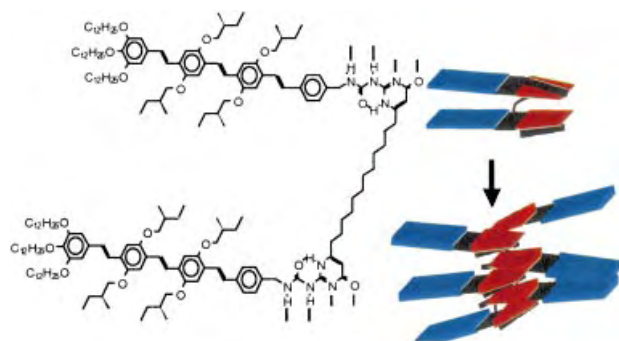
B. M. Trost,* O. Dirat, J. Dudash, Jr.,
E. J. Hembre 3658–3660

An Asymmetric Synthesis of C-2-*epi*-
Hygromycin A

Keywords: asymmetric catalysis •
asymmetric synthesis • natural products •
palladium • total synthesis

Angew. Chem. **2001**, *113*, 3770–3772

A combination of the well-defined character of π -conjugated oligomers and the material properties of polymers is displayed by the supramolecular hydrogen-bonded π -conjugated architectures of the title compounds (see scheme). These compounds have been successfully used for the first time in electronic devices.



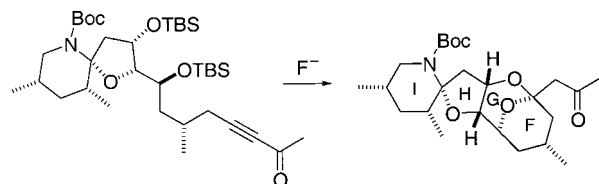
A. El-ghayoury, A. P. H. J. Schenning,
P. A. van Hal, J. K. J. van Duren,
R. A. J. Janssen,*
E. W. Meijer* 3660–3663

Supramolecular Hydrogen-Bonded
Oligo(*p*-phenylene vinylene) Polymers

Keywords: electronic devices •
fullerenes • hydrogen bonds •
polymers • supramolecular chemistry

Angew. Chem. **2001**, *113*, 3772–3775

A stereocontrolled synthesis of the C26–C40 domain of the azaspiracid shellfish toxins containing the intricate FGHI ring system has been achieved by the deployment of novel methods for heterocycle synthesis (see scheme). Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.



C. J. Forsyth,* J. Hao,
J. Aiguade 3663–3667

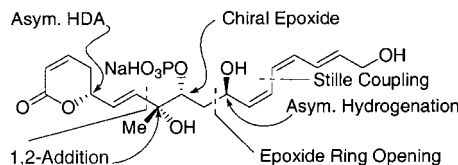
Synthesis of the (+)-C26–C40 Domain of
the Azaspiracids by a Novel Double
Intramolecular Hetero-Michael Addition
Strategy

Keywords: azaspiracid •
natural products • synthetic methods •
total synthesis

Angew. Chem. **2001**, *113*, 3775–3779



The most selective protein phosphatase inhibitor identified to date, fostriecin was synthesized in a highly convergent manner by a chiral building block approach (see picture). Three of the four stereocenters were introduced by using catalytic methods, including novel and practical applications of asymmetric hetero-Diels–Alder (HDA) and hydrolytic kinetic resolution reactions.



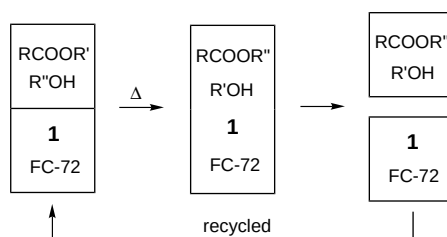
D. E. Chavez,
E. N. Jacobsen* 3667–3670

Total Synthesis of Fostriecin (CI-920)

Keywords: antitumor agents •
asymmetric catalysis •
Diels–Alder reactions • epoxides •
enzyme inhibitors • total synthesis

Angew. Chem. **2001**, *113*, 3779–3782

There is no need for the recovery of the catalyst in the fluororous biphasic transesterification catalyzed by $[\{\text{Cl}(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_2\text{SnOSn}(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_2\text{Cl}\}_2]$ (**1**; see scheme), which results in quantitative conversions and yields. An FC-72 solution of the dimeric fluoroalkyldistannoxane **1** can be recycled repeatedly without having to recover the neat catalyst.



J. Xiang, S. Toyoshima, A. Orita,
J. Otera * 3670–3672

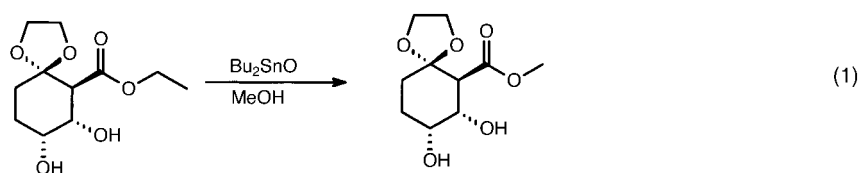
A Practical and Green Chemical Process: Fluoroalkyldistannoxane-Catalyzed Biphasic Transesterification

Keywords: fluorinated ligands • homogeneous catalysis • synthetic methods • tin • transesterification

Angew. Chem. **2001**, *113*, 3782–3784



An extraordinarily versatile transesterification of simple or highly functionalized esters of aliphatic and aromatic carboxylic acids in high yields is catalyzed by dibutyltin oxide [Eq. (1)]. The reaction is compatible with several functional groups, for example, acetals, ketals, aliphatic bromides, enol ethers, urethanes, as well as free hydroxy, phenolic, and amino groups, and even with water.



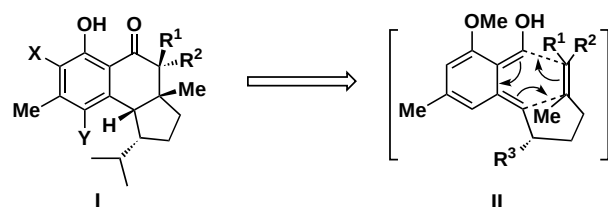
P. Baumhof, R. Mazitschek,
A. Giannis * 3672–3674

A Mild and Effective Method for the Transesterification of Carboxylic Acid Esters

Keywords: homogenous catalysis • synthetic methods • tin • transesterification

Angew. Chem. **2001**, *113*, 3784–3786

A streamlined and general method for the construction of benzannulated systems such as **I** involves the intramolecular Diels–Alder reaction of photochemically generated hydroxy-*o*-quinodimethanes, for example, **II**. The method was optimized to set the stage for the synthesis of the naturally occurring hamigerans.



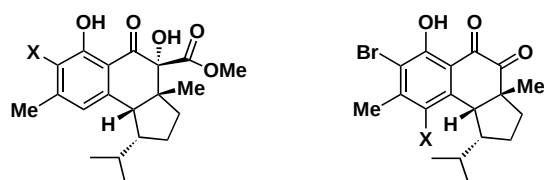
K. C. Nicolaou,* D. Gray,
J. Tae 3675–3678

Total Synthesis of Hamigerans: Part 1. Development of Synthetic Technology for the Construction of Benzannulated Polycyclic Systems by the Intramolecular Trapping of Photogenerated Hydroxy-*o*-quinodimethanes and Synthesis of Key Building Blocks

Keywords: cycloaddition • natural products • photochemistry • quinodimethanes • total synthesis

Angew. Chem. **2001**, *113*, 3787–3790

The synthesis of libraries of natural products is important for chemical biology studies. With this in mind, the intramolecular Diels–Alder reaction of photochemically generated hydroxy-*o*-quinodimethanes was used to produce the naturally occurring hamigerans **1–4** and several of their epimers.



1: X = H : debromohamigeran A **3:** X = H : hamigeran B
2: X = Br : hamigeran A **4:** X = Br : 4-bromohamigeran B

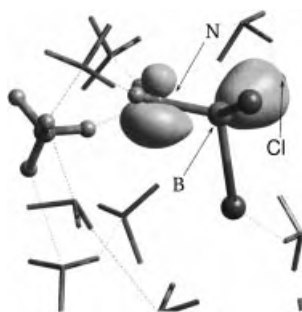
K. C. Nicolaou,* D. Gray,
J. Tae 3679–3683

Total Synthesis of Hamigerans: Part 2. Implementation of the Intramolecular Diels–Alder Trapping of Photochemically Generated Hydroxy-*o*-quinodimethanes; Strategy and Completion of the Synthesis

Keywords: cycloaddition • natural products • photochemistry • quinodimethanes • total synthesis

Angew. Chem. **2001**, *113*, 3791–3795

Contrary to the concerted two-step mechanism in the gas phase, the ammonolysis of boron trichloride in excess ammonia in the liquid phase follows an ionic three-step mechanism, according to a Car–Parrinello molecular dynamics investigation. The pair of electrons in the N–H bond becomes a lone electron pair on the N atom, whereas the electrons in the B–Cl bond leave the ionic intermediate together with the Cl atom (see picture).



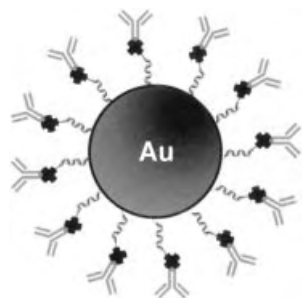
S. Reinhardt, C. M. Marian,*
I. Frank 3683–3685

The Influence of Excess Ammonia on the Mechanism of the Reaction of Boron Trichloride with Ammonia—An ab initio Molecular Dynamics Study

Keywords: density functional calculations • molecular dynamics • reaction mechanisms • solvent effects • solvolysis

Angew. Chem. **2001**, *113*, 3795–3797

A supramolecular construction kit comprises DNA-functionalized gold nanoparticles, covalent DNA–streptavidin conjugates, and biotinylated antibodies and allows the generation of functional nanoparticle reagents (see schematic illustration). The combination of specific antibodies and DNA-stabilized colloidal gold is applicable for the detection of antigens attached to a chip.



C. M. Niemeyer,* B. Ceyhan 3685–3688

DNA-Directed Functionalization of Colloidal Gold with Proteins

Keywords: analytical methods • DNA • nanostructures • proteins • supramolecular chemistry

Angew. Chem. **2001**, *113*, 3798–3801

The macroscopic shape of the starting material is retained during the solid/gas reaction between iron and gaseous SiCl_4 , which leads to the formation of iron silicide FeSi (as well as FeCl_2 , which is gaseous under the reaction conditions (1000°C)): If, for example, an iron wire spiral (see bottom of picture) is used, the reaction product FeSi also retains this spiral form (top).



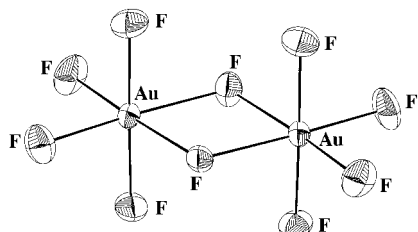
M. Binnewies,* A. Meyer,
M. Schütte 3688–3690

The Unusual Formation of Iron Silicide by Reaction of Iron with SiCl_4

Keywords: iron • silicon • solid-state reactions

Angew. Chem. **2001**, *113*, 3801–3803

The only pentafluoride with a dimeric structure is gold pentafluoride (see structure). According to calculations it has the highest fluoride-ion affinity and thus is the strongest Lewis acid known to date. It decomposes in HF under its own acidity to give AuF_3 and F_2 .



I.-C. Hwang, K. Seppelt* ... 3690–3693

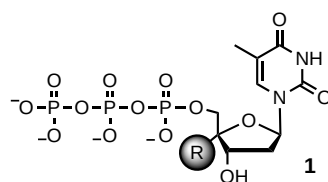
Gold Pentafluoride: Structure and Fluoride Ion Affinity

Keywords: ab initio calculations • fluorides • gold • superacidic systems

Angew. Chem. **2001**, *113*, 3803–3805



Do enzyme–sugar interactions contribute to DNA-polymerase fidelity? With the novel chemical probes **1** ($\text{R} = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), which are used by a DNA polymerase more selectively than the natural counterpart ($\text{R} = \text{H}$), insights are obtained into the influence of enzyme–sugar interactions on the selectivity of the enzyme.



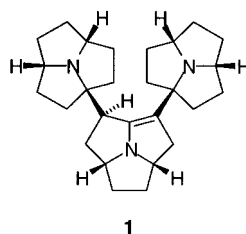
D. Summerer, A. Marx* 3693–3695

DNA Polymerase Selectivity: Sugar Interactions Monitored with High-Fidelity Nucleotides

Keywords: bioorganic chemistry • DNA polymerases • DNA recognition • DNA replication • nucleotides

Angew. Chem. **2001**, *113*, 3806–3808

A vicelike grip on a proton is exerted by the unusual nonacyclic product **1**, which forms spontaneously in a unique enamine trimerization that occurs when azatriquinenamine is heated in the presence of a proton source. pK_a measurements and computational modeling of the proton affinity substantiate the superbasic character of the trimer.



M. Mascal,* M. Lera, A. J. Blake,
M. Czaja, A. Kozak, M. Makowski,
L. Chmurnyński 3696–3698

The Azatriquinenamine Trimer—
A Novel Proton Chelate

Keywords: ab initio calculations •
 enamines • polycycles • receptors •
 superbases

Angew. Chem. **2001**, *113*, 3809–3811



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

* Author to whom correspondence should be addressed



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In the communication by **V. Thuillier, M. Famulok, and co-workers** (*Angew. Chem. Int. Ed.* **2000**, 39, 4369–4373), a correction is necessary in Figure 3: The authors noticed that clone D16-05 contains an additional C residue in position 42 between G41 and G43 (5'-end of the sequence region shown in orange). This mutation slightly alters the computer-generated secondary structure of the point mutant D16-05 to the folding shown in Figure 3 b. The RNA decoys incubated with D16-05 (Figure 3 a, lanes 7, 8, 10, and 11) did not contain C42 because they were transcribed from a template DNA that was obtained by means of PCR with a 5' primer that lacks C42. The authors therefore repeated the analysis represented in Figure 3 with the correct primers. The analysis revealed that constructs 10 and 11 in Figure 3 a can effectively restore the cleavage activity. As a consequence, the previous statement that helix I (red) plays an important structural role in doxycycline binding is still valid but it now appears that the effect of helix I can be exerted in a sequence-independent manner. All other conclusions of this communication remain unaffected..

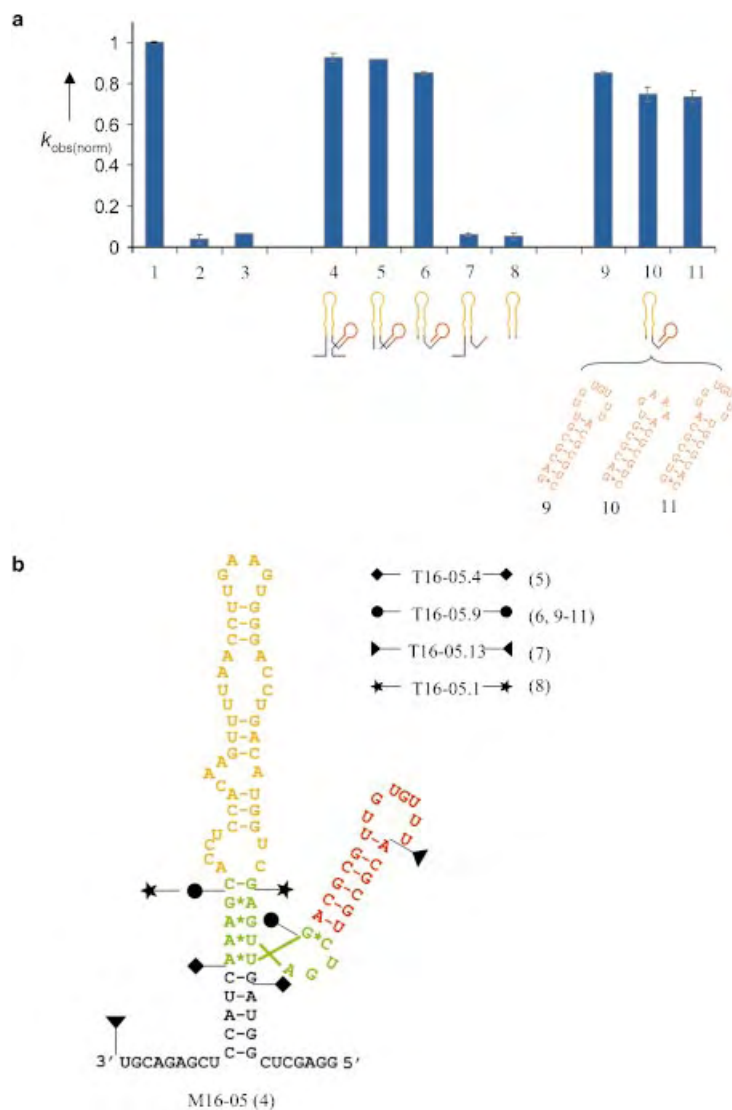


Figure 3. Determination of the minimal sequence of clone D16-05. **a)** Relative activity $k_{\text{obs(norm)}}$ of the cleavage reaction under various conditions (always in the presence of 1 μM tRNA as an unspecific competitor). 1: Cleavage activity of D16-05 (1 nM). 2: Same in the presence of 200 nM **1**. 3: Same as in 2 in the presence of 2.0 μM unselected pool as an unspecific competitor. 4–8: Same as in 2 in the presence of 2.0 μM cleavage inactive point mutant M16-05 (4), construct T16-05.4 (5), construct T16-05.9 (6), construct T16-05.13 (7), construct T16-05.1 (8). 9–11: Same as in 2 in the presence of 2.0 μM T16-05.9 with the depicted variations in helix I. **b)** Computer-generated secondary structure of the point mutant D16-05. The various marker symbols flank the sequences of the truncated versions tested. To enable T7-transcription two guanosine residues, which are not shown here, were inserted into the 5'-position of the truncated constructs. Orange: The original randomized region; red: constant region from the HHR (helix I); green: catalytic core. The guanosine residue shaded in black shows the point-mutation C–G. The numbers in parentheses refer to the numbering in (a).

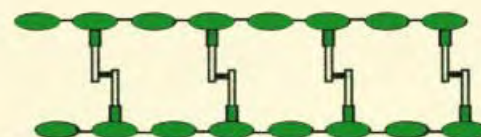
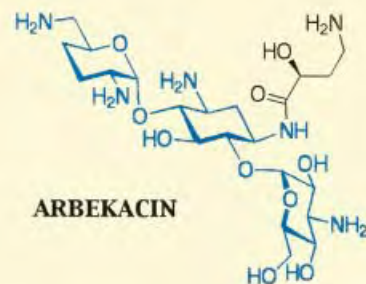
In the communication by **D. Zhao and co-workers** in Issue 11, 2001, pp. 2166–2168, two relevant references were not cited, for which the authors apologize: a) A. K. Cheetham, G. Férey, T. Loiseau, *Angew. Chem.* **1999**, 111, 3466–3492; *Angew. Chem. Int. Ed.* **1999**, 38, 3268–3292; b) N. Guillou, Q. Gao, M. Nogues, R. E. Morris, M. Hervieu, G. Férey, A. K. Cheetham, *C.R. Acad. Sci. Ser. IIc* **1999**, 2, 387–392.

Table 1 in the communication by **J. T. Groves, S. Shaik, and co-workers** in Issue 15, 2001, pp. 2874–2878 contains an incorrect sign. The first energy datum in entry 2 should be +0.07 kcal mol^{−1} and not −0.07.



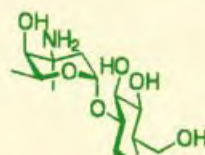
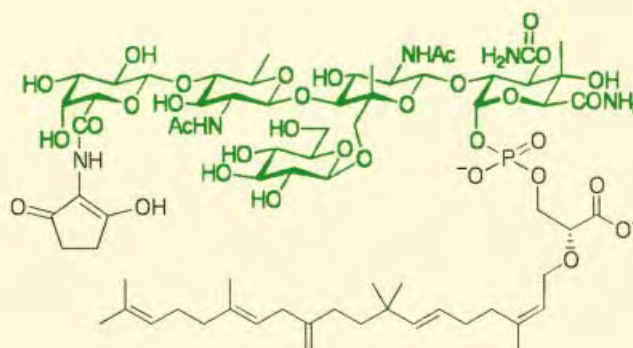
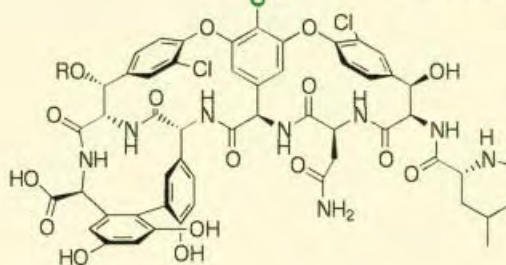
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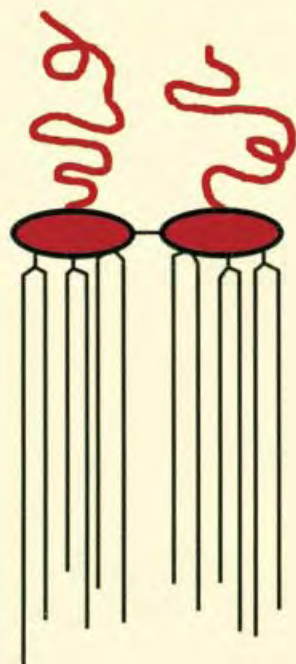


PEPTIDOGLYCAN

LIPOPOLYSACCHARIDE

**VANCOMYCIN**

MOENOMYCIN



Carbohydrate-Based Antibiotics: A New Approach to Tackling the Problem of Resistance

Thomas K. Ritter and Chi-Huey Wong*

Recent interest in the problem of antibiotic resistance has led to the identification of new targets and strategies for antibiotic discovery. Among these efforts, the development of small molecules as antibiotics to target carbohydrate receptors or carbohydrate-modifying enzymes represents a new direction. This review covers recent

work in this regard and discusses the impact of each strategy on the development of drug resistance. Particularly interesting targets include unique cell-surface carbohydrates, the transglycosylase involved in peptidoglycan biosynthesis, and bacterial RNA. With a greater understanding of the genome of different bacteria as well as advan-

ces in functional genomics and proteomics, we can expect the discovery of a variety of targets for the development of novel antibiotics.

Keywords: antibiotics • carbohydrates • enzyme inhibitors • peptidoglycan • RNA

1. Introduction

Antibiotics are bacterial or fungal products that inhibit the growth of other organisms. To date, the term antibiotics often includes synthetically produced antibacterial substances. Penicillins, the first major class of antibiotics, were introduced in the 1940s and 1950s. They were hailed as miracle drugs that eliminate bacteria without doing much harm to the cells of the treated individuals. Nevertheless, as a result of the saturation of the market, many large pharmaceutical companies lost interest in the development of antibiotic drugs and instead focused on chronic diseases. Through mutation and exchange of genes, however, bacteria have continued to develop resistance not only to single but also to multiple antibiotics.^[1, 2] Strains of at least three bacterial species that cause life-threatening diseases (*Enterococcus faecalis*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa*) have developed resistance to all available antibiotics. Enterococci, which are known to exchange resistance genes quite easily, have been able to transfer their resistance to *Staphylococcus aureus* in the laboratory. *S. aureus* is a particularly virulent organism that causes a wide range of diseases, and the fear is that they will eventually do so in nature as well.^[3] Two major factors are known to aggravate the problem of antibiotic resistance:

overuse of antibiotics in humans and animals, and noncompliance to the course of treatment by patients. Both the long-term exposure to low doses and the failure to finish a prescription encourage more resistant bacterial strains to flourish. Bacterial resistance to an antibiotic drug is mediated by one or more of the following processes:^[4, 5]

1. Prevention of the drug from reaching its target either by active efflux from or by reduced uptake into the cell, as well as by sequestration of the antibiotic by protein binding.
2. Deactivation of the antibiotic by enzymatic modification.
3. Modification of the drug's target, thereby eliminating or reducing the binding of the antibiotic.
4. Metabolic bypass of the inhibited reaction.
5. Overproduction of the antibiotic target.

Of these mechanisms, the first three represent the most common processes that enhance bacterial resistance to antibiotics (Figure 1). The widespread occurrence of such resistance mechanisms has renewed industrial interest in this field. Currently available antibacterial drugs act on only a small number of targets (see Section 2), and all experience resistance problems. To overcome these resistance problems efficiently, the identification of new targets as well as the improvement of existing drugs will be necessary.

Carbohydrates are found ubiquitously in nature as building blocks of the structural framework of cells, as sources of metabolic energy, and as key components of various intercellular recognition processes.^[6, 7] It is therefore not surprising that various existing antibiotics are based on carbohydrates, that is, they contain a glycan portion in their structure or they

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E-mail: wong@scripps.edu

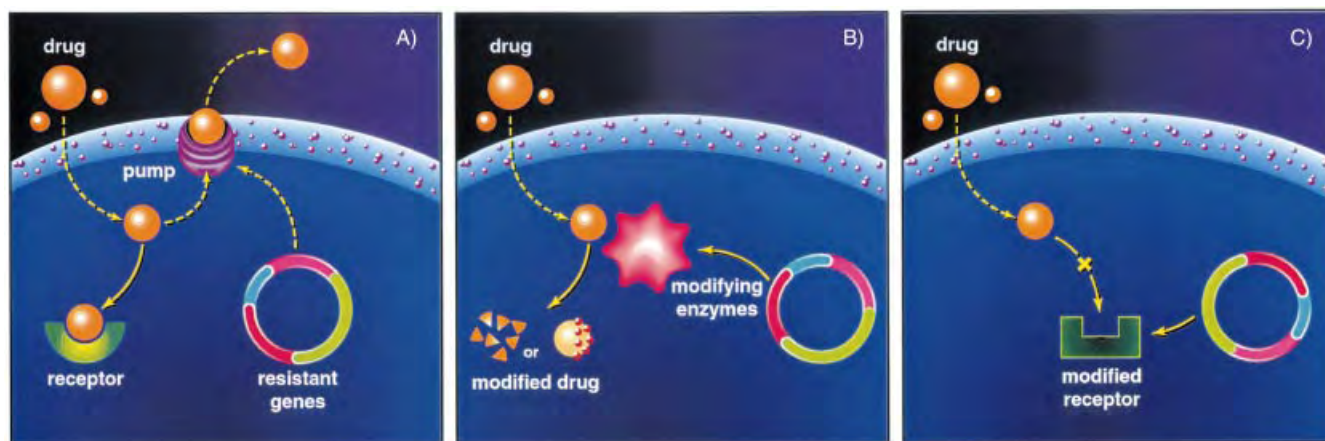


Figure 1. Mechanisms of bacterial drug resistance: A) active efflux; B) enzymatic modification of the drug; C) modification of target receptor or enzyme.

are non-carbohydrate molecules that target an enzyme or receptor associated with carbohydrate synthesis, metabolism, or recognition. Most of these carbohydrate-based antibiotics occur naturally or are semisynthetic. Although the development of carbohydrate-based therapeutics appears to have great potential, it has been hampered by a series of obstacles.^[8] Carbohydrates are densely functionalized with hydroxy groups of similar reactivity, leading to difficulties in their synthesis. They often bind their targets with a relatively low affinity. Furthermore, medicinal chemists consider complex carbohydrates as an uninteresting class of molecules for drug development, since carbohydrates are usually too complex for process development and their bioavailability is hampered as they are too hydrophilic. They are generally not stable enough to allow oral administration. One way to overcome these problems is to design mimics of carbohydrates that have improved properties with regard to stability, specificity, affinity, and synthetic availability.^[9, 10] These carbohydrate mimics potentially allow the targeting of the

numerous natural processes in which glycans are involved, without causing the problems that arise from the undesirable properties of carbohydrates.

2. Site of Action of Antibiotics

Antibiotics are most commonly classified by target and mechanism of action. In this respect, antibiotics that interfere with the biosynthesis and function of the bacterial cell envelope represent a primary target for drug development. Historically, bacteria have been classified as Gram-positive or Gram-negative, based on the cell envelope structure (Figure 2). The cytoplasm of Gram-positive bacteria is encapsulated by the plasma membrane. This phospholipid bilayer is surrounded by the cell wall, which consists of a polysaccharide/polypeptide framework, known as peptidoglycan or murein. The surface of Gram-positive bacteria is studded with teichoic acids (phosphodiester polymers) that often

Chi-Huey Wong received his B.S. and M.S. degrees from the National Taiwan University, and his Ph.D. in Chemistry with G. W. Whitesides from the Massachusetts Institute of Technology in 1982. He then moved with Professor Whitesides to Harvard University as a postdoctoral fellow for another year. He was on the chemistry faculty at Texas A&M University from 1983 to 1989, and has been Professor and held the Ernest W. Hahn Chair in Chemistry at The Scripps Research Institute since 1989. His current interests are in the areas of bioorganic and synthetic chemistry as well as biocatalysis, with a specific focus on the development of new synthetic chemistry based on enzymatic and chemo-enzymatic reactions, the study of carbohydrate-mediated biological recognition, and the development of mechanism-based inhibitors of enzymes and carbohydrate receptors.



C.-H. Wong



T. K. Ritter

Thomas K. Ritter was born in Bühl (Germany) in 1972. He first studied at the University of Constance, before moving to Portland State University (Oregon), where he carried out research under the guidance of D. H. Peyton and received his M.S. in 1998 for his work on paramagnetic NMR spectroscopic studies of metalloproteins. Since then he has been working in the group of C.-H. Wong at The Scripps Research Institute in La Jolla (California) using synthetic organic chemistry to study biological systems, in particular the biosynthesis of bacterial cell walls.

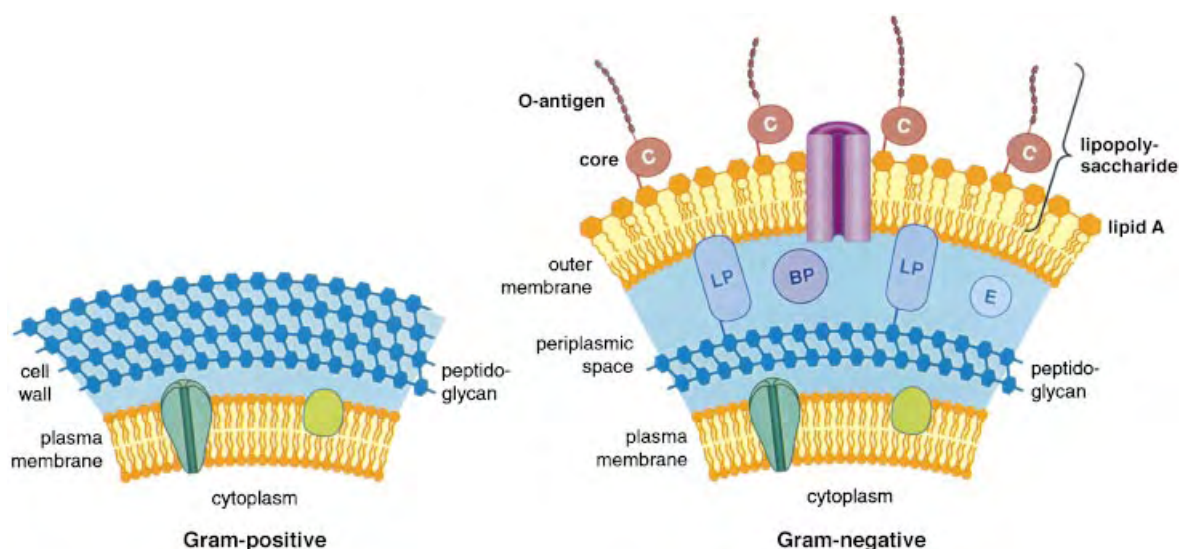


Figure 2. The cell envelope of Gram-positive and Gram-negative bacteria. Gram-positive bacteria have a thicker peptidoglycan layer than that of Gram-negative bacteria, but lack the outer membrane at the cell surface.

terminate in lipopolysaccharides (LPS). In contrast, Gram-negative bacteria are surrounded by two phospholipid bilayers (inner and outer membrane), which are separated by an aqueous compartment (periplasmic space). LPS represent the major component of the outer leaflet of the Gram-negative bacterial outer membrane. The periplasmic space contains a peptidoglycan layer as well as proteins that transport sugar and other nutrients. As a result of the importance of the cell envelope for the viability of bacteria, antibiotics that disrupt its integrity have been employed clinically for decades. Numerous mechanisms toward this end exist, with the inhibition of peptidoglycan biosynthesis perhaps being one of the most effective. The peptidoglycan layer provides the strength and rigidity of the cell envelope of bacteria, which allows them to live in a hypotonic environment and gives them their characteristic shape. Antibiotic-induced defects lead to cell lysis as a result of the inability of the bacteria to cope with the internal osmotic pressure. The biosynthetic pathway of peptidoglycan provides an attractive target for antibiotics, as it has no counterpart in mammalian cells. Other mechanisms geared towards the disruption of the cell envelope include the inhibition of LPS biosynthesis and pore formation in the bacterial membranes.

The prokaryotic translational machinery is the target of the majority of known antibiotics, probably because of the complexity of the ribosome, which makes it vulnerable to disruption in many ways. The crystal structure of the prokaryotic ribosome has only recently been

solved.^[11–13] It is composed of two unequal subunits: the large (50S) subunit consists of a 5S and a 23S rRNA molecule and 31 polypeptides, whereas the small (30S) subunit contains a 16S rRNA and 21 different polypeptides. The translation of mRNA into a protein commences with the formation of the initiation complex: in prokaryotes, the 30S and 50S ribosomal subunits and formylmethionine-tRNA assemble on a mRNA molecule. The ribosome then elongates the polypeptide in a multistep reaction cycle (Figure 3). Aminoacyl-tRNA binds to the A site; subsequently the growing polypeptide chain is transferred from the P-site tRNA to the aminoacyl-tRNA in the A site. Transfer of the resulting uncharged P-site tRNA out of the ribosome, and translocation (movement of the peptidyl tRNA from the A site to the P site) then complete the cycle. Finally, binding of two release factors to the termination codon induces transfer of the peptidyl group to

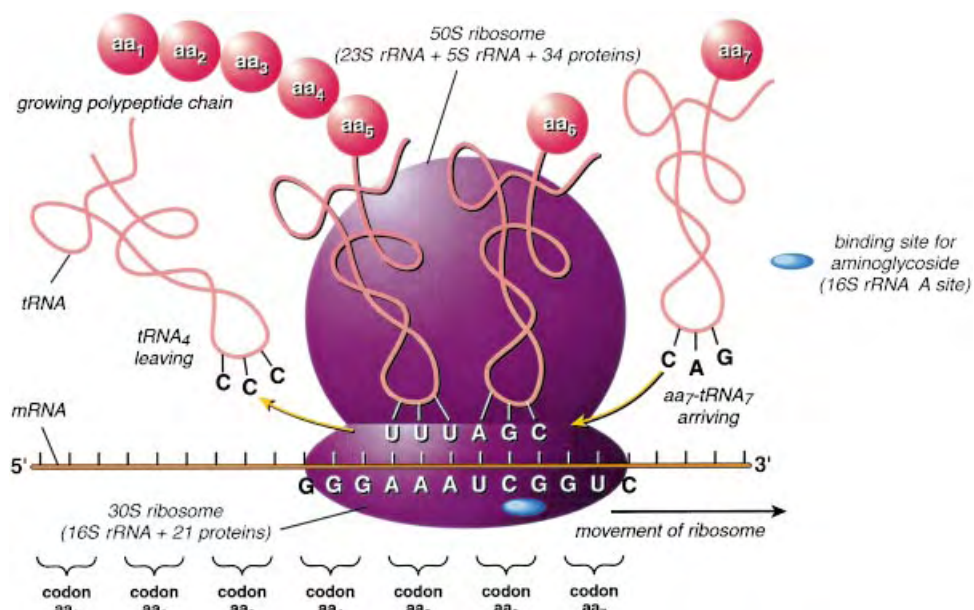


Figure 3. Ribosomal protein synthesis and the 16S rRNA A site for the binding of aminoglycosides.

water rather than to an aminoacyl-tRNA. The aminoglycoside and tetracycline antibiotics inhibit translation by binding to the small ribosomal subunit, whereas the macrolide antibiotics, chloramphenicol, and the oxazolidinones, a relatively new class of synthetic antibiotics, target the large subunit. In addition to the two major classes, there are antibiotics that affect RNA synthesis (rifamycins), DNA topoisomerase inhibitors (quinolones, 2-pyridones),^[14, 15] and the so-called antimetabolites (sulfonamides, trimethoprim) that interfere with folic acid metabolism.

3. Antibiotics That Target the Cell Envelope

3.1. LPS

In higher animals and humans, the release of LPS, also known as endotoxins, upon treatment with antibacterial agents may invoke septic shock. This further leads to an inflammatory response, resulting in numerous deaths in intensive-care units worldwide. A late treatment with conventional antibiotics will lead to acceleration of LPS release and therefore aggravation of the disease. Strategies for the control of LPS-mediated pathophysiological disorders include methods that interfere with LPS/serum or LPS/cell receptor interactions (e.g. LPS antibodies and LPS antagonists) or with the production and secretion of inflammatory mediators.^[16] Additionally, agents that interfere with the biosynthesis of LPS are bacteriocidal or at least inhibit bacterial growth, thus resulting in higher susceptibility to the action of other antibiotics. Moreover, such agents might lower the risk of Gram-negative sepsis by reducing the amount of endotoxins released when other antibiotics are administered simultaneously.

The structure of endotoxins consists of three regions (Figure 4). The lipid region (lipid A) consists of a GlcNAc–GlcNAc disaccharide that is modified by phosphates at the 1- and 4'-positions as well as by a variable number of fatty acids. This phosphoglycolipid is linked to a 3-deoxy-D-manno-octulosonic acid (KDO) unit of the core oligosaccharide, which varies from species to species. A repeating oligosaccharide polymer, the O-antigen, extends from the core oligosaccharide. The smallest LPS structure that is required for continued bacterial growth consists of lipid A and two

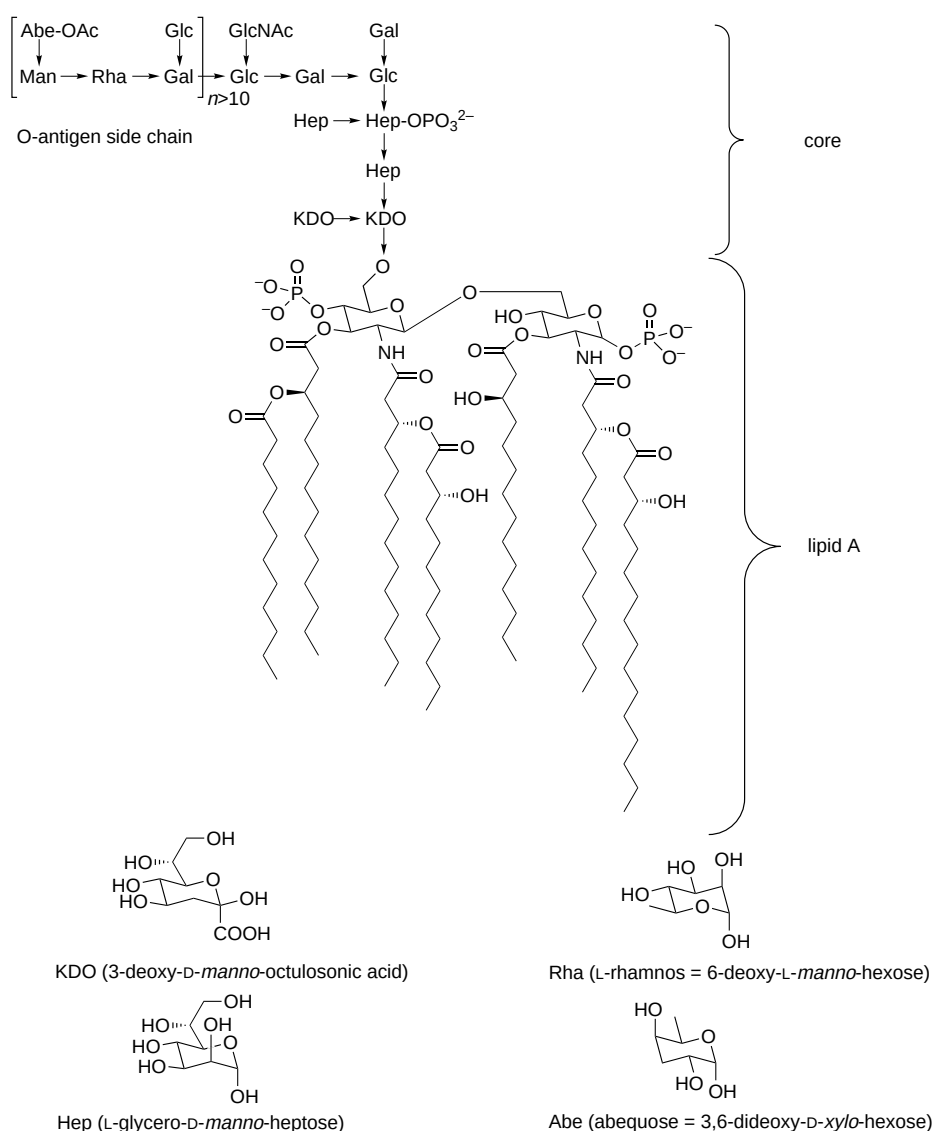
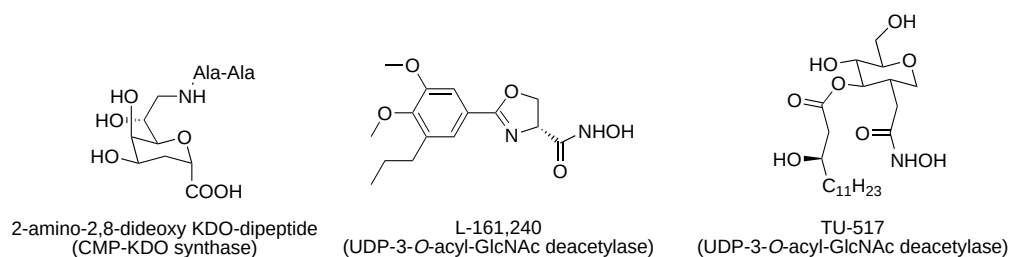


Figure 4. Lipopolysaccharide (LPS) of *Salmonella typhimurium* (GlcNAc = N-acetylglucosamine).

KDO moieties. The pathological effects seen upon the release of LPS can be induced by its lipid A region alone.

One of the strategies that has been investigated towards the inhibition of LPS biosynthesis involves targeting the unique enzyme CMP-KDO synthetase, which activates KDO as cytidyl nucleotide prior to incorporation into the LPS layer. Although KDO exists as four different tautomers in solution, only the β -pyranose form can act as a substrate for CMP-KDO synthetase.^[17] The 2-deoxy analogue of KDO is locked in the β -pyranose conformation and acts as a competitive inhibitor of the synthetase. 2,8-Dideoxy-8-amino KDO was found to be an even more potent inhibitor in vitro; therefore dipeptide conjugates were synthesized through the 8-amino group to facilitate transport across the membrane by peptide permeases. The 2,8-dideoxy-8-amino KDO dipeptides (Scheme 1) exhibited minimum inhibitory concentrations (MICs) of 5–100 $\mu\text{g mL}^{-1}$, depending on the species and agent tested.^[17] The requirement for active aminopeptidases for activity suggests that these conjugates act as prodrugs that release the KDO analogue inhibitor once inside the cell. In an



Scheme 1. Inhibitors of LPS biosynthesis. The targets are indicated in parentheses.

extension of this study, C-glycosyl derivatives of 2-deoxy KDO were synthesized.^[18] However, the introduction of any substituent at the C2 position of KDO resulted in almost complete loss of inhibitory activity against CMP-KDO synthetase. No further development was reported with regard to these approaches.

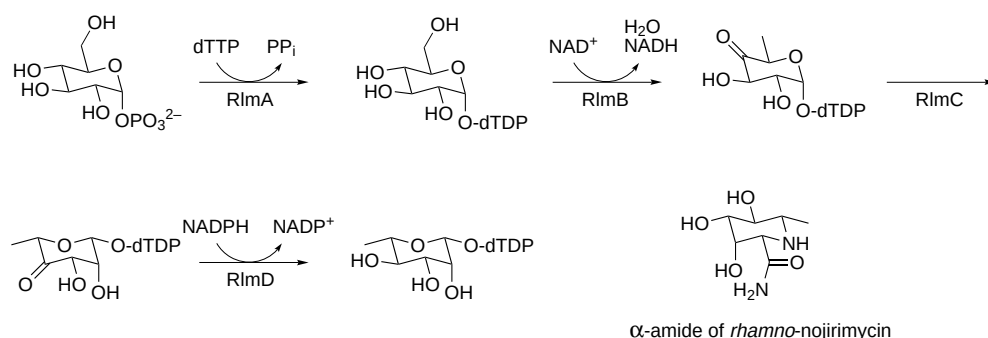
L-glycero-D-manno-Heptose (Hep) is the second sugar of the core oligosaccharide that is highly conserved among several genera of bacteria, but not found in mammalian cells. The recent structural determination of ADP-Hep 6-epimerase, an enzyme of the Hep biosynthetic pathway, along with the mechanistic conclusions drawn from its structure may allow the design of mechanism- and structure-based inhibitors that have antibiotic activity.^[19] Although these approaches, that is, the inhibition of the enzymes involved in the synthesis, activation, and transfer of KDO and Hep (the unique components of the core oligosaccharide) are interesting and certainly a new direction, they have so far not resulted in any new drugs.

A different strategy towards the inhibition of LPS production is to target the biosynthesis of lipid A, and some inhibitors have been reported (Scheme 1). Screening and subsequent optimization led to the discovery of hydroxamic acid derivatives that inhibit UDP-3-O-acyl-GlcNAc deacetylase (LpxC).^[20] The hydroxamic acid moiety is thought to inhibit the deacetylase by chelating a metal ion in the active site, thereby mimicking a pyrophosphate group. The most active compound, L-161,240, had an MIC of about $1 \mu\text{g mL}^{-1}$ against *E. coli* and rescued mice from an *E. coli* infection that was 100% fatal without treatment. In a more rational approach, hydroxamic acid moieties were attached to the 2-amino group of monosaccharides that resemble a portion of the LpxC substrate.^[21] Compounds that feature a long alkyl chain, such as TU-517, exhibited a wider spectrum of antibacterial activity than the hydroxamic acids obtained by simple screening.

A more specific strategy than targeting the biosynthesis of core oligosaccharide and lipid A is the inhibition of enzymes involved in the biosynthesis of the O-antigens, as these vary from species to species. Deoxysugars are frequently found in

O-antigens and L-rhamnose is one of the most common components. Incorporation of L-rhamnose into the cell wall occurs through its activated form, dTDP-L-rhamnose. This precursor is synthesized in four steps (Scheme 2):^[22] coupling of glucose-1-phosphate with dTTP (deoxythymidine triphosphate) is followed by the

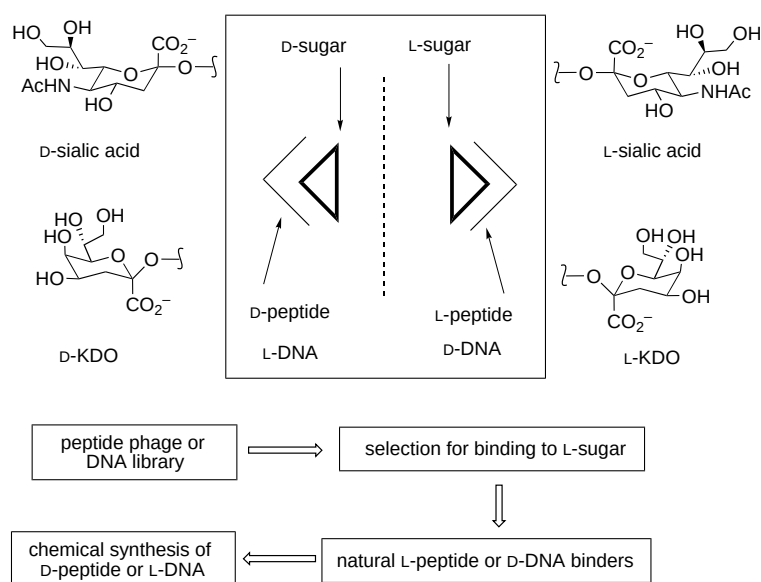
action of an NAD^{+} -dependent 4,6-dehydratase, epimerization at the 3- and 5-positions, and reduction. The enzymes that catalyze this pathway represent an appealing target, since humans do not synthesize dTDP-L-rhamnose. Micromolar concentrations of the analogues of *rhamno*-nojirimycin and



Scheme 2. The dTDP-L-rhamnose biosynthetic pathway and one of its inhibitors (RlmA = glucose-1-phosphate thymidyl transferase, RlmB = dTDP-D-glucose 4,6-dehydratase, RlmC = 6-deoxy-D-xylo-4-hexulose 3,5-epimerase, RlmD = dTDP-6-deoxy-L-xylo-4-hexulose reductase).

related trihydroxypiperic acid derivatives were shown to inhibit the biosynthesis of dTDP-L-rhamnose.^[23] The recent structural work on the second, third, and fourth enzyme of the dTDP-L-rhamnose pathway could soon make a structure-based approach towards the inhibition of these enzymes possible.^[24–26]

A new approach to the development of antibacterial agents that also makes use of the unique cell-surface carbohydrates, is the design of D-peptides, L-DNA, or L-RNA as synthetic receptors (Figure 5). These enantiomers of the natural L-peptides and D-nucleic acids are resistant to enzymatic degradation and are thus more stable in the circulation. To discover such enantiomeric oligomers, one can take advantage of biological replication and evolution methods by using phage display and DNA or RNA evolution.^[27] Phage display has been used to select short peptides that bind small molecules such as dioxin^[28] and biotin^[29] with moderate affinities, and it may be possible to obtain similar binding to sugars. In a recent demonstration of this strategy, a phage peptide display was used to identify L-peptides that bind to L-sialic acid or L-KDO. The corresponding D-peptides can be synthesized chemically and are expected to bind the natural D-sugars. Initial studies have identified peptides on phage that binds sialic acid with a dissociation constant in the nanomolar range.^[30] This strategy is complementary to the traditional carbohydrate-based vaccine approach.^[31]



The negative charge of the phosphate substituents of lipid A provides the initial site of interaction of some cationic peptide antibiotics (e.g. defensins, magainins, cecropins).^[32] These cationic peptides are amphipathic, that is, they have both a hydrophobic and a hydrophilic part. The presence of positively charged residues gives them an affinity for LPS that is higher than that of the metal ions that normally bind the LPS phosphate groups. Thus, the hydrophobic face of the antibiotic is positioned to disturb the integrity of the outer membrane, thus allowing insertion of the antibiotic into the membrane and formation of channels ("self-promoted uptake"). These pores promote leakage from the periplasm and increased uptake of antimicrobial compounds that act in synergy with the perturbing peptide. Additionally, the ability to bind to LPS gives these peptide antibiotics anti-endotoxic properties.

3.2. Peptidoglycan

Peptidoglycan biosynthesis^[33] (Figure 6) commences with the transfer of an enolpyruvyl group from phosphoenolpyruvate (PEP) to UDP-*N*-acetylglucosamine (UDP-GlcNAc). The NADPH-dependent reduction of the resulting unsaturated acid gives UDP-*N*-acetylmuramic acid (UDP-MurNAc). Three amino acid residues, L-Ala, D-Glu, and L-Lys (in Gram-positive bacteria) or *meso*-diaminopimelic acid (*m*DAP in Gram-negative bacteria) are then attached sequentially in ATP-dependent reactions to the lactic acid residue of UDP-MurNAc. This is followed by the coupling of

a preformed dipeptide, usually D-Ala-D-Ala, to the peptide terminus. The D-amino acids are synthesized either from L-amino acids under racemase catalysis, or from α -ketoglutarate in a reaction catalyzed by a D-amino acid aminotransferase. In the next step, MurNAc-pentapeptide phosphate is transferred from its UDP derivative to undecaprenyl phosphate, a carrier molecule embedded in the cytoplasmic membrane. A second GlcNAc residue is then coupled at the 4-position of MurNAc-pentapeptide. In many Gram-positive bacteria, the formation of the disaccharide is followed by the addition of several amino acids (usually glycines) to the ϵ -amino group of Lys. At this point, the GlcNAc-MurNAc peptide is translocated across the cytoplasmic membrane to the cell surface by an unknown mechanism. Here, the disaccharide units are polymerized by the action of several transglycosylases. Finally, transpeptidases catalyze the attack of the terminal side-chain amino group of *m*DAP (Gram-negative bacteria) or the amino terminus of the oligo-Gly linker (Gram-positive bacteria) at the peptide bond between the two D-Ala residues in a neighboring peptide chain, resulting in crosslinking with a concomitant loss of D-Ala.

Each of these enzymes represents a target for antibiotic development. The most commonly used antibiotics (the

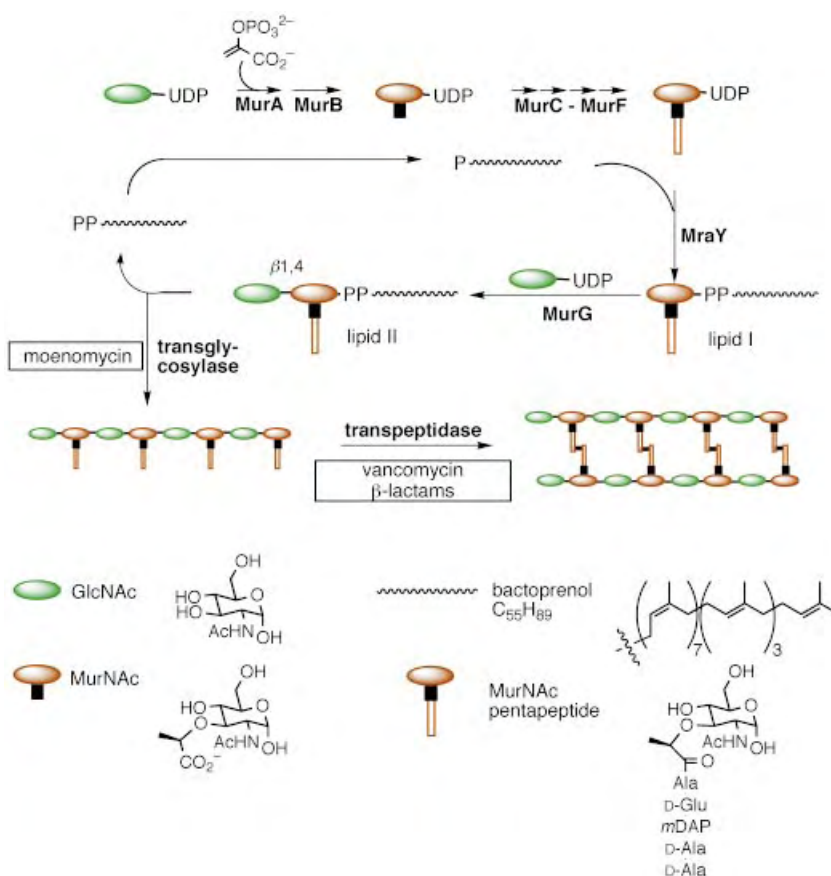


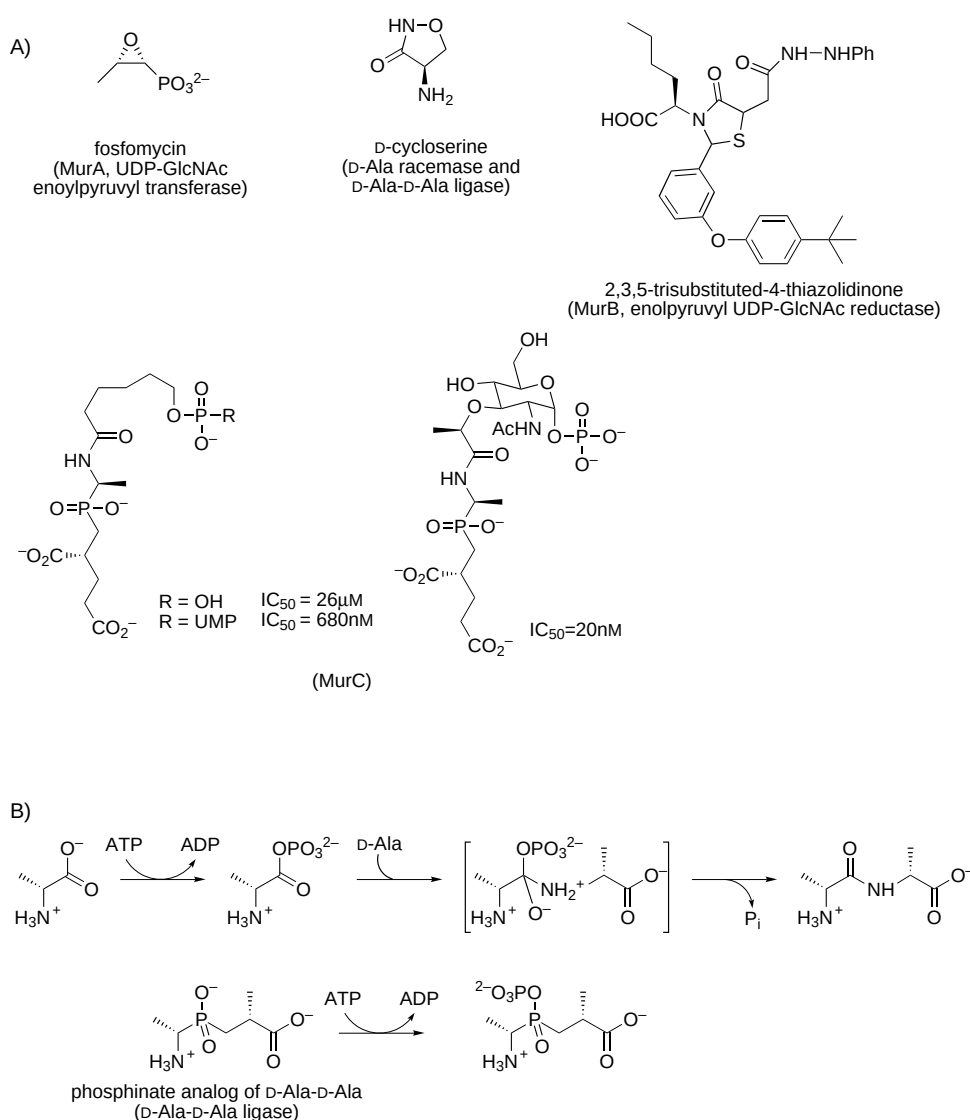
Figure 6. Biosynthesis of peptidoglycan (UDP = uridine diphosphate, Mur = muramic acid, MurNAc = *N*-acetylmuramic acid, P = phosphate substituent, MraY = translocase, *m*DAP = *meso*-diaminopimelic acid).

penicillins and cephalosporins) target the enzyme transpeptidase that catalyzes the crosslinking step. However, the widespread occurrence of resistance against these antibiotics as a result of the induction of β -lactamases, which catalyze the hydrolysis of the β -lactam moiety, has increased the significance of antibiotics that target the earlier steps in the peptidoglycan biosynthetic pathway (Scheme 3). Fosfomycin, an analogue of PEP, is an irreversible inhibitor of UDP-GlcNAc enolpyruvyl transferase (MurA). The crystal structure of the MurA/fosfomycin complex revealed that the antibiotic was covalently bound to a cysteine residue in the active site. This indicates that inactivation arises from the attack of the cysteine thiol at the epoxide moiety of fosfomycin.^[34] The enolpyruvyl-UDP-GlcNAc reductase (MurB) has received attention only recently, and a first series of inhibitors has been found.^[35] Diastereomeric mixtures of the reported 2,3,5-trisubstituted 4-thiazolidinones were designed to mimic the pyrophosphate moiety of the MurB substrate. The enzymes MurC-F, which are responsible for the sequential addition of amino acid residues to the lactic acid of

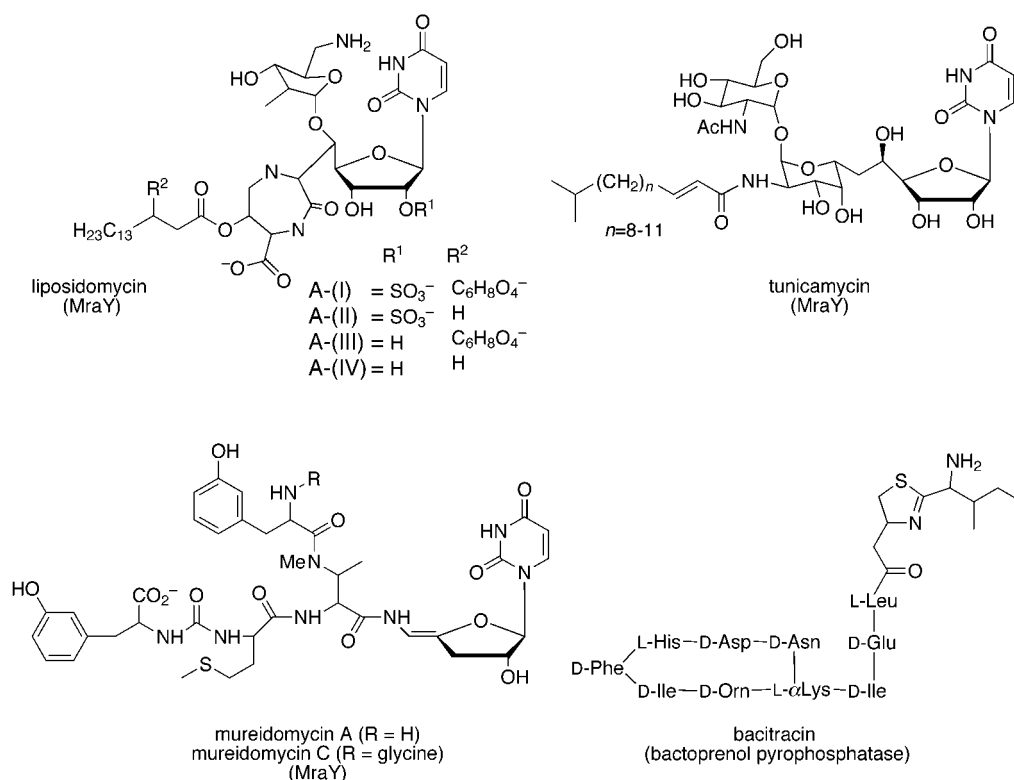
MurNAc, as well as the D-Ala-D-Ala ligase (Ddl) all catalyze the formation of peptide bonds. Inhibitors of these enzymes mimic the tetrahedral intermediates of the ligase reaction by incorporation of a phosphorus-containing group in place of the peptide bond.^[36] Recent structural and mechanistic studies of Ddl have revealed the mechanistic aspect of a phosphinate analogue that acts as a transition-state mimic of the reaction.^[37] D-Ala-D-Ala racemase and Ddl are also targeted by the antibiotic D-cycloserine.^[38] This antibiotic shows competitive inhibition of both enzymes and is thought to be a structural analogue of D-Ala. First generation inhibitors against MurD and MurE consisted of a phosphate group or UDP connected through a simple alkyl linker to the peptide group that mimicked the transition state.^[39, 40] Substitution of the alkyl linker with the native MurNAc residue increased the potency of the inhibitors by several orders of magnitude.^[41] Bacitracin, a cyclic peptide, inhibits the recycling of the carrier lipid by complexation to its pyrophosphate moiety in the presence of magnesium ions.^[42]

Several classes of nucleoside antibiotics inhibit the

phospho-MurNAc-pentapeptide translocase (MraY).^[43] These include tunicamycin, the liposidomycins, and the mureidomycins (Scheme 4). Although tunicamycin is a fairly potent inhibitor, its selectivity for MraY is low. Tunicamycin also inhibits N-linked glycan formation of the precursors of mammalian glycoproteins, thus causing toxicity problems. In contrast, mureidomycins and liposidomycins exhibit excellent selectivity for MraY.^[44, 45] In spite of their potent in vitro activity against MraY, liposidomycins showed only weak activity against bacteria. Transportation into cells might be limited by the hydrophilic sulfate moiety. Different medium components allowed the isolation of new liposidomycin analogues that lack the sulfate and/or 3-methylglutamic acid moiety.^[46, 47] Not only did these new analogues selectively inhibit MraY, but they were also more potent than their natural, more hydrophilic counterparts.^[46] An initial study towards the identification of the pharmacophore of the liposidomycins has been undertaken by superimposing their lowest energy conformation on the nucleoside substrate, UDP-MurNAc-pentapeptide.^[48] Mo-



Scheme 3. A) Inhibitors of the early stages of peptidoglycan biosynthesis (targets are indicated in parentheses); B) the D-Ala-D-Ala ligase reaction.



Scheme 4. Inhibitors of MraY (translocase) and of bactoprenol pyrophosphatase.

lecular overlap analysis indicated that the ribosamine sugar of the liposidomycins mimics the pyrophosphate group of UDP-MurNAc-pentapeptide. The nucleoside ribosamine core of the liposidomycins was synthesized and showed fair inhibitory activity. For a more complete structure–activity relationship (SAR) study, the elucidation of the role of each functional group present in the liposidomycins is required. Furthermore, analogues of the mureidomycins were synthesized in an attempt to identify their mechanism of inhibition.^[49] A structurally unique feature of the mureidomycins is the central enamide functionality that connects the nucleoside moiety to the peptide portion of the molecule. Enamides are known to tautomerize under acidic conditions to reactive *N*-acylimminium ions. It has been hypothesized that a nucleophilic attack at this reactive species in the active site leads to the covalent modification of the enzyme. However, the lack of reactivity of simple nucleoside structures that contain the unusual mureidomycin enamide functionality indicates that this moiety may not be involved in the slow binding inhibition of MraY by the mureidomycins.

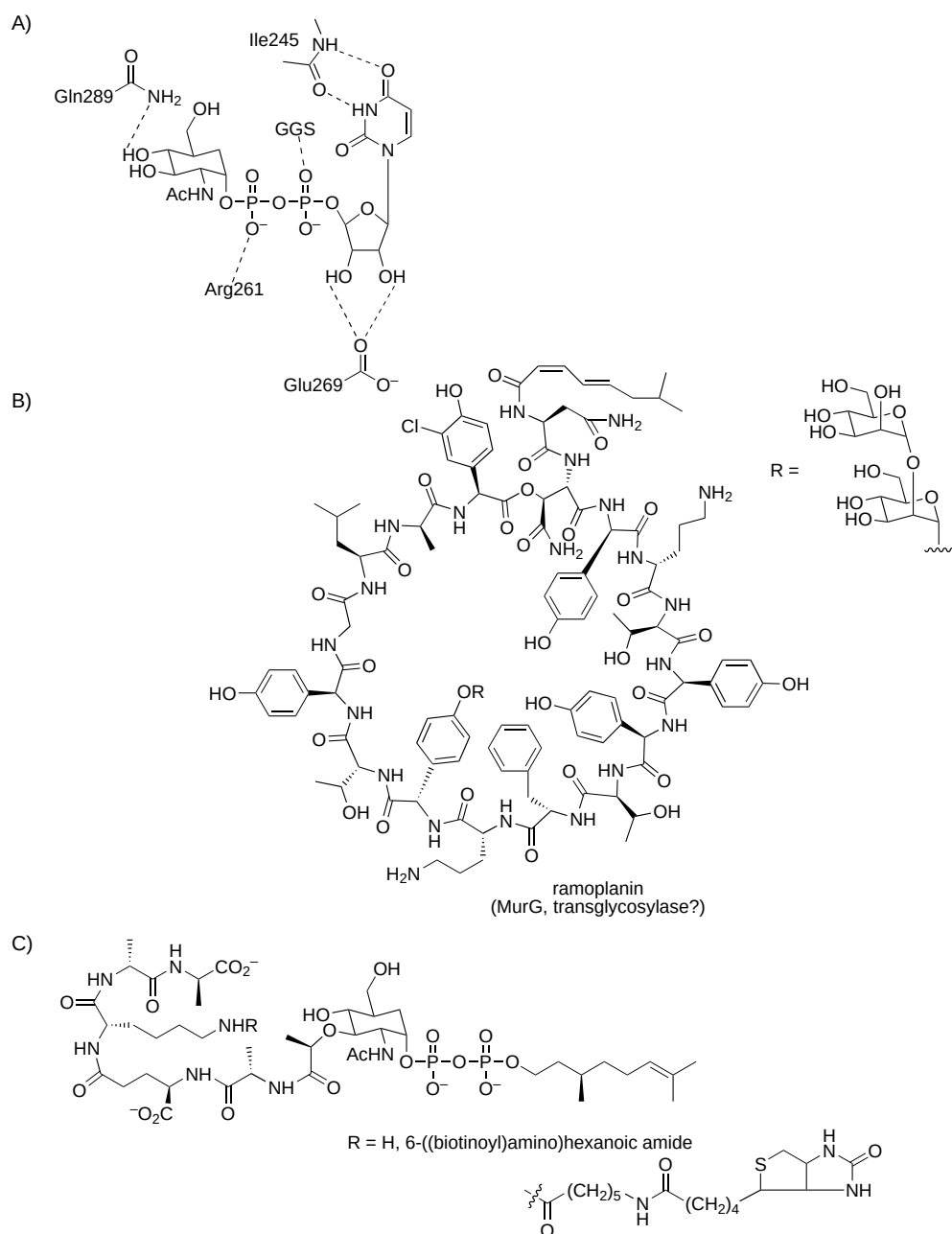
Ramoplanin, a glycopeptide, is the only known natural occurring inhibitor of the GlcNAc transferase (MurG) (Scheme 5).^[50] The development of synthetic inhibitors of MurG has been hampered by difficulties in obtaining the enzyme and its substrate, which are present in cells in only small quantities. Recently, however, MurG has been successfully isolated^[51] and its crystal structure has been solved.^[52] Furthermore, a simplified analogue of lipid I has been shown to act as a substrate, thus greatly improving the feasibility of a MurG assay.^[53] The synthetic substrate differs from lipid I only in that the 55-carbon undecaprenol chain has been

replaced by the ten-carbon chain of citronellol. Additionally, a biotin-labeled derivative was synthesized to simplify the assaying procedure, thus paving the way for the design and evaluation of new synthetic MurG inhibitors. With this new methodology available, MurG was kinetically characterized,^[51] and the site of inhibition of ramoplanin was reinvestigated.^[54] Results from this study indicated that ramoplanin's main mode of action may be the inhibition of transglycosylase, instead of the inhibition of MurG which had been postulated earlier.

Among the enzymes involved in the biosynthesis of peptidoglycan, the transglycosylase, which is responsible for the polymerization of disaccharide units, is perhaps the most interesting target for several reasons. The enzyme

is located on the cell surface, thus making it easily accessible to small molecular drugs. In addition, the polysaccharide backbone always remains intact in wild-type and resistant strains. New antibiotics that target the transglycosylation step may therefore be less prone to resistance development. Transglycosylase activity cannot be assigned to a single enzyme. Within the family of the penicillin-binding proteins (PBPs) of *E. coli*, several members with transglycosylase activity have been identified. Some of the PBPs are bifunctional and also catalyze transpeptidation. A systematic study of mutants that lacked all possible combinations of eight PBPs confirmed the absolute requirement of at least PBP1A or 1B for the viability of the bacteria.^[55] In addition to the bifunctional PBPs, monofunctional transglycosylases exist in bacteria,^[56] but their role in cellular peptidoglycan synthesis is not known. The same difficulties that were encountered in the development of MurG inhibitors are also prominent in studies of transglycosylation.^[57] Activity against transglycosylases is generally detected in a cumbersome and somewhat ambiguous assay format.^[58] There is a high-throughput screen available for transglycosylase; however, it can only detect compounds with high affinity to PBPs, as it relies on competition with the high-affinity phosphoglycolipid moenomycin.^[59]

Natural products that inhibit transglycosylation (Scheme 6) can be categorized into two classes: 1) those that directly inhibit the enzymes (e.g. moenomycin), and 2) those that bind lipid II, the substrate of transglycosylation (e.g. type B lantibiotics, glycopeptide antibiotics). The three-dimensional structure of the phosphoglycolipid moenomycin, which is employed as a growth promoter in animal nutrition, has been



Scheme 5. GlcNAc (MurG): A) interactions between the donor substrate and the enzyme (determined by X-ray crystal structure analysis), B) a MurG inhibitor, C) structure of acceptor derivatives used in a MurG assay.

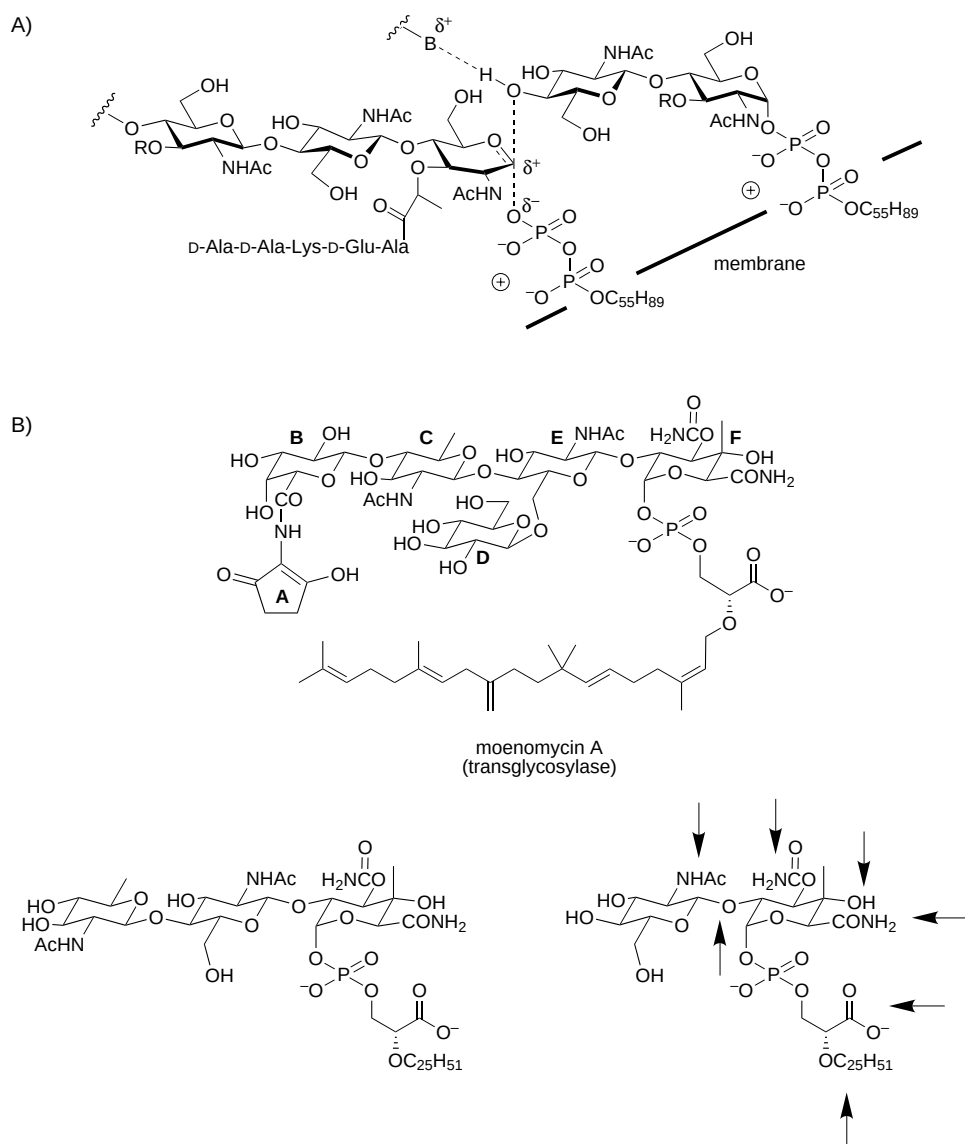
determined^[60] and extensive SAR studies have been carried out.^[61, 62] The moenomycins and analogues with at least three sugar units (C, E, F) are active *in vivo* against Gram-positive bacteria. Derivatives composed of only two sugars (E, F) are not active against antibiotics, but do inhibit transglycosylase *in vitro*, provided they have the correct substitution pattern. All functional groups on the F ring, the acetamide functionality of the E ring, and the lipid chain carboxylate and phosphate moiety are crucial for the activity. Unfortunately, the mechanism by which moenomycin mimics the natural substrates of transglycosylation is not clear upon examination of its structure. Rational design of more effective antibiotics based on the moenomycin core structure is therefore not trivial. However, a combinatorial library of novel disaccharides

based on moenomycin has been synthesized, in which four key positions, the 3- and 4-substituents of the F ring, the 2-substituent of the E-ring, and the lipid side chain, were structurally explored (Scheme 7).^[63] This study led to the discovery of a class of disaccharides with two aromatic substituents which inhibits peptidoglycan biosynthesis *in vitro*, are active as antibiotics, and exhibits an activity profile that is distinct from moenomycin.^[64] Several inhibitors of transglycosylation that incorporate long alkyl chains to mimic the membrane anchor of lipid II and moenomycin were rationally designed. Phosphate,^[65, 66] phosphonate,^[66, 67] and thiazoline derivatives^[68] of MurNac and GlcNac-MurNac disaccharides have been pursued, but none of these molecules have efficiently inhibited transglycosylation. This result, in combination with the SAR studies on moenomycin, as well as the combinatorial moenomycin disaccharide library, indicates that small mono- and disaccharides probably do not provide a sufficient number of interaction sites for tight binding to the enzymes that catalyze transglycosylation.

Lantibiotics are a class of peptide antibiotics that contain the unusual amino acids lanthionine and methyllan-

thionine and form intramolecular thioether linkages (Figure 7).^[69, 70] They interact with docking molecules in the cytoplasmic membrane, for example, lipid II.^[71, 72] The binding was not antagonized by D-Ala-D-Ala, which indicates an alternative binding mode to that of vancomycin (see Scheme 8). The lantibiotics can be subdivided into two classes, according to their mode of action. Type A lantibiotics (e.g. nisin) form pores in the cytoplasmic membrane upon binding to the docking molecules,^[73] whereas type B lantibiotics (e.g. mersacidin, actagardine) directly interfere with peptidoglycan biosynthesis by inhibiting transglycosylation.^[74]

During the last decade, the glycopeptide antibiotics have been intensively investigated and several reviews on this class of molecules have been published.^[75, 76] Two glycopeptide

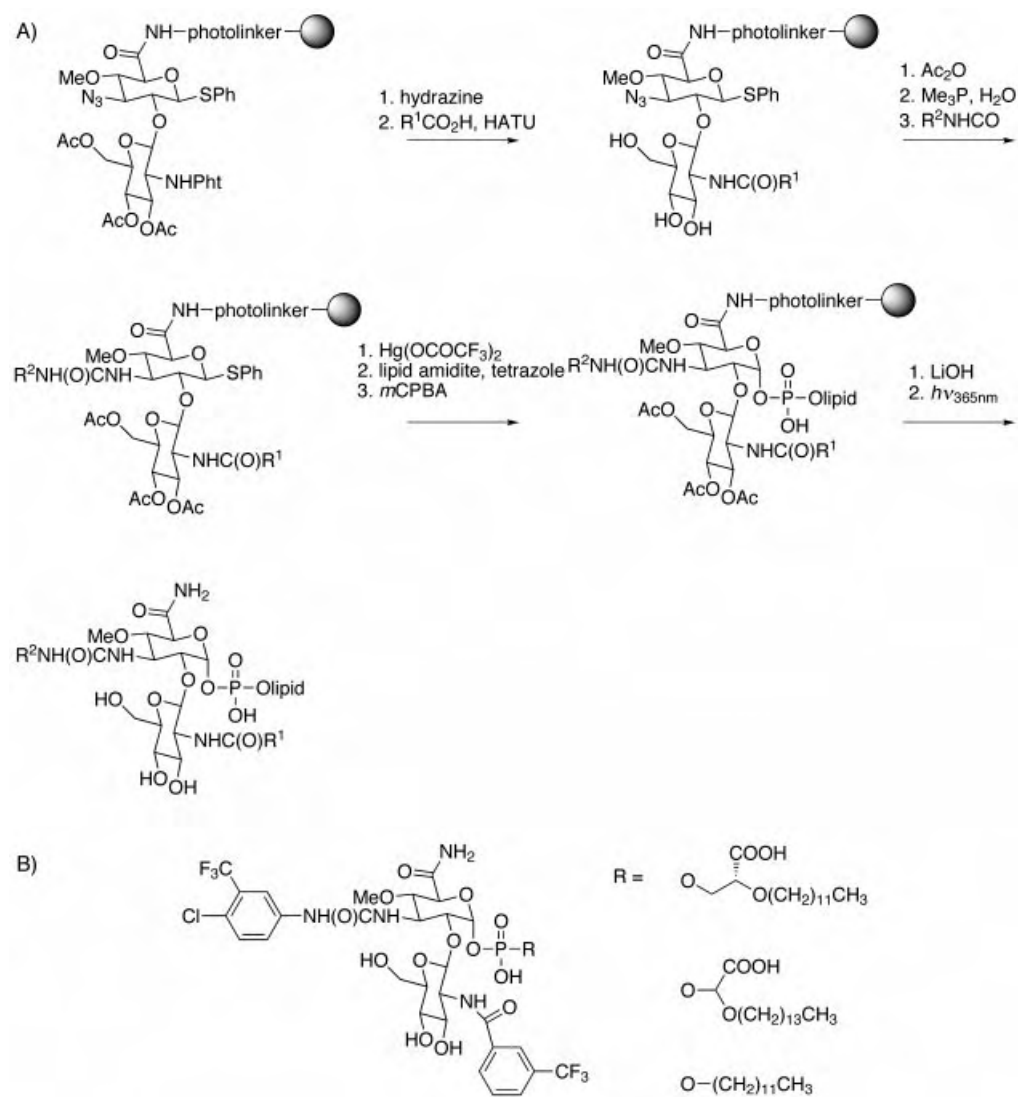


Scheme 6. The transglycosylase reaction: A) proposed transition state, B) moenomycin A and two simplified derivatives. The arrows indicate structural elements that were identified from SAR studies as essential for activity.

antibiotics, vancomycin and teicoplanin, are in clinical use and are often referred to as last-resort drugs, because of their utility in treatment of infections by bacteria that are resistant to many other classes of antibiotics, in particular methicillin-resistant *S. aureus* (MRSA) (Scheme 8). The mechanism of the glycopeptide antibiotics is well understood: the cyclic peptide portion binds noncovalently to the D-Ala-D-Ala termini of lipid II and immature peptidoglycan, thereby preventing transglycosylation and cross-linking of the peptide side chains (Scheme 9).^[77] Resistance against vancomycin occurs when bacteria change the composition of the peptide portion of peptidoglycan.^[78] Resistant strains that feature D-lactate or D-serine as the terminal amino acid have been isolated. In both cases, the hydrogen-bonding pattern between the cyclic peptide of the drug and the peptide termini of peptidoglycan is disturbed, leading to lower affinity binding, and therefore resistance. Even though the SAR of the glycopeptide antibiotics has been studied extensively,^[79] the

modifications necessary to improve the affinity for the peptide termini of vancomycin-resistant bacteria are not clear. Moreover, such altered antibiotics could be rendered useless in a short amount of time as a result of a further change in the peptide portion of peptidoglycan by the evolving bacteria. In contrast to the well-established binding mechanism of aglycon-peptidoglycan interaction, the role of the carbohydrate portion of glycopeptide antibiotics remains unclear. In vitro activity of vancomycin is affected minimally by removal of the sugar substituents; in vivo activity, however, is significantly reduced, which indicates the importance of the glycan for a favorable pharmacokinetic profile.^[79] A comparative NMR spectroscopic study of vancomycin and its aglycon has demonstrated that the vancomycin disaccharide influences the conformation of the cyclic peptide. In particular, the alignment of the amide protons, which participate in the hydrogen-bonding network with the cell-wall precursors, differs between the two structures, thus indicating the possible role of glycosylation in maintaining the bioactive conformation.^[80] A further task of the carbohydrate in dimerization has been suggested. Glycopeptide antibiotics are known to dimerize, thus leading to an increased activity as a result of multivalent effects. The tendency to dimerize and the anti-

biotic activity are stronger in A82846B (vancomycin plus one additional carbohydrate substituent) than in vancomycin itself, which indicates that the carbohydrate substituent may be involved in noncovalent dimer formation.^[81] The concept of multivalency as a mechanism of glycopeptide antibiotic action has been investigated in more detail with synthetic covalent dimers of vancomycin (Scheme 10).^[82, 83] These dimers not only bind to short peptides that terminate in D-Ala or D-lactate more strongly than to the corresponding monomers, they also showed increased activity against vancomycin-resistant enterococci (VRE). A trimeric vancomycin analogue that features a trifunctional amine as core, was found to bind a synthetic trimeric D-Ala-D-Ala peptide with a dissociation constant of 4×10^{-17} M, the tightest association known among low molecular weight organic species.^[84] A vancomycin polymer has been synthesized by the introduction of an olefin-containing substituent, followed by polymerization with Grubbs catalyst.^[85] This polymer also



Scheme 7. A combinatorial library based on moenomycin. a) Synthetic scheme (HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate, *mCPBA* = *meta*-chloroperoxybenzoic acid), b) some of the most active library members.

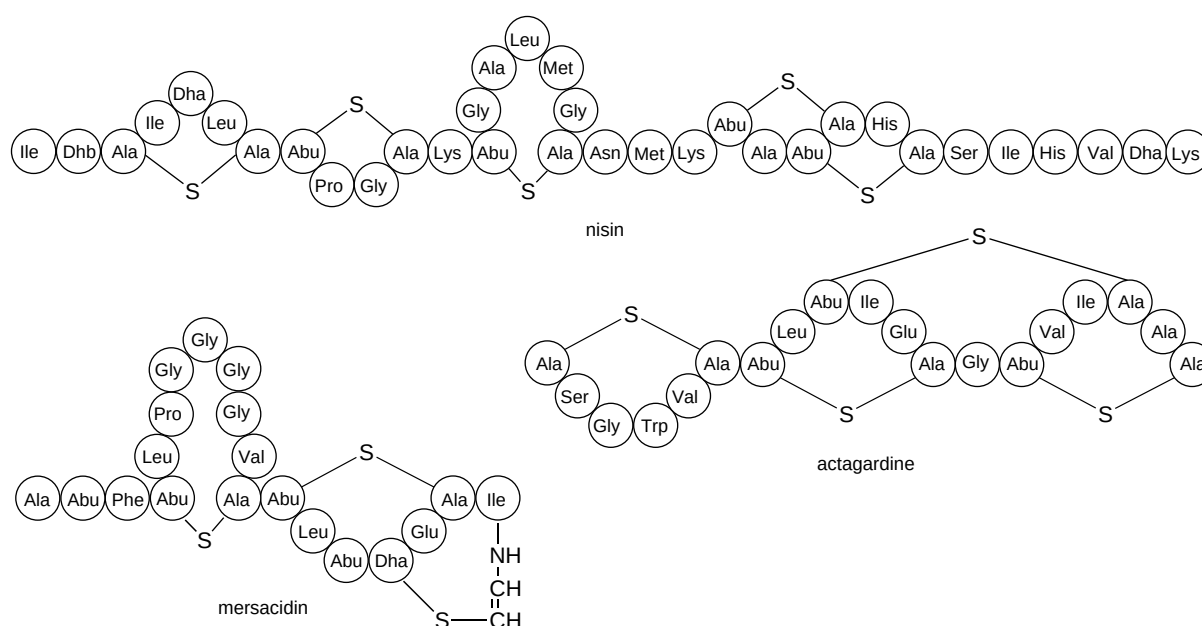
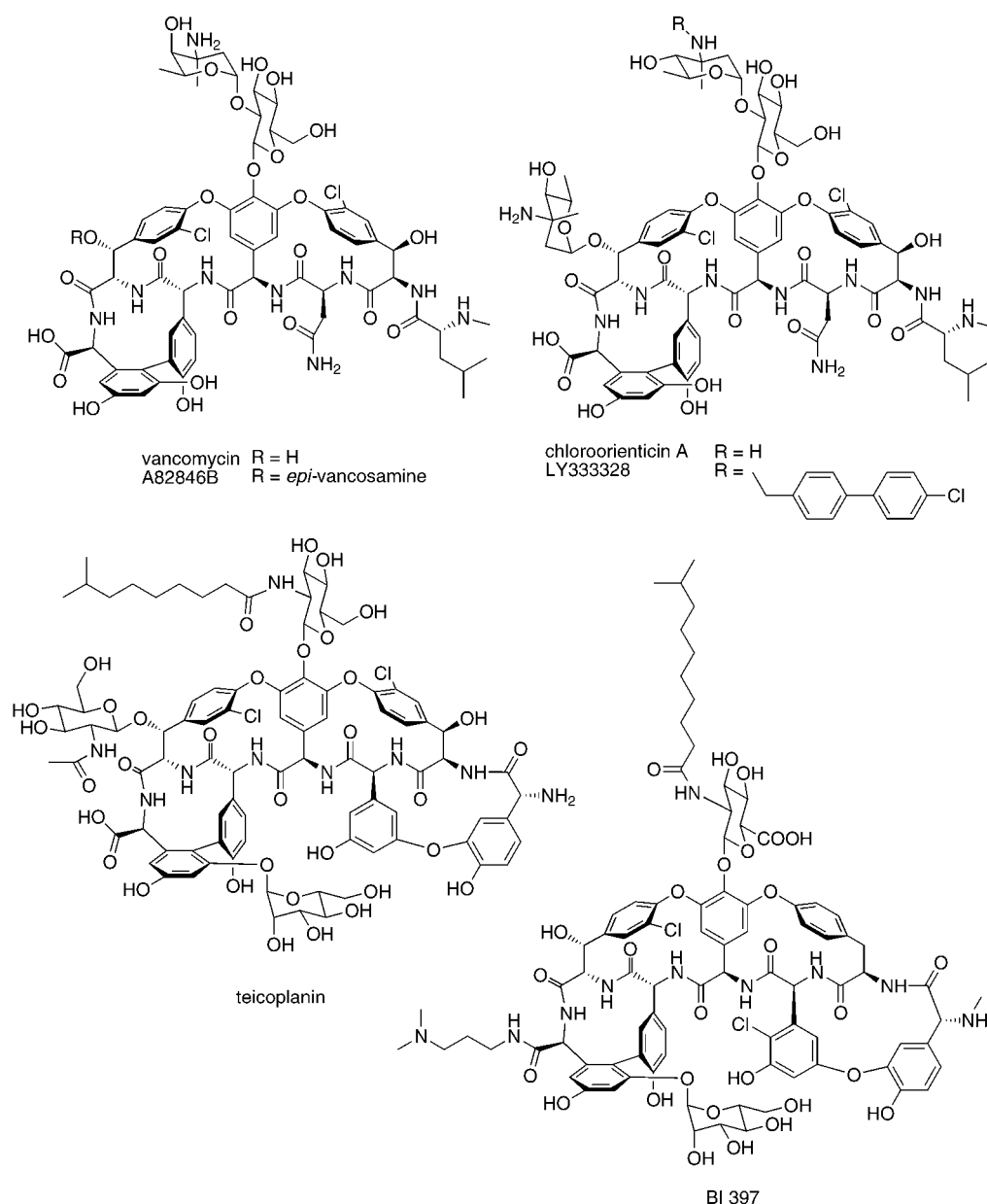


Figure 7. Lantibiotics (Dha = 2,3-didehydroalanine, Dhb = 2,3-didehydrobutyrine, Abu = α -aminobutyric acid, Ala-S-Ala = lanthionine, Abu-S-Ala = 3-methylanthionine).



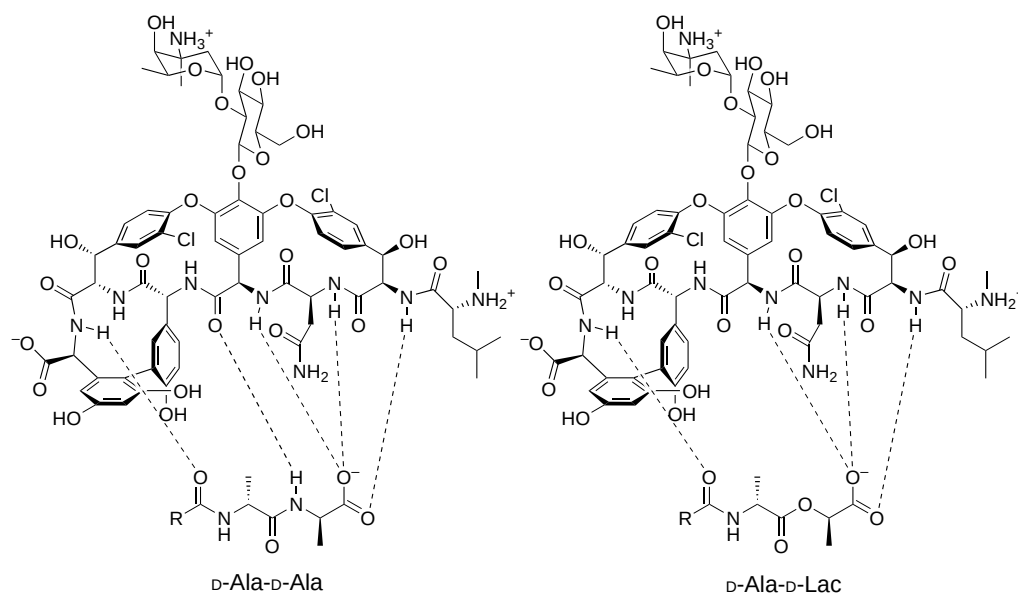
Scheme 8. Important glycopeptide antibiotics.

showed a significantly increased activity against VRE. In a “dynamic target-driven combinatorial synthesis,”^[86] the greater formation constant of vancomycin dimers in the presence of its target was exploited to find a potent vancomycin derivative dimer with the optimal linker length (Scheme 11).^[87] To this end, eight compounds (vancomycin, desleucyl vancomycin, β -alanine desleucyl vancomycin, and asparagine desleucyl vancomycin, each with a C_4 or a C_6 olefin tether attached to their terminal sugar substituent) were dimerized with Grubbs catalyst in the presence of a Lys-D-Ala-D-Ala tripeptide. Preferential formation of dimers that contained the native vancomycin aglycon structure and short tether lengths was observed, and these compounds were also most active against a range of enterococci and staphylococci. Indeed, the most active dimers had drastically improved activities against an intermediate vancomycin-resistant strain of *S. aureus* and a VRE strain. The correlation between

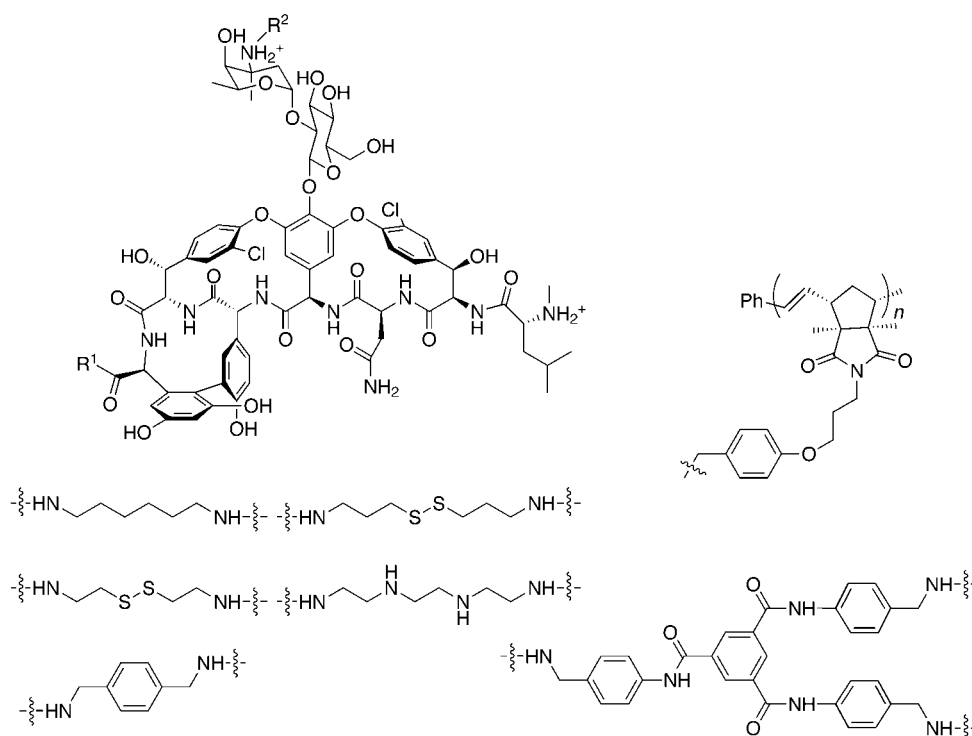
dimerization rate enhancement and antibiotic activity demonstrates the usefulness of the target-accelerated combinatorial synthesis concept in predicting biological properties.

Several studies have been focused on modifying the carbohydrate portion of glycopeptide antibiotics. Hybrids between the aglycon part of vancomycin and various sugars were produced *in vitro* and *in vivo* by using cloned glycosyltransferases.^[88] Chemical modifications of the carbohydrate portion were mainly carried out on the terminal sugar substituent of vancomycin, referred to as vancosamine.^[89] The vancosamine amino functionality can be modified selectively without the protection of the other vancomycin functional groups. Although N-acylation led to only slight improvements in activity, N-alkylation had a more profound effect. The activity of vancomycin against VRE could be significantly improved by the incorporation of long-chain alkyl and aryl substituents. These hydrophobic moieties can act as anchors by inserting into the plasma membrane. This leads to an effective increase in the concentration of the antibiotic at the site of transglycosylation. The hydrophobic substitution also enhances dimerization, but it

has not been demonstrated that an enhancement in dimerization has a direct correlation with an increase in antibiotic activity. The activity of one of the most active N-alkylated analogues (chlorobiphenyl desleucyl vancomycin) is independent of binding to the peptide terminus of peptidoglycan, thus identifying transglycosylase as its target.^[90] This result implies that the modified saccharide is a key determinant for activity. Indeed, the disaccharide portion of chlorobiphenyl-vancomycin with a simple aryl substituent in place of the aglycon unit showed some inhibition of transglycosylase.^[91] The glycopeptide antibiotic LY333328, a vancomycin derivative that features both the chlorobiphenyl side chain and the additional sugar substituent of A82836B, is highly efficient against MRSA and VRE and is now in clinical trials.^[92, 93] BI 397, a new semisynthetic derivative of teicoplanin, is a complex of six related structures, which differ only in the structure of the N-acyl side chain of the N-acylaminoglu-



Scheme 9. The binding of vancomycin to the D-Ala-D-Ala termini of cell wall precursors is mediated through five hydrogen bonds. Substitution of the terminal D-Ala with D-Lac in vancomycin-resistant strains results in the loss of one hydrogen bond, and thus the binding affinity is decreased 1000-fold.



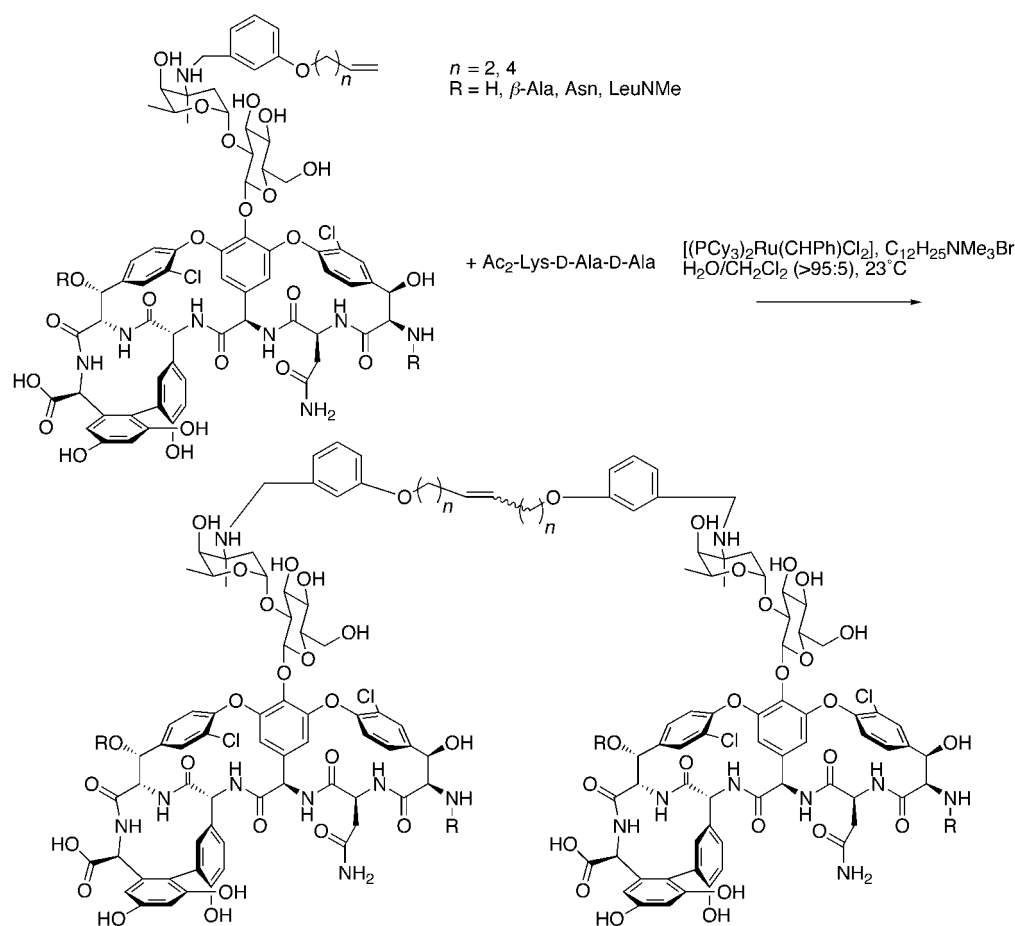
Scheme 10. Vancomycin dimers, trimer, and polymer (R^1 = linker attachment in the dimer and trimer; R^2 = linker attachment in polymer).

curonic acid substituent. It is more active *in vitro* against staphylococci than vancomycin and teicoplanin, including some teicoplanin-resistant strains.^[94] Furthermore, lower dosages with a reduced number of daily treatments were necessary to reduce the bacterial loads in a model study of staphylococcal endocarditis in the heart of a rat.

Mycobacteria, a class of Gram-positive bacteria that include the causative agents of tuberculosis and leprosy, are known to be resistant to a large number of common anti-

biotics. This resistance is thought to be caused by the impermeability of their cell walls, which differ from those of other Gram-positive bacteria in several ways.^[95] The peptidoglycan of mycobacteria is covalently linked to mycoylarabinogalactan (mAG) by means of a phosphodiester bond. mAG consists of D-galactofuranoses, D-arabinofuranoses, and mycolic acids, ($\approx$ C-90 branched fatty acids) which extend perpendicularly to the arabinogalactan/peptidoglycan layer. Surface glycolipids intercalate into the mycolic acid layer to form a pseudo lipid bilayer. Somewhat embedded into the mycoylarabinogalactan/peptidoglycan framework is the key surface molecule involved in the virulence and immunopathogenesis of mycobacterial diseases, lipoarabinomannan

(LAM). Both mAG and LAM contain D-arabinofuranose residues, which are otherwise extremely rare in nature and thus good targets for antibiotics. Ethambutol, a naturally occurring inhibitor of arabinosyltransferase,^[96] is used in the therapy of tuberculosis, and is specific in its antibiotic effects against mycobacteria (Scheme 12). Because of the relatively low activity and severe side-effects of ethambutol, synthetic inhibitors of arabinosyltransferase have been investigated, including ethambutol-sugar hybrids^[97] and aza analogues of



dimers in order of abundance	MIC ($\mu\text{g}/\text{ml}$) against VRE
(LeuNMe) C_2 -(LeuNMe) C_2	2
(LeuNMe) C_2 -(β -Ala) C_2	8
(LeuNMe) C_2 -(LeuNMe) C_4	4
(β -Ala) C_4 -(β -Ala) C_4	8
(LeuNMe) C_4 -(LeuNMe) C_4	>16
(β -Ala) C_2 -(β -Ala) C_2	>16
vancomycin	>100

Scheme 11. Target-accelerated combinatorial synthesis of dimers of vancomycin analogues.

arabinofuranose.^[98] Unfortunately, none of these molecules exhibited properties superior to those of ethambutol.

Galactofuranose, the second component of mAG, is also mostly restricted to mycobacteria. It is incorporated as the activated form, UDP-galactofuranose, which is synthesized by the unique enzyme UDP-galactopyranose mutase. The recent structural investigations of this enzyme may make its exploitation as an antibiotic target possible.^[99]

4. Antibiotics That Target Prokaryotic Protein Biosynthesis

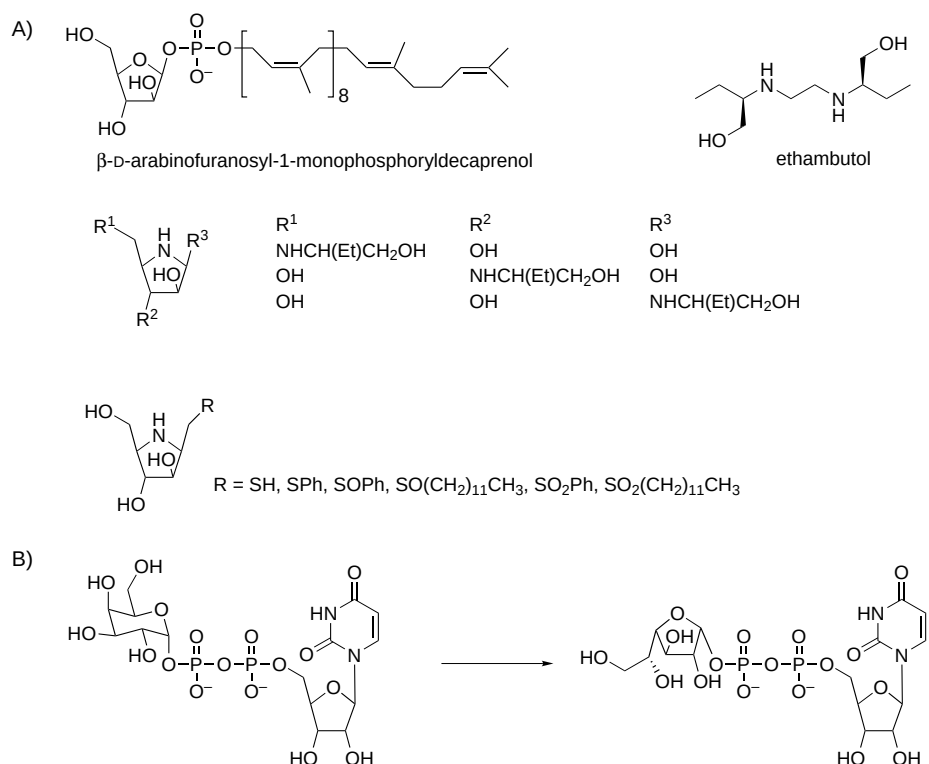
4.1. Macrolide Antibiotics

Macrolides are secondary metabolites that are structurally diverse, exhibit a variety of activities, and consist of a branched-chain fatty acid formed into a macrocyclic ring

(Scheme 13). Typically one or more deoxysugars are attached to the macrolide core structure, and the sugar moiety is often essential for the activities. Erythromycin A, a 14-membered macrolide, has been known for almost fifty years and has provided an effective antibiotic therapy against Gram-positive pathogens much of the time, especially as an alternative for patients that are allergic to β -lactam antibiotics. A new interest in the macrolide antibiotics has been sparked by the introduction of semisynthetic erythromycin A derivatives. For example, 9-(*S*)-erythromycyl amines have potent in vitro activity against a variety of Gram-positive bacteria; however, they are only poorly absorbed by humans after oral administration. Dirithromycin, a 9-*N*-11-*O*-oxazine derivative, which is metabolized into erythromycylamine, is as active in vitro as the erythromycylamines but exhibits better pharmacokinetic properties.^[100] Clarithromycin (6-OMe erythromycin)^[101] and azithromycin,^[102] the first member of the azalide family, are more stable than their parent compound in an acid medium and are therefore tolerant to oral administration. Furthermore, azithromycin has extended the spectrum of the macrolide antibiotics to Gram-negative species.

All macrolide antibiotics are thought to function by binding to the 23S subunit of ribosomal RNA, where they interact with hairpin 35 in domain II and with the peptidyl transferase loop in domain V.^[103] They stimulate the dissociation of peptidyl tRNA from the ribosome during translocation, thus resulting in the premature termination of the peptide chain.

The biosynthesis of macrolides and other polyketides resembles the synthesis of fatty acids in many ways.^[104] Both are assembled from two-carbon acyl units by complex enzyme systems: polyketide synthetases (PKS) and fatty acid synthetases (FAS), respectively. Type I PKS are giant, multifunctional proteins that feature separate modules with FAS-like activities. Each of these modules consists of three to six catalytic domains. They are typically used in a noniterative way, that is, each module is responsible for the synthesis of one specific part of the polyketide, whereas the linear module



Scheme 12. A) The arabinosyltransferase donor, the naturally occurring inhibitor ethambutol, and some synthetic derivatives, B) the UDP-galactopyranose mutase reaction.

arrangement specifies the structure of its polyketide product. Type II PKS consist of several, largely monofunctional proteins, and each PKS complex is used iteratively for all synthetic steps. Type I and II PKS are generally involved in the synthesis of macrolides and fused aromatic ring systems (e.g. tetracyclines), respectively. However, exceptions are known: for example, fungal type I PKS also synthesize aromatic polyketides. Additionally, some PKS are responsible for the synthesis of polyethers and polyenes.

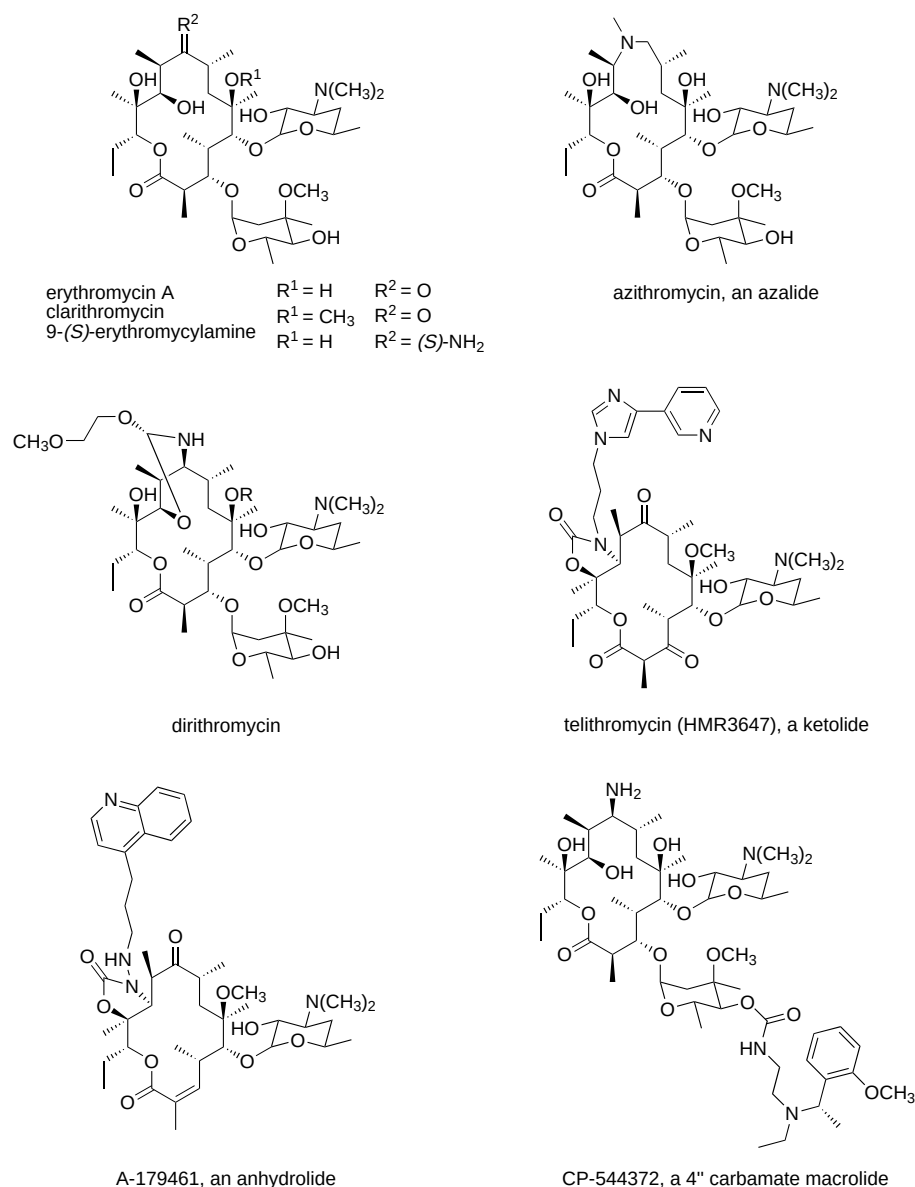
The biosynthesis of macrolides can be divided into four phases: priming, initiation, elongation, and termination.^[105] In the priming phase, the acyl carrier proteins (ACP) of the individual modules are charged with prosthetic phosphopantothienoyl groups. These provide a flexible tether, which terminates in a thiol group and is the site of attachment of the monomer and growing chain intermediates. The chain growth is then initiated by the transfer of a monomer unit from acyl-CoA to the first ACP. Elongation occurs by means of Claisen-like condensation reactions of additional acyl building blocks with the growing chain. Each PKS module contains up to three additional FAS-like domains for the reduction of the ketone, dehydration, and reduction of the resulting conjugated double bond. The presence or absence of these domains, in addition to the variation in acyl building blocks accounts for the structural diversity of the macrolides. Finally, a thioesterase domain catalyzes an intramolecular attack, which results in the release of the cyclic macrolactone. This macrolide core structure is then typically altered by modifying enzymes such as hydroxylases, glycosyltransferases, and methyltransferases. The biosynthesis of erythromycin A is illustrated in Figure 8.

The linear, modular organization of the PKS has been exploited in the synthesis of designed macrolides and aromatic polyketides.^[106, 107] Through the inactivation or substitution of certain catalytic domains, unnatural structures could be obtained as predicted by prior knowledge of domain function.^[108, 109] Extension of this methodology to alter multiple carbon centers in a single molecule allowed the synthesis of a fifty-membered macrolide combinatorial library.^[110] Such an undertaking would have been impractical by chemical synthetic methods alone.

Although the biosynthesis of polyketides can successfully provide variants of macrolide core structures, several major obstacles complicate the study of the deoxysugar components. Even though the genes that code for the biosynthetic proteins of deoxysugars are part of the overall macrolide gene cluster, their identification is a challenge as they are scattered at both ends of

the PKS cluster, along with genes that encode for regulatory and aglycon-modifying enzymes. Furthermore, assignment of genes to a particular glycosylation enzyme is difficult in macrolides with more than one sugar substituent. Progress in the area of cloning, overexpression, and molecular assembly of the genes, and implications for the mechanism of the biosynthesis of deoxysugars have been extensively reviewed.^[111–114]

A major obstacle in the study of deoxysugars has been the complicated synthesis of activated nucleoside diphosphate deoxysugars that have been postulated as biosynthetic intermediates. Glycosyltransferases transfer a specific carbohydrate from its corresponding sugar nucleotide to the acceptor hydroxy group. The chemical synthesis of 2-deoxysugar nucleotides is particularly challenging, largely because the stereochemistry at the anomeric center cannot be controlled through the neighboring-group effect. Once synthesized, the activated sugar nucleotides are highly unstable as they are prone to hydrolysis and 1,2-elimination. However, enzymatic methods may make a wide variety of sugar nucleotides accessible. For example, the substrate specificity of an α -D-glucopyranosyl phosphate thymidyltransferase was investigated.^[115] Most of the twelve glycosylphosphates tested (all possible α -D-hexoses and monodeoxy- α -D-glucoses) provided an appreciable amount of the condensation product with both TTP and UTP. Interestingly, the substrate specificity seemed to be governed by the preferred conformation of the sugar substrate. The significance of these findings lies in the fact that they provide substrate sets for the further development of in vitro glycosylation systems. The general feasibility of incorporating unnatural sugar substitu-



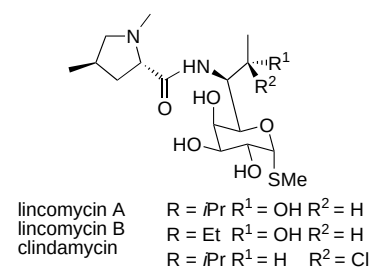
Scheme 13. The structures of some macrolide antibiotics.

ents into macrolide antibiotics had been demonstrated earlier for methymycin, a polyketide that bears a single sugar substituent, desosamine, as well as for other systems. In *streptomyces venezuelae*, desosamine is synthesized and attached to the methymycin aglycon by a series of eight gene products, DesI – VIII (Scheme 14). As predicted, the deletion of one of methymycin's *N*-methyltransferases (DesVI) led to an analogue with an amino instead of a dimethylamino substituent at the 3-position of the deoxysugar.^[116] Transformation of an aminotransferase gene (*calH*) involved in the biosynthesis of calicheamicin into a methymycin-producing strain successfully provided a methymycin–calicheamicin hybrid,^[117] whereas the transformation of two genes from the streptose pathway (*strM* and *strL*) resulted in a methymycin aglycon that bears an L-rhamnose substituent, thus demonstrating the promiscuity of the glycosyltransferase DesVII.^[118] An extension of these methodologies may soon allow combinatorial biosynthetic approaches that

give diverse macrolides that incorporate modified sugar substituents on various polyketide structures.

Polyketide deoxysugar substituents have traditionally been thought to affect pharmacokinetic properties, such as adsorption, distribution, metabolism, and excretion (ADME). More recently, additional roles of the sugar substituents have been considered. Deoxygenated sugars have a balance of hydrophilic and hydrophobic groups, which are pre-organized on a rigid pyran ring scaffold and have the potential to participate in target recognition. The involvement of deoxysugars in the recognition of binding sites has primarily been studied for deoxysugar-containing antitumor drugs that target DNA. DNA molecules can easily be synthesized and are more stable than RNA. Additionally, the helical and relatively stable conformation of DNA in solution facilitates NMR spectroscopic studies. For example, it was shown that the oligosaccharide chain of calicheamicin is embedded in the minor groove of duplex DNA, thereby positioning the active aglycon enediyne unit for cleavage.^[119] The participation of deoxysugar substituents in the recognition of RNA sequences by macrolide antibiotics remains to be demonstrated.

The lincosamides are another class of RNA-binding antibiotics that include a carbohydrate in their structure. The semisynthetic clindamycin



has replaced the naturally occurring lincomycins clinically because of its higher activity and reduced side-effects. Macrolides, lincosamides, and group B streptogramins have overlapping binding sites on the 50S ribosomal subunit. Full cross-resistance between the groups (MLS_B resistance), which is mediated by specific base methylation of the 23S RNA, is therefore observed for these three antibiotic families. This modification of ribosomal RNA is catalyzed by the Erm

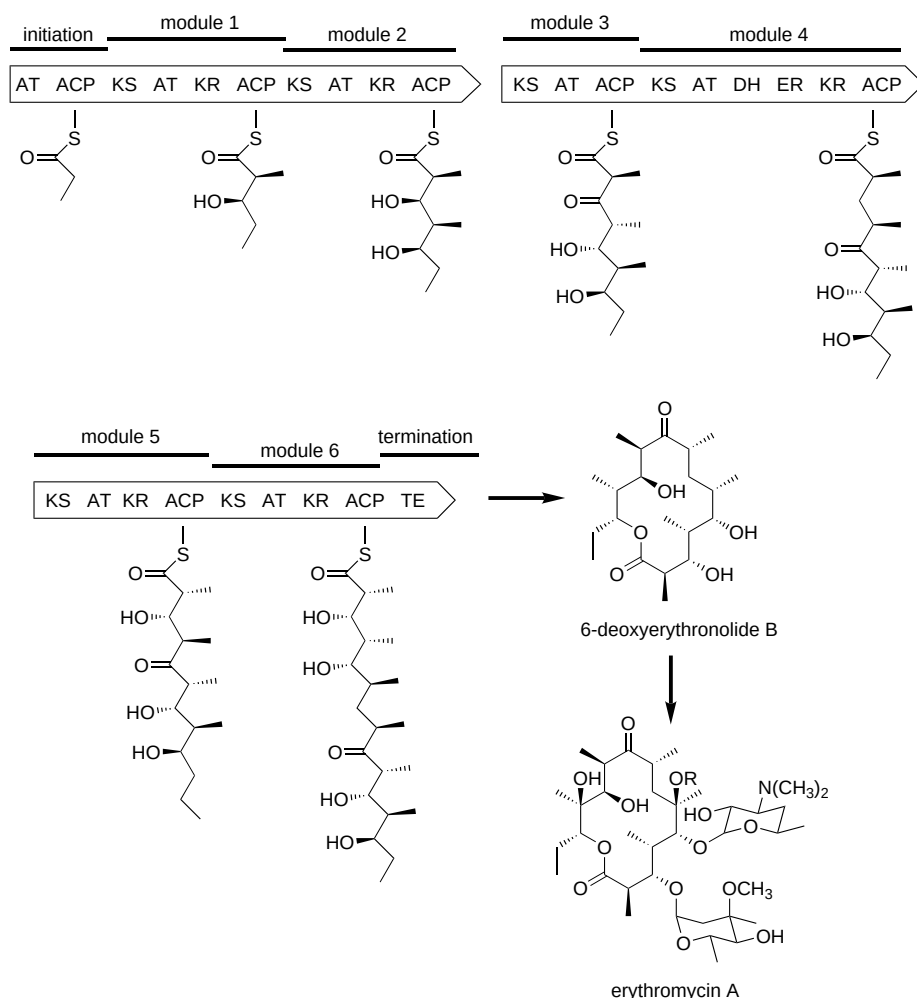


Figure 8. Illustration of the function of a modular polyketide synthetase, with the biosynthesis of erythromycin A shown as an example (AT = acyl transferase, ACP = acyl-carrier protein, KS = ketosynthase, KR = ketoreductase, DH = dehydratase, ER = enoyl reductase, TE = thioesterase).

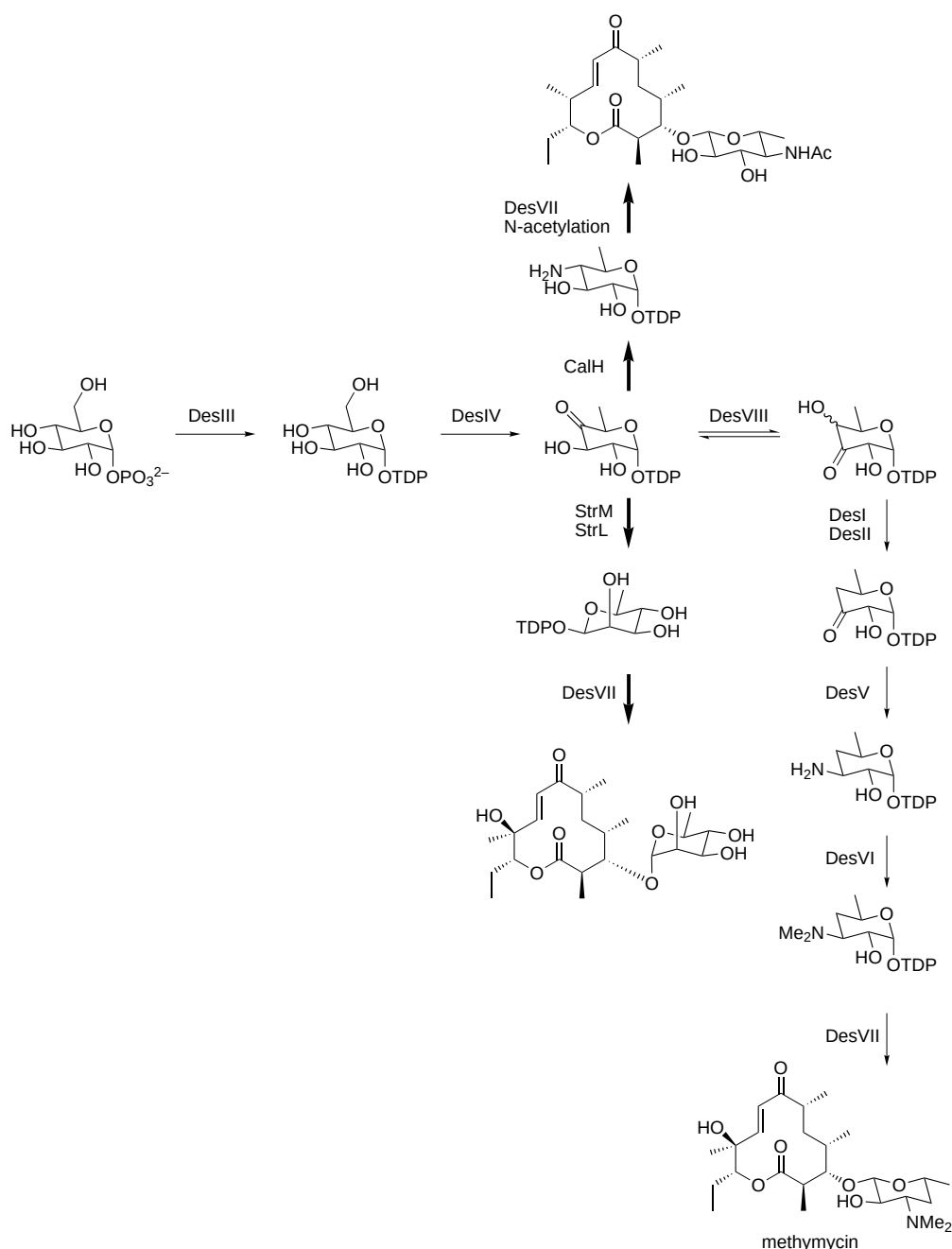
(erythromycin ribosome methylation) family of methyltransferases.^[120] A large number of compounds were screened for activity against these enzymes and a group of seemingly unrelated chemicals were found to selectively inhibit ErmC.^[121] However, none of these inhibitors potentiated the ability of erythromycin to prevent ErmC-containing *S. aureus* from generating acute infections in mice. The interaction of small molecules with the Erm family of methyltransferases were probed in an NMR spectroscopic based screen, and a series of substituted triazines were identified as compounds that increase the activities of lincosamides and group B streptogramins.^[122] The lead triazines were optimized by the parallel synthesis of a large number of analogues, and resulted in structures that inhibited the RNA methyltransferase at micromolar concentrations. Resistance to macrolide antibiotics can also result from two non-MLS_B resistance mechanisms: chemical modifications (phosphorylation, glycosylation, esterification) and active efflux systems across the membrane (associated with the *metE* determinant) (see Figure 1).

Ketolides are the 3-descladinoyl-3-oxocarbamate analogues of erythromycin or clarithromycin, many of which

feature an additional 11,12-cyclic carbamate moiety.^[123] The ketolide telithromycin (formerly known as HMR-3647) is not only less prone to induce resistance than other macrolide antibiotics, but also displays good pharmacokinetic parameters in vivo, as well as a high therapeutic efficacy in mice that were infected with respiratory pathogens.^[124] Furthermore, anhydrolides, in which a carbon–carbon double bond was introduced at the C2–C3 position,^[125] and 4''-carbamate macrolides^[123] have similar in vitro activities as those of the ketolides.

4.2. Aminoglycosides

Aminoglycosides consist of a six-membered carbocyclic nucleus (aminocyclitol) with a varying number of sugar substituents (Scheme 15). This core is most commonly 2-deoxystreptamine, but other aminocyclitols such as streptidine (streptomycins), actinamine (spectinomycins), and fortamine (fortimicins) occur. The aminoglycosides are generally classified according to their attached amino sugar groups. For example, three amino sugars are attached to the central 2-deoxystreptamine in the neomycin family, whereas members of the kanamycin and gentamicin families bear only two sugar substituents. The aminoglycosides function as inhibitors of protein translation by binding to the highly conserved A-site sequence of the small 30S ribosomal subunit (Figures 9 and 10). The structure of paromomycin, a member of the neomycin group, complexed to the A site of a model oligonucleotide hairpin has been solved by using NMR spectroscopy.^[126] The aminoglycosides provide hydrogen-bond donors that are preorganized on the sugar ring scaffold and interact with conserved nucleotides in the RNA. Aminoglycoside binding in the major groove within a pocket created by a mismatched A–A base pair and a single unpaired adenine induces a conformational change that stabilizes the tRNA–A site complex.^[127] Prevention of efficient proofreading then results in erroneous proteins. The accumulation of mutant membrane proteins compromises the integrity of the bacterial envelope, which then allows the uptake of larger quantities of aminoglycosides and results in further misreading and eventually in cell lysis. A change in the RNA conformation is also crucial for the mode of action of the aminoglycoside spectinomycin.^[128] The RNA conformational change induced by spectinomycin inhibits the translocation of tRNA from the A site to the P site, the same step that is targeted by the macrolide antibiotic erythromycin (see Section 4.1).



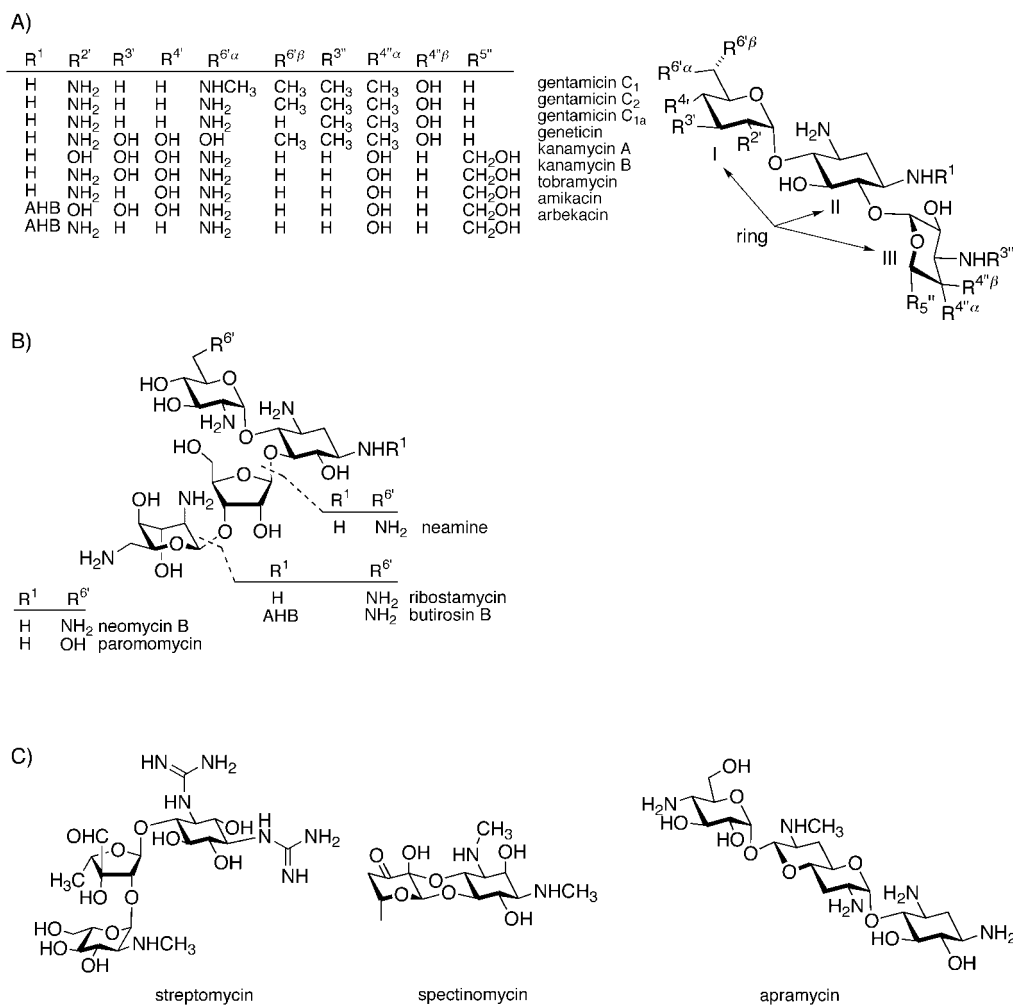
Scheme 14. The biosynthesis of methymycin in *streptomyces venezuelae*. The bioengineered synthesis of new macrolides that bear designed sugar moieties is indicated by the bold arrows.

Aminoglycoside derivatives have been synthesized to investigate the structural features that are responsible for their activity. Simple aminols were found to bind to miniature constructs of the A-site region, thus suggesting that the 1,3-aminol moiety represents the essential pharmacophore of aminoglycosides.^[129, 130] Monosaccharides with the 1,3-hydroxyamine substitution pattern of aminoglycosides bind to phosphodiester and the Hoogsteen face of guanosine,^[129] which is consistent with the results from the structural studies of the paromomycin—A site complex (Figure 10).^[126] A library of 6-deoxy-6-amino GlcNAc derivatives was synthesized to further investigate the activity based largely on the 1,3-hydroxyamine motif.^[131] Since the exact location of the

idose ring IV in the paromomycin-RNA complex could not be defined by using NMR spectroscopy,^[126] its role in the binding event was investigated with a series of neomycin B derivatives with modified at the idose ring.^[132] Compounds in which ring IV was replaced with amines on flexible linkers were antibiotically as active as neomycin B. However they bind less specifically to an isolated A-site hairpin than a negative control, which indicates that the idose ring scaffold is necessary for the correct placement of the positive charge. The naturally occurring neamine is the simplest effective aminoglycoside antibiotic and has been explored as a nucleus for the synthesis of new aminoglycoside derivatives.^[133] These analogues feature a variety of amino substituents attached to the 5-hydroxy group of 2-deoxystreptamine. Despite binding more strongly than neamine to an isolated A-site model hairpin, some of the analogues were weaker antibiotics. Their antibiotic activity correlated better with the *in vitro* inhibition of translation (assayed by means of a luciferase reporter gene) and antibiotic activity. The apparent differences in the binding affinity of the aminoglycoside for the A site, whether isolated in a model oligonucleotide or in the context of the ribosome, may be the result of a number of factors. For example, contacts to neighboring ribosomal proteins might stabilize

aminoglycoside binding or the surrounding ribosome may have structural effects on the A site. During the development of a fluorescence assay of RNA binding, it was observed that aminoglycosides modified with a fluorescent reporter group bind to RNA A site constructs with a higher affinity than that of their parent molecules.^[134] This increase in affinity was attributed to the intercalating properties of the fluorescent dye. A systematic study of this effect led to the discovery of a paromomycin–thiazole orange hybrid with a 41-fold higher affinity than paromomycin itself, while still exhibiting specificity for the A site.^[135]

Resistance mechanisms against aminoglycosides include efflux-mediated processes and enzymatic modification of the



Scheme 15. Some natural and semisynthetic aminoglycoside antibiotics: A) Gentamicin and kanamycin aminoglycosides (AHB = aminohydroxybutane), B) neomycin aminoglycosides, C) other aminoglycosides.

drugs or the target site (RNA methylation). N-acetylation, O-phosphorylation, and O-nucleotidylation processes catalyzed by aminoglycoside acetyltransferases (AAC), phosphotransferases (APH), and adenylation (AAD) are the clinically most important mechanisms.^[136] A large variety of semisynthetic aminoglycoside antibiotics have been developed to overcome such resistance mechanisms.^[137] Particularly problematic is the bifunctional AAC(6')-APH(2'') present in multiple-drug-resistant *S. aureus* and *S. epidermidis* strains, which has rendered most aminoglycosides useless against these pathogens. Arbekacin, a semisynthetic kanamycin derivative, is a notable exception; a small number of MRSA strains with a moderate level of arbekacin resistance have been clinically isolated, but no highly resistant strains have occurred.^[138] The low susceptibility of arbekacin to modifying enzymes is not only a consequence of the 1-*N*-aminohydroxybutyryl group and the absence of hydroxy groups at the 3' and 4' positions, but also of the fact that arbekacin retains its activity after acetylation by several AACs. In a mechanism-based approach to overcome inactivation by APH(3'), 2'-nitro derivatives of neamine and kanamycin were synthesized (Scheme 16).^[139] The 3'-phosphorylated compounds that arise from the action of the

modifying enzyme undergo elimination to generate nitroalkenes, which presumably undergo a Michael addition of the active-site nucleophiles. In spite of their APH(3')-inhibiting properties, these compounds were not effective in reversing aminoglycoside resistance. The APH(3') resistance enzyme was avoided by synthesizing a 3'-oxo-kanamycin derivative.^[140] The hydrolyzed form of this ketone is a substrate for APH(3'). The resulting 3'-phospho derivative is unstable and expected to eliminate phosphate, thereby regenerating the antibiotic. This aminoglycoside modification lowered the MIC in the presence of the resistant enzyme APH(3')-Ia by an order of magnitude.

In a surface plasmon resonance (SPR) spectroscopic study, neamine was found to bind the A-site sequence with a 2:1 stoichiometry, each with a dissociation constant of approximately 10 μM .^[141] Various dimers were therefore constructed to identify a bivalent aminoglycoside that would bind to the A site with high affinity owing to the simultaneous ligation to both binding sites. Dimers coupled through a flexible hydrophilic linker possessed a significantly increased antibiotic activity against neamine. A nearly linear relationship between the IC₅₀ of translation inhibition and the MIC values validated translation as the

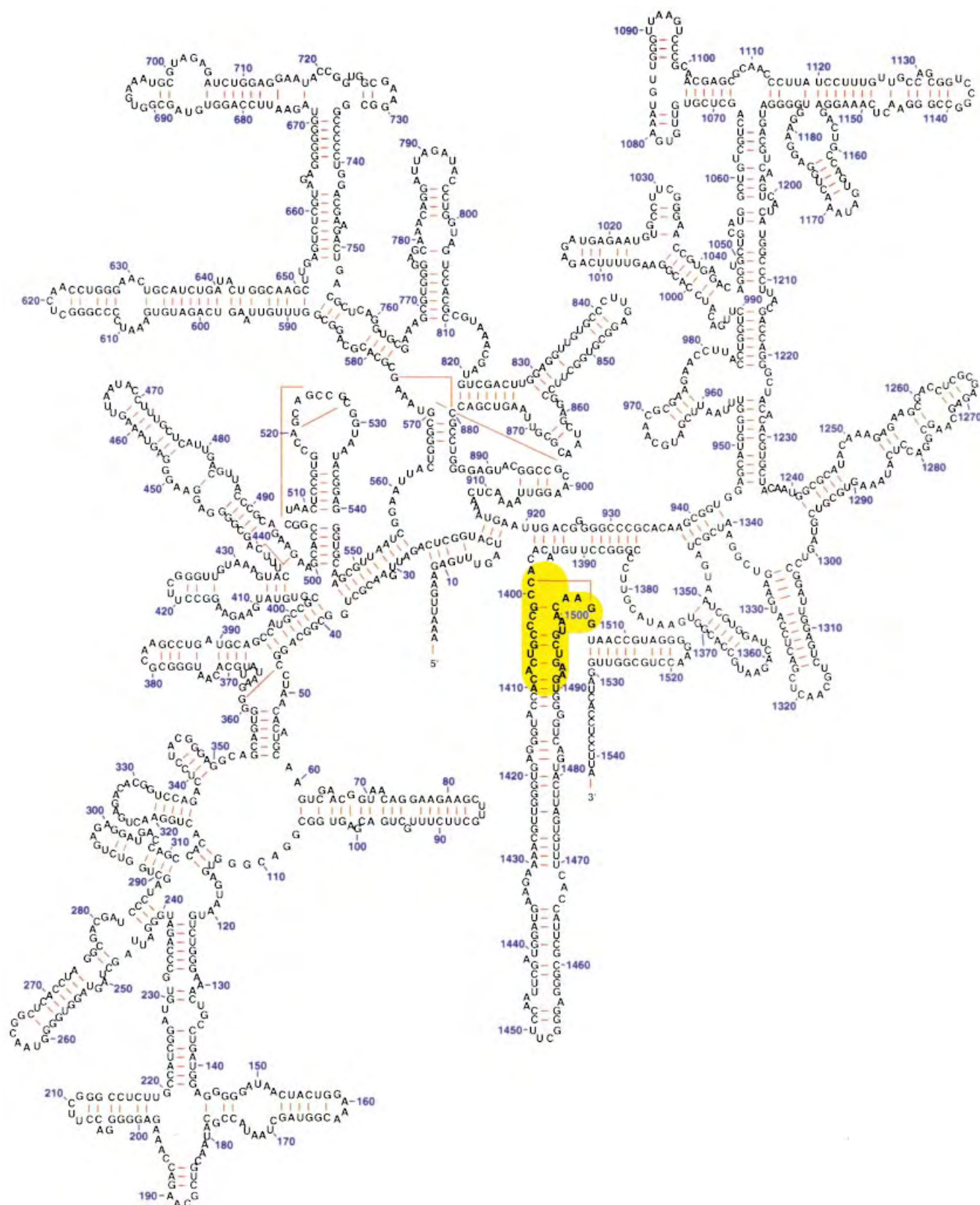


Figure 9. The ribosomal 16S RNA sequence and the A site (yellow) for aminoglycoside binding.

target of this new class of aminoglycoside antibiotics. Interestingly, several of these neamine dimers also were found to be inhibitors of the APH(2'') activity of the bifunctional

APH(2'')-AAC(6') aminoglycoside-modifying enzyme. These dimeric neamine constructs therefore represent a new strategy toward thwarting the resistance to aminoglycosides.

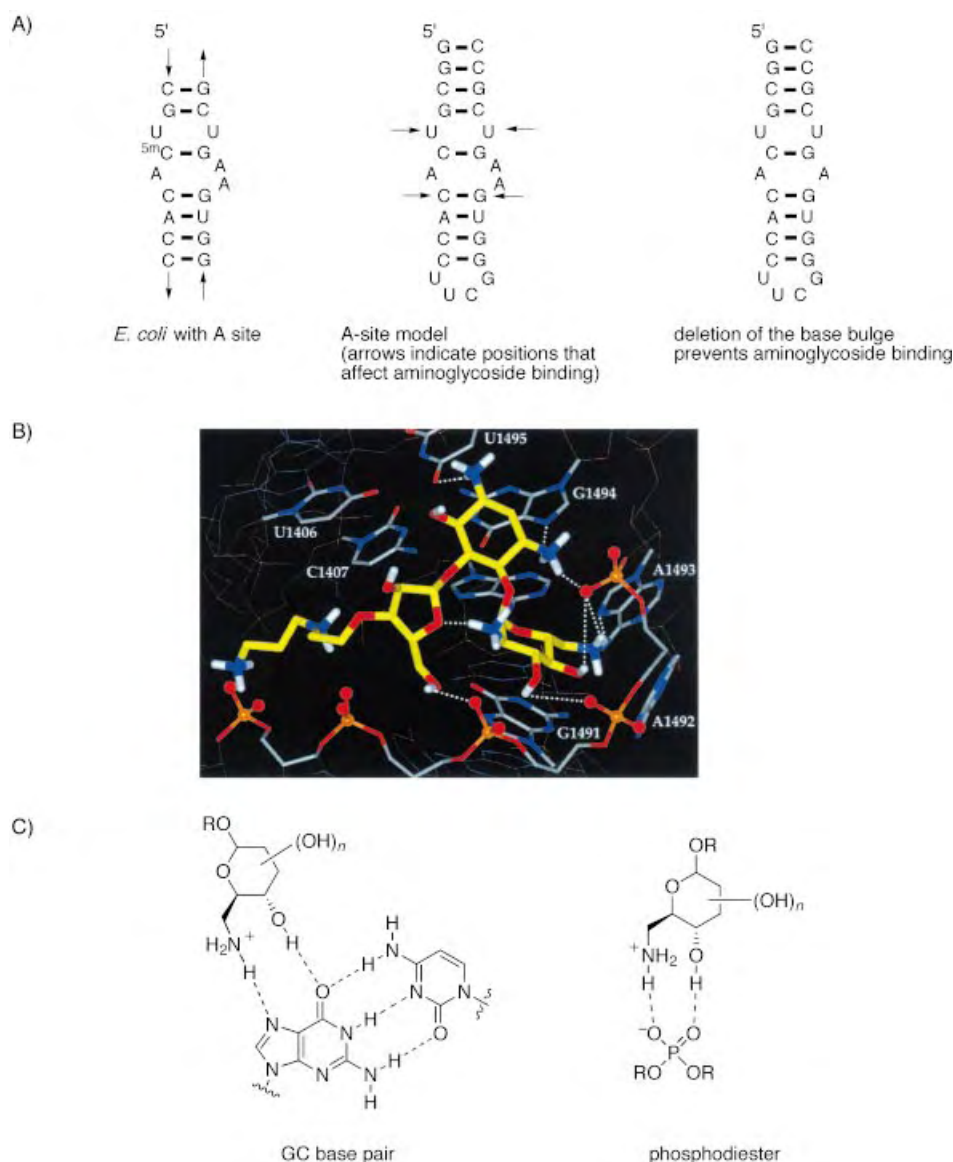


Figure 10. A) RNA sequences related to the ribosomal decoding A site, B) structure of paromomycin complexed to the A site, determined by using NMR spectroscopy, C) putative modes of the interactions of hydroxyamines with phosphodiester and with the Hoogsteen faces of the GC base pairs.

4.3. Everninomycins

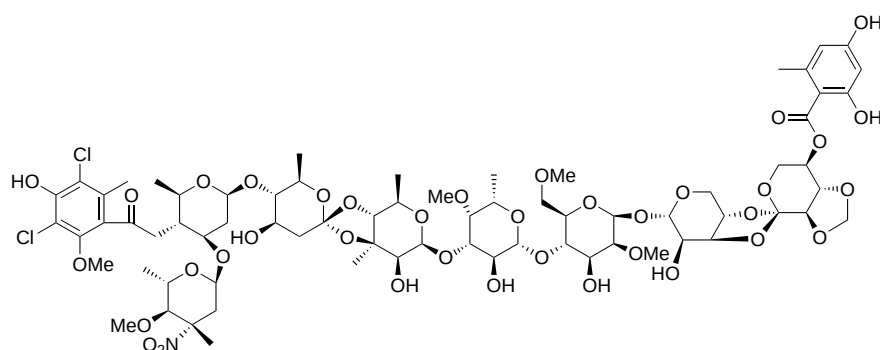
The everninomycins, for example, everninomycin 13,384-1, are a class of complex oligosaccharide antibiotics. They are part of the orthosomycin family, which feature one or more

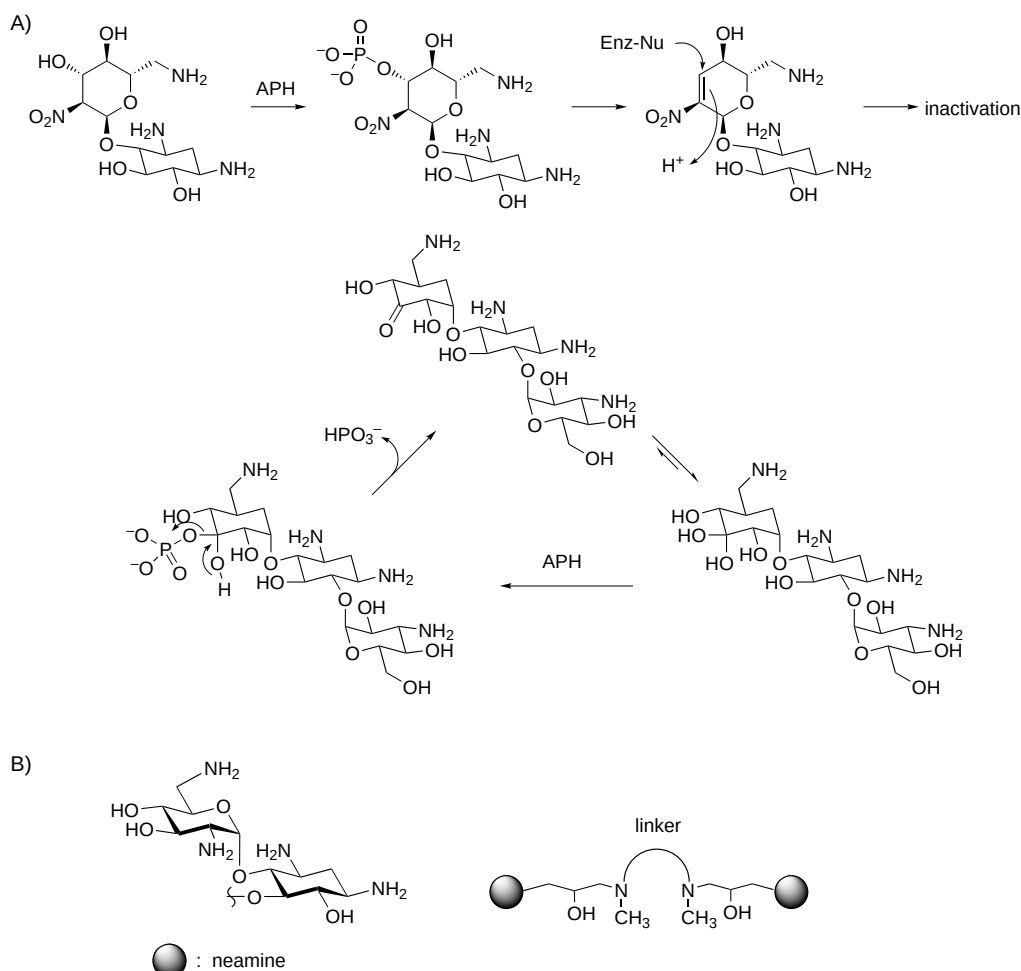
orthoester linkages.^[142] Their complex structure has attracted the interest of synthetic organic chemists and a total synthesis has been reported.^[143] The everninomycin antibiotics are thought to inhibit RNA to protein translation by preventing the assembly of the initiation complex. Everninomycins are active both in vitro and in vivo against MRSA and VRE; however, the first members of this class were toxic. Ziracin, a cyclodextrin complex of everninomycin 13,384-1 which was proven to be safe in vivo, and analogues thereof are being developed for clinical trials.^[144]

4.4. RNA as a Drug Target

Recently, there has been an increased interest in the potential of RNA as a target for small-molecule drug discovery and aminoglycosides have served as a paradigm for this approach.^[145, 146] Protein synthesis, mRNA maturation, and ribonucleoprotein–RNA interactions are generally considered as the most promising points of interaction. As RNA functional domains are more highly conserved than the shapes of enzyme-active sites, drug resistance is expected to develop at a slower pace. For example, type I human immunodeficiency virus (HIV-I) has rapidly developed resistance to enzyme inhibitors. RNA-based antiviral targets offer a potential solution to this problem. Aminoglycosides were shown to disrupt the interaction between a *trans*-activating region (TAR) and its cognate peptide (Tat),^[147] as well as between a Rev-response element (RRE) and the viral transactivator protein (Rev).^[148] These regulatory interactions are necessary for viral replication. The synthesis of a library of neamine-based derivatives by using four-component Ugi reactions resulted in the discovery of compounds that bind RRE more effectively than neamine.^[149]

Since binding of the Rev peptide to RRE induces a single base bulge, it was suggested that an aminoglycoside–intercalator hybrid might have a very high affinity for RRE.^[150] Indeed, a neomycin–acridine conjugate is the strongest known competitive inhibitor of Rev–RRE binding with an affinity that is only two times lower than that of the Rev peptide. In cystic fibrosis, a point





Scheme 16. Strategies to overcome aminoglycoside resistance caused by modifying enzymes. A) Mechanism-based approaches, b) aminoglycoside dimers (APH = aminoglycoside phosphotransferase).

mutation introduces a stop codon into the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The addition of aminoglycosides to an *in vitro* protein expression system for mutant CFTR promoted the read-through of the stop codon.^[151] Fusion genes that arise from chromosomal translocation are thought to be the cause of certain forms of cancer. Antisense agents to the breakpoints of these genes have been shown to inhibit cancer growth.^[152, 153] A library of neamine derivatives was tested for their binding affinities to two of these fusion genes, namely PAX3-FKHR and Bcr-Abl.^[154] Polyamine-substituted neamine derivatives were found to be the most efficient binders, with dissociation constants in the submicromolar range. Based on their affinities, it is reasonable to believe that aminoglycosides can potentially act as regulators of gene expression. Furthermore, the aminoglycoside antibiotics also act as inhibitors of catalytic

RNAs, such as the group I intron,^[155] the hammerhead ribozyme,^[156] and the ribozymes of the hepatitis delta virus (HDV).^[157]

With recent and future advances in functional genomics research and the revelation of the genomes of different species, unique RNA sequences will be identified as new drug targets. Aminoglycosides may serve as the primary source of small molecules for the identification of new leads to target RNA. The development of efficient combinatorial methods for the synthesis of aminoglycosides thus represents a new direction. The programmable one-pot oligosaccharide synthesis methodology,^[158] which gives relatively easy access to oligosaccharides, should be applicable to the synthesis of aminoglycoside libraries. In combination with the tools used in genomic and proteomic research (Figure 11), this may allow the discovery of molecules that target RNA and the evaluation of their selectivity.

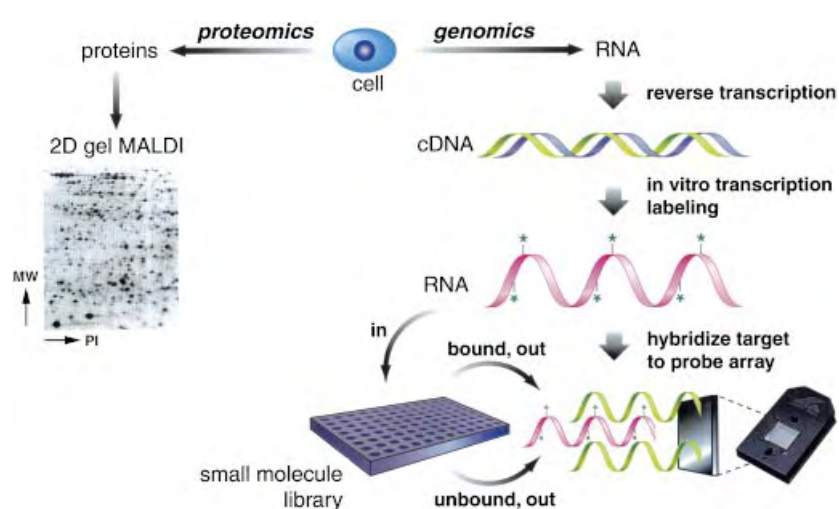


Figure 11. RNA binding analysis by using genomic and proteomic tools. Proteomics: Comparison of the proteome (visualized on a 2D gel, MW = molecular weight, PI = isoelectric point) before and after incubation of the cell with the molecule under investigation. A subsequent analysis of the affected proteins by MALDI (matrix-assisted laser-desorption/ionization) mass spectrometry facilitates the identification of selective inhibitors of translation. Genomics: Labeling of the complete pool of RNA present in a cell (through reverse transcription and *in vitro* transcription labeling of the resulting cDNA) is used to detect the specific binding of small molecules to RNA.

5. Summary and Outlook

The development of new antibiotics to tackle the problem of antibiotic resistance has emerged as an important area of drug discovery. The carbohydrate-based approach described herein represents a relatively new strategy, and several targets appear to be interesting candidates for antibiotic discovery. New methods that recently emerged in carbohydrate research have not only advanced the field, but have also created a new direction in antibiotic development. With a greater understanding of the genome of different bacterial species and with advances in functional genomics and proteomics, additional targets for antibiotics are expected to be identified.

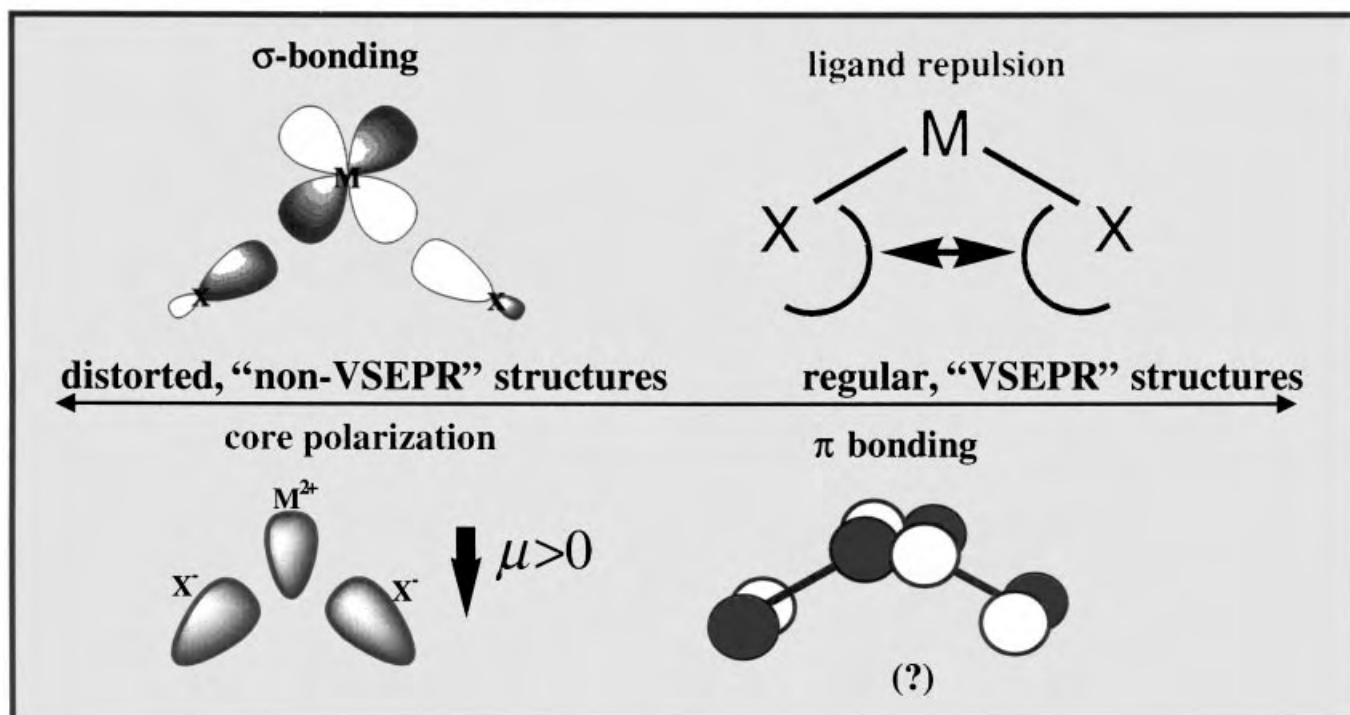
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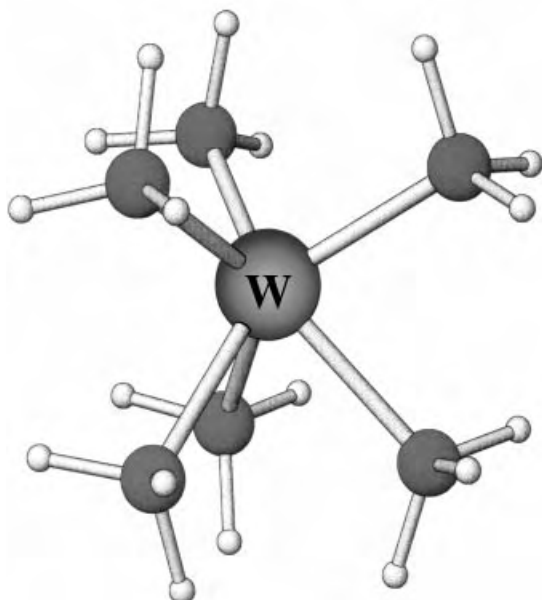
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The fascinating structures of systems with formal d^0 configurations may be traced back largely to the interplay of four factors:



Examples include the distorted trigonal-prismatic structure of $[W(CH_3)_6]$ (see picture), bent structures of gaseous alkaline earth dihalides, and those of many more molecules and solids.



The structural distortions have important consequences for homogeneous and heterogeneous catalysis, bioinorganic chemistry, and materials properties.

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“Non-VSEPR” Structures and Bonding in d^0 Systems

Martin Kaupp*

Dedicated to the memory of Marco Häser (1961–1997)

Under certain circumstances, metal complexes with a formal d^0 electronic configuration may exhibit structures that violate the traditional structure models, such as the VSEPR concept or simple ionic pictures. Some examples of such behavior, such as the bent gas-phase structures of some alkaline earth dihalides, or the trigonal prismatic coordination of some early transition metal chalcogenides or pnictides, have been known for a long time. However, the number of molecular examples for “non-VSEPR” structures has increased dramatically during the past decade, in particular in the realm of organometallic chemistry. At the same time, various theoretical models have been discussed, sometimes controversially, to explain the observed, unusual structures. Many d^0 systems are important in homogeneous and heterogeneous catalysis, biocatalysis (e.g. molyb-

denum or tungsten enzymes), or materials science (e.g. ferroelectric perovskites or zirconia). Moreover, their electronic structure without formally nonbonding d orbitals makes them unique starting points for a general understanding of structure, bonding, and reactivity of transition metal compounds. Here we attempt to provide a comprehensive view, both of the types of deviations of d^0 and related complexes from regular coordination arrangements, and of the theoretical framework that allows their rationalization. Many computational and experimental examples are provided, with an emphasis on homoleptic mononuclear complexes. Then the factors that control the structures are discussed in detail. They are a) metal d orbital participation in σ bonding, b) polarization of the outermost core shells, c) ligand repulsion, and

d) π bonding. Suggestions are made as to which of the factors are the dominant ones in certain situations. In heteroleptic complexes, the competition of σ and π bonding of the various ligands controls the structures in a complicated fashion. Some guidelines are provided that should help to better understand the interrelations. Bent’s rule is of only very limited use in these types of systems, because of the paramount influence of π bonding. Finally, computed and measured structures of multinuclear complexes are discussed, including possible consequences for the properties of bulk solids.

Keywords: bond theory • d^0 complexes • density functional calculations • transition metals • VSEPR Model

1. Introduction

The development of improved models for chemical bonding has always benefited from specific cases in which the existing models fail. One well-known example is the failure of the widely used valence-shell electron-pair-repulsion (VSEPR^[1]) model and also of simple ionic models to predict the bent structures of some of the molecular dihalides of the heavy alkaline earth metals (Ca, Sr, and Ba) in the gas phase.^[2–10] Many more complexes with a formal d^0 configuration of the

central metal (and also with d^1 and d^2 configurations) have since been found, both experimentally and computationally, which do not conform to the simple structural models. These interesting “non-VSEPR” d^0 systems and the electronic factors that control their shapes are the topic of this article.

Figure 1 shows the part of the periodic table, in which metals with a formal d^0 configuration may be found. The configuration assignment is based on the usual oxidation state formalism, which assumes a heterolytic distribution of the bonding electrons in favor of the ligands.^[11] The number of different metals for which such a configuration is possible is remarkable indeed, and ranges from the heavier members of “main” Groups 1 and 2 through the genuine transition metals Groups 3–8 to the lanthanides, and even to the later members of the actinides.^[12, 13] Many compounds with a formal d^0 configuration are of practical importance, for example, as

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Table 1. Preferred structures of the monomeric alkaline earth dihalides [MX₂].^[a]

X:	F	Cl	Br	I
M:				
Be	linear	linear	linear	linear
Mg	linear	linear	linear	linear
Ca	quasilinear	quasilinear	quasilinear	quasilinear
Sr	bent ($\Delta E_{\text{lin}} = 6.6$)	quasilinear	quasilinear	quasilinear
Ba	bent ($\Delta E_{\text{lin}} = 20.9$)	bent ($\Delta E_{\text{lin}} = 6.8$)	bent ($\Delta E_{\text{lin}} = 4.5$)	quasilinear

[a] Linearization energies ΔE_{lin} [kJ mol⁻¹] are from Configuration interaction singles-doubles (CISD) calculations.^[5] Species for which computed energy changes are below approximately 4 kJ mol⁻¹ upon angle changes of more than 20° around linearity have been termed “quasilinear”.

linear versus bent structures of these molecules, mainly based on the results of *ab initio* calculations^[4, 5] (the various available experimental techniques all have their problems with the quantitative structure determination in the case of shallow potential-energy surfaces^[5, 10]). As expected, the Be and Mg dihalides are linear. However, the halides of the heavier metals deviate increasingly from a rigid linear structure, the heavier the metal and the lighter the halogen is.^[2] As a result, [BaF₂]^[*] may be called genuinely bent, with a linearization energy of about 20 kJ mol⁻¹, whereas several other “intermediate” species should be better termed “quasilinear” in view of energy changes below approximately 4 kJ mol⁻¹ upon bond-angle changes over more than 20°. ^[4, 5] These computational results confirmed the more qualitative conclusions of the early electric quadrupole deflection (EQD) experiments of Klemperer et al.,^[2] which initiated the interest in the shapes of the gaseous alkaline earth dihalides. The quantum-chemical calculations may thus be considered to have settled the long-standing dispute on the structures of these molecules. We note in passing that the use of even larger basis sets and a better inclusion of electron correlation than in these studies are expected to give an even slightly larger preference to bent arrangements (as well as slightly shorter bond lengths in some of the systems).

The lanthanides in their +II oxidation state may be considered to be valence isoelectronic with the heavy alkaline earth compounds. Consequently, their gaseous dihalides are also bent, or at least they exhibit a relatively flat bending potential curve (i.e. they are quasilinear). This structure has been confirmed at various computational levels^[19] (again, various experimental techniques give partly inconclusive results, but EQD experiments indicate bent structures for the difluorides^[20]). The alkaline earth dihydrides have been studied computationally as the simplest model systems for the dihalides.^[3, 7–9] While [CaH₂]^[3, 7–9] should be considered quasilinear, the heavier homologues are increasingly bent. For example, [BaH₂] was computed^[3] to have a bending angle of around 119° and a linearization energy of more than 25 kJ mol⁻¹. Thus, it is slightly more bent than [BaF₂]. A

[*] Note: molecular metal compounds will be considered as coordination complexes and thus written in square brackets.

matrix-isolation infrared (IR) and density functional study has found bent structures also for almost all lanthanide dihydrides.^[21]

A computational comparison of a range of [MX₂] complexes^[6] (M = Ca, Sr, Ba; X = Li, BeH, CH₃, NH₂, OH, F) has indicated that the dimethyl complexes [M(CH₃)₂] also exhibit an even larger tendency to bend than the corresponding difluorides, for reasons we will discuss in Section 3.8. Indeed, Eaborn et al.^[22] have prepared a number of unsolvated [MR₂] complexes (M = Ca, Eu, Yb) with very bulky alkyl ligands (R = C[Si(CH₃)₃]₃) and structurally characterized them by X-ray diffraction. All of these compounds exhibit bent structures in the solid state. In the case of the alkaline earth diamides [M(NH₂)₂], a significant dependence of the bending on the orientation of the amide group has been found computationally,^[6] a point we will discuss in detail in Section 3.8. Complex potential-energy surfaces have been computed for the [M(CN)₂] molecules, with side-on coordination and bent structures dominating for M = Sr, Ba.^[23]

If we regard the cyclopentadienyl ligand as occupying one coordination site at the metal, the Group 2 and lanthanide(II) metallocenes [MCp₂] (Cp = η⁵-C₅H₅) may also be viewed as dicoordinate [MX₂] complexes. Indeed, the observation^[24, 25] of bent solid-state structures of a number of substituted, base-free alkaline earth and lanthanide(II) metallocenes stimulated considerable interest, although it could not be ruled out that intermolecular contacts may be partly responsible for the bending. Gas-phase electron diffraction (GED) studies also suggested bent structures.^[26] *Ab initio* calculations on [MCp₂] at the MP2 level^[27] indicated bent minimum-energy structures for M = Sr, Ba, Sm, Eu, but linear structures for M = Ca, Yb (see refs. [26d, 28] for further computations). In all cases the bending potential was extremely shallow, and thus these complexes should best be classified as quasilinear, with shallow potential-energy surfaces. As a consequence, the problem of shrinkage effects^[10] makes a reliable determination of the bending angles by GED difficult for such systems.

In contrast, calculations on the isoelectronic but more covalently bonded, hypothetical cations [MCp₂]⁺ (M = Sc, La)^[29] indicated significantly bent arrangements with large linearization barriers. Thus, the preference for bent structures increases with increasing covalency (cf. Section 3.7). Bent structures have also been computed for the heteroleptic model systems [CpM(NH)] (M = Y, La).^[30] Similarly, the cations [YH₂]⁺,^[31c] [ScF₂]⁺,^[9f, 32] and [ScH₂]⁺^[32, 33] have been computed to be significantly bent. Small angles and large linearization energies have been found computationally and partly experimentally for [MO₂] (M = Ti, Zr, Hf).^[34–36] Even more strongly bent structures have been found for the ions [MO₂]⁺ (M = Nb, Ta).^[37] and were predicted for the hypothetical [MO₂]²⁺ (M = Mo, W).^[38] Earlier Hartree–Fock–Slater calculations also gave a significantly bent structure for [CeO₂],^[7] but this method probably overestimates the bending.^[39]

d⁰ Systems with neutral ligands may also exhibit bent structures, with relatively shallow bending potentials but quite low bending angles. This has been found computationally for the hypothetical cations [M(L)₂]^{m+} (M^{m+} = Ca²⁺, Sr²⁺, Ba²⁺, Ra²⁺, Sc³⁺, Y³⁺, La³⁺; L = HF, H₂O, NH₃).^[40] Even the

corresponding Group 1 cations $[\text{Rb}(\text{L})_2]^+$ and $[\text{Cs}(\text{L})_2]^+$ were computed to exhibit deviations from linearity, albeit with extremely shallow potential wells.^[40b] The same holds for the bis(diethyl ether) complexes.^[41]

2.2. Pyramidal Tricoordinate Complexes

The importance of ligand repulsion increases with increasing coordination numbers (cf. discussion in Section 3.7). The conditions for the pyramidalization of tricoordinate complexes are therefore already significantly more restrictive than those for the bending of dicoordinate species. Thus, Group 3 or lanthanide trihalides tend to be planar^[13, 19, 32, 42, 43] (ref. [10] provides extensive further literature) or only very slightly pyramidalized, with shallow potential wells (“quasiplanar”). Slightly pyramidalized structures in the solid state have been found for a number of substituted rare earth metal tris(amido)^[44, 45] and tris(phenolato)^[46] complexes. However, the available evidence (e.g. NMR spectra in solution^[44] or disorder in the solid-state structures^[44–46]) indicates that the barrier to planarity must be small. Planar structures are expected for the corresponding isoelectronic Group 2 $[\text{MX}_3]^-$ ions.

In contrast to the trihalides, significantly pyramidal structures have been computed for hydrido species such as $[\text{ScH}_3]$,^[32] $[\text{LaH}_3]$,^[42c] several other lanthanide trihydrides (supported by matrix IR data^[21]), $[\text{TiH}_3]^+$ ^[32] and $[\text{ZrH}_3]^+$,^[31c] or for the trialkyl ions $[\text{Ti}(\text{CH}_3)_3]^+$ ^[32] and $[\text{Ta}(\text{CH}_3)_3]^{2+}$.^[47] Indeed, the unsolvated trialkyl complexes $[\text{M}\{\text{CH}(\text{Si}(\text{CH}_3)_2)\}_3]$ ($\text{M} = \text{La}, \text{Sm}$) have been found experimentally to be distinctly pyramidal in the solid state.^[48] This greater preference for pyramidal structures with hydride or alkyl ligands is to a large extent a result of the absence of π bonding^[32] (cf. Section 3.8). The computed preference for pyramidal structures of species such as the ion $[\text{TiCp}_2\text{R}]^+$ ($\text{R} = \text{alkyl}$) has been suggested^[49] as a possible origin of the syndiotacticity of propene polymerization using related metallocene catalysts (see also ref. [50]). In contrast, model calculations gave planar structures for neutral species like $[\text{ScCp}_2\text{R}]$ or $[\text{TiCp}_2\text{R}]$, and a correspondingly lower stereospecificity was considered.^[49] Some more computational examples for pyramidal heteroleptic Group 3 and Group 4 complexes have been provided.^[30, 51] Pyramidal structures have also been computed for the hypothetical cations $[\text{ML}_3]^{m+}$ ($\text{M}^{m+} = \text{Sr}^{2+}, \text{Ba}^{2+}, \text{La}^{3+}$; $\text{L} = \text{H}_2\text{O}, \text{NH}_3$)^[40a,b] (and $[\text{Ln}(\text{MeCN})_3]^{3+}$ ^[52]). For the more covalent Group 6 systems $[\text{CrO}_3]$, $[\text{MoO}_3]$, and $[\text{WO}_3]$, calculations indicated significantly pyramidal structures^[53–55] (see also refs. [30, 56] for further examples).

2.3. Tetracoordinate Complexes

Deviations from conventional “VSEPR” structures are least likely for tetracoordination, as both ligand repulsion and covalent considerations lead to a large preference for tetrahedral arrangements. Indeed, tetrahedral structures dominate the tetracoordination of d^0 complexes. Hybridization arguments (cf. Section 3.5) suggest a square pyramid

(with the metal at the apex) or a trigonal pyramid (with the metal at the basis) as possible alternatives to the tetrahedron.^[31c] However, these configurations have considerably larger ligand repulsion. DFT calculations on the $[\text{NbH}_4]^+$ ion indicate a square pyramidal structure as lowest-energy minimum.^[57] Already for the heavier homologue $[\text{TaH}_4]^+$, the tetrahedron is computed to be lowest in energy, with the square pyramid about 30 kJ mol^{-1} above.^[31c] While $[\text{Ti}(\text{CH}_3)_4]$ has been computed to be tetrahedral, its distortion requires considerably less energy than for analogous main group compounds.^[58] Interesting deviations from an ideal tetrahedron may be found for tetracoordinate complexes when inequivalent ligands are present (see Section 4.1).

2.4. Square-Pyramidal Pentacoordinate Complexes

The VSEPR model predicts the trigonal-bipyramidal (TBP-5) structure to be the most stable arrangement for pentacoordinate d^0 complexes. However, even for main group compounds, square-pyramidal (SP-5) structures are only very slightly higher in energy (usually by a few kJ mol^{-1}). As a result, many $[\text{MX}_5]$ main group complexes are fluxional, often by the well-known Berry-pseudorotation pathway^[59] (see ref. [60] for early reviews and excellent bonding discussions). The same behavior, that is, a TBP-5 minimum and low-lying SP-5 transition states, is found for d^0 pentahalides, both experimentally^[61] and computationally^[62] (see also ref. [60a]).

In contrast, the TBP-5 structure has been computed to be only a higher-order saddle point for $[\text{TaH}_5]$, more than 80 kJ mol^{-1} above the SP-5 minimum.^[62] This preference for an SP-5 arrangement survives for $[\text{Ta}(\text{CH}_3)_5]$ ^[62–64] which is experimentally known and has been structurally characterized by GED.^[64] Among other factors, the larger ligand repulsion compared to the hydride (see discussion in Section 3.7) reduces the TBP-5 versus SP-5 energy difference (MP2 calculations give ca. 30 kJ mol^{-1} ,^[62, 63] recent DFT calculations provide ca. 53 kJ mol^{-1} ^[65]). Based on ab initio calculations, it has been suggested^[66] that the activation barrier for unimolecular methane elimination from $[\text{M}(\text{CH}_3)_5]$ ($\text{M} = \text{Nb}, \text{Ta}$), to give Schrock-type carbene complexes, is enhanced significantly by the fact that the ground states have SP-5 structures, whereas the transition states for the elimination reaction are closer to TBP-5. The recently reported structure^[58] of the $[\text{Ti}(\text{CH}_3)_5]^-$ ion in the solid state ($[\text{Li}(\text{Et}_2\text{O})_2][\text{Ti}(\text{CH}_3)_5]^-$) is remarkable, as it exhibits two crystallographically different ion pairs. Of these, one is closer to SP-5, the other closer to TBP-5. Calculations for the free anion indicate SP-5 to be lower than TBP-5 by only about 10 kJ mol^{-1} .^[58] A structure close to SP-5 has been found by X-ray diffraction for another $[\text{TaR}_5]$ alkyl complex ($\text{R} = \text{CH}_2\text{-}p\text{-C}_6\text{H}_4\text{CH}_3$).^[67] The d^1 complex $[\text{Mo}(\text{CH}_3)_5]$ has recently also been found to favor SP-5, and computations suggest that the stabilization relative to TBP-5 is large.^[65]

Interesting computational results are available for some further hypothetical hydride complexes: For the ion $[\text{TiH}_5]^-$, an SP-5 minimum has been calculated by DFT methods, with

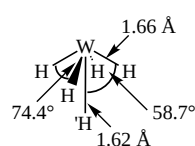


Figure 2. DFT-optimized lowest-energy structure of $[\text{WH}_5]^+$.^[31c]

the TBP-5 approximately 30 kJ mol⁻¹ less stable.^[68] The more ionic $[\text{HfH}_5]^-$ prefers TBP-5, probably in part because of ligand repulsion (cf. Section 3.7).^[57] In contrast, DFT calculations for the cation $[\text{WH}_5]^+$ suggest an unusual “umbrella-like” C_{4v} structure to be lowest in energy (Figure 2), but with several other low-lying minima

(including the SP-5 structure) at less than 10 kJ mol⁻¹ higher energy^[31c] (see also ref. [57]).

Another interesting result is the computational observation of low-lying transition states of C_{2v} symmetry for the interconversion of equivalent SP-5 minima in $[\text{TaH}_5]$ (Figure 3).^[62] These transition structures may be classified as edge-bridged tetrahedral (EBT-5).^[68] Therefore, this system has

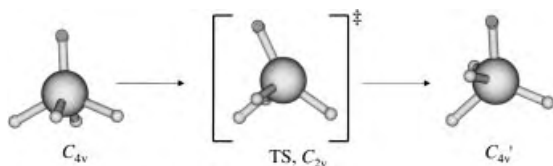


Figure 3. Low-lying C_{2v} symmetrical transition states (TS) on the energy surface of $[\text{TaH}_5]$.^[62]

been predicted to be fluxional, in spite of the high energy of the TBP-5 structure.^[62] Similar pivoting mechanisms may be expected for other five-coordinate d⁰ complexes (as confirmed, for example, by computations^[68] on the $[\text{TiH}_5]^-$ ion). Related EBT-5 arrangements may even become minima on the potential-energy surface for heteroleptic five-coordinate systems including both σ - and π -donor ligands^[68, 69] (see Section 4.2).

2.5. Nonoctahedral Hexacoordinate Complexes

The increasing number of known nonoctahedral hexacoordinate d⁰, d¹, and d² complexes represents probably the most spectacular failure of the traditional structure models in this area of the periodic table. The octahedron, which is clearly favored by ligand repulsion,^[70] has been, and still is by far the predominant geometry for this coordination number, both in main group and in transition metal chemistry. It remains the dominant coordination mode even for most d⁰ $[\text{MX}_6]$ complexes, for example, with X = halide,^[10, 62, 71] OR,^[72] NR₂,^[73]. However, as has been pointed out,^[71] there are indications that the energy difference between octahedral and trigonal-prismatic arrangements for such d⁰ systems is already considerably lower than for typical main group species, that is, the complexes are less rigid towards intramolecular rearrangements (presumably via D_{3h} transition states; however, see ref. [70]). A controversy arose,^[62, 74–76] about whether the structure of $[\text{CrF}_6]$ is octahedral or trigonal prismatic. This was mainly because the computational treatment of electron correlation is relatively difficult for this 3d system with a low HOMO–LUMO gap. The experimental information was also controversial. However, meanwhile both experiment^[77]

and theory^[62, 76] agree with an octahedral structure. The conversion from octahedron into trigonal prism is computed^[62, 76] to require actually somewhat higher energy than, for example, in $[\text{WF}_6]$.^[78] Table 2 summarizes activation barriers

Table 2. Relative energies [kJ mol⁻¹] between D_{3h} and O_h structures of Group 6 hexahalide complexes.^[a]

	Cr	Mo	W
F	61.6	27.1	42.9
Cl	56.4	62.6	78.7
Br	–[b]	61.9	74.9
I	–[b]	–[b]	66.4

[a] DFT calculations, see appendix. The O_h structure has been characterized as a minimum, whereas the D_{3h} structure is a transition state. [b] No self-consistent field (SCF) convergence within O_h symmetry at this computational level.

calculated for the trigonal twist of the Group 6 hexahalides. The regular trigonal prism is generally a transition state for this process (for $[\text{CrBr}_6]$, $[\text{CrI}_6]$, and $[\text{MoI}_6]$, the DFT calculations did not converge for the O_h structure). Notably, with Mo and W, the barrier is larger for the heavier halogens than for fluorine (Section 3.8). For a given halogen, the barrier is larger with W than with Mo (Section 3.7). Obviously, these numbers indicate that a trigonal twist is much more facile than for main group hexahalide complexes, for which the barriers range typically from 100 to 300 kJ mol⁻¹,^[71] and thus dissociative processes become likely alternative pathways for ligand scrambling.

The earliest experimental examples of trigonal-prismatic coordination of early transition metals were provided by the extended solid-state structures of various d⁰, d¹, and d² metal chalcogenides and pnictides (e.g. for the mineral molybdenite, MoS_2). An early overview on these solid-state compounds, and a very perceptive discussion of their electronic structure, has been given by Huisman et al.^[79] (see also discussion in ref. [70]). Although the stoichiometric composition often does not lead directly to a d⁰–d² configuration of the metal, the local electronic situation may well correspond to it. Strongly distorted octahedral metal coordination is ubiquitous in binary or ternary Group 4–6 oxides, e.g. for ZrO_2 , WO_3 , MoO_3 , BaTiO_3 , or KNbO_3 .^[80, 81] These examples are relatively clear-cut d⁰ cases. The distortions have been studied extensively in many cases because of their impact on technologically important materials properties. Such extended solid-state structures will be discussed in more detail in Section 5.

The first molecular d⁰ complexes with trigonal-prismatic (or close to prismatic) structures were those of dithiolate (or diselenolate) chelate ligands,^[82–85] originally with an unsaturated organic backbone (dithiolene or diselenolene^[86] ligands). In this case, the nature of bonding is delocalized, and the assignment of a formal oxidation state and d configuration

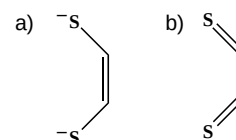


Figure 4. Two extreme bonding situations for dithiolene chelate ligands: a) dianionic dithiolene, b) neutral dithiodiketone.

is not straightforward (Figure 4 shows two extreme formulations of the state of the ligands). A formal treatment of the ligands in their dianionic form is advantageous for our present purpose^[85], and gives a d^0 electron count for tris(dithiolene) systems such as $[\text{Mo}(\text{S}_2\text{C}_2\text{H}_2)_3]$ or $[\text{Nb}(\text{S}_2\text{C}_2\text{H}_2)_3]^-$.^[87] Meanwhile, a significant number of nonoctahedral complexes with saturated dithiolates^[83, 88] have been structurally characterized. Their bonding may be discussed in somewhat simpler terms. Part of the ongoing interest in dithiolate and dithiolene complexes is related to the importance of dithiolene coordination for the molybdopterin cofactor of various oxidase and reductase enzymes^[84, 89–91] (Section 4.4). More recently, the first nonoctahedral hexacoordinate complexes of monodentate thiolate ligands have been reported.^[92]

Typically, the structures found for tris(dithiolate), hexathiolate or tris(dithiolene) complexes, and for related complexes of more unsymmetrical ligands, may be assigned, at least approximately, C_3 symmetry. Depending on the actual electron configuration, on the type of ligand, on the metal, and on counter-ion contacts, these structures cover the entire

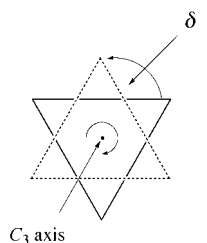


Figure 5. Definition of trigonal twist angles δ along C_3 axis for tris(dithiolene) and related systems intermediate between octahedron and trigonal prism.

range from octahedral to trigonal prismatic coordination. Whether a structure is closer to the trigonal prismatic or octahedral (“trigonal antiprismatic”) extreme may often be expressed most conveniently in terms of a trigonal-twist angle δ between the two appropriate trigonal faces (Figure 5).^[82–84] For monodentate ligands, $\delta = 0^\circ$ and $\delta = 60^\circ$ denote clearly the trigonal prismatic and antiprismatic limits, respectively. For chelate ligands, the octahedral limit has to be set at $\delta < 60^\circ$, depending on the ligand bite angle (ca. 49° for a typical bite angle of ca. 81°).^[93] The angle between *trans* coordination sites will in this case

be around 170° rather than 180° . This has to be compared to a typical *trans* angle of about 136° for a regular trigonal prism.

Complexes with unsaturated dithiolene ligands exhibit structures closer to the trigonal prism than those of saturated dithiolate ligands. This is related to π bonding (Section 3.8). A particularly fascinating set of systems is provided by compounds containing the $[\text{M}(\text{ndt})_3]^-$ ion ($\text{M} = \text{Nb}, \text{Ta}$; $\text{ndt} = \text{norbornane-}exo\text{-}2,3\text{-dithiolate}$).^[94] Depending mainly on the counter ions, several unusual structures are possible, in one of which the three chelate ligands coordinate in nonequivalent modes.^[94] In this case, the distortion is more in the direction of a bicapped tetrahedron than of a trigonal prism. Similar types of distortion have been observed^[95] and are more important for heteroleptic complexes (Section 4.3).

Most of the early discussions of the nonoctahedral structures of tris(dithiolene) complexes have focused on the notion of some special property of the ligands, for example, on the idea of “interligand bonding”,^[86a, 96] rather than on a genuine preference of the central metal for a prismatic coordination (however, see refs. [70, 79]). In view of the more recent observations of nonoctahedral complexes with simpler, monodentate ligands (see below), it is now clear that tris(dithio-

lene) and related complexes may be understood along the general lines set out in Section 3.

Apart from complexes of sulfur-based ligands, various complexes of other chelate ligands have been found to exhibit structures along the octahedral/prismatic twist coordinate. Examples are the tris(dialkoxide) complexes $[\text{W}(\text{OCH}_2\text{CH}_2\text{O})_3]$ ($\delta \approx 37^\circ$)^[97] and $[\text{W}(\text{OCMe}_2\text{CMe}_2\text{O})_3]$ ($\delta \approx 34^\circ$).^[98] which are more on the octahedral side. More on the prismatic side are tris(9,10-phenanthrene-quinone)molybdenum,^[99] tris(buta-1,3-diene)molybdenum,^[100, 101] tris(*ortho*-xylyl)tungsten,^[102] tris(methylvinylketone)tungsten^[103] (all $\delta \approx 0^\circ$), or the recently characterized tris(4,4',5,5'-tetramethyl-2,2'-bisphosphinine)tungsten ($\delta \approx 15^\circ$; Figure 6).^[104] In all of these cases, we may arrive at a formal d^0 con-

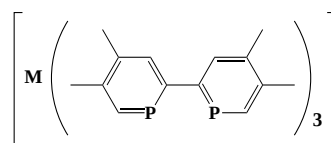


Figure 6. Group 6 tris(4,4',5,5'-tetramethyl-2,2'-bisphosphinine) complexes.^[104]

figuration of the metal by regarding the chelate ligands in their dianionic form. For the butadiene ligand, this would lead to a metallacyclopentene-type rather than to a butadiene π -complex bonding situation (Figure 7). Therefore, one might expect shorter central than terminal C–C bonds, as

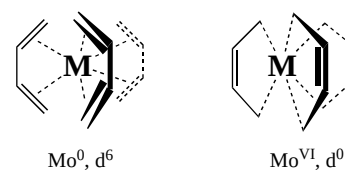


Figure 7. Two limiting resonance structures and formal d configurations for $[\text{Mo}(\text{bd})_3]$ ($\text{bd} = 1,3\text{-butadiene}$).

is common for butadiene complexes of early transition metals.^[105] The available experimental data^[100, 101] indicate short terminal and long central bonds. However, these distances are probably unreliable. Recent DFT and MP2 calculations give the expected shorter central bonds.^[106] The structures of tris(*ortho*-xylyl)tungsten^[102] and tris(methylvinylketone)tungsten^[103] exhibit short central bonds and thus support a first approximation as d^0 complexes with chelating dialkyl and enolate ligands, respectively. Similar to the situation for dithiolene ligands (see above), one may generally approach the bonding either by starting from a neutral ligand and then include extensive π backbonding, or from a dianionic ligand and then include π delocalization within the ligand (Section 3.8).^[70]

In the 1980s, calculations predicted trigonal-prismatic structures (distorted, C_{3v} , or regular, D_{3h}) for simple hydride systems such as $[\text{TiH}_6]^{2-}$, $[\text{VH}_6]^-$, or $[\text{CrH}_6]$ ^[107] (see refs. [31, 62, 71, 74, 108, 109] for further, related computational studies). The first experimental example of a trigonal-prismatic complex with only simple monodentate ligands was

then provided by the solid-state structure of the $[\text{Zr}(\text{CH}_3)_6]^{2-}$ ion (further coordinated by $[\text{Li}(\text{tmeda})]^+$ counter ions; TMEDA = *N,N,N',N'*-tetramethylethylenediamine).^[110] This observation spurred considerable interest. Subsequently, the neutral, valence-isoelectronic analogue hexamethyltungsten, $[\text{W}(\text{CH}_3)_6]$, received most of the attention, both experimentally^[111–113] and computationally^[31, 62, 114, 115] (the model system $[\text{WH}_6]$ and related species were also studied theoretically^[31, 62, 71, 74, 108, 114]). While $[\text{W}(\text{CH}_3)_6]$ had been prepared in 1973 by Wilkinson and co-workers,^[116] its structure had always been assumed to be octahedral.^[116, 117] A GED study could then clearly rule out an octahedral arrangement.^[111] A regular trigonal prism was favored (with D_{3h} skeleton), but a distortion of the skeleton towards C_{3v} could not be excluded. Initial Hartree–Fock (HF) optimizations supported the D_{3h} structure.^[62] Calculations that include electron correlation later showed the skeleton to be distorted to C_{3v} symmetry (slightly tilted methyl groups reduce the overall symmetry to C_3).^[114, 115] However, the system is fluxional, because a regular prismatic D_3 -symmetrical transition state is only about 20 kJ mol^{−1} higher in energy and thus allows a rapid flipping process.^[114, 115] Indeed, the VALBOND force-field calculations of Landis et al.^[31] (Section 3.5) had even earlier suggested a distorted prism and fluxional behavior. The C_{3v} skeleton has been confirmed independently^[112, 113] by a low-temperature X-ray diffraction study (see Figure 8 for a comparison of computed and experimental structure parameters). Among other things, the fluxional nature of $[\text{W}(\text{CH}_3)_6]$ ^[114, 115] accounts for the relatively simple NMR spectra^[111, 116, 117] at room temperature.

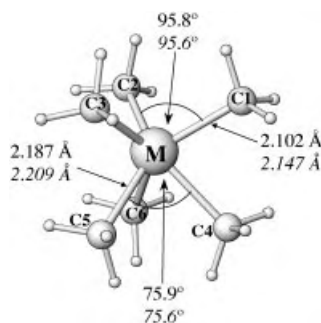


Figure 8. Comparison of experimental^[113] and computed^[114, 115] structure parameters for $[\text{W}(\text{CH}_3)_6]$. Computed parameters in italics. Experimental values have been averaged over three formally equivalent positions, and over the two molecules within the unit cell.

Meanwhile, the structures of several further d⁰–d² hexamethyl complexes have been studied, both experimentally^[113] and computationally.^[115] DFT calculations have indicated the mono- and dianionic d⁰ complexes $[\text{M}(\text{CH}_3)_6]^-$ ($\text{M} = \text{V}, \text{Ta}$) and $[\text{M}(\text{CH}_3)_6]^{2-}$ ($\text{M} = \text{Ti}, \text{Zr}, \text{Hf}$) to have regular trigonal prismatic structures, whereas neutral and cationic complexes $[\text{M}(\text{CH}_3)_6]$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) and $[\text{M}(\text{CH}_3)_6]^+$ ($\text{M} = \text{Tc}, \text{Re}$) distort to C_3 structures (with C_{3v} heavy-atom skeleton) to varying extents.^[115] $[\text{Nb}(\text{CH}_3)_6]^-$ was computed to be a borderline case, just on the brink of distortion^[115] (X-ray data confirm a slight distortion and show considerable thermal motion^[113]). A regular prism was confirmed by X-ray dif-

fraction for $[\text{Ta}(\text{CH}_3)_6]^-$.^[113] Adding one or two electrons to the system quenches the distortion effectively, and thus d¹ $[\text{Re}(\text{CH}_3)_6]$ and $[\text{Tc}(\text{CH}_3)_6]$, as well as d² $[\text{M}(\text{CH}_3)_6]$ ($\text{M} = \text{Ru}, \text{Os}$), have been predicted to prefer regular prisms^[114, 115] (an unusual C_{2v} structure was predicted computationally for $[\text{OsH}_6]$ ^[109]). Indeed, while the initial X-ray structure determination for $[\text{Re}(\text{CH}_3)_6]$ had suggested a slightly distorted arrangement,^[112] a more recent, better refinement confirms a regular prism.^[113] Very recently, Roessler and Seppelt^[118] reported the structure of $[\text{Mo}(\text{CH}_3)_6]$ and confirmed the computationally predicted C_3 structure^[115] with a slightly larger distortion than that of the tungsten analogue. Most notably, in none of these cases can a distorted or regular octahedral structure compete energetically with the prismatic arrangements.

Partly because of β -hydrogen elimination as a potential low-energy pathway for decomposition, no further d⁰ $[\text{MR}_6]$ complexes with simple alkyl ligands are known. However, regular trigonal prismatic structures were also observed by X-ray diffraction for the aryl complexes $[\text{TaPh}_6]^-$ and $[\text{Ta}(\text{tolyl})_6]^-$.^[119] Even more recently,^[120] the anionic acetylide complexes $[\text{Ta}(\text{tBu}_3\text{SiC}\equiv\text{C})_6]^-$ and $[\text{M}(\text{tBu}_3\text{SiC}\equiv\text{C})_6]^{2-}$ ($\text{M} = \text{Zr}, \text{Hf}$) were examined in form of the salts $\text{K}[\text{Ta}(\text{tBu}_3\text{SiC}\equiv\text{C})_6]$, $[\text{K}(\text{crypt } 2.2.2.)][\text{Ta}(\text{tBu}_3\text{SiC}\equiv\text{C})_6]$, $[\text{Li}(\text{tBu}_3\text{SiC}\equiv\text{C})_3][\text{Ta}(\text{tBu}_3\text{SiC}\equiv\text{C})_3]$, and $[\text{Li}(\text{tBu}_3\text{SiC}\equiv\text{C})_3]_2\text{M}$ ($\text{M} = \text{Zr}, \text{Hf}$; crypt 2.2.2. = 4,7,13,16,21,24-hexaoxa-1,10-diaza-bicyclo[8.8.8]hexacosane). While the bulky substituted acetylide ligands provide complexes closer to the trigonal prismatic extreme for the two tantalum systems (twist angles $\delta = 18^\circ$), the more ionic Zr and Hf dianions exhibit almost regular octahedra. DFT and calculations on the simpler model complexes $[\text{Ta}(\text{C}\equiv\text{CH})_6]^-$ and $[\text{Zr}(\text{C}\equiv\text{CH})_6]^{2-}$ gave structures closer to the regular prism, but with the octahedron at lower relative energy for the dianion compared to the monoanion.^[120]

2.6. Higher Coordination Numbers

For coordination numbers above six, there should be no significant surprises. Ligand–ligand repulsion is expected to dominate and to favor regular structures. Moreover, even the simplest structure models allow several different coordination arrangements (Figure 9) that usually do not differ much energetically. Nevertheless, we may ask to what extent additional electronic factors favor certain structures?

The only experimental examples of seven-coordinate, exclusively σ -bonded d⁰ complexes are the ions $[\text{M}(\text{CH}_3)_7]^-$ ($\text{M} = \text{Mo}, \text{W}$).^[118, 121] Both exhibit a singly capped distorted octahedral structure (SCO-7; C_{3v} skeleton), which has also been found in ab initio calculations to be the lowest-energy structure for $[\text{MH}_7]^-$ ($\text{M} = \text{Mo}, \text{W}$)^[31d, 57, 122] The SCO-7 arrangement is “allowed” by the VSEPR model because it has relatively low ligand–ligand repulsions, in fact lower than those of the two alternative structures, the singly capped trigonal prism (SCTP-7) and the pentagonal bipyramid (PB-7). On the other hand, the structural parameters of the underlying distorted octahedra for $[\text{M}(\text{CH}_3)_7]^-$ are in striking agreement with one of the lower-lying stationary points on the

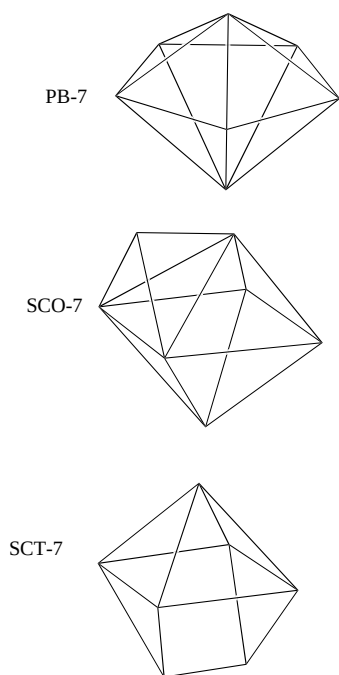


Figure 9. Preferred polyhedra for heptacoordination.

potential-energy surface computed for the hexamethyl complexes.^[114, 115] This suggests that in addition to ligand repulsion there may also be some electronic factors that favor the SCO-7 structure. These structures contrast to those of heptacoordinate main group compounds such as $[\text{IF}_7]$, which usually prefer PB-7 (with distortions in the equatorial plane).^[122, 123] Of the experimentally known d^0 heptafluorides, $[\text{ReF}_7]$ ^[124] apparently prefers a distorted PB-7,^[125] whereas $[\text{WF}_7]^-$ and $[\text{MoF}_7]^-$ favor the SCO-7.^[126] The dianions $[\text{NbF}_7]^{2-}$ and $[\text{TaF}_7]^{2-}$ have been found to exhibit the SCTP-7,^[127] whereas the PB-7 apparently is again favored for the trianions $[\text{ZrF}_7]^{3-}$ and $[\text{HfF}_7]^{3-}$ ^[128] (clearly, interactions with the counter ions are expected to be large for the polyanions).

The most notable computational result in this context is the finding that the SCO-7 is *strongly* favored (by ca. 150 kJ mol^{-1}) over PB-7 for $[\text{WH}_7]^-$, whereas the energy difference is only about 4 kJ mol^{-1} for $[\text{WF}_7]^-$ and around 18 kJ mol^{-1} for $[\text{MoF}_7]^-$.^[122] This provides further support for the importance of electronic factors. More specifically, as the pentagonal bipyramid exhibits a 180° bond angle between the apical ligands, this arrangement is unfavorable for predominantly σ -bonded d^0 systems (Sections 3.4 and 3.5). Furthermore, it appears possible that π bonding is less effective for these high coordination numbers, because of competition with the σ bonds for the same metal orbitals (Section 3.8 and 4.1).

Nonclassical structures are most likely for simple hydrides, and quantum-chemical calculations on these systems are most easily carried out. Calculations on $[\text{TcH}_7]$ favor a C_{2v} structure that might be described best as distorted SCTP-7.^[57] For ReH_7 , a further slight distortion of this polyhedron was computed.^[57] MP2-optimizations for the cations $[\text{MH}_7]^+$ ($M = \text{Ru}, \text{Os}$) converged towards nonclassical dihydrogen complexes and thus may not be compared directly.^[57] If we regard the η^5 -cyclopentadienyl ligand as occupying one coordination site,

an experimentally known heteroleptic analogue of a d^0 $[\text{MH}_7]$ system is provided by $[\text{ReCpH}_6]$ (see also Section 4).^[129] This system favors a structure derived from PB-7, but with the equatorial hydrogens bent away by more than 110° from the Cp ligand (which is a strong π donor, Sections 3.8. and 4). Calculations indicate SCO-7 to be higher in energy by about 66 kJ mol^{-1} .^[130]

Ab initio calculations on $[\text{OsH}_8]$ and $[\text{MH}_8]^-$ ($M = \text{Tc}, \text{Re}$) indicate that irregular C_s structures are favored ($[\text{RuH}_8]$, $[\text{RhH}_8]^+$, and $[\text{IrH}_8]^+$ converge towards dihydrogen complexes).^[57] σ Bonding disfavors the more symmetrical eight-coordinate arrangements, the dodecahedron (D_{2d}) and square antiprism (Section 3.4).^[57] A distorted square-antiprismatic D_{2d} structure has been predicted computationally for $[\text{OsF}_8]$.^[131] While a similarly distorted structure has been observed for the $[\text{TaF}_8]^{2-}$ ion in $\text{Na}_2[\text{TaF}_8]$,^[132] a regular square antiprism was found for the d^0 $[\text{WF}_8]^{2-}$ and the d^1 $[\text{ReF}_8]^{2-}$ ions.^[133] The d^1 octaalkyl complex, $[\text{Re}(\text{CH}_3)_8]^{2-}$ exhibits an almost regular square antiprism structure.^[121] Finally, the nine-coordinate systems $[\text{IrH}_9]$, $[\text{MH}_9]^-$ ($M = \text{Ru}, \text{Os}$), and $[\text{MH}_9]^{2-}$ ($M = \text{Tc}, \text{Re}$) are computed to prefer tricapped trigonal prisms, D_{3h} symmetry (with low-lying C_{4v} transition states),^[57] as found also experimentally^[134] for the latter two systems.

3. Bonding Descriptions and Models

In the previous section, we have summarized computational and experimental evidence indicating that a considerable variety of homoleptic d^0 complexes exhibit structures that do not obey the VSEPR model nor simple electrostatic considerations. We will now discuss the factors that lead to these “non-VSEPR structures”, as well as those factors that favor the more regular structures. Figure 10 illustrates the four

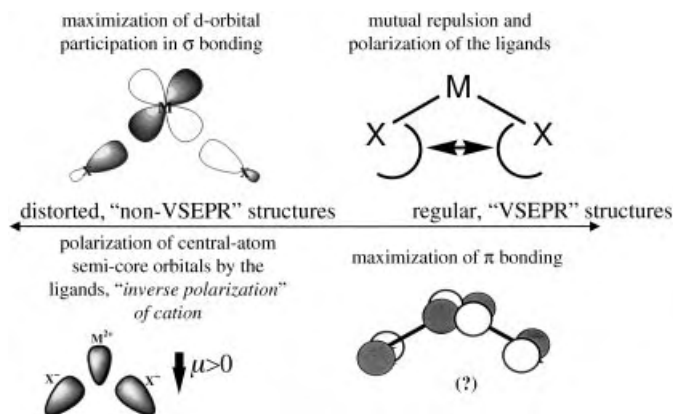


Figure 10. Illustration of the four important factors that control the structural preferences of d^0 complexes. The question mark for π bonding indicates that there are cases where π bonding may actually favor the “non-VSEPR” structures (see Section 3.8).

major influences that need to be considered. Of these, core polarization and d-orbital participation in σ bonding have been found to favor the non-VSEPR arrangements, whereas ligand repulsion and π bonding tend to act against them. However, the effect of π bonding is more complicated and

may even favor distorted structures (Section 3.8). Core polarization and σ bonding, and the models commonly employed to deal with them, are discussed in Section 3.1–3.6, ligand repulsion is addressed in Section 3.7, and π bonding in Section 3.8.

3.1. The “Classical” Models: Core Polarization versus d-Orbital Involvement?

Let us start again with the first examples given in Section 2, the bent structures of some alkaline earth dihalides. Historically, two very different explanations had been offered for the bent arrangements, which at first sight appear to be very difficult to reconcile. a) Klemperer and co-workers^[2] explained the bent structures within the framework of a polarized-ion model (although they did not rule out other possible reasons).^[135] Thus, as shown in Figure 11, a large,

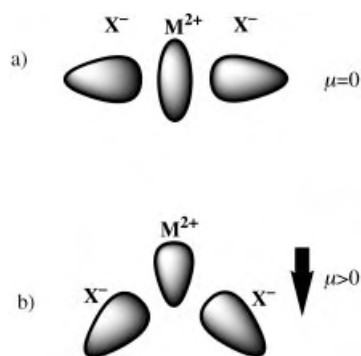


Figure 11. Schematic display of the polarized-ion model explanation of bending of alkaline earth dihalides. a) At a linear structure the system has no permanent dipole moment, and there is no stabilization because of interactions of the induced dipole of the cation with charge or dipole moment of the anions. b) At bent structures, a permanent dipole moment allows stabilizing charge–dipole and dipole–dipole interactions involving the induced dipole moment of the cation.

polarizable cation may be polarized by the anions. This is sometimes referred to as “inverse polarization”, in contrast to the more common polarization of anions by cations. Only a system with a bent structure possesses a permanent dipole moment and thus exhibits nonvanishing charge–dipole and dipole–dipole interactions involving the dipole polarizability of the cation. These interactions will therefore stabilize the bent relative to the linear arrangement. This model has later been put on a more quantitative basis by Guido and Gigli,^[136] using a Rittner-type approach,^[137] and it was tested by other workers.^[5, 7, 8] b) An alternative, covalent bonding model has been considered in detail by Hayes,^[138] and by Coulson^[139] (an even earlier, very perceptive discussion has been given by Skinner,^[140] prior to the discovery^[2] of the bent structures). While the lighter metals Be and Mg have only valence ns and np orbitals at their disposal for covalent bonding, the heavier metals Ca, Sr, and Ba may employ their “inner” $(n-1)d$ orbitals^[141, 142] (note the contrast to the “outer” nd orbitals that are frequently—most often unnecessarily—invoked in the qualitative discussion of “hypervalency” of the heavier

p-block main group elements^[143]). The highest occupied σ -bonding molecular orbital in these molecules has σ_u symmetry in the linear $D_{\infty h}$ structure and b_2 symmetry in the bent C_{2v} structure. Thus, as shown in Figure 12, while a valence

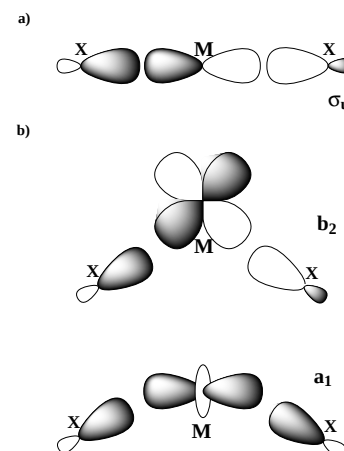


Figure 12. The d-orbital participation model^[138, 139] to explain linear versus bent structures of the alkaline earth dihalides. a) Participation of a metal np orbital in the σ_u HOMO favors a linear structure (e.g. for the Be and Mg dihalides). b) Participation of a metal $(n-1)d$ orbital in the b_1 HOMO favors a bent structure (e.g. for the Ca, Sr, and Ba dihalides).

p orbital is best for the formation of a linear structure, a d orbital may only participate at a bent structure (optimally at a bond angle of 90°). Depending on the availability of such “inner” d orbitals, covalent σ -bonding contributions would thus favor either a linear structure (e.g. for the Be and Mg systems) or a bent one (for Ca, Sr, and Ba). The symmetrical σ -bonding combination (of σ_g/a_1 symmetry), which also should be considered, has optimum overlap for a linear structure. However, the slight loss of overlap for this MO is expected to be greatly over compensated by the gain in overlap for the antisymmetric combination. These arguments may be extended in a straightforward manner to higher coordination numbers (see discussions of molecular orbital and valence-bond models in Sections 3.4 and 3.5, respectively).

3.2. Core Polarization and d-Orbital Involvement!

For a long time, these two models were discussed controversially. However, a careful analysis of results from ab initio calculations on $[MX_2]$ complexes indicated that a) the cation polarization and d-orbital participation arguments both are valid as two contributing aspects of the phenomenon,^[3–5, 8] and b) the two aspects are not strictly separable.^[144] The latter point may be appreciated best when considering radial density plots of the atomic valence and semi-core orbitals, shown for barium in Figure 13: The dipole polarizability, and thus the magnitude of any possible “inverse polarization” of a Ba^{2+} ion is largely determined by the outermost semi-core 5p atomic orbitals (AOs). For Ba^{2+} , the “inner” $(n-1)d$ orbitals invoked in the covalent models are

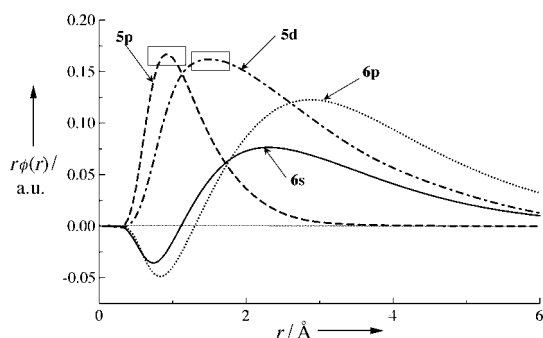


Figure 13. Radial distribution functions of atomic pseudo-valence orbitals for barium. Results of HF calculations with a small-core ECP and (6s6p5p1f) valence basis set. The 5p and 6s radial densities are from the ^1S ground state. The 5d and 6p radial densities have been computed for the lowest-lying ^3D and ^3P excited states, respectively. See ref. [145] for similar results for the calcium atom. Shaded boxes highlight the closeness of the maxima of the 5p and 5d curves.

the 5d orbitals. These orbitals have the same principal quantum number as the outermost core orbitals, and consequently their radial maxima are found in rather similar regions (Figure 13). This has been shown to be even more pronounced for the “3d metal” calcium.^[145] Thus, in spite of a significant energy difference between these $(n-1)p$ and $(n-1)d$ orbitals (e.g. the HF orbital energies of the 5p semi-core orbitals computed for $[BaH_2]$ are in the range 23.5–24 eV, the valence orbitals near 7.5–8 eV), a clear geometrical separation of “semi-core” and valence space is not possible. Similar arguments hold for all transition metals (as well as for the lanthanides) and in particular for the early ones. Thus, it has been shown many times that in an effective-core-potential (ECP) ansatz,^[146] the semi-core $(n-1)p$ orbitals have to be treated together with the valence orbitals to get accurate results.^[147] In the present context this means that a structure change resulting from involvement of the $(n-1)d$ orbitals in bonding will invariably influence the semi-core $(n-1)p$ orbitals. Turning the argument around, a polarization of the $(n-1)p$ semi-core orbitals involves generally the mixing of $(n-1)d$ -type orbitals into the wavefunction (the d -type basis functions have been termed “virtual orbitals of the core”^[8, 145]). This represents a fundamental break down, in this region of the periodic table, of the chemists’ usual valence-electron-only view.

In this context, it appears appropriate to term core polarization and d -orbital participation “two sides of the same coin”.^[8] Szentpály and Schwerdtfeger proposed the use of cation and anion softness as a unifying criterion, as this depends both on polarizability and the relative energies of different valence states.^[8] Unfortunately, a quantitative analysis indicates that the proposed criterion does not account for the structures of the entire series of alkaline earth dihalides.^[5] In spite of the inherent difficulties, there have been attempts to analyze, as far as possible, the influence of the two individual factors, core polarization and d -orbital participation, on the structural preferences of these alkaline earth $[MX_2]$ molecules. The most detailed analyses have been carried out for the simple dihydride model systems ($X = H$),^[3] where complicating π -bonding contributions are absent. Various ECP

approaches have been compared, with different ECP core sizes, with and without additional core-polarization potentials (CPP^[148]), and with different sizes of valence basis sets. It turned out that, for example, the bent structure of $[BaH_2]$ is not reproduced with a frozen-core 2-valence-electron ECP ansatz for the metal (i.e. the innermost 54 electrons of barium are replaced by the ECP), even with a large metal d -orbital valence basis set.^[3] Only when a CPP is added to simulate the polarization of the core by the valence electrons,^[148] is a bent structure observed.^[3] On the other hand, even with a CPP, such a 2-valence-electron ECP calculation fails to provide significantly bent structures when the metal basis does not contain d functions with large exponents (corresponding to genuine $(n-1)d$ orbitals just as for the transition metals).^[3]

This indicates that both core polarization and d -orbital participation act simultaneously to favor bent structures in these systems (keeping in mind that the two factors are not strictly separable, see above). Other investigations have supported this view,^[4, 5, 8] for example, a comparison of bending-force constants obtained from a polarized ion model or from the *ab initio* values,^[5] or analyses of model-core potential calculations.^[4] Investigations of $[BaX_2]$ molecules^[149] within Häser’s elegant one-center expansion analysis procedure^[150] of the one-particle density matrix have indicated clearly that the d -type metal populations have to be classified partly as genuinely “valence-type” as opposed to pure core-polarization contributions. This provides support for a “boundary role” of the heavy Group 2 atoms between main group elements, lanthanide, and transition metals.^[3–5]

Obviously, the relative importance of core polarization versus d -orbital participation will depend on a) the metal, b) the nature of the ligands, and c) the overall charge of the system. Consider, for example, the alkali metal complex $[Cs(H_2O)_2]^+$, which calculations show to be bent, albeit with an extremely shallow bending potential.^[40b] Clearly, covalent bonding contributions are very small in this system, and it appears more natural here to invoke the large polarizability of the cesium cation. Slightly bent structures of ionic compounds with large anions can be considered in a similar fashion, they are bent mainly because of the polarization of the central ion.^[151]

On the other hand, if we move into the transition metal series, the importance of the covalent bonding contributions increases dramatically with increasing oxidation state and formal charge of the metal center. At the same time, core polarizability diminishes. Landis et al.^[31c] have compared calculations with different ECP core sizes for the system $[WH_6]$. They found the distorted trigonal-prismatic structure for this complex to be favored even with an ECP including the $(n-1)s$ and $(n-1)p$ orbitals in the frozen core (“large-core” ECP). They concluded that core polarization is not very important for the structural preferences, which are then exclusively because of the covalent bonding contributions. As a note of caution, we have to mention that our own comparisons of “large-core” and “small-core” metal ECPs for $[W(CH_3)_6]$ and similar complexes indicate a large *overestimate* of the energetic preferences for distorted structures, and of the structural distortions, when using a large core. This is a result of the above mentioned fundamental break down of

core-valence separation in these systems, which makes “large-core” ECP approaches unreliable quantitatively,^[147] and which also does not allow a strict separation of core polarization and covalent bonding (see above). Nevertheless, it may be argued convincingly^[31c] that in such relatively covalent systems the d-orbital participation in σ bonding is generally more important than the influence of core polarization in determining the “non-VSEPR” structures.

3.3. Cases for an “Extended VSEPR Model”?

Recently, Gillespie, Bader, and co-workers have studied the Laplacian of the charge density, $\Delta\rho$,^[152] as a basis to discuss “non-VSEPR” structures of the alkaline earth $[\text{MX}_2]$ compounds,^[153] and of some more covalent d⁰ systems.^[154] The $\Delta\rho$ distribution does clearly show a nonspherical form of, for example, the Ba^{2+} ion in bent $[\text{BaH}_2]$.^[153a] Indeed, similar results had been obtained^[144] with the electron-localization function (ELF^[155]). Such plots show very nicely that, in spite of the formal noble-gas electron configuration, the central atom in such d⁰ systems is significantly nonspherical.

Gillespie et al. argued further^[153, 154] that the observed maxima (attractors) in $-\Delta\rho$ allow the explanation of the distorted structures: the ligands are positioned as far removed as possible from maxima in the vicinity of the central atom, these maxima are termed “core charge concentrations”. More generally, these workers had argued that maxima in $-\Delta\rho$ may be seen as a manifestation of the bonding and nonbonding electron pairs of Lewis theory (more recently termed electron pair “domains”^[1d,e]), and thus also as a fundamental basis of an “extended VSEPR model”.^[152] Based on their calculations, Gillespie et al. then claimed^[153, 154] that the observed Laplacian distributions show core-polarization to be the origin of the distorted structures, thus confirming an argument advanced earlier for the failure of the VSEPR model for transition metal compounds, that is, the nonspherical shape of the metal core.^[1c-e]

Unfortunately, this view is a gross oversimplification. It neglects the more complicated situation delineated in Section 3.2, in which core polarization and d-orbital participation in covalent bonding are two contributing aspects of the problem, which moreover are not completely separable. As we discussed above, the exclusive focus on core polarization becomes increasingly less tenable the more covalent the bonding is. Moreover, very recently Bader et al. had to conclude^[154c] that “core charge concentrations” in $-\Delta\rho$ of $[\text{TiCl}_2(\text{CH}_3)_2]$ are found even when a *frozen* spherical metal atomic core density is added to a “large core” ECP valence density. This obscures effectively any relation of these maxima in $-\Delta\rho$ to the core-polarization model, and it remains to be seen what their true significance is.

A more general weakness of the extended VSEPR model is that it lacks transparency and does not appear to be predictive: to obtain the $\Delta\rho$ distribution, a detailed quantum-chemical calculation has to be carried out, using the correct structure as input! Then the observed attractors in $-\Delta\rho$ may be used for a subsequent justification of the input structure. The usefulness of this approach is clearly quite

limited, and no simple rules have emerged yet from these studies, which would allow structure predictions without the need for explicit calculations. Sometimes, incorrect structures have been employed as an input for analyses, thus invalidating the conclusions. For example, a regular trigonal-prismatic structure has been employed in the analysis of $[\text{Cr}(\text{CH}_3)_6]$,^[153a] whereas accurate calculations clearly support a distorted prism.^[115] Similarly, a distorted octahedron has previously been used in Laplacian analyses of the structure of the $[\text{ClF}_6]^-$ ion,^[156] whereas accurate calculations indicate a regular octahedron.^[157] Generally speaking, it may not be sufficient to know the charge density at a given molecular structure, but we need to know what factors have lead to this structure and charge density.^[158]

We emphasize that analyses of “observable-based” quantities such as $\Delta\rho$ or ELF do provide very valuable insights into the bonding of complex systems. However, an “extended VSEPR model”, even though based on such important quantities, does not presently appear to be suitable to rationalize or predict the structures of transition metal compounds in any detail. The exclusive focus on core polarization and ligand repulsion distracts from other important factors, such as the competition between σ - and π -bonding interactions (see Sections 3.4–3.8, 4.1).

3.4. Molecular Orbital (MO) Descriptions: Second-Order Orbital Mixing and Symmetry Arguments

The covalent bonding aspects favoring the “non-VSEPR” structures may be cast nicely^[62, 63, 74, 107] into the language of perturbation molecular orbital (PMO) theory.^[159] Thus, the bent structure of $[\text{BaH}_2]$ may be considered to arise from a stabilization of the b_2 HOMO upon bending by mixing in metal d_{yz} character in second-order perturbation theory (see Figure 12). This corresponds to Hayes’ modified Walsh diagrams^[138] for the alkaline earth dihalides including d orbitals (reasonable Walsh diagrams for ionic systems may be obtained^[5] from ab initio wavefunctions when using Davidson’s “internally consistent self-consistent-field” orbitals^[160]). Similar PMO arguments may be used for other coordination numbers, for example, for square-pyramidal pentacoordinate,^[62, 63] or for distorted or regular trigonal-prismatic hexacoordinate complexes.^[63, 74] Figure 14 shows a correlation diagram for the $O_h \rightarrow D_{3h} \rightarrow C_{3v}$ distortion of a d⁰ $[\text{MH}_6]$ system, as obtained in ref. [62] from extended-Hückel-type calculations. The HOMO at the octahedral structure is a t_{1u} orbital, with participation of metal p orbitals. The LUMO is the well-known t_{2g} orbital. In this situation the participation of metal d orbitals in metal–ligand σ bonding is very unsatisfactory. Symmetry lowering to D_{3h} allows more interactions of metal d orbitals with appropriate ligand orbitals. Further symmetry reduction to C_{3v} , as computed for $[\text{WH}_6]$, finally allows the metal d_{z^2} orbital to participate in bonding (the qualitative scheme in Figure 14 may overestimate the role of the metal p orbitals). Two preconditions for these distortions are a) a small energy gap between the occupied and virtual orbitals that are to be mixed upon symmetry lowering, and b) not too much energy raising for lower-lying MOs (this

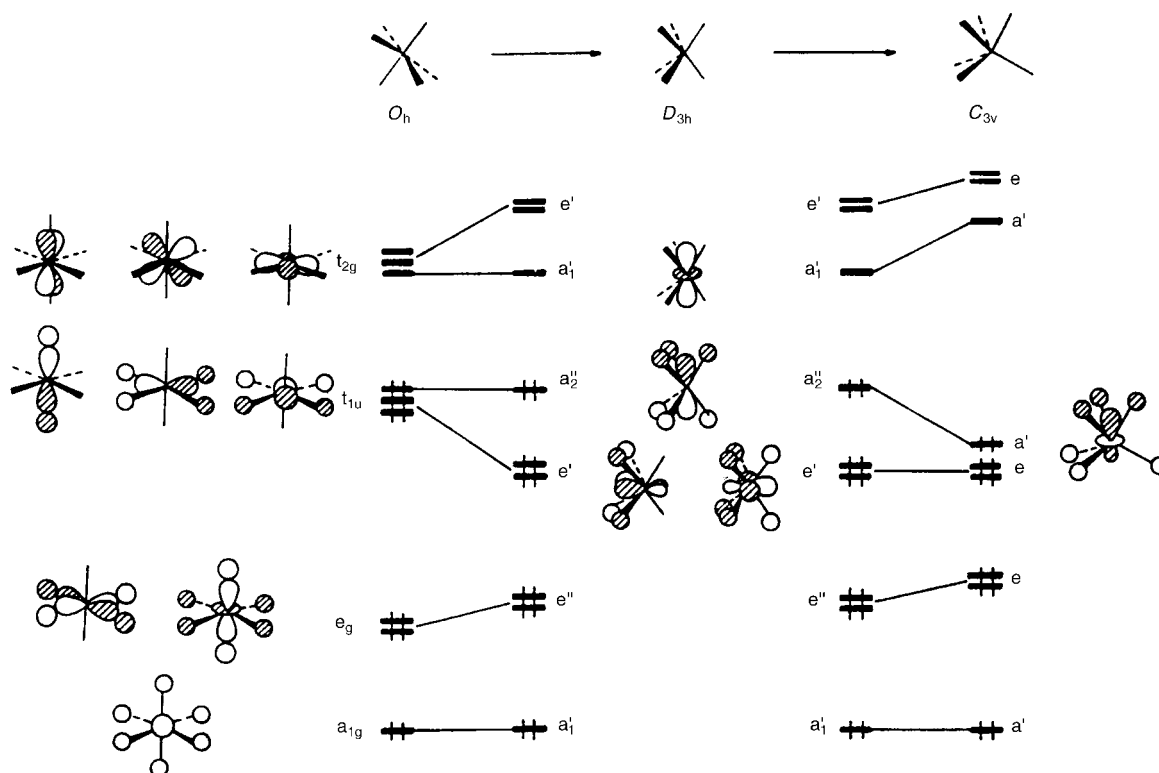


Figure 14. Qualitative MO correlation diagram for a purely σ -bonded d^0 $[\text{MH}_6]$ system (reproduced with permission from ref. [62]).

corresponds to the ligand repulsion aspect discussed in Section 3.7). π Bonding (Section 3.8) enters this picture by a destabilization of the t_{2g} LUMO at O_h symmetry, thus raising the relevant energy difference and opposing the symmetry lowering.

The limitations of the PMO picture are clear: the contribution of core polarization is not incorporated in this scheme, as it is typically restricted only to the valence MOs of the highest energy. Obviously, as discussed above, this restriction becomes less and less important the more covalent the bonding situation, and the more dominant the d-orbital participation aspect is. Indeed, the extended-Hückel model, from which most of the PMO interpretations derive, is applicable only to relatively nonpolar bonds.

Symmetry lowering by orbital mixing in electronically nondegenerate systems is sometimes referred to as a second-order Jahn–Teller (SOJT) effect.^[159] One may argue about the theoretical justification of the SOJT argument^[161, 162] outside the scope of the PMO model (see discussion in ref. [157]). A loose orbital-type definition of the SOJT concept would also qualify the bent (pyramidal) structures of, for example, the H_2O (NH_3) molecules as a consequence of an SOJT effect,^[159] even though the HOMO–LUMO gaps at the linear (planar) structures are appreciable. Thus, while a second-order perturbation theory argument is clearly a very useful way to view the covalent aspects of the “non-VSEPR” structures of d^0 systems, we are reluctant to employ the SOJT label.

A simple generalization of many of the above considerations is to say that lower symmetry of the coordination arrangement allows more metal d- and ligand orbitals to match in symmetry, and thus to provide stronger σ -bonding interactions. This statement may be found, in different disguises,

in many previous works.^[3–5, 7–9, 34, 50, 62, 70, 74, 79, 108a, 109, 138–140] Formalizations, applicable to simple homoleptic transition metal hydride and alkyl complexes, have recently been given by Bayse and Hall,^[57] and by King.^[163] Similar to the valence-bond concept of Landis (Section 3.5), the bonding is assumed to be dominated by the metal $(n-1)d$ and ns orbitals. Metal np -orbitals are only of secondary importance, at least for systems up to a valence-electron count of 12,^[57] as for most of the d^0 systems discussed here. For a given structure, metal s and d orbitals, and ligand σ -bonding orbitals are classified with respect to the irreducible representations of the appropriate point group. This provides symmetry allowed or forbidden structures, depending on how many metal and ligand orbitals match. Further criteria, such as ligand repulsion, have to be employed to discriminate between different “allowed” coordination arrangements. Table 3 provides “allowed” symmetries for d^0 $[\text{MH}_k]$ ($k=3-6$).^[57] Note, for example, that the regular octahedron for $[\text{MH}_6]$, the trigonal bipyramid for $[\text{MH}_5]$, the trigonal planar structures for

Table 3. “Symmetry-allowed” structures for d^0 MH_n complexes.^[a]

	Structures
$[\text{MH}_3]$	$D_{3h}, C_{3v}, C_{2v}, C'_{2v}$
$[\text{MH}_4]$	$T_d, D_{2d}, C_{4v}, C_{3v}, C_{2v}, C'_{2v}, C''_{2v}$
$[\text{MH}_5]$	$C_{5v}, C_{4v}, C_{2v}, C'_{2v}$
$[\text{MH}_6]$	C_{5v}, C_{3v}, C'_{3v}
$[\text{MH}_7]$	$C_{5v}, C_{3v}, C'_{3v}, C_{2v}, C''_{2v}$
$[\text{MH}_8]$	$D'_{2d}, C_{4v}, C'_{2v}, C''_{2v}, C'''_{2v}$
$[\text{MH}_9]$	$D_{3h}, D'_{3h}, C_{4v}, C_{3v}, C'_{3v}, C'_{2v}$

[a] See ref. [57]. Further structures with lower symmetry are possible. Primed entries indicate more than one structure of a given point group, as described by Bayse and Hall.^[57]

[MH₃], or the linear structures for [MH₂], are not allowed. At these more symmetric structures, metal d orbitals and ligand orbitals have insufficient match in σ -bonding interactions. In contrast, T_d symmetry is “allowed” for d⁰ [MH₄] complexes.^[57]

π Bonding may be included without problem in the MO framework (see Section 3.8), an advantage over the simple valence-bond model described in Section 3.5. On the other hand, many canonical (delocalized) molecular orbitals may have to be considered for larger systems. This limits the application of the MO description as a basis for “back-of-the-envelope” arguments, and explicit computations may be required.

3.5. A Simple Valence-Bond Model

Landis and co-workers^[31] have explained the “non-VSEPR” structures of a considerable variety of simple homoleptic hydride and alkyl complexes using straightforward valence-bond arguments. Considering d⁰ [MR_k] systems (R = H, alkyl) to be well-represented by k two-center two-electron bonds, and assuming that the bonding contribution by the metal valence p orbitals is negligible, the metal–ligand bonds may be regarded as originating from the interaction of k metal sd^{k-1} hybrids with the corresponding ligand AOs. The bonding with the ligands is optimized for minimal overlap between the different sd^{k-1} hybrids at the metal (Figure 15). This overlap leads to certain optimum bond angles. For example, the bonds in [BaH₂] would be qualified as being made up from metal sd -hybrid orbitals and hydrogen 1s orbitals, and thus an optimum angle of 90° would be predicted (this relatively ionic system may already be outside the scope of the model, see below). Similarly, the bonds in [WH₆] may be thought to be formed by metal sd^5 hybrids.^[31] Figure 15

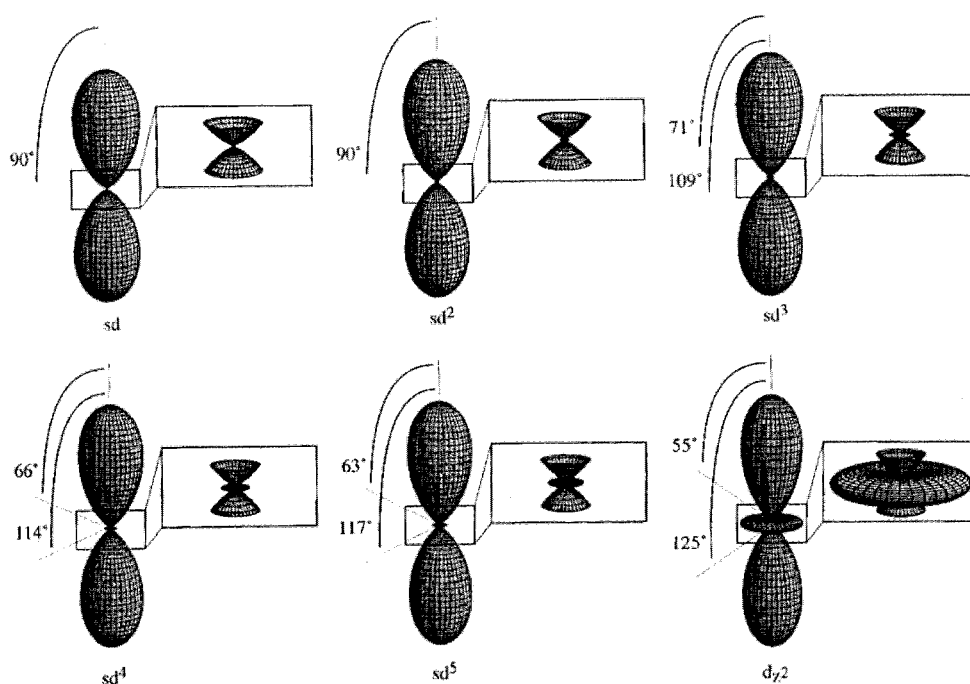


Figure 15. Optimum “inter hybrid angles” for sd^n hybrids (reproduced with permission from ref. [31c]).

shows clearly that in this case the preferred interhybrid angles are 63° and 117°, far from the 90° and 180° required for an octahedron. This approach leads to a number of preferred coordination arrangements (cf. “symmetry-allowed structures” in the MO models given in Section 3.4). Among these one may then again discriminate further by other criteria, such as ligand repulsion. In this respect, the above MO models and the Landis’ VB ansatz are rather similar. Differences arise in the treatment of metal p orbitals once the valence electron count of 12 at the metal is exceeded. While Bayse and Hall^[57] prefer to include metal p orbitals in these cases, Landis et al. treat these “hypervalent” cases using three-center bonding.^[31c] A general discussion has thus started on the importance of the outer metal p orbitals in transition metal chemistry (see also ref. [17]), in analogy to the much older discussion on the participation of outer d orbitals in main group chemistry.^[143, 164] However, for the present d⁰ systems it is usually sufficient to restrict the description to the d and s orbitals (exceptions have to be considered for coordination numbers seven and higher, or for extensive π bonding).

The preferred bond angles in simple alkyl and hydride transition metal complexes have been reproduced remarkably well by the simple VB model. Landis et al. have incorporated this “VALBOND” ansatz into a molecular-mechanics framework to model the angular-energy dependence around the central metal.^[31] Indeed, VALBOND calculations had correctly predicted^[31a,b] the distorted trigonal-prismatic structure of [W(CH₃)₆] prior to independent experimental^[112, 113] and ab initio^[114, 115] confirmation. Moreover, the inexpensive VALBOND method may be used conveniently in molecular-dynamics calculations and thereby has provided radial distribution curves for [W(CH₃)₆] and for [Ta(CH₃)₅]^[31a] in good agreement with GED experiments.^[64, 111]

Obviously, the simple valence-bond model must have severe limitations, most of which have already been discussed by Landis and co-workers.^[31] Core polarization is clearly not incorporated. As for the above mentioned PMO model, this becomes a less problematic approximation the more covalent the bonding. The model appears to work well for simple homoleptic hydride and alkyl complexes, that is, systems which are well described by localized σ bonding only. It may be extended to “hypervalent” complexes by including covalent–ionic resonance,^[31c] but it will become less useful for more strongly delocalized systems. As yet there have been no systematic applications of the model to transition metal systems including π bonding. Undoubtedly, valence-bond descriptions will be less straightforward in such cases,

just as they tend to become clumsy for main group compounds when the bonding becomes more complex. The appreciable importance of π bonding for the structural preferences of d^0 complexes will be discussed in Sections 3.8 and 4.1.

Another implicit assumption of the simple valence-bond ansatz is the orthogonality of the metal hybrid orbitals employed. In other words, a comparable radial extent of the metal $(n-1)d$ and ns orbitals is assumed such that only angular overlap needs to be considered.^[31] Only in the case of orthogonal hybrids does a clear-cut relationship hold between the hybrid-orbital composition and the bond angles. Kutzelnigg^[164, 165] has discussed in detail that hybrid orthogonality holds only when the AOs involved have the same overlap with the ligand orbitals, that is, they must have a comparable radial extent. For example, the condition of orthogonal hybrids does not hold for compounds of the heavier p-block elements, where the valence s orbitals are considerably more contracted than the valence p orbitals. In this case, the popular relations between hybrid composition and bond angles (e.g. $sp^3 \rightarrow 109.5^\circ$, $sp^2 \rightarrow 120^\circ$, $sp \rightarrow 180^\circ$) cease to apply.^[164] As a typical example, the assumption of sp hybrids for linear $[HgX_2]$ complexes is far from reality, as the bonding is almost exclusively derived from the metal s orbitals, with very little p-orbital participation.^[150, 166]

As yet, there have been no systematic studies of hybrid orthogonality for transition metal compounds. Natural population analyses (NPA^[167]) suggest that the hybrid compositions for simple, relatively covalent hydride complexes often conform quite well to the expectations of the simple valence-bond model.^[31c] Our own experience indicates that already for the somewhat more polar bonds in alkyl complexes,^[69, 114, 115] the s-orbital participation in bonding is frequently *less* than that implied by the simplest valence-bond descriptions (however, the population analyses confirm the underlying assumption of the model^[31] that the valence p-orbital participation in bonding is usually small in these systems). The more ionic the bonding, the less we may expect hybrid orthogonality to hold. Thus, for example, the basic valence-bond description will be less accurate for classical Werner-type coordination complexes.^[31c] Landis et al. also point out that the size of $(n-1)d$ and ns orbitals will be less compatible for 3d than for 4d or 5d complexes.^[31c]

The simple valence-bond model will thus certainly be less widely applicable than, for example, the PMO approach. The great appeal of the model, however, lies in its simplicity. Moreover, the valence-bond approach appears to be particularly well suited as a basis for the parametrization of angular terms in molecular-mechanics force fields throughout the periodic table.^[31, 168]

3.6. On the Isolobal Analogy Between Main Group and Early Transition Metal Compounds: A Little Caveat

A very useful way to break down conceptually complex transition metal systems into smaller fragments is the isolobal principle.^[169] Two molecular fragments are termed isolobal, if their most important frontier MOs have similar shapes, orientations, and energies. This approach has been partic-

ularly efficient in relating the typically more complex transition metal systems to somewhat better understood main group compounds.^[159, 169] The considerations of the previous two sections allow us to discuss a little caveat (restriction) that needs to be kept in mind when applying the isolobal analogy to compare main group and early transition metal complexes.

Consider the two radical species $[SiH_3]$ and $[ZrH_3]$ (Figure 16), which contain the central atoms from Groups 14 and 4 of the periodic table, respectively. Both molecules are

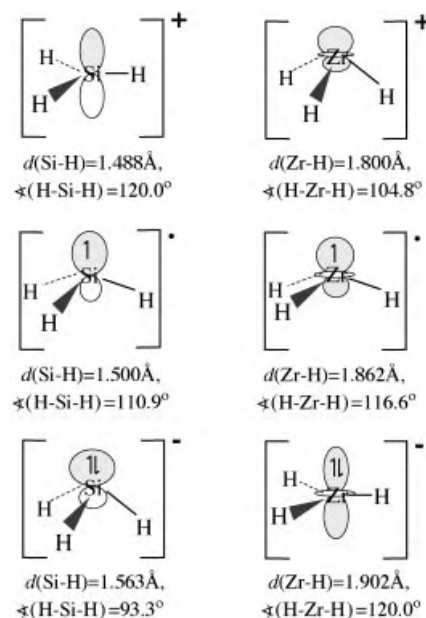


Figure 16. Opposite structural and electronic behavior of the SiH_3 and ZrH_3 fragments upon addition or removal of one electron. Structure parameters pertain to DFT optimizations (see appendix).

computed to be pyramidal, and they both have one singly occupied nonbonding orbital of comparable energy pointing away from the three hydrogen substituents. As a good approximation we may consider these two fragments as being isolobal. However, let us examine the structural changes occurring upon removal or addition of one electron from or to these systems. The p-block main group cation $[SiH_3]^+$ is planar, as the s-orbital participation in bonding is maximized by leaving a p_z orbital perpendicular to the molecular plane empty (in valence-bond language, neglecting hybrid non-orthogonality,^[164, 165] one would usually speak of sp^2 hybridization). Addition of one or two electrons to the system leads to increasing pyramidalization, as it is favorable for the now occupied nonbonding orbital to acquire more s character. In contrast, the $[ZrH_3]^+$ ion prefers a pyramidal structure, to maximize d-orbital participation (in valence-bond language, the metal may be considered to use sd^2 hybrids for bonding^[31]). Adding electrons to the system reduces the pyramidalization, as the nonbonding electrons attempt to acquire maximum d character. As a result, the hypothetical $[ZrH_3]^-$ ion is planar, with the nonbonding electron pair in a d_{z^2} orbital perpendicular to the molecular plane. Thus, while one would at first sight undoubtedly qualify the neutral $[EH_3]$ fragments as being isolobal, the structural behavior of the two systems

upon addition or removal of one electron is just the opposite, because of the different composition of the dominant valence orbitals.

3.7. The Role of Ligand Repulsion

The repulsion of bonding and nonbonding electron pairs is at the heart of the VSEPR model. Ligand repulsion is thus the most obvious factor that favors the conventional VSEPR structures and opposes the distortions. The nature of the repulsion may be both electrostatic (in particular for significantly polar bonds) and steric (mainly Pauli exchange repulsion). It is usually not straightforward to extract the magnitude of such repulsions directly from quantum-chemical calculations in a quantitative manner, although various schemes have been proposed to estimate, for example, Pauli exchange repulsion.^[170] The systematic comparison of compounds with different metals, ligands, coordination numbers, and net charges provides some insight into the importance of ligand repulsion for the structural preferences. Ligand repulsion is probably also the chemically most intuitive of the factors involved. For example, it is clear that, all other things being equal, ligand repulsion increases rapidly for larger coordination numbers.

Our prototype dicoordinate systems, the alkaline earth dihalides, are more on the electrostatic side. The analysis of their bending force constants in terms of a polarized-ion model has provided an estimate of the Coulomb-repulsion and anion-polarization contributions that favor the linear arrangements.^[5] Thus, for example, the anion–anion repulsion in the calcium dihalides is considerably more pronounced than for the corresponding Sr and Ba species, because of the shorter anion–anion distances involved. Therefore, the calcium dihalides are at best quasilinear, in spite of a large driving force towards a bent structure (a result of d-orbital participation and metal core polarization).^[5]

The leading anion–anion repulsion terms may be removed when replacing the anionic halide ligands by neutral ligands such as HF, H₂O, or NH₃. Indeed, complexes like [Ba(H₂O)₂]²⁺ have been computed to exhibit even lower bending angles than [BaF₂] or [BaH₂], in spite of their much smaller covalent bonding contributions and very shallow bending potential curves.^[40] As a result, tricoordinate cations such as [Ba(H₂O)₃]²⁺ are still slightly pyramidal,^[40] while anionic species such as [BaX₃][−] (X = H, F) are expected to be genuinely planar.

Within the range of the more covalent d⁰ systems, it has also been shown that an increasing negative charge on the ligands disfavors the “non-VSEPR” arrangements. Thus, the preference for nonoctahedral structures of 3d⁰ hexahydride systems increases along the series [ScH₆]^{3−} < [TiH₆]^{2−} < [VH₆][−] < [CrH₆] < [MnH₆]⁺.^[71, 108c] Similar results were obtained in DFT calculations for Group 4–7 hexamethyl complexes, [M(CH₃)₆]ⁿ (*n* = −2, −1, 0, +1).^[115] Only the cationic and neutral complexes prefer distorted trigonal prisms, whereas the mono- and dianionic systems have regular trigonal-prismatic structures (of the three Group 5 monoanions, only the 4d species [Nb(CH₃)₆][−] shows some tendency to distort).

While the octahedron is far from competitive for any of these hexamethyl complexes, its energy relative to the minimum structure is lowest for the dianions.^[115] Experimentally, the [Zr(CH₃)₆]^{2−} and [Ta(CH₃)₆][−] ions prefer a regular trigonal prism,^[110, 113, 119] whereas [W(CH₃)₆]^[112] and [Mo(CH₃)₆]^[118] are distorted (see Section 2.5). As the anionic systems have the most ionic bonding and bear significant negative charge on the methyl ligands, it appears reasonable to assume that increased electrostatic repulsion between the ligands prevents a distortion of the prism. However, at the same time the more ionically bonded anionic systems show the largest HOMO–LUMO gap at the regular prismatic structure^[114, 115] (as discussed in Section 3.4, a small gap is important for the second-order orbital mixing upon distortion).^[159]

Similar arguments have been invoked for the structural preferences of tris(dithiolene) complexes: a better match of the energy of ligand and metal valence orbitals for the more covalent complexes was made responsible for their larger deviations from an octahedron, for example, along the series [Zr(S₂C₆H₄)₃]^{2−}, [Nb(S₂C₆H₄)₃][−], [Mo(S₂C₆H₄)₃]^[171] (see also ref. [172]). This result shows that it is difficult to completely separate these influences. Another comparison may be made between the neutral [Ta(CH₃)₅] and monoanionic [Ti(CH₃)₅][−]. The computed preference for the square-pyramidal over the trigonal-bipyramidal structure is considerably reduced for the Ti^[58] than for the Ta^[62, 63] complex. The hybridization of the ligand donor atom affects its electronegativity. For example, the structures of hexaacetylide d⁰ complexes tend to be in between octahedral and prismatic,^[120] whereas hexaalkyl complexes are more clearly prismatic. This difference may again be attributed to both a) larger ligand repulsion, because of the more polar M–C bonding in acetylides, and b) a larger gap between occupied and unoccupied MOs.

Interestingly, the bond polarity (and also the HOMO–LUMO gap) is larger for 5d than for 4d complexes, a result of the relativistic expansion^[173] of the 5d orbitals. Relativity reduces metal–ligand covalency and thereby increases ligand repulsion.^[115] As a consequence, [Mo(CH₃)₆] for example, exhibits a more strongly distorted trigonal-prismatic structure than the heavier congener [W(CH₃)₆]^[115, 118] (the trigonal distortion of octahedral [MoX₆] complexes is also easier than that of their homologous [WX₆] species, see Table 2). In contrast, the distortion has been predicted to be less pronounced for [Cr(CH₃)₆], partly because of the smaller ligand–ligand distances and thus the larger ligand repulsion.^[115] Similarly, the 4d complex [Nb(CH₃)₆][−] is on the borderline to a distorted prism, whereas the 5d analogue [Ta(CH₃)₆][−] clearly exhibits a regular prism structure.^[113, 115] As another experimental example, we note that for the two tris(dithiolene) systems [M(S₂C₆H₄)₃][−] (M = Nb, Ta), the 4d niobium system exhibits a structure that is considerably closer to the trigonal-prismatic extreme than that of its 5d tantalum homologue.^[95, 174] Computational studies on the [MH₄]⁺ ion (M = Nb, Ta) give preference to an unusual square-pyramidal structure for the 4d system but to the tetrahedron for the 5d complex.^[31c, 57] Further examples of such 4d/5d comparisons in the regime of extended solid-state structures will be discussed in Section 5.

d⁰-Metallocenes provide further examples, in which reduced negative charge on the ligands corresponds nicely with more distorted structures. While the neutral Ca, Sr, Ba, Eu, Sm, and Yb metallocenes [MCp₂] are shown by calculations to have at most quasilinear structures,^[27] the hypothetical isoelectronic cations [LaCp₂]⁺ and [ScCp₂]⁺ have been computed to be significantly bent.^[29] Similar comparisons can be made essentially for all examples discussed in Section 2: the more covalent the bonding, the larger the deviations from the conventional “VSEPR structures”. In all cases it is difficult to separate the covalent and the ligand-repulsion contribution to the structural preferences (note the exceptional behavior of systems with neutral ligands^[40]). Moreover it is also frequently difficult to separate the influences of ligand repulsion from those of π bonding (see Section 3.8).

Actual steric interactions in the sense of Pauli exchange repulsion become more important the more covalent the system gets. Obviously the size of the ligands may then be particularly important. A striking example is provided by substituted alkaline earth and lanthanide(II) metallocenes. While several permethylated complexes [MCp₂^{*}] (M = Sm, Eu, Yb, Ba; Cp^{*} = η^5 -C₅(CH₃)₅) have been found to exhibit bent structures in the solid state (keeping in mind possible influences by intermolecular interactions, see Section 2.1), larger alkyl substituents on the cyclopentadienyl rings eventually force linear metallocene structures as a consequence of the steric bulk of the ligands.^[25]

It has been suggested^[26b] that the ring–ring distances in [MCp₂^{*}] (Cp^{*} = C₅Me₅) complexes are such that there may also be attractive van der Waals (vdW) interactions between the methyl groups on different rings. Indeed, it has been claimed, based on molecular-mechanics calculations,^[175] that such vdW forces may be responsible for the bent [MCp₂^{*}] structures. It is unclear how reliable such estimates are. For example, a recently reported bent structure for a triple-decker sandwich without alkyl substituents at the central C₈H₈ ring has been taken as evidence *against* the importance of vdW attractions.^[176] Even if weak attractive interactions are important, this implies that the other factors involved (covalent bonding, core polarization, ligand repulsion) act together to provide a very shallow bending potential curve,^[27] such that the weak dispersive forces may become decisive. These arguments are certainly not applicable to the hypothetical cationic systems [MCp₂]⁺ (M = Sc, La), which have been predicted to be strongly bent.^[29] Here the covalent-bonding contributions undoubtedly dominate the bending process.

We note in passing, that the accurate ab initio treatment of systems with bulky ligands becomes increasingly cumbersome for larger systems. Recent methodological developments suggest, however, that such steric contributions to the structural preferences for large systems may be modeled reasonably well by integrated quantum-mechanics/molecular-mechanics (QM/MM) approaches.^[177] Thus, while the electronically demanding part of the system (e.g. the immediate coordination sphere of the metal) is described at a sufficiently high ab initio level, more remote parts of the molecule (e.g. parts of bulky ligands) may be treated at a molecular-

mechanics or lower quantum-chemical level of theory. A notable example of a QM/MM treatment for some heteroleptic d⁰ systems has been given by Barea et al.^[178] (see also Section 4.2). As another example of the influence of steric repulsion, recent DFT calculations also indicated a significant effect on the preferred coordination arrangement of a d⁰ *cis*-diimido complex, when PH₃ was substituted for P(CH₃)₃.^[179]

3.8. The Influence of π Bonding

π Bonding is considerably more important in early, high-valent transition metal complexes than for analogous (formally single-bonded) main group compounds.^[180–182] This is easily understandable when we consider the orbitals available at the central atom. In p-block main group compounds, the *outer* d orbitals are too large and too high in energy to be available as efficient acceptors for π bonding. Thus, in the absence of regular p _{π} –p _{π} bonding, it is mainly negative hyperconjugation that allows some π character to mixed into the bonds, at the expense of some σ bonding to the neighboring substituents.^[183] In contrast, the coordinative unsaturation of early, high-valent transition metal complexes arises from the availability of low-lying *inner* d orbitals. This point has to be kept in mind to appreciate the potential influence of π bonding on structure (see also Section 4).

Besides ligand repulsion, π bonding is usually considered to be the second important factor that opposes a deviation from the VSEPR-conforming structures. This had already been noted by Jolly and Marynick^[32] for di- and tricoordinate systems (e.g. for [ScX₂]⁺ or [ScX₃]), and by Kang et al.^[62, 74] for [MX₅] and [MX₆] systems with X = H, F (ref. [107] gives an even earlier, related discussion). In both cases, the hydride species adopt “non-VSEPR” structures (bent dicoordinate, pyramidal tricoordinate, square pyramidal pentacoordinate, distorted trigonal prismatic hexacoordinate), whereas the fluorides favor the regular VSEPR arrangements.^[32, 62, 74] While one might attribute this to the larger ionicity of the fluorides, which leads to increased anion–anion repulsion (see Section 3.7), there is further evidence which points to the importance of π bonding (see below).

It appears that π bonding favors structures closer to the VSEPR requirements in most homoleptic systems. However, there are also a number of cases, with strong π -donor ligands, for which π bonding has been considered to *increase* the deviations from the VSEPR-type arrangements. The most well-known case is the strongly bent [MoO₂]²⁺ unit found in many heteroleptic “molybdenyl” complexes. Calculations at various degrees of sophistication^[38, 184] have suggested that the *cis* configuration with relatively small O–Mo–O angles (typically around 103°), also found in the isolated [MoO₂]²⁺ fragment,^[38] is partly caused by more efficient π bonding in the *cisoid* structure. Similar arguments may be applied to other dioxo, trioxo, or disulfido systems, for example, to chromyl complexes, [CrO₂X₂]. This tendency is also frequently discussed in the context of a large *trans* effect for strong π -donor ligands.^[15]

We are thus facing the seemingly paradoxical situation that π bonding is considered to increase the bond angle in systems

such as [ScF₂]⁺ (compared to [ScH₂]^{+[32]}) but to decrease the angle in [MoO₂]²⁺ and related species.^[38, 184] To rationalize these findings, we have recently studied the interdependence of π bonding and bond angles in some detail by analyses of natural localized molecular orbitals (NLMOs^[167]) as functions of bond angle for some simple model complexes.^[180] Figure 17 shows those (canonical, delocalized) metal d orbitals which

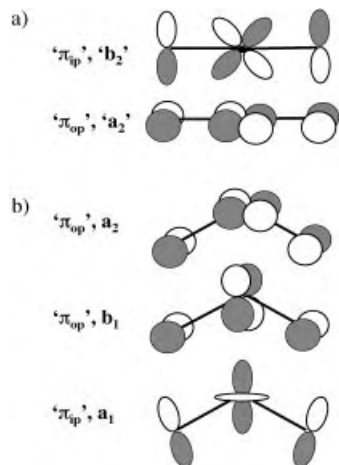


Figure 17. Metal d orbitals available for π bonding in d⁰ MX₂ complexes. a) At an X-M-X angle of 180°. b) At X-M-X angles < 180° (cf. refs. [38, 180, 184]). Symmetry labeling as appropriate for C_{2v} point group; ip = in plane, op = out-of-plane.

may potentially act as π acceptors in linear and bent d⁰ [MX₂] systems, respectively (cf. also refs. [38, 184]). In the case of cylindrical π donors such as oxo or halide ligands, four π -type lone pairs have to share two metal d orbitals in a linear arrangement (Figure 17a). Upon bending, the in-plane component of the former d $_{\pi}$ set (d_{yz}, b₂ in C_{2v} symmetry) has essentially no overlap with the ligand π orbitals, and we will disregard it in the following. In contrast, the overlap of the out-of-plane component (d_{xy}, a₂ in C_{2v} symmetry, see Figure 17b) decreases only very slowly when reducing the angle. Thus, initially we expect a significant loss of in-plane π bonding and a very slight loss of out-of-plane π bonding. However, at smaller angles two more metal orbitals become accessible for π bonding: the d_{xz} orbital (of b₁ symmetry) becomes out-of-plane π bonding, whereas at even smaller angles a hybrid dominated by the d_{z²}-orbital (a₁ symmetry) becomes in-plane π bonding (Figure 17b; note that π_{ip} and σ bonding contributions are not easily separable in such systems, as they involve MOs of the same symmetry). These two orbitals are the ones that have been invoked as reasons for the small angles of the [MoO₂]²⁺ fragment.^[38, 184]

Thus, π bonding is expected to depend in a nontrivial way on the bond angle, and of course also on the σ - and π -bonding ability of the ligands (and of the metal). Analyses of the “weak π -donor” prototype system [ScF₂]⁺ indicated that the overall π -bonding covalency at the bent equilibrium structure is lower than at the linear structure, and therefore π bonding might be considered to favor the linear structure. In contrast, in the “strong π -donor” model [ZrO₂] the sum of in-plane and out-of-plane π bonding apparently favors the bent arrange-

ment, in agreement with the above mentioned notions for molybdenyl systems. But in both cases, [ScF₂]⁺ and [ZrO₂], the slopes of the NLMO “covalency” curves around the equilibrium structures indicated that π bonding tends to favor smaller angles.^[180] Thus, even in such apparently simple systems, the interrelations between π bonding and bond angles are far from trivial, because of the variety of metal d orbitals and ligand orbitals involved. In more complicated systems, the bonding to additional ligands may further alter the situation significantly (cf. Section 4.1).^[180]

In a recent DFT study, in-plane π bonding (π_{ip} bonding) was held responsible for the bent structures of alkaline earth metallocenes.^[185] While the significantly bent structures found in that study appear to be an artifact^[180] of the unbalanced basis sets employed in the calculations, one may indeed consider such interactions in the case of genuinely bent metallocene structures. Of course the discrimination between π_{ip} and σ bonding will be even more difficult in these cases than in the models discussed above. A similar type of π interaction at strongly pyramidalized structures of rare earth trihalides has been considered in Extended-Hückel calculations.^[186] Unfortunately, the computed pyramidal structures again appear to have been artifacts of the theoretical approach employed. Similar arguments have been put forward to explain the pyramidal structure of the MoO₃ molecule.^[55]

The clearest indication for π bonding may be obtained when different conformations are possible. HF calculations on the series of simple alkaline earth [MX₂] molecules (M = Ca, Sr, Ba; X = Li, BeH, BH₂, CH₃, NH₂, OH, F) have indicated^[6] the largest degree of bending in the absence of π bonding, for example, for the dimethyl complexes [M(CH₃)₂] (for a given metal), whereas the linearization energies decrease from X = CH₃ to X = F (see Figure 18a). Moreover, the diamide species [M(NH₂)₂] (M = Sr, Ba) show a strong dependence of the linearization energy and bending angle on the orientation of the NH₂ ligands. As shown in Figure 18b, a C_{2v} arrangement with the amide hydrogen atoms in the N-Ba-N molecular plane is the most stable structure and has the smallest N-Ba-N

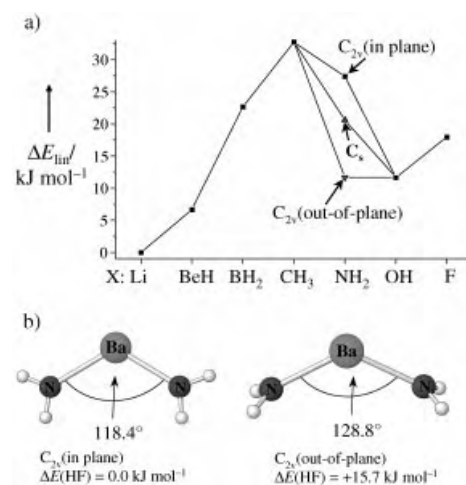


Figure 18. a) Linearization energies of [BaX₂] molecules (HF results from ref. [6]). Different entries for [Ba(NH₂)₂] pertain to different conformations (see (b)). b) Computed structure parameters for two rotamers of [Ba(NH₂)₂].

angle, around 118° (and the largest linearization energy, ca. 27 kJ mol^{-1}). Rotation of the two amide groups out of the plane costs approximately 16 kJ mol^{-1} and increases the angle by about 7° .^[6] This amounts to a surprisingly large rotational barrier for such an ionic system and indicates clearly the presence of π bonding. In the in-plane configuration, loss of π_{ip} bonding upon bending is avoided, and out-of-plane π bonding is retained (see above). Therefore, this arrangement is the most stable one, and the bending angle is coupled significantly to the amide group conformation. Somewhat stronger, cylindrical π donors such as cyclopentadienyl ligands appear to disfavor bending even more, with the result that, for example, the alkaline earth and lanthanide(II) metallocenes $[\text{MCp}_2]$ are quasilinear.^[27]

Within the PMO model of Section 3.4, the effect of π donation enters by a destabilization of some of the unoccupied orbitals of the more highly symmetrical structure.^[62, 74, 107, 159] Thus, in the MO Scheme of an O_h symmetrical d^0 $[\text{MX}_6]$ complex, the replacement of purely σ -donating hydride or alkyl ligands by σ/π -donating halide ligands results in a significant destabilization of the π -antibonding t_{2g} LUMO (see Figure 14). As a consequence, the gap between the t_{1u} HOMO and t_{2g} LUMO increases, and the second-order mixing of these two MOs upon distortion to a trigonal prism becomes less favorable.^[62, 74, 107] Therefore, simple d^0 hexahalides such as $[\text{WF}_6]$ or $[\text{WCl}_6]$ are octahedral, whereas the corresponding hexahydride and hexamethyl complexes prefer structures derived from a trigonal prism (Section 2.5). Again, one might attribute these differences simply to the larger ionicity and thus to larger electrostatic anion–anion repulsions in the halides. In this case, however, the distortion from an octahedron to a trigonal prism would be expected to require the largest energy for the most ionic systems, that is, with fluoride ligands. In disagreement with this expectation, our DFT calculations^[78] (see Table 2) indicate almost twice the barrier for the trigonal twist of the tungsten or molybdenum chlorides or bromides than for the respective fluorides (our results for $[\text{WF}_6]$ agree well with those of previous ab initio or DFT calculations^[62, 187]). Thus, the prismatic structure is almost twice as favorable energetically for the fluoride as for the chloride, in spite of the much larger ionicity of the former (e.g., computed NPA metal charges at the O_h minima are $+0.05$, $+0.25$, $+1.91$, and $+2.23$ for $[\text{MoCl}_6]$, $[\text{WCl}_6]$, $[\text{MoF}_6]$, and $[\text{WF}_6]$, respectively). Moreover, an NPA/NLMO analysis^[188] shows clearly that both a) π bonding at the octahedral structure, and b) the loss of π bonding upon distortion to a prism are much more pronounced for the chloride than for the fluoride. Thus, the π -donor abilities of the ligands appear to be more important here than the bond ionicities. This has the interesting consequence that successive alkyl substitution in mixed compounds $[\text{W}(\text{CH}_3)_m\text{X}_{6-m}]$ leads to a transition from octahedral to prismatic structure at lower m value for $\text{X}=\text{F}$ than for $\text{X}=\text{Cl}$ (see Section 4.2).^[78] These results are consistent with a recent study on metal–chalcogen bonding in related d^0 complexes.^[181] DFT calculations for a series of homologous complexes $[\text{OsO}_3\text{E}]$, $[\text{MCl}_3\text{E}]$ ($\text{M}=\text{V}$, Ta), and $[\text{MCl}_4\text{E}]$ ($\text{M}=\text{Cr}$, Mo , W , Re) with $\text{E}=\text{O}$, S , Se , Te , indicated that the strength of the $\text{M}-\text{E}$ σ bonds decreased from $\text{E}=\text{O}$ to $\text{E}=\text{Te}$. However, the $\text{M}-\text{E}$ π bonding ex-

hibited the maximum strength for $\text{E}=\text{S}$, Se . Relative to the σ -bond strength, the importance of π bonding increased even to $\text{E}=\text{Te}$.^[181]

Halide ligands are moderate cylindrical π donors, whereas hydride and alkyl ligands are σ donors (slightly modified^[189] by agostic interactions for alkyl ligands^[63, 107, 114, 115, 189]). One may thus ask what structural preferences may be induced by single-sided π -donor ligands. One example has already been given above when discussing the alkaline earth $[\text{M}(\text{NH}_2)_2]$ complexes.^[6] Somewhat less clear-cut examples, which are particularly important in the regime of six-coordinate d^0 complexes, are thiolate ligands (see also Section 2.5). While an SR ligand has in principle two lone pairs available for bonding to the metal, the bending of the $\text{M}-\text{S}-\text{R}$ moiety leads to considerable sulfur s character for the in-plane lone pair (Figure 19). Thus, only the lone pair perpendicular to the $\text{M}-\text{S}-\text{R}$ plane remains truly effective as a π donor. Figure 20 shows the DFT-optimized structure of the model complex $[\text{Mo}(\text{SH})_6]$ (see

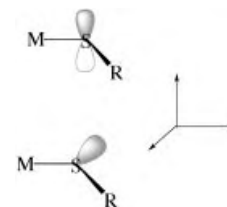


Figure 19. Formally non-bonded sulfur orbitals in a bent metal–thiolate fragment. Only the out-of-plane lone pair (top) is a suitable π donor, whereas the in-plane lone pair (bottom) obtains significant s character.

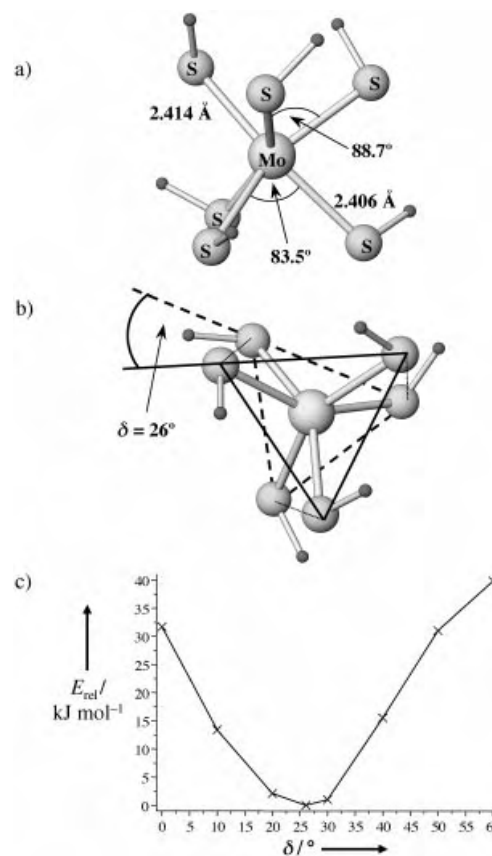


Figure 20. DFT optimized structure of the $[\text{Mo}(\text{SH})_6]$ model complex. a) Side view with key structural parameters. b) Top view showing the twist angle δ between the two triangular faces. c) Computed energy profile along the twist angle coordinate. The curve is the result of a “relaxed scan”, in which the twist angle has been changed step-wise and, for a given twist angle, all other structural parameters have been fully optimized. See appendix for computational methods.

ref. [92] for experimentally observed homoleptic d⁰ complexes of monodentate thiolates). The structure has C₃ symmetry, and its trigonal twist angle $\delta = 26^\circ$ (Section 2.5) indicates that it lies between the octahedral ($\delta = 60^\circ$) hexahalides and the trigonal prismatic ($\delta \approx 0^\circ$) hexaalkyl structures. The energy profile in Figure 20c shows that the system is intermediate between octahedron and prism also from an energy point of view. Obviously, replacement of halide by thiolate is one way of partially switching off π -bonding contributions in such [MX₆] d⁰ complexes.

Similar considerations hold for the experimentally relevant chelating dithiolate ligands. As discussed in Section 2.5, for a given metal the complexes of the unsaturated dithiolene ligands appear to be closer to the trigonal prismatic extreme than their saturated dithiolate analogues^[82, 83] (or of monothiolates^[92]). Recent model calculations on the dithiolene complexes [M(S₂C₂H₂)₃] (M = Mo, W) give twist angles $\delta \approx 0^\circ$.^[104] It appears reasonable to attribute this difference to the partial involvement of the sulfur lone-pair orbitals in intra-ligand π bonding and thus to reduced metal–ligand π -bonding contributions for the unsaturated dithiolene systems^[104] compared to saturated dithiolates (keeping in mind the boundary conditions set to the twist angles by the bite angles of the bidentate ligands; Section 2.5). A further frequent distortion in dithiolene complexes is the nonplanarity of the ligands. Among other things, this has been attributed to improved overlap, in the nonplanar arrangement, of the sulfur π -type lone pairs with the metal d_{z²} orbital in the trigonal prismatic arrangement.^[190]

A structure close to trigonal prismatic has recently also been found for the complex [W(4,4',5,5'-tetramethyl-2,2'-bisphosphinine)₃]^[104] (see Figure 6). For this system, the approximate ligand symmetry does indeed provide single-sided phosphorus π donors (we assume a dianionic formulation of the chelate ligand). The donor ability of the π -type lone pair should, however, be reduced because of delocalization within the ligand. For saturated phosphanide ligands, the interesting question arises, whether a pyramidal or a planar geometry around phosphorus will be found. While the former case would correspond essentially to a σ -only donor, significant π bonding would be expected for the latter case. Such systems thus appear to be attractive targets for computational and experimental studies (see also Section 5).

As mentioned in Section 2.5, the view of a d⁰ complex with dianionic ligands is one extreme of a continuous description of the electronic structure of dithiolene complexes or related systems such as the above mentioned tris(bisphosphinine) complex, tris(buta-1,3-diene)molybdenum,^[100, 101] tris(*ortho*-xylyl)tungsten,^[102] or tris(methylvinylketone)tungsten.^[103] At the d⁰ extreme, a minimization of ligand-to-metal π bonding by delocalization of the relevant ligand lone-pair orbitals throughout an unsaturated chelate-ligand framework provides a driving force towards a prismatic structure. On the other hand, many years ago Hoffmann et al. approached the problem from the opposite extreme, and started from a d⁶ system with neutral ligands.^[70] They identified strong metal-to-ligand π back bonding to ligand orbitals of the appropriate symmetry as a means to move the structure away from the ubiquitous octahedron. Obviously, maximum back bonding

will bring us back to the other extreme, a regular or distorted trigonal prismatic structure with d⁰ metal configuration and dianionic ligands (see also Figure 7). This continuum of bonding descriptions provides part of the fascination of dithiolene and related ligands.

Finally, we may speculate on the importance of π bonding in various extended solid-state structures known with trigonal-prismatic coordination at the metal center.^[79] The coordinating main group atoms are typically connected to more than one metal center, and their mutual orientations are restricted by the solid-state arrangement of the atoms. Thus it appears likely that the ligand lone-pair orbitals are not fully available for π bonding. This might explain the large variety of cases with trigonal-prismatic metal coordination in early transition metal chalcogenides, pnictides, and related systems. On the other hand, π bonding may in some cases enhance the distortions (see above). Such considerations may become important, for example, for distortions of octahedral coordination in extended oxide structures (Section 5).

4. Heteroleptic Systems

We have up to now concentrated on homoleptic complexes, as the major aim has been to discuss the general bonding features of d⁰ species. Most of the compounds of practical interest, for example, in catalysis or bioinorganic chemistry, are heteroleptic systems. With the basic underlying factors reasonably well understood for the simpler homoleptic systems, future interest will concentrate on heteroleptic complexes. We will in this Section discuss some bonding features and structural peculiarities which need to be considered when dealing with more complicated d⁰ systems. We will first focus on some simple tetracoordinate molecules (Section 4.1) to highlight the influence of π bonding and electronegativity on bond angles. We will then turn to a number of interesting penta- and hexacoordinate systems that provide hints of what the future may bring in this field (Sections 4.2–4.4).

4.1. May Bent's Rule be Extended to Transition Metal Chemistry?

Let us examine briefly what considerations come into play when we have mixed sets of ligands. Two factors to be kept in mind are a) the different electronegativity and b) the relative σ - and π -bonding capabilities of the ligands (a third factor is the steric requirements). A suitable starting point is the distorted tetrahedral structure of [Ti(CH₃)₂Cl₂]. Computation^[191] and GED^[192] both indicate the C–Ti–C and Cl–Ti–C angles to be lower than the ideal tetrahedral value, and the Cl–Ti–Cl angle to be larger (Figure 21 a). This is just opposite to what is normally observed in main group compounds, for example, for [Si(CH₃)₂Cl₂] (Figure 21 b).^[191b, 193] Here the angle between the less electronegative alkyl ligands is larger than tetrahedral whereas the Cl–Si–Cl angle is smaller.

Structures of such main group compounds are often explained by Bent's rule.^[194] It states that the bonds to the

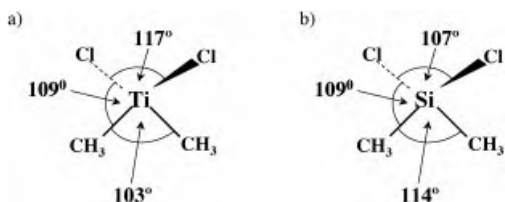


Figure 21. Bond angles from GED for a) $[\text{Ti}(\text{CH}_3)_2\text{Cl}_2]$ and b) $[\text{Si}(\text{CH}_3)_2\text{Cl}_2]$ (from refs. [191, 193]).

more electronegative substituents have more p character and thus make smaller angles, whereas the bonds to the less electronegative substituents obtain more s character and thus make larger angles (the valence p orbitals of the central atom are higher in energy and have a larger radial extent than the valence s orbitals).

Is it possible to extend Bent's rule to transition metal compounds? Jonas et al. argued,^[191b] on the basis of natural bond orbital (NBO) hybridization analyses, that in this case Bent's rule has to be rephrased. As the $(n-1)d$ orbitals are lower in energy and have a smaller radial extent than the ns orbitals, the bonds to the less electronegative ligands tend to acquire more d character and thus make lower angles, whereas the bonds to the more electronegative ligands have larger s character and thus make larger angles. This has been criticized by McGrady et al.,^[192] and by Landis et al.^[31c] In particular, Landis et al. argue that their orbital strength functions for the appropriate sd^k hybrids^[31] show a preference for *larger* bond angles with increasing k , that is, with increasing d character. Thus, the less electronegative ligands should make larger angles, in agreement with Bent's rule! They further argue that the "inverse Bent's rule" structures of $[\text{Ti}(\text{CH}_3)_2\text{Cl}_2]$ and of related compounds may be explained instead within a valence-bond picture by invoking ionic resonance structures (this would imply *lower* d character in the Ti–C than the Ti–Cl bonds).^[31c]

Could Ti–Cl π bonding be responsible for the large Cl–Ti–Cl angles and thus resolve these contradictions? McGrady et al. rejected this possibility,^[16, 192] based on the fact that related systems with strong π donors such as $[\text{CrO}_2\text{F}_2]$ exhibit *small* angles between the π -donor ligands. However, as discussed in Section 3.8 the interrelation between π bonding and bond angles may be complicated in d^0 systems, because of the involvement of both in-plane and out-of-plane π bonding.^[180] For example, for the "weak π -donor case" $[\text{ScF}_2]^+$, π bonding favors a linear arrangement over the bent equilibrium structure, whereas for the "strong π -donor case" $[\text{ZrO}_2]$, the opposite is true. For the present, heteroleptic pseudotetrahedral systems, the out-of-plane π bonding (π_{op}) will now in addition have to compete with the σ bonding to the additional ligands (e.g. in $[\text{Ti}(\text{CH}_3)_2\text{Cl}_2]$, $\pi_{\text{op}}(\text{Ti}-\text{Cl})$ bonding competes with $\sigma(\text{Ti}-\text{C})$ bonding).

The detailed analysis of NLMO compositions and of NBO deletion analyses has indicated indeed, that the overall effect of Ti–Cl π bonding in $[\text{Ti}(\text{CH}_3)_2\text{Cl}_2]$ favors a large Cl–Ti–Cl angle.^[180] In contrast, in $[\text{CrO}_2\text{F}_2]$ and related systems with strong π donors and weakly donating competing ligands, the overall dependence of the bond angle on π bonding (the sum of in-plane and out-of-plane contributions) appears to be low,

and thus the σ -bonding framework may dictate the small O–M–O angles.^[180] Upon introduction of stronger σ donors as ancillary ligands, for example, in the model system $[\text{CrO}_2\text{H}_2]$, in-plane M–O π bonding again starts to favor larger O–M–O angles.^[80] Indeed, the O–Re–O angles in $[\text{CH}_3\text{ReO}_3]$ have experimentally been found to be 113° , larger than the ideal tetrahedral angle (with C–Re–O angles of 105.6°).^[195] Clearly, the preferred angles reflect not only the specific character of the π -donor ligands, but also the σ -donor abilities of additional ligands present. This conclusion should also apply to other coordination numbers (see Sections 4.2 and 4.3).

Considerable further computational data on heteroleptic tetracoordinate complexes are available, which provide typical bond angles. For example, recent DFT calculations on d^0 and d^2 alkylidyne complexes $[\text{M}(\equiv\text{CH})(\text{CH}_3)_2(\text{X})]$, and of bis(alkylidene) complexes $[\text{M}(=\text{CH}_2)_2(\text{CH}_3)(\text{X})]$, studied the influence of the ligands X on the computed bond angles.^[196] Schrock-type carbene^[197] and carbyne^[198] complexes were studied systematically by MP2 calculations.

In view of the considerable importance of π bonding for their structural preferences, $[\text{Ti}(\text{CH}_3)_2\text{Cl}_2]$, $[\text{CrO}_2\text{F}_2]$, and similar complexes are not well suited to decide on the validity of Bent's rule in d^0 complexes. It would be better to compare heteroleptic systems without significant π -bonding contributions, but with significantly different electronegativities of the ligands. The choice of suitable models is rather limited. In ref. [180], the titanium complexes $[\text{TiH}_2(\text{CF}_3)_2]$, $[\text{Ti}(\text{CH}_3)_2(\text{CF}_3)_2]$, $[\text{Ti}(\text{SiH}_3)_2(\text{CH}_3)_2]$, and $[\text{Ti}(\text{SnH}_3)_2(\text{CH}_3)_2]$, as well as their silicon analogues were compared in DFT calculations. In the first case, the difference in substituent electronegativities is too small. The second and third system exhibit an inverse Bent's rule structure, but their silicon analogues also violate Bent's rule (probably the match of orbital size overrides the electronegativity differences^[180]). Only the last system exhibits an inverse structure with titanium but a regular structure with silicon. It appears difficult to derive an extension of Bent's rule to d^0 systems from these examples. On the other hand, the potential usefulness of the rule would appear to be very limited anyway, because of the typically very large importance of π bonding for the bond angles (see Section 3.8).^[180]

4.2. Pentacoordinate Heteroleptic Systems

Many of the factors discussed in Section 4.1 will also apply to other coordination numbers. Some examples of heteroleptic tricoordinate complexes have already been mentioned in Section 2.2. Clearly, the overall situation will become more complicated for higher coordination numbers, simply because more metal and ligand orbitals, as well as more potentially important geometrical structures have to be considered. Two recent computational studies have independently dealt with the structures of heteroleptic pentacoordinate complexes of the type $[\text{MX}_2\text{R}_3]$ ^[68] and $[\text{MXR}_4]$,^[69] where X denotes a σ -/ π -donor ligand and R an essentially pure σ -donor ligand.

The main impetus for the first study^[68] was the great importance of metallocene complexes of the type $[\text{MCp}_2\text{R}_3]$, in polymerization catalysis. Indeed, the $\eta^5\text{-C}_5\text{H}_5$ ligand may be considered a strong cylindrical π -donor X (Section 2.1). The typical structures of such pentacoordinate complexes, which appear to be also relevant for the transition state of stereospecific chain propagation in olefin polymerization,^[199]

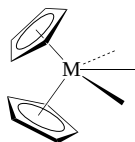


Figure 22. Preferred EBT-5 structure of $[\text{MCp}_2\text{R}_3]$ complexes.^[68]

are shown in Figure 22 (many theoretical studies have dealt with the orbitals of bent metallocenes; see for example ref. [50]). Ward et al. termed this structure *edge-bridged-tetrahedral* (EBT-5)^[68] and studied many systems with related $[\text{MX}_2\text{R}_3]$ ligand arrangements, both by quantum-chemical calculation and by structure-correlation analysis. Starting from a trigonal bipyramid (TBP-5) the EBT-5 structure is reached by a reverse Berry pseudorotation. Detailed comparison of the d⁰ MR_5 case (for which the EBT-5 structure is already a low-lying transition state,^[62, 63, 68] see Section 2.4) and the $[\text{MX}_2\text{R}_3]$ case demonstrated clearly how the π -donor character of X favors EBT-5 over SP-5 (which lies along the regular Berry pathway). The stronger the π -donors, the larger the stabilization is. The

structure-correlation analysis of published structures indicated many examples at different stages of the reverse Berry pathway.^[68] $[\text{ReO}_2(\text{CH}_3)_3]$ is a clear-cut case for which a gas-phase EBT-5 structure has been determined recently (Figure 23).^[200] The small C-Re-C angles are particularly obvious. Interestingly, the O-Re-

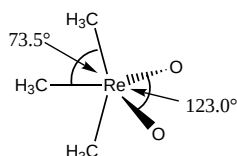


Figure 23. Gas-phase structure of $[\text{Re}(\text{CH}_3)_3\text{O}_2]$.^[200]

O angle is larger than the 120° required by a regular trigonal bipyramid. This provides further support for the influence of the character of the ancillary σ -donor ligands on the bond angles (Section 4.1). In this case the strong σ -donor methyl ligands may lead to the observed preference for a larger O-Re-O angle. Weaker π -donor ligands may not be sufficient to force a nonclassical structure. For example, a regular TBP-5 with both chloride ligands in the axial positions was found by electron diffraction for $[\text{Nb}(\text{CH}_3)_3\text{Cl}_2]$.^[16, 201]

We studied the $[\text{MXR}_4]$ system, in particular the structure of $[\text{WO}(\text{CH}_3)_4]$ and of related d⁰ and d¹ systems.^[69] While DFT calculations showed the hydride model system $[\text{WOH}_4]$ to exhibit strong deviations from a regular SP-5 structure (with the π -donor ligand in apical position), the distortions of the alkyl complex proceed along a rather shallow potential-energy surface. Nevertheless, the calculations show clearly that the regular SP-5 (C_{4v} symmetry) is not a minimum in these systems. Two directions of distortions were identified (Figure 24). One leads to a coordination arrangement that is close to the EBT-5 structure of Ward et al.^[68] and exhibits C_s symmetry (C_s -1). The second distortion pathway leads to a different C_s structure (C_s -2) which may in fact become the lowest-energy structure for strong π -donor ligands X,^[202] and for the d¹ model complex $[\text{ReOH}_4]$.^[69] While the EBT-5-type

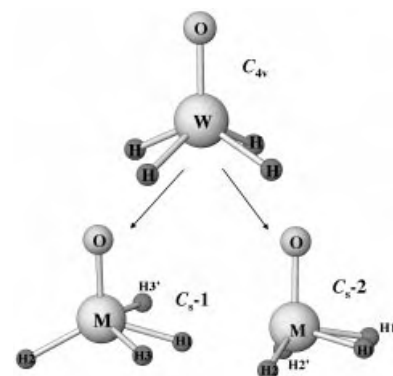


Figure 24. Possible distortions of the square pyramid for d⁰ and d¹ $[\text{MXR}_4]$ complexes.^[69]

arrangement provides three inequivalent sets of ligands R, two sets are obtained along the alternative distortion pathway.^[69] Both types of distortions help to reduce antibonding interactions at the C_{4v} high-symmetry structure, which arise from the competition of M-X π bonding and M-R σ bonding. And both directions appear to provide closely comparable magnitude of stabilization.^[69]

The available evidence on $[\text{MX}_3\text{R}_2]$ systems indicates that the third π -donor brings us back into the regime of the TBP-5. However, there are significant differences depending on the type of σ and π donors. Thus, in the solid-state structure of the complex $[\{(\text{CH}_3)_2\text{N}\}_3\text{Zr}(\text{SiPh}_2\text{tBu})_2]^-$, the three π -donor amide ligands are in equatorial position.^[203] In contrast, two of the three π -donor chloride ligands in the gas-phase structure of $[\text{Nb}(\text{CH}_3)_2\text{Cl}_3]$ apparently are in axial positions, with *cis* Cl-Nb-Cl angles of about 96.5°.^[16]

4.3. Hexacoordinate Heteroleptic Systems

Distortions from the regular octahedron in heteroleptic hexacoordinate d⁰ complexes have played an important historical role in drawing the attention of theoreticians to possible deviations from the usual structures. For example, the strongly distorted octahedral structures of $[\text{TiRCl}_3(\text{dmpe})]$ ($\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$; $\text{dmpe} = (\text{CH}_3)_2\text{P}(\text{CH}_2)_2\text{P}(\text{CH}_3)_2$) initiated some of the earliest theoretical studies of nonoctahedral d⁰ systems.^[74, 107] Since then many more complexes have been studied, both experimentally and theoretically, in which different types of deviations from the regular octahedron are apparent. Generally, it is more difficult to discuss complexes with chelate ligands, as the preferred bite angle of the ligand may strongly influence the structure of the system, and works either against or with the electronic preferences of the central metal (Section 2.5).

The conceptually easiest distortions are probably those of unsymmetrical chelate ligands that remain largely along the trigonal twist discussed in Section 2.5. Examples are too numerous to be discussed here in detail.^[84, 103, 204] It appears likely that the averaged σ - and π -donor abilities and bond ionicities of both inequivalent sides of the chelate ligand determine the twist angle. More interesting distortions are

those in which formally equivalent chelate ligands coordinate in inequivalent modes (see Section 2.5).^[94, 95] An interesting distorted trigonal-prismatic (C_{3v} symmetrical) system with one tridentate and three monodentate ligands is provided by [(tbn)Ta(CH₃)₃] (tbn = tribenzylidenemethane).^[47]

In Section 3.8 we have discussed the effect of replacing a cylindrical π -donor such as a halide by an effectively single-sided π -donor such as thiolate. This leads us into the range of structures intermediate between octahedron and trigonal prism, typically along the trigonal-twist pathway (see also Section 2.5). A recent DFT study explored a different route into this “no-man’s-land”:^[78] starting from [WCl₆] or [WF₆], the halides were successively replaced by methyl ligands, to provide the heteroleptic series [WX_{6-n}(CH₃)_n] ($n = 1 - 5$). The question was, how the structures proceed from the octahedral preference in [WX₆] to the distorted trigonal prism of [W(CH₃)₆]. As indicated in Section 3.8, the trigonal prism has been computed to be a transition state for the trigonal twist in the hexahalides, approximately 80 kJ mol⁻¹ and 43 kJ mol⁻¹ above the O_h structure for [WCl₆] and [WF₆], respectively (the smaller difference for the fluoride being a result of the less efficient π bonding). Already after the first substitution of a halide by a methyl ligand ([WX₅CH₃]) this energy difference has almost vanished. Now a distorted octahedral minimum is only about 20 kJ mol⁻¹ more stable than a trigonal-prismatic transition state for X = Cl, whereas the calculations already gave a very slight preference (by ca.

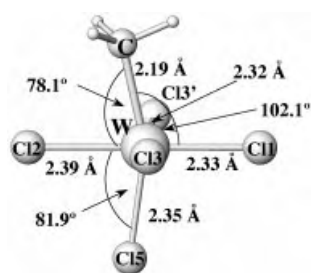


Figure 25. Distorted octahedral minimum structure computed for [WCl₅CH₃].^[78]

multiple substitution by methyl groups, the possibility of different isomers arises. Two minima of almost identical energy have been found computationally for [WCl₄(CH₃)₂]. One is a distorted *trans* octahedron of C_{2v} symmetry (analogous to the structure in Figure 25), whereas the second has C_2 symmetry and is intermediate between the trigonal prism and the *cis* octahedron. The structures of all of these complexes are presumed to be highly fluxional. Already with three methyl ligands, there appears to be a clearer preference for the trigonal prism, with the presence of different isomers of similar energy.^[78] This preference is further enhanced upon substitution of the remaining halides by methyl groups, with no particularly surprising structures found along the way.^[206] These computational data mark some of the possible intermediate structure situations in heteroleptic systems. Depending on the actual combination of σ -donor and single- or double-faced π -donor ligands, we may expect a considerable variety of coordination ar-

rangements. Very recently, Seppelt et al.^[207] succeeded in carrying out initial solid-state structure determinations for four heteroleptic systems, [MoOCH₃(CH₃)₅], [WCl(CH₃)₅], [Mo(OCH₃)₂(CH₃)₄], and [MoCl(OCH₃)₂(CH₃)₃]. While the first three complexes are close to the trigonal-prismatic limit, the latter complex appears to prefer a distorted octahedral arrangement, which resembles strikingly a low-lying transition state computed for [WCl₃(CH₃)₃].^[78]

The type of distortions indicated in Figure 25 had already been observed earlier experimentally in a series of d⁰ complexes of composition [M(OAr)₂(H)₂LX] (M = Nb, Ta; L = P(CH₃)₂Ph, X = Cl, OAr).^[208] and they have been the target of two independent computational studies on simplified model systems^[209, 210] (see also ref. [107]). In these complexes, the two *trans* hydride ligands are bent characteristically towards the phosphane ligand L, away from the π -donor X ligand (Figure 26). With *trans* H-M-H angles of around 125–135°, the distortion is more pronounced than that computed for the *trans* alkyl ligands in the above mentioned [WCl₄(CH₃)₂] (ca. 144°).^[78] Replacement of the hydride ligands in these complexes by chloride ligands does not completely remove the bending but reduces it to a much less dramatic magnitude (*trans* Cl-M-Cl angles ca. 165°). The computational studies identified clearly the interplay between a maximization of the π bonding to ligand X and optimization of the σ overlap between the hydride ligands and appropriately hybridized metal d orbitals.^[209, 210] Replacing X by a pure σ -donor ligand does not remove the distortion but reduces the energy preference for bending towards L. In several cases the calculations indicated the possible existence of a second isomer with the hydrides bent towards X.^[210] The latter isomers became the preferred ones when X was replaced by a π -acceptor (see also ref. [18]).

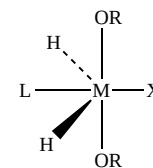


Figure 26. Distorted octahedral structures found for heteroleptic complexes [M(OR)₂(H)₂LX] (M = Nb, Ta; L = P(CH₃)₂Ph, X = Cl, OAr).^[208–210] While R = aryl group in the experimentally studied systems, DFT calculations employed R = H.

The results of these studies confirm a preference for angles below 90° and below 180° between *cis* and *trans* σ -donor ligands, respectively (see also Section 3.4 and 3.5). At the same time, the distortions allow the competing π -donor ligands to enhance their bonding to the metal. These conclusions are consistent with more general notions about the alleviation, by structural distortions, of conflicts between different π -donor ligands (or between σ - and π -donor ligands) competing for a given set of metal d orbitals.^[211] The prototypical example for this type of competition is that discussed for distorted octahedral dioxomolybdenum complexes, in which the two strong π -donor oxo ligands prefer a *cisoid* arrangement (Section 3.8), and the two weakest co-ligands are located *trans* to the oxo ligands, with typically small angles between them^[211a, 212] (see also ref. [179] for a theoretical study on a *cis* diimido complex).

Either structures close to the trigonal prism or characteristically distorted octahedral arrangements have been found

for the complexes $[MX_2(Me_4taen)]$ ($Me_4taen = 5,7,12,14$ -tetramethyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,13-tetraene; $M = Zr, Hf$).^[213] The cavity of the tetradentate macrocyclic ligand Me_4taen is too small to completely enclose the metal. The additional ligands X are attached in a *cis* arrangement on one side of the macrocycle. The dihedral angles are close to the trigonal prismatic extreme for $X = Cl, CH_2Ph$, with the ligands X each pointing in between two of the nitrogen atoms of the macrocycle. In contrast, in complexes with presumably stronger π -donors^[213] ($X = N(CH_3)_2, OtBu$) the ligands X eclipse almost two of the macrocyclic nitrogens, creating an octahedral structure distorted in the direction of a doubly capped tetrahedron.

An interesting example of a d² complex with five σ -donors and one π - σ -donor is provided by $[CpOsH_5]$.^[214] Calculations indicate a strongly distorted pseudo-octahedral structure with the equatorial hydrogens strongly bent away (by ca. 115°) from the apical Cp ligand, to enhance their σ bonding to the metal.^[215] The system is thought to fluctuate even at low temperatures, via low-lying trigonal prismatic transition states.^[215]

A very different class of heteroleptic d⁰ systems may be derived from more strongly ionic complexes of the heavier alkaline earth metals ($M = Ca, Sr, \text{ and } Ba$) or of the lanthanides. For example, in a series of complexes $[M(N\text{-carbazolyl})_2(L)_n]$, a clear transition from a mutual *trans* arrangement of the formally anionic carbazolyl ligands in $[Ca(N\text{-carbazolyl})_2(pyridine)_4]$ via a bent *transoid* arrangement in $[Sr(N\text{-carbazolyl})_2(NH_3)(dme)_2]$ to a *cis* arrangement in $[Ba(N\text{-carbazolyl})_2(dme)_3]$ was found by X-ray diffraction ($dme = 1,2$ -dimethoxyethane).^[216] Based on the increasingly bent structures of the gas-phase alkaline earth dihalides with increasing atomic number of the metal (see Section 2.1), it has been suggested that the same effects (small covalent σ -bonding contributions involving metal d orbitals and core polarization, Sections 3.1 and 3.2) survive when additional weakly bonded, neutral co-ligands are present.^[216] This idea has been supported by ab initio calculations on the model complexes $[M(NH_2)_2(HF)_4]$ ($M = Ca, Ba$). While the calcium complex prefers an almost regular octahedral structure with *trans* NH_2 ligands, the barium complex favors a distorted *cis* arrangement. Even for the less stable *trans* structure, the N-Ba-N angle was computed to be only about 146° (the energy differences involved are in the range of only ca. 10 kJ mol⁻¹).^[216] It appears that the electronic requirement to have the two anionic ligands in a bent arrangement dominates over the requirements of the additional neutral ligands (provided the latter are not too bulky) in controlling the preferred structure. This is consistent with a distinction between regular covalent and dative bonding.^[217] Some more experimental examples in agreement with these ideas have been provided.^[216] Recently, a number of hexacoordinate bithiolate and bisselenolate complexes $[M(thf)_4EMes_2^*]$ ($M = Ca, Sr, Ba$; $E = S, Se$; $Mes^* = 2,4,6\text{-}tBu_3C_6H_2$) have been structurally characterized.^[218] While the Ca, Sr, and Ba complexes all exhibit a *transoid* arrangement of the anionic thiolato or selenolato ligands, the X-M-X angle decreases from Ca to Ba, and from selenolate to thiolate complexes, consistent with the above discussion.

4.4. Mononuclear Molybdenum and Tungsten Enzymes

We have already mentioned examples, in which the “non-VSEPR structures” of certain d⁰ complexes were considered relevant for practical questions, for example, for the stereospecificity of olefin polymerization (Section 2.2), or in the context of α -elimination of alkyl compounds to produce carbene complexes (Section 2.4). Another case, in which the nonclassical structure preferences of d⁰ systems are of potential interest, is the fascinating field of molybdenum and tungsten enzymes. We will disregard here the multinuclear molybdenum nitrogenases but will concentrate on the mononuclear active sites of the other large class of molybdenum enzymes and the closely related tungsten enzymes.^[89, 90] In these enzymes, sometimes referred to as oxomolybdenum (oxotungsten) or oxotransferase enzymes, the single metal atom is coordinated by a unique bioligand termed pterin cofactor. Most notably, the coordination is of the dithiolene type, and this is one of the reasons for the large amount of research carried out on dithiolene complexes (Section 2.5). In their oxidized state, the active sites of the enzymes feature Mo^{VI} and W^{VI}, respectively, that is, they may be assigned a d⁰ configuration.

Hille^[89] has classified the known molybdenum enzymes broadly into three families, based on the known structural features of their active site. In the M^{VI} state, the “xanthine oxidase family” and the “sulfite oxidase family” both exhibit *one* chelating dithiolene (pterin) ligand, two terminal oxo (or sulfido) ligands, and one or two additional ligands. The structures determined may be termed distorted octahedral, partly because of the specific requirements of the strong π -donor oxo- and/or sulfido-ligands. These active sites fit well the category of d⁰ dioxo complexes discussed above (Section 4.3), and a considerable number of synthetic model complexes has been structurally characterized^[211, 212] or studied computationally.^[211, 219]

In contrast, the “dimethylsulfoxide (DMSO) reductase family”^[89] of molybdenum enzymes exhibits coordination by *two* pterin ligands, usually in a bischelating dithiolene mode (Figure 27). The additional ligands X and Y may be one oxo, sulfido, or selenido ligand (or potentially protonated forms like hydroxy or aqua ligands) plus one monoanionic ligand coming from the protein surroundings, for example, serinate, cysteinate, or selenocysteinate. Because of the restricted π -donor abilities of dithiolene ligands (Section 3.8), “non-VSEPR structures” are most likely for this last family of molybdenum enzymes, or for related tungsten active sites. Indeed, based on recent protein X-ray structure determinations, several of the active sites studied have been termed “distorted trigonal prismatic”.^[89, 90]

In particular, the following cases have been discussed: 1) the structure of formate dehydrogenase H of *Escherichia coli*, where the two additional co-ligands to molybdenum(vi) center were either hydroxy and seleno-cysteinate, or nitrite and seleno-cysteinate (nitrite is considered an inhibitor, closely

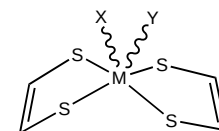


Figure 27. General coordination pattern of the Mo^{VI} active sites of molybdenum enzymes in the DMSO reductase family.^[89]

analogous to the substrate formate).^[220] 2) The structure of DMSO reductase from *Rhodobacter sphaeroides*, where the two co-ligands to the Mo^{VI} center have been considered to be one oxo and one serinate ligand.^[221] 3) The structure of the tungsten(vi) active site of aldehyde ferredoxin oxidoreductase from *Pyrococcus furiosus*,^[222] the structure of which has been considered to be very close to that of the Mo active center of DMSO reductase from *Rhodobacter sphaeroides* (see above).

Unfortunately, in none of these crystallographic studies of proteins is the structural resolution obtained sufficiently high to unequivocally discriminate near-octahedral or near-trigonal-prismatic coordination of the metal center. Nor does the additional spectroscopic information allow this classification to be made. Structure analyses of synthetic model complexes with suitable ligand combinations could provide the necessary insight, but as yet the data is limited for systems with a d⁰ metal center, two dithiolene ligands and two appropriate additional co-ligands.^[223–226] Those [M(dt)₂XY] model complexes studied crystallographically (dt = dithiolene-type ligand; X, Y = monodentate co-ligands) had either two oxo ligands,^[223, 224] or one oxo ligand plus a “monoanionic” ligand like alkoxide, siloxide, or chloride.^[225, 226] In all cases, the structures may be best characterized as distorted octahedral.

Based on the predominantly trigonal-prismatic structures of tris(dithiolene) complexes (Section 2.5) and the structural role of π bonding (Section 3.8), we can speculate about possible structures of [M(dt)₂XY] complexes. In particular, we expect that complexes in which X and Y are relatively weak π donors (that is, not oxo or sulfido ligands) will be closest to the trigonal-prismatic extreme. Thus, for example, the combination between a monoanionic co-ligand X (e.g. serinate, cysteinate, seleno–cysteinate) and a monoanionic (e.g. hydroxide, nitrite) or neutral (e.g. H₂O) co-ligand Y might provide a suitable electronic situation for a prismatic structural preference.^[227] Clearly, in the actual situation in the protein, hydrogen bonding may further modify the π - and σ -donor abilities of the ligands. It is presently an open question, to what extent the structure preference of the active site of such molybdenum or tungsten enzymes may alter the reactivity of the system. However, as the fully reduced d² states (Mo^{IV}, W^{IV}) of the enzymes are likely to exhibit structures derived from the square pyramid (SP-5), it is not unlikely that oxo-transfer or related reactions will be modified in going from a distorted trigonal prismatic to an octahedral structure of the oxidized state.

5. Multinuclear d⁰ Complexes: Moving towards the Extended Solid

As discussed in Section 2.5, the first “non-VSEPR” cases observed for d⁰–d² systems were extended solid-state structures with trigonal-prismatic metal coordination.^[79] It is to be expected that the factors discussed in Sections 2–4 may also be relevant for other extended solid-state systems. All other things being equal, an increase in coordination number increases ligand repulsion and thus tends to decrease the tendency towards nonclassical structures. In the case of MoS₂ and its relatives, the large covalency of metal–ligand σ bond-

ing obviously helps to stabilize the prismatic coordination even in the bulk material (Section 3.7).^[79] However, there are indications that even relatively small covalent-bonding contributions may be sufficient to have an influence on the structural preferences. Multinuclear complexes may be considered as intermediate states of aggregation, between molecule and extended solid. They are thus a convenient starting point for our discussion.

Still on the covalent side, some di- and trinuclear thiolato complexes of Ti and Zr should be mentioned, in which the central metal adopts either a distorted or a regular trigonal-prismatic coordination geometry.^[92b,c] As discussed in Section 3.8, it appears likely that the influence of π bonding may be diminished compared to corresponding mononuclear analogues, as angular constraints do not allow the π -type lone pairs on sulfur to participate fully in bonding. A related heteroleptic example is provided by the trimer [(Me₂N)₃Zr(μ -H)(μ -NMe₂)₂]₃Zr, in which the central metal is in a trigonal prismatic and the outer metals in a trigonal antiprismatic environment.^[228]

DFT^[36] and HF^[229] calculations have dealt with the monomers, dimers, and trimers of [TiO₂]. The electrostatically most favorable planar, doubly bridged D_{2h} structure (Figure 28a) is not a minimum on the dimer potential-energy surface, and it distorts to a C_{2h} structure (Figure 28b), with trigonal-pyramidal metal coordination. However, a triply bridged structure with C_{3v} symmetry (Figure 28c) is even more favorable energetically. Related structures have been computed for the trimer, [Ti₃O₆]^[36, 229] and for its zirconium analogue.^[230] In bulk TiO₂ modifications, Ti is octahedrally coordinated, but with deviations from the ideal polyhedron (the distortions are most notable in the brookite structure^[80]). The 4d homologue ZrO₂ is also polymorphic. Except for the high-temperature cubic form, the coordination of the metal is highly irregular. In the low-temperature monoclinic modification (cf. the mineral baddeleyite; the same structure is realized by HfO₂), the metal is irregularly coordinated by seven oxygen neighbors.^[80, 81, 231, 232] Ionic models have not performed well in describing the phase transitions of ZrO₂.^[233] This has been taken as evidence for the importance of Zr–O covalency in describing the low-symmetry structures.^[234] The phase transitions of ZrO₂ are of tremendous technological importance, as they are intrinsically related to the mechanical properties of zirconia (ZrO₂), one of the most widely used ceramic materials.^[235] A vast literature exists on various factors affecting the stability of the different phases, which include the stabilization of the cubic structure by impurities. A review of this field is beyond the scope of the present article.

The more covalent MoO₃, and particularly WO₃, also

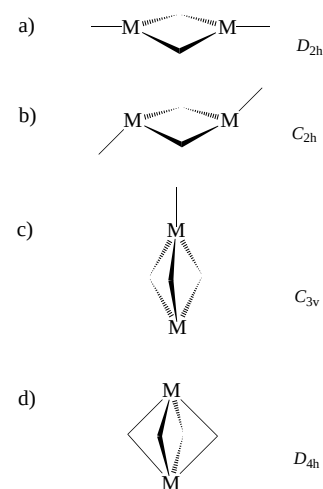


Figure 28. Preferred structures for d⁰ [M₂X₄] systems.^[232]

exhibit a strikingly rich structural chemistry, again with highly unsymmetrical coordination of the metal center in many cases.^[80, 81, 232, 236] And again, the structural distortions are coupled to important technological applications (e.g. WO₃ is used in electrochromic devices,^[237] and MoO₃ is an important oxidation catalyst^[238]). In most cases, the metal coordination environment may be described as distorted octahedral. In several phases of WO₃, and in the metastable β -MoO₃,^[236] the metal is displaced towards a face of the oxygen octahedron. An extended-Hückel study,^[239] and several more recent HF and DFT studies^[55, 240] have dealt with the instability of the high-symmetry cubic ReO₃-type structure for WO₃ or MoO₃. The preference for lower coordination symmetry in the d⁰ systems has in all cases be traced to improved covalent M–O interactions. While the extended-Hückel work of Wheeler et al. emphasized the π -type interactions,^[240] more recent HF solid-state calculations suggested that also the metal-oxygen σ bonding is improved in the lower-symmetry structures.^[240a] Both notions are consistent with the discussions in Section 3. Notably, the deviations from a regular octahedral coordination are more pronounced for the 4d system MoO₃,^[236] than for the 5d system WO₃, probably because of the relativistic expansion of the 5d orbitals and the resulting larger bond ionicity and band gap in the tungsten compound (Section 3.7). Addition of one electron, to give a formal metal d¹ configuration, stabilizes the classical cubic structures of ReO₃ or of NaWO₃, with regular octahedral metal coordination. This has been traced to M–O antibonding contributions from the conduction band.^[239, 240b]

In close relationship to the distorted structure of WO₃ are the ferroelectric d⁰ perovskites.^[241] The prototype is BaTiO₃, one of the economically most important ceramic materials, because of its ferroelectric transition near room temperature. At normal pressure, BaTiO₃ exhibits three phase transitions.^[242] Notably, in the thermodynamically most stable low-temperature rhombohedral phase, the titanium atom has shifted towards one of the faces of the distorted oxygen coordination octahedron (the other ferroelectric transitions correspond to movements towards a corner or an edge, respectively). In this and related cases, the computed band gap increases upon distortion of the cubic structure.^[243] Regarding the origin of the low-symmetry distortions, the same considerations apply as for WO₃ or MoO₃ above. Wheeler et al.^[239] have classified the distortions as representative for a more general picture of second-order Jahn–Teller distortions. More recent DFT studies also emphasized the improved covalent M–O bonding in the distorted structures^[243] (unfortunately, in most chemistry textbooks, the distortions are still rationalized as being because the “Ti⁴⁺ ion” is too small to adequately fill the octahedral interstices).

Among the other ferroelectric perovskites, we should mention KNbO₃, which exhibits the same series of ferroelectric phase transitions upon cooling, and the same distorted metal coordination in the low-temperature phases as BaTiO₃,^[244] caused by the same tendency to improve M–O covalency. Interestingly, the heavier 5d homologue, KTaO₃, does not distort from the high-symmetry cubic perovskite form, even at very low temperatures.^[245] However, a soft phonon mode^[246] indicates that KTaO₃ is just on the brink of

also favoring a low-symmetry distortion (it has been termed an “incipient ferroelectricum”). The dielectric properties of unrestricted solid solutions of KNbO₃ and KTaO₃ (a pseudobinary alloy termed “KTN”) may be adjusted conveniently by concentration.^[247] Ferroelectric behavior is already found at Nb concentrations above 1%. We may again attribute the differences between the 5d and 4d systems to slightly more ionic bonding in the former (caused by the relativistic expansion of the 5d orbitals), as well as to the related larger band gap (3.79 eV in KTaO₃^[248] relative to 3.3 eV in KNbO₃^[249]), which disfavors a “second-order Jahn–Teller distortion” (Sections 3.7 and 3.4, respectively). Similar differences apply to the comparison of LiNbO₃ and LiTaO₃. While both substances are known to exhibit one ferroelectric phase transition, the transition temperature is lower for LiTaO₃ (950 K) than for LiNbO₃ (1480 K), consistent again with a shallower well on the potential surface for the Ta compound.^[250] Ferroelectrically distorted structures have recently been found also for CsTaQ₃ (Q = S, Se, Te).^[251] A detailed appreciation of the vast amount of experimental and theoretical work centered on the ferroelectric distortions in perovskites and related materials is outside the scope of this article.

Many further d⁰ oxides exhibit low-symmetry distortions of the metal coordination environment. Examples are the complex structural chemistry exhibited by Nb₂O₅ or Ta₂O₅ (again with notable differences between the 4d and 5d system^[80]), the Group 3 sesquioxides (e.g. Sc₂O₃, Y₂O₃, La₂O₃), numerous iso- and heteropolyions of Nb, Ta, Mo, and W, or the rich structural chemistry of the vanadates. Even the different structures of the 4d oxide Tc₂O₇ and the 5d oxide Re₂O₇ in the solid state should be mentioned in this context. A detailed discussion of the extensive literature on these compounds is beyond the scope of this article (see, for example, ref. [80]).

Herein we have concentrated mainly on the local bonding environment of the d⁰ metal, and therefore we have not considered long-range Coulombic interactions in detail. Moreover, the structural distortions of the metal coordination sphere are intrinsically coupled to those of the neighboring unit cells (this touches also the question of first- and second-order phase transitions). The structures are undoubtedly influenced by packing effects and thus by the relative sizes of the different atoms. Nevertheless, it is clear that the covalent bonding aspects discussed in Sections 2–4 have a high impact on the structural preferences, and thus on the materials properties of these substances. The discussion of the structural chemistry of d⁰ oxides would benefit from a better consideration of covalent bonding.

Structures similar to [Ti₂O₄] (see above) have been found for the ionic dimeric compounds of the heavier alkaline earth metals. HF calculations on the dihydride dimers indicated the triply bridged C_{3v} structure (Figure 28c) to be lowest in energy for [Sr₂H₄], and in particular for [Ba₂H₄], followed by the doubly bridged C_{2h} structure (Figure 28b) with pyramidal metal coordination environment.^[252] Even a quadruply bridged D_{4h} structure with no terminal ligands (Figure 28d) has been computed to be almost as viable energetically as the ground-state structure for the heavier metals. The regular D_{2h} structure (Figure 28a) is preferred slightly for [Ca₂H₄] and

strongly for the Be and Mg systems but is not a minimum for $[\text{Sr}_2\text{H}_4]$ or $[\text{Ba}_2\text{H}_4]$. Very similar results have been obtained in recent DFT calculations on the difluoride and dichloride dimers,^[253] with increasing preference for the triply bridged structure with the heavier metals and lighter halogens. This is exactly the same type of tendency found for the bending of the monomers (Section 2.1).

Experimental examples for these types of structure preferences encompass oligomeric diamides, diphosphanides, and dialkoxides of the heavier alkaline earth metals: the dimers of bulky diamides, $[\text{M}[\text{N}(\text{SiMe}_3)_2]]_2$, exhibit the doubly bridged structure, with increasing pyramidalization of the metal center (C_{2h} heavy-atom skeleton) along the series $\text{Ca} < \text{Sr} < \text{Ba}$.^[254] In contrast, the corresponding phosphanides $[\text{M}[\text{P}(\text{SiMe}_3)_2]]_2$ exhibit significantly reduced P–M π bonding, a result of the preferred pyramidalization around phosphorus atoms. Indeed, the known X-ray structures indicate triply bridged structures (Figure 28c), but with additional solvent molecules attached to the open metal site.^[255] Further examples of these triply bridged types of dimers, and of related larger aggregates, are provided by a number of alkoxides of the heavier alkaline earth metals.^[256]

Will the “non-VSEPR” preferences of alkaline earth MX_2 compounds also survive in the bulk solid? In this context, the covalent σ -donor hydride ligands are the most likely candidates for unusual coordination. Indeed, the solid-state structures of the heavy alkaline earth and lanthanide(II) dihydrides exhibit remarkably unsymmetrical metal coordination, typically described as a very irregular 6+3 or 7+2 coordination in a distorted PbCl_2 structure type.^[80, 81] There appears to be no good reason based on ionic bonding forces alone that would explain these unusual structures. The unsymmetrical metal coordination in many lead dihalides or related compounds with the PbCl_2 structure type may be rationalized by the stereochemical activity of the metal lone pair. It seems likely that the irregular structures of the heavy Group 2 dihydrides in the bulk phase are because of d-orbital participation in σ bonding and to core polarization. These are the same factors that make the monomeric and dimeric molecules violate the usual structure rules.

The dihydrides are not alone in exhibiting irregular structures in the bulk solid. While ionic bonding forces appear to dominate the regular structures of alkaline earth and lanthanide(II) difluorides, the other barium halides, as well as EuCl_2 and SmCl_2 , have PbCl_2 -type structures similar to the hydrides, with very unsymmetrical coordination of the metal center.^[80, 81] Wells noted that “The alkaline earth halides are surprisingly complex from a structural viewpoint, the twelve compounds exhibiting at least six different structures.”^[80] Complex structural situations also pertain to the known Group 3 and lanthanide(III) trihalides. For example, LaCl_3 and LaBr_3 , as well as many 4f trichlorides and trihydroxides, prefer the UCl_3 structure type, which is related to the PbCl_2 -type. Even the fluorides tend to exhibit irregular coordination. It is notable, for example, that the highly irregular YF_3 structure type is the same as that also adopted by the main group fluorides TlF_3 and $\beta\text{-BiF}_3$,^[80] where the unsymmetrical metal coordination might be attributed to stereochemically active lone pairs.

6. Final Remarks

The number of examples of “non-VSEPR structures” of d^0 and related systems provided in Sections 2–5 show that we are not dealing with a mere curiosity or exotic phenomenon. In many cases, the low-symmetry distortions appear to be related to important processes, for example, in homogeneous or heterogeneous catalysis (e.g. olefin polymerization or oxide-surface catalyzed oxidations), in bioinorganic chemistry (e.g. molybdenum enzymes), or in materials research (e.g. ferroelectric oxides). Future research will bring us more examples, in particular of heteroleptic complexes with numerous applications. We also have to accept that even those complexes that obey the classical structural models, may nevertheless exhibit potential-energy surfaces that differ sharply from those of related main group compounds. It is therefore mandatory that improved bonding principles are provided for such systems. These models should enable the preparative chemist, the catalyst designer, or the materials researcher to predict structure, reactivity, and properties of high-valent early transition metal compounds with good accuracy.

While the bonding in homoleptic, σ -bonded complexes appears to be well described by relatively simple MO or VB models, in conjunction with ligand repulsion (Sections 3.1–3.7), the influence of π bonding on structure (in particular on bond angles and conformation) needs further scrutiny before we will understand all its intricacies (Section 3.8). This holds in particular for heteroleptic complexes, where the outcome of the competition between σ -bonding and σ -/ π -bonding ligands for the metal d orbitals is still hard to predict, because of the multitude of possible solutions, and often a result of relatively small energy differences between different structures (Section 4). Once the structural preferences have been put on a firm theoretical basis, our understanding of reactivity and stereoselectivity will benefit as well, for example, in the case of the molybdenum enzymes discussed in Section 4.4. Another area that deserves more work, also from a quantum-chemical point of view, are the multinuclear complexes, and the bulk phases discussed in Section 5. It appears possible that many solid-state structures, that up to now defy clear-cut interpretations, will become tractable along the lines set out in Section 3.

Generally, quantum-chemical calculations have played an enormously important role in uncovering the concepts described in Section 3 (and in Section 4.1). Moreover, the quantitative accuracy of modern *ab initio* or DFT calculations in structure predictions has been shown to rival experiment in many cases. In future we will need even better tools, in particular to extract suitable, improved qualitative chemical models from such quantitative calculations.

7. Appendix: Details of the DFT Calculations

All molecular calculations performed specifically for the present paper have been carried out with the Gaussian94 program,^[257] at the same computational level used in

refs. [69, 114, 115]. That is, the gradient-corrected BP86 functional^[258] was used with quasirelativistic small-core metal ECPs,^[147a, 259] and also with ECPs for the main group atoms F, Cl, and S.^[260] Valence basis sets employed were of the sizes (8s7p6d)/[6s5p3d] for the transition metals,^[147a, 259] and (4s4p1d)/[2s2p1d] for the p-block main group atoms.^[260, 261] Hydrogen basis sets were of the size (4s)/[2s]^[262] augmented by one p-function ($\alpha = 1.0$) for hydrogen atoms directly bound to the metal center. NPA and NBO analyses^[167] have been carried out with the built-in subroutines of the Gaussian 94 program.^[257]

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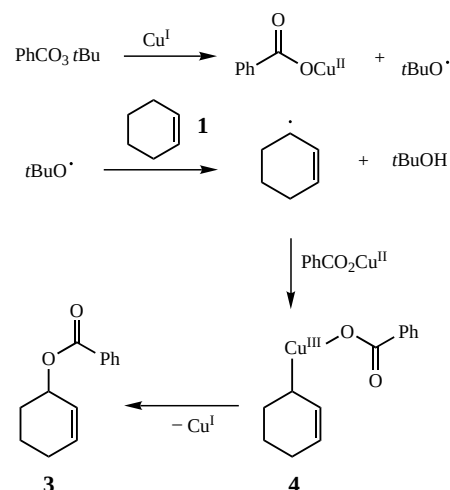
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Catalytic Allylic Oxidation of Alkenes Using an Asymmetric Kharasch–Sosnovsky Reaction

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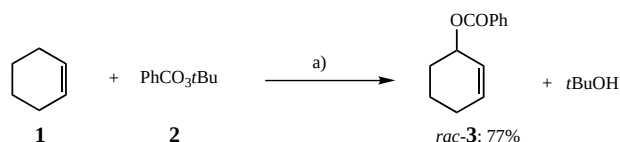
Abstract: Kharasch and Sosnovsky reported the allylic oxidation of alkenes to give racemic allylic benzoates. This could be achieved efficiently using a *tert*-butyl perester as the oxidant, in the presence of a copper or cobalt salt. The use of C_2 -symmetric bis(oxazoline) ligands in the presence of copper(I) triflate with cyclic olefinic substrates gave the first synthetically useful asymmetric variant. The enantioselective control was good (up to 84% *ee*) although yields were variable. In all cases the facial preference of the newly formed C–O bond was the same giving an *S* configuration at the allylic stereocenter. Lower stereocontrol was observed for large-ring alkenes and substantially reduced enantioselectivities were found with open-chain alkenes. This reaction has been further screened using a variety of bis(oxazoline) and proline-derived ligands, which give a direct correlation between the chirality of the ligand and the enantioselectivity obtained. Individual substrates were found to be extremely sensitive to both the ligand structure and copper salt used as well as the presence of additives such as zinc, hydrazine, and molecular sieves.

reaction was more efficient using a copper salt. It was proposed that the reaction occurred via a radical mechanism, which was suggested to proceed in a concerted manner, with the copper center being intimately involved in the C–O bond forming step through the allyl cuprate, **4** (Scheme 2).^[1] When



Scheme 2. Proposed mechanism for the allylic oxidation of **1**.

Some of the recent developments in the asymmetric allylic oxidation of alkenes have stemmed from a seminal report by Kharasch and Sosnovsky in the late 1950s.^[1] They originally showed that allylic oxidation of alkenes, such as cyclohexene (**1**), could efficiently occur using a *tert*-butyl perester **2** as the oxidant, in the presence of a copper or cobalt salt to give allylic benzoates in good yield (Scheme 1). In most cases, the

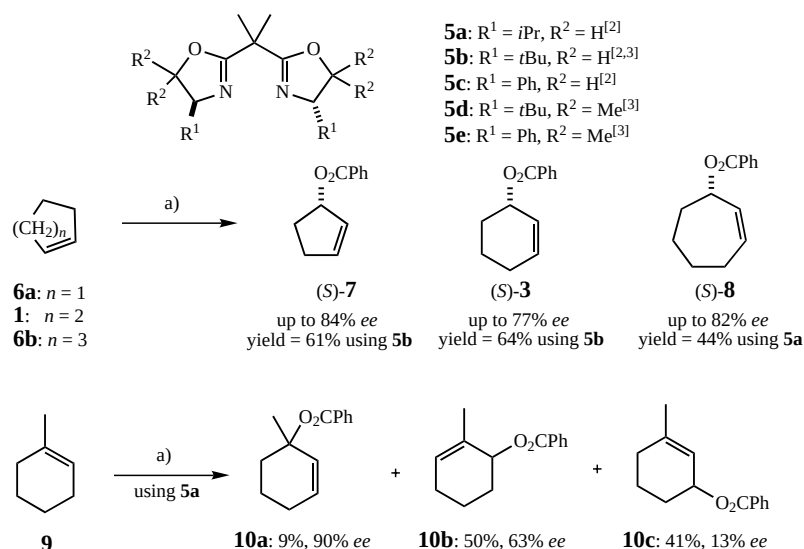


Scheme 1. The Kharasch-Sosnovsky reaction: a) cupric 2-ethylhexoate or CuBr, 80 °C, benzene.

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the reaction was performed in the presence of an aliphatic acid, the ester of this acid was obtained rather than the corresponding benzoate.

In view of the potential utility of such a synthetic transformation, it does seem remarkable that the first synthetically useful asymmetric variant was only reported in the mid 1990s, independently by the groups of Pfaltz,^[2] Andrus,^[3] and Katsuki.^[4] Pfaltz^[2] and Andrus^[3] and their co-workers both employed the same series of enantiomerically pure C_2 -symmetric bis(oxazoline) groups (**5a–e**) as the ligand in the presence of copper(I) triflate with cyclic olefinic substrates (Scheme 3). The enantioselective control was generally good (up to 84% *ee*) although yields were somewhat more variable. In all cases the facial preference of the newly formed C–O bond was the same, giving an *S* configuration at the newly formed allylic stereocenter. It was clear from these initial studies that a small change in the substituent R^2 (incorporated to prevent oxidation adjacent to the oxygen atom to improve catalyst stability) had a dramatic effect on the resulting

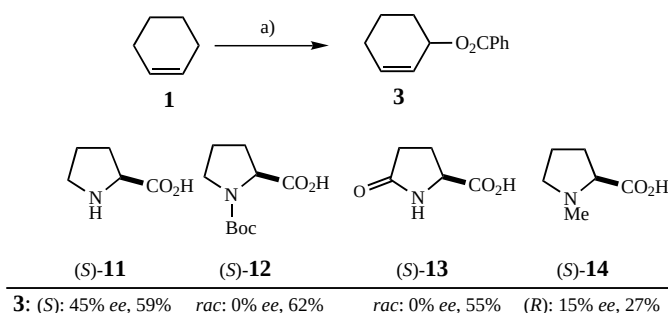


Scheme 3. Allylic oxidation of cycloalkenes using a C_2 -symmetric bis(oxazoline) ligand **5**: a) $PhCO_3tBu$, $CuOTf$ (5 mol %), chiral ligand **5a–e** (6–8 mol %); OTf = trifluoromethanesulfonate.

stereocontrol; for example, changing from oxazoline **5b** to **5d** resulted in the enantioselectivity dropping from 70 to 42% *ee* for the synthesis of benzoate **7**. Unfortunately there was no clear pattern to indicate which oxazoline-based ligand would give superior control over a wide range of cycloalkenes, and consequently systematic screening appeared to be the best method of choosing a particular catalyst for a given alkene. High levels of enantioselectivity were obtained for simple cyclopentene, cyclohexene, and cycloheptene rings. However, for larger rings such as cyclooctene, little stereocontrol was observed. Andrus also examined the allylic oxidation of two open-chain alkenes (allylbenzene and 1-octene) and found that although the facial preference was no different than for the cyclic cases, the enantioselectivity was substantially lower. Surprisingly for these substrates, higher levels of enantioselectivity were obtained at higher temperature. Pfaltz further investigated the regioselectivity of this process by allylic oxidation of 1-methylcyclohexene (**9**) and found as expected the formation of a secondary radical was preferred. However, the regiocontrol was rather poor leading to a regioisomeric mixture of benzoates **10a–c** with moderate to good enantioselectivity (Scheme 3).

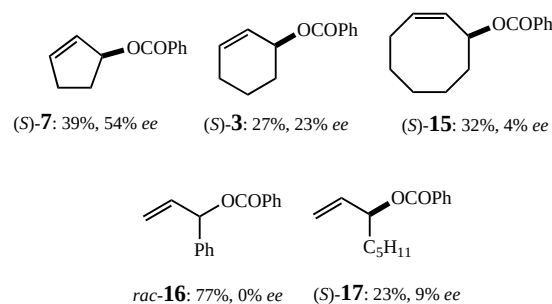
Some success was also reported for proline and proline derived ligands.^[5–7] Muzart and co-workers probed the activity of a series of copper(i) catalysts with proline **11** or proline-like ligands **12–14** for the oxidation of cyclohexene (**1**). They have clearly shown that there is a correlation between the coordinating ability of the chiral ligand (to the copper atom) and the enantioselectivity observed. By lowering the σ -donor ability of the nitrogen atom through delocalization (into either an *exo*- or *endo*-carbonyl group) in **12** and **13**, the facial selectivity was lost (Scheme 4). The use of **14**, the simple *N*-methylated derivative of (*S*)-proline, resulted in the return of some facial control, although rather intriguingly this was in the opposite sense to the natural amino acid **11**. A series of cyclic and acyclic alkenes were systematically screened against the optimum conditions found for **11**, as the chiral

ligand. In keeping with the findings of the Pfaltz and Andrus groups it was found that the more conformationally rigid the alkene the better the stereocontrol. Consequently cyclic alkenes gave better control than open-chain alkenes (Scheme 5). Further investigations into the rate of addition of the perester to the reaction mixture and the nature of the active catalyst indicated that a CuL_2 complex was largely responsible for the activity and optimum conditions were found to require the oxidant, $PhCO_3tBu$, to be added in a single portion.^[5] Investigations were also made into the effect of the structural nature and acidity of the capturing carboxylic acid (RCO_2H). For strong organic acids, such as CF_3CO_2H no oxidation occurred, whereas sterically demanding acids such as pivalic acid ($R = tBu$), did provide the highest levels of asymmetric induction (52% *ee*) albeit with very low yield (6.5%).



Scheme 4. Yield and enantioselectivity in the production of **3** by the allylic oxidation of **1** using proline-based ligands **11–14**. a) Cu_2O (2 mol %), chiral ligand **11–14**, $PhCO_3tBu$ (70% aq.); *Boc* = *tert*-butoxycarbonyl.

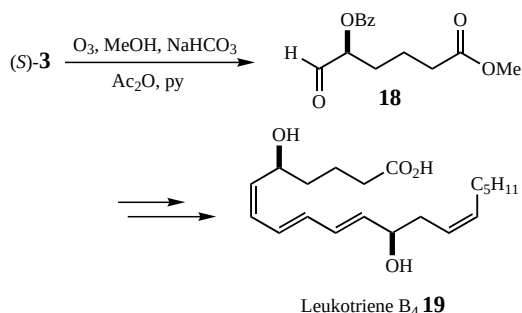
Feringa and co-workers have investigated the use of substituted proline variants on this oxidation procedure using **1** as a substrate and propionic acid as the capturing carboxylic acid.^[7] They have shown that the addition of an excess of copper bronze (or zinc) as a co-reductant was required for high yields and enantiomeric excesses, in addition to excess **11**. This procedure was also very sensitive to the copper salt with copper(ii) acetate proving to be most effective; a structurally well defined bis(aqua)-(*S*)-prolinato- Cu^{II} complex $[Cu^{II} \cdot (H_2O)_2 \cdot (S)\text{-proline}]$ was found to behave in an



Scheme 5. The yields and enantiomeric excesses for a variety of synthesized allylic benzoates **3, 7, 15–17**.

identical manner to the in situ prepared catalyst. (*S*)-Proline (**11**) was similarly found to be the most reliable ligand giving better facial control; any attempt at protecting the nitrogen lone pair only served to lower the enantiomeric excess although when a strained four-membered azetidine-2-carboxylic acid was used, moderate levels of enantioselectivity returned. Feringa has also shown that the yield of cyclohexenyl propionate was affected by the structural nature of the perester oxidant although the enantiomeric excesses were much less influenced. This presumably indicates that the rate of perester decomposition has to fit smoothly and efficiently into the catalytic cycle otherwise the yields are compromised.

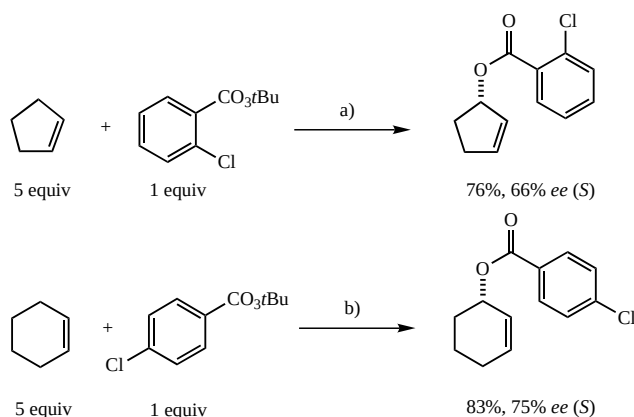
Subsequent studies have developed these initially successful ligand sets. Structural modifications in ligand architectures and peracid oxidant have led to significant improvements, both in terms of yield and enantiomeric excess. Andrus probed the effect of using electron deficient peresters in the presence of the bis(oxazoline) ligands previously reported. Weakening of the perester bond would be expected to lead to more rapid bond homolysis with concomitant increase in the rate of formation of copper(II) benzoate and *tert*-butoxy radical.^[8] This strategy was successfully applied to the synthesis of oxoester **18**, a formal intermediate in the synthesis of leukotriene B₄ (Scheme 6). In line with previous reports this methodology was found to be sensitive to the nature of the copper(I) salt, the ligand structure, and the perester employed (Scheme 7). In both cases copper(I) hexafluorophosphate



Scheme 6. A formal synthesis of Leukotriene B₄; py = pyridine.

(CuPF₆) was found to be the salt of choice, which presumably indicates that a more Lewis acidic copper complex leads to a higher degree of stereocontrol because of more efficient binding of the intermediate allylic radical in the stereochemistry-determining step. The choice of perester and ligand were also found to be important for optimum yield and enantiomeric excess, however, as in previous studies systematic screening of both reagents was required.

Andrus and co-workers have further probed the effect of additional stereogenicity in the bis(oxazoline) backbone by employing the diastereoisomeric biaryl atropisomeric oxazolines **20**, (Scheme 8).^[9, 10] The wider bite angle between the two nitrogen atoms and the copper center was expected to improve selectivity for both ligands, by forcing the reacting allyl and benzoate groups

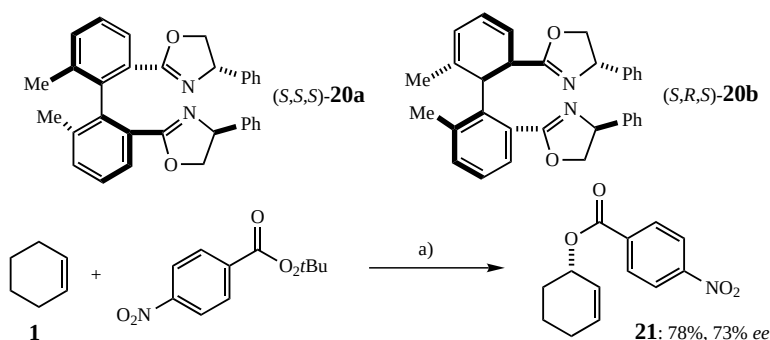


Scheme 7. Allylic oxidation of cyclopentene and cyclohexene using bis(oxazoline) ligands **5**: a) CuPF₆ (15 mol %), chiral ligand **5b**, MeCN, −20 °C, 7 days; b) CuPF₆ (15 mol %), chiral ligand **5c**, MeCN, −20 °C, 7 days.

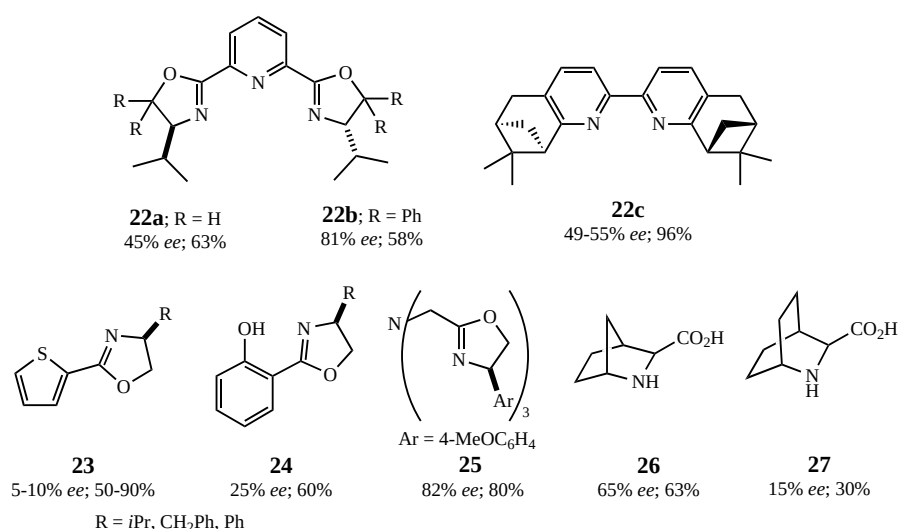
closer together in **4**. However, it was found that the (*S,S,S*)-oxazoline **20a** gave much better stereocontrol than the related (*S,R,S*) stereoisomer **20b** (76 % yield, 0 % *ee*). This trend does not appear to be limited to the phenyl substituent within the oxazoline framework of **20**, although the phenyl substituent in **20a** gave better facial control for cyclohexene than either a benzyl or *tert*-butyl substituent. In contrast for cyclopentene the presence of a benzylic group proved to be slightly superior. The absolute stereochemistry in the product allylic ester was remarkably predictable; the (*S*)-configuration being formed exclusively.

Singh and DattaGupta have also extended this methodology by using the tridentate pyridine-based oxazoline **22a** and **22b**.^[11] The stereoselectivity was shown to be better using the more substituted oxazoline **22b** for the benchmark cyclohexene oxidation (63 % yield, 81 % *ee*). The optimized reaction conditions, involving the in situ reduction of copper(II) using hydrazine, followed by the addition of 4 Å molecular sieves, were also effective for cyclopentene (70 % yield, 59 % *ee*). The more flexible cycloheptene and cyclooctene gave poor levels of asymmetric induction, although the facial control appeared to be independent of the ring size of the starting alkene (Scheme 9).

Kočovský and co-workers have recently found that a bipyridine based ligand **22c** gave better control for larger cycloalkenes (e.g., cycloheptene (62–75 % *ee*)) than smaller



Scheme 8. Enantioselective allylic oxidation of **1** using an atropisomeric oxazoline **20**: CuPF₆ (10 mol %), chiral ligand **20a** (10 mol %), MeCN, −20 °C, 5 days.



Scheme 9. Yields and enantiomeric excesses for the enantioselective oxidation of cyclohexene.

carbocyclic rings such as cyclopentenes (49% *ee*) and cyclohexene (49–55% *ee*) (Scheme 9).^[12]

Feringa and Zondervan have also investigated the heteroatom topography of a limited series of substituted oxazolines to probe the effect of the nature of the donor atom within the ligand (Scheme 9). Although the softer oxazoline ligand **23**, gave high conversions, the enantioselectivity was low.^[13] Slightly higher facial control was observed for the harder phenolic donor **24**, which may indicate that a more strongly coordinated transition state for the copper(III) intermediate **4**, leads to higher stereocontrol, although conversions were only moderate. In the same study the allylic oxidation of cyclohexene by copper(II) (*S*)-proline based complexes was investigated. Moderate enantiocontrol (up to 60% *ee*) was observed using the naturally available **11** as the chiral ligand. Surprisingly the addition of an additive, anthraquinone, resulted in an increase in the facial selectivity, but only when *tert*-butyl hydroperoxide was used as the oxidant. Using the softer ligand (*S*)-thiaphene **23** caused both the yield and stereoselectivity to be reduced, as did all their other ligand modifications. A negative nonlinear effect was observed for (*S*)-proline itself, that was interestingly reversed to a positive nonlinear effect in the presence of anthraquinone. Although no definitive conclusion as to the nature of the active catalyst was made, it does seem clear from this limited study that a fundamental change in mechanism or structure of the catalyst occurs on addition of the anthraquinone additive.

In spite of Feringa's assertions that modification of the (*S*)-proline skeleton would not result in improved catalyst performance,^[13] Andersson and Södergren investigated the effect of introducing a rigid cyclic framework in ligands based on the proline skeleton using a diastereoselective Diels–Alder approach, **26** and **27** (Scheme 9).^[14] The bicyclic [2.2.1] ligand **26** gave better stereocontrol than the original (*S*)-pro-

line in the allylic oxidation of cyclohexene (63% yield, 65% *ee*), however, simple addition of an extra methylene unit in **27** caused a dramatic reduction in the facial control.

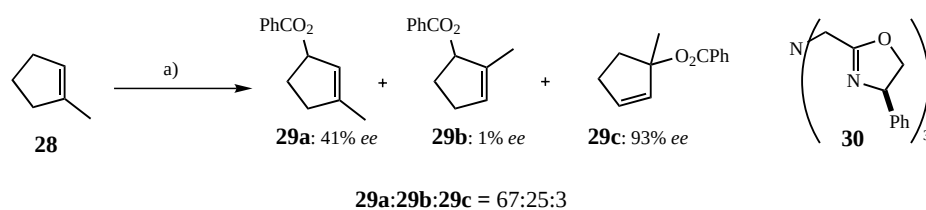
Following his initial report,^[4] Katsuki has further demonstrated the C₃-symmetric oxazoline **30** (Scheme 10) to be an extremely effective ligand for the stereoselective oxidation of cyclopentene. During this study it was discovered that the enantiomeric excess of the product, such as benzoate **3**, decreased as the reaction time became longer.^[15] The simple addition of 4 Å molecular sieves to the acetone reaction mixture suppressed this racemization leading to 83% yield and 76% *ee*. Reduction in temperature was further shown to increase the

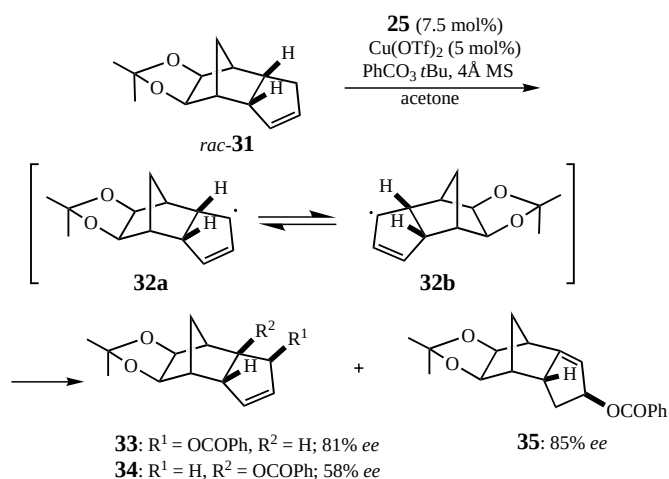
enantioselectivity (up to 93% *ee*) although the yields dropped dramatically. These optimized conditions were also shown to be effective for other cyclic alkenes, although the selectivity and turnovers were inferior. Although, recently, the selectivity has been improved using the related oxazoline **25** (Scheme 9).

The regioselective oxidation of 1-methylpentene (**28**), in keeping with the earlier findings of Pfaltz and co-workers,^[2] produced three positional isomeric allylic benzoates **29a–c**, with dramatically different enantiomeric excess (Scheme 10). The enantioselectivity was evidently dependent on the structural nature of the intermediate allylic radical. No oxidation of the allylic methyl C–H unit was observed.

Katsuki and Kohmura have also elegantly shown that this procedure can be extended towards the deracemization of racemic substituted cyclopentenes **31** to give the enantiomerically enriched allylic benzoates **33** (81% *ee*), **34** (58% *ee*), and **35** (85% *ee*) in an overall 38% yield (Scheme 11).^[16, 17] The reaction must proceed via an interconverting pair of enantiomeric allylic radicals **32a** and **32b**. The C₃-symmetric tris(oxazoline) **30** gave the best facial control, whereas, the more common C₂-symmetric based oxazoline ligand **5** gave lower levels of control.

Currently, there are a only limited number of applications of this methodology, primarily because of the infancy of this asymmetric reaction.^[8] In view of the potential utility and versatility of this transformation within organic synthesis, it seems likely that further applications will soon appear. Before this can occur, a generic catalytic system is clearly required. Presumably this will follow on from better mechanistic

Scheme 10. Regioselective oxidation of **28**: a) Cu(OTf)₂–**30** (5 mol %), PhCO₂tBu, acetone, 0 °C.



Scheme 11. The deracemization of alkene *rac*-**31** using an allylic oxidation strategy. Ratio **33**:**34**:**35** = 57:24:19; yield 38%; MS = molecular sieves.

understanding of the complex reaction and the role of particular additives. In addition, some general problems need addressing, such as the requirement for high alkene concentrations, the long reaction times and apparent substrate restrictions before the potential of this reaction can be truly realized.

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Encapsulated, Sandwiched, or Sticking Out: Closed-Shell Interactions of d¹⁰ Metal Centers with Thallium(I)

Lutz H. Gade*

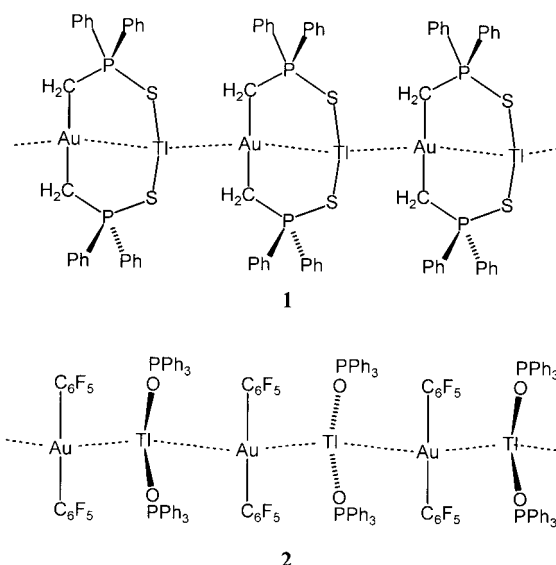
Closed-shell metal–metal contacts are ubiquitous in the structural chemistry of the heavy, late transition metal and p-block elements.^[1] The attractive interaction between these heavy-metal centers in molecules and solids, which determines their structures, has early on led to the notion of significant but essentially noncovalent bonding. Phenomenologically labeled first as “aurophilic” for gold(I) compounds,^[2] later more generally as “metallophilic” for the attractive forces between d⁸, d¹⁰, and s² metal centers,^[1, 3] the physical interpretation of this type of interaction initially remained disputed. The work of Pykkö and his co-workers has only recently led to a clarification of the nature of these “metallophilic” interactions. As was shown in a series of detailed theoretical studies, they represent a correlation effect which at long intermetallic distances is essentially a “classical” dispersion force.^[4, 5] This dispersive (van der Waals) attraction is frequently reinforced by electrostatic components as well as a charge–transfer type dispersive contribution.^[6]

Monovalent gold and thallium, possessing d¹⁰ and s² configurations and thus representing the closed-shell species referred to above, mark the two extremes of metallophilic attraction. The interaction between Au^I centers may be comparable to strong hydrogen bonds (up to 46 kJ mol^{−1}) and has enabled, for instance, the spectacular gold “clustering” reported by Schmidbaur’s group.^[2] On the other hand, the relative weakness of the attraction between Tl^I centers, estimated to lie below 20 kJ mol^{−1}, has lent a certain ambiguity to the interpretation of the the solid-state structures of this element.^[7]

Whereas the “metallophilic” attraction between d¹⁰ metal centers is enhanced by the relativistic contraction of the s- and p-electron shells (along with the destabilization of the d-orbitals),^[4] the relativistic contribution to the closed-shell interaction between s² metal centers such as Tl^I actually weakens their dispersive attraction.^[8] It is thus not surprising that the observation of “metallophilic” attraction between thallium(I) centers strongly depends upon the absence of

competing intra- and intermolecular interactions, such as electrostatic attraction or repulsion or the van der Waals interactions with aromatic rings.^[9] However, combining d¹⁰ metal centers and Tl^I has led to a series of stable adducts, the metal–metal contacts for some being additionally supported by electrostatic attraction.

The first example of such a thallium(I)–d¹⁰ metal interaction in the infinite chains of [AuTl(mtp)]_∞ **1** (mtp = CH₂P(S)Ph₂[−]; Scheme 1), which are based on both dispersive

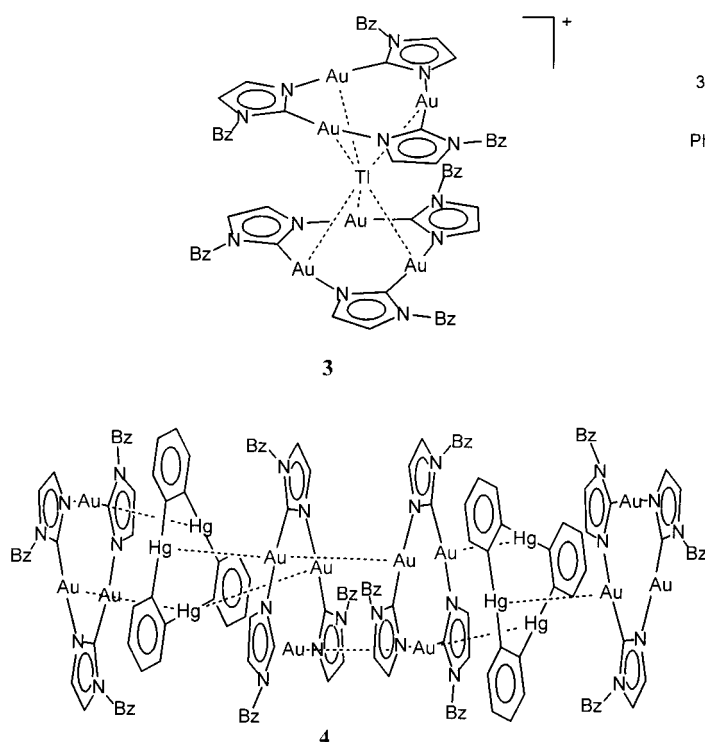


Scheme 1. The Au–Tl chains of [AuTl(mtp)]_∞ (mtp = [CH₂P(S)Ph₂][−]) **1** and [Tl(OPPh₃)₂][Au(C₆F₅)₂] **2**.

and electrostatic (“acid–base”) attraction between the metal centers, was reported by Fackler et al. more than a decade ago.^[10] Recently, Laguna and his co-workers found a related metal chain structure **2** derived from [Tl(OPPh₃)₂]⁺ and [Au(C₆F₅)₂][−].^[11] Whereas neither of the individual molecular components are emissive, the heterometallic aggregate displays a characteristic luminescence, similar to that of Fackler’s complex **1**. The importance of the metallophilic aggregation for the photophysical properties of the compounds in question is a central aspect of current research in this area and has been reviewed previously.^[12]

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The type of aggregation through dispersive and electrostatic (Lewis acid–base) attraction observed in the metal chains discussed above has led to spectacular sandwich structures if planar trinuclear gold(I) complexes are combined with Ti^+ salts. The cyclic trinuclear complex $[\text{Au}(\mu\text{-C}^2, \text{N}^3\text{-bzim})]_3$ ($\text{C}^2, \text{N}^3\text{-bzim}$ = 1-benzylimidazolate) forms sandwich “clusters” **3** in the presence of Ti^+ , in which the thallium ions are located between the planar units and form contacts with six AuI centers in a distorted trigonal-prismatic coordination (Scheme 2).^[13] The sandwich units themselves further

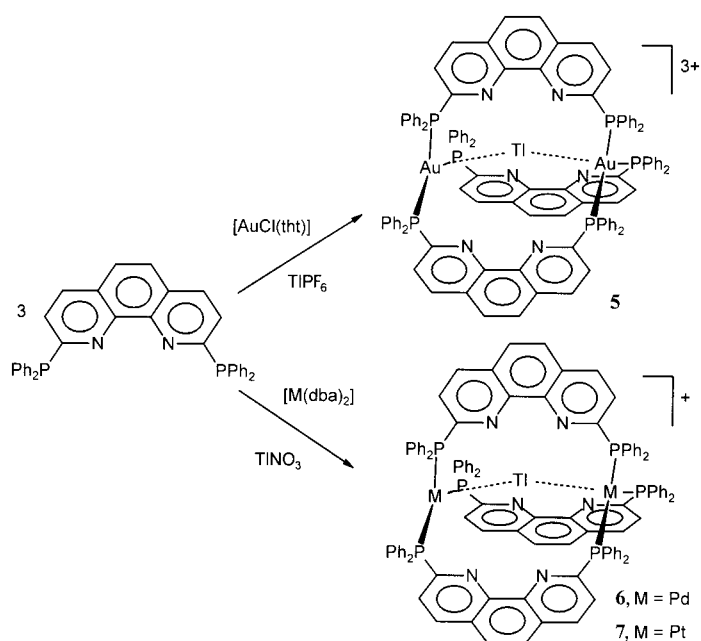


Scheme 2. The $(\text{Au}_3)_2\text{Ti}$ sandwich structures in $[\text{Ti}\{\text{Au}(\mu\text{-C}^2, \text{N}^3\text{-bzim})\}_3]^+$ **3** and the columnar aggregate of $[\{\text{Au}(\mu\text{-C}^2, \text{N}^3\text{-bzim})\}_3\{\text{Hg}(\mu\text{-C}_6\text{F}_4)\}_3]^+$ **4**.

aggregate through Au–Au interactions to form infinite columnar structures obeying an $\text{Au}_3\text{-Ti-Au}_3\text{-Au}_3\text{-Ti-Au}_3$ stacking pattern. A related stacking pattern, based on $d^{10}\text{-d}^{10}$ attractions, was observed upon co-crystallization of $[\text{Au}(\mu\text{-C}^2, \text{N}^3\text{-bzim})]_3$ and the trinuclear mercury complex $[\text{Hg}(\mu\text{-C}_6\text{F}_4)]_3$.^[14] In the columnar structure found in a single crystal X-ray diffraction study of **4**, Hg–Au distances of as short as 3.24 Å indicate metallophilic attraction, which is additionally supported by the electrostatic attraction of the metal-basic (electron-rich) gold triangle and the metal-acidic (electron-poor) trimercury unit (Scheme 2). However, it is thought that these sandwich-type aggregates dissociate in solution and are thus only observed in the crystal, as is the case for the heterometal chains discussed above.

Catalano and co-workers have now shown that Ti^+ ions may bind fairly strongly to d^{10} metal centers and that this type of metal–metal contact pertains in solution. In a series of metal-binding experiments of a new class of metallocryptands, they found a facile uptake and incorporation of in particular Ti^+ . In the host molecules a binding cavity is created by linking two

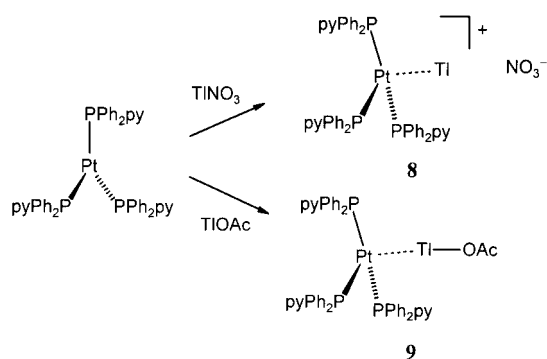
three-coordinate Au^{I} , Pd^0 , or Pt^0 complex fragments with three 2,9-diphosphanylphenanthrolines (“ P_2phen ”) molecules acting as bridging ligands (Scheme 3).^[15–17]



Scheme 3. Aggregation of the metallocryptates $[\text{Ti}\{\text{Au}_2(\text{P}_2\text{phen})\}_3]^{3+}$ **5**, $[\text{Ti}\{\text{Pd}_2(\text{P}_2\text{phen})\}_3]^{3+}$ **6**, and $[\text{Ti}\{\text{Pt}_2(\text{P}_2\text{phen})\}_3]^{3+}$ **7** (tht = tetrahydrothiophene, dba = dibenzylideneacetone).

It is remarkable that Ti^+ enters the $[\text{Au}_2(\text{P}_2\text{phen})_3]^{2+}$ cage and forms short Au–Ti contacts in **5**, in spite of the positive charges of the metal centers in both the host molecule and the guest ions. This rules out a simple electrostatic component in this attraction, which is thought to be entirely due the “metallophilic” van der Waals attraction between the metal centers. The repulsion between ionic components only becomes a destabilizing factor on going from monovalent thallium to the isoelectronic divalent lead. In order to incorporate the Pb^{2+} ions, the neutral host cages $[\text{Pd}_2(\text{P}_2\text{phen})_3]$ and $[\text{Pt}_2(\text{P}_2\text{phen})_3]$ were employed, in which the Pd^0 and Pt^0 centers actually bear relatively high electron densities at the metal center, in part located above and below the L_3M planes.^[17]

While the complexation of Ti^+ within the cryptand cages may at first sight appear to favor the relatively strong binding and may obscure the the actual strength of the individual metal–metal interactions, a very recent study of the reaction of the three-coordinate mononuclear platinum(0) complexes $[\text{Pt}(\text{PPh}_2\text{py})_3]$ with thallium(I) salts (Scheme 4) led to the isolation and structural characterization of the thallium adducts **8** and **9** containing direct Pt–Ti bonding in the solid (Figure 1).^[18] In fact, ^{205}Tl and ^{195}Pt NMR studies in solution have established the stability of these heterometallic complexes in solution, while fast-atom bombardment (FAB) mass spectrometry established their integrity in the gas phase. That there is significant bonding interaction between Ti and Pt in these molecules is also evident from the striking changes of their chemical properties upon coordination of the thallium cations to the d^{10} metal centers. While the triphosphanepla-



Scheme 4. Formation of the Tl–Pt complexes **8** and **9** (py = pyridine).

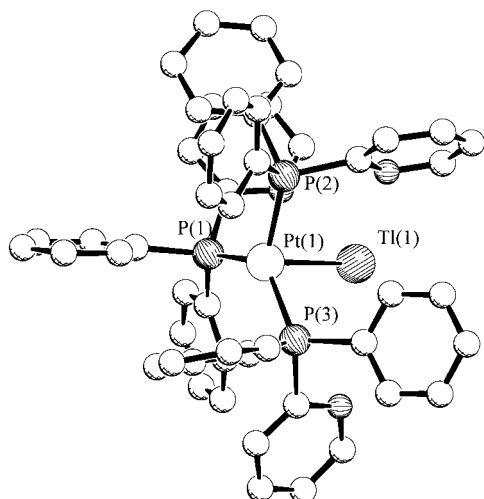


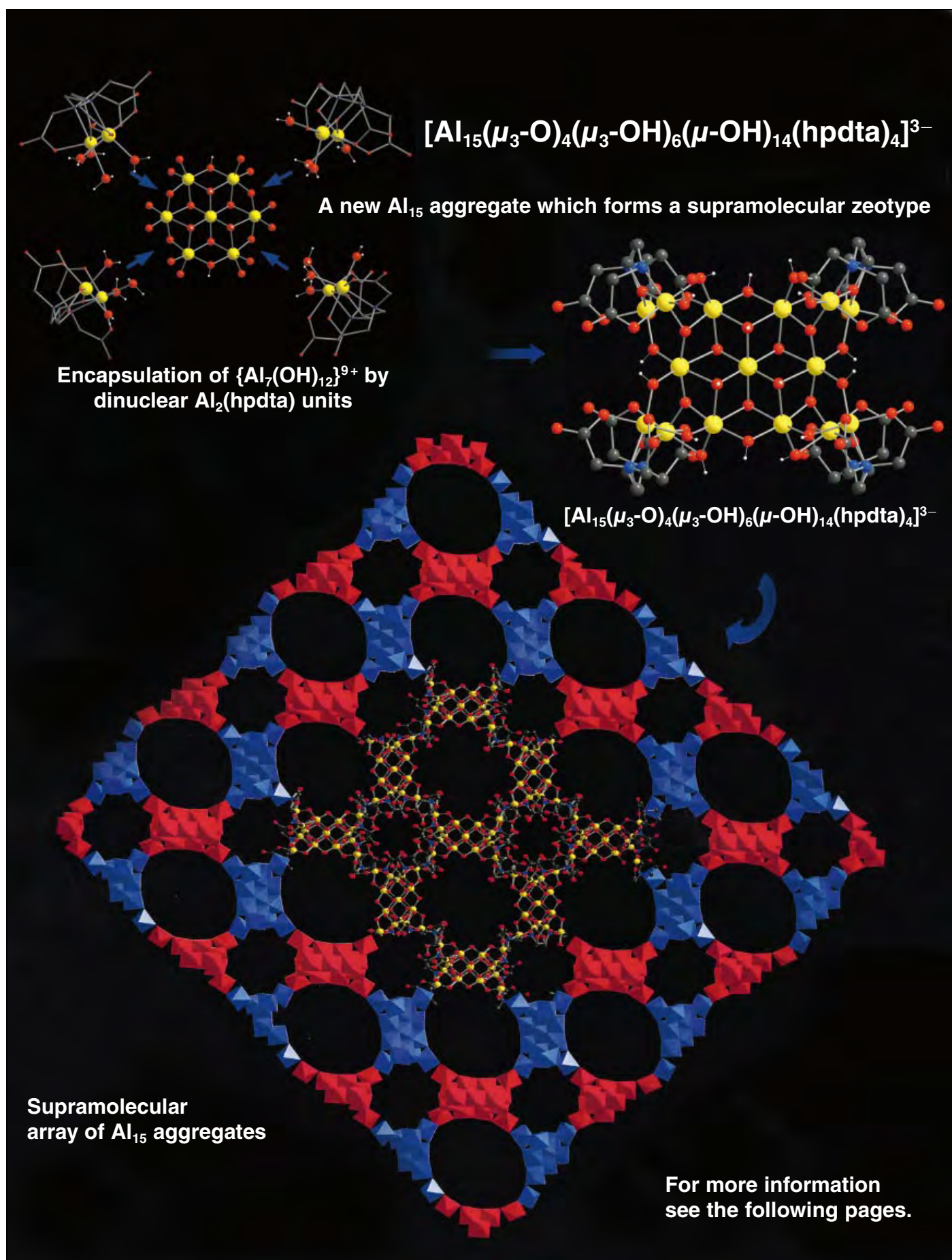
Figure 1. Molecular structure of $[\text{Tl-Pt}(\text{PPh}_2\text{py})_3]^+$ in **8**.

tinum(0) compounds are highly susceptible to oxidation by O_2 , this is not the case for the heterodinuclear derivatives. Further, in contrast to the trigonally coordinated platinum complexes, **8** and **9** are nonemissive.

This formation of stable adducts through metallophilic bonding of $d^{10}s^2$ ions such as Tl^+ to palladium(0) and platinum(0) makes one wonder about the generality of this phenomenon. It was therefore of interest to find out whether single mercury(0) atoms (which are isoelectronic with Tl^+) bind in a similar way to a tris(phosphane)platinum complex. Catalano and co-workers have very recently reported such an inclusion of a single mercury atom within their metallocryptand cage.^[19] This exciting observation adds a new aspect to the classical experiments on the clustering of mercury metal with Pt^0 fragments bearing isocyanide, phosphane, or CO ligands reported by the groups of Yamamoto and Venanzi almost two decades ago.^[20] It may also lead us to reconsider the general suitability of mercury addition to Pt and Pd catalysts in a standard experiment to distinguish molecular from colloidal catalysis.^[21] Strong adduct formation of a closed-shell atom or ion with a zerovalent mononuclear complex is expected to at least modify the activity of the catalytic system.

It will be interesting to see whether the metallocryptand approach developed in Catalano's group will be extended to include the complex formation of more inert closed-shell "guests" such as heavy noble-gas atoms.^[22]

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**[Al₁₅(μ₃-O)₄(μ₃-OH)₆(μ-OH)₁₄(hpdta)₄]³⁻—
A New Al₁₅ Aggregate Which Forms a
Supramolecular Zeotype****

Wolfgang Schmitt, Elham Baissa, Alexander Mandel,
Christopher E. Anson, and Annie K. Powell*

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

The chemistry of aluminum(III) in aqueous solution is largely driven by the high charge density of the small Al³⁺ ion. This property leads to extensive hydrolytic processes and this has been utilized in the preparation of a number of aggregated oxyhydroxy species containing from thirteen to thirty aluminum centers.^[1–4] Such cluster aggregates are of interest both in the investigation of Al^{III} hydrolysis, which is relevant to environmental and biological situations where the metal ion is present, and also as a means of producing small and reactive hydroxide-rich aggregates which might be useful for promoting or even catalyzing hydrolytic reaction chemistry. Amongst the examples of purely inorganic aggregates is the Al₁₃ cluster [AlO₄Al₁₂(OH)₂₄(H₂O)₁₂]⁷⁺,^[1] which has the Keggin ion structure, and the related and largest Al^{III} aggregate so far crystallographically characterized [AlO₄Al₁₂(OH)₂₄(H₂O)₁₂]₂–[Al₄(OH)₈(H₂O)₆]¹⁸⁺.^[2] There are two further, related Al₁₃ species, the purely inorganic [Al₁₃(OH)₂₄(H₂O)₂₄]¹⁵⁺ and the cluster formed in the presence of the ligand heidi (H₃heidi = N(CH₂COOH)₂(CH₂CH₂OH)) [Al₁₃(OH)₁₈(heidi)₆(H₂O)₆]³⁺.^[3, 4] In these two compounds the structure of the Al-oxyhydroxide core corresponds to the brucite-type structure. This type of structure has also been observed in the Fe₁₉ aggregates formed with heidi and the related Me-heidi and Et-heidi ligands which have methyl and ethyl groups, respectively, on the α-C atom of the hydroxyethyl moiety.^[5, 6] The encapsulation of such core aggregates in organic shells offers the possibility of modifying packing arrangements through changes to the organic part and also allows for the preparation of hybrid materials where regions with different polarities can be incorporated into the same structure. For example, the purely inorganic Al₁₃ clusters crystallize with a dense packing that optimizes the hydrogen-bonding interactions and gives a substance with a density of 1.78 g cm^{–3}, whereas the hybrid Al₁₃-heidi clusters crystallize in a trigonal space group; the molecules are hexagonally packed in layers which stack into columns with parts of the heidi ligands forming spacers between the layers. This arrangement gives a relatively open structure with a density of only 1.35 g cm^{–3}. Another way of viewing such Al₁₃ aggregates is to take the basic close-packed brucite core structure of

{Al₇(OH)₁₂}⁹⁺ and to regard the encapsulating portion as consisting of a ring of six Al-ligand units, each of which is connected to the core by double bridges containing oxygen atoms: in the case of the inorganic “naked” aggregate these are both hydroxides, whilst for the Al-heidi compound there is one hydroxide plus one alkoxide bridge from the hydroxyethyl side chain of the ligand.

We find that when we use the ligand hpdta (H₅hpdta = HOCH₂[CH₂N(CH₂COOH)₂]₂), which has two iminodiacetic acid moieties linked by a 2-hydroxypropane group, the dinucleating alkoxide side chain is now placed between two iminodiacetate units and leads to a different arrangement of the Al-ligand units on the periphery. In this case hydrolytic reactions lead to the isolation of Al₁₅ cluster aggregates. Single-crystal structure analyses on two examples, **1a** and **2**, reveal that the cluster anions, [Al₁₅(μ₃-O)₄(μ₃-OH)₆(μ-OH)₁₄(hpdta)₄]³⁻ possess the same type of core as the Al₁₃ structures, but this is now captured by four dinuclear {Al₂(hpdta)} units in which the Al^{III} centers are bridged by the alkoxide function of the ligand. One aluminum ion of each unit is connected to the core by two hydroxide bridges, the other by one hydroxide and a μ₃-oxide ligand. The latter case corresponds to the deprotonated form of one of the peripheral hydroxides of the inner {Al₇(OH)₁₂}⁹⁺ core (Figure 1).

This different ligand coordination at the periphery of the aggregates combined with a templating effect from the organic base used in the hydrolysis leads to a packing arrangement in which the aggregates are arranged in such a way as to create two types of channel running through the structure parallel to the *c* axis (Figure 2). We find that this overall structure can be reproduced using both piperazine (**1a**) and ethylenediamine (**2**) as the templating hydrolyzing base. The structure of **1a** is better defined in terms of the solvent content of the large channels and we confine our attention to this for further discussion. The smaller channels are mainly lined with noncoordinated oxygen atoms of the hpdta ligands and contain the countercations, which appear to act as templates for the observed structure. An oxonium cation lies at the center of a distorted square of such carboxylate oxygen atoms, each of which originates from a different cluster unit. At any one time, the oxonium cation can form hydrogen bonds to three of these four oxygen atoms, and dynamic disorder is presumably in operation here.

Alternating with the H₃O⁺ ions in these smaller channels are piperazinium ions (pipzH₂⁺); the N-H protons of these piperazinium ions are also involved in hydrogen bonding to carboxylate oxygen atoms from different clusters. The cations thus play an important role in maintaining the supramolecular structure. The larger channels are principally lined with arrays of hydroxyl groups from the cluster cores but there are also carboxylate oxygen atoms and methylene groups from the peripheral ligands on the cluster present. These larger channels are filled with neutral water and base molecules. In this way we can see how the incorporation of an organic ligand into the outer shell of the aggregate allows for the separation of the structure into areas of different polarities.

Overall the Al₁₅ units pack to form a supramolecular array which reproduces aspects of the structural features of zeolites such as Linde A and other such molecular sieves. If we

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[**] H₅hpdta = HOCH₂[CH₂N(CH₂COOH)₂]₂.

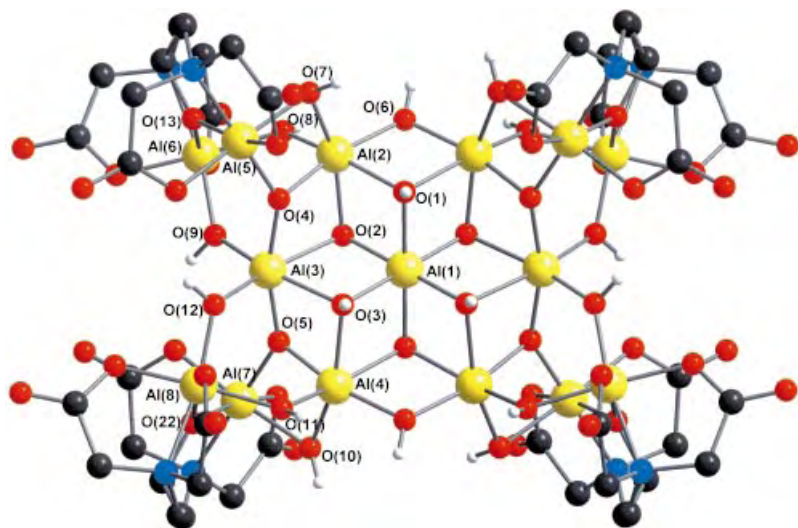


Figure 1. The supramolecular structure of the cluster ion $[\text{Al}_{15}(\mu_3\text{-O})_4(\mu_3\text{-OH})_6(\mu\text{-OH})_{14}(\text{hpda})_4]^{3-}$ in **1a**. The hydrogen atoms on the peripheral ligands are omitted for clarity. Al–O bond lengths (Al–O–Al angles) are in the ranges: 1.847(3)–2.083(3) Å (92.3(1)–101.7(2)°) for Al–(μ_3 -OH); 1.824(3)–1.969(4) Å (92.5(1)–130.0(2)°) for Al–(μ_2 -OH); 1.753(3)–1.841(3) Å (101.8(2)–142.8(2)°) for Al–(μ_3 -O). The Al–N bond lengths are in the range 2.036(4)–2.116(4) Å.

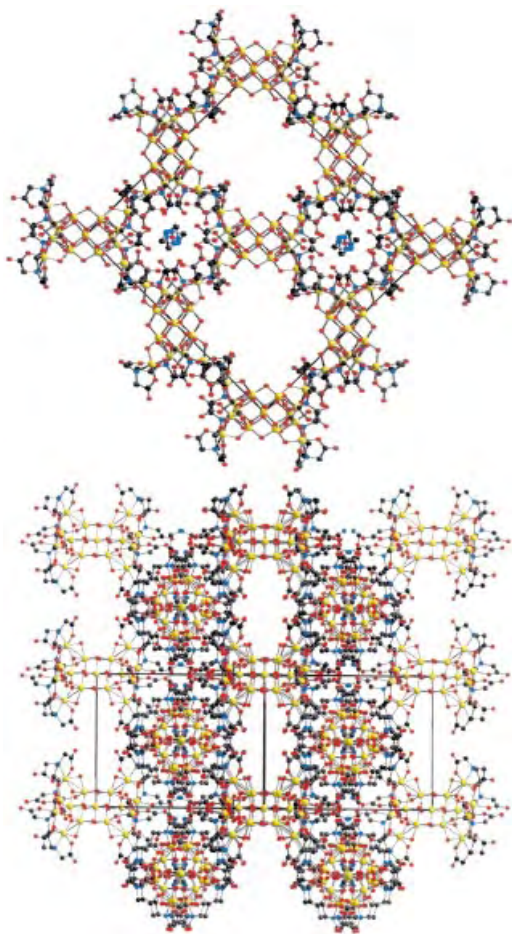


Figure 2. The supramolecular array of the Al_{15} cluster in **1a** (Al yellow, O red, N blue, C black). The protonated base and water molecules in the smaller channels act as a template and stabilize the structure. The solvent and base molecules have been omitted from the larger channels for clarity. The top view is looking down the *c* axis, the lower view is a projection on to [110] and shows the side entrances to the large channels.

examine the size and shape of the larger channels we find these are an average of about 11 Å in diameter and are connected together by cavities running perpendicular with diameters of about 5 Å (Figure 2). The available space within these interlinked larger channels can be calculated as 4494 Å³, or 36.7 % of the total unit cell volume.^[7] In the crystal structure analysis of compound **1a** the solvent and base molecules in the larger channels were relatively well-defined and we were able to assign the electron density to forty-one water molecules and one base molecule per aggregate to give an overall formula of $(\text{pipzH}_2)(\text{H}_3\text{O})[\text{Al}_{15}(\mu_3\text{-O})_4(\mu_3\text{-OH})_6(\mu\text{-OH})_{14}(\text{hpda})_4] \cdot \text{pipz} \cdot 41 \text{H}_2\text{O}$. This assignment takes into account the results of the CHN analysis and also seems reasonable when we look at the hydrogen-bonding interactions between the water molecules and the hydroxy groups of the cluster. Thus, we can readily identify three strongly hydrogen-bonded water molecules per cluster surface which are hydrogen-bonded to further water molecules with the very center of the channels containing twofold

disordered base and water molecules (Figure 3a). Thermal analysis on this compound substantiates this further and shows that by 300 °C all the solvent molecules have been lost from the sample. Beyond this temperature the rest of the organic residues are driven off to give Al_2O_3 .

In the light of the results of the differential thermal analysis (DTA) experiments we decided to investigate the crystal structures of single crystals which had been heated to 150 °C for 4 h and at 200 °C overnight in an oven. The sample which had been heated to 200 °C proved to be extremely hygroscopic and although it was possible initially to observe some very diffuse diffraction spots, the crystal deteriorated too rapidly to allow for the collection of a data set. This result indicates that the structure is capable of taking up solvent molecules extremely readily. The sample which was heated to 150 °C retained its integrity and we were able to collect and analyze a full data set on this (compound **1b**). The structure solution reveals that the overall supramolecular framework structure remains the same, but a significant amount of solvent from the larger channels has been lost (Figure 3). Not surprisingly, it is the less strongly bound molecules in the centers of the channels which have disappeared so that 1 piperazine molecule and about 18 water molecules are lost per cluster from the 1 piperazine and 41 water molecules originally present (Figure 3b).

These results show how it is possible to create supramolecular arrays of aluminum-oxyhydroxy aggregates that display zeotypic structures and properties. The structural similarities to zeotypic systems are even more striking when the structure is viewed in a polyhedral representation (Figure 4). Some of the giant polyoxomolybdate wheels synthesized in the research group of Müller can form supramolecular arrays containing nanoscale channels that are produced by the concentric stacking of the units with the phosphinic acid derived ligands captured within the channels.^[8] In our case it is

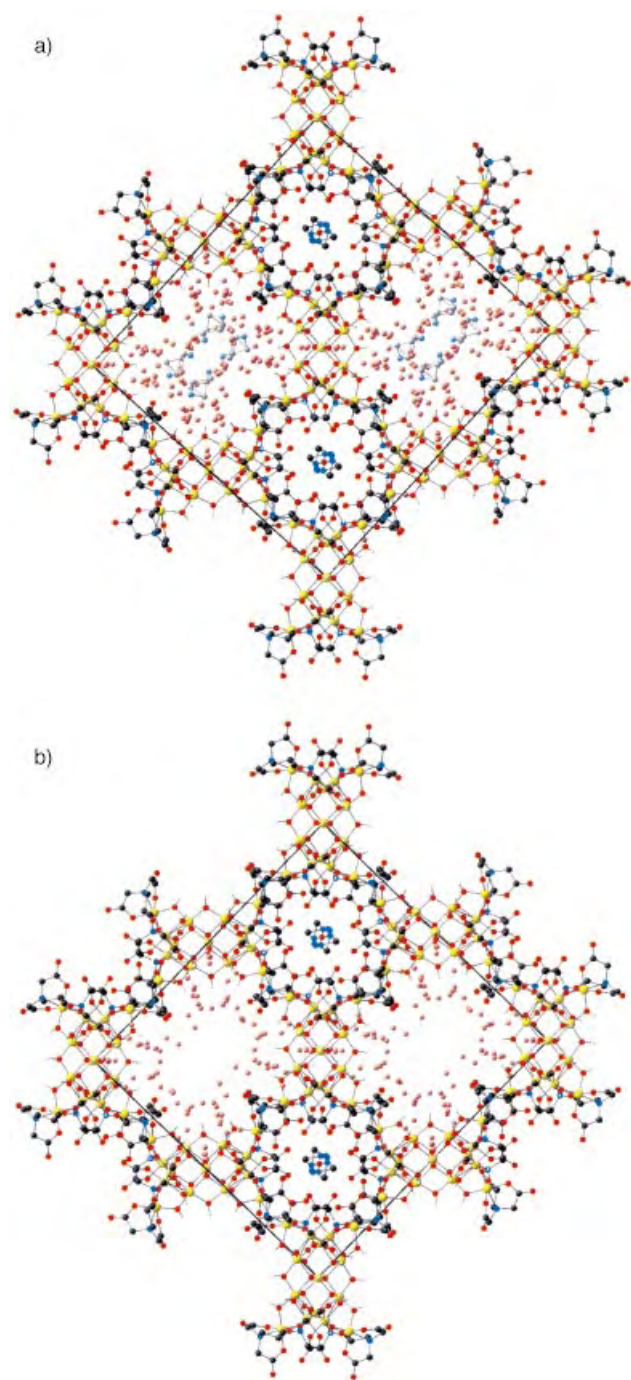


Figure 3. a) The structure of a freshly prepared crystal (colors as for Figure 2). The paler shaded atoms are the solvent and base molecules in the large channels. b) The structure of a crystal heated at 150 °C for 4 h showing the loss of the central molecules from the large channels.

the direct interaction of the oxonium and base-derived cations with the hpdta ligands on the outside of the aggregates which stabilizes the “host” channel structure observed. These interactions are such that the supramolecular structure is maintained even when the guest molecules (water and base) are driven from the large host channels. Of particular relevance for possible future applications is the ability to construct such a hybrid material from well-defined nanoscale alumina-derived building blocks. We are not aware of any

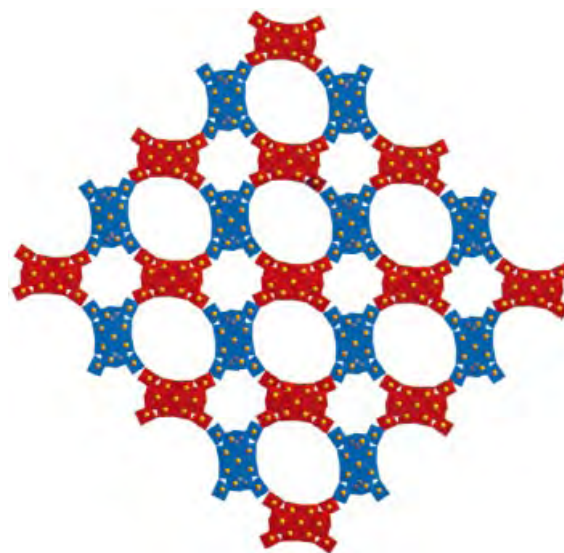


Figure 4. Polyhedral representation of the supramolecular cluster structure looking down the *c*-axis. The blue clusters are in a plane half a unit cell length below the plane containing the red clusters.

similar structure based on hybrid molecular aggregates. Perhaps even more interesting could be the possible hydrolytic activation or catalytic reactions using suitably sized substrates within the hydroxide-rich cavities of this structure; this is an area we are now poised to explore.

Experimental Section

Synthesis: Compound **1** was prepared from 2-hydroxypropane-1,3-diamine-*N,N,N',N'*-tetraacetic acid (*H₃hpdt*a, 1.66g, 5 mmol) dissolved in a mixture of H₂O (30 mL) and an aqueous piperazine solution (1M, 20 mL). The resulting solution was added with stirring to a solution of aluminum nitrate nonahydrate (7.5 g, 20 mmol) dissolved in H₂O (50 mL). The pH was adjusted to 8.85 by the dropwise addition of an aqueous piperazine solution (1M). Addition of dimethylacetamide (100 mL) followed by slow evaporation of the solvent gave colorless crystals of **1** after approximately 8 days. Elemental analysis (%) calcd for C₅₂H₁₆₁Al₁₅N₁₂O₉₂ (which corresponds to the crystallographically determined formulation with the loss of 9 water molecules from the structure): C 21.92, H 5.77, N 5.9; found: C 21.99, H 6.19, N 6.01; IR (KBr): $\tilde{\nu}$ = 3455 (vs,br), 2969 (sh), 1692 (vs), 1650 (vs), 1392 (s), 1085 (m), 1051 (m), 970 (m), 917 (ms), 754 (ms), 641 cm⁻¹ (s).

Compound **2** was prepared in a similar manner to compound **1** but ethylenediamine was used as base.

Thermal analysis: The differential thermal analysis (DTA) and the differential thermogravimetry (DTG) experiments were carried out using a Netzsch STA 409C system. The measurement was performed in an oxygen atmosphere with a flow rate of 50 Lh⁻¹. Sample **1a** (4.7 mg) was heated in a crucible to 1000 °C at a heating rate of 2 Kmin⁻¹. Between room temperature and 300 °C, two overlapping processes corresponding to the loss of solvent of crystallization were observed: 20–140 °C (15 % mass loss, DTG curve centered at ca. 55 °C) and 140–300 °C (11 % mass loss, DTG curve centered at ca. 190 °C). Between 300 and 370 °C, oxidation of the ligands (46 % mass loss, DTG curve centered at ca. 345 °C) in an exothermic process led to the formation of Al₂O₃.

X-ray crystallography for 1a and 1b:^[11] Data were collected at 200 K on a Bruker SMART Apex diffractometer with graphite-monochromated MoK α radiation. Semi-empirical absorption correction with SADABS.^[9] Structure solution by direct methods and refinement with SHELXTL.^[10] **1a**: (C₅₂H₁₇₉Al₁₅N₁₂O₁₀₁ 2706.19 g mol⁻¹): colorless octahedron 0.30 × 0.25 × 0.20 mm, orthorhombic, space group *Pccn*, *a* = 26.8226(14), *b* = 28.2975(15), *c* = 15.5604(8) Å, *V* = 11810.5(11) Å³, *Z* = 4, ρ_{calcd} = 1.68 g cm⁻³, *F*(000) = 6312, μ (MoK α) = 0.260 mm⁻¹. 57679 reflections were

measured ($4.0 < 2\theta < 55.6^\circ$), of which 13778 were unique ($R_{\text{int}} = 0.0862$). Refinement against F^2 to $wR_2 = 0.2438$, $S = 1.068$ (all data), R_1 (9753 reflections with $I > 2\sigma(I)$) = 0.0916. 858 parameters, 18 restraints; all non-H atoms were anisotropic apart from some of the disordered solvent molecules; hydroxy hydrogen atoms were located and refined. The unit cell was close to tetragonal ($P4_2/nm$) but no twinning was observed. **1b**: ($C_{48}H_{133}Al_{15}N_{10}O_{83}$, 2583.34 g mol $^{-1}$): colorless octahedron $0.35 \times 0.30 \times 0.30$ mm, orthorhombic, space group $Pccn$, $a = 26.871(3)$, $b = 28.001(3)$, $c = 15.5309(17)$ Å, $V = 11686(2)$ Å ^{3} , $Z = 4$, $\rho_{\text{calcd}} = 1.47$ g cm $^{-3}$, $F(000) = 5400$, $\mu(\text{MoK}\alpha) = 0.238$ mm $^{-1}$. 56757 reflections were measured ($4.2 < 2\theta < 56.1^\circ$), of which 13542 were unique ($R_{\text{int}} = 0.0733$). The crystal quality was significantly poorer than for **1a**. Refinement against F^2 to $wR_2 = 0.3459$, $S = 1.101$ (all data), R_1 (9859 reflections with $I > 2\sigma(I)$) = 0.1237. 776 parameters, 10 restraints; all non-H atoms in the cluster and counterions were anisotropic. Some disordered solvent waters were assigned partial occupancies.

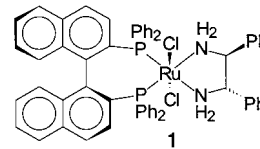
Crystal data for **2**: ($C_{38}H_{84}Al_{15}N_{24}O_{74}$; 2706.19 g mol $^{-1}$): colorless octahedron $0.14 \times 0.07 \times 0.06$ mm, tetragonal, space group $P4_2/nm$, $a = 27.979(3)$, $c = 15.623(2)$ Å, $V = 12230.1(24)$ Å ^{3} , $Z = 4$, $\rho_{\text{calcd}} = 1.47$ g cm $^{-3}$, $F(000) = 5548$, $\mu(\text{MoK}\alpha) = 0.230$ mm $^{-1}$. Data were collected at 293 K on a Rigaku R-Axis IIC area detector diffractometer with graphite-monochromated MoK α radiation. 56705 reflections were measured ($4.1 < 2\theta < 50.8^\circ$), of which 5737 were unique ($R_{\text{int}} = 0.2335$). Structure solution by direct methods; refinement against F^2 (SHELXTL^[10]) to $wR_2 = 0.1886$, $S = 1.125$ (all data), R_1 (2450 reflections with $I > 2\sigma(I)$) = 0.0604. 484 parameters; all non-H atoms in the cluster and counterions were anisotropic. The solvent molecules were heavily disordered, and only those directly H-bonded to the cluster could be modeled realistically; the solvent content is likely to be similar to that in **1a** and the parameters given here only refer to the atoms which were located during the refinement.

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Noyori's Hydrogenation Catalyst Needs a Lewis Acid Cocatalyst for High Activity**

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The asymmetric hydrogenation of simple ketones^[1] in isopropyl alcohol by using *trans*-RuCl $_2$ [(*S,S*)-binap][(*S,S*)-dpn] **1** (binap = [1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane)]); dpn = diphenylethylenediamine), an excess of an inorganic base, and 10–50 bar H $_2$ at 30–60°C is remarkable in several respects: quantitative chemical yield within hours, enantiomeric excesses (*ee*) up to 99%, high chemoselectivity for carbonyl over olefin reduction, and a substrate-to-catalyst ratio (S/C) > 100 000. The combination of desirable features makes this catalytic reaction of great practical interest.^[2] Moreover, the catalytic cycle is mechanistically novel, with most of the attention having been focussed on the step in which the ketone is reduced. Much less attention has been devoted to the cleavage of hydrogen to form the active ruthenium hydride. However, it is this step that differentiates the new class of hydrogen-cleaving Ru^{II} catalysts from the structurally similar transfer hydrogenation Ru^{II} complexes.^[3,4] We report herein an experimental study of the mechanism of catalytic hydrogenation with **1** which shows that the catalyst requires the presence of alkali metal cations, or more generally, a Lewis acid, as a cocatalyst for efficient turnover.



The preparation and purification of Noyori's catalyst **1** as well as the other reagents used in this study is described in the Supporting Information. Solution-phase reactivity studies were performed in thick-walled Pyrex pressure tubes fitted with a Bourdon-tube manometer on a stainless-steel head fitted with high-pressure valves (Whitey SS-43MA-S4, specified up to 200 bar). The solution (typically 2.9 mL) was degassed by three freeze-pump-thaw cycles, and then magnetically stirred in a temperature-controlled oil bath. The apparatus was found to be leak-proof over 48 h with up to 6 bar H $_2$. Test reactions with **1** (3 mg), *t*BuOK (10 equiva-

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- [11] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163561–163563. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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

lents), and acetophenone (660 mg, 2000 equivalents) in isopropyl alcohol (2.9 mL, 2.0 M with respect to the ketone) for 4 h under H₂ (5 bar) and at 50 °C afforded (*R*)-1-phenylethanol quantitatively with 90% *ee*.^[5] The rather low S/C value of 2000, which corresponds to a millimolar concentration of catalyst, was chosen to adjust the reaction rate to a convenient range. After confirmation that the hydrogenation proceeded as expected, kinetic studies were performed by monitoring the rate of H₂ consumption over several hours, with or without various additives.

Although the conversion of the pressure drop per unit time to turnover frequency (TOF) requires a precise cell volume, the pressure drops themselves do serve as a relative rate measurement.^[6] For each measurement, an initial rate was recorded, which was defined as the rate within the first 15 min after temperature equilibration and saturation with H₂ to 5 bar (*t*₀). The second rate corresponds to the maximum rate of H₂ consumption (*t*₁). The results in Table 1 must be considered with a particular equilibrium in mind. If one considers the p*K*_a values of isopropyl alcohol (18)^[7] and the conjugate acid of DBU (11.8; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene)^[8], then one can calculate the protonated fraction of DBU, and hence the concentration of isopropoxide, as a function of DBU concentration in neat isopropyl alcohol. For a 1 mM solution of **1** in isopropyl alcohol, 100 equivalents of DBU would give approximately 1 mM isopropoxide (one equivalent with respect to **1**). Interestingly, for a thousandfold decrease in catalyst concentration to 1 μM, 100 equivalents of DBU would result in approximately 30 equivalents of isopropoxide relative to catalyst. Similarly, for a 1 mM and 1 μM solution of catalyst, 1000 equivalents of DBU would generate roughly 3 and 100 equivalents of isopropoxide, respectively. In other words, both DBU and isopropoxide are present as bases when DBU is added to isopropyl alcohol, so that even in the (hypothetical) limiting case in which DBU only promotes dehydrochlorination but does not participate further except through

its contribution to the isopropoxide concentration, one has at least one equivalent of isopropoxide.

Table 1 shows several clear results: 1) although a base is needed for dehydrohalogenation of **1**, alkoxide alone is insufficient for high activity—an alkali metal cation is also necessary; 2) the experiments that involved crown ethers show that the alkali metal cation is needed for turnover, and not only for initiation; 3) the alkali metal cations influence the activity in the order K > Na ~ Rb > Li; 4) an increase in the alkali metal cation concentration with a constant amount of base results in a higher activity.

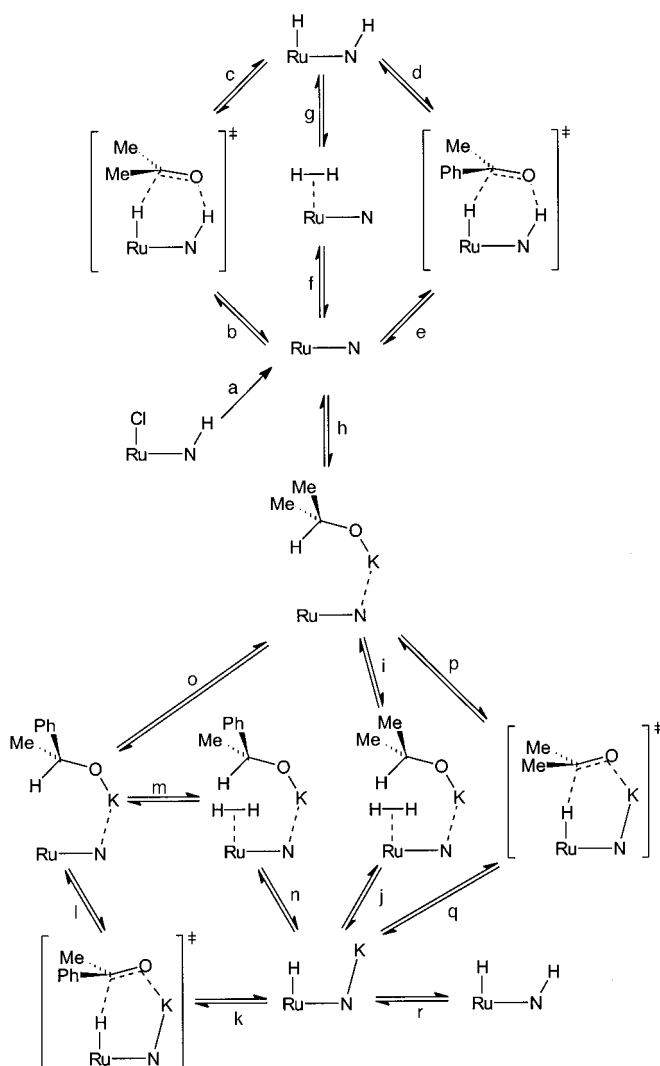
The above-mentioned properties of hydrogenation catalysts of the same family as **1** require an explanation. Noyori et al. have proposed a novel mechanistic explanation for the reversible hydride transfer from Ru^{II}–amine complexes to secondary alcohols. This mechanism rationalizes the activity and selectivity of the transfer hydrogenation catalysts, typically (arene)Ru(diamide) complexes and differs sharply from the accepted mechanism for rhodium- and iridium-catalyzed hydrogenations.^[9] The proposed mechanism is supported by the isolation of the presumed intermediates,^[10] as well as by computational evidence,^[11,12] and is at least plausible for transfer hydrogenation. The proposal does not, however, explain why **1** and its close relatives can cleave hydrogen and why they have such a high activity with an S/C ratio in excess of 1 000 000.

Scheme 1 shows the mechanism for transfer hydrogenation as well as for hydrogen-cleaving routes, both with and without a Lewis acid cocatalyst, which is consistent with the experimental results in Table 1. The reaction depicted is the reduction of acetophenone in isopropyl alcohol with a potassium alkoxide as the inorganic base. Because even the hydrogenation reactions catalyzed by **1** are performed in isopropyl alcohol, and the hydride transfer from the activated form of **1** to acetophenone is the microscopic reversal of a putative dehydrogenation of a secondary alcohol, one can infer that **1** uses hydrogen rather than isopropyl alcohol as a

Table 1. Relative rate of H₂ consumption [bar h⁻¹] in the catalytic hydrogenation of acetophenone with **1** for various conditions and additives.^[a]

Entry	Conditions [equiv]	Rate at <i>t</i> ₀	<i>t</i> ₁ [min]	Addition at <i>t</i> ₁ [equiv]	Rate at <i>t</i> ₁	<i>t</i> ₂ [min]	Addition at <i>t</i> ₂ [equiv]	Rate at <i>t</i> ₂
1	10 <i>t</i> BuOK	2.8	30	–	3.6	–	–	–
2	2 <i>t</i> BuOK	1.8	60	400 [18]crown-6	0.8	75	450 <i>t</i> BuOK	1.0 (at <i>t</i> ₂ = 135)
3	100 DBU, 10 KBAF	0.45	180	10 [18]crown-6	0.00	240	10 KBAF	0.20
4	100 DBU, 10 NaBAF	0.20	165	10 [18]crown-6	< 0.05	315	10 KBAF	> 0.10
5	10 <i>t</i> BuOLi	1.40	60	–	2.00	–	–	–
6	10 <i>t</i> BuONa	2.00	30	–	2.80	–	–	–
7	10 <i>t</i> BuOK	2.80	30	–	3.60	–	–	–
8	10 <i>t</i> BuORb	2.00	30	–	2.60	–	–	–
9	100 DBU	0.00	150	–	0.00	–	–	–
10	100 DBU, 10 LiBAF	0.00	120	–	0.00	–	–	–
11	100 DBU, 10 NaBAF	0.20	60	–	0.30	–	–	–
12	100 DBU, 10 KBAF	0.45	30	–	0.50	–	–	–
13	100 DBU, 10 RbBAF	0.20	60	–	0.30	–	–	–
14	100 DBU, 100 LiBAF	0.23	60	–	0.16	–	–	–
15	100 DBU, 100 NaBAF	3.00	40	–	3.63	–	–	–
16	100 DBU, 100 KBAF	3.33	30	–	6.00	–	–	–
17	1000 DBU, 100 NaBAF	4.00	40	–	4.44	–	–	–
18	1000 DBU, 100 KBAF	4.29	30	–	7.20	–	–	–

[a] Each row describes an experiment which proceeds with the designated addition of a reagent or rate measurement at the marked time. Quantities of base and additives are expressed in mole equivalents relative to **1**. All reactions were performed at 5 bar H₂ pressure at 50 °C. BAF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate anion.



Scheme 1. Elementary steps in a unified mechanism for the reduction of acetophenone by both isopropyl alcohol (above) or H_2 (below), catalyzed by a ruthenium–amine complex: a) $-\text{HCl}$; b) $+$ isopropyl alcohol; c) $-\text{acetone}$; d) $+$ acetophenone; e) $-\text{1-phenylethanol}$; f) $+\text{H}_2$; g) $-$; h) $+\text{iPrOK}$; i) $+\text{H}_2$; j) $-\text{isopropyl alcohol}$; k) $+\text{acetophenone}$; l) $-$; m) $+\text{H}_2$; n) $-\text{1-phenylethanol}$; o) $+\text{isopropyl alcohol}$, $-\text{1-phenylethanol}$; p) $-$; q) $-\text{acetone}$; r) $+\text{iPrOK}$, $-\text{isopropyl alcohol}$. The base is taken to be potassium isopropoxide, although the role of the potassium cation could be played by another suitable oxophilic Lewis acid.

hydride source,^[13] because hydrogen cleavage is faster than dehydrogenation of isopropyl alcohol. In other words, for the catalytic cycle that involves the earlier transfer catalysts (upper half of Scheme 1), step g cannot compete with step b, even if the binding of H_2 (step f) is favorable. A process that accelerates hydrogen cleavage until it dominates the competing isopropyl alcohol dehydrogenation must lead to a catalyst such as **1**, which is more active than the previous transfer catalysts, as shown by the higher turnover frequency and S/C ratios.

The accelerated cleavage of hydrogen corresponds to a dominance of steps j and n over step p (Scheme 1). The key to understanding the acceleration lies in the activation of H_2 in related systems.^[14] The reaction itself is presumably related to that in Wilkinson's ruthenium catalyst,^[15] which is interestingly accelerated in aqueous solutions by alkali metal cations.^[16] Whereas hydrogen typically binds only weakly to

neutral 16-electron Ru^{II} complexes, some cationic complexes bind H_2 quite strongly, for example, $[\text{CpRu}(\text{dmpe})(\text{H}_2)]^+$ is stable in hot THF, with H_2 being displaced only slowly in refluxing acetonitrile.^[17] Moreover, hydrogen coordinated to Ru^{II} can be strongly activated to heterolysis if the metal center is made sufficiently electron deficient, that is, if the complex is mono- or dicationic, but nevertheless capable of back-donation into the $\sigma_{\text{H-H}}^*$ orbital of hydrogen. The $\text{p}K_{\text{a}}$ value of bound H_2 in $[\text{CpRu}(\text{dmpe})(\text{H}_2)]^+$ was measured by Heinekey and co-workers^[18] to be 5. Similarly, Morris and co-workers^[19] found a $\text{p}K_{\text{a}}$ value of 9.2 for $[\text{Cp}^*\text{Ru}(\text{dppm})(\text{H}_2)]^+$. The variation of the $\text{p}K_{\text{a}}$ values of H_2 in the complex $[\text{CpRu}(\text{L})_2\text{H}_2]^+$ (L = phosphanes) correlates systematically with electron deficiency at the ruthenium center.^[20] Dicationic Ru^{II} complexes^[21] show even more extreme behavior with respect to H_2 . The same effect has been suggested to be operative in certain hydrogenases.^[22]

Given that the ruthenium amide complexes (Ru-N ; Scheme 1) are neutral, one would expect them to bind H_2 substantially more poorly than their cationic congeners. Moreover, the bound hydrogen should be substantially less acidic than in $[\text{CpRu}(\text{dmpe})(\text{H}_2)]^+$. Step g) in Scheme 1 shows the deprotonation of bound hydrogen by the amide ligand. How basic is the amide nitrogen? There are no quantitative data available, but one may make an estimate by using two procedures. First, one can model the coordination of the amine to a Ru^{II} center on the protonation of a primary amine to form the corresponding ammonium cation. A decrease in the $\text{p}K_{\text{a}}$ value from ~ 30 to ~ 10 is observed—a change of 20 orders of magnitude,^[23] which is consistent with the effect seen in other Ru- and Os- amine complexes.^[24] Alternatively, if one observes that the activation of **1** requires 10 equivalents of potassium alkoxide when the concentration of **1** is 1 mM, but 10000 equivalents of base for a 1 μM solution of **1**, then, with the assumption that full activation is represented by approximately 90% deprotonation of the N-H moiety, one can calculate a $\text{p}K_{\text{a}}$ value of 14 for the ruthenium–amine complex.^[25]

The lack of significant hydrogen cleavage in the absence of alkali metal cations indicates that the ruthenium amide moiety (Ru-N) is not sufficiently basic to cleave hydrogen efficiently enough to compete with the alternative isopropyl alcohol dehydrogenation reaction.^[26] On the other hand, the coordination of the alkali metal cation to the N atom of the ruthenium amide should withdraw electron density from the amide ligand, and hence from the ruthenium center, thus rendering the coordinated hydrogen more acidic. Moreover, the product of the previous cycle of reduction, a ruthenium amide with coordinated potassium alkoxide, places the basic alkoxide in an ideal position to deprotonate the coordinated hydrogen through a six-membered cyclic transition state (Scheme 1, step n).

As a last question, one may speculate as to why the alkali metal cation accelerated reaction occurs for **1**, but not for the structurally related transfer catalysts. The X-ray crystal structure of **1** and the MMX-optimized calculated structure (Figure 1) show that the N-H moiety that is almost *syn*-periplanar to the Ru-Cl (later Ru-H) bond has the amine proton situated between two face-to-face aryl rings. One of

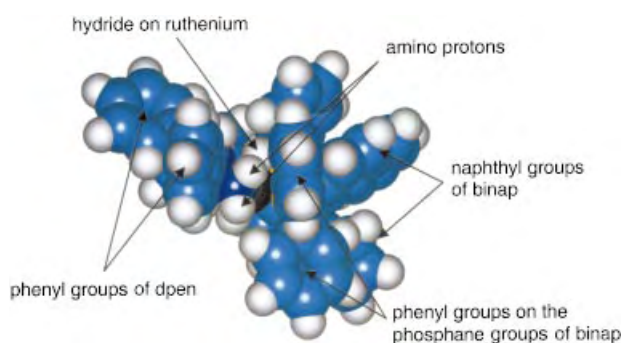


Figure 1. Structure of *trans*-[RuH₂[(*S*)-binap][(*S,S*)-dppe]] calculated by using molecular mechanics with the MMX forcefield, viewed along a N–Ru bond. See text for details.

the aryl rings belongs to the dppe moiety and the other to the binap group. The center-to-center distance between the two rings is approximately 5.6 Å, and the midpoint between the rings lies around 2 Å from the nitrogen atom. When the amine ligand is deprotonated, the amide nitrogen and the two aryl rings form a preorganized cation binding site for potassium, based on cation–arene interactions.^[27] Similar albeit not catalytic structures,^[28] in which alkali metal cations are π -bound to aryl groups in Ru or Os complexes have been crystallographically characterized, thus supporting the plausibility of the present hypothesis in the Noyori-type complexes. The observed order for reaction acceleration, $K > Na \sim Rb > Li$, would also be explained by the conjecture that a potassium-specific binding site is coincidentally created in **1** by the aryl groups of the two ligands on the ruthenium. Lewis acidity alone would have predicted $Li > Na > K > Rb$. Interestingly, the crown ether experiments for hydrogenation catalyzed by **1**/*t*BuOK are less clearcut than the equivalent ones that use **1**/DBU/KBAF (Table 1, entries 2 and 3). A likely explanation is that crown ether sequestration of K^+ in the former case not only removes the alkali metal cation, but also breaks up the aggregation and ion-pairing^[29] of *t*BuOK with a concomitant increase in the alkoxide basicity and partial compensation for the reduced H₂ consumption rate. The effect would be absent in the latter case.

The bimetallic, binuclear mechanism with a cooperative action of two metal centers is reminiscent of the role of bimetallic intermediates in the alkylation of ketones and in CO₂ fixation reactions investigated by Floriani and co-workers.^[30] Also similar are the cross-coupling reactions of Grignard reagents with acyl chlorides in the presence of transition metal chelates studied by Uhlig and co-workers,^[31] and the “flip-flop” mechanism for anionic coordination polymerization of epoxides by zinc and aluminum catalysts.^[32] Perhaps the most interesting parallel is that between the key hydride transfer (step k) and the corresponding step in the asymmetric catalytic reduction of ketones by BH₃·THF in the presence of chiral oxazaborolidine catalysts, reviewed by Corey et al.,^[33] and other reductions with complex metal hydrides.^[34] The major difference is that the present ruthenium systems can cleave hydrogen as well as deliver the hydride efficiently to the ketone substrate.

The combination of a nonionic base with an alkali metal salt (that is soluble in isopropyl alcohol and that contains a

noncoordinating anion) allows the separation of base effects from those of the cations. The surprising dependence of catalytic turnover in Noyori’s hydrogenation catalyst on the presence of alkali metal cations suggests a mechanism in which an accidental cation-binding site leads to an enhanced cleavage of the coordinated hydrogen. The resulting acceleration of direct hydrogenation relative to transfer hydrogenation gives **1** its remarkable activity. Further work to exploit this mechanism is underway.

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Bioreduction of AuCl_4^- Ions by the Fungus, *Verticillium sp.* and Surface Trapping of the Gold Nanoparticles Formed**

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The area of nanotechnology, which spans the synthesis of nanoscale matter, understanding/utilizing their exotic physicochemical and optoelectronic properties, and organization of nanoscale structures into predefined superstructures, promises to play an increasingly important role in many key technologies of the new millennium.^[1] As far as the synthesis of nanoparticles is concerned, there is an ever-growing need to develop clean, non-toxic, and environmentally friendly ("green chemistry") synthetic procedures. Consequently, researchers in the field of nanoparticle preparation have been looking at biological systems for inspiration. The above factors, combined with academic curiosity, has lead to the development of biomimetic approaches for the growth of advanced materials. Many organisms, both unicellular and multicellular, are known to produce inorganic materials either intra- or extracellularly,^[2] examples include magnetotactic bacteria (which synthesize magnetite nanoparticles),^[3] diatoms (which synthesize siliceous materials),^[4] and S-layer bacteria (which produce gypsum and calcium carbonate layers).^[5]

Even though microbes have been used with considerable success in biotechnological applications, such as remediation of toxic metals,^[6] reports on their use in the synthesis of nanomaterials are extremely limited. Beveridge and co-workers have demonstrated that nanoscale gold particles

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readily precipitate in bacterial cells on incubation of the cells with Au^{3+} ions.^[7] A study of the growth of Au nanoparticles by using *Bacillus subtilis* 168 revealed the precipitation of non-crystalline Au particles which subsequently transformed into crystalline octahedral gold containing sulfur and phosphorus.^[7b] More recently, Klaus-Joerger, and co-workers have demonstrated that placing the bacteria *Pseudomonas stutzeri* AG259 (isolated from a silver mine) in a concentrated aqueous solution of AgNO_3 , resulted in the reduction of the Ag^+ ions and formation of silver nanoparticles of well-defined size and distinct morphology within the periplasmic space of the bacteria.^[8] Furthermore, they have shown that biocomposites of nanocrystalline silver and the bacteria, when thermally treated, yield a carbonaceous material with interesting optical properties for potential application in functional thin-film coatings.^[9] Herein, we demonstrate that exposure of the fungus, *Verticillium sp.* (AAT-TS-4), to aqueous AuCl_4^- ions results in reduction of the metal ions and formation of gold nanoparticles of around 20 nm diameter. The gold nanoparticles are formed on both the surface and within the fungal cells (on the cytoplasmic membrane) with negligible reduction of the metal ions in solution. To our knowledge, this is the first demonstration of the use of eukaryotic organisms in the biological synthesis of noble metal nanoparticles such as gold.

Figure 1 A shows the *Verticillium sp.* fungal cells after removal from the culture medium and before immersion in HAuCl_4 solution, the pale yellow color of the fungal cells can

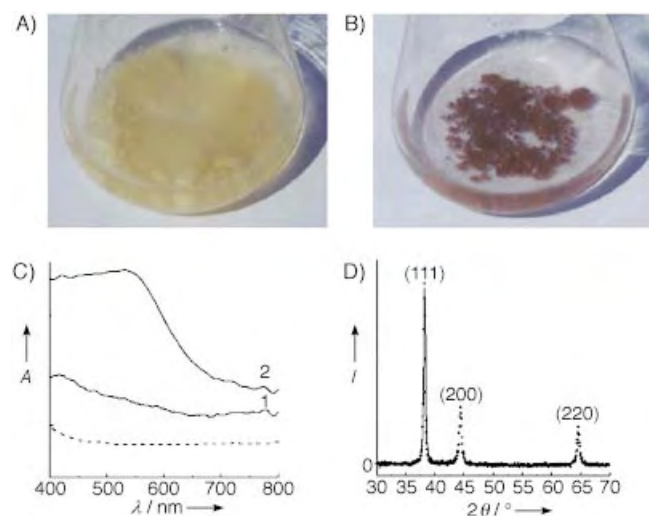


Figure 1. A) *Verticillium* fungal cells after removal from the culture medium. B) *Verticillium* fungal cells after exposure to 10^{-4}M aqueous solution of HAuCl_4 for 72 h. C) UV/Vis spectra recorded from biofilms of the *Verticillium* fungal cells before (curve 1) and after exposure to 10^{-4}M aqueous HAuCl_4 solution for 72 h (curve 2). The spectrum recorded from the HAuCl_4 solution after immersion of the fungal cells for 72 h is shown for comparison (dashed line). D) XRD pattern recorded from an Au nano-*Verticillium* biofilm formed on a Si(111) wafer. The principal Bragg reflections are identified.

clearly be seen. After exposure to aqueous solution of HAuCl_4 the fungal cells are vivid purple which indicates the formation of Au nanoparticles in the cells (Figure 1 B); the aqueous HAuCl_4 medium is colorless, which indicates that extracellular reduction of AuCl_4^- ions has not occurred. Gold

nanoparticles absorb radiation in the visible region of the electromagnetic spectrum (ca. 520 nm) because of excitation of surface plasmon vibrations giving gold nanoparticles striking colors in various media.^[10] The UV/Vis spectra show no evidence of absorption in the range 400–800 nm for the as-harvested fungal cells, the fungal cells exposed to AuCl_4^- ions show a distinct absorption at around 540 nm (Figure 1 C). This absorption is close to that observed for thin films of gold nanoparticles grown by different techniques.^[10, 11] Just as for the as-harvested fungal cells the UV/Vis spectrum of the aqueous HAuCl_4 solution after immersion of the fungal cells shows no discernible absorption in the 540 nm region. This result supports the visual evidence (Figure 1 B) that no extracellular reduction of the AuCl_4^- ions occurred. Further evidence for the intracellular formation of gold nanoparticles is provided by X-ray diffraction (XRD) analysis of the Au nano-*Verticillium* biofilm deposited on a Si substrate (Figure 1 D). The presence of intense peaks corresponding to the (111), (200), and (220) Bragg reflections of gold (identified in the diffraction pattern) agree with those reported for gold nanocrystals.^[12] An estimate of the mean size of the gold nanoparticles formed in the cells was made by using the Debye–Scherrer equation by determining the width of the (111) Bragg reflection.^[13] The size of the gold nanoparticles was thus determined to be about 25 nm.

The presence of mycelia covered with well-dispersed gold nanoparticles can be observed by scanning electron microscopy (SEM; Figure 2 A). The gold nanoparticles appear to be

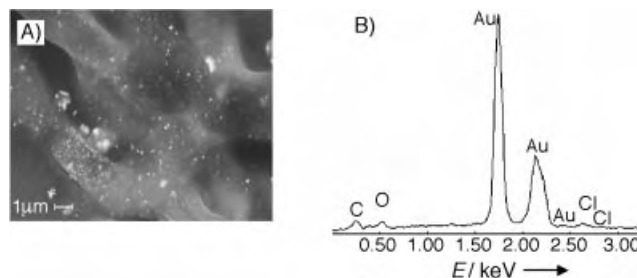


Figure 2. A) SEM image of a biofilm of the *Verticillium* fungal cells deposited on an Si(111) wafer after immersion of the cells in aqueous 10^{-4}M HAuCl_4 solution for 72 h. B) Spot-profile EDX spectrum recorded from one of the gold nanoparticles shown in Figure 2 A.

on the surface of the mycelia. A spot-profile energy-dispersive analysis of X-rays (EDX) of one of the gold nanoparticles shows the presence of strong signals from the gold atoms together with weaker signals from C, O, and Cl atoms (Figure 2 b). The C and O signals arise from X-ray emission from proteins/enzymes either directly bound to the gold nanoparticle or in the vicinity of the particle, while the presence of a weak Cl signal indicates the presence of a small fraction of AuCl_4^- ions in the region being investigated.

To understand, albeit tentatively, the mechanism of formation of the gold nanoparticles in the biofilm, knowing the location of the gold nanoparticles relative to the fungal cells is important. This is conveniently done by transmission electron microscopy (TEM) analysis of thin sections of the Au nano-*Verticillium* cells (Figure 3). At lower magnification, a number

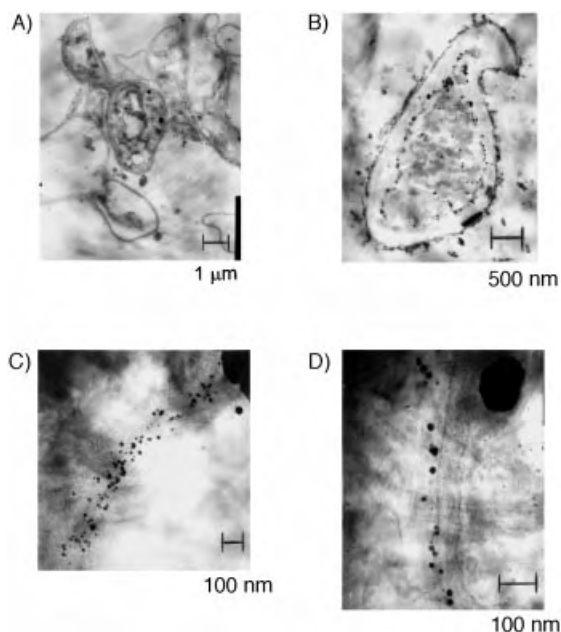


Figure 3. TEM images at different magnifications (A–D) of thin sections of stained *Verticillium* cells after reaction with AuCl_4^- ions for 72 h.

of *Verticillium* cells can be seen (Figure 3A). Careful inspection of the picture shows extremely small particles of gold organized on the walls of the cells. Larger particles of gold are seen within the cells and are considerably smaller in number. Figure 3B shows a TEM image of a single cell in which the gold nanoparticles are formed both on the cell wall (outer boundary) as well as on the cytoplasmic membrane (inner boundary). The number of gold nanoparticles is clearly higher on the cytoplasmic membrane than on the cell wall. As observed in Figure 3A, a very small percentage of larger gold particles is observed within the cytoplasm. Selected area diffraction analysis of a single gold particle (data not shown) revealed diffuse rings with lattice spacings in excellent agreement with those expected for gold. From many TEM images of single *Verticillium* cells a statistical analysis of the size of gold nanoparticles formed both on the cell wall and on the cytoplasmic membrane gave an average gold nanoparticle size of 20 ± 8 nm. Note that in this analysis, the bigger gold particles (often larger than 100 nm, Figure 3C and D) have been excluded.

Higher magnification TEM images of one of the cells show the highly organized assembly of gold nanoparticles on the membrane (Figure 3C and D). The large number of the gold nanoparticles on the membrane surface is striking—this marks a significant departure from bacterial cells, where often not more than 10–15 nanoparticles are observed in one cell.^[8] Of note is that the size distribution of gold nanoparticles produced using *Verticillium sp.* is much narrower than that observed for silver particles produced in bacteria.^[8] The higher magnification TEM thin-section image (Figure 3D) shows the gold nanoparticles are mostly spherical but that there are a few triangular and hexagonal particles. The cytoplasmic membrane is clearly seen in Figure 3D and a large, quasi-hexagonal gold particle is observed within the cytoplasm.

The full potential for using micro-organisms for the synthesis of nanoscale matter may be realized if the ability of the cells to multiply (and thus cover large surface areas with nanomaterials) is not compromised by the presence of metal ions. Consequently, a small number of the *Au nano-Verticillium* cells were removed from the biofilm and placed in the culture medium on an agar plate. Within a week, the seed fungal cells had multiplied to cover the surface of the agar plate of diameter 8 cm (picture shown in the Supporting Information) thus clearly demonstrating that the AuCl_4^- ions and Au nanoparticles do not lead to cell death.

While the exact mechanism of the formation of gold nanoparticles by reaction with the fungal cells is not understood, based on our and other results we speculate as follows: Esumi et al. have shown that sugar persubstituted (amidoamine)dendrimers spontaneously reduce AuCl_4^- ions, which leads to the formation of gold nanoparticles bound to the dendrimers.^[14] We have demonstrated the reduction of AuCl_4^- ions by silanol groups and entrapment of the gold nanoparticles within the pores of mesoporous MCM-41 silicate matrices.^[15] To rule out the reduction of AuCl_4^- ions by sugars in the cell wall, reaction of the metal ions with different genera of fungi, such as *Fusarium oxysporum*, *Colletotrichum gloeosporioides*, and *Curvularia lunata* were carried out in a manner identical to that for *Verticillium sp.* No intracellular reduction of the AuCl_4^- ions was observed in these cases, thus ruling out a nonspecific mechanism for the growth of the nanoparticles. Indeed, that most of the gold nanoparticles are observed to form on the cytoplasmic membrane of *Verticillium* cells (Figure 3) rules out the role of cell-wall sugars in the reduction of the AuCl_4^- ions. Since the nanoparticles are formed on the surface of the fungal cells and not in solution, we believe the first step involves trapping of the AuCl_4^- ions on the surface of the fungal cells. This could occur by electrostatic interaction with positively charged groups (such as, lysine residues) in enzymes present in the cell wall of the mycelia. Thereafter, the gold ions are reduced by enzymes within the cell wall leading to the aggregation of the metal atoms and formation of gold nanoparticles. TEM analysis of thin sections also shows the presence of gold nanoparticles on the cytoplasmic membrane (Figure 3B, D), which indicates that some of the AuCl_4^- ions/small gold particles diffuse across the cell wall and are localized on the cytoplasmic membrane. It is possible that enzymes present in the cytoplasmic membrane also participate in the reduction of the gold ions. A detailed structural analysis of single *Verticillium* cells is currently underway as part of efforts to elucidate the mechanism of formation of gold nanoparticles by reduction of AuCl_4^- ions.

In conclusion, the bioreduction of aqueous AuCl_4^- ions by the fungus *Verticillium sp.* has been demonstrated. The reduction of the noble metal ions occurs on the surface of the mycelia as well as on the cytoplasmic membrane leading to the formation of gold nanoparticles of fairly well-defined dimensions and good monodispersity. The nanoparticles are bound to the surface of the fungal cells and may be used for other applications including catalysis and as precursors for synthesis of coatings for electronic applications. This fungal-mediated green chemistry approach towards the synthesis of

gold nanoparticles has many advantages, such as the ease with which the process can be scaled up, economic viability, possibility of covering large surface areas by suitable growth of the mycelia etc. The shift from bacteria to fungi as a means of developing natural "nano-factories" has the added advantage that processing and handling of the biomass would be much simpler. Further, compared to bacteria, fungi are known to secrete much higher amounts of proteins, thereby significantly increasing the productivity of this biosynthetic approach. Application of such bio-nanocomposites in catalysis and other electronic applications are currently being pursued.

Experimental Section

The acidophilic fungus, *Verticillium sp.*, was isolated from the Taxus plant and maintained on potato-dextrose agar slants at 25 °C. The fungus was grown in 500 mL Erlenmeyer flasks each containing MGY media (100 mL), composed of malt extract (0.3%), glucose (1.0%), yeast extract (0.3%), and peptone (0.5%) at 25–28 °C under shaking (200 rpm) for 96 h. After 96 h of fermentation, mycelia were separated from the culture broth by centrifugation (5000 rpm) at 10 °C for 20 min and the settled mycelia were washed three times with sterile distilled water. Some of the harvested mycelial mass (10 g) was re-suspended in sterile distilled water (100 mL) in 500 mL conical flasks at pH = 5.5–6.0 and to this suspension an aqueous solution of chloroauric acid (HAuCl₄, 100 mL, 10^{−4} M) was added. The whole mixture was put into a shaker at 28 °C (200 rpm) and left for 72 h. The bio-transformation was monitored by visual inspection of the biomass as well as measurement of the UV/Vis spectra from the fungal cells. Films of the fungal cells (both before and after exposure to AuCl₄[−] ions for 72 h) for UV/Vis spectroscopy, X-ray diffraction, and SEM studies were prepared by solution casting the fungal cells onto quartz and Si(111) substrates and thoroughly drying the films in a flow of N₂. UV/Vis spectroscopy measurements of the films on quartz were made on a Shimadzu dual-beam spectrophotometer (model UV-1601PC) operating in the reflection mode at a resolution of 2 nm. Since the films of the bio-nanocomposite were rough, the results are not quantitative and have been used merely to detect the presence of gold nanoparticles in the biomaterial. UV/Vis spectra of the aqueous HAuCl₄ solution after reaction with the *Verticillium* cells for 72 h were also recorded in the transmission mode on the same instrument. SEM and EDX measurements of the fungal cells after formation of the gold nanoparticles were carried out on a Leica Stereoscan-440 scanning electron microscope equipped with a Phoenix EDX attachment. Since the images obtained for the as-prepared Au nano-*Verticillium* biofilms were good, no sputtering of either gold or carbon was required. EDX spectra were recorded in the spot-profile mode by focusing the electron beam onto one of the gold nanoparticles present on the surface of the mycelial cells. XRD studies of the Au nano-fungus biofilm on Si(111) substrates were carried out in the transmission mode on a Philips PW 1830 instrument operating at 40 kV voltage and a current of 30 mA with Cu_{Kα} radiation.

Thin sections of the *Verticillium* cells, after reaction with AuCl₄[−] ions in the manner described above, were prepared for TEM analysis as follows: approximately 1 mm³ aliquots of the Au nano-*Verticillium* biomass were taken and fixed in 2.5% glutaraldehyde in distilled water for 2 h at room temperature. After fixation, the cells were sedimented (1500 rpm, 10 min) and washed three times with distilled water. Without postfixation, the pellet was subjected to dehydration with 30, 50, 70, and 90% ethanol for 15 min at each concentration followed by two changes in absolute ethanol. Since ethanol is poorly miscible with epoxy resins, propylene oxide was used as a linking agent. The dehydrated pellet was kept in propylene oxide for 15 min following which the infiltration of the resin was carried out by placing the pellet in a 1:1 mixture of propylene oxide and Epon 812 overnight at room temperature. Embedding was carried out by using a mixture of the resin (Epon 812) and hardeners (DDSA: dodecynyl succinic anhydride and MNA: methyl nadic anhydride) in the ratio 1:1.5. To this, two drops of trimethylaminomethyl phenol (DMP30) was added to accelerate the polymerization process. Polymerization was carried out using this mixture at 60 °C for 3 days. Ultrathin sections were cut using an ultramicrotome (Leica Ultracut UCT) and were taken on copper TEM

grids (40 μm × 40 μm mesh size). The sections were slightly stained with uranyl acetate and lead citrate prior to TEM analysis. TEM measurements were carried out on a JEOL Model 1200EX instrument operating at an accelerating voltage of 60 kV. A low operating voltage was used to minimize damage to the thin sections by electron beam heating.

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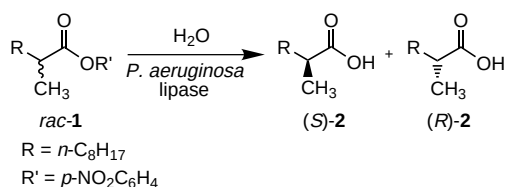
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Directed Evolution of an Enantioselective Enzyme through Combinatorial Multiple-Cassette Mutagenesis

Manfred T. Reetz,* Stephanie Wilensek, Dongxing Zha, and Karl-Erich Jaeger

In 1997 we demonstrated that the methods of directed evolution of functional proteins^[1–4] can be applied successfully in the quest to create enantioselective enzymes for use in organic synthesis.^[5] The combination of suitable mutagenesis and gene-expression methods with high-throughput assays for determining the enantioselectivity of thousands of enzyme mutants forms the basis of a fundamentally new concept in the area of asymmetric catalysis. In only four cycles of random mutagenesis based on the error-prone polymerase chain reaction (epPCR) and high-throughput screening of about 8000 enzyme variants the selectivity factor E ^[6] of the lipase-catalyzed hydrolytic kinetic resolution of ester **1** was increased from 1.1 (with the wild-type enzyme) to 11 (with



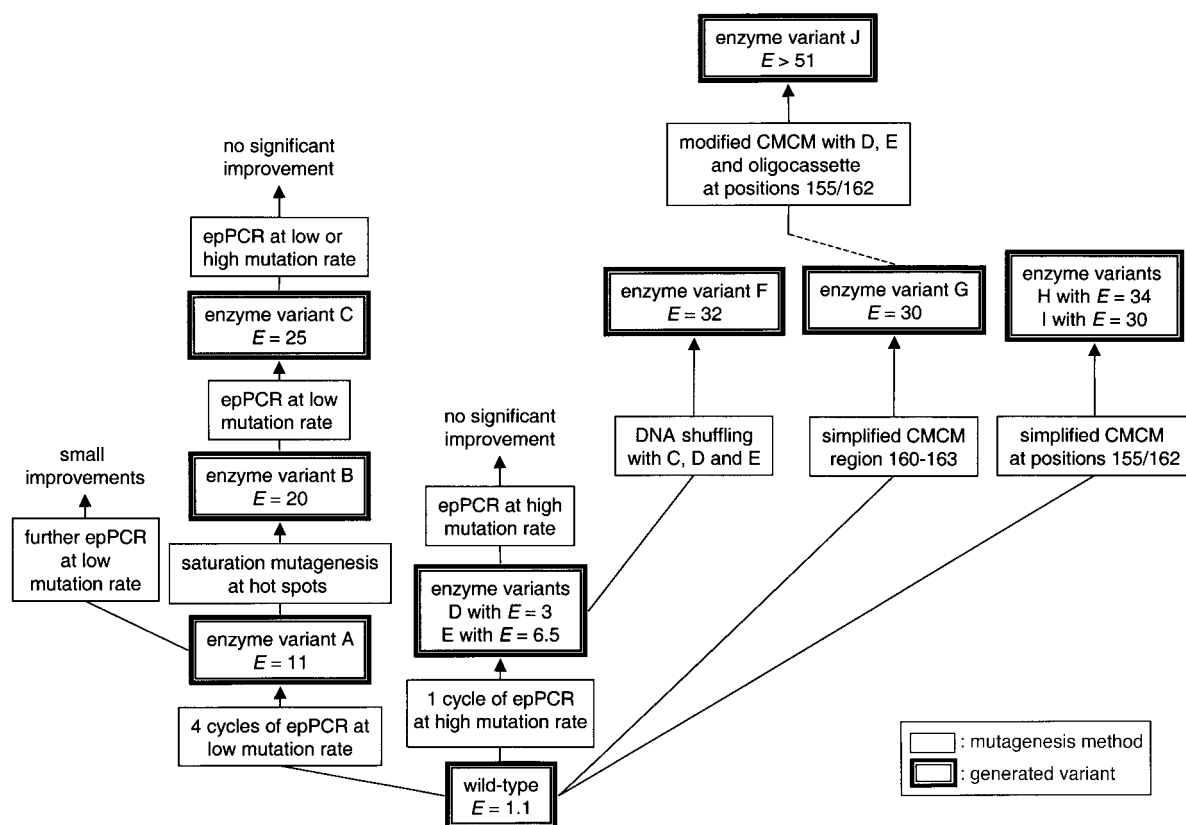
enzyme variant A; Scheme 1, bottom left) in favor of the *S* acid **2**. The epPCR experiments were conducted with the gene of the bacterial lipase from *Pseudomonas aeruginosa* at a low mutation rate corresponding to an average of one amino acid substitution per enzyme. This particular lipase is composed of 285 amino acids, a number that needs to be considered when calculating the theoretical protein-sequence space.^[7] Since only small improvements in enantioselectivity were observed in further rounds of epPCR, saturation mutagenesis was applied at sensitive positions (“hot spots”, identified by amino acid sequencing) of the improved enzyme variants, which led to the identification of a variant B displaying significantly increased enantioselectivity ($E = 20$; Scheme 1, middle left).^[8] When another cycle of epPCR was added on top of this, variant C ($E = 25$) with five mutations (V47G, V55G, S149G, S155F, and S164G) was obtained (Scheme 1, left). However, the strategy of alternating epPCR and saturation mutagenesis seems to have limitations, since further experiments of this kind did not result in significant improvements. We now show

for the first time that recombinant methods are viable tools in improving the enantioselectivity of an enzyme.

Since the hitherto best enzyme variant C was evolved on the basis of incremental improvements brought about sequentially by small changes (single amino acid exchanges), it might be argued that back-crossing with DNA shuffling^[3] could improve the functional properties of the enzyme by eliminating mutations which might have a negative effect in concert with the rest of the mutations. However, upon applying DNA shuffling with the wild-type gene and the mutant gene encoding variant C, no significant improvements were observed. In order to create altered genetic material of higher diversity which is not a result of small incremental changes for subsequent utilization in DNA shuffling, the wild-type gene was subjected to epPCR at a considerably higher mutation rate, which corresponded to about three amino acid exchange events per enzyme molecule.^[7] Upon screening 15000 variants several hits were found which had three mutations and displayed enhanced *S* selectivity relative to the wild-type, for example, variant D (with the mutations S53P, C180T, and G272A; $E = 3$) and variant E (D20N, S161P, and T234S; $E = 7$). The two relevant genes plus the gene encoding variant C were then subjected to DNA shuffling (fragment size 30–50 base pairs (bp)). This experiment turned out to be much more successful than the previous DNA shuffling because it provided a small pool of very enantioselective enzyme variants; the best one (variant F) had five mutations (V47G, S149G, S155F, S199G, and T234S) and showed an E value of 32 (Scheme 1, right).

Although further navigation in protein-sequence space^[7] on the basis of epPCR, saturation mutagenesis, and/or DNA shuffling might well be successful, we decided to attempt other types of methodological developments by turning to cassette mutagenesis^[4] with a simplified version of combinatorial multiple-cassette mutagenesis (CMCM).^[9] The original form of CMCM as described by Cramer and Stemmer is a special type of DNA shuffling which was applied in the area of functional antibodies and which allows the generation of mutant-gene libraries in which the wild-type gene and cassettes composed of defined sequences are randomized.^[9a] On the basis of our previous experiments concerning the identification of hot spots, the positions around amino acid number 160 appeared to constitute a hot region.^[5, 8] Since cassette mutagenesis should not be applied to exceedingly large regions,^[4] we restricted it to positions 160–163. Mutagenesis was performed using only the wild-type gene and a single oligocassette was synthesized by employing equimolar amounts of nucleotide mixtures (simplified CMCM). This ensures saturation at all four positions. Upon screening a library of 5000 variants, several enantioselective enzymes were found, with the best one (variant G with $E = 30$) being characterized by the mutations E160A, S161D, L162G, and N163F (Scheme 1, right). Since earlier work had shown that the introduction of glycine often has beneficial effects,^[8] we focused on mutation L162G. Having previously identified position 155 as another important hot spot,^[5b] we inserted a cassette (size: 69 bp) with double saturation at positions 155 and 162 into the wild-type gene. Accordingly, these two positions were saturated with equimolar nucleotide mixtures

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Scheme 1. Schematic representation of the directed evolution of enantioselective enzymes (lipase variants) which catalyze the hydrolytic kinetic resolution of ester **1**.

in a simplified CMCM process. Following expression and screening two very enantioselective variants were identified: Variants H (S155S, L162G) and I (S155V, L162G) which displayed *E* values of 34 and 30, respectively (Scheme 1, right). In both cases the mutation L162G is conserved, which substantiates earlier speculations concerning the positive role of this particular amino acid substitution.^[8]

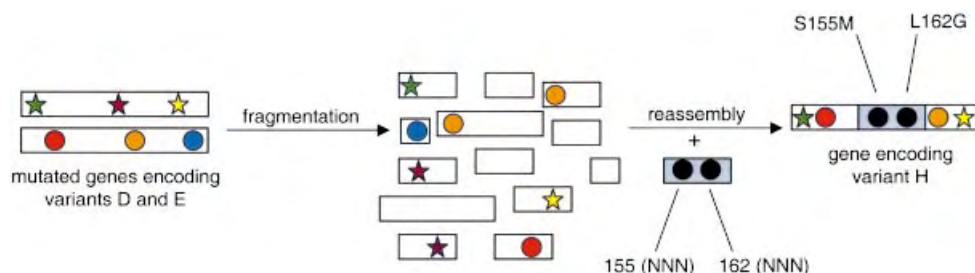
This type of search program restricts the accessible protein-sequence space considerably. We therefore decided to extend it by developing a strategy based on the extension of the CMCM principle. This was accomplished by performing DNA shuffling^[3, 9a] with mutant genes encoding enzyme variants D and E and an oligocassette with simultaneous saturation at positions 155 and 162 (Scheme 2). This ensures the possibility of maximum recombination. Indeed, this approach turned out to be successful because several highly enantioselective

enzymes were found, among them variant J with six exchanged amino acids (D20N, S53P, S155M, L162G, T180I, and T234S). The *E* value of > 51 (*ee* ≥ 95% at 24% conversion) means that the enantioselectivity has almost been doubled (Scheme 1, top right).

This work demonstrates that appropriate forms of recombinant methods are successful in the directed evolution of enantioselective enzymes. We have learned that protein-sequence space with respect to enantioselectivity is best explored by undertaking three steps: 1) Generation of mutants by epPCR at a high-mutation rate; 2) identification of hot regions and spots in the enzyme by epPCR and substantiation of them by simplified CMCM; and 3) extension of the process of CMCM^[9] to cover a defined region of protein sequence space. Less than a total of 40 000 enzyme variants were screened.^[10] We are currently applying this protocol in

the directed evolution of other enantioselective enzymes,^[11] but also expect it to be useful in the evolutionary improvement of other enzyme properties.

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Scheme 2. Extended CMCM in the evolution of an *S*-selective lipase variant J; see Scheme 1, right (green star: position 20; purple star: position 161; yellow star: position 234; red circle: position 53; orange circle: position 180; blue circle: position 272).

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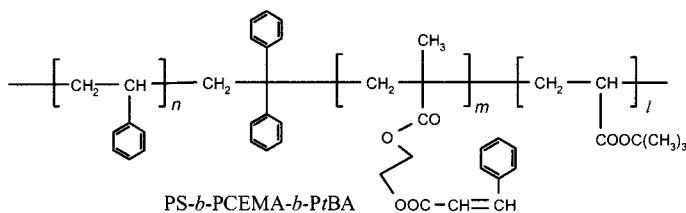
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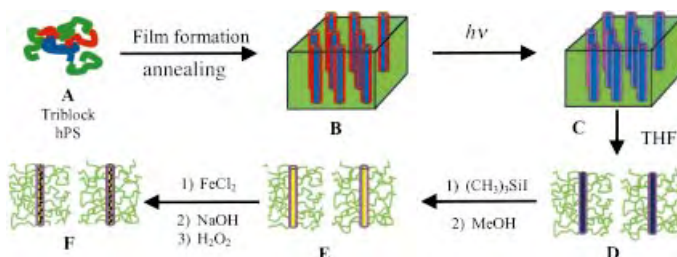
Superparamagnetic Triblock Copolymer/ Fe_2O_3 Hybrid Nanofibers**

Xiaohu Yan, Guojun Liu,* Futian Liu, Ben Zhong Tang, Han Peng, Alexander B. Pakhomov, and Catherine Y. Wong

Block copolymers self-assemble in bulk to form various intricate nanometer-sized block segregation patterns.^[1] Block-segregated structures of diblock copolymers have been processed chemically to yield nanofibers,^[2,3] nanospheres,^[4] and nanochannels in thin films.^[5,6] Here we report on the preparation of polymer/ Fe_2O_3 hybrid nanofibers by processing films of the triblock copolymer polystyrene-*block*-poly(2-cinnamoyloxyethyl methacrylate)-*block*-poly(*tert*-butyl acrylate) or PS-*b*-PCEMA-*b*-PtBA.



The preparation involved the self-assembly of the blocks in thin films into concentric PCEMA and PtBA cylinders dispersed in a matrix of PS (A $\rightarrow$ B in Scheme 1). The cylindrical structures were then locked in by photo-cross-linking the PCEMA shells (B $\rightarrow$ C). Dissolving the films in THF yielded individual nanofibers with PS coronas, PCEMA middle layers, and PtBA cores (C $\rightarrow$ D). Nanotubes with PAA-lined cores [PAA = poly(acrylic acid)] were obtained by cleaving the *tert*-butyl groups from PtBA (D $\rightarrow$ E). Producing Fe_2O_3 nanoparticles in the PAA cores yielded solvent-dispersible superparamagnetic block copolymer/inorganic hybrid nanofibers (E $\rightarrow$ F).



Scheme 1. Preparation of the triblock copolymer/ Fe_2O_3 hybrid nanofibers (see text for details).

The triblock copolymer used consisted of 690 styrene, 170 CEMA, and 200 *t*BA units. Films were obtained by evaporating a toluene solution containing the triblock copolymer and a homopolystyrene (hPS) standard. Figure 1 shows a trans-

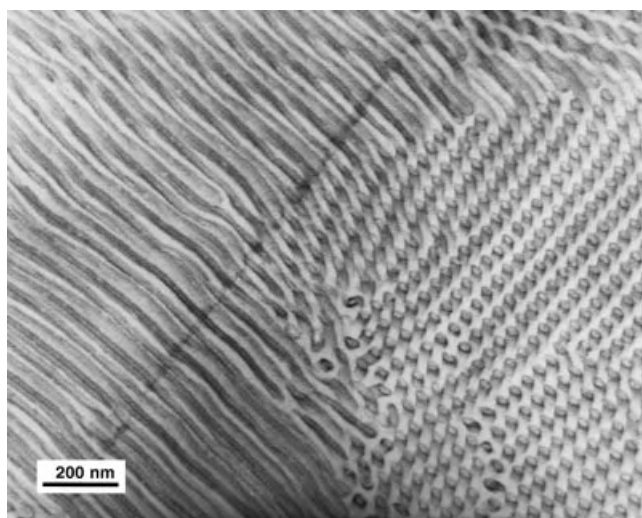


Figure 1. TEM image of a 50-nm-thick section of a PS-*b*-PCEMA-*b*-PtBA/hPS film. The sample was stained with OsO_4 vapor. TEM was performed at 70 kV with a Hitachi H-7000 instrument.

mission electron microscopy (TEM) image of a 50-nm-thick section of such a film stained with OsO_4 . On the right of the image, concentric ellipses with short stems dominate. These represent projections of cylinders, deformed along the microtoming direction, with PCEMA shells and PtBA cores aligned slightly off the normal direction of the image. The PCEMA shells appear darker, because OsO_4 reacted with PCEMA selectively. The diameter of such PtBA cores is about 20 nm, which is smaller than the average contour length of about 50 nm for the PtBA chains. On the left of Figure 1 some cylinders lie in the plane of the picture.

The PCEMA was cross-linked by dimerization between CEMA units of different chains with light from a mercury lamp that had passed through a 290-nm cut-off filter.^[7] A typical CEMA conversion of 22 %, measured by FTIR spectroscopy, was used in this study. Such irradiated triblock/hPS films disintegrated in THF under gentle stirring due to the separation of cross-linked cylindrical domains and

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formation of isolated nanofibers in THF. The cleavage of the *tert*-butyl groups was accomplished by a method used extensively by us in the past.^[2] It involved treating the PS-*b*-PCEMA-*b*-PtBA nanofibers with (CH₃)₃SiI and then decomposing the excess (CH₃)₃SiI with methanol containing about 2% water. Quantitative removal of the *tert*-butyl groups was confirmed by FTIR studies, and the morphologies of the PS-*b*-PCEMA-*b*-PtBA nanofibers and PS-*b*-PCEMA-*b*-PAA nanotubes were confirmed by TEM studies.

A literature method^[8] was followed to load the PAA-lined PS-*b*-PCEMA-*b*-PAA nanotubes with presumably γ -Fe₂O₃. After Fe₂O₃ loading, the nanofiber dispersion became red. Nanofibers prepared after Fe₂O₃ loading had a Fe₂O₃ content of about 0.28 g per gram of nanofibers, as determined by thermogravimetric analysis. These fibers remained dispersed for days in THF or other organic solvents that solubilize PS. Figure 2a shows a TEM image of such fibers sprayed onto carbon-coated copper grids. Since the fibers were not stained before TEM observation, Fe₂O₃ must constitute the visible part of the fibers. The diameter of the Fe₂O₃-impregnated portion is about 20 nm, which is the same as that of the PtBA

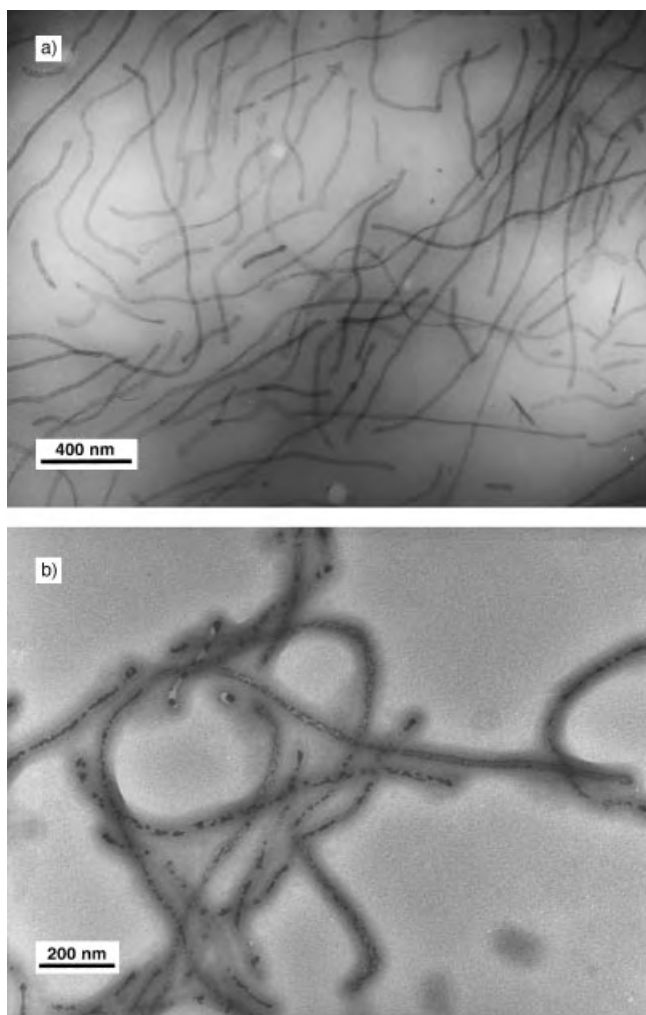


Figure 2. TEM images of triblock/Fe₂O₃ hybrid nanofibers at different magnifications. A THF solution of the sample was aspirated onto a carbon-coated copper grid to prepare the specimen. The samples were not stained.

cores shown in Figure 1 and suggests synthesis of Fe₂O₃ inside the PAA cores. Figure 2b shows an image of the hybrid fibers taken at a higher magnification. The encapsulating layers are clearly visible here.

We obtained electron-diffraction data for the Fe₂O₃ particles. Due to the similarity of the interplanar distances in the different crystalline forms of Fe₂O₃, we could not conclude unambiguously that the particles were γ -Fe₂O₃. Figure 3a

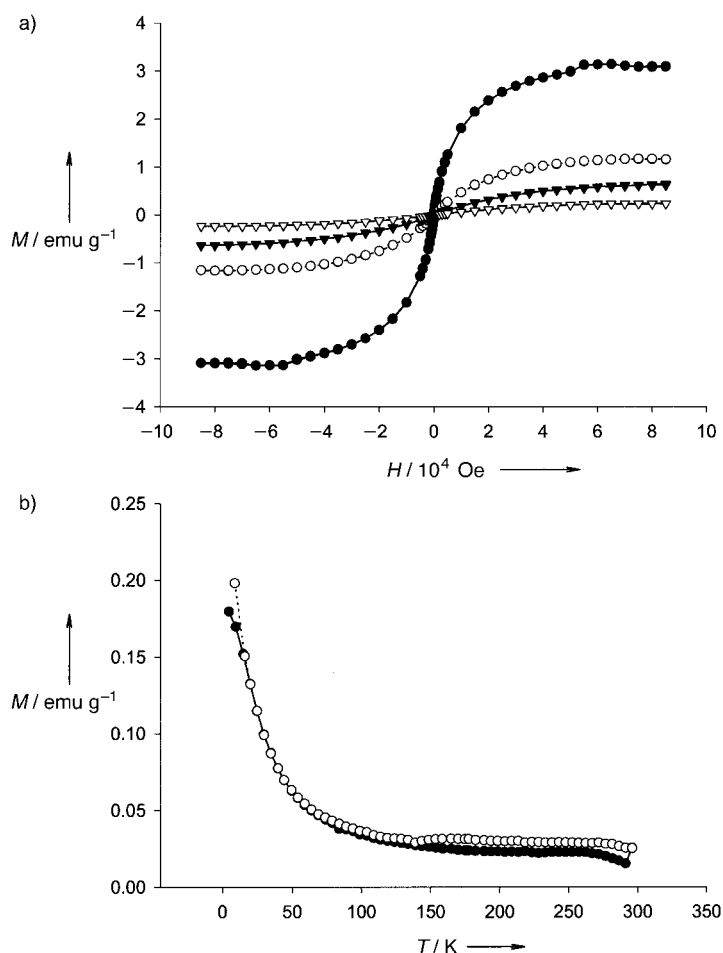


Figure 3. a) Magnetization curves of the hybrid nanofibers at 300 K (∇), 200 K ($\blacktriangledown$), 100 K ($\circ$), and 10 K ($\bullet$). b) Magnetization at 500 G as a function of temperature under ZFC ($\bullet$) and FC ($\circ$) conditions.

shows magnetization curves for the hybrid nanofibers, measured with a SQUID magnetometer (Quantum Design MPMS-5S) at 10, 100, 200, and 300 K. Only at 10 K was measurable coercivity obtained, that is, the particles are superparamagnetic. However, the saturation magnetization at 300 K was low (0.24 emu per gram of hybrid nanofibers or 0.86 emu per gram of iron oxide), but it increased with decreasing temperature and reached about 11.4 emu per gram of Fe₂O₃ at 10 K. Figure 3b depicts the variation in the magnetization of a hybrid fiber sample at 500 G as a function of temperature under zero-field-cooled (ZFC) and field-cooled (FC) conditions. While the field of 500 G was applied after the sample had been cooled to 10 K in the ZFC case, the field was applied

at room temperature before sample cooling to 10 K and then warming to 300 K again in the FC case. For γ -Fe₂O₃ particles prepared previously in polymer matrices,^[9] the ZFC magnetizations at low temperature were much lower than the FC magnetizations, because the particles became magnetically frozen, and their magnetic moment could not flip and align rapidly along the direction of the applied field under ZFC conditions. Only above a blocking temperature^[10] could the spins flip, and the ZFC magnetization then coincided with the FC magnetization. Such a blocking temperature is definitely not observed in our case in the range 10–300 K. The drastic increase in saturation magnetization with decreasing temperature and a blocking temperature below 10 K suggest that our Fe₂O₃ particles are small (that is, <5 nm). Small particles were probably formed due to the use of THF/water rather than water as the solvent during Fe₂O₃ preparation. Alternatively, the abnormal behavior may be due to contamination of the magnetic γ -Fe₂O₃ by other forms of Fe₂O₃.

Due to the low magnetization of the hybrid fibers at room temperature, the as-made fibers may not be useful as magnetic materials. The more gratifying aspect is the ability of the inorganic particles to modify the properties of the polymer fibers. For example, we dispersed the hybrid fibers in a mixture consisting of 28.9 wt% of THF, 58.7 wt% of styrene, 10.4 wt% of divinylbenzene, and 2.0 wt% of benzoyl peroxide in an NMR tube. After the mixture had equilibrated in the uniform 4.7-T field of a Varian XL-200 NMR spectrometer for 3 h at room temperature, the temperature was raised to 70 °C to gel the matrix. Figure 4 shows a

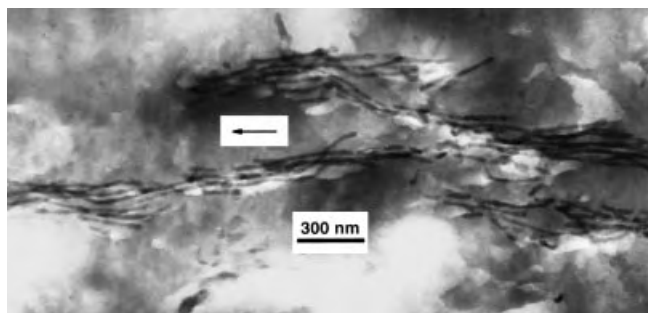


Figure 4. Side view of the hybrid fibers aligned in the magnetic field. The rugged background is due to partial shattering of cross-linked PS during microtoming.

representative TEM image of a thin section microtomed from the cylindrically shaped sample thus gelled in the NMR tube. The hybrid fibers are aligned along the direction of the magnetic field (arrow). Since no alignment or bundling was observed for the PS-*b*-PCEMA-*b*-PAA nanotubes under similar conditions, alignment of the hybrid nanofibers was probably due to the magnetic anisotropy of the Fe₂O₃ particles produced in the PAA-lined cores of the triblock tubes. Further experiments will involve obtaining the magnetization curves of such aligned fibers parallel and perpendicular to their axial direction to determine this anisotropy.^[11]

We also examined the phase-segregation properties of solutions of the hybrid nanofibers and the PS-*b*-PCEMA-*b*-

PAA nanotubes in THF after solvent evaporation with and without an applied magnetic field. Figure 5 shows a TEM image of a thin section obtained after microtoming such a film that was dried immediately next to the NMR solenoid. The magnetic fibers are not fully aligned here because of the weaker field, but phase separation occurred. No phase

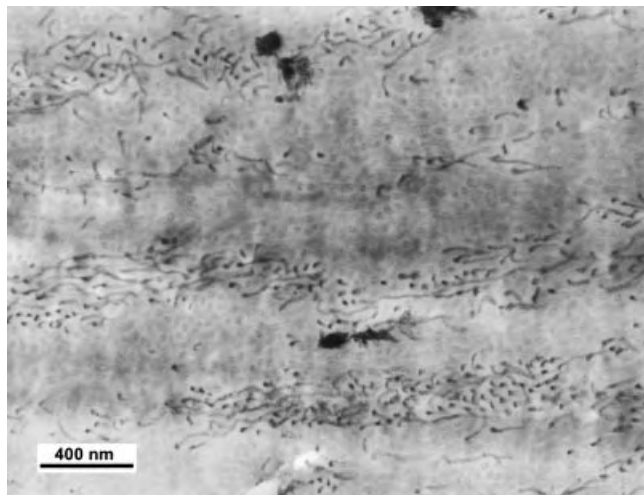


Figure 5. TEM images of a 50-nm-thick section of a PS-*b*-PCEMA-*b*-PAA nanotube and hybrid fiber film dried in a magnetic field. The sample was not stained.

separation was observed when such a sample was dried in the absence of an applied magnetic field. This is in agreement with the fact that the enthalpy of mixing of the hybrid fibers and tubes should be close to zero under such circumstances. The more intriguing aspect is that the fibers and tubes formed alternating multilayers (Figure 5). We do not yet know whether we can make periodically spaced layers. Films containing such layers may serve as photonic crystals.^[12]

In summary, we have produced solvent-dispersible PAA-lined PS-*b*-PCEMA-*b*-PAA nanotubes and polymer/Fe₂O₃ hybrid nanofibers. Such hybrid fibers aligned and segregated from the PS-*b*-PCEMA-*b*-PAA nanotubes in a magnetic field. Superparamagnetic particles were prepared previously in polymer films,^[9, 13] polymer gel particles,^[14] in microemulsion droplets,^[15] and in lipid vesicles.^[16] Preparation of magnetic nanofibers in the channels of ion-track-etched membranes^[11] or anodized alumina^[17] and in tubes of conductive polymers has also been reported.^[18] To our knowledge, this the first report on the preparation of superparamagnetic Fe₂O₃ nanoparticles in solvent-dispersible block copolymer nanotubes.

Experimental Section

The triblock copolymer was prepared by anionic polymerization by following procedures used by us previously to synthesize PS-*b*-PCEMA^[2] and PCEMA-*b*-PrBA^[5] diblock copolymers. Light scattering in chloroform using the measured specific refractive index increment of 0.122 mL g⁻¹ yielded a weight-average molecular mass of 1.42×10^5 g mol⁻¹ for the sample. Comparing intensities of the ¹H peaks of the three blocks gave *n*:*m*:*l* = 1.00:0.25:0.29. Gel-permeation chromatography in THF with a poly(methyl methacrylate) standards gave a polydispersity of 1.13 for the

triblock copolymer. Triblock copolymer films were obtained by evaporating a concentrated toluene solution of the copolymer and a hPS standard ($\bar{M}_w = 2500 \text{ g mol}^{-1}$, $\bar{M}_w/\bar{M}_n = 1.09$) in a mass ratio of 1.00/0.40 over 3 d. The films were then annealed at 120 °C for one week. To incorporate Fe_2O_3 , an excess of FeCl_2 was equilibrated with the nanotubes with PAA-lined cores in deoxygenated THF. The excess FeCl_2 was removed after precipitation of the Fe^{2+} -impregnated tubes into methanol. The trapped Fe^{2+} was then treated with NaOH in THF containing 2 % water to form iron(II) hydroxide or oxide. Fe_2O_3 was prepared by oxidizing the iron(II) hydroxide or oxide with hydrogen peroxide.

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Thermally Stable Homogeneous Catalysts for Alkane Dehydrogenation**

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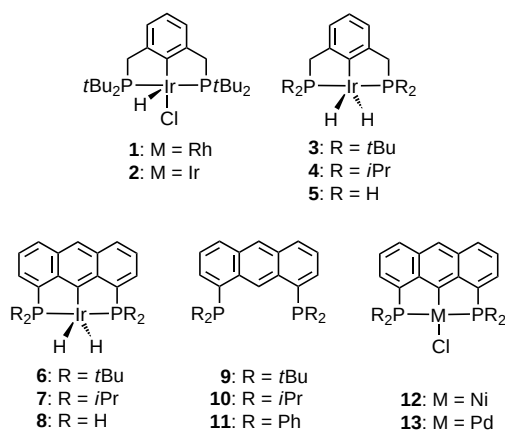
Dedicated to Professor Heinz A. Staab on the occasion of his 75th birthday

Thermostable homogeneous catalysts have three major advantages: the first is that less reactive substrates, for which the kinetics require high temperatures, can be transformed to products; second, they expand the field of homogeneous catalysis to include more endothermic processes, for which the thermodynamics require high temperatures; the third benefit is facile catalyst separation by distillation of educts and products. A process where such catalysts would definitely show great promise is the C–H activation of alkanes in homogeneous solution with dehydrogenation to alkenes and hydrogen.^[1] However, thermostable homogeneous catalysts for endothermic processes are almost nonexistent^[2] and the synthesis of suitable organometallic coordination compounds seemed destined to be abandoned because of complex instability at high temperatures.^[3] This trend was reversed with the introduction of tridentate coordination compounds^[4] in the form of PCP pincer complexes $[\text{MCl}(\text{H})\{\text{C}_6\text{H}_3(\text{CH}_2\text{PrBu})_2-2,6\}]$ (**1**, **2**)^[5] and their subsequent conversion into $[\text{M}(\text{H})_2\{\text{C}_6\text{H}_3(\text{CH}_2\text{PrBu})_2-2,6\}]$ and $[\text{M}(\text{H})_4\{\text{C}_6\text{H}_3(\text{CH}_2\text{PrBu})_2-2,6\}]$ ($\text{M} = \text{Rh}, \text{Ir}$).^[6, 7] The transition metal dihydrides, especially the iridium compounds **3** and **4**, are thermally stable up to 200 °C and are reactive to aliphatic and cycloaliphatic C–H bonds.^[7]

An even higher thermostability can be expected for “anthraphos” complexes **6** and **7** which are obtained by replacing the benzylic PCP pincer ligands with anthracene-

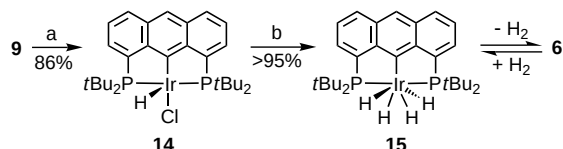
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1,8-diphosphanes **9** and **10**.^[8] The rigidity and chemical inertness of the polycyclic aromatic ligand backbone resulted in remarkably stable cyclometallated complexes **12** and **13** formed from anthraphos **11**.^[9] This observation prompted us to synthesize **6** and to investigate its application as a thermostable homogeneous catalyst for alkane dehydrogenation.

Anthraphos **9** was prepared similarly to **11**^[9b] by direct nucleophilic substitution of 1,8-difluoroanthracene with two equivalents of potassium di-*tert*-butylphosphide (*t*Bu₂PK, dioxane/THF 5/1, reflux, 1 h, 80% yield).^[10, 11] In analogy to the preparation of **2**^[5a] the reaction of **9** and IrCl₃·3H₂O in 2-propanol/water gave **14** (red crystal powder, m.p. 196°C (differential scanning calorimetry; DSC), dec. 308°C (DSC), 86%, Scheme 1). Reduction of **14** under an atmosphere of



Scheme 1. a) IrCl₃·3H₂O, 2-propanol/water (15/2), reflux 24 h; b) NaH, THF, sonication, 12 h.

hydrogen gave mixtures of the yellow iridium tetrahydride **15** and the red iridium dihydride **6**. By saturating solutions of such mixtures with hydrogen the equilibrium was shifted towards **15** and by evaporating the solvent under vacuum the red solid of pure **6** was obtained in >95%.

The structures of the anthraphos complexes **14**, **15**, and **6** are unambiguously revealed by their NMR spectroscopic data and by comparison with the data of the corresponding PCP pincer complexes **2** and **3**.^[5a, 6b,c] In accordance with the structure of **14**, in which the chloride is situated in the anthracene plane and the hydride perpendicular to that plane, the ¹H and ¹³C NMR spectra show two sets of signals for each of the two different types of *tert*-butyl groups (apparent C_s symmetry). On the other hand, all four *tert*-butyl groups are equivalent for **15** and **6** showing apparent C_{2v} symmetry. In ³¹P NMR spectra with {¹H}offset (proton decoupling with exception of the hydride region) the number of hydrogen atoms bound to iridium is indicated by the signal splitting (**14**: δ =

66.8 (d, ²J_{H,P} = 10.0 Hz), **15** δ = 76.4 (quint, ²J_{H,P} = 9.5 Hz), **6**: δ = 92.3 (t, ²J_{H,P} = 9.5 Hz)).

Whereas the pincer iridium dihydrides **3** and **4** are instantaneously decomposed above 200°C,^[7] the anthraphos compound **6** in alkane solution was found to be stable at 250°C and to catalyze the dehydrogenation of, for example, cyclododecane to *cis/trans*-cyclododecene (1/2.4) and hydrogen at this temperature (Figure 1).^[12] To our knowledge this

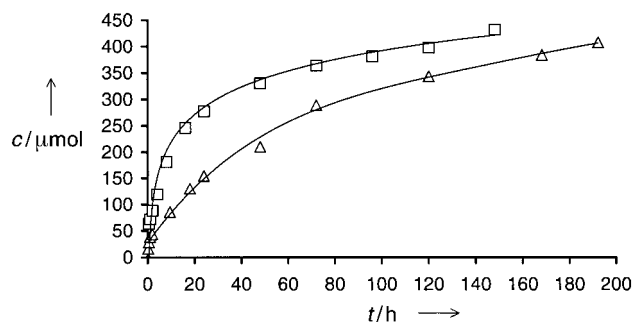


Figure 1. Formation of cyclododecene (total, *cis/trans* 1/2.4, μmol) in the dehydrogenation of cyclododecane catalyzed by **6** (3.3 μmol) at 230°C (Δ) and 250°C (□). Experiments were performed under argon in glass vessels which allowed release of hydrogen. For gas chromatography (GC) analysis, catalyst-free samples were prepared by vacuum transfer and recondensation.

represents the highest thermostability yet reported for an organometallic homogeneous catalyst. At 250°C the initial turn over frequency (TOF) was 40 h⁻¹ and the turn over number (TON) of 136 was reached after 148 h. At 230°C an initial TOF of 30 h⁻¹ and a TON of 126 after 192 h was observed. With increasing olefin formation the rate decreases, but apparently because of the high temperature the dehydrogenation does not come to a complete standstill as was observed with pincer complexes **3** and **4** at 200°C.^[13] However, if the initial TOF for dehydrogenation of cyclooctane at 150°C is compared, the reactivity of **6** at this low temperature is found to be about one order lower than for **3** and about two orders lower than for **4**.

The reaction mechanism of catalytic alkane dehydrogenation requires that the alkane makes contact with the metal center of the catalyst. A conformationally flexible catalyst molecule should be appropriate to simulate the rate-determining step for reactions at high temperatures. In addition, the relative accessibility of the metal center, which can be determined by calculating the accessible molecular surface (*ams*),^[14, 15] is a very simple approach for rationalizing the relative activities of catalysts. During the two-step procedure the conformational flexibility of the catalyst molecule is introduced by generating a “super molecule”, which is a superposition of all relevant conformers within a certain energy range (*E* < 3 kcal mol⁻¹). In the second step, Connolly’s method^[16] is applied to this super molecule. The resulting *ams* can be regarded as a measure of the minimal accessible surface at the center considered. Figure 2 shows this surface for catalysts **3**, **4**, **6**, and **7**. The lower reactivity of the anthraphos catalyst **6** compared to the pincer catalysts **3** and **4** is reflected in its distinctly smaller *ams* value (legend to

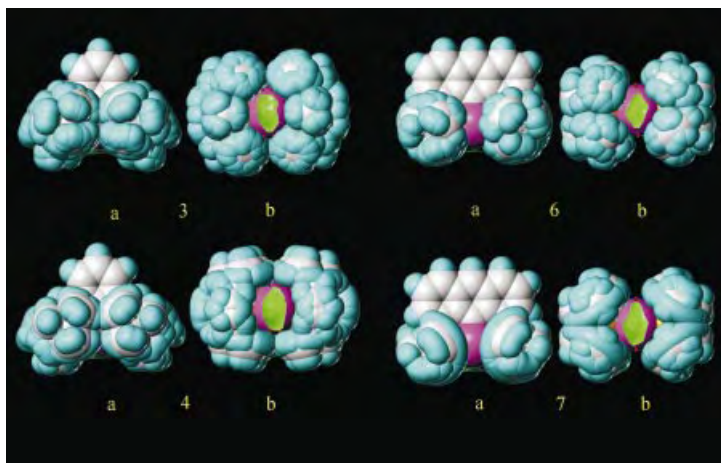


Figure 2. Accessible molecular surface (*ams*) at the Ir (purple) center. The “super-molecular” fragments (no hydride atoms) of **3**, **4**, **6**, and **7** are shown in top (a) and front view (b) with the *ams* in green. Size of the *ams* at the Ir center: *ams* (**3**) = 5.6 Å² (1258 conformers superimposed); *ams* (**4**) = 5.7 Å² (2234 conformers), *ams* (**6**) = 3.5 Å² (50 conformers), *ams* (**7**) = 5.1 Å² (1428 conformers). Size of the *ams* at the Ir center for the most stable conformation (not shown): *ams*_{stable}(**3**) = 8.9 Å², *ams*_{stable}(**4**) = 11.8 Å², *ams*_{stable}(**6**) = 5.9 Å², *ams*_{stable}(**7**) = 6.5 Å².

Figure 2). The models of **3** and **4** take into account the two equilibrating enantiomeric conformers as pictured in Figure 3. On the other hand, anthrapphos catalyst **7** is expected to possess a reactivity similar to **3** and **4**. At low to moderate temperatures the equilibrium structure of the catalyst molecule should gain more importance and in this case the relative catalyst reactivities might better correlate to the corresponding accessibility (*ams*_{stable}). These values show greater differ-

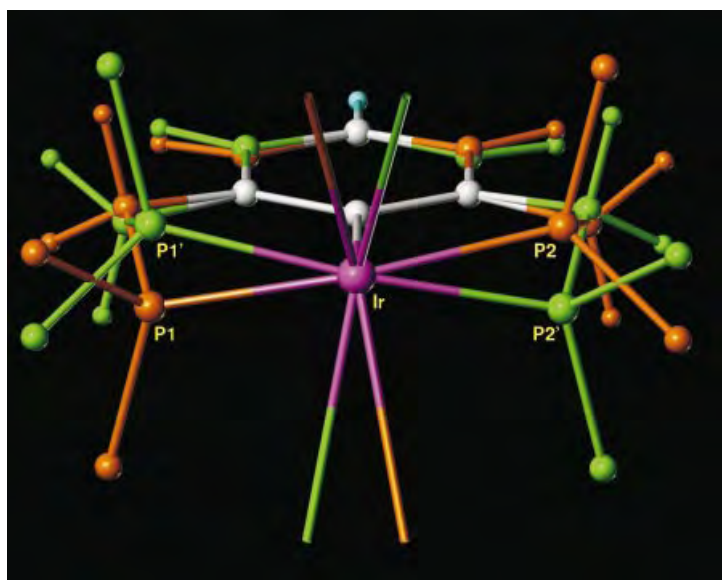
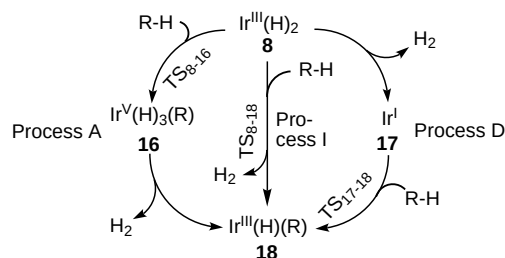


Figure 3. Superposition of the two enantiomers of a pincer IrP₂ fragment. One enantiomer is drawn in brown with P1 and P2 and the other in green with P1' and P2'. The best fit was obtained by superposition of Ir, the metallated carbon atom, and the two *ortho*-C atoms. The endpoints of the sticks at the Ir atom mark for each enantiomer the free coordination sites D which complement the trigonal-bipyramidal coordination geometry at the metal center (distance Ir...D: 2.5 Å). This also allows for a description of their positions relative to that of the corresponding *ams* in Figure 2.

ences between **3** and **4** (**6** and **7**) as well as between **3** and **6** (**4** and **7**) than the *ams* used for the reaction at high temperatures.

The transition states (TS) of the catalytic alkane dehydrogenation were investigated by density functional theory (DFT) techniques by using ethane and the anthrapphos iridium dihydride **8** (phosphorous substituents R = H) as models for the reaction.^[17–24] Although the B3LYP method generally produces excellent results, calculations by higher level ab initio methods, such as coupled cluster with single and double excitations (CCSD) suggest that B3LYP underestimates the stability of the higher oxidation states.^[25] Calibration of CCSD and DFT methods for Ir^V and Ir^{III} suggests that the BP86 functional produces energy differences closer to the more accurate CCSD methods.^[25] The final energies reported here are BP86 energies with zero point and thermal correction from the B3LYP frequency calculations.

Based on experimental and theoretical work^[6, 7, 13, 26] on the related pincer iridium dihydrides **3–5**, it is well established that the Ir^{III}(H)₂ complex exchanges the alkane (RH) and dihydrogen (H₂) to form an Ir^{III}(R)(H) complex, then transfers a β H to form the olefin complex Ir^{III}(R')(H)₂, and lastly releases the olefin (R') to reform the starting complex. However, the details of the formation of Ir^{III}(R)(H) from Ir^{III}(H)₂ and alkane (RH) are not completely clear. Scheme 2 shows three routes for this reaction: an associative process (A) through an Ir^V intermediate, an interchange process (I) through an (RH)/(H₂) exchange transition state, and a dissociative process (D) through an Ir^I intermediate.



Scheme 2. Alternative pathways investigated by DFT calculations for the model reaction of anthrapphos Ir(H)₂ **8** and ethane (RH): A: associative; I: interchange; D: dissociative.

For both model catalysts, the anthrapphos Ir(H)₂ **8** studied here and the previously investigated pincer Ir(H)₂ **5**, the route with the lowest internal energy (lowest barriers and most stable intermediates) passes through the associative path (A). However, an alternative dissociative path (D) would be favored at high temperatures because of its more favorable entropy.^[27]

As we began our investigation of the anthrapphos model catalyst **8** and examined the relative energies of the A and D paths, we discovered an unexpected TS for an interchange mechanism (I). The structure of this TS is shown in Figure 4. The most difficult step, highest ΔG[‡], on the alternative paths (A and D) involves oxidative addition of the alkane (RH) to Ir^{III}(H)₂ and Ir^I respectively. Between room temperature (298 K) and 523 K, the TS for the I path has a lower free

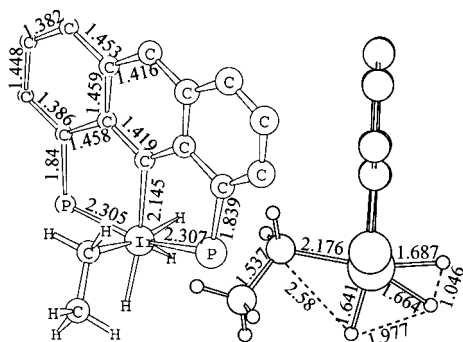


Figure 4. Calculated transition state (TS₈₋₁₈) for the interchange mechanism (I) in Scheme 2.

energy ($\Delta G^\ddagger$) than the most difficult step on either of the other paths, A or D (Table 1). Although the I path is more favorable throughout this temperature range, at the operating temperature (523 K) of this catalyst all three mechanisms have a similar $\Delta G^\ddagger$. Perhaps, this similarity is connected to the efficiency of these systems for alkane dehydrogenation. Furthermore, because of this similarity in $\Delta G^\ddagger$, one expects

Table 1. Calculated thermodynamic parameters [kcal mol⁻¹] at 298.15 K and 523.15 K.

Species ^[a]	ΔH	ΔH	$\Delta G^\ddagger$	$\Delta G^\ddagger$
	298 K	523 K	298 K	523 K
reactant 8	0.0	0.0	0.0	0.0
TS ₈₋₁₆ (A)	10.88	10.03	23.11	33.15
intermediate 16	3.8	4.14	17.04	27.08
TS ₈₋₁₈ (I)	8.23	6.57	19.26	29.06
intermediate 17	32.72	31.11	22.16	15.53
TS ₁₇₋₁₈ (D)	30.85	27.74	30.19	32.45
product 18	26.28	24.29	25.41	26.84

[a] See Scheme 2 for nomenclature. Energies include ethane (RH) and molecular hydrogen (H₂) as appropriate.

that the dynamics of the reaction will involve sampling the entire range of A, I, and D pathways. Therefore, arguments about whether the mechanism is A or D may be irrelevant.

The experimental and theoretical results presented demonstrate the uniqueness of anthrapphos ligands for the development of thermostable homogeneous catalysts.

Experimental Section

14: A suspension of **9** (40 mg, 0.086 mmol) and IrCl₃·3H₂O (31 mg, 0.088 mmol) in 2-propanol/water (8 mL; 15/2) was stirred at room temperature for 12 h and subsequently heated at reflux for 24 h. After the red suspension was cooled to -20 °C, the precipitate was collected by filtration and dried in high vacuum to yield 51 mg (86%) of a red crystal powder, m.p. 196 °C (DSC), dec. 308 °C (DSC); ³¹P{¹H} NMR (243 MHz, [D₆]benzene, 25 °C): δ = 66.8 (s); ¹H NMR (600 MHz, [D₆]benzene, 25 °C): δ = 7.90 (s, 1H; 10-H), 7.89 (d, ³J_{H,H} = 7.5 Hz, 2H; 4-, 5-H), 7.71 (m, 2H; 2-, 7-H), 7.24 (dd, ³J_{H,H} = 8.0 Hz, ³J_{H,H} = 7.2 Hz, 2H; 3-, 6-H); 1.44 ("t", ²J_{H,P} ≈ 6.9 Hz, 18.0H; *t*Bu), 1.49 ("t", ²J_{H,P} ≈ 7.0 Hz, 18H; *t*Bu), -41.14 (t, ²J_{H,P} = 12.5 Hz, 1H; IrH); ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 155.5 (s, br.; C-9), 150.6 (s, "t", ²J_{C,P} = 29.2 Hz; C-8a, C-9a), 138.7 (s, "t", ²J_{C,P} = 38.4 Hz; C-1, C-8), 132.2 (s, "t", ²J_{C,P} = 12.8 Hz; C-4a, C-10a), 130.9 (d; C-4, C-5), 130.4

(d; C-2, C-7), 124.7 (d, d, ²J_{C,P} = 7.2 Hz; C-3, C-6), 119.0 (d; C-10), 39.4 (s, "t", ²J_{C,P} = 20.0 Hz; *t*Bu); 36.9 (s, "t", ²J_{C,P} = 22.0 Hz; *t*Bu), 30.5 (q br.; *t*Bu), 30.3 (q br.; *t*Bu); MS (70 eV): *m/z* (%): 694 (52) [*M*⁺ with ³⁵Cl and ¹⁹³Ir, isotopic pattern as calcd], 658 (100) [*M*⁺ - HCl], 599 (23), 546 (74), 486 (54), 430 (92); HRMS: calcd for C₃₀H₄₄ClIrP₂: 694.223961, found: 694.224630; elemental analysis (%) calcd for C₃₀H₄₄ClIrP₂: C 51.90, H 6.39, found: C 49.83, H 6.30.

15 and 6: A suspension of **14** (10.0 mg, 0.015 mmol) and NaH (3.36 mg) in THF (6 mL) was sonicated under an atmosphere of H₂ for 12 h. Evaporation of THF, extraction of the residue with hexane, filtration of the hexane solution, and evaporation yielded mixtures of solid **15** and **6** in > 95%. Under 3 bar hydrogen pressure dissolved mixtures of **15** and **6** were converted into yellow solutions of **15**, whereas evaporation of the solvent in high vacuum yielded the red solid of **6**.

15: C₃₀H₄₇IrP₂ (661.86 g mol⁻¹); ³¹P{¹H} NMR (243 MHz, [D₆]benzene, 25 °C): δ = 76.4 (s); ¹H NMR (600 MHz, [D₈]toluene, 25 °C): δ = 8.01 (s, 1H; 10-H), 7.88 (d, ³J_{H,H} = 8.6 Hz, 2H; 4-, 5-H), 7.73 (m, 2H; 2-, 7-H), 7.26 (dd, ³J_{H,H} = 8.6 Hz, ³J_{H,H} = 7.4 Hz, 2H; 3-, 6-H), 1.36 ("t", ²J_{H,P} ≈ 7 Hz, 36H; *t*Bu), -8.31 (t, ²J_{H,P} = 9.0 Hz, 4H; IrH₄); ¹³C NMR (151 MHz, [D₈]toluene, 25 °C): δ = 147.2 (s, "t", ²J_{C,P} = 32 Hz; C-8a, C-9a), 145.4 (s, "t", ²J_{C,P} = 36 Hz; C-1, C-8), 132.9 (s, "t", ²J_{C,P} = 12 Hz; C-4a, C-10a), 131.0 (d; C-4, C-5), 129.0 (d; C-2, C-7), 124.5 (d, d, ²J_{C,P} ≈ 8 Hz; C-3, C-6), 119.8 (d; C-10), 34.8 (s, "t", ²J_{C,P} = 23.0 Hz; *t*Bu), 30.6 (q, "t", ²J_{C,P} = 8.0 Hz; *t*Bu), signal of C-9 not observed.

6: C₃₀H₄₅IrP₂ (659.84 g mol⁻¹); ³¹P{¹H} NMR (243 MHz, [D₈]toluene, 25 °C): δ = 92.3 (s); ¹H NMR (600 MHz, [D₈]toluene, 25 °C): δ = 8.02 (s, 1H; 10-H), 7.91 (d, ³J_{H,H} = 8.2 Hz, 2H; 4-, 5-H), 7.80 (m, 2H; 2-, 7-H), 7.33 (dd, ³J_{H,H} = 8.2 Hz, ³J_{H,H} = 6.8 Hz, 2H; 3-, 6-H), 1.32 ("t", ²J_{H,P} ≈ 6.8 Hz, 36H; *t*Bu), -20.10 (t, ²J_{H,P} = 12.0 Hz, 2H; IrH₂); ¹³C NMR (151 MHz, [D₈]toluene, 25 °C): 152.4 (s, "t", ²J_{C,P} = 32 Hz; C-8a, C-9a), 146.7 (s, "t", ²J_{C,P} = 33 Hz; C-1, C-8), 133.3 (s, "t", ²J_{C,P} = 13 Hz; C-4a, C-10a), 130.9 (d; C-4, C-5), 130.1 (d; C-2, C-7), 124.7 (d, d, ²J_{C,P} ≈ 8 Hz; C-3, C-6), 121.0 (d; C-10), 36.3 (s, "t", ²J_{C,P} = 21.0 Hz; *t*Bu), 30.5 (q, "t", ²J_{C,P} = 7.0 Hz; *t*Bu), signal of C-9 not observed.

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Nickel-Catalyzed Homoallylation of Aldehydes in the Presence of Water and Alcohols**

Masanari Kimura, Akihiro Ezoe, Shuji Tanaka, and Yoshinao Tamaru*

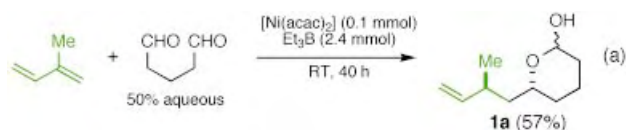
By virtue of their high polarity, a wide variety of allylic metal and metalloid (e.g., B, Si, Sn) complexes can serve as nucleophilic reagents toward carbonyl compounds;^[1] some allylations can be successfully performed even in the presence of water under Barbier conditions.^[2] On the other hand, because of their low polarity, the homoallylic metals that are capable of undergoing a nucleophilic addition reaction are likely to be limited to some electropositive main group metals (e.g., Li, Mg).^[3] Accordingly, reactions with these homoallylic metals should be performed with care under strictly water-free conditions and could be applied effectively to those compounds that do not possess an acidic hydrogen.

Here, we disclose that even in the presence of water and alcohols, nickel complexes serve as a catalyst to promote homoallylation of aldehydes with 1,3-dienes. The reaction proceeds under essentially the same conditions as those reported recently from these laboratories for a nickel-catalyzed homoallylation of carbonyl compounds with dienes in the presence of a stoichiometric amount of Et₃B.^[4–6] These two reactions, that is, in the presence and in the absence of water, provide bishomoallyl alcohols in comparable yields

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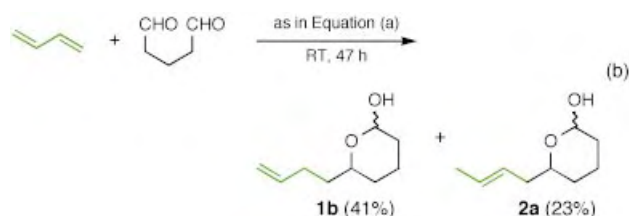
[**] We thank Mr. Y. Ohhama, NMR Facility, for his outstanding technical assistance. Financial support from the Ministry of Education, Science, Sports, and Culture, Japanese Government, Grant-in-Aid for Scientific Research B, is acknowledged.

with the same sense of stereoselectivity and regioselectivity. For example, isoprene (4.0 mmol) reacted with glutaraldehyde (1.0 mmol) regioselectively at the C1 position and stereoselectively to provide **1a** in 57% yield as a single



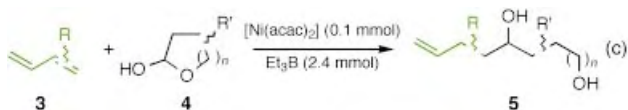
isomer, which is 1,3-*anti* with respect to a tetrahydropyranyl oxygen and a methyl group, when exposed to [Ni(acac)₂] (0.1 mmol, acac = acetylacetonato) and Et₃B (2.4 mmol) in THF (5 mL) at room temperature for 40 h [Eq. (a)]. Glutaraldehyde is stable in water and commercially available as an aqueous solution.^[7] In the above reaction, a 50% aqueous solution was used as received; it follows that the homoallylation could be performed successfully in the presence of about six equivalents of water.

Butadiene reacted with glutaraldehyde (50% aqueous) similarly well and provided the expected homoallylation product **1b** in reasonable yield [Eq. (b)]; however, as noted



previously,^[4] butadiene was the only exception among the dienes examined so far that furnished such an allylation product as **2a** as a minor component.

Encouraged by the compatibility of the [Ni(acac)₂]/Et₃B/diene/aldehyde system with water, we next examined the applicability of the system to the homoallylation of cyclic hemiacetals **4** [Eq. (c)]. To achieve homoallylation of cyclic



hemiacetals with a homoallylic metal, one would anticipate that two equivalents of the reagent would be required; the first equivalent to abstract the hydrogen atom, the second to effect a nucleophilic addition to the aldehyde of ω -metalloxyaldehyde, which might be present as a component of an equilibrium mixture with 2-metalloxy-1-oxacycloalkane. To our surprise, the homoallylation of cyclic hemiacetals proceeded successfully under identical conditions to those for the homoallylation of aldehydes,^[4] that is, use of extra amounts of [Ni(acac)₂], Et₃B, and dienes was not necessary (Table 1). Furthermore, unsymmetrical dienes, such as isoprene (**3b**) and methyl sorbate (**3d**), reacted regioselectively at the C1 and C2 positions, respectively. The stereoselectivity was also

excellent; **3b** provided 1,3-*anti* isomers **5b** and **5e** exclusively (Table 1, runs 2 and 5) and **3d** afforded 1,2-*anti* isomers **5d** and **5g** as a single diastereomer (Table 1, runs 4 and 7), irrespective of the ring size of **4**. The reactivity decreases in the order of 2-hydroxytetrahydrofuran (**4a**), 2-hydroxytetrahydropyran (**4b**), and 2-hydroxy-5,6-benzo-1-oxacyclohexane (**4c**) (cf., Table 1, runs 3, 6, and 8). Indeed, a small amount of **4c** (13%) remained unchanged even after 78 h at room temperature (Table 1, run 8).

Reduction of **1a** with NaBH₄ afforded a diol **5e**, the IR and ¹H NMR spectra of which were identical in all respects to those of the product obtained in run 5, Table 1. The 1,3-*anti* structure of **5e** was derived from that of a lactone derivative **6a** on the basis of NOE experiments (Figure 1, See Exper-

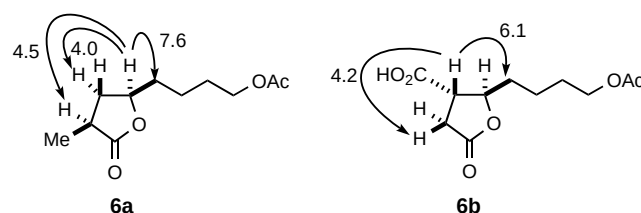


Figure 1. Selected NOE data (% increment) of **6a** and **6b** derived from **5e** and **5g**, respectively.

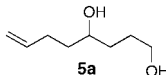
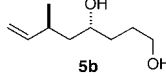
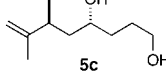
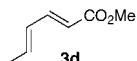
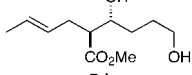
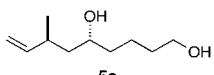
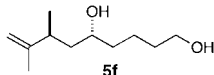
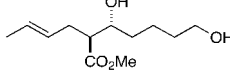
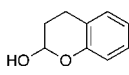
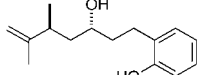
imental Section). The 1,2-*anti* structure of **5g** was also established based on that of the lactone derivative **6b** (Figure 1).

In conclusion, we have demonstrated that a catalytic system of [Ni(acac)₂]/diene/Et₃B efficiently promotes homoallylation of a 50% aqueous solution of glutaraldehyde and cyclic hemiacetals at room temperature. Unsymmetrical dienes react regio- and stereoselectively and provide bishomoallyl alcohols with excellent 1,2- and 1,3-*anti* asymmetric induction. These reaction features may be ideal for modification of sugars and greatly contribute to carbohydrate and related chemistry. The low toxicity and low cost of the reagents and the mild reaction conditions are of particular interest from an environmental and an economic point of view.

Experimental Section

anti-5-Hydroxy-7-methyl-8-nonen-1-ol (**5e**) (run 5, Table 1): Into a flask containing [Ni(acac)₂] (25.7 mg, 0.1 mmol) purged with N₂ were successively added dry THF (5 mL), isoprene (400 μ L, 4.0 mmol), 2-hydroxytetrahydrofuran (102.1 mg, 1.0 mmol),^[8] and Et₃B (2.4 mmol, 1M hexane) by syringe. The homogeneous mixture was stirred at room temperature for 62 h. After dilution with EtOAc, the mixture was washed with 2M HCl, saturated NaHCO₃, and then with brine. The aqueous phases were combined and saturated with NaCl, and then extracted three times with EtOAc. The combined organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography over silica gel (hexane/EtOAc, 2/1, v/v) to provide **5e** (108.5 mg, 63%). IR (neat film): $\tilde{\nu}$ = 3332 (s), 1639 (m), 1057 (m), 995 (m), 910 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, TMS): δ = 1.02 (d, *J* = 6.6 Hz, 3H), 1.36–1.63 (m, 10H), 2.33 (m, 1H), 3.65 (t, *J* = 6.2 Hz, 2H), 4.94 (dd, *J* = 1.5, 10.3 Hz, 1H), 5.03 (br dd, *J* = 1.5, 17.2 Hz, 1H), 5.78 (ddd, *J* = 7.7, 10.3, 17.2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz, TMS): δ = 20.3, 21.7, 32.7, 35.6, 37.3, 44.5, 62.9, 70.4, 112.9, 145.2; HRMS calcd for C₁₀H₂₀O₂: 172.1463; found *m/z* (%): 172.1462 (*[M*⁺], 6), 157 (3), 154 (3), 129 (13), 116 (100); elemental analysis calcd (%) for C₁₀H₂₀O₂: C 69.72, H 11.70; found: C 69.32, H 11.52.

Table 1. Et₃B-promoted, Ni⁰-catalyzed homoallylation of cyclic hemiacetals **4a–c** with 1,3-dienes **3a–d**.^[a]

Run	Diene 3	Hemiacetal 4	<i>t</i> [h]	Product 5	Yield [%]
1	 3a	 4a	24	 5a	63 ^[b]
2	 3b	4a	22	 5b	83
3	 3c	4a	23	 5c	88
4	 3d	4a	46	 5d	64
5	3b	 4b	62	 5e	63
6	3c	4b	40	 5f	99
7	3d	4b	72	 5g	51
8	3c	 4c	78	 5h	82 ^[c]

[a] Reaction conditions: A homogeneous solution of **3** (4 mmol), **4** (1 mmol), [Ni(acac)₂] (0.1 mmol), and Et₃B (2.4 mmol in 1 M hexane) in THF (5 mL) was stirred under N₂ at room temperature for the period of time indicated. [b] In addition to **5a**, an allylation product, *trans*-6-octene-1,4-diol, was isolated in 23 % yield. [c] Yield based on 87 % conversion of **4c**.

cis- γ -(4-Acetoxybutyl)- α -methyl- γ -butyrolactone (**6a**): A solution of **5e** (86.1 mg, 0.5 mmol) in dichloromethane (5 mL) was cooled to -78°C , and ozone was bubbled through until a blue color appeared (ca. 10 min). The excess of ozone was removed by a flow of N₂. The mixture was allowed to warm to room temperature. Into this solution were added AcOH (2 mL), H₂O (0.2 mL), concentrated H₂SO₄ (0.2 mL), and 30 % H₂O₂ (1 mL). The mixture was stirred at room temperature for 1 h and then at 60°C for 5 h. The mixture was diluted with EtOAc, washed with saturated NaHCO₃ and then brine, and dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography over silica gel (hexane/EtOAc, 8/1, v/v) to provide **6a** (61.1 mg, 57 %). IR (neat film): $\tilde{\nu}$ = 2939 (s), 1755 (s), 1737 (s), 1244 (s), 1168 (s), 1002 (m), 927 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, TMS): δ = 1.27 (d, *J* = 7.0 Hz, 3H), 1.51 (td, *J* = 12.5, 10.6 Hz, 1H), 1.42–1.80 (m, 6H), 2.05 (s, 3H), 2.49 (ddd, *J* = 5.3, 8.8, 12.5 Hz, 1H), 2.68 (ddq, *J* = 8.8, 12.5, 7.0 Hz, 1H), 4.07 (t, *J* = 6.6 Hz, 1H), 4.34 (ddt, *J* = 7.7, 10.6, 5.3 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 15.1, 20.9, 22.0, 28.4, 35.2, 35.9, 37.4, 64.1, 78.2, 171.1, 179.3; HRMS calcd for C₁₁H₁₈O₄: 214.1205; found *m/z* (%): 214.1227 ([*M*⁺], 17), 196 (59), 125 (72), 95 (100).

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High-Resolution NMR Spectroscopy of the β -Amyloid(1–28) Fibril Typical for Alzheimer's Disease

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One of the major markers of Alzheimer's disease (AD) is the extracellular deposition of fibrous protein aggregates, called senile or amyloid plaques, in brain tissue.^[1] Even though a causal link between plaque formation and AD has not been firmly established, increasing evidence suggests that amyloid deposition may play a critical role in the neurodegenerative process.^[2] The major component of amyloid plaques is the 39- to 42-aminoacid β -amyloid peptide (β -AP) which is deposited in the form of protease-resistant amyloid fibrils.^[3]

Knowledge of the β -AP fibril structure is essential for understanding the abnormal assembly and deposition of this peptide in AD and could lead to the rational design of therapeutic agents for the prevention or even disaggregation of the fibrils. Furthermore, elucidation of the structure of β -AP fibrils would be an important step towards understanding the propagating structure of other fibrillar proteins involved in systemic amyloidoses, all of which form fibrils with very similar morphology and histochemical properties.^[4]

Fortunately, the highly ordered structure of β -AP fibrils can be replicated in vitro by using synthetic β -APs of various lengths,^[5] a fact that has allowed systematic structural studies. Electron microscopy has revealed that amyloid fibrils are rigid, nonbranching, with lengths exceeding 1 μ m and diameters in the order of 10 nm.^[6] X-ray diffraction measurements from amyloid fibrils showed the "cross- β " pattern characteristic for an extended β -sheet structure with polypeptide chains running perpendicular to the long axis of the fibril and interchain hydrogen bonds roughly parallel to this axis.^[7]

Since amyloid fibrils are noncrystalline, insoluble, high molecular weight aggregates, they are intractable to study by the usual high-resolution structural methods, like X-ray crystallography and solution NMR spectroscopy, and, therefore, atomic details of their structure remained unknown until

recently. Interestingly enough, most of the structural models proposed for the amyloid fibril are based on an antiparallel β -sheet organization.^[6b, 7d, 8] These structural models, however, are largely derived from molecular modeling and are unconstrained by experimental data. Experimental support for the antiparallel arrangement of the strands is limited to IR spectroscopy and specifically to the observation of a weak amide I vibrational band near 1690 cm^{-1} ^[9] which has been assigned to antiparallel β -sheets by empirical studies of model peptides and by theoretical studies.^[10]

The application of solid-state NMR techniques to the elucidation of the structure of amyloid fibrils is of critical importance because solid-state NMR spectroscopy is uniquely capable of providing high-resolution, site-specific structural constraints at the level of specific interatomic distances and torsion angles.^[11] The applications reported so far have utilized ^{13}C -labeled peptides and have determined ^{13}C - ^{13}C dipolar couplings and hence ^{13}C - ^{13}C distances. The first set of measurements on β -AP fibrils was carried out on a doubly ^{13}C -labeled nine-residue β -AP(34–42) fibril and, in combination with molecular modeling, the antiparallel structure was proposed.^[12] Recently, additional experiments on seven-residue β -AP(16–22) indicated an antiparallel β -sheet structure as well.^[13] However, experiments carried out with longer peptide fibrils provide solid experimental evidence for a parallel β -sheet structure. Specifically, ^{13}C - ^{13}C dipolar couplings were determined in singly ^{13}C -labeled β -AP(10–35) fibrils^[14] as well as in full-length β -AP(1–40) fibrils.^[15] In both studies, the measured distance between labeled carbons was approximately 5 Å, a fact which is in agreement with a parallel β -sheet with residues in exact register. The different results in the case of β -AP(34–42)^[12] and β -AP(16–22)^[13] are attributed to the limited length of the peptide chain.^[11]

We now report high-resolution magic angle spinning (HR-MAS) ^1H NMR studies on the β -AP(1–28) fibrils. β -AP(1–28) readily forms fibrils in vitro that are similar in ultrastructure to the in vivo amyloid and aggregate into large bundles that resemble those of senile plaque cores.^[5d,e, 6b, 16] The spectral resolution achieved with the HR-MAS method, which is applied to systems that maintain some degree of motional freedom,^[17] enabled the application of two-dimensional NMR spectroscopy and the assignment of the spectra on the basis of total correlation (TOCSY) and nuclear Overhauser effect (NOESY) experiments. To our knowledge, this is the first time that high-resolution ^1H NMR data are reported for amyloid fibrils. The data are in agreement with an in-register, parallel organization of the fibrils.

NMR samples were prepared in 90 % H_2O /10 % D_2O under conditions described for rapid fibril formation.^[5f] Evidence for full fibrillization was obtained through optical polarizing microscopy of the fibrillized sample after staining with Congo red. Strong green-yellow birefringence, that is characteristic of amyloid fibrils,^[18] was observed from more than 95 % of the sample indicating full fibrillization (microscope image provided as Supporting Information). In addition, no signals were observed in either a usual liquid-state 500 MHz ^1H NMR spectrum or a circular dichroism spectrum of the sample indicating that the HR-MAS signals really come from amyloid fibrils.

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The identification of most of the spin systems was unambiguously achieved from amide proton TOCSY connectivities (Figure 1). The assignment of resonances to

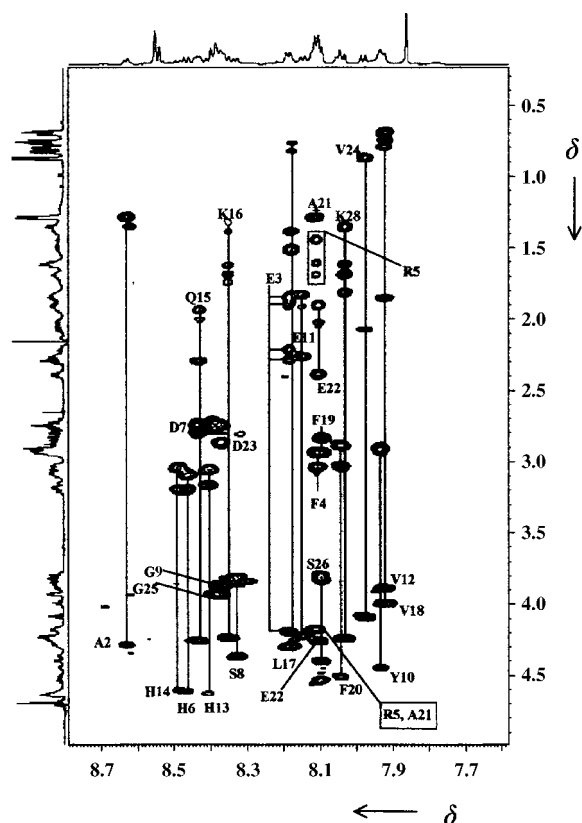


Figure 1. Region of a TOCSY spectrum of β -AP(1–28) fibrils ($\text{H}_2\text{O}/\text{D}_2\text{O}$ 9:1, 300 K, 600 MHz, mixing time 80 ms) with assignments of intraresidue connectivities.

individual amino acids was accomplished by the combined analyses of the $\alpha\text{H}_i\text{-NH}_{i+1}$ connectivities in the fingerprint regions of the TOCSY and NOESY spectra and ascertained by the examination of the $\beta\text{H}_i\text{-NH}_{i+1}$ connectivities. The complete assignments for the ^1H resonances of all amino acid residues are provided as Supporting Information.

All NOEs recorded in the NOESY spectra and their relative intensities are presented in Figure 2. $\alpha\text{H}_i\text{-NH}_i$ and $\alpha\text{H}_i\text{-NH}_{i+1}$ connectivities are present over the full length of

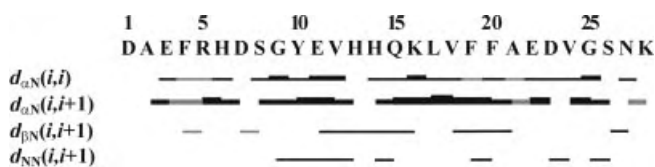


Figure 2. Visualization of NOE connectivities measured for β -AP(1–28) fibrils ($\text{H}_2\text{O}/\text{D}_2\text{O}$ 9:1, 300 K). The intensities of NOE crosspeaks are indicated by the thickness of the bars, grouped into strong, medium, weak, and very weak. Where unambiguous assignment was not possible because of peak overlap, NOE connections are drawn with gray boxes.

the peptide. Weak $\text{NH}_i\text{-NH}_{i+1}$ NOEs were observed for residues 9–13, 14/15, 19/20, 23/24, and 25/26, as shown in the contour plot of the NH–NH region (Figure 3). No long-range NOEs were observed.

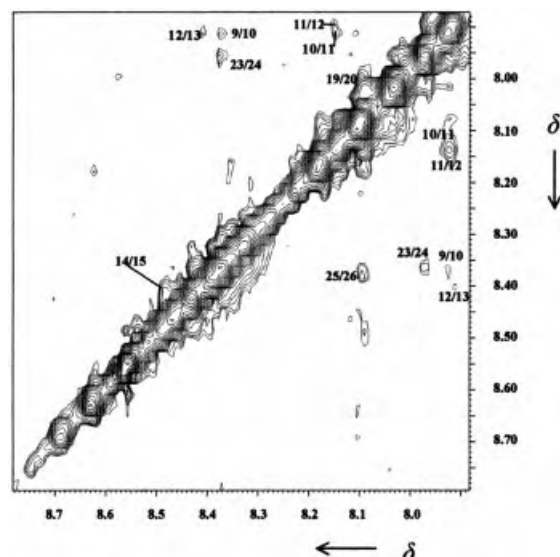


Figure 3. NH–NH region of a 150-ms NOESY spectrum of β -AP(1–28) fibrils ($\text{H}_2\text{O}/\text{D}_2\text{O}$ 9:1, 300 K, 600 MHz) showing some weak sequential $\text{NH}_i\text{-NH}_{i+1}$ connectivities.

The presence of strong $\alpha\text{H}_i\text{-NH}_{i+1}$ connectivities combined with the relatively weaker $\alpha\text{H}_i\text{-NH}_i$ crosspeaks and the absence of $\alpha\text{H}_i\text{-NH}_{i+3}$ and $\alpha\text{H}_i\text{-}\beta\text{H}_{i+3}$ connectivities is in agreement with a β -sheet structure.^[19] Regarding the basic structural issue of a parallel or an antiparallel arranged β -sheet, the absence of NOEs between α -protons of adjacent strands is in agreement with a parallel arrangement since the distance $d_{\alpha\alpha}$ is 2.3 Å in the case of the antiparallel β -sheet and 4.8 Å in the case of a parallel β sheet.^[19] Furthermore, the presence of weak consecutive $\text{NH}_i\text{-NH}_{i+1}$ NOESY crosspeaks for residues 9 to 24 agrees with the in-register, parallel structure. As can be seen from Figure 4, this structure

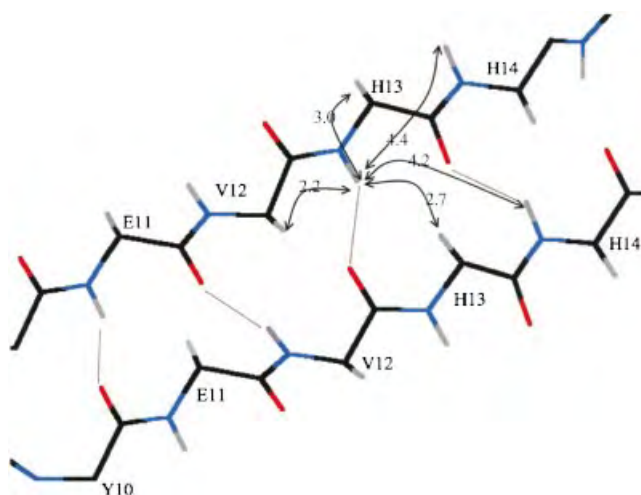


Figure 4. Two strands of β -AP(1–28) (only residues 10–14 are shown; C = black, O = red, N = blue, H = gray) in an in-register, parallel β -sheet arrangement. As shown with dotted lines, in this arrangement hydrogen bonds form between residue i of a given peptide strand and residues $i - 1$ and $i + 1$ of the neighboring strand. Distances corresponding to recorded NOEs are given in Å on curved arrows. The structure was calculated for β -AP(1–28) using Macromodel software, and the interatomic distances derived are in complete agreement with those in the literature.^[19]

incorporates the observed NOE data well. If the strands were not in register, interstrand NOEs between amide protons at various positions in the peptide chain should exist, however, all the recorded NH-NH NOEs are between adjacent peptides.

The presence of consecutive NH_i-NH_{i+1} NOEs for residues 9 to 26 could also be explained by a continuous turn in the structure forming an open loop. This hypothesis cannot be excluded; however, it is not in agreement with the existing literature on the β -sheet structure of β -AP(1–28) fibrils.^[5d,e, 6b, 16]

The lack of NH-NH connectivities for residues 1–8 may indicate structural disorder in the N-terminal part of the peptide. It has already been demonstrated that the first ten residues of the amyloid peptide are not required for fibril formation in vitro;^[20] so it appears plausible that the N-terminal residues may extend outside the ordered β -sheet core.

Our results, suggestive of a parallel, in-register arrangement of the β -AP(1–28) fibrils, are in agreement with the solid-state ¹³C NMR results recently reported on the structure of the β -AP(10–35)^[14] and the full-length β -AP(1–40)^[15] fibrils. HR-MAS ¹H NMR spectroscopy proves to be a powerful tool for probing amyloid fibril structure since it provides solid experimental evidence for the precise arrangement of the individual β -APs in the amyloid fibril, an issue that was until recently elusive. Hopefully, the elucidation of the structure of the β -AP fibrils will provide clues as to the mechanism of amyloid assembly in Alzheimer's disease and will identify potential targets for controlling the aggregation process.

Experimental Section

β -AP(1–28) (H-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-OH) was purchased from AnaSpec Inc. and was >95% pure. 0.5 mg were dissolved in 20 μ L of 90% H₂O/10% D₂O. At that concentration, fibril formation is very rapid.^[5d]

HR-MAS ¹H NMR spectra were obtained with a Bruker AVANCE 600 (DRX) spectrometer. A 4-mm HR-MAS probe was used together with a rotor containing an inner spacer in order to improve B_0 homogeneity and spinning stability as well as to improve the suppression of solvent signals. The spinning rate was 6 kHz, and the temperature was stabilized at 300 K. TOCSY spectra were obtained with a spectral width of 6613 Hz in both dimensions, a mixing time of 80 ms, 512 t_1 increments, 32 scans, and 2 K t_2 data points. The NOESY spectra were obtained with the same spectral parameters and mixing times of 80, 150, 200, and 250 ms. Suppression of the water peak was performed with presaturation.

For the Congo red staining procedure, the NMR sample was diluted 1:10 with H₂O for easier handling. Aliquots of the NMR sample were air-dried on glass slides, dehydrated for 5 min with 80% ethanol, and stained for 20 min with 5% Congo red prepared in 80% ethanol saturated with NaCl.^[21] Excess Congo red was removed by washing with 90% ethanol. The stained samples were examined for green-yellow birefringence using an upright microscope (Zeiss Axioplan 2) equipped with polarizers. Images were acquired using a $\times 40$ objective (Plan-Neofluar) and a Peltier-cooled CCD color camera (Hitachi KP-C571).

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A Demonstration of Anion Templatation and Selectivity in Pseudorotaxane Formation**

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In recent years progress in the synthesis of rotaxane and catenane architectures has reached the stage at which their design is both a function of whether the components of these systems can be interlocked and what function the assembled products possess.^[1] Control over the relative disposition of the constituents in the final structure, their co-conformations,^[2] is usually a derivative of the residual noncovalent interactions initially employed to construct them. Examples of the interactions applied for these purposes to date include hydrogen bonding, π stacking, metal–ligand dative bonding, and hydrophobic binding between species which are neutral or cationic in nature.^[3] With few exceptions, the participation of anions in the formation of interpenetrated and interlocked molecular entities has largely been unexplored and they are rarely incorporated as an operative feature in the resulting ensembles.^[2, 4] The ubiquitous nature of anions in both natural and synthetic systems should make their application in the synthesis of mechanically bonded assemblies highly valuable. Here we report the formation of a [2]pseudorotaxane that is templated selectively by chloride and, to a lesser extent, bromide anions.

We have approached the integration of anionic species into a pseudorotaxane superstructure by employing the chloride ion itself as a central core, about which two coordinating ligands are orthogonally disposed (Figure 1). Crabtree and co-



Figure 1. Proposed anion template. Hydrogen bond donating ligands are represented in red and blue, the chloride anion in green.

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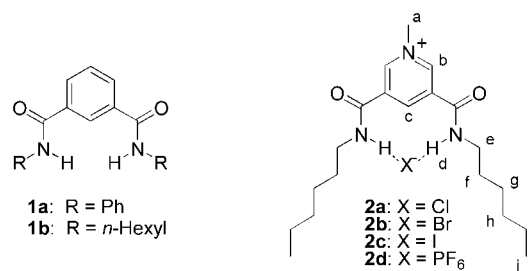
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workers have shown that simple isophthalamide molecules such as **1a** (Scheme 1) are receptors for anions in chloroform.^[5] In particular, fluoride and chloride ions bind more strongly to these receptors than bromide and iodide ions as a result of their size complementarity with the hydrogen-bond donor

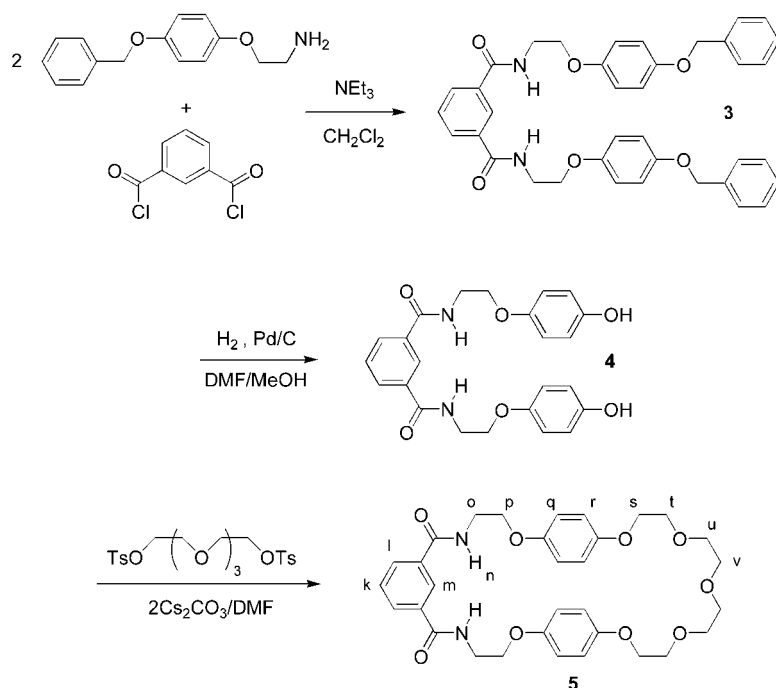


Scheme 1. Structure of hydrogen bond donating ligands **1a** and **b**, as well as the ion pair threads **2a–d**.

cleft created by the amide groups and their mutually *ortho* aryl proton. Unfortunately for our purposes, these receptors bind the halides with a 1:1 stoichiometry that is unsuitable for the formation of the desired template. The utilization of a cationic receptor as one of the ligands in the system could potentially solve this problem. Thus, **2⁺** should include a chloride anion much more tightly in its cleft as a consequence of the increased acidity of the protons involved in substrate binding and the favorable electrostatics provided by the cationic nature of the pyridinium ring. This enhancement can be demonstrated by the large downfield ¹H NMR shifts observed in acetone for only protons c and d of **2⁺** in the series **2d–2a** ($\Delta\delta = 1.59$ and 1.67 , respectively). The resulting tight ion pair leaves the chloride anion with an empty meridian that could bind another neutral hydrogen bond donor ligand in the absence of a competitive solvent. In fact, a ¹H NMR titration of **1b** with **2a** in acetone produced a 1:1 association constant of 100 M^{-1} , while the same treatment of **1b** with **2d** produced no detectable change in the system.^[6]

The second component of the system, macrocycle **5**, was designed to act as the wheel through which **2a** would thread to form the [2]pseudorotaxane. It was anticipated that the isophthalamide fragment incorporated within the macrocyclic cavity would satisfy the coordinatively unsaturated chloride ion. In addition, the hydroquinone and polyether functionality should stabilize the pyridinium cation in the interpenetrated structure. Compound **5** was synthesized in three steps (Scheme 2) beginning with the facile condensation of known 2-(4-benzyloxy)phenoxyethylamine^[7] and commercially available isophthaloyl dichloride to yield **3**. The benzyl protecting groups were removed catalytically and the resulting diol **4** was treated with tetraethylene glycol di-*p*-tosylate and Cs₂CO₃ in DMF to give the final product.

The first indication that **2a** threads through macrocycle **5** in acetone came from the observation of a charge-transfer absorption at approximately 370 nm in the UV/Vis spectrum upon the admixture of one equivalent of each of these two colorless components (Figure 2). The resulting pale yellow color, which can be attributed to π stacking between the pyridinium and hydroquinone rings, is not produced when **2b–d** are mixed with **5**.



Scheme 2. Synthesis of macrocycle **5**. Ts = tosyl = toluene-4-sulfonyl.

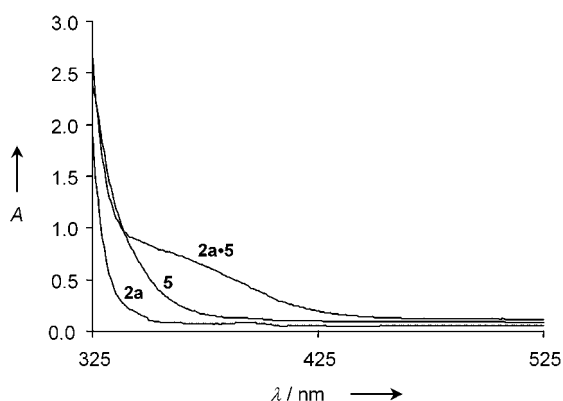


Figure 2. UV/Vis spectra of **2a**, **5**, and **2a·5** in acetone.

Examination of the ^1H NMR spectra of 1:1 mixtures of **5** with each of **2a–d** in acetone revealed complexation-induced shifts in all cases. Table 1 summarizes some of the larger shifts that occur in the aryl and amide protons of the components. The most apparent trend is the marked increase in the size of the shifts of both species in the series **2d** < **2c** < **2b** < **2a**. The effects of π stacking on the aryl protons of both the pyridinium (protons b and c) and hydroquinone (protons q and r) rings is evident in the upfield shifts they display. The

increase in these shift values as the anion decreases in size indicates a concomitant increase in the ability of the cation to reside within the macrocyclic ring. The upfield shifts of protons c and d, relative to the free ion pairs, are most likely also a result of the polarization of the anion towards the hydrogen-bond donors of the macrocyclic ring which reduces the strength of the hydrogen bonds to the cationic donors. Indeed, protons m and n do display downfield shifts indicative of hydrogen bonding to the anion. Once again, these values increase as the anion becomes smaller, more polarizing, and a better fit for the anion “pocket” created in the pseudorotaxane superstructure.

In order to determine the overall strength of these interactions macrocycle **5** was titrated with threads **2a–d** in acetone and association constants were determined by monitoring the shift of the hydroquinone protons r.^[6] Table 1 shows that the association constants measured display the same trend as the magnitudes of the shifts, with pseudorotaxane formation being templated preferentially by a chloride anion. These results give a chloride selectivity of approximately 37:1 over iodide, although there is a difference of just 0.39 Å between the ionic radii of the two anions.

Further proof of the [2]pseudorotaxane structure of the complex **2a·5** is found in the solid state. Pale yellow crystals of the [2]pseudorotaxane were grown by slow diffusion of diisopropyl ether into a 1:1 solution of the two components in chloroform.

The ^1H NMR spectrum of the crystals dissolved in acetone is identical to that of a solution of a 1:1 mixture of the separate compounds. Single-crystal X-ray analysis^[8] reveals the ion pair **2a** threaded through the cavity of the macrocycle in the manner intended (Figure 3 and 4). The chloride ion engages in six hydrogen bonds with the two hydrogen bond donor clefts of the thread and macrocycle (N–Cl: 3.33–3.47 Å, C–Cl: 3.42 and 3.54 Å), and sits within 0.07 Å of the planes of both clefts described by these atoms which intersect at 90°. The C_2 axis of the pyridinium ring forms an angle of 145° with the C_2 axis of the isophthaloyl ring. This arrangement results in the amide protons forming a coordination sphere around the chloride ion similar to that of a trigonal bipyramid with an unoccupied axial position. The pyridinium ring is π stacked between the hydroquinone rings of the macrocycle (mean plane separation: 3.35 and 3.43 Å, centroid–centroid separation: 3.70 and 3.54 Å, angles formed by the ring planes: 1.2 and 3.1°, respectively) and the

Table 1. Association constants (K_a), free energies of complexation (ΔG), and selected ^1H NMR shifts of **2a–d** with **5** in $[\text{D}_6]\text{acetone}$ at 298 K.

Complex	$K_a [\text{M}^{-1}]$	$-\Delta G [\text{kJ mol}^{-1}]$	Chemical shift ($\Delta\delta$) ^[a]						
			H_b	H_c	H_d	H_m	H_n	H_q	H_r
5·2a	2400	19.3	−0.35	−0.98	−1.02	0.65	0.51	−0.24	−0.41
5·2b	700	16.2	−0.17	−0.53	−0.51	0.44	0.27	−0.15	−0.31
5·2c	65	10.3	−0.05	−0.13	−0.11	0.09	0.05	−0.01	−0.09
5·2d	35	8.81	−0.01	0.00	−0.04	0.02	0.01	0.00	−0.05

[a] Shifts determined from 1:1 mixtures at a concentration of $2.5 \times 10^{-3} \text{ M}$.

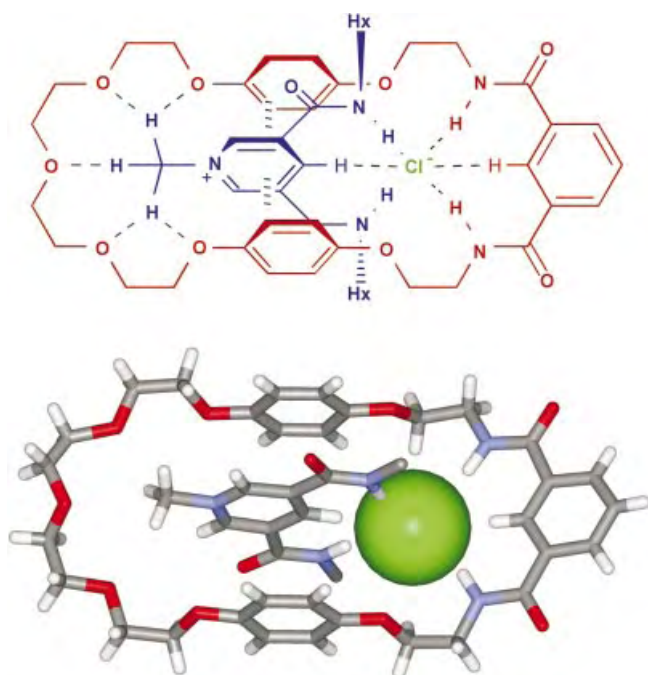


Figure 3. Solid-state structure of **2a**·**5**. Top: Schematic representation of the [2]pseudorotaxane highlighting the interactions between the components. Bottom: Stick representation of the crystal structure. The outermost five carbon atoms and hydrogen atoms of the hexyl chains have been removed and the chloride anion shown as a CPK sphere for clarity.

N-methyl group of the pyridinium cation is stabilized by C–H···O hydrogen bonds with the polyether oxygen atoms (C–O 3.20–3.46 Å).

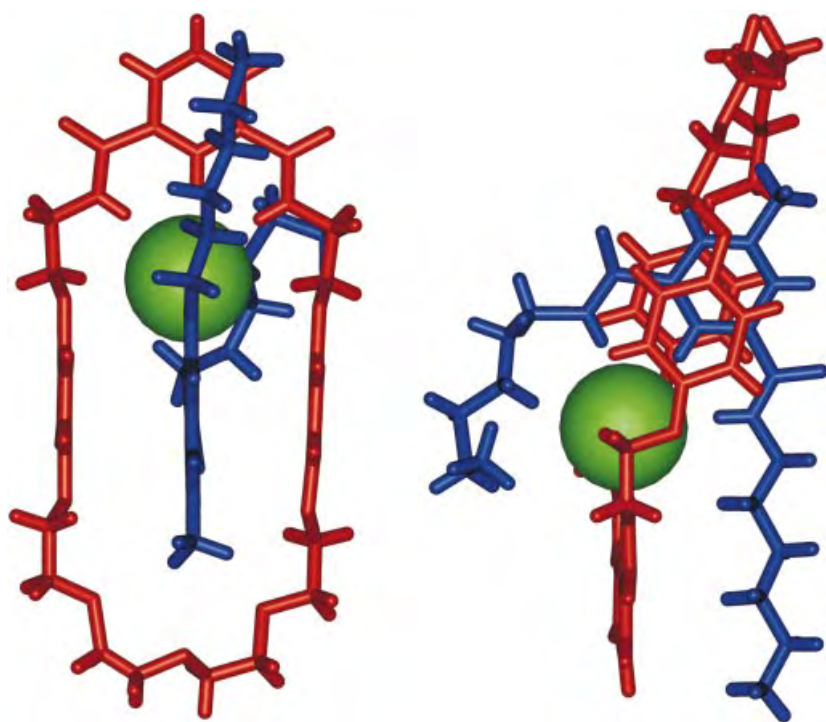


Figure 4. Stick representations of the solid-state structure of **2a**·**5** (blue: **2**⁺, red: **5**, green: Cl[−]). Left: view through the annulus of the macrocyclic ring; right: view in the plane of the macrocyclic ring. The chloride anion is represented as a CPK sphere for clarity.

These results produce a picture of pseudorotaxane formation in which the macrocycle binds **2a** through both first- and second-sphere coordination of the chloride ion. Replacement of chloride by a larger anion destabilizes the entire recognition motif. This process leads to mismatch with both the anion binding pocket created by the four amide groups and, as a result, the ability of the cation to reside within the macrocyclic ring. Thus, the entire structure of the [2]pseudorotaxane hinges on the nature of the anion involved in the binding event. We are currently involved in the application of this template to the construction of rotaxanes and catenanes and anticipate that interlocked compounds based on this protocol will display unique properties in the realms of anion recognition and anion-controlled movement of their constituent parts.

Experimental Section

3,5-Pyridinedicarbonyl chloride was synthesized by a literature procedure^[9] from commercially available 3,5-pyridinedicarboxylic acid.

N,N-Bis(*n*-hexyl)-3,5-pyridinedicarboxamide: A solution of 3,5-pyridinedicarbonyl chloride (1 g, 4.90 mmol) in dichloromethane (25 mL) was added over 30 min to a stirred solution of hexylamine (0.677 g, 5.88 mmol), triethylamine (0.607 g, 6.00 mmol), and dichloromethane (50 mL) cooled to 0°C. The reaction was allowed to proceed for a further 2 h and then warmed to room temperature. The solution was washed with aqueous citric acid (2 M, 4 × 50 mL). The organic layer was dried with MgSO₄ and evaporated to give the desired product as a white solid (1.47 g, 87%). ¹H NMR (300 MHz, CDCl₃, TMS): δ = 9.02 (s, 2 H, *o*-ArH), 8.48 (s, 1 H, *p*-ArH), 7.77 (br m, 2 H, NH), 3.41 (m, 4 H, α-CH₂), 1.59 (m, 4 H, β-CH₂), 1.28 (m, 12 H, γ, δ, ε-CH₂), 0.84 (m, 6 H, CH₃).

2c: *N,N*-Bis(*n*-hexyl)-3,5-pyridinedicarboxamide (1.00 g, 3.00 mmol) and methyl iodide (4.26 g, 30.0 mmol) were added to chloroform (50 mL) and refluxed for 24 h. Addition of the resulting solution to diethyl ether (250 mL) gave **2c** as a bright yellow solid (1.18 g, 83%). ¹H NMR (300 MHz, [D₆]acetone, TMS): δ = 9.99 (s, 1 H, H_c), 9.62 (s, 2 H, H_b), 9.06 (br s, 2 H, H_d), 4.78 (s, 3 H, H_a), 3.44 (m, 4 H, H_e), 1.70 (m, 4 H, H_f), 1.34 (m, 12 H, H_{g-i}), 0.89 (m, 6 H, H_j); elemental analysis calcd for C₂₀H₃₄IN₃O₂: C 50.53, H 7.21, N 8.84; found: C 50.30, H 7.31, N 8.95.

2a: A solution of **2c** (1.00 g, 2.10 mmol) in acetone/water (10 mL) was passed through an Amberlite IRA-400(Cl) ion-exchange column that was pretreated with aqueous 1 N HCl. Evaporation of the eluent gave **2a** as a white solid (0.670 g, 87%). ¹H NMR (300 MHz, [D₆]acetone, TMS): δ = 10.90 (s, 1 H, c), 10.06 (br s, 2 H, H_d), 9.51 (s, 2 H, H_b), 4.78 (s, 3 H, H_a), 3.40 (m, 4 H, H_e), 1.68 (m, 4 H, H_f), 1.34 (m, 12 H, H_{g-i}), 0.89 (m, 6 H, H_j); elemental analysis calcd for C₂₀H₃₄ClN₃O₂: C 62.56, H 8.93, N 10.94; found: C 62.57, H 8.95, N 11.02.

2b: A solution of **2c** (1.00 g, 2.10 mmol) in chloroform (50 mL) was washed with an aqueous 1 M NH₄Br solution (8 × 50 mL) until the organic phase was completely colorless. The organic layer was dried with MgSO₄ and evaporated to give **2b** as a white solid (0.720 g, 80%). ¹H NMR (300 MHz, [D₆]acetone, TMS): δ = 10.55 (s, 1 H, H_c), 9.65 (br s, 2 H, H_d), 9.56 (s, 2 H, H_b), 4.79 (s, 3 H, H_a), 3.42 (m, 4 H, H_e), 1.70 (m, 4 H, H_f), 1.34 (m, 12 H, H_{g-i}), 0.89 (m, 6 H, H_j); elemental analysis calcd for C₂₀H₃₄BrN₃O₂: C 56.07, H 8.00, N 9.81; found: C 56.10, H 8.39, N 9.80.

2d: A solution of **2c** (1.00 g, 2.10 mmol) in methanol (4 mL) was added to a saturated aqueous solution of NH₄PF₆ (10 mL). The resulting mixture was heated to its boiling point and reduced to approximately 2/3

volume. Cooling the solution gave **2d** as a white crystalline precipitate (0.881 g, 85%). ¹H NMR (300 MHz, [D₆]acetone, TMS): δ = 9.58 (s, 2H, H_b), 9.31 (s, 1H, H_c), 8.39 (brs, 2H, H_d), 4.78 (s, 3H, H_a), 3.48 (m, 4H, H_e), 1.64 (m, 4H, H_f), 1.33 (m, 12H, H_g); 0.88 (m, 6H, H_j); elemental analysis calcd for C₂₀H₃₄F₆N₃O₂P: C 48.68, H 6.94, N 8.52; found: C 48.59, H 6.98, N 8.58.

3: 2-(4-Benzyloxy)phenoxyethylamine (4 g, 16.4 mmol) and triethylamine (2.02 g, 20.0 mmol) were dissolved in dichloromethane (100 mL) and cooled to 0 °C. A solution of isophthaloyl dichloride (1.66 g, 8.20 mmol) in dichloromethane (50 mL) was added over 30 min, which resulted in the formation of a white precipitate. The mixture was stirred for a further 2 h and then filtered and washed with dichloromethane (2 × 25 mL) and methanol (2 × 25 mL) to yield **3** as a white solid (5.06 g, 92%). ¹H NMR (300 MHz, [D₆]DMSO, TMS): δ = 8.78 (brs, 2H, NH), 8.34 (s, 1H, isophth.-CH), 7.98 (d, J = 7.6 Hz, 2H, isophth.-CH), 7.55 (t, J = 7.6 Hz, 1H, isophth.-CH), 7.37 (m, 10H, benzyl-CH), 6.90 (m, 8H, phenyl-CH), 5.02 (s, 4H, benzyl-CH₂), 4.06 (t, J = 5.9 Hz, 4H, OCH₂), 3.61 (m, 4H, NCH₂).

4: A mixture of **3** (2 g, 3.24 mmol) and Pd/C (0.2 g) in DMF/methanol (100 mL, 4:1) was stirred under an H₂ atmosphere for 24 h. Celite (10 g) was added and the mixture filtered through a pad of celite to give a light yellow solution. The solution was evaporated under vacuum to give **4** as an off-white solid (1.36 g, 96%). ¹H NMR (300 MHz, [D₆]DMSO, TMS): δ = 8.91 (s, 2H, OH), 8.77 (brs, 2H, NH), 8.35 (s, 1H, isophth.-CH), 7.98 (d, J = 8.2 Hz, 2H, isophth.-CH), 7.56 (t, J = 8.2 Hz, 1H, isophth.-CH), 6.79 (d, J = 8.8 Hz, 4H, phenyl-CH), 6.66 (d, J = 8.2 Hz, 4H, phenyl-CH), 4.10 (t, J = 5.9 Hz, 4H, OCH₂), 3.60 (m, 4H, NCH₂).

5: A solution of **4** (1 g, 2.29 mmol) and tetraethylene glycol di-*p*-tosylate (1.15 g, 2.29 mmol) in DMF (100 mL) was added to a stirred mixture of Cs₂CO₃ (1.57 g, 4.81 mmol) in DMF at 60 °C over a period of 24 h. The resulting mixture was stirred and heated for a further 24 h and cooled to room temperature. Filtration and evaporation of the solvent under vacuum gave a brown oil which was extracted with hot chloroform (2 × 100 mL). The chloroform was reduced to a light brown oil, which was purified by chromatography on silica gel (ethyl acetate) to give **5** as a white solid (0.368 g, 27%). ¹H NMR (300 MHz, [D₆]acetone, TMS): δ = 8.31 (s, 1H, H_m), 8.03 (m, 4H, H_i, H_a), 7.56 (t, J = 7.7 Hz, 1H, H_k), 6.83 (m, 8H, H_q, H_r), 4.12 (t, J = 5.0 Hz, 4H, H_p), 4.02 (m, 4H, H_s), 3.78 (m, 8H, H_o, H_l), 3.63 (m, 8H, H_u, H_j); elemental analysis calcd for **5** · H₂O C₃₂H₄₀N₂O₁₀: C 62.73, H 6.58, N 4.57; found: C 62.69, H 6.56, N 4.51.

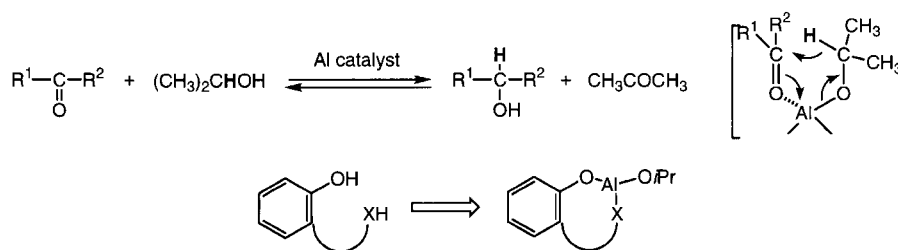
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- [6] All titrations were performed with the concentration of receptor or host (**1b** or **5**) held at 2.5×10^{-3} M and following the movement of the appropriate protons upon addition of **2a–2d**. In the case of **1b** data was obtained by observation of both the amide and mutually *ortho* aryl protons; both methods gave the same K_a values within experimental error. Association constants were determined from the data using the program EQNMR (M. J. Hynes, *J. Chem. Soc. Dalton Trans.* **1993**, 311–312) and fit 1:1 binding models. The estimated errors in all cases were less than 10%.
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Practical Approach to the Meerwein–Ponndorf–Verley Reduction of Carbonyl Substrates with New Aluminum Catalysts**

Takashi Ooi, Hayato Ichikawa, and Keiji Maruoka*



Scheme 1. General schemes for Meerwein–Ponndorf–Verley reduction of carbonyl compounds and the development of new aluminum catalysts.

The Meerwein–Ponndorf–Verley (MPV) reaction, which involves a reversible hydride transfer via a six-membered transition state, has long-been recognized as a particularly mild reduction method that has several attractive features.^[1–3] The reaction is operationally very simple, uses inexpensive, non-toxic, and nonhazardous reagents such as $\text{Al}(\text{O}i\text{Pr})_3$ and $i\text{PrOH}$, and is compatible with a broad range of functional groups present in the substrate.

However, these advantages seem to be canceled out by the usual need for relatively drastic reaction conditions because of the poor reactivity of the traditional $\text{Al}(\text{O}i\text{Pr})_3/i\text{PrOH}$ catalyst system, for which continuous removal of acetone is necessary to shift the equilibrium and hence undesirable side reactions seem inevitable. Accordingly, a number of modern variants of metal alkoxide/hydride source combinations have been elaborated to allow the classical methodology to regain an appropriate place in organic synthesis.^[4–7] Although our recently introduced catalytic procedure with bidentate aluminum alkoxides certainly contributed to such an endeavor, it unfortunately requires *sec*-phenethyl alcohol as a hydride donor for smooth reduction of simple acyclic aliphatic ketones.^[8] This constitutes a major difficulty (especially in the reduction of aromatic ketones), and prompted us to make further effort to bring out the inherent potential in the MPV reduction for practical use. Herein we report our preliminary results on the development of new aluminum alkoxides that can be employed for the efficient catalytic MPV reduction of various ketone substrates (including aromatic ketones). These reactions, which proceed under mild reaction conditions and in which $i\text{PrOH}$ functions as a convenient hydride source, provide a simple yet practical method for carbonyl reduction.

Our strategy for the development of a readily accessible, highly active aluminum catalyst was based on the modification of simple aluminum phenoxide through introduction of an additional heteroatom-containing functionality on the *ortho* position of the parent phenol aromatic ring as schematically illustrated in Scheme 1. Attempted reduction of acetophenone as a representative substrate in the presence of diisopropoxyaluminum phenoxide (10 mol%) (prepared in situ from phenol, Me_3Al , and $i\text{PrOH}$) and $i\text{PrOH}$ as a hydride source (5 equiv) in CH_2Cl_2 at 25 °C for 5 h resulted in total

recovery of the starting ketone (Table 1, entry 1), and use of salicylic acid as an aluminum ligand gave none of the desired *sec*-phenethyl alcohol (Table 1, entry 2). Although the reactivity was slightly enhanced by aluminum isopropoxides derived from catechol and *o*-(methanesulfonylamino)phenol, it was far from a synthetically satisfactory level (Table 1, entries 3 and 4). However, use of the phenol possessing a trifluoromethanesulfonamide functionality improved the yield of *sec*-phenethyl alcohol (30%) and a similar result was obtained with the 2,2'-biphenol-based catalyst (46%) (Table 1, entries 5 and 6),^[9] which led us to consider the possibility of combining the two structural characteristics. The synthesis of 2-hydroxy-2'-(trifluoromethanesulfonylamino)biphenyl (**1**) was thus pursued starting from phenol. Interestingly, treatment of acetophenone with 10 mol% of catalyst, prepared from **1**, Me_3Al , and $i\text{PrOH}$, in CH_2Cl_2 at 25 °C for 5 h produced the corresponding secondary alcohol in 65% yield (Table 1, entry 7). Here, tuning of the perfluoroalkyl group of the sulfonamide moiety afforded a beneficial effect on the catalyst activity. Thus, the reaction under the influence of the

Table 1. Catalytic MPV reduction of acetophenone with various aluminum catalysts.^[a]

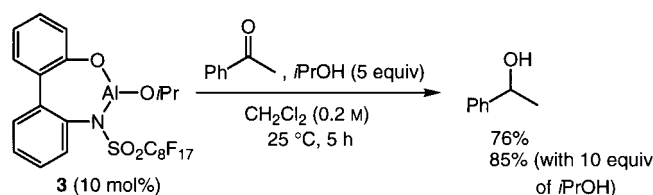
Entry	R	$i\text{PrOH}$ [equiv]	Yield [%] ^[b]
1	H	5	n.r. ^[c]
2	COOH	5	n.r. ^[c]
3	OH	5	8
4	NHSO_2CH_3	5	9
5	NHSO_2CF_3	5	30
6		5	46
7		5	65
8		5	76
9	2	10	85

[a] The MPV reduction of acetophenone was conducted with several aluminum catalysts (10 mol%) and $i\text{PrOH}$ (distilled from CaH_2) in freshly distilled CH_2Cl_2 at 25 °C for 5 h. [b] Yield of isolated product. [c] n.r. = no reaction.

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aluminum isopropoxide **3** (Scheme 2), which was derived from 2-hydroxy-2'-(perfluorooctanesulfonylamino)biphenyl (**2**), gave rise to *sec*-phenethyl alcohol in 76% yield and,



Scheme 2. Efficient catalytic MPV reduction of acetophenone in the presence of the new aluminum alkoxide **3**.

eventually, the yield of the alcohol was improved to 85% by using 10 equivalents of *i*PrOH (Table 1, entries 8 and 9, respectively).^[10]

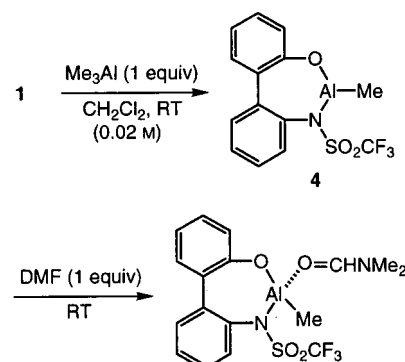
A variety of ketone substrates were examined for this optimized catalytic MPV reduction with **3** and the results are summarized in Table 2. As expected, cyclic ketones such as 4-phenylcyclohexanone can be reduced instantaneously to 4-phenylcyclohexanol quantitatively (*cis/trans* = 17:83) (Table 2, entry 1). Simple aliphatic ketones were also found to be efficiently converted to the corresponding secondary alcohols in excellent yields (Table 2, entries 2 and 3). Moreover, the present catalytic system based on the newly developed aluminum catalyst allows smooth hydride transfer from *i*PrOH to various aromatic ketones (Table 2, entries 4–7).

Table 2. Catalytic MPV reduction of ketone substrates with new aluminum catalyst **3**^[a] and scale-up experiments with 5 g of starting ketones.^[b]

Entry	Substrate	Conditions [°C]	[h]	Yield ^[c] [%]	Scale-up reaction conditions [°C]	[h]	yield [%] ^[c]
1		25	0.5	99 ^[d]	25	2	99 ^[d]
2	$\text{CH}_3(\text{CH}_2)_6\text{COCH}_3$	25	5	97	25	5	94
3	$(\text{CH}_3(\text{CH}_2)_3)_2\text{C}=\text{O}$	25	5	92	25	5	91
4		25	3.5	85	25	5	82
5		25	5	99	25	5	98
6		25	1	99	25	3.5	99
7		25	5	97	25	9	95

[a] The MPV reduction of various ketone substrates was effected with **3** (10 mol %) and *i*PrOH (10 equiv, distilled from CaH_2) in freshly distilled CH_2Cl_2 (0.2 M) under the indicated reaction conditions. [b] The reaction was carried out in reagent grade CH_2Cl_2 (1.0 M) and distilled *i*PrOH (10 equiv) in the presence of **3** (5 mol %), prepared from $\text{Al}(\text{O}i\text{Pr})_3$ and **2**, under the given conditions. [c] Yield of isolated product. [d] The *cis/trans* ratio was 17:83.

To gain information about the actual structure of the new aluminum catalyst, we prepared the complex of the catalyst precursor **4** with DMF as a model example (Scheme 3), and



Scheme 3. Preparation of the model complex **4**-DMF.

the structure was determined by single-crystal X-ray diffraction analysis, which revealed a dimeric structure with unique pentacoordinate aluminum centers (Figure 1).^[11, 12] Thus, the formation of the expected seven-membered cyclic structure was unambiguously verified. Notably, the trifluoromethyl moiety was found to be located away from the aluminum center, suggesting that the introduction of the perfluoroalkyl group essentially provides an electronic effect rather than a steric one.

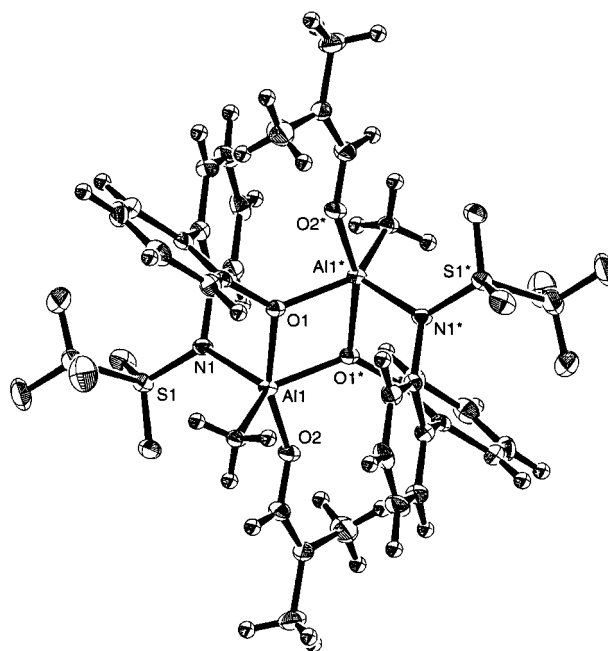


Figure 1. Structure of the **4**-DMF complex (ORTEP representation).

Based on the results, we then conducted scale-up experiments to illuminate the practical aspect of our approach, and first examined the possibility of using $\text{Al}(\text{O}i\text{Pr})_3$ as an aluminum source to avoid the rather troublesome handling of Me_3Al . Fascinatingly, simple mixing of 10 mol % each of commercially available $\text{Al}(\text{O}i\text{Pr})_3$ ^[13] and **2** in CH_2Cl_2 at room

temperature, followed by treatment with *i*PrOH (10 equiv) and acetophenone at 25 °C for 5 h resulted in the formation of *sec*-phenethyl alcohol in 82 % yield,^[14, 15] indicating the intervention of extremely facile ligand exchange.^[16] With this simple yet efficient process in hand, the reactions with 5 g of the starting ketones were undertaken with a lower catalyst loading (5 mol %), which scarcely affect the outcome of the catalysis. The results included in Table 2 demonstrate the potential utility of the present method.^[17] Importantly, these product yields were achieved at high substrate concentration (1.0 M) with reagent grade CH₂Cl₂, which also simplifies the operations of this MPV reduction procedure.

In summary, we have devised an essentially new aluminum alkoxide that exerts high catalytic activity with *i*PrOH as a hydride donor in the MPV reduction of various ketone carbonyl groups. This is the most reactive aluminum-based catalyst reported so far and has remarkable potential for practical use. Further improvement of the reactivity and development of an asymmetric version of the reaction are currently under investigation in our laboratory.

Experimental Section

Scale-up reaction with acetophenone: 2-Hydroxy-2'-(perfluorooctanesulfonylamino)biphenyl (1.39 g, 2.1 mmol) and Al(O*i*Pr)₃ (0.43 g, 2.1 mmol)^[13] were placed in a dry, two-neck flask with a Teflon-coated stirring bar under argon, and CH₂Cl₂ (42 mL, reagent grade purchased from Wako Chemical Co., Ltd.) was introduced. The resulting mixture was stirred for 15 min at room temperature and then 2-propanol (31.3 mL, 412 mmol) distilled from CaH₂ was introduced at the same temperature and stirring was continued for an additional 15 min. Freshly distilled acetophenone (5 g, 41.6 mmol) was added at 25 °C and the reaction solution was stirred for 5 h. This solution was poured into 1 N HCl and extracted three times with diethyl ether. The ethereal extracts were washed with brine and dried over Na₂SO₄. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (*H* = 12 cm, ϕ = 7 cm, acetone/hexane = 1:9 as eluant) gave *sec*-phenethyl alcohol (4.15 g, 34.0 mmol; 82 % yield). The ligand, 2-hydroxy-2'-(perfluorooctanesulfonylamino)biphenyl, can be recovered by subsequent elution with ethyl acetate. In addition, purification of the reduction product by vacuum distillation is also recommended.

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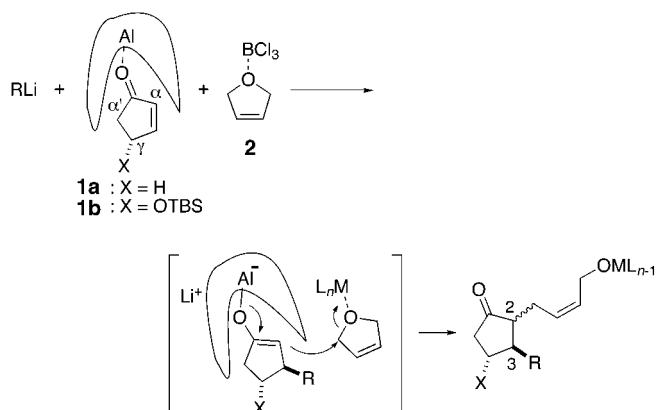
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- [9] Attempted reduction of acetophenone with previously reported (2,7-dimethyl-1,8-biphenylenedioxy)bis(diisopropoxyaluminum)^[8] (10 mol %) as a catalyst under otherwise identical conditions produced *sec*-phenethyl alcohol in 35 % yield.
- [10] The requisite aluminum ligand **2** can be readily prepared from phenol in five steps: 1) NaH, methoxymethyl chloride (MOMCl), THF (99 %); 2) BuLi, ether, then B(OMe)₃, H₃O⁺ (85 %); 3) 2-bromoaniline, Pd(OAc)₂, PPh₃, K₂CO₃, DME (70 %); 4) BuLi, *N,N,N',N'*-tetramethyl-1,2-ethylenediamine (TMEDA), C₆F₁₇SO₂F, diethyl ether (50 % with recovery of the starting material); 5) HCl, MeOH (99 %). Spectroscopic characterization of **2**: ¹H NMR (CDCl₃, 400 MHz): δ = 7.92 (s, 1H; NH), 7.65 (dd, *J* = 1.6, 8.0 Hz, 1H; ArH), 7.32–7.47 (m, 4H; ArH), 7.26 (dd, *J* = 1.6, 8.0 Hz, 1H; ArH), 7.09 (dt, *J* = 1.2, 7.6 Hz, 1H; ArH), 6.95 (dd, *J* = 1.0, 8.2 Hz, 1H; ArH), 5.44 (s, 1H; OH); IR (KBr): $\tilde{\nu}$ = 3476, 3194, 1489, 1440, 1408, 1356, 1269, 1232, 1213, 1205, 1182, 1155, 1065, 935, 835, 752 cm⁻¹; MS: *m/z* (%): 667 [*M*⁺], 184 (100), 156, 154; HRMS calcd for C₂₀H₁₀F₁₇NO₃S: 667.0109 [*M*⁺], found: 667.0106 [*M*⁺]; elemental analysis calcd (%) for C₂₀H₁₀F₁₇NO₃S: C 36.00, H 1.51, F 48.40, N 2.10; found: C 35.71, H 1.35, F 48.32, N 2.40.
- [11] Crystal structure data for the complex **4**–DMF collected at 123 K: C₃₄H₃₆Al₂F₆N₄S₂O₈, *M_r* = 860.75, monoclinic, space group *P*2₁/*c*, *a* = 9.4834(7), *b* = 9.4378(7), *c* = 21.375(1) Å, β = 97.856(3)°, *V* = 1895.2(2) Å³, *Z* = 2, ρ_{calcd} = 1.508 g cm⁻³, *R_i* = 0.063. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-165945. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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- [13] Purchased from Aldrich Chemical Co., Ltd. (99.99 % purity).
- [14] This simple method resulted in a slight decrease of the chemical yield probably due to the incomplete catalyst formation, which is technically inevitable at present.
- [15] Attempted use of other representative metal alkoxides as catalyst under similar reaction conditions gave the following results: 58 % with Gd(O*i*Pr)₃; 51 % with Sm(O*i*Pr)₃; 0 % with Zr(OR)₄ (*R* = *i*Pr, *t*Bu).
- [16] As expected, attempted reduction of acetophenone with Al(O*i*Pr)₃ (10 mol %) and *i*PrOH (10 equiv) in CH₂Cl₂ at 25 °C for more than 5 h showed no evidence of the product formation.
- [17] For the result of the scale-up reaction with acetophenone, see Experimental Section.

Novel Three-Component Coupling Using Aluminum Tris(2,6-diphenylphenoxide) (ATPH): The Same Synthetic Strategy Leads to *trans*- and *cis*-Jasmonates

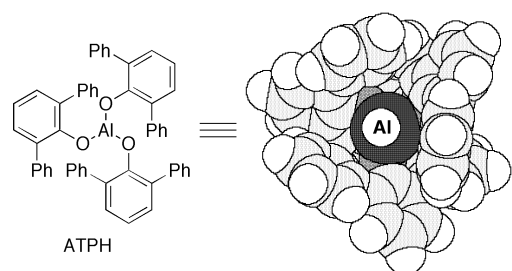
Susumu Saito, Satoko Yamazaki, and Hisashi Yamamoto*

One-pot three-component coupling^[1] is an important procedure in organic synthesis and provides a powerful and rapid means for construction of the prostaglandin^[2] and jasmonate^[3] families. Here we report on a novel strategy for three-component coupling (Scheme 1), which involves the



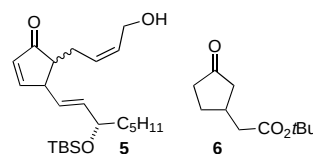
Scheme 1. Three-component coupling using ATPH. TBS = *tert*-butyldimethylsilyl.

combined use of: 1) an organolithium reagent (RLi); 2) aluminum tris(2,6-diphenylphenoxide) (ATPH;^[4] see space-filling model) cyclopentenone complexes **1a** and **1b**; and 3) 2,5-dihydrofuran (DHF)·BCl₃ complex (**2**). This approach leads efficiently to both *trans*- and *cis*-jasmonate derivatives.



Precomplexation of a solution of ATPH (1.05 equiv) in toluene with 2-cyclopenten-1-one (**3a**; 1.0 equiv) at -78°C was followed by treatment with a solution of isopropenyllithium (1.1 equiv) in DME. After 1 h, sequential addition of DHF (5.0 equiv) and BCl₃ (2 equiv) gave three-component

coupling product **4**, which was isolated in a yield of 71 % (2,3-*trans*-**4**/2,3-*cis*-**4** = 3.5:1; 2'*E*/2'*Z* = 1:99). The formation of **4** was not observed before treatment with BCl₃.^[5] The addition of a mixture of DHF and BCl₃ gave a yield and selectivity comparable to those achieved by sequential addition. Other alkenyl- and alkynyllithiums, as well as lithium enolates, are well suited to this process and give the corresponding products in moderate to high yields with complete retention of the original *Z* configuration (Table 1). The even more labile cyclopentenone **3b** was also compatible with these basic conditions (entries 3 and 6), but scant 2,3-*cis/trans* selectivity was observed with 2-alkylethenyllithiums (entries 2 and 3). The 2,3-*cis* selectivity increases in the order isopropenyl- < crotyl- < alkynyllithium, that is, with decreasing size of the organolithium reagents (each prepared in DME) (entries 1, 2, and 5).^[6]



Tetrahydrofuran was also used as an alkylating agent in place of DHF (Table 2), but in some cases the stereoselectivity was different from that with DHF. For instance, in the case of isopropenyllithium, the 2,3-*cis* product predominated with THF (Table 2, entries 2–4),^[6, 7] while the 2,3-*trans* product was formed selectively with DHF (Table 1, entries 4–6). However, both DHF and THF gave the 2,3-*cis* product almost exclusively with 1-hexynyllithium (Table 1, entry 1; Table 2, entry 1).^[6, 7] The TBSOTf·THF complex gives better 2,3-*cis* selectivity than BCl₃·THF (Table 2, entries 2–4). Both THF and DHF showed a general trend to give high 2,3-*trans* selectivity with lithium enolates (Table 1, entries 8 and 9; Table 2, entries 5–7).^[8]

With this new method in hand, various *trans*- and *cis*-jasmonate derivatives can be obtained in a few steps by assembling commercially available compounds. For example, stereo- and regioselective methylation of diphenylphosphate **8** (Scheme 2), readily obtained from *trans*-**7**, was effected by using trimethylzincate and a catalytic amount of Fe^{III} (Me₂Zn + MeMgBr (2 + 2 equiv); [Fe(acac)₃]: 1 mol %)^[9] at -78°C to give *tert*-butyl jasmonate **9** (2,3-*trans/cis* > 20:1) together with small amounts of stereo- (2'*Z*/2'*E* = 97:3; **10**, 2 %) and regioisomers (S_N2/S_N2' = 87:13; **11**, 11 %); the total yield of isomers was 87 %, and the isomeric purity of **9** was 85 %).^[10] The ketone and ester groups remained intact under these conditions. Subsequent displacement of a *tert*-butyl group (HCO₂H, RT) led to quantitative formation of *trans*-jasmonic acid.

Likewise, methyl *cis*-jasmonate was easily accessible from three-component coupling product **12** (2,3-*cis/trans* = 7.5:1 and 71 % yield from **3a**). After separation of the diastereomers (to 2,3-*cis/trans* = 99:1), a similar phosphorylation–methylation^[9] sequence (Scheme 3) caused only slight epimerization at C2 and gave **13** (2,3-*cis/trans* = 31:1) in a reasonable overall yield together with moderate amounts of stereo-

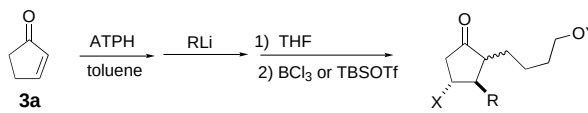
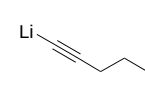
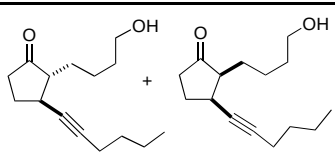
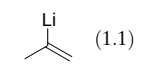
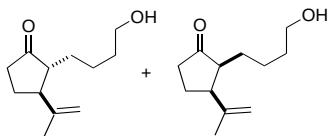
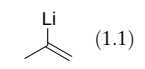
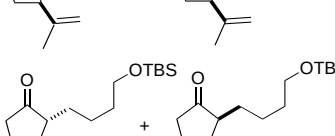
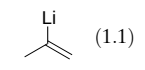
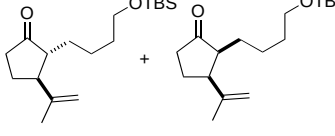
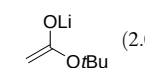
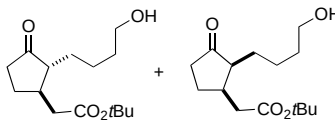
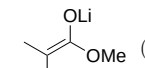
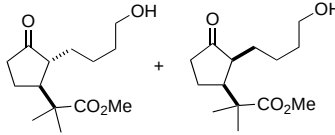
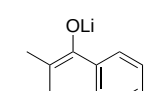
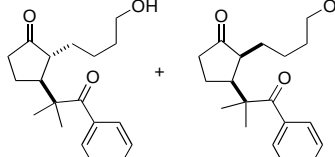
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Table 1. Three-component coupling of RLi, **1a** (or **1b**), and DHF·BCl₃ complex.^[a]

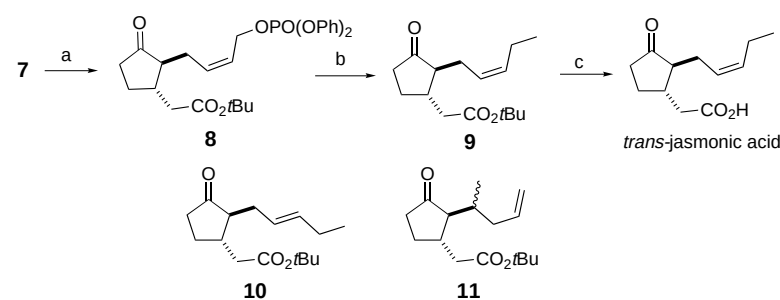
3a: X = H 3b: X = OTBS					
Entry	RLi [equiv] ^[b]	Ketone	Conditions [°C, h] ^[c, d]	Products	Yield [%] (2,3- <i>trans</i> /2,3- <i>cis</i>) ^[e]
1	(1.1)	3a	−78, 2.5; −40, 2		44 (1:11)
2	(1.1)	3a	−78, 5; −40, 0.5		57 (1.2:1)
3	(1.2)	3b	−78, 20; −40, 10		46 (1:1) ^[f]
4	(1.1)	3a	−78, 17.5; −40, 3		59 (4.4:1)
5	(1.1)	3a	−78, 1.5; −40, 3		71 (3.5:1)
6	(1.1)	3b	−78, 168		66 (79:11:10) ^[g]
7	(2.0)	3a	−78, 18; −40, 2		69 (>20:1) ^[h]
8	(2.0)	3a	−78, 19		47 (>20:1)
9	(2.0)	3a	−78, 19; −40, 3		32 (>20:1)

[a] Unless otherwise specified, the reaction was performed with a solution of ATPH (1.05 equiv) in toluene, cyclopentenone (1.0 equiv), organolithium (RLi), BCl₃ or *tert*-butyldimethylsilyl triflate (TBSOTf), and DHF. [b] Each was prepared from the corresponding alkyne, bromide, or tin reagent with BuLi (entries 1–6) or from carbonyl compounds and lithium diisopropylamide (LDA; entries 7–9) in DME (entries 1–3 and 5) or diethyl ether (entries 4 and 6–9). [c] The following conditions were used: BCl₃ (2.0 equiv) + DHF (5.0 equiv). [d] The indicated reaction temperatures and times are for the three-component coupling process. [e] Yields of isolated, purified product. The diastereoselectivity was determined by ¹H and ¹³C NMR spectroscopy. See also ref. [7]. [f] Elimination product **5** (7%) was also obtained. [g] 2,3-*trans*,3,4-*trans*/2,3-*cis*,3,4-*trans*/2,3-*trans*,3,4-*cis*. [h] Protonated product **6** (27%) was obtained.

Table 2. Three-component coupling of RLi, ATPH·3a (1a), and THF·Lewis acid.^[a]

					
Entry	RLi [equiv] ^[b]	Alkylating agent ^[c]	Conditions [°C, h] ^[d]	Products	Yield [%] (2,3- <i>trans</i> /2,3- <i>cis</i>) ^[e]
1	 (1.1)	A	−78, 2.5; −40, 2		44 (1: >20)
2	 (1.1)	A ^[f]	−78, 7.5		77 (1:2.7)
3	 (1.1)	A	−78, 2		85 (1:3.2)
4	 (1.1)	B	−78, 2; −40, 2.5		74 (1:4.0)
5	 (2.0)	A	−78, 15		43 (>20:1)
6	 (2.0)	A	−78, 15		54 (>20:1)
7	 (2.0)	A	−78, 15		57 (>20:1)

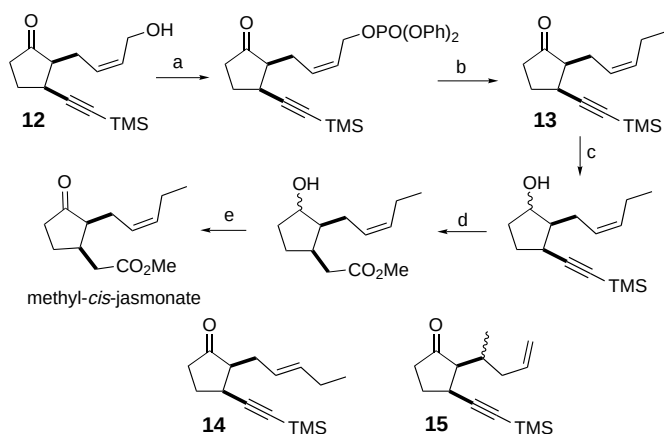
[a] Unless otherwise specified, the reaction was performed with a solution of ATPH (1.05 equiv) in toluene, cyclopentenone (1.0 equiv), organolithium (RLi, THF solution), and BCl₃ or TBSOTf. [b] Each was prepared from the corresponding alkyne, bromide, or tin reagent with BuLi (entries 1–4). Enolates were prepared by using LDA (entries 5–7). [c] The following conditions were used: A) BCl₃ (2.0 equiv) + THF (123 equiv); B) TBSOTf (7.0 equiv) + THF (123 equiv). Organolithiums or enolates were prepared in THF. [d] The indicated reaction temperatures and times are for the three-component coupling process. [e] Yields of isolated, purified products. The diastereoselectivity was determined by ¹H and ¹³C NMR spectroscopy. See also ref. [7]. [f] BCl₃ (1.1 equiv) was used.



Scheme 2. Synthesis of *trans*-jasmonic acid. Reagents and conditions: a) Et₃N, ClPO(OPh)₂, DMAP, CH₂Cl₂, −20°C, 90%; b) Me₃ZnMgBr, [Fe(acac)₃] (1 mol %), THF, −78°C, <87%; c) HCO₂H, RT, >99%. DMAP = 4-(dimethylamino)pyridine, acac = acetyl acetone.

(2'Z/2'E = 90:10; **14**, 7%) and regioisomers (S_N2/S_N2' = 84:16; **15**, 14%); the total yield of isomers was 86%, and the isomeric purity of **13** was 73%.^[10] Reduction of the ketone carbonyl group was followed by hydroboration of the trimethylsilylacetylene^[11] and subsequent oxidation. The resulting crude carboxylic acid was selectively methylated, and reoxidation of the remaining hydroxy group would lead to methyl *cis*(*epi*)-jasmonate^[12] by the method previously described.^[13]

In summary, the present coupling was successful under strongly basic conditions, which is



Scheme 3. Synthesis of methyl *epi(cis)*-jasmonate. Reagents and conditions: a) Et₃N, ClPO(OPh)₂, -20 °C, 84 %; b) Me₃ZnMgBr, [Fe(acac)₃] (5 mol %), THF, -78 °C, <86 %; c) NaBH₄, MeOH, 0 °C, 91 % (1,2-*cis*:2,3-*cis*:1,2-*trans*:2,3-*cis* = 3.2:1); d) (C₆H₁₁)₂BH, THF, 0 °C; H₂O₂, NaOH, MeOH/benzene, 0 °C; TMSCHN₂, MeOH, 0 °C, 48 %; e) see ref. [12]. TMS = trimethylsilyl.

otherwise difficult to achieve. The synthetic potential of ATPH may originate from: 1) The effective Michael addition of organolithium reagents due to both steric (prevention of 1,2-addition and α - and/or γ -deprotonation) and electronic (activation of the β -position) influence of ATPH;^[4e] and 2) the novel reactivity of the resulting ATPH enolates, which undergo either 2,3-*cis*- or -*trans*-selective alkylation by the DHF/Lewis acid complexes. This eventually accommodated the *Z* geometry of the new double bond in the α chain.

Experimental Section

Representative procedure for the reaction of ATPH·**3a**, isopropenyllithium, and BCl₃·DHF: **3a** (42 μ L, 0.5 mmol) was added to a solution of ATPH (0.53 mmol) in toluene (5.0 mL) at -78 °C under an argon atmosphere. After 20 min, isopropenyllithium [generated by treatment of a solution of isopropenyltributyltin (194 mg, 0.59 mmol) in DME (5.0 mL) with a solution of *n*BuLi (1.66 M, 0.33 mL, 0.55 mmol) in hexane at -78 °C followed by stirring at 0 °C for 12 min and cooling to -78 °C] was transferred by cannula to the solution of ATPH·**3a** at -78 °C. The reaction mixture was stirred at this temperature for 45 min. To this mixture were then added DHF (0.189 mL, 2.5 mmol) and a solution of BCl₃ (1.0 M, 1.0 mL, 1.0 mmol) in hexane. After 1.5 h, the reaction mixture was warmed to -40 °C, stirred for 3 h, quenched with aqueous NaHCO₃, filtered through a Celite pad, and extracted with Et₂O. The organic layer was dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on silica gel to give **4** (69.4 mg, 71 %) as a pale yellow oil. *trans*-**4**: IR (neat): $\tilde{\nu}$ = 3434, 2950, 1734, 1456, 1377, 1148, 1015, 895 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 5.74–5.63 (m, 1H), 5.58–5.41 (m, 1H), 4.87 (dt, 2H, *J* = 12.3, 1.2 Hz), 4.16 (dd, 2H, *J* = 6.6, 2.1 Hz), 2.57–2.03 (m, 8H), 1.76 (s, 3H), 1.78–1.63 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ = 219.8, 144.9, 130.5, 128.6, 112.0, 58.0, 52.1, 48.8, 37.8, 26.4, 24.5, 19.0; elemental analysis (%) calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34; found: C, 74.09; H, 9.64. *cis*-**4**: ¹H NMR (CDCl₃, 300 MHz): δ = 4.90 (s, 1H), 4.72 (s, 1H), 4.18–4.04 (m, 2H), 2.97–2.90 (m, 1H), 1.70 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ = 219.8, 144.2, 130.1, 129.8, 112.4, 58.1, 51.7, 46.4, 36.4, 24.5, 23.4, 22.4.

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- [5] This means that neither Li^I nor Al^{III} is the activating agent for DHF.
- [6] At present, we do not have a reasonable explanation for these unprecedented 2,3-*cis* selectivities, which might be ascribed to steric influence of ATPH.
- [7] The diastereoselectivity (2,3-*cis*:2,3-*trans*) of three-component coupling products was determined by ¹H and ¹³C NMR spectroscopy, as well as several *cis* and *trans* equilibration experiments (HCl, MeOH, RT). We found that ¹³C NMR spectroscopy could be a powerful tool for establishing the relative stereochemistry at the 2,3-vicinal carbon atoms of 2,3-disubstituted-1-cyclopentanones. In general, ¹³C NMR chemical shifts of C1' and C1'' of the *cis* adducts appear upfield due to the greater shielding effects compared to those in the *trans* products. For example, *cis*- and *trans*-2,3-dimethylcyclopentanones show δ = 9.5 (2-Me (C1')) and 14.8 (3-Me (C1')), and δ = (2-Me (C1')) and 19.1 (3-Me (C1')), respectively (J. B. Stothers, C. T. Tan, *Can. J. Chem.* **1974**, 52, 308); methyl *epi*-jasmonate, *cis*: δ = 23.0 (2-CH₂ (C1')), 33.7 (3-CH₂ (C1')); *trans*: δ = 25.6 (2-CH₂ (C1')), 37.7 (3-CH₂ (C1')) (L. Crombie, K. M. Mistry, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1981). We also found that the equilibrium reached an inherent static point depending on the size of the 3-substituent. Thus, the equilibrium lies on the *trans* side in the order of bulkiness: isopropenyl (*cis:trans* = 1:25) > crotyl (*cis:trans* = 1:11) > 1-hexynyl (*cis:trans* = 1:1.6).
- [8] In general, the concomitant formation of Michael addition products such as **6** through enolate protonation was a major side reaction. Considerable formation of this type of product (ca. 30 %) was observed in several cases (Table 1, entries 8, and 9; Table 2, entries 1, and 5–7). It is highly unlikely that the *trans* selectivity is due to the work-up procedure, since the same conditions were used throughout the work (see Experimental Section).
- [9] The details of this new stereo- and regioselective method for the alkylation of allylic phosphates by the combined use of trialkyl- or tetraalkylzincates and Fe^{III} or Fe^I catalysts will be reported elsewhere.
- [10] These selectivities (S_N2 vs S_N2'; 2'E vs 2'Z; 2,3-*cis* vs 2,3-*trans*) were determined by ¹H and ¹³C NMR spectroscopy and GC-MS.
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Angew. Chem. 2000, 112, 581; Angew. Chem. Int. Ed. 2000, 39, 569. Other approaches to methyl *cis*-jasmonate are cited therein. See also ref. [3a].

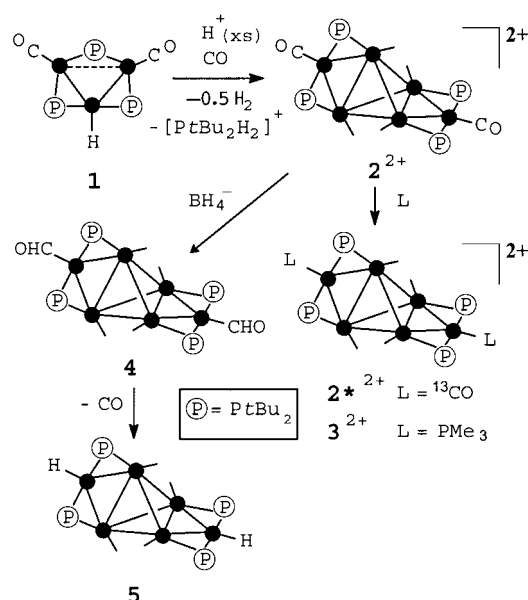
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The First Platinum Formyl, a Member of a Series of Hexanuclear Clusters Exhibiting a Rare Structure**

Piero Leoni,* Fabio Marchetti, Lorella Marchetti, Marco Pasquali, and Silvia Quaglierini

A large number of platinum clusters have been reported in the past decades.^[1] Nevertheless, only two hexanuclear structures have been authenticated by X-ray crystallography: the trigonal-prismatic $[\text{Pt}_6(\mu\text{-CO})_6(\text{CO})_6]^{2-}$ ^[2a] and the octahedral $[\text{Pt}_6(\text{CO})_6(\mu\text{-dppm})_3]^{2+}$ (dppm = bis(diphenylphosphanyl)methane).^[2b] In addition, the decanuclear $[\text{Fe}_4\text{Pt}_6(\text{CO})_{22}]^{2-}$,^[3] arising from the orthogonal dimerization of two $[\text{Pt}_3(\text{CO})_3\{\mu_2\text{-Fe}(\text{CO})_4\}_2]^-$ triangles, contains a tetrahedral Pt core, two opposite edges of which are each bridged by another platinum atom. We have discovered a facile route to platinum clusters having this unusual structure.^[4] The precursor $[\text{Pt}_6(\text{CO})_6(\mu\text{-PtBu}_2)_4](\text{CF}_3\text{SO}_3)_2$ (**2**) was prepared by treating the trinuclear hydrido cluster $[\text{Pt}_3(\text{H})(\text{CO})_2(\mu\text{-PtBu}_2)_3]$ (**1**)^[5] with an excess of triflic acid under a CO atmosphere (Scheme 1).

Figure 1 shows an ORTEP view of the cation **2**²⁺, which exhibits overall D_{2d} symmetry.^[7] Complex **2** is air-stable, thermally robust (decomp 228 °C), and remains unchanged, even under forcing conditions, in the presence of CO (100 °C, 100 atm, 12 h) or H₂ (80 °C, 90 atm, 6 h). Interestingly, **2** reacts with ¹³CO to give $[\text{Pt}_6(\text{CO})_4(^{13}\text{CO})_2(\mu\text{-PtBu}_2)_4](\text{CF}_3\text{SO}_3)_2$ (**2***), the product of selective substitution of the carbonyl ligands attached to the two “apical” atoms Pt2 and Pt5. A similar remarkable regioselectivity was also observed in the reactions of **2** with PMe₃ or NaBH₄ to give $[\text{Pt}_6(\text{CO})_4(\text{PMe}_3)_2(\mu\text{-PtBu}_2)_4](\text{CF}_3\text{SO}_3)_2$ (**3**), and $[\text{Pt}_6(\text{CO})_4(\text{CHO})_2(\mu\text{-PtBu}_2)_4]$ (**4**), respectively. The structures of **2***, **3**, and **4** can be clearly assigned on the basis of elemental analyses and IR and NMR spectra. For example, the four bridging P nuclei are still



Scheme 1. Synthesis and further reactions of **2**.

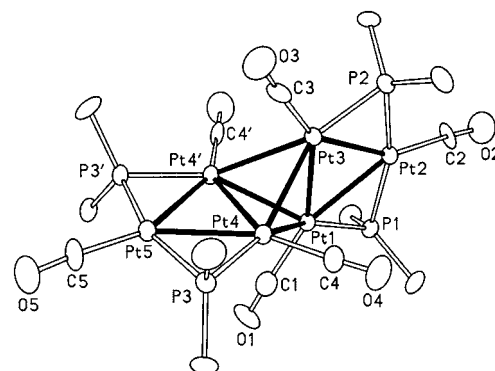


Figure 1. Molecular structure of **2**²⁺.^[7] Methyl groups are omitted for clarity (thermal ellipsoids at 30% probability; symmetry code: ' = x, -y, z). Selected bond lengths [Å] and angles [°]: Pt1-Pt2 2.758(1), Pt1-Pt3 2.667(1), Pt1-Pt4 2.841(1), Pt2-Pt3 2.762(1), Pt3-Pt4 2.841(1), Pt4-Pt4' 2.666(1), Pt4-Pt5 2.756(1); Pt3-Pt1-Pt2 61.17(3), Pt1-Pt2-Pt3 57.79(3), Pt1-Pt3-Pt2 61.04(3), Pt3-Pt1-Pt4 62.00(3), Pt1-Pt3-Pt4 62.00(3), Pt1-Pt4-Pt3 56.00(3), Pt1-Pt4-Pt4' 62.01(2), Pt3-Pt4-Pt4' 62.01(2), Pt4'-Pt4-Pt5 61.071(15), Pt4-Pt5-Pt4' 57.86(3).

isochronous and in the ³¹P{¹H} NMR spectrum they give rise to a central singlet (doublet in **3**, ²J(P_μ, P_{term}) = 13 Hz) flanked by a complex set of ¹⁹⁵Pt satellites, very similar to those observed for **2**. Strong similarities were also observed in the main features of the ¹⁹⁵Pt{¹H} NMR spectra, which still show only two signals and hence rule out all other possible isomers.

Complex **4** is of particular interest, being the first platinum formyl, and its structure was unequivocally confirmed by comparison of its spectra with those of the labeled $[\text{Pt}_6(\text{CO})_4(^{13}\text{CHO})_2(\mu\text{-PtBu}_2)_4]$ (**4***). In particular, the triplet for the formyl group at δ = 18.9 (³J(H,P) = 14 Hz) in the ¹H NMR spectrum of **4** splits as expected in **4*** (brdt, ¹J(C,H) = 152 Hz) for coupling with the adjacent ¹³C nucleus (Figure 2a, b). The same coupling is exhibited by a doublet at δ = 244.6 for the formyl C atom in the proton-coupled ¹³C NMR spectrum of **4*** (Figure 2c, d).^[6a] Furthermore, a

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

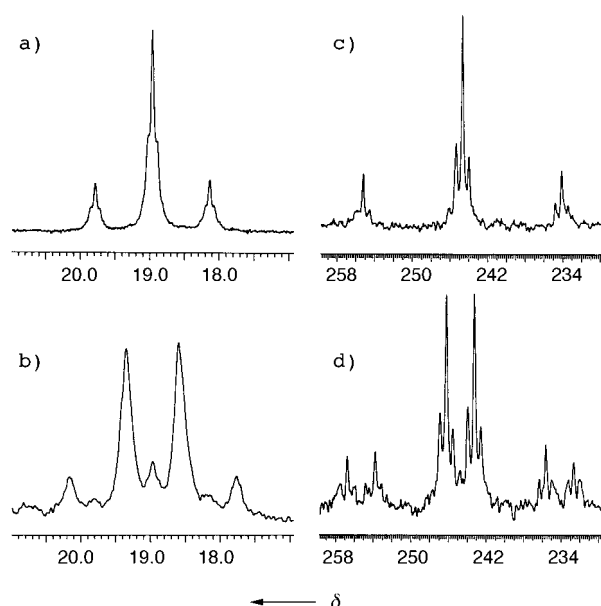


Figure 2. Formyl signals in the ^1H NMR spectra of **4** (a) and **4*** (b), and in the proton-decoupled (c) and -coupled (d) ^{13}C NMR spectra of **4***.

$\nu_{\text{C=O}}$ band at 1604 cm^{-1} in the IR spectrum of **4** shifts to 1574 cm^{-1} in the spectrum of **4***.^[6a]

Metal formyls are suggested to be important intermediates in the metal-catalyzed reduction of carbon monoxide.^[6] Complex **4** exhibits relatively high thermal stability (decarbonylation in toluene to give the dihydrido cluster $[\text{Pt}_6(\text{H})_2(\text{CO})_4(\mu\text{-PtBu})_4]$ (**5**) occurs in 5 h at 60°C and in 36 h at room temperature). Finally, to the best of our knowledge, metal diformyls were previously unknown.

Experimental Section

2: $\text{CF}_3\text{SO}_3\text{H}$ (0.4 mL, 4.5 mmol) was added to a red solution of **1** (614 mg, 0.57 mmol; prepared as previously described^[5]) in CHCl_3 (20 mL). After 2 h the flask was filled with CO (1 atm) and the reaction mixture stirred for 0.5 h; the solvent was evaporated and the residue was suspended in THF/ Et_2O . Complex **2** was isolated as a red solid (353 mg, 56%). Elemental analysis (%) calcd for $\text{C}_{40}\text{H}_{72}\text{F}_6\text{O}_{12}\text{P}_4\text{Pt}_6\text{S}_2$: C 21.7, H 3.27; found: C 21.7, H 3.26. **2*** was prepared by dissolving **2** in $[\text{D}_6]\text{acetone}$ under a ^{13}CO atmosphere. After 24 h the solution contained a 1:10 mixture of **2** and **2***. Selected data for **2** [**2***]: $^{31}\text{P}\{^1\text{H}\}$ NMR (80.9 MHz, $[\text{D}_6]\text{acetone}$, 25°C): $\delta = 383.7$ (s, with ^{195}Pt satellites); ^1H NMR (200 MHz, $[\text{D}_6]\text{acetone}$, 25°C): $\delta = 1.62$ (vt, $^3J(\text{H,P}) + ^5J(\text{H,P}) = 8\text{ Hz}$); $^{195}\text{Pt}\{^1\text{H}\}$ NMR (42.8 MHz, $[\text{D}_6]\text{acetone}$, 25°C): $\delta = -4960$ (m, 2Pt [dm, $^1J(\text{C,Pt}) \approx 1750\text{ Hz}$]), -3203 (4Pt); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, CH_3CN , 25°C): $\delta = 206.1$ (weak brs, with satellites, 4CO), 185.8 (weak brs, with satellites, 2CO [in $[\text{D}_6]\text{acetone}$, 185.4 , strong t, $^2J(\text{C,P}) = 4.7\text{ Hz}$, with satellites, $^1J(\text{C,Pt}) = 1750\text{ Hz}$, $^2J(\text{C,Pt}) = 144\text{ Hz}$]), 48.5 (s, with satellites, PC), 32.3 (s, CH_3); IR (CH_2Cl_2): $\tilde{\nu} = 2089$ (2 CO [2040]), 2056 cm^{-1} (4 CO).

3: PMe_3 (8 μL , 0.077 mmol) was added to a solution of **2** (60 mg, 0.027 mmol) in CH_2Cl_2 (2 mL). After 1 h at room temperature, most of the solvent was evaporated; addition of Et_2O (8 mL) caused the precipitation of **3** as an orange powder (44 mg, 70% yield). Elemental analysis (%) calcd for $\text{C}_{44}\text{H}_{90}\text{F}_6\text{O}_{10}\text{P}_6\text{Pt}_6\text{S}_2$: C 22.8, H 3.92; found: C 22.6, H 3.95. Selected spectroscopic data: $^{31}\text{P}\{^1\text{H}\}$ NMR (80.9 MHz, CDCl_3 , 25°C): $\delta = 337.4$ (d, $^2J(\text{P,P}) = 13\text{ Hz}$, with satellites, $\mu\text{-P}$), -13.7 (t, $^2J(\text{P,P}) = 13\text{ Hz}$, with satellites, $^1J(\text{P,Pt}) = 3370\text{ Hz}$, $^2J(\text{P,Pt}) = 333\text{ Hz}$, P_{term}); ^1H NMR (200 MHz, CDCl_3 , 25°C): $\delta = 2.46$ (d, $^2J(\text{H,P}) = 10.2\text{ Hz}$, with satellites, $^3J(\text{H,Pt}) = 40\text{ Hz}$, PCH_3), 1.50 (vt, $^3J(\text{H,P}) + ^5J(\text{H,P}) = 7\text{ Hz}$, CCH_3); $^{195}\text{Pt}\{^1\text{H}\}$ NMR (42.8 MHz, CDCl_3 , 25°C): $\delta = -2914$ (m, 4Pt), -5218 (m, 2Pt, $^1J(\text{Pt,P}) = 3370\text{ Hz}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, CDCl_3 , 25°C): $\delta = 45.7$ (s, with satellites, CCH_3), 32.5 (s, CCH_3), 25.0 (d, $^1J(\text{C,P}) = 38\text{ Hz}$, with satellites, $^2J(\text{C,Pt}) = 54\text{ Hz}$, PCH_3); IR (CDCl_3): $\tilde{\nu} = 2030\text{ cm}^{-1}$.

4: NaBH_4 (44 mg, 1.16 mmol) was added to a solution of **2** (152 mg, 0.0685 mmol) in MeOH (15 mL). Complex **4** precipitated as a violet solid (84 mg, 64%). Elemental analysis (%) calcd for $\text{C}_{38}\text{H}_{74}\text{O}_6\text{P}_4\text{Pt}_6$: C 23.7, H 3.88; found: C 23.5, H 3.90. **4*** was prepared as above, starting from **2***. Selected spectroscopic data for **4** [**4***]: $^{31}\text{P}\{^1\text{H}\}$ NMR (80.9 MHz, CD_2Cl_2 , 25°C): $\delta = 316.3$ (s, with satellites); ^1H NMR (200 MHz, CD_2Cl_2 , 25°C): $\delta = 18.9$ (t, $^3J(\text{H,P}) = 14\text{ Hz}$, with satellites, $^2J(\text{H,Pt}) = 332\text{ Hz}$, CHO [br dt, $^1J(\text{H,C}) = 152\text{ Hz}$, with satellites]), 1.31 (vt, $^3J(\text{H,P}) + ^5J(\text{H,P}) = 7\text{ Hz}$, CCH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, CD_2Cl_2 , 25°C): $\delta = [244.6$ (s) (H coupled: d, $^1J(\text{C,H}) = 152\text{ Hz}$) with satellites, $^1J(\text{C,Pt}) = 1062\text{ Hz}$, $^2J(\text{C,Pt}) = 68\text{ Hz}$]; $^{195}\text{Pt}\{^1\text{H}\}$ NMR (42.8 MHz, C_6D_6 , 25°C): $\delta = -4642$ (m, 2Pt), -2570 (m, 4Pt). IR (CD_2Cl_2): $\tilde{\nu} = 2006$ (C=O), 1608 [1574] (C=O) cm^{-1} .

5: A violet solution of complex **4** (50 mg, 0.026 mmol) in toluene (2 mL) was heated at 70°C ; the solution became red. After 6 h the solvent was evaporated and the red cluster **5** was suspended in acetone and collected by filtration (27 mg, 56%). Elemental analysis (%) calcd for $\text{C}_{36}\text{H}_{74}\text{O}_4\text{P}_4\text{Pt}_6$: C 23.2, H 4.00; found: C 23.3, H 3.98; $^{31}\text{P}\{^1\text{H}\}$ NMR (80.9 MHz, C_6D_6 , 25°C): $\delta = 342.0$ (s, with satellites); ^1H NMR (200 MHz, C_6D_6 , 25°C): $\delta = 1.41$ (vt, $^3J(\text{H,P}) + ^5J(\text{H,P}) = 7\text{ Hz}$, CCH_3), -0.09 (m, with satellites, $^1J(\text{H,Pt}) = 1385\text{ Hz}$, PtH); $^{195}\text{Pt}\{^1\text{H}\}$ NMR (42.8 MHz, C_6D_6 , 25°C): $\delta = -5146$ (m, 2Pt [dm, $^1J(\text{Pt,H}) = 1384\text{ Hz}$, in the H-coupled spectrum]), -2822 (m, 4Pt).

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Short Hydrogen Bonds, Circular Dichroism, and Over-Estimates of Peptide Helicity**

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Short polypeptide fragments from proteins were once believed to be unstructured. The observation of structure in the C peptide (connecting peptide) from the N terminus of ribonuclease A has spawned the widespread study of the structure of peptides in solution.^[1] Their structure is often characterized by using circular dichroism (CD) spectroscopy, in part because helical peptides have a distinctive CD spectrum, with a positive peak at 190 nm, and negative peaks at 208 nm and 220 nm (or 222 nm). As discussed recently,^[2] the average fractional helicity, f_H , of an N-residue peptide may be related to the observed mean residue molar ellipticity at 220 nm, $[\theta]_{220}$, by Equation (1).

$$f_H = \frac{[\theta]_{220}}{[\theta_{H\infty}]_{220} \left(1 - \frac{k}{N}\right)} \quad (1)$$

$[\theta_{H\infty}]_{220}$ is the ellipticity of an infinitely long, completely helical peptide and k is an end-effect correction, the value of which is ~ 3 . Estimated values for $[\theta_{H\infty}]_{220}$ range from $-37\,000$ ^[3] to $-44\,000$ deg cm² dmol⁻¹.^[4] The recent report^[2] of peptides of the type AcHel-(Ala₄Lys)_{*n*}Ala₂-NH₂ exhibiting values of $[\theta]_{220}$ more negative than $-44\,000$ and as low as $-55\,000$ deg cm² dmol⁻¹ is thus quite startling, and has obvious implications concerning the application of Equation (1) to interpret CD measurements. Herein, we rationalize the observation of unprecedented ellipticity at 220 nm by using recently improved theoretical methods for calculating the circular dichroism of polypeptides.

In the discussion of their observation of unprecedented intensity at 220 nm, Kemp and co-workers remarked that the $n\pi^*$ band at 220 nm has yet to be satisfactorily modeled by theory.^[2] Although this comment was correct at the time, the situation has changed. We have used ab initio calculations on *N*-methylacetamide in a continuum model of solvent to realize an improved description of the electronic states and transitions of the amide chromophore in proteins.^[5] Using a set of parameters derived from the ab initio calculations, the matrix method for calculation of the CD of polypeptides,^[6] and coordinates from X-ray structures, we have been able to reproduce $[\theta]_{220}$ for a set of 29 proteins with a correlation of ~ 0.9 .^[7] Comparable improvements have also been achieved using semiempirical parameters.^[8] Our calculations consider only the $n\pi^*$ and $\pi\pi^*$ transitions of the amide backbone chromophore. Contributions from higher-energy transitions are ignored, as are all transitions from side-chain chromophores or disulfide bridges. Whilst the calculations are not fully quantitative and tend to underestimate $[\theta]_{220}$ by about

10%, they are sufficiently accurate to explore semiquantitatively the dependence of $[\theta]_{220}$ on the precise geometry of the residues in a helical peptide.

Two potentially important features of the experimental study by Kemp and co-workers are the use of ethylene glycol as a co-solvent and a variation in temperature, which can fall as low as 253 K.^[2] Ab initio calculations have suggested that ethylene glycol promotes the formation of strong (and short) hydrogen bonds.^[9] Detailed modeling of possible conformations of AcHel-(Ala₄Lys)_{*n*}Ala₂-NH₂ in mixed solvents is beyond the scope of this report. However, we present calculated CD spectra for a range of helical conformations of a model polyalanine peptide, which suggest that the observed anomalous CD may be because of the formation of short hydrogen bonds.

Spectroscopic calculations may be quite sensitive to the precise conformation of the peptide chain. Therefore, it is important to prepare representative structures carefully. The macromolecular modeling software CHARMM was used.^[10] Minimizations of the blocked peptide, Amn-Ala₂₀-Cbx, were performed within the generalized Born continuum solvent model, with parameters appropriate for water.^[11] We have examined typical geometries for the α , 3_{10} , and π helices. Peptides with α -helical ($\phi = -48^\circ$, $\psi = -57^\circ$; and $\phi = -63^\circ$, $\psi = -41^\circ$), 3_{10} -helical ($\phi = -60^\circ$, $\psi = -30^\circ$), and π -helical ($\phi = -57^\circ$, $\psi = -70^\circ$) conformations were built for a range of main-chain hydrogen-bond lengths from $d_{O-N} = 2.5$ Å to $d_{O-N} = 3.8$ Å (d_{O-N} is the oxygen–nitrogen separation) in increments of 0.1 Å. Two α -helical geometries were examined. One, with dihedral angles $(-48^\circ, -57^\circ)$, is the classical Pauling–Corey helix; the second has dihedral angles $(-63^\circ, -41^\circ)$ close to the mean values observed in helices in proteins.^[12]

To generate the desired geometry, constraint potentials were used for both the dihedral angles and the hydrogen-bond distances. Force constants for the constraints with values of 500, 1000, and 2000 kcal mol⁻¹ Å⁻² (kcal mol⁻¹ rad⁻² for the angle constraints) were explored. We identified the values that gave structures in which the deviation from the desired dihedral angles was within 1° and hydrogen-bond distances within 0.1 Å. We chose the values that met the criteria across the range of hydrogen-bond distances and led to conformations with the lowest energy.

The peptide studied by Kemp and co-workers probably adopts an α -helical conformation. Figure 1 shows that first principles CD calculations predict a marked linear relationship between hydrogen-bond length and $[\theta]_{220}$, the intensity at 220 nm. For completeness, we have also investigated 3_{10} and π helices. They show trends similar, if less pronounced, to the α helix. A very intense band at 220 nm suggests the presence of short hydrogen bonds. Shortening from a conventional oxygen–nitrogen separation of about 3.0 Å to 2.8 Å or 2.7 Å is predicted to lead to a sizable enhancement of the intensity at 220 nm.

From the potential-energy surfaces calculated using constrained minimization within the generalized Born continuum solvent model (Figure 2) and the corresponding Boltzmann populations, the changes in temperature in the experimental system from 333 K to 253 K cannot entirely account for the

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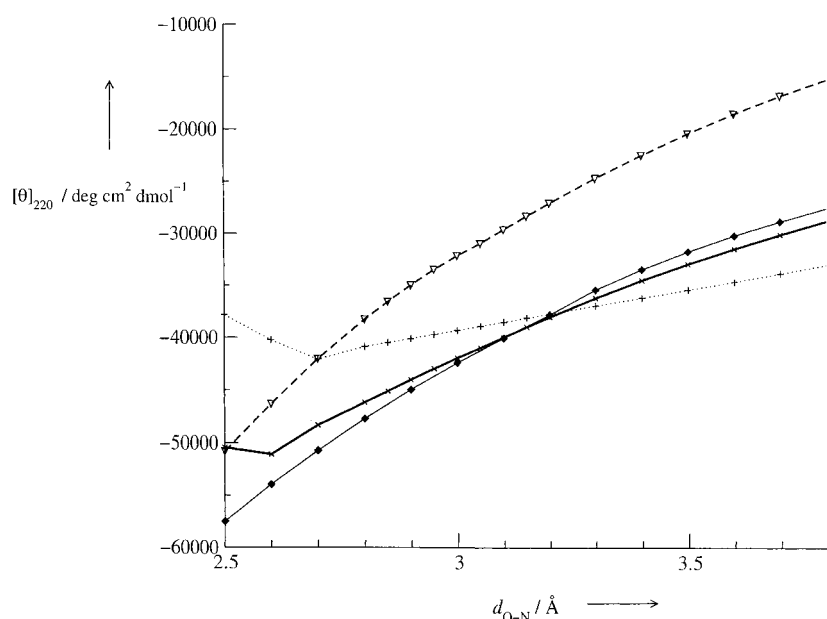


Figure 1. Mean residue ellipticity at 220 nm, $[\theta]_{220}$, calculated as a function of main-chain hydrogen-bond length for different helices, d_{O-N} : (∇) = 3_{10} helix (-60° , -30°); (+) = π helix (-57° , -70°); ($\times$) = α helix (-48° , -57°); ($\blacklozenge$) = α helix (-63° , -41°).

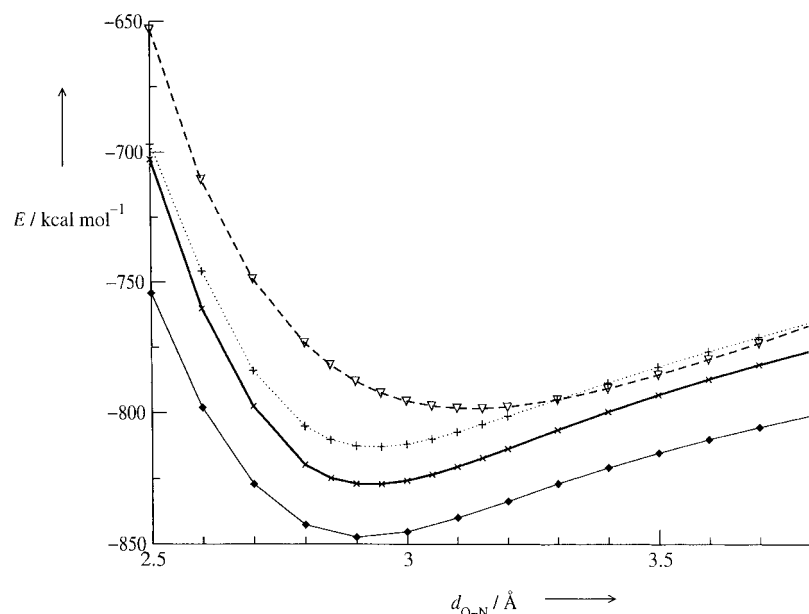


Figure 2. The potential energy, E , calculated as a function of main-chain hydrogen-bond length for different helices in water, d_{O-N} : (∇) = 3_{10} helix (-60° , -30°); (+) = π helix (-57° , -70°); ($\times$) = α helix (-48° , -57°); ($\blacklozenge$) = α helix (-63° , -41°).

large changes in $[\theta]_{220}$. However, an explanation is suggested by ab initio calculations on the solvent influence on peptide hydrogen-bond stability in water, ethanol, ethylene glycol, and trifluoroethanol.^[9] This investigation of hydrogen-bond strength with the interaction with one or more solvent molecules found a significant cooperative effect strengthening the hydrogen bond in the presence of certain high-polarity solvent molecules, which selectively bind to the helical conformation of peptides.

In a helical peptide, solvent molecules can hydrogen bond to unsatisfied hydrogen-bonding valences at the termini of the helix. Hydrogen-bonding valences within the core are satis-

fied by main-chain hydrogen bonds. Solvent molecules may be able to hydrogen bond directly to core amide residues. However, even if they do not, recent theoretical work^[13] suggests that there is a high degree of cooperativity in chains of hydrogen-bonded amides, which may provide a mechanism for propagating short hydrogen bonds along a helix.

Thus, calculations of the CD of helical peptides from first principles indicate that $[\theta]_{220}$ is sensitive to the main-chain hydrogen-bond length. Changes in the hydrogen-bond lengths alter the distances, orientation, and interactions between the electronic excited states on different amides. Detailed analysis of our matrix-method calculations suggests that these interactions and their variation with hydrogen-bond length are quite sensitive to the particular geometry of the peptide chain. In the Pauling–Corey helices, the predominant effect of a shorter hydrogen bond is to increase the interaction between the $\pi\pi^*$ electric transition dipole moments of the two hydrogen-bonded peptide groups. In the other α -helical geometry that we examined, shorter hydrogen-bond lengths increase the interaction between the $n\pi^*$ transition on one amide group with the $\pi\pi^*$ transition on the subsequent amide along the chain. Whilst the change in the intensity at 220 nm is the most striking feature of the experimental data, there are also significant changes at 208 nm. The precise geometry of the peptide is unknown and it may be that both mechanisms play a role in modifying the CD spectrum.

Ab initio calculations provide strong evidence that ethylene glycol promotes short hydrogen bonds. Thus, we propose that the unprecedented intensity observed by Kemp and co-workers for a helical peptide in a water/ethylene glycol solvent is a result of short hydrogen bonds. Similar observations of intense CD in trifluoroethanol/water and in aqueous salt (NaCl) solutions have also been reported.^[2] Short hydrogen bonds may be

significant in the former; the effect of salt is perhaps less clear. The short hydrogen-bond hypothesis might be tested experimentally through NMR spectroscopy measurements or theoretically by molecular dynamics simulations of the peptide in explicit solvent. In the latter case, however, a typical potential based on pair-wise additive interactions may not be adequate, as noted by Guo and Karplus.^[9]

Our calculations demonstrate that short hydrogen bonds will influence the CD spectra of peptides. They present one plausible explanation for the origin of anomalously high ellipticity. Other factors may also be important. Woody has suggested^[14] that the interaction of the charged lysine residues

with amide carbonyl oxygen atoms is likely to lead to strong mixing of the $n\pi^*$ and $\pi\pi^*$ transitions in those amide groups.

In conclusion, some helical structures formed by simple polypeptides in solution may have unusually short main-chain hydrogen bonds. Our calculations indicate that the helicity of such peptides will be over-estimated by CD analysis based on literature calibration of helical content. Whilst much is still to be established, if short hydrogen bonds can form under certain conditions, the use of CD to estimate helicity will have to be complemented by another experimental probe that is sensitive to hydrogen-bond length.

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Orientation Dependence of Energy Transfer in an Anthracene–Porphyrin Donor–Acceptor System**

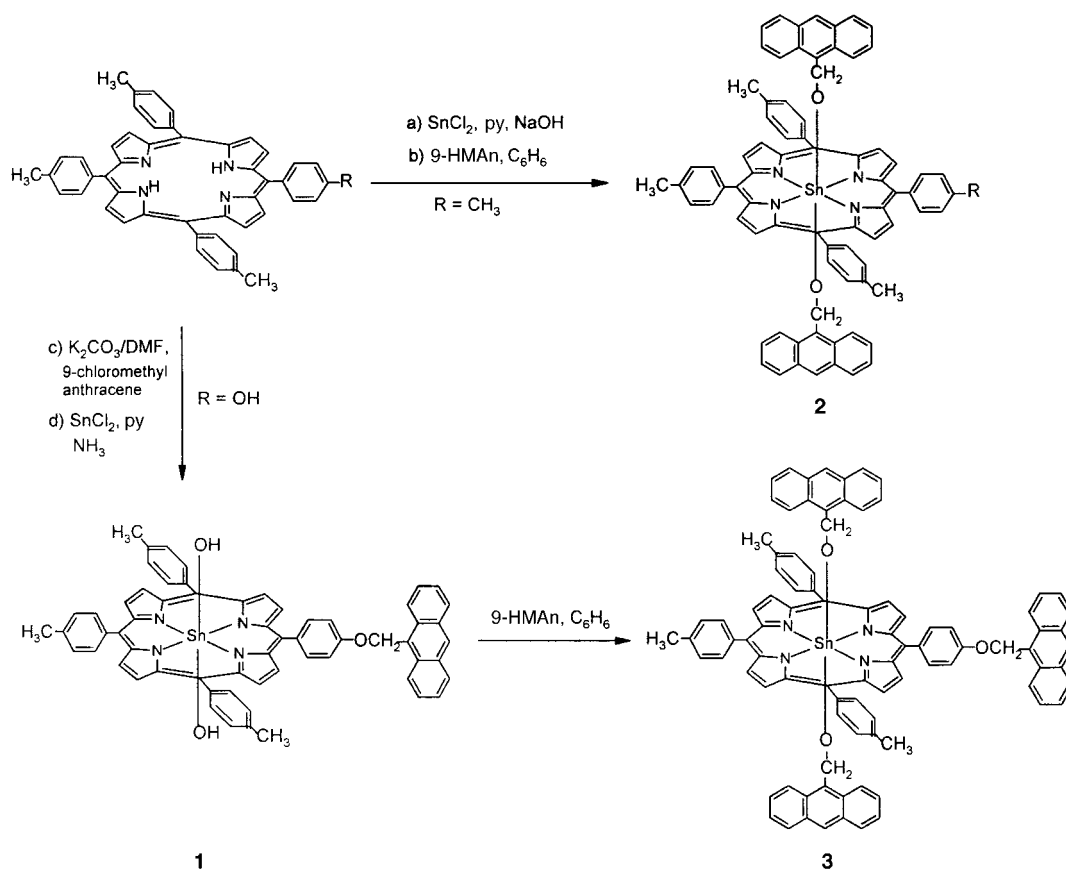
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The rates of electronic energy transfer (EET) reactions mediated by both dipole–dipole and electron-exchange mechanisms have long been postulated to be critically dependent, amongst other things, on the distance and mutual orientation between the donor and acceptor moieties.^[1, 2] Recent experimental validation of these theoretical predictions comes from energy-transfer studies carried out with rationally designed, photochemically active donor–acceptor (D–A) assemblies.^[3] Amongst such D–A systems, those based on the porphyrinoid class of chromophores are of relevance to the present work. A number of studies carried out with the covalently/noncovalently linked porphyrin–porphyrin^[3b,c, 4] and porphyrin–nonporphyrinic chromophore^[5] assemblies have dealt with the effect of D–A distance on the rates of EET reactions but, relatively less attention has been paid to the corresponding orientation effects. In addition, to our knowledge, orientation dependence of EET has not been unequivocally demonstrated in a porphyrin-based system where the donor and the acceptor subunits are disposed at two distinctly different orientations in a given D–A ensemble. Here, we demonstrate the orientation dependence of energy transfer in a simple, porphyrin-based, D–A system **3** where the donor anthracene subunits are linked both at the axial and peripheral sites of a tin(IV) porphyrin scaffold, Scheme 1. Fluorescence-emission and excitation spectra reveal that light absorbed by the “peripheral” anthracene unit of **3** is efficiently transferred to the porphyrin but, that absorbed by the “axial” anthracene subunits is not.

The syntheses of **3** and the corresponding “reference” compounds **1** (where the anthracene subunit occupies only a peripheral position) and **2** (where the anthracene subunits occupy only the axial sites) are illustrated in Scheme 1. These new porphyrins have been characterized by elemental analysis, UV/Vis, ¹H and ¹³C NMR spectroscopy, and electrochemical methods. In the ¹H NMR spectra, the spacer methylene protons connecting the porphyrin and anthracene chromophores of **1** resonate at $\delta = 6.33$, whereas the corresponding axial methylene protons of **2** resonate at $\delta = 5.65$ as a result of the ring-current effect exerted by the basal porphyrin macrocycle. In the spectrum of **3**, resonances arising from the two peripheral and the four axial methylene protons are at $\delta = 6.32$ and 5.62, respectively. The UV/Vis spectra of **1**, **2** and **3** (in CH₂Cl₂) are nearly equivalent to the summation of the

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Scheme 1. Synthesis of the three D–A systems investigated; py = pyridine.

spectra recorded for 1:1, 1:2, and 1:3 equivalents (mole/mole) of 5,10,15,20-tetra(*p*-tolyl)porphyrinato tin(IV) dihydroxide ($[(\text{ttp})\text{Sn}^{\text{IV}}(\text{OH})_2]$) and anthracene (or 9-hydroxymethyl anthracene (9-HMAAn)), respectively (Figure 1 a). These spec-

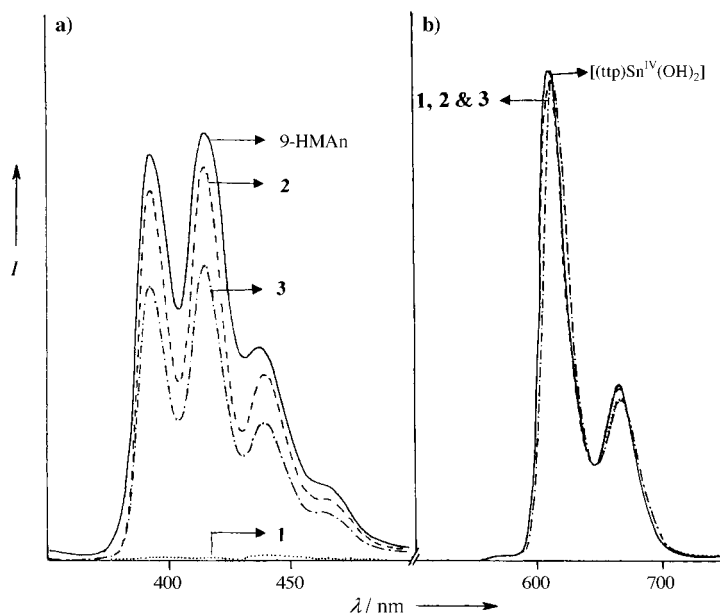


Figure 1. a) Fluorescence spectra of equiabsorbing solutions (O.D. = 0.14) of 9-HMAAn, **1**, **2**, and **3** in CH_2Cl_2 ($\lambda_{\text{ex}} = 250 \text{ nm}$); b) fluorescence spectra of equiabsorbing solutions (O.D. = 0.18) of $[(\text{ttp})\text{Sn}^{\text{IV}}(\text{OH})_2]$, **1**, **2**, and **3** in CH_2Cl_2 ($\lambda_{\text{ex}} = 525 \text{ nm}$); O.D. = optical density.

trophic data indicate that electronic communication between the porphyrin and the axial/peripheral anthracene π ring systems in these D–A systems is quite insignificant. UV/Vis data additionally suggest that there is scope to individually address the photophysical properties of the porphyrin and anthracene chromophores of **1–3** by excitation either in the 500–600 nm region or at $< 300 \text{ nm}$, respectively.

Irradiation into the porphyrin absorption band (525 nm) of CH_2Cl_2 solutions of these molecular systems resulted in fluorescence quantum yields that are close ($\Phi = 0.047–0.048$) to the quantum yield of $[(\text{ttp})\text{Sn}^{\text{IV}}(\text{OH})_2]$ ($\Phi = 0.048 \pm 0.004$), Figure 1 b. On the other hand, excitation at the anthracene absorption maximum (250 nm) resulted in quenching of fluorescence for **3** ($\Phi = 0.21 \pm 0.01$) and also **1** ($\Phi < 0.001$) compared to the fluorescence of 9-HMAAn ($\Phi = 0.32 \pm 0.02$). Interestingly, fluorescence arising from the anthracene sub-units of **2** was largely unaffected ($\Phi = 0.29 \pm 0.02$) under similar experimental conditions, Figure 1 a.^[6] The quenching efficiencies (% $Q = \{[\Phi_{9\text{-HMAAn}} - \Phi_{1,2,\text{or } 3}]/\Phi_{9\text{-HMAAn}}\} 100$) for the anthracene units of **1–3** are estimated ($\pm 7\%$) to be ~ 99 , 9, and 34, respectively.

Fluorescence life times ($\pm 10\%$) of the anthracene chromophores ($\lambda_{\text{ex}} = 250 \text{ nm}$, $\lambda_{\text{em}} = 400 \text{ nm}$) of these D–A systems are: **1**, 0.16 ns ($\sim 100\%$); **2**, 2.14 ns (100%), and **3**, 0.62 ns (31%) and 2.28 ns (69%), the values in the parentheses are the relative amplitudes obtained while fitting the data to one/two exponential decay functions. The one-exponential decays observed for tin(IV) porphyrin based D–A systems **1** and **2** are

unlike those of the several free-base porphyrin–anthracene systems reported by us earlier.^[7] The biexponential fluorescence decay observed for the latter systems, in which the porphyrin and anthracene are connected by a flexible $-\text{OCH}_2-$ linkage (at the “peripheral sites”), has been interpreted in terms of the presence of two different D–A conformers (“closed” and “extended”) that do not equilibrate within the life time of the fluorophore. Clearly, the single exponential decay of the analogous tin(IV) porphyrin based systems **1** and **2** indicates that such a conformational equilibrium does not play a significant role in these cases.^[8] Based on the data of **1** and **2**, the biexponential decay of **3** can be rationalized in terms of the presence of two different ground-state D–A orientations (unquenched axial and quenched peripheral) in this system.

Excitation of both **3** and **1** at 250 nm resulted in the appearance of well-defined porphyrin emission bands in the 600–700 nm region; this was not the case for **2**. In addition, overlap of the corrected and normalized excitation spectra (emission collected at the porphyrin emission maximum, 665 nm) with the corresponding absorption spectra reveals that fluorescence quenching is entirely a result of the energy transfer in these two D–A systems (Figure 2). The energy-

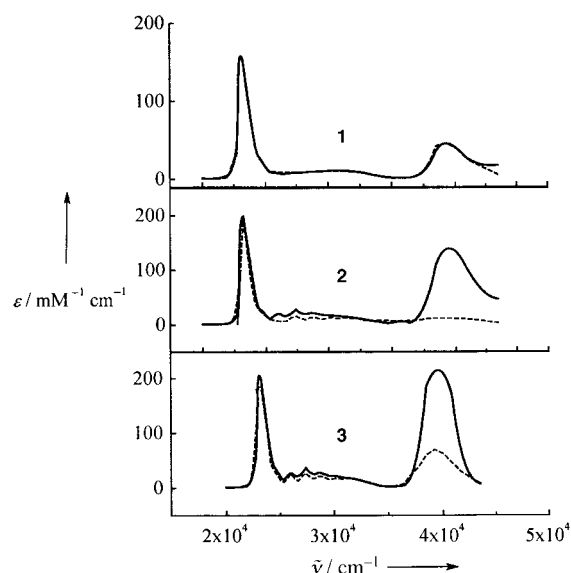


Figure 2. Overlay of the excitation (---) and absorption (—) spectra of **1**–**3** in CH_2Cl_2 ($\lambda_{\text{em}} = 665 \text{ nm}$). The excitation spectra were corrected for the instrument response function and were normalized with respect to the absorption spectra between $22\,222$ – $25\,000 \text{ cm}^{-1}$.

transfer efficiencies (%E) for **1** (99 ± 7) and **3** (25 ± 3) are quite close to the corresponding %Q values (see above). There was no indication of any energy transfer in **2** (see Figure 2, %E = 5 ± 2) consistent with the high fluorescence observed for this system.

Thus, energy transfer is lacking in **2** (where the donor subunits are *exclusively* at the axial positions), almost quantitative in **1** (where the donor subunit is *exclusively* at the peripheral site), and is approximately 30% in **3** (where two donor subunits are at the axial site and one at the peripheral position). Clearly, energy transfer to the porphyrin is strongly favored ($\sim 100\%$) from the peripheral anthracene

and is quite inefficient ($\sim 0\%$) from the axial anthracene in these D–A systems. It should be noted here that the peripheral anthracene subunit of **3** absorbs only one third of the incident light at the excitation wavelength. Thus, a near 30% quenching observed for this system amounts, actually, to %E ~ 100 from the peripheral anthracene to the porphyrin.^[9]

Having demonstrated the orientation dependence of EET in these D–A systems, it is pertinent to explore the origin of this novel effect. The Dexter's exchange mechanism requires the presence of electronic communication between the donor and acceptor species (via orbital overlap).^[2] However, the ^1H NMR and UV/Vis data discussed above indicate that such interaction in these intramolecular porphyrin–anthracene compounds is quite insignificant. Therefore, we chose to analyze the EET in **3** by the dipole–dipole mechanism, according to which the rate of EET, k_{Forster} , is given by Equation (1).^[1]

$$k_{\text{Forster}} = [8.8 \times 10^{-25} \kappa^2 \Phi_D J_{\text{Forster}}] / [n^4 \tau R^6] \quad (1)$$

In Equation (1) n is the solvent refractive index, Φ_D and τ are the fluorescence quantum yield and the fluorescence lifetime of the isolated donor (anthracene), J_{Forster} is the Forster's overlap integral representing emission of anthracene and absorption of the acceptor ($[(\text{ttp})\text{Sn}^{\text{IV}}(\text{OH})_2]$) components, R is the D–A center-to-center distance, and κ^2 is the so-called orientation factor. While J_{Forster} ($= 1.2 \times 10^{-13} \text{ cm}^6 \text{ mol}^{-1}$), Φ_D ($= 0.24$) and τ (5.2 ns) are the same for both axially and peripherally substituted situations, the center-to-center distances between the tin(IV) ion and the axial and equatorial anthracene rings in **3** are estimated to be 6.5 and 9.5 Å, respectively.^[10] We thus note that, assuming the same κ^2 ($= 2/3$, for a random D–A orientation), the Forster energy transfer to the porphyrin should, in principle, be more conducive from the axial anthracenes than it is from the peripheral anthracene according to Equation (1).^[11] This is clearly not the case as revealed by the %E values given above. Thus, κ^2 [Eq. (2)] plays a key role in determining the directionality of EET in **3**.

$$\kappa^2 = [\cos \gamma - 3 \cos \alpha \cos \beta]^2 \quad (2)$$

In Equation (2) α and β are the angles made by the transition dipoles of anthracene (axial/peripheral) and porphyrin with the line joining the centers of the transitions and γ is the angle between the two transition dipoles. While the transition dipole of the emitting ^1S state of anthracene lies on the short axis of the molecule,^[12] that of porphyrin is known to lie along a line joining two opposing pyrrole nitrogens.^[13] Thus, the near perpendicular juxtaposition of the donor and acceptor transition dipoles when the anthracenes occupy the axial sites and the near coplanar situation when the anthracene is linked at the peripheral site seem to be modulating the κ^2 in such a way that the energy transfer is nearly absent in **2** and is almost quantitative in **1**.^[14] The unique behavior of compound **3**, wherein the anthracene donors are connected both at the axial and peripheral sites is thus self explanatory.

In summary, to our knowledge, D–A compound **3** is the first porphyrin-based system wherein the donor species are

connected both at the axial and peripheral positions of the macrocycle. Energy transfer occurs only from the peripheral anthracene to the porphyrin in this system. We believe that realization of such an orientation dependence of EET would amount to demonstration of unidirectionality of the energy transfer event.^[15]

Experimental Section

Materials were obtained from either Aldrich Chemicals (USA) or BDH (India). Measurements of absorption, steady-state fluorescence and excitation, and ¹H and ¹³C NMR spectra (200 or 400 MHz) and also the time-resolved fluorescence decays were carried out as detailed previously.^[7, 16] Fluorescence quantum yields (Φ) were estimated using either 5,10,15,20-tetraphenylporphyrinato zinc(II) (for λ_{ex} = 525 nm, porphyrin band) or anthracene (λ_{ex} = 250 nm, anthracene band) as standards.

Syntheses: **1** (0.05 g, 0.05 mmol; obtained, in 82 % yield, by tin insertion into 5-(4-(9-methoxy anthracenyl)phenyl)-10,15,20-tri(*p*-tolylporphyrin)) and 9-HMAN (0.05 g, 0.24 mmol) were dissolved in dry C₆H₆ (20 mL). The resulting mixture was refluxed under a nitrogen atmosphere for 12 h. Solvent was evaporated under reduced pressure and the residue was redissolved in minimum amount of CHCl₃ and purified by flash column chromatography on an alumina column. The purple (second) fraction was collected by eluting with CHCl₃. Evaporation of the solvent and recrystallization from CHCl₃/hexane afforded **3** in 73 % yield.

Compound **2** was synthesized by refluxing [(ttp)Sn^{IV}(OH)₂] and 9-HMAN in benzene and purified in a manner analogous to that described above for **3**. Yield: 74 %.

Characterization (selected data) **3**: ¹H NMR (200 MHz, CDCl₃, 25 °C, TMS): δ = 9.25 (m, 8H, β -pyrrole), 8.58 (m, 4H, anthracene), 8.38 (m, 8H, anthracene), 8.18 (m, 9H, tolyl and anthracene), 8.05 (m, 6H, tolyl and anthracene), 7.55 (m, 16H, tolyl and anthracene), 6.32 (s, 2H, -OCH₂, peripheral), 5.65 (s, 4H, -OCH₂, axial), 2.75 (s, 9H, CH₃); ¹³C NMR (50 MHz, CDCl₃, 25 °C, TMS): 63.4 (-OCH₂, peripheral), 57.2 (-OCH₂, axial); UV/Vis (CH₂Cl₂): λ_{max} [nm] (log ϵ): 607 (4.15), 565 (4.12), 525 (3.50), 429 (5.36), 255 (5.36); elemental analysis (%) calcd for: C₉₂H₆₆N₄O₃Sn: C 79.25, H 4.77, N 4.02; found: C 79.11, H 4.62, N 4.55; cyclic voltammetry: $E_{1/2}$ (CH₂Cl₂, 0.1M TBAP (tertabutyl ammonium perchlorate)); [V] versus SCE (saturated calomel electrode): 1.60, 1.38, -0.92, -1.32.

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[8] Note that the possibility of the presence of short-lived components, the life times of which are within the instrument response function can not be ruled out.

[9] This analysis implicitly assumes that singlet energy migration between the axial and equatorial anthracenes in **3** is negligible.

[10] Molecular structures of these compounds have been modeled using the PM3 calculations. The PM3 minimized structures reveal that, at the axial sites of **3** (and also **2**), the dihedral angle Sn-O-C-C_{anthracene} and the angle Sn-O-C are 165.5° and 120.8°, respectively. The corresponding dihedral angle C_{meso}-O-C-C_{anthracene} and the angle C_{meso}-O-C, at the peripheral sites of **3** (and also **1**), are 104.4° and 125.6°, respectively. Thus, there is a near perpendicular juxtaposition of the porphyrin and the axial anthracene subunits in **3**, probably because the corresponding “nonperpendicular” orientations are sterically unfavorable in this crowded system. By contrast, changing the dihedral angle between the porphyrin and equatorial anthracene can potentially generate many energetically close rotamers that are not sterically unfavorable.^[7]

[11] Indeed, assuming that κ^2 = 2/3, the energy-transfer rate from the axial anthracene to the porphyrin has been estimated to be an order of magnitude faster than it is from the peripheral anthracene (calculations were performed using PhotochemCAD: H. Du, R.-C. A. Fuh, J. Li, L. A. Corkan, J. S. Lindsey, *Photochem. Photobiol.* **1998**, 68, 141).

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[14] The value of κ^2 estimated for the PM3 minimized structure is as low as 0.0004 for the porphyrin–axial-anthracene pair and is quite high (1.28) for the porphyrin–peripheral-anthracene pair. However, given the “semi-rigid” nature of the link between the two chromophores in **3**, our estimation of the magnitudes of the κ^2 values may not be rigorous. Nonetheless, the above analysis suggests that the directionality conditions of the dipole–dipole mechanism clearly do not favor Förster energy transfer between the axial anthracenes and the basal porphyrin. Notwithstanding this, other explanations (e.g. those involving the tin(IV) center) that do not invoke the κ^2 dependence of energy transfer and yet rationalize the absence of energy transfer in the axial direction in **2** and **3** cannot be ruled out altogether.

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Design and Synthesis of a Protein Catenane**

Liang Z. Yan and Philip E. Dawson*

The structural characterization of thousands of proteins has revealed over 550 different backbone topologies.^[1] Interestingly, none of these proteins form a backbone structure that can be described as topologically linked. Examples of knotted and catenated structures have been observed within a single peptide chain through disulfide bonds and cofactors,^[2] a handful of linear “knotted” proteins have been described.^[3] Recently, the bacteriophage HK97 capsid^[4, 5] was found to be composed of a network of interlocking protein subunits connected through a side chain isopeptide bond. Here, we describe the design and synthesis of the first protein with topologically linked backbone structure, a protein [2]catenane.

In contrast to proteins, interlocked macromolecules represent an intensely studied area of supramolecular chemistry,^[6] and natural and synthetic DNA molecules form both knotted and catenane structures.^[7] Catenanes have been synthesized by both statistical and template-directed strategies.^[6] Since proteins have evolved to fold into defined three-dimensional structures, a folding-directed strategy was devised. The tetramerization domain of the tumor suppressor protein p53 (residues 325–356) has been structurally characterized by crystallographic and NMR methods.^[8, 9] The structure can be described as a “dimer of dimers” in which the repeated dimer unit consists of two antiparallel β -strands and two antiparallel α -helices (Figure 1). These structures are formed by the

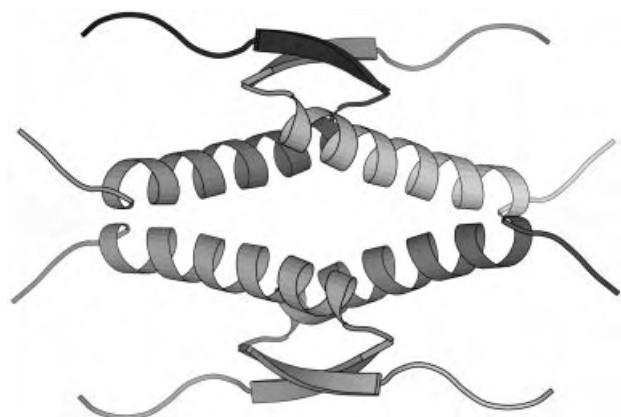


Figure 1. Structure (Molscript plot^[24]) of the tetramerization domain of the tumor suppressor protein p53. The backbone is represented as a ribbon to highlight the interlocking structure of the dimers.

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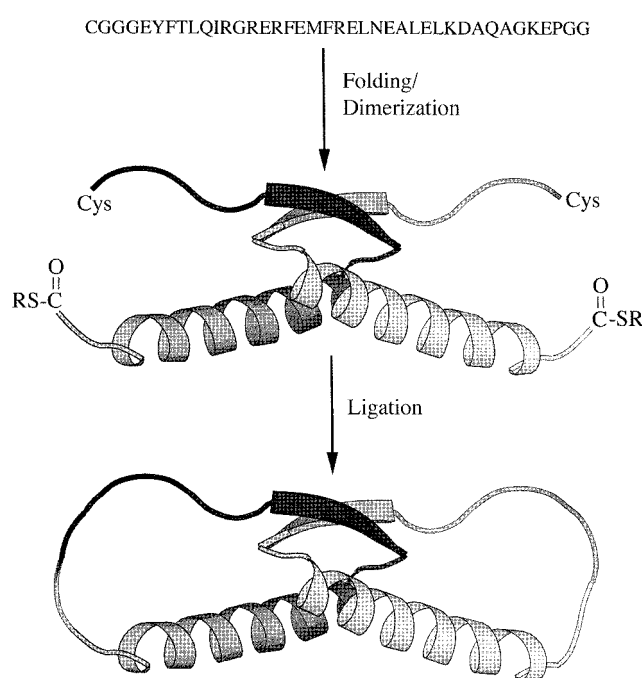
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

folding of the peptides in an intertwined manner that has been described as a bisecting U motif.^[10] It was reasoned that if the N- and C-termini of each folded peptide could be joined to form a cyclic peptide, the polypeptides would become interlocked, creating a catenane structure.

To form a peptide bond between the N- and C-termini of the p53 peptides following folding, a highly chemoselective reaction is necessary. Native chemical ligation utilizes the rapid and specific reaction of an N-terminal cysteine residue with a C-terminal α -thioester group to form a native amide bond. This reaction is mediated by thioester exchange followed by a rapid S to N acyl shift.^[11] If the N-terminal Cys and C-terminal thioester groups are on the same polypeptide, cyclic products (e.g. cyclic peptides and proteins) can be generated with remarkable efficiency.^[12, 13]

The synthetic strategy for the assembly of the p53 catenane is described in Scheme 1. Since protein dimerization and folding are rapid^[14] compared to the native chemical ligation



Scheme 1. Synthetic design of the p53 catenane.

reaction at pH 6, the p53 peptides should assemble before circularizing. The resulting structure is expected to consist of two p53 catenanes folded together to form a dimer of catenanes. A polypeptide corresponding to residues 325–361 with an N-terminal CGG extension and a C-terminal thioester was synthesized by standard solid-phase protein synthesis using butyloxycarbonyl protecting groups (Boc-SPPS) on a thioester resin. The folding and ligation of the CGG-p53-COSR polypeptide was highly efficient, yielding a single major peak by HPLC after 6 h (Figure 2a).^[15]

Since [2]catenanes are held together by a mechanical bond, they are a single molecular compound which cannot dissociate into separate components without breaking at least one covalent bond. Consistent with this structure, the observed molecular weight of 8971.5 Da by ESI-MS corresponded to

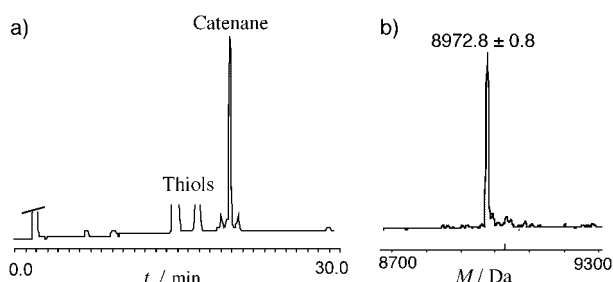


Figure 2. Synthesis of p53 catenane. a) HPLC trace of crude reaction mixture after 6 h. b) Electrospray mass spectrum of the major peak, deconvoluted to a single mass.

two cyclic p53 peptides (Figure 2b). An alternative structure that would have the same mass is a cyclic dimer. To confirm the catenane structure, a partial cleavage at the single cysteine residue was performed by cyanylation followed by aminolysis.^[16] Analysis of the cleavage products by HPLC and ESI-MS detected only linear monomer (4529 Da), cyclic monomer (4487 Da), and cyanylated cyclic monomer (4511 Da) products. The presence of cyclic monomer and absence of linear dimer products is consistent with the interlocked structure.

The folded structure of the p53 catenane was characterized by circular dichroism. The CD spectrum of the p53 catenane (Figure 3) has the same minima as that of the linear form although the mean residual ellipticity is significantly higher

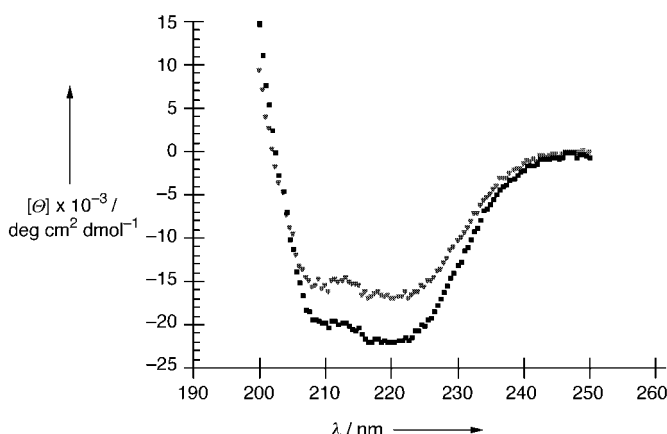


Figure 3. Circular dichroism spectra of linear (▼) and catenated (■) p53 tetramerization domains.

for the catenane structure. This enhancement could result from structural differences in the CGG-linker or from the region corresponding to the “ends” of the linear p53 peptides.^[17] Two p53 catenanes are expected to fold together to form a dimer of catenanes of 17942 Da. Consistent with this folded conformation, a molecular weight of 16250 Da was determined by analytical ultracentrifugation.

Linear proteins can be stabilized by engineered disulfide bonds and by tethering dimeric proteins.^[18, 19] The resulting increase in stability has been attributed to reduction in entropy and the resulting destabilization of the unfolded state.^[20] By analogy, the p53 catenane was expected to be more stable than the linear p53 tetramer as a result of peptide cyclization and topological linking. As anticipated, the linear p53 tetramer started denaturing at about 60 °C with a T_m of

83 °C, while the p53 catenane was folded up to 98 °C, as monitored by CD at 222 nm. Interestingly, the p53 catenane is significantly stabilized even though only one of the dimer interfaces is topologically linked.^[21]

The design and synthesis of the p53 protein catenane demonstrates a novel method for assembling and stabilizing proteins. The protein folding-assisted assembly of the linear polypeptide chains followed by backbone circularization using native chemical ligation should be applicable to the entire family of bisecting U proteins using synthetic or biologically expressed C-terminal thioester peptides. In addition, other homo- or heterodimeric proteins may be accessible to topological engineering through the use of appropriate peptide linker sequences. Protein catenanes may find application in many areas of protein science including the study of folding and dynamics and the development of novel protein materials.

Experimental Section

Peptide synthesis and assembly: The polypeptide corresponding to CGGGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPGG was synthesized manually using established *in situ* neutralization protocols for Boc-SPPS^[22] on a thioester resin.^[23] The crude peptide was purified by reversed-phase HPLC, and characterized by ESI-MS: 4704.3 ± 1.0 Da. The purified linear peptide (3.5 mg) was dissolved in a solution (1.5 mL; pH 7.5) containing 0.1 M NaH₂PO₄ and 1 mM EDTA, and benzyl mercaptan (30 μL; 2%) and thiophenol (30 μL; 2%) were added; the final ligation mixture was pH 6. The circularized product was purified by HPLC. (1.6 mg, 47% recovered yield). ESI-MS: 8971.5 ± 1.5 Da.

Cyanylation and aminolysis: The cyclic product (1.6 mg, 0.18 μmol) and 1-cyano-4-(dimethylamino)pyridinium tetrafluoroborate (CDAP) (63.4 μg, 0.27 μmol) were dissolved in a solution (1.2 mL; pH 2.3) containing degassed 6 M guanidine and 0.1 M AcOH for 20 min at 25 °C. After desalting by HPLC, the cyanylated peptides (0.4 mg) were treated with 3.0 M ammonia (0.2 mL) at 0 °C for 20 min. The following species were found by ESI-MS: 8972.0 ± 1.3, 4528.8 ± 1.0, 4512.1 ± 0.3, 4486.6 ± 0.8 Da.

Circular dichroism and thermal denaturation: The CD spectra were recorded on an Aviv spectropolarimeter with a 2-mm pathlength cuvette. Samples were prepared in 0.1 M NaH₂PO₄ (pH 6.4), and concentrations were determined by amino acid analysis. Thermal denaturation was monitored by CD at 222 nm from 2 °C to 98 °C in increments of 2 °C with 2 min equilibration.

Analytical ultracentrifugation: Experiments were carried out in a Beckman XL-A analytical ultracentrifuge at 20 °C with a rotor speed of 25 000 rpm and detection at 254 nm. Samples were prepared in 0.1 M NaH₂PO₄ (pH 6.4). The data were edited by using XL-A software.

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A Highly Efficient Chain-Extension Process in the Systematic Syntheses of Carotenoid Natural Products**

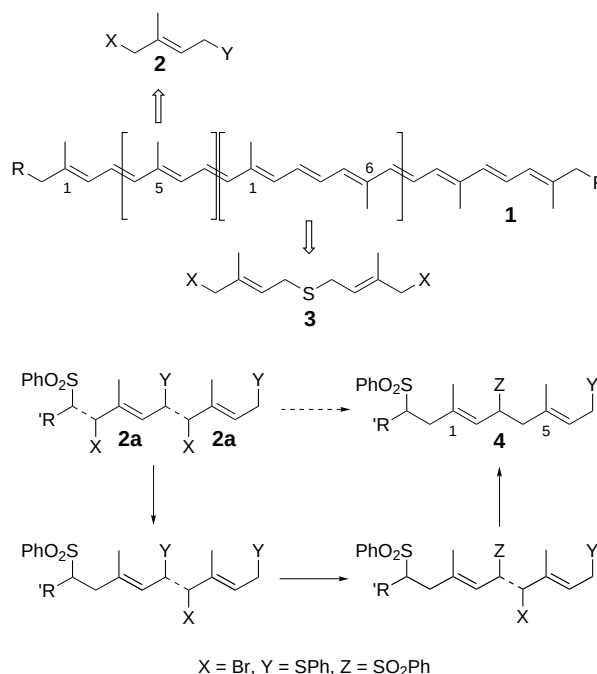
Minkoo Ji, Hojin Choi, Minsoo Park, Minyong Kee, Young Cheol Jeong, and Sangho Koo*

Dedicated to Professor Masato Koreeda on the occasion of his 60th birthday

Nature adopts isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAP) as building blocks for de novo syntheses of various isoprenoids, such as terpenoids, steroids, and carotenoids.^[1] Enzymatic assembly of these basic C₅ units provides a diverse range of natural products. We are currently searching for such a mimic for IPP or DMAP in the

chemical syntheses of isoprenoids, especially for carotenoids,^[2] which show antioxidant activities for low-density lipoprotein and which are widely used as natural pigments. Certain carotenoids, such as lycopene,^[3] also lower the propensity for humans to develop prostate cancers.

Carotenoids **1** have the general structure of two consecutive methyl groups attached to a conjugated polyene chain in either a 1,5 or 1,6 arrangement (Scheme 1). The symmetrical



Scheme 1. Generalized disconnection of the carotenoid structure **1** into the chain-extension unit **2** and the chain-termination unit **3**, as well as the proposed chain-extending process by repeated use of **2a**.

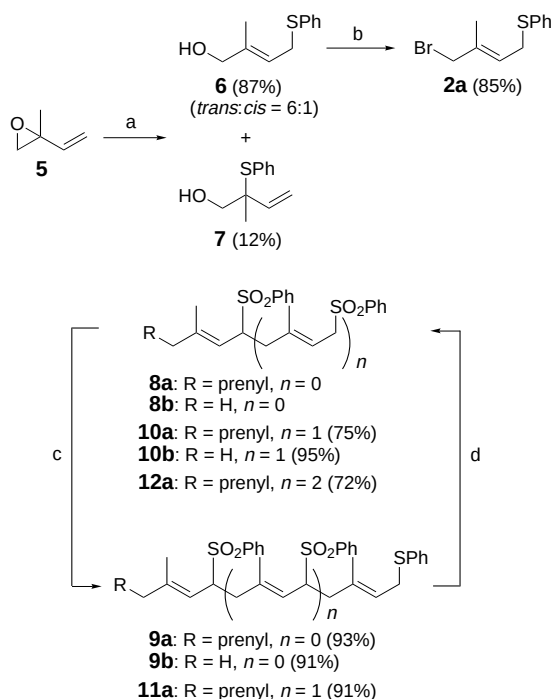
carotenoid structure can be divided into three parts for a systematic construction of such compounds: the chain-initiating unit, the chain-extending unit, and the chain-terminating unit. The Julia sulfone olefination protocol^[4] is a perfect methodology to put the three components together, and allylic sulfone compounds were thus selected as the initiating unit. It was envisioned that bifunctionalized C₅ prenyl compound **2** might be an efficient chemical mimic for IPP or DMAP as a chain-extending unit, insofar as X is a good leaving group and Y can be easily transformed to a sulfonyl group. The carbanion-stabilizing ability of Y should be much less than that of the sulfonyl group of the chain-initiating unit to prevent the unfavorable base-promoted halide elimination process from occurring in compound **2**. It was thus appropriate to use 4-bromo-3-methyl-2-butenyl phenyl sulfide **2a** (X = Br, Y = SPh in **2**) to meet the above criteria. Repeated use of this chain-extending unit **2a** with each additional oxidation step to produce the corresponding sulfone would then produce the required 1,5-dimethyl-substituted carbon skeleton, such as structure **4**. This compound could accomplish the chain-extension process. We have already demonstrated that bis(haloallylic) sulfide **3** is a stable substitute for highly unstable 1,8-dihalo-2,7-dimethyl-2,4,6-octatriene in β -caro-

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tene synthesis,^[5] and it could serve as the chain-terminating unit in carotenoid syntheses.

Contrary to the easily obtainable chain-initiating allylic sulfones, not much chemistry has been known for 4-hydroxy-3-methyl-2-butenyl phenyl sulfide (**6**),^[6] which is an apparent precursor to **2a** as a chain-extension unit. We herein report a highly efficient and practical method of synthesizing **6** by a Cu^I-catalyzed opening reaction of isoprene monoxide (**5**) with benzenethiol in DMF (Scheme 2). The use of the Cu^I salt and



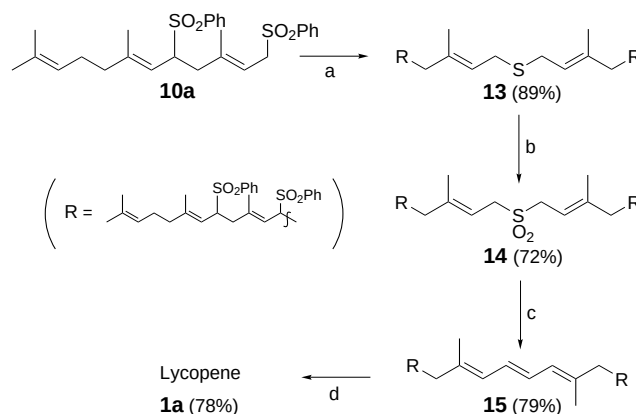
Scheme 2. The chain-extension process: preparation of the chain-extension unit **2a** and the chain-extended allylic sulfones **10** and **12**. Reaction conditions: a) PhSH and Cu^I (0.025 equiv) in DMF, b) PBr₃ in diethyl ether, c) *n*BuLi in THF at –78 °C then **2a**, d) LiNbMoO₆ (0.05 equiv) and H₂O₂ (2.5 equiv) in MeOH.

DMF in this epoxide-opening reaction was crucial in that the allylic opening product **6** was obtained as the major product (87 %) with a high *trans* selectivity (6:1 *trans*:*cis*). A small amount (12 %) of the side product **7**, which arose from the opening at the more-substituted carbon end of epoxide **5**, was also obtained. Hydroxyallylic sulfide **6** was then easily converted into **2a** (85 %) with PBr₃.

The chain-extension process by repeated use of **2a** has proven to be highly efficient and practical (Scheme 2). The carbanions of readily available allylic sulfones of geranyl **8a** and prenyl **8b** coupled with **2a** to produce the chain-extended thio-sulfone compounds **9a** (93 %) and **9b** (91 %), respectively, in excellent yields. Subsequent oxidation of the sulfur atom with the composite metal oxide catalyst LiNbMoO₆^[7] and H₂O₂ produced the corresponding disulfones **10a** (75 %) and **10b** (95 %) without any formation of the undesirable, but expected, epoxidation products. The initiating allylic sulfones have been elongated by five carbon atoms by this reaction sequence. This procedure was then repeated for disulfone **10a** to provide trisulfone **12a** (72 % from **11a**) via thio-disulfone

11a (91 %). This process can be repeated many times to reach the required number of carbon atoms in the allylic sulfone units.

The chain-extended allylic sulfones can couple with the chain-terminating bis(haloallylic) sulfide **3** to give rise to the required carbon skeletons for various carotenoid syntheses. As an example, the chain-elongated allylic disulfone **10a** from geranyl sulfone **8a** coupled with bis(bromoallylic) sulfide **3** to provide compound **13** which was required for the synthesis of lycopene (**1a**; Scheme 3). The dianion of disulfone **10a** was



Scheme 3. A representative example of carotenoid syntheses by coupling the chain-extended allylic sulfone **10a** and the chain-terminating bis(bromoallylic) sulfide **3**: synthesis of lycopene. Reaction conditions: a) *n*BuLi (2 equiv) in THF at –78 °C then **3** (X = Br, 0.5 equiv), b) LiNbMoO₆ (0.05 equiv) and H₂O₂ (2.5 equiv) in MeOH, c) KOH in *t*BuOH and CCl₄, d) NaOEt in refluxing EtOH.

generated by the addition of *n*BuLi (2 equiv) at –78 °C in THF and then treated with **3** (0.5 equiv) at that temperature to give **13** in 89 % yield. It only required several functional-group transformations to obtain a fully conjugated carotenoid polyene chain **1** from the coupling product **13**. The central sulfur atom of **13** was oxidized to a sulfone (72 % yield) by the composite metal oxide (LiNbMoO₆) and H₂O₂ oxidant system. A Ramberg–Bäcklund reaction^[8] on the resulting diallylic sulfone unit of **14** provided the conjugated triene moiety at the center of **15** (79 % yield). A base-promoted (EtONa/EtOH) elimination of the four sulfonyl groups^[9] in **15** then produced the fully conjugated polyene chain, lycopene (**1a**), in 78 % yield.^[10]

In conclusion, we have developed a general synthetic method for the carotenoid polyene chain structure **1** which highlighted the use of 4-bromo-3-methyl-2-butenyl phenyl sulfide (**2a**) as a chain-extension unit in the Julia sulfone olefination reaction. We also demonstrated the usefulness of bis(haloallylic) sulfide **3** as a chain-termination unit and as a stable substitute for the highly unstable α,ω -dihalotriene. This polyene chain synthesis, which was exemplified for lycopene, is sufficiently general to be utilized for the synthesis of any carotenoid structure. Furthermore, this concept may well be applied to the syntheses of conducting organic compounds comprising a fully conjugated polyene chain.

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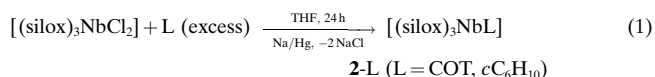
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Dehydrogenation of $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_8)$ ($\text{silox} = t\text{Bu}_3\text{SiO}$) to $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_6)$ and Its Subsequent Alkene-to-Alkylidene Rearrangement**

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The observed pyridine ring-opening of $[(\text{silox})_3\text{Nb}(\eta\text{-C}_5\text{H}_5\text{N})]$ ($\text{silox} = t\text{Bu}_3\text{SiO}$) to $[(\text{silox})_3\text{Nb}=\text{CHCH}=\text{CHCH}=\text{CHN}=\text{Nb}(\text{silox})_3]$, and related picoline chemistry^[1,2] suggested that carbon–carbon bond scission might occur by similar pathways. 1,3,5,7-Cyclooctatetraene (COT) was considered a prime candidate for ring opening because of its lack of resonance stabilization energy, but in binding to two $[(\text{silox})_3\text{Nb}]$ units, COT functions as an aromatic dianion, which directs the chemistry toward C–H bond activation, dehydrogenation, and a subsequent alkene-to-alkylidene rearrangement.

Reduction of $[(\text{silox})_3\text{NbCl}_2]$ (**1**)^[3] with Na/Hg in THF with three equivalents of COT present resulted in the isolation of brown $[(\text{silox})_3\text{Nb}(\eta\text{-C}_8\text{H}_8)]$ (**2**-COT, 40 %) [Eq. (1)].

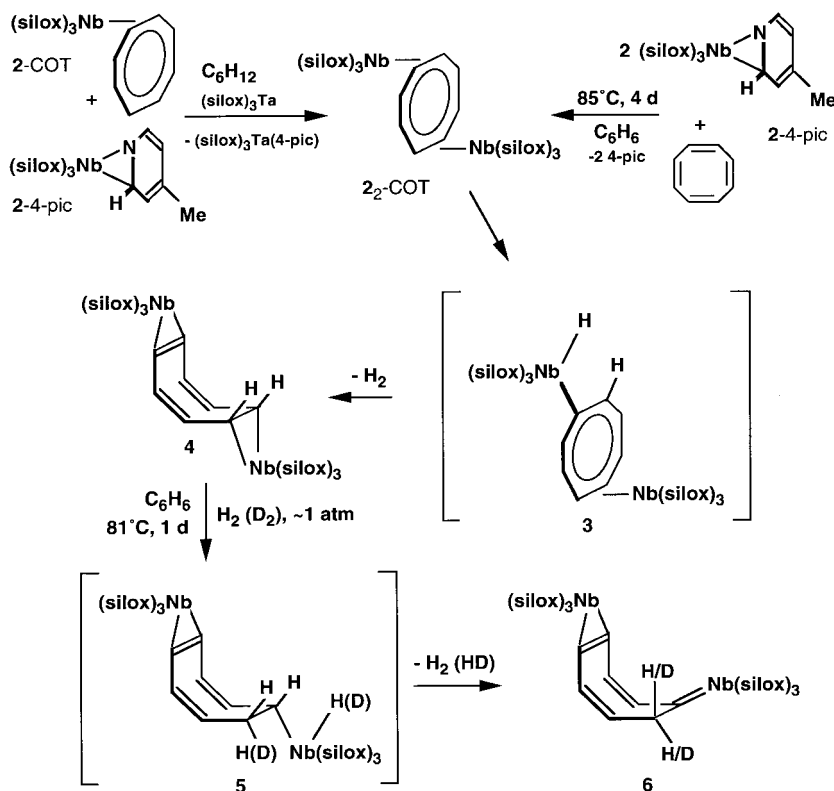


Abstraction of 4-picoline from $[(\text{silox})_3\text{Nb}(\eta\text{-C},N\text{-4-MeC}_5\text{H}_4\text{N})]$ (**2**-4-pic) by $[(\text{silox})_3\text{Ta}]^{[2]}$ in the presence of **2**-COT afforded $[(\text{silox})_3\text{Ta}(\eta\text{-4-pic})]$ and burgundy, crystalline $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_8)$ (**2**-COT, 33 %, Scheme 1). The synthesis of **2**-COT must occur under mild conditions to avoid further reaction (vide infra). An X-ray crystal structure determination of **2**-COT^[4,5] revealed the $[(\text{silox})_3\text{Nb}]$ moieties ($d(\text{Nb}-\text{C}) = 2.20(5) \text{ \AA}$ (av))^[6,7] in an *anti*- η^2,η^2 -configuration about a planar COT ligand, although disorder problems hampered further analysis. The insolubility of **2**-COT in unreactive hydrocarbon solvents prevented spectral characterization.

Upon thermolysis of two equivalents of $[(\text{silox})_3\text{Nb}(\eta\text{-C},N\text{-4-MeC}_5\text{H}_4\text{N})]$ (**2**-4-pic) and COT, **2**-COT and presumably **2**-COT were generated in situ, and dehydrogenation led to the gold-brown cyclooctatriene^[8] complex, $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_6)$ (**4**; Scheme 1). Although **4** was isolated in 50 % yield, ^1H NMR spectroscopy revealed the conversion to be > 95 % when the reaction was monitored in a sealed tube (C_6D_6). Olefin substitution reactions of **2**-4-pic, such as the synthesis of the 1-butene complex, $[(\text{silox})_3\text{Nb}(\eta^2\text{-C}_4\text{H}_8)]$ (**2**-

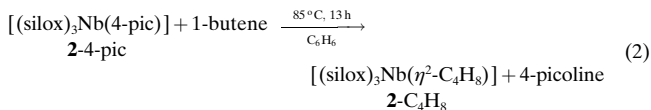
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Scheme 1. Synthesis of **2**₂-COT and its subsequent reactions to give **6**.

C_4H_8 [Eq. (2)], had been previously established,^[2] and provided a practical synthesis of **4**.



Direct thermolysis of **2**₂-COT also afforded **4**, but in lesser purity. The single-crystal X-ray structure determination of **4** is shown in Figure 1.^[5, 9] 1,2-Alkyne ligation ($d(\text{Nb}-\text{C}) = 2.091(8), 2.092(9) \text{ \AA}$; $d(\text{C}-\text{C}) = 1.364(14) \text{ \AA}$) is distinct from

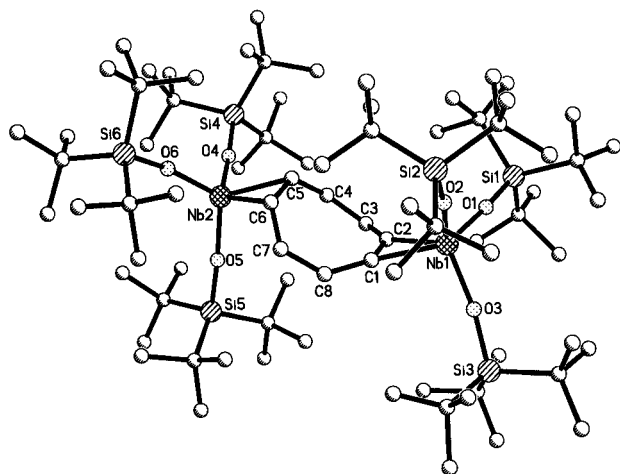


Figure 1. Molecular structure of **4**. Selected distances [$\text{\AA}$] and angles [$^\circ$]: Nb1-O 1.903(31) av, Nb2-O 1.912(47) av; Nb1-C1-C8 150.9(7), Nb1-C2-C3 152.3(8), Nb1-C1-C2 71.4(5), Nb1-C2-C1 71.4(5), C2-C1-C8 136.7(9), C1-C2-C3 135.7(9), Nb2-C5-C4 111.2(6), Nb2-C6-C7 124.3, Nb2-C5-C6 72.6(6), Nb2-C6-C5 70.7(6), C4-C5-C6 131.3(9), C5-C6-C7 135.8(9).

5,6-alkene binding ($d(\text{Nb}-\text{C}) = 2.153(10), 2.177(9) \text{ \AA}$; $d(\text{C}-\text{C}) = 1.335(12) \text{ \AA}$) as the near planarity of the C8-C1-Nb-C2-C3 atoms attests.

The reversibility of the **2**₂-COT $\rightarrow$ **4** conversion was probed by thermolysis of **4** under H_2 . Instead, dihydrogen catalyzed the rearrangement of **4** to the orange alkydine-yne complex, $[(\text{silox})_3\text{Nb}]_2(\eta^1;\eta^2\text{-4,5-C}_8\text{H}_6)$ (**6**, Scheme 1). Although **6** was isolated in about 40% yield, the reaction was observed to be virtually quantitative when monitored in a sealed tube by ^1H NMR spectroscopy; without dihydrogen, the conversion took three days at 155°C . The single-crystal X-ray structure determination of **6** is shown in Figure 2.^[5, 10] The alkyne is slightly skewed ($d(\text{Nb}-\text{C}) = 2.056(10), 2.145(11) \text{ \AA}$), the niobium-alkylidene bond length of $1.971(10) \text{ \AA}$ is normal,^[1, 11] and the methylene is a substituent on the alkydine moiety.

When $[(\text{silox})_3\text{Nb}]_2(\eta^1;\eta^2\text{-4,5-C}_8\text{H}_5\text{D})$ (**6**-D) was synthesized from **4** and D_2 in a sealed tube, its ^1H NMR spectrum revealed that the intensity of the methylene resonance at $\delta = 4.70$ was halved, consistent with the incorporation of one deuterium atom. The overlapping

doublet of triplets at $\delta = 6.31$ assigned to a proton adjacent to the methylene group became a doublet of doublets, and HD (solution) was observed as a 1:1:1 triplet at $\delta = 4.42$ (C_6D_6). Variable-temperature ^1H NMR resonance experiments provided evidence in solution for the ring pucker observed in the solid-state structure of **6**. Decoalescence of the CHH' group into two broad resonances was attributed to a ring inversion barrier of $\Delta G^\ddagger = 10.7(3) \text{ kcal mol}^{-1}$. The labeling experiment is consistent with hydrogenation of the alkene of **4** to form transient alkyl-hydride **5**, followed by an α -H-abstraction^[12] by the hydride to give the alkydine **6** (see Scheme 1,). The hydrogenation of **4** may occur through a

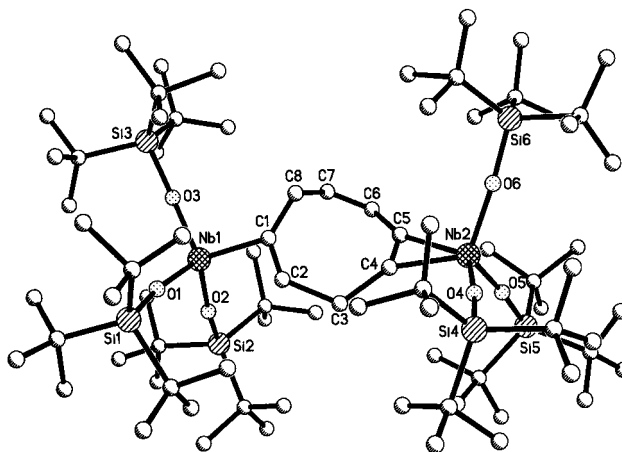
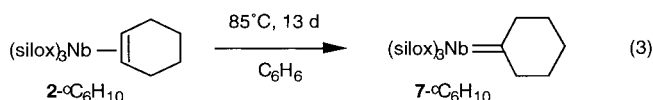


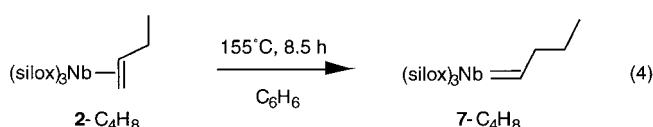
Figure 2. Molecular structure of **6**; C8 is the the methylene group. Selected distances [$\text{\AA}$] and angles [$^\circ$]: Nb1-O 1.897(23) av, Nb2-O 1.900(30) av; Nb1-C1-C2 107.0(8), Nb1-C1-C8 129.2(8), C1-C8-C7 108.5(9), Nb2-C4-C3 149.4(8), Nb2-C5-C6 156.8(8), Nb2-C4-C5 77.5(7), Nb2-C5-C4 69.3(7), C3-C4-C5 129.0(10), C4-C5-C6 132.2(11).

standard H_2 (D_2) oxidative addition to the putative Nb^{III} -alkene center of **4** followed by insertion to give **5**, or by a mechanistically indistinguishable σ -bond metathesis path.

The COT dehydrogenation and rearrangement reactions prompted an investigation of simple olefin complexes. Extended thermolysis of $[(\text{silox})_3\text{Nb}(\eta^2\text{-}C_6H_{10})]$ (**2**- C_6H_{10} , [Eq. (1)], 40%) induced the rearrangement to the cyclohexylidene complex, $[(\text{silox})_3\text{Nb}=\text{C}(\text{CH}_2)_4\text{CH}_2]$ (**7**- C_6H_{10} , 69% yield) [Eq. (3)]. Likewise, rearrangement of 1-butene



complex $[(\text{silox})_3\text{Nb}(\eta^2\text{-}C_4H_8)]$ (**2**- C_4H_8) to the butylidene complex $[(\text{silox})_3\text{Nb}=\text{CH}(\text{CH}_2)_2\text{CH}_3]$ (**7**- C_4H_8) was evidenced [Eq. (4)]. Thermolyses under H_2 led to olefin hydrogenation.



As Scheme 1 indicates, a logical dehydrogenation sequence involves C–H bond activation of **2**-COT to give an intermediate alkenyl–hydride (**3**), followed by a β -H abstraction by the hydride^[13–15] to afford **4** and dihydrogen. An alternative path requires β -H elimination to a d^0 alkyne–dihydride intermediate and subsequent elimination of H_2 . Upon C–H bond activation, the COT likely remains a planar dianion in the alkenyl hydride (**3**) derived from **2**-COT. A β -abstraction by the niobium hydride of **3** is aided by the favorable geometry of the planar COT, whose β -hydrogen atom is jammed into the Nb center ($\angle \text{Nb-C-C} \sim \angle \text{C-C-H} \sim 112.5^\circ$); β -abstractions are known to be exquisitely sensitive to geometry.^[13] An alkene-to-alkylidene transformation^[16–20] would incur a disruption in the resonance stabilization energy of the $C_8H_8^{2-}$ ligand of **2**-COT. As Figure 1 reveals, the dehydro-COT ligand of **4** has lost its dianionic character, hence its rearrangement to the alkylidene occurs rather than another dehydrogenation. Investigations continue into the mechanism of the olefin-to-alkylidene (e.g., **4** $\rightarrow$ **6**, **2**- C_4H_8 $\rightarrow$ **6**- C_4H_8 and **2**- C_6H_{10} $\rightarrow$ **6**- C_6H_{10}) rearrangements that provide a rationale for the generation of olefin metathesis catalysts.

Experimental Section

All manipulations were performed by using either glovebox (N_2) or high-vacuum techniques (Ar), and dried, deoxygenated solvents.

2-COT: A 50 mL flask was charged with $[(\text{silox})_3\text{NbCl}_2]$ (**1**) (1.00 g, 1.23 mmol), 1,3,5,7-cyclooctatetraene (386 mg, 3.70 mmol), 0.9% Na/Hg (2.1 equiv, 70 mg Na in 7.75 g Hg) and THF (20 mL) at 77 K. Upon stirring at 23°C for 28 h, dark brown **2**-COT (410 mg, 40%) was obtained from cold (-78°C) diethyl ether. ^1H NMR (C_6D_6 , 23°C , TMS): $\delta = 1.23$ (s, 8H; $t\text{Bu}$), 5.64 (s, 8H; C_8H_8); $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 24.18$ ($C(\text{CH}_3)_3$), 31.35 ($C(\text{CH}_3)_3$), 112.17 (HC); elemental analysis calcd (%) for $C_{44}H_{80}Si_3O_3Nb$: C 62.7, H 10.6; found: C 60.4, H 10.1.

2- C_6H_{10} : A 100 mL flask charged with **1** (1.50 g, 1.85 mmol), 0.65% Na/Hg (2.1 equiv, 89 mg Na in 13.76 g Hg), C_6H_{10} (3 mL), and THF (30 mL, 77 K). Upon stirring at 23°C for 12 h, green **2**- C_6H_{10} (600 mg, 40%) was obtained

from hexanes. ^1H NMR (400 MHz, C_6D_6 , 23°C , TMS): $\delta = 1.25$ (s, 8H; $t\text{Bu}$), 1.50–1.86 (m, 4H; C_7H_2), 2.38–2.66 (m, 4H; C_7H_2), 2.78 (m, 2H; C_8H); $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 23°C): $\delta = 23.90$ ($C(\text{CH}_3)_3$), 25.07 (C_7), 28.46 (C_8), 31.21 ($C(\text{CH}_3)_3$), 70.76 (C_8); elemental analysis calcd (%) for $C_{42}H_{91}Si_3O_3Nb$: C 61.4, H 11.2; found: C 61.2, H 11.0.

2-COT: A 25 mL vial was charged with a mixture of $[(\text{silox})_3\text{Nb}(\text{4-pic})]$ (**2**-4-pic) (209 mg, 0.252 mmol) and $[(\text{silox})_3\text{Ta}]$ (208 mg, 0.252 mmol). The mixture was dissolved in C_6H_{12} (5 mL), shaken vigorously for 2 min, and left undisturbed for 45 min; a solution of **2**-COT (230 mg, 0.252 mmol) in cyclohexane (3 mL) was added. The solution turned dark burgundy after it had been shaken vigorously for 30 s. Burgundy **2**-COT precipitated (260 mg, 33%) from this solution after it had been left to stand undisturbed for 24 h.

4: A 25 mL flask charged with **2**-4-pic (500 mg, 0.600 mmol), 1,3,5,7-cyclooctatetraene (0.5 equiv, 31 mg, 0.30 mmol), and benzene (20 mL) was refluxed at 85°C for four days. Golden brown **4** was isolated from pentane (232 mg, 50%). ^1H NMR (C_6D_6 , 23°C , TMS): $\delta = 1.25$ (s, 8H; $t\text{Bu}$), 1.33 (s, 8H; $t\text{Bu}$), 3.19 (s, 2H; $\text{Nb}(\eta^2\text{-CHCH})$), 6.81 (m, 2H; $-\text{CH}=\text{}$), 6.98 (m, 2H; $-\text{CH}=\text{}$); $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 23.94$ ($C(\text{CH}_3)_3$), 23.18 ($C(\text{CH}_3)_3$), 31.39 ($C(\text{CH}_3)_3$), 31.43 ($C(\text{CH}_3)_3$), 80.16 ($\text{Nb}(\eta^2\text{-CHCH})$), 125.42, 129.07 ($\text{CH}=\text{CH}$).

2- C_4H_8 : A 50 mL bomb flask was charged with **2**-4-pic (500 mg, 0.600 mmol), C_6H_6 (20 mL), and 1-butene (ca. 5 equiv) at 77 K and placed in an 85°C oil bath for 13 h. Green **2**- C_4H_8 (385 mg, 81%) was isolated upon removal of the volatiles. ^1H NMR (C_6D_6 , 23°C , TMS): $\delta = 1.24$ (s, 8H; $t\text{Bu}$), 1.35 (t, 3H; CH_3), 1.73 (m, 1H; $\text{CH}_2=\text{CH}-$), 1.95 (dd, 1H; $\text{CH}_2=\text{CH}$), 2.5 (m, 1H; $\text{CH}_2=\text{CH}$), 2.69 (m, 2H; CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 21.14$ (CH_3), 23.85 ($C(\text{CH}_3)_3$), 31.11 ($C(\text{CH}_3)_3$), 33.82 (CH_2), 70.12, 84.02 ($\text{CH}_2=\text{CH}$); elemental analysis calcd (%) for $C_{40}H_{80}Si_3O_3Nb$: C 60.4, H 11.3; found: C 60.3, H 11.3.

6: A 50 mL bomb charged with **4** (80 mg, 0.050 mmol), benzene (10 mL) and H_2 (500 Torr; 77 K) was placed in a 70°C oil bath for about two days. Crystallization from pentane at -78°C afforded orange **6** (30 mg, 40%). ^1H NMR (C_6D_6 , 23°C , TMS): $\delta = 1.27$ (s, 8H; $t\text{Bu}$), 1.32 (s, 8H; $t\text{Bu}$), 4.70 (br d, $^3J = 8$ Hz, 2H; CH_2), 6.31 (dt, $^3J = 10$, 8 Hz, 1H; $\text{CH}_2\text{CH}=\text{}$), 7.20 (d, $^3J = 10$ Hz, 1H; $-\text{CH}=\text{}$), 8.30 (d, $^3J = 11$ Hz, 1H; $\text{Nb}=\text{CCH}=\text{CH}-$), 5.70 (d, $^3J = 11$ Hz, 1H; $-\text{CH}=\text{}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 23°C): $\delta = 23.36$ ($C(\text{CH}_3)_3$), 23.45 ($C(\text{CH}_3)_3$), 30.68 ($C(\text{CH}_3)_3$), 30.90 ($C(\text{CH}_3)_3$), 41.82 (CH_2), 111.75, 132.34, 134.73, 137.43 ($-\text{C}=\text{}$), 206.63, 211.54 (NbCC).

7- C_6H_{10} : A 50 mL glass bomb charged with **2**- C_6H_{10} (600 mg, 0.732 mmol) and benzene (25 mL) was placed in an 85°C bath for 13 days. Green **7**- C_6H_{10} (415 mg, 69%) was obtained from pentane. ^1H NMR (C_6D_6 , 23°C , TMS): $\delta = 1.16$ (m, 2H; C_8H_2), 1.28 (s, 8H; $t\text{Bu}$), 1.59 (m, 4H; C_7H_2), 3.78 (m, 4H; C_7H_2); $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 23.67$ ($C(\text{CH}_3)_3$), 26.96 (C_8), 29.12 (C_7), 31.07 ($C(\text{CH}_3)_3$), 40.99 (C_8), C_9 not observed; elemental analysis calcd (%) for $C_{42}H_{91}Si_3O_3Nb$: C 61.6, H 11.9; found: C 60.9, H 11.8.

7- C_4H_8 : A 50 mL bomb charged with **2**- C_4H_8 (350 mg, 0.440 mmol) and benzene (20 mL) was heated at 155°C for 8.5 h. Red **7**- C_4H_8 (90 mg, 26%) was obtained from cold (-78°C) Et_2O . ^1H NMR (C_6D_6 , 23°C , TMS): $\delta = 0.86$ (t, $J = 7.2$ Hz, 3H; CH_3), 1.12 (m, 2H; CH_2), 1.29 (s, 8H; $t\text{Bu}$), 3.49 (m, $J = 7.2$ Hz, 2H; CH_2), 8.17 (bs, 1H; $\text{Nb}=\text{CH}$); $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 13.74$ (CH_3), 26.71 (CH_2), 23.96 ($C(\text{CH}_3)_3$), 30.99 ($C(\text{CH}_3)_3$), 44.10 (CH_2), 249.0 ($\text{Nb}=\text{C}$, HMQC); elemental analysis calcd (%) for $C_{40}H_{80}Si_3O_3Nb$: C 60.4, H 11.3; found: C 60.2, H 11.4.

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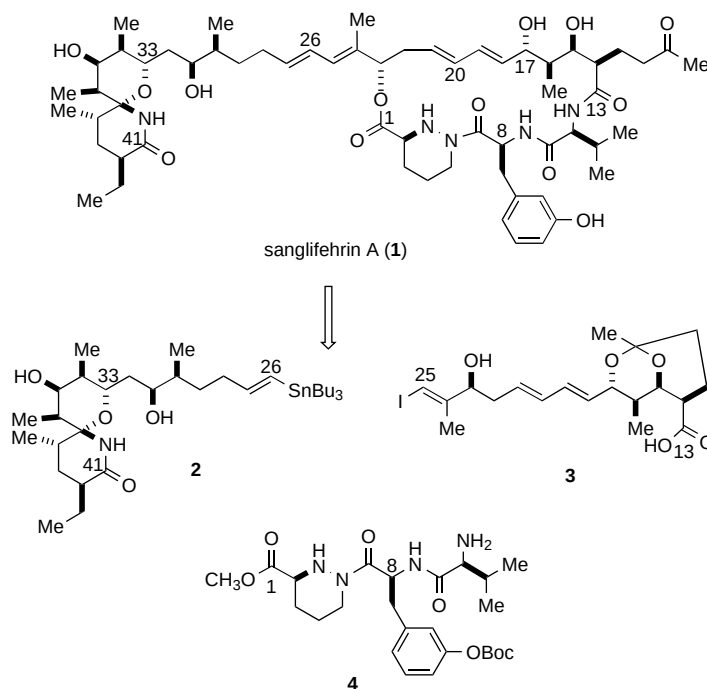
- independent; $R1 = 0.0793$ ($I > 2\sigma(I)$), $wR2 = 0.1523$; $\mu = 0.332 \text{ mm}^{-1}$ (SADABS); full-matrix, least-squares on F^2 .
- [5] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163099 (**2**), CCDC-163100 (**4**), and CCDC-163101 (**6**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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- [10] **6**· C_6H_6 : monoclinic, $P2_1/c$; $a = 24.6813(4)$, $b = 17.6046(3)$, $c = 25.4832(4) \text{ \AA}$, $\beta = 116.96(1)^\circ$; $V = 9869.5(3) \text{ \AA}^3$; $Z = 4$, $H_{171}C_{86}O_6Si_6Nb_2$; $T = 173(2) \text{ K}$; $\lambda = 0.71073$; 56059 reflections, 21816 independent; $R1 = 0.0864$ ($I > 2\sigma(I)$), 14073 reflections, $wR2 = 0.2119$; $\mu = 0.368 \text{ mm}^{-1}$ (SADABS); full-matrix, least-squares on F^2 .^[5]
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Enantioselective Total Synthesis of the Cyclophilin-Binding Immunosuppressive Agent Sanglifehrin A**

Maosheng Duan and Leo A. Paquette*

The sanglifehrins are structurally unusual Streptomyces metabolites discovered in a soil sample from Malawi.^[1] The A factor **1** holds particular interest because of its strong cyclophilin-binding properties and remarkable capability to inhibit the proliferation of B and T cells. Since neither FK binding protein binding activity nor calcineurin-inhibiting capability is displayed, **1** exerts its powerful immunosuppressive action in a manner quite different from that adopted by cyclosporin A, FK506, and rapamycin.^[2, 3] The complex structural and stereochemical features associated with **1** and its congeners, ultimately corroborated by partial^[4] and total synthesis,^[5] have provided a bevy of challenging opportunities for de novo molecular assembly.

Recent synthetic efforts in this laboratory have resulted in the successful acquisition of certain subunits central to the construction of sanglifehrin A (**1**) in convergent and highly enantiocontrolled fashion.^[6] Herein, we report useful refinements in these protocols as well as the successful conjoining of components **2–4** to arrive at **1** having all of its seventeen stereogenic centers properly installed.

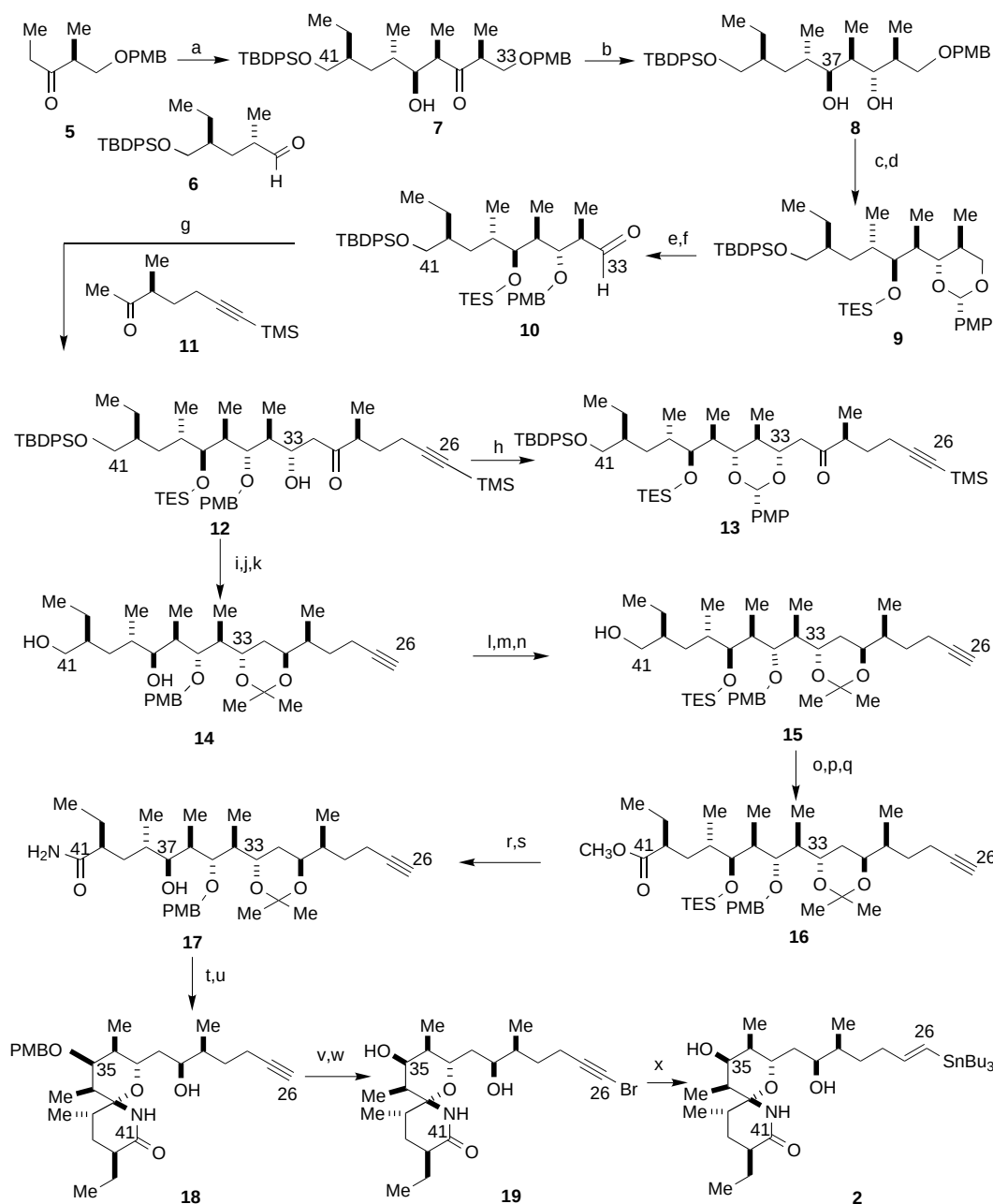


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The key elements present in **1** are clearly a spirolactam fragment, a 22-membered macrolactone, an uncommon tripeptide array, and contiguous centers of chirality along C14–C17 as well as C33–C38. Retrosynthetically, **2** was expected to derive from a sequence of enantiocontrolled aldol condensations prior to more advanced backbone assembly (Scheme 1). To this end, we first focused on generation of the tin(II) enolate of *S*-**5**^[7] and its condensation with the previously

described aldehyde **6**^[6a] under conditions of substrate control.^[8] As expected, *Re*-face selectivity was exercised preferentially (*ds* 92:8) and **7** was thus generated. *anti*-Diol **8** was next obtained by hydroxy-directed reduction involving tetramethylammonium triacetoxyborohydride,^[9] this step serving as a prelude to differentiation of the two OH groups by DDQ oxidation under kinetic control.^[10] Selective O-silylation at C37 could then be accomplished as in **9**. The controlled



Scheme 1. Synthesis of the western spirolactam sector **2**. Reagents and conditions: a) $\text{Sn}(\text{OTf})_2$, Et_3N , CH_2Cl_2 , -78°C , then **6**, -78°C , 5 h, 73%; b) $\text{Me}_4\text{NBH}(\text{OAc})_3$, HOAc , CH_3CN , -25°C to 0°C , overnight, 82%; c) DDQ, 4-Å MS, CH_2Cl_2 , 0°C , 10 h, 85%; d) Et_3SiCl , imidazole, DMF, 50°C , 3 h, 99%; e) $i\text{Bu}_2\text{AlH}$, THF, 0°C , 1 h, 86%; f) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C ; Et_3N , 95%; g) (+)-DIPCl, Et_3N , diethyl ether, 0°C ; then **11**, -78°C to -20°C , 36 h; 30% H_2O_2 , pH 7.0 buffer, MeOH, 0°C , 48%; h) DDQ, 4-Å MS, CH_2Cl_2 , 0°C to RT, 2 h, 65%; i) $\text{Me}_4\text{NBH}(\text{OAc})_3$, CH_3CN , HOAc , -25 to 0°C , 91%; j) 2,2-dimethoxypropane, acetone, PPTS, overnight, 97%; k) $\text{Bu}_4\text{N}^+\text{F}^-$, THF, overnight, 100%; l) pivaloyl chloride, pyr, DMAP, 20°C , 1 h, 81%; m) Et_3SiCl , imidazole, DMF, 50°C , 3 h, 97%; n) $i\text{Bu}_2\text{AlH}$, CH_2Cl_2 , -78°C , 2 h, 90%; o) Dess–Martin periodinane, CH_2Cl_2 , 0°C , 1 h; p) NaClO_2 , NaH_2PO_4 , $\text{Me}_2\text{C}=\text{CHMe}$, $i\text{BuOH}$, H_2O ; q) CH_2N_2 , EtOAc , 97% for three steps; r) Me_2AlNH_2 , CH_2Cl_2 , 40°C , 39 h, 71%; s) $\text{Bu}_4\text{N}^+\text{F}^-$, THF, RT, 3 h, 97%; t) Dess–Martin periodinane, CH_2Cl_2 , 20°C , 45 min, 98%; u) camphorsulfonic acid, CH_2Cl_2 , MeOH, 78%; v) DDQ, CH_2Cl_2 , H_2O , 4 h, 94%; w) NBS, AgNO_3 , acetone, 30 min, 97%; x) $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$, Ph_3P , Bu_3SnH , THF, 10 min, RT, 70%; DIPCl = *B*-chlorodiisopinocampheylborane; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; PPTS = pyridinium *p*-toluenesulfonate; NBS = *N*-bromosuccinimide.

reduction of **9** with diisobutylaluminum hydride proceeded regioselectively^[11] to deliver the primary alcohol and make possible the generation of aldehyde **10** by Swern oxidation. For installation of the C26–C32 extension, **10** was coupled to **11** in a second asymmetric aldol reaction mediated by (+)-*B*-chlorodiisopinocampheylborane in the presence of triethylamine.^[12] To confirm that the stereoinduction at C33 had

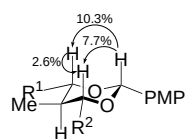
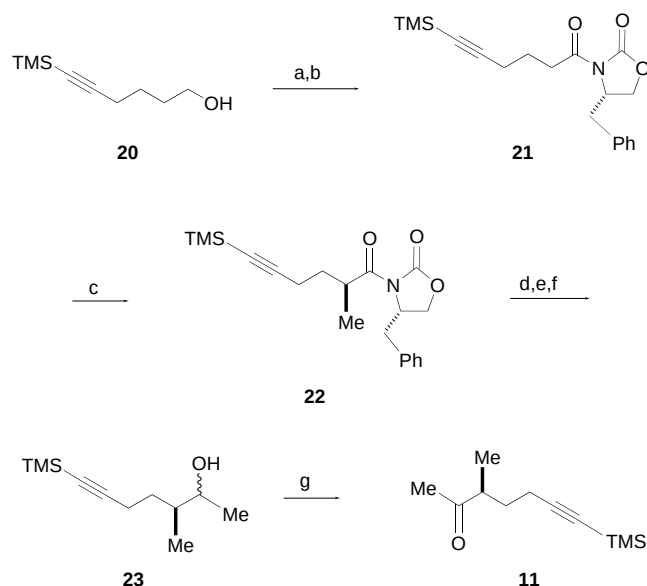


Figure 1. NOE interactions observed for **13** at 500 MHz in CDCl₃ solution.

indeed proceeded in the desired manner, **12** was oxidatively cyclized to the 1,3-dioxane **13**, ¹H NMR analysis of which unequivocally corroborated the equatorial projection of all four ring substituents as shown in Figure 1.

Preparation of the required acetylenic ketone **11** was initiated by sequential oxidation of **20**^[13] to the carboxylic acid level with pyridinium chlorochromate (PCC), generation of the mixed anhydride with pivaloyl chloride in the presence of triethylamine, and condensation with (*S*)-4-(phenylmethyl)-1,3-oxazolidin-2-one^[14] (Scheme 2). Following highly enantio-



Scheme 2. Synthesis of ketone **11**. Reagents and conditions: a) PCC, DMF, 20 °C, 24 h, 72 %; b) (CH₃)₃CCOCl, Et₃N, THF, –40 °C to 0 °C, then LiCl, (*S*)-4-(phenylmethyl)-1,3-oxazolidin-2-one, 20 °C, overnight, 94 %; c) NaN(SiMe₃)₂, THF, –78 °C; CH₃I, –78 °C to –40 °C, 69 %; d) LiBH₄, diethyl ether, H₂O, 0 °C, 1 h, 74 %; e) (COCl)₂, DMSO, CH₂Cl₂, –78 °C; Et₃N, 0 °C, 100 %; f) CH₃MgBr, diethyl ether, 20 °C, 92 %; g) (COCl)₂, DMSO, CH₂Cl₂, –78 °C; Et₃N, 0 °C, 94 %.

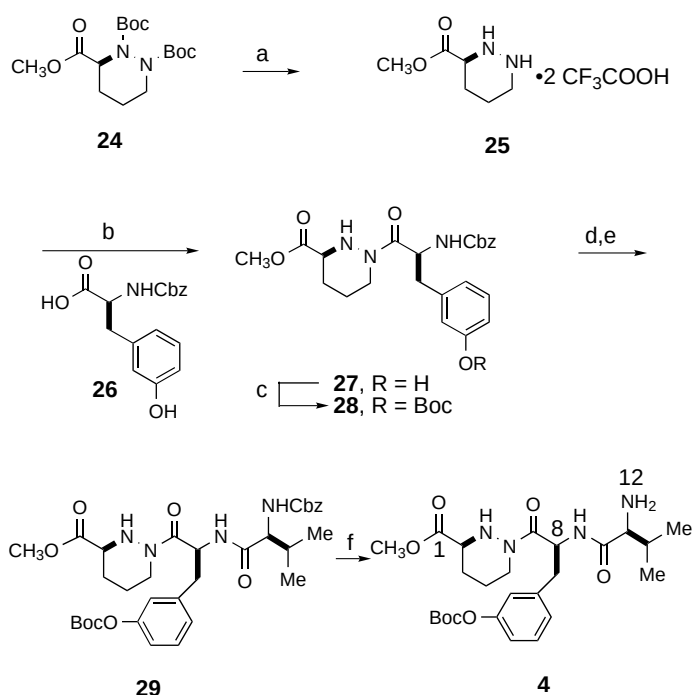
selective α -methylation of the enolate of **21**, the methyl ketone **11** was generated by conventional methods in an overall yield approximating 70 %.

At this juncture, it was becoming increasingly clear that **12** might well serve as a suitable precursor of spirolactam **3**. We could now attempt directed triacetoxyborohydride reduction in advance of suitable incorporation of the resulting *trans*-1,3-diol array into an acetonide ring. With this maneuver accomplished, it proved an easy matter to rid the molecule of its three different silyl protecting groups in a single operation upon exposure to tetrabutylammonium fluoride

(TBAF) in THF. Gratifyingly, **14** was isolated in 92 % yield. Significantly, the secondary hydroxy group in **14** could be selectively protected as in **15**, thereby facilitating arrival at methyl ester **16**.

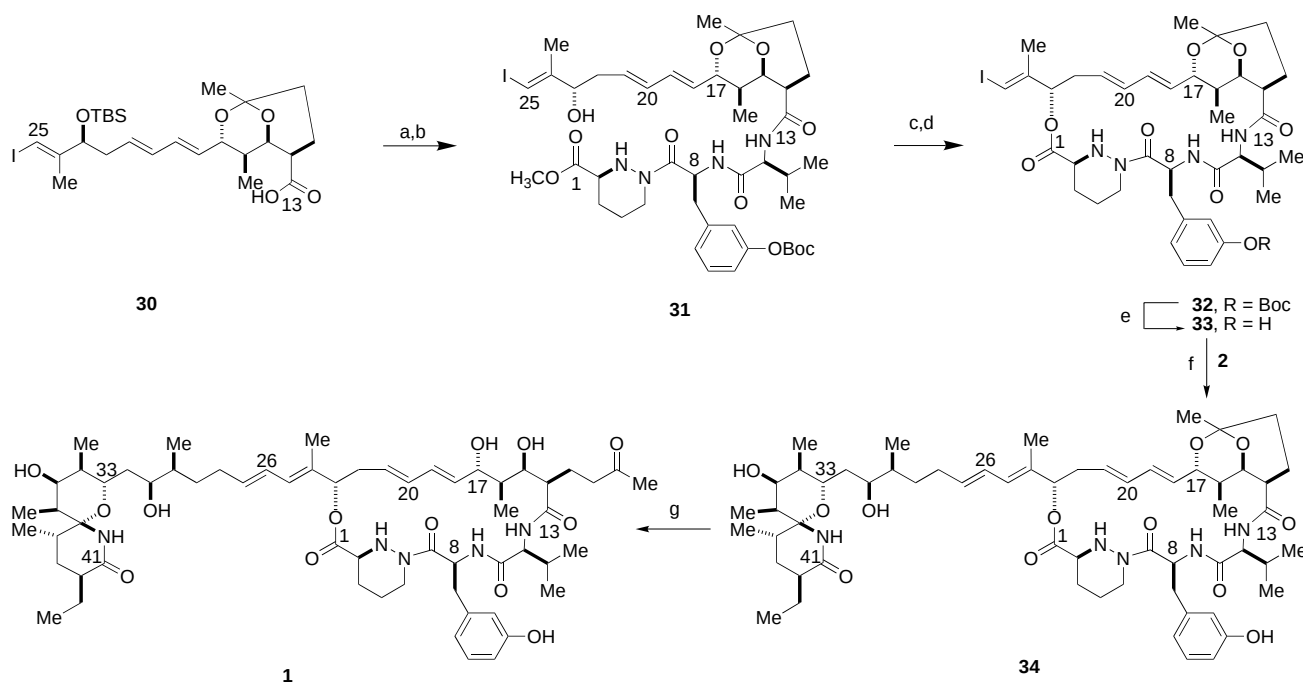
The carboxamide structural motif was next introduced by treatment of **16** with freshly prepared dimethylaluminum amide in CH₂Cl₂ at the reflux temperature.^[15] Subsequent removal of the triethylsilyl (TES) protecting group in the presence of fluoride ion, oxidation of the C37 hydroxy group with the Dess–Martin periodinane reagent,^[16] and acid-catalyzed ring closure gave rise predominantly to the [5.5]spirolactam **18** with exceptional efficiency (78 %; diastereomeric ratio 8:1). The two-step conversion of **18** to **19** proved uneventful, thereby setting the stage for conversion to the (*E*)-vinylstannane **2**.

On the tripeptide front, modifications to our original route^[6a] were made to improve efficiency in the required penultimate deprotection step. To this end, the known bis-Boc protected piperazic acid methyl ester **24**^[4a] was converted to salt **25** by reaction with trifluoroacetic acid in CH₂Cl₂ at room temperature (Scheme 3). Direct acylation of **25** at its less



Scheme 3. Synthesis of the tripeptide domain **4**. Reagents and conditions: a) CF₃COOH, CH₂Cl₂, RT, 3 h; b) **26**, HBTU, Et₃N (3.1 equiv), CH₃CN, 2 h, RT, 76 % over two steps; c) (Boc)₂O, Et₃N, DMAP, CH₂Cl₂, RT, 84 %; d) H₂, 10 % Pd/C, C₂H₅OH; e) Cbz-L-valine, HBTU, Et₃N (1 equiv), CH₃CN, 20 °C, 1.5 h, 98 % over two steps; f) H₂, 10 % Pd/C, C₂H₅OH, 98 %; DMAP = 4-dimethylaminopyridine; Cbz = benzyloxycarbonyl; HBTU = *O*-benzotriazole-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; (Boc)₂O = di-*tert*-butyl dicarbonate.

hindered nitrogen atom with the derivatized (*S*)-*m*-tyrosine **26**^[17] was most effectively accomplished by using HBTU and triethylamine in acetonitrile.^[18] Following optimization of the step **27**→**28**, it proved convenient to effect hydrogenolytic removal of the Cbz group in preparation for smooth incorporation of the Cbz-L-valine fragment. Catalytic reduc-



Scheme 4. Completion of the synthesis of **1**. Reagents and conditions: a) tetra-*n*-butylammonium fluoride, THF, 0 °C to RT, 94%; b) **4**, HATU, *i*Pr₂NEt, CH₃CN, 0 °C to RT, 5 h, 67%; c) LiOH, THF, H₂O, 0 °C, 1 h, 100%; d) EDC, *i*Pr₂NEt, 4-PPy, CH₂Cl₂, 10^{−3} M, 0 °C to RT, overnight, 21%; e) Me₃SiOTf, 2,6-lutidine, CH₂Cl₂, 20 °C, 1.5 h, 73%; f) [PdCl₂(CH₃CN)₂], DMF, RT, 6 h, 40%; g) *p*-toluenesulfonic acid (1 equiv), boric acid (5 equiv), THF, RT, 10 h, 30%; HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; 4-PPy = 4-pyrrolidinopyridine; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

tion of **29**, obtained in this manner without observable epimerization, furnished the targeted **4** and set in motion the final stages of the total synthesis.

The previously reported carboxylic acid **30**^[6b] served as the third subunit. Following its desilylation, tripeptide **4** was regioselectively attached at C13 by the action of HATU and Hünig's base,^[19] thereby furnishing **31** (Scheme 4). With **31** in hand, its methyl ester was chemoselectively saponified with lithium hydroxide in aqueous THF under conditions known not to induce possible loss of enantiomeric homogeneity.^[4a] Exposure of the hydroxy acid so formed to EDC/*i*Pr₂NEt/4-PPy in CH₂Cl₂ at high dilution (~10^{−3} M) then furnished **32** in 21% yield. At this point, the time had arrived to unmask the phenolic hydroxyl. After some trial and error, the capability of trimethylsilyl triflate and 2,6-lutidine in CH₂Cl₂^[20] to deliver **33** was recognized.

We could now attempt the critical Stille coupling intended to merge the two large fragments while establishing the exocyclic *E,E* cumulated diene chromophore.^[21] As foreshadowed by the success realized in our recent synthesis of polycavernoside A,^[22] the use of [PdCl₂(CH₃CN)₂] in DMF at room temperature afforded the sanglifehrin acetal **34** (40%). Finally, the acidic hydrolysis of **34** with one equivalent of *p*-toluenesulfonic acid and five equivalents of boric acid as recommended by Metternich and co-workers^[4b, 23] furnished **1**, the spectral and chromatographic properties of which duplicated those exhibited by the authentic natural substance.

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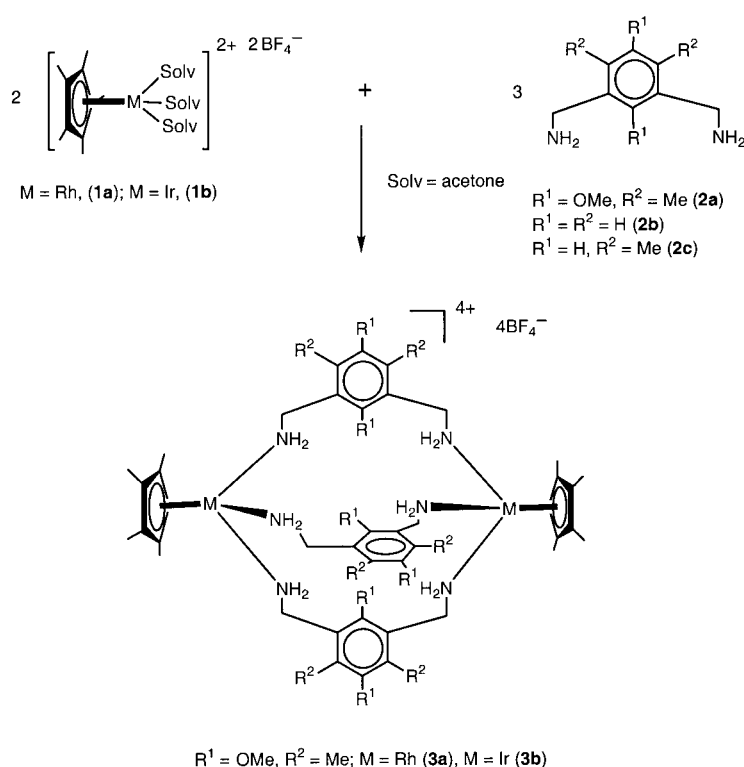
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Rational Design and X-ray Molecular Structure of the First Irido-Cryptand and Encapsulation of a Tetrafluoroborate Anion**

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In memory of John A. Osborn

Supramolecular systems obtained by assembling molecular subunits through noncovalent interactions have been the focus of recent intense investigations.^[1] In the last decade there has been a blossoming in the preparation of inorganic and organometallic macrocycles which have shown particular promise in the supramolecular chemistry of host–guest interactions.^[2] Cryptands, which are the most fascinating macrobicyclic systems, possess intramolecular cavities that are available for the encapsulation of ionic guests.^[3] In a spectacular demonstration by Lehn and co-workers a bis-(tren) chelate receptor was used to encapsulate fluoride anions.^[4] Recently Bowman-James and co-workers have elegantly shown that a bicyclic polyammonium receptor can encapsulate two nitrate anions.^[5] Although the chemistry of organic cryptands is steadily expanding, less is known about metallocryptands.^[6] Herein we report a rational high-yield (70–85%) strategy for preparing organometallic cryptands that is based on iridium coordination chemistry (Scheme 1)



Scheme 1. General synthetic strategy for metallocryptands.

and demonstrate their properties as anion hosts. Although the coordination chemistry of cations is well developed, the chemistry of anion encapsulation is still in its infancy.^[7] only one example of a metallo-helicate encapsulating a PF_6^- ion has been described by Steel and co-workers and two supramolecular tetrahedron complexes encapsulating a BF_4^- ion have been reported by the groups of Huttner, and Ward and McCleverty.^[8] To our knowledge no metallo-cryptate that encapsulates a polyfluoroanion has so far been reported.

The novelty of our work is the use of $[\text{Cp}^*\text{M}(\text{Solv})_3][\text{BF}_4]_2$ ($\text{Cp}^* = \text{C}_5(\text{CH}_3)_5$, $\text{M} = \text{Rh}$, Ir , $\text{Solv} = \text{acetone}$) (**1a**, **b**) complexes^[9] as “tripod connectors”. These compounds possess piano-stool structures in which the $\eta^5\text{-Cp}^*$ ligand remains firmly attached, whereas three weakly bound acetone molecules occupy the three legs of the tripod. In this work we have used diamines that were designed to coordinate to two different tripod connectors rather than to chelate to a single metal center. We sought the spontaneous and cooperative self-assembly of metallocryptands by combining two metal fragments and three diamines (Scheme 1).

To demonstrate the viability of our strategy we prepared the bidentate ligand 1,3-bis(aminomethyl)-2,5-dimethoxy-4,6-dimethylbenzene (**2a**). Significantly, treatment of three equivalents of the diamine **2a** with two equivalents of tripod connectors **1a** or **1b**, prepared in situ, affords in one-pot reactions the rhodium and iridium cryptands $[(\text{Cp}^*\text{M})_2(\text{2a})_3][\text{BF}_4]_4$ (**3a** and **3b**), respectively, in 77–85% yield. The ^1H and ^{13}C NMR data recorded in CD_3CN are consistent with the proposed formulas. Most remarkably, the resonances ascribed to the protons of the amino groups appear at very different fields: at $\delta = 5.12$ (td, $J = 11.5$, 4.4 Hz, 1H) and at $\delta = 1.41$ (brt, 1H) for **3a** and at $\delta = 5.91$ (td, $J =$

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11.5, 4.5 Hz, 1H) and at $\delta = 2.40$ (brt, 1H) for **3b**. These different amine resonances are consistent with a rather asymmetric structure. The folding of the ligands was confirmed by a single-crystal X-ray diffraction study (Figure 1).^[10] As expected, cryptand **3b** is made up of three connecting

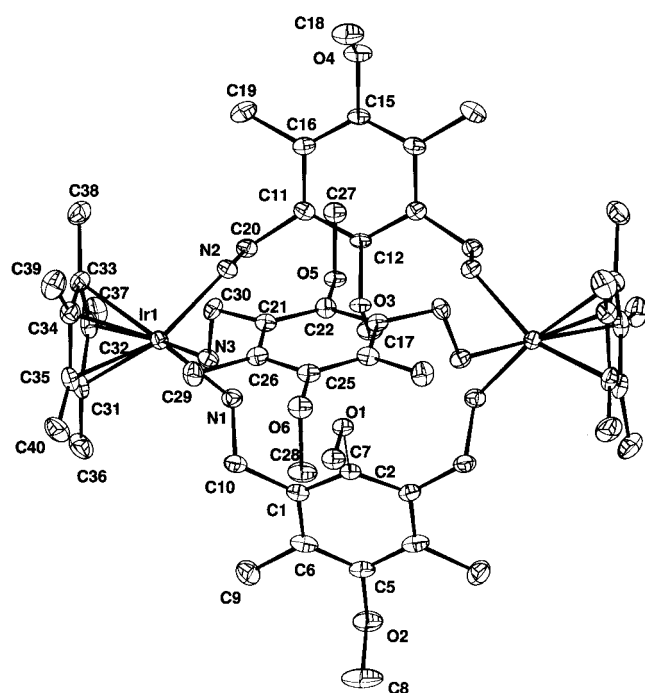


Figure 1. Crystal view of the cationic part of the metallocryptand **3b** with atom numbering system. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Ir1–N1 2.189(7), Ir1–N2 2.141(7), Ir1–N3 2.143(7), Ir1–C31 2.177(9), Ir1–C32 2.161(9), Ir1–C33 2.188(9), Ir1–C34 2.157(9), Ir1–C35 2.160(9); N1–Ir1–N2 84.1(3), N1–Ir1–N3 81.8(3), N2–Ir1–N3 82.5(3).

diamine ligands **2a** that bridge the two “Cp*Ir” moieties. Each metal center adopts a three-legged piano stool described by the three (–NH₂) groups of **2a** and the (η^5 -Cp*) coordinated ligand. It is clear that the three bidentate diamines and the two iridium centers describe an internal cavity, with both extremities are capped by the iridium fragments.

The Ir...Ir distance in **3b** is 8.17 Å, while the average O...O distance between the internal methoxy groups is 3.56 Å. All the BF₄[–] ions are located outside the metallomacrocyclic cavity, perhaps because of the steric hindrance presented by the internal methoxy groups. The ¹⁹F NMR spectrum of **3b** recorded in CD₃CN showed a sharp singlet at $\delta = -150$ which was attributed to free BF₄[–] ions.^[8b, 11]

Our next synthetic tactic was to prepare other metallocryptands without methoxy groups on the interior of the cavity, so as to leave more room for anionic guests. Thus, three equivalents of 1,3-bis(aminomethyl)benzene (**2b**) or the methylated derivative (**2c**) were combined with two equivalents of **1b**, prepared in situ, to afford the off-white complexes **4** and **5**, respectively, in 70–75 % yield. Complexes **4** and **5** were fully characterized by spectroscopic analyses (¹H, ¹³C, ¹⁹F NMR, IR) and elemental analysis. In contrast to what was seen for **3**, the ¹H NMR spectra of **4** and **5** recorded in

CD₃CN showed that the metallomacrocycles are fully symmetric: for example, the protons of the coordinated amino groups resonated as one large triplet at $\delta = 5.24$ for **4** and at $\delta = 5.12$ for **5**. Remarkably, the ¹⁹F NMR spectra of both **4** and **5** recorded in CD₃CN showed not only the presence of a singlet at $\delta = -149.5$, which were attributed to free BF₄[–] ions (as observed for **3b**; see above), but also another signal at $\delta = -44.7$ for **4** and at $\delta = -46.2$ for **5**. These latter resonances were attributed to an encapsulated and hydrogen-bonded BF₄[–] ion, respectively. Most remarkably, the ¹³C NMR spectra of **4** and **5** showed a doublet at $\delta = 132.7$ ($J_{C-F} = 10.8$ Hz) for **4** and at $\delta = 134$ ($J_{C-F} = 9.4$ Hz) for **5**. These resonances are ascribed to the three aromatic carbon atoms C(2), each of which is concluded to be close to one ¹⁹F nucleus of the BF₄[–] ion. Thus, selective ¹⁹F decoupling experiments were carried out on **4** while recording the ¹³C{¹⁹F} spectra: when the ¹⁹F signal at $\delta = -44.7$ was irradiated, the signal attributed to C(2) in the ¹³C spectrum became a singlet (Figure 2). Similar results were also obtained for complex **5**.

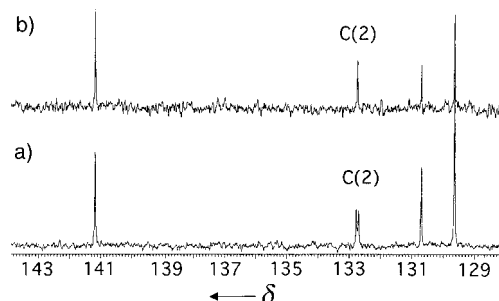


Figure 2. Section of the NMR spectra of **4**, a) ¹³C{¹H} and b) ¹³C{¹⁹F, ¹H}, showing a direct interaction between C(2)-H and one ¹⁹F nucleus of the encapsulated BF₄[–] ion.

This observation suggests that on the time scale of the NMR experiment the BF₄[–] ion remains encapsulated within the cryptate, but is tumbling within the cavity rather than being locked in one orientation. Although all attempts to obtain diffractable crystals of **4** have so far been unsuccessful, the unusual spectroscopic results and the ¹⁹F decoupled experiments, when taken together, suggest strongly the formation of the first iridium cryptates of the formula [BF₄[–] ⊂ (Cp*Ir)₂(**2b**)₃][BF₄]₃ (**4**) and [BF₄[–] ⊂ (Cp*Ir)₂(**2c**)₃][BF₄]₃ (**5**; Figure 3).

It is suggested that the BF₄[–] ion is strongly held by the polarizable protons of the coordinated amino groups bringing it close to the C(2)-H groups of the bidentate ligand (Figure 3). In this work, crucial ¹³C, and ¹⁹F NMR analyses and decoupling experiments, reveal the details of the supramolecular templation process in solution.

In conclusion, we have reported a rational synthetic strategy for formation of metallocryptands that is based on iridium and rhodium coordination chemistry. The cavity size of these metallocryptands can be varied, depending on the bridging diamine ligands used. Most notably, the synthesis of the cryptate complexes **4** and **5** was made possible by increasing the accessibility of the cavity. Further investigations are ongoing on this and related metallocryptand systems

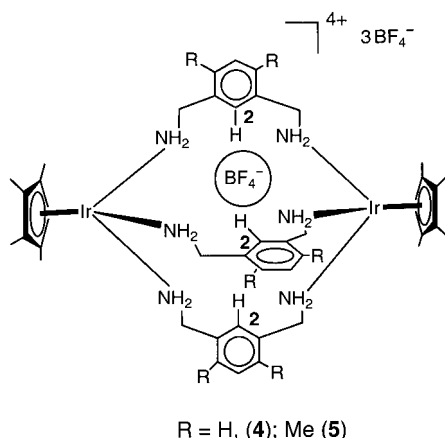


Figure 3. Schematic drawing of the Ir-cryptates **4** and **5**.

to obtain better and more selective hosts for a variety of anionic guests.

Experimental Section

All experimental manipulations were carried out under argon using Schlenk tube techniques

3b: A solution of AgBF_4 (195 mg, 1.0 mmol) in acetone (10 mL) was added to $[(\eta^5\text{-C}_5\text{Me}_5)\text{Ir}(\mu\text{-Cl})\text{Cl}]_2$ (199 mg, 0.25 mmol) in acetone (20 mL). This resulted in the rapid formation of a white precipitate of AgCl . The reaction mixture was stirred for 15 min. then the resulting orange solution of $[(\eta^5\text{-C}_5\text{Me}_5)\text{Ir}(\text{acetone})_3][\text{BF}_4]_2$ was filtered into a dry Schlenk tube kept under argon. A solution of **2a** (110 mg, 0.75 mmol) in $\text{C}_2\text{H}_4\text{Cl}_2$ (10 mL) was then added to this orange solution and the mixture was stirred for 1 h, during which the solution became lighter and a white precipitate was obtained. This compound was separated and washed several times with Et_2O and dried under vacuum, to give 353 mg of **3b** (85% yield). ^1H NMR (400 MHz, CD_3CN): δ = 5.91 (td, 6H, NH_2), 4.06 (td, 6H, CH_2), 3.65 (s, 9H, CH_3O), 3.43 (t, 6H, CH_2), 2.82 (s, 3H, CH_3O), 2.46 (s, 18H, CH_3), 2.40 (brt, 6H, NH_2), 1.95 (s, 30H, $\eta^5\text{-C}_5(\text{CH}_3)_5$). Elemental analysis calcd for $\text{C}_{35}\text{H}_{90}\text{O}_6\text{N}_6\text{Ir}_2\text{B}_4\text{F}_{16} \cdot \text{C}_3\text{H}_6\text{O}$: C 40.48, H 5.62, N 4.88; found: C 41.26, H 5.63, N 5.14.

3a: was prepared in a similar way to that described for **3b**. Yield 77% (276 mg). ^1H NMR (400 MHz, CD_3CN): δ = 5.12 (td, 6H, NH_2), 4.01 (td, 6H, CH_2), 3.65 (s, 9H, CH_3O), 3.33 (t, 6H, CH_2), 2.78 (s, 3H, CH_3O), 2.47 (s, 18H, CH_3), 1.93 (s, 30H, $\eta^5\text{-C}_5(\text{CH}_3)_5$), 1.41 (brt, 6H, NH_2). Elemental analysis calcd for $\text{C}_{35}\text{H}_{90}\text{O}_6\text{N}_6\text{Rh}_2\text{B}_4\text{F}_{16} \cdot \text{C}_3\text{H}_6\text{O}$: C 45.16, H 6.27, N 5.45; found: C 46.06, H 6.45, N 5.55.

4: This irido-cryptate was prepared in acetone at room temperature following the above procedure, but using the diamine ligand **2b**. Yield 70% (247 mg). ^1H NMR (400 MHz, CD_3CN): δ = 7.39–7.50 (m, 12H, aromatic-H), 5.24 (brt, 12H, NH_2), 3.91 (brs, 12H, CH_2), 1.85 (s, 30H, $\eta^5\text{-C}_5(\text{CH}_3)_5$). Elemental analysis calcd for $\text{C}_{44}\text{H}_{66}\text{N}_6\text{Ir}_2\text{B}_4\text{F}_{16} \cdot \text{C}_3\text{H}_6\text{O}$: C 38.43, H 4.94, N 5.72; found: C 38.66, H 5.17, N 6.16

5 was prepared in a similar fashion to that of **4** but using the diamine ligand **2c**. Yield 75% (280 mg). ^1H NMR (400 MHz, CD_3CN): δ = 7.26–7.06 (m, 6H, aromatic-H), 5.12 (brt, 12H, NH_2), 3.83 (brs, 12H, CH_2), 1.84 (s, 30H, $\eta^5\text{-C}_5(\text{CH}_3)_5$). Elemental analysis calcd for $\text{C}_{50}\text{H}_{78}\text{N}_6\text{Ir}_2\text{B}_4\text{F}_{16}$: C 40.17, H 5.62, N 5.26; found: C 39.04, H 5.47, N 5.59.

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High Turnover Numbers for the Catalytic Selective Epoxidation of Alkenes with 1 atm of Molecular Oxygen**

Yoshiyuki Nishiyama, Yoshinao Nakagawa, and Noritaka Mizuno*

Catalytic epoxidation of alkenes has attracted much attention both in industrial processes and in organic syntheses, because epoxides are among the most useful synthetic intermediates. Epoxidation of alkenes can be carried out by various techniques with various oxidants. However, stoichiometric (noncatalytic) epoxidation is still widely used, and large amounts of byproducts, particularly salts, are formed. For example, propylene oxide has been produced commercially by alkaline dehydrochlorination of propylene chlorohydrin with formation of large amounts of metal salts.^[1–3] The utilization of molecular oxygen for a catalytic epoxidation without reducing reagents or radical initiators is a rewarding goal, because molecular oxygen has the highest content of active oxygen, and no byproducts are formed from it, in contrast to various other oxidants.^[4–13] However, only a few ideal homogeneous epoxidations of alkenes with molecular oxygen at 1 atm without reducing reagents or radical initiators have been achieved, because organic ligands of the catalysts are degraded or the catalysts act as stoichiometric oxidants.

Therefore, a high catalyst turnover number (TON) is a key. The catalytic activity of polyoxometalates has attracted much attention, because their acidic and redox properties can be controlled at the atomic or molecular level. The strong acidity and oxidizing power of polyoxometalates have led to many studies on homogeneous and heterogeneous catalysis.^[13–16] The additional attractive and technologically significant

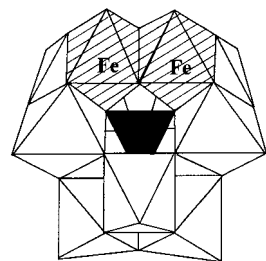


Figure 1. Polyhedral representation of γ - $\text{SiW}_{10}\text{Fe}_2(\text{OH})_{12}\text{O}_{38}^{6-}$ (**1**). The two iron atoms are represented by shaded octahedra. The WO_6 moieties occupy the white octahedra, and an SiO_4 group is shown as the internal black tetrahedron.

aspect of polyoxometalates in catalysis is their inherent stability towards oxygen donors.^[17–19] We used the Keggin-type diiron-substituted silicotungstate **1** (Figure 1) as a catalyst precursor for the selective epoxidation of alkenes with molecular oxygen at 1 atm and found that this epoxidation can be catalyzed with high TONs. The catalyst is thus able to use molecular oxygen as an oxidant, and raises the prospect of using this type of inorganic catalyst for industrial epoxidation processes.

Figure 2 shows the time course of the oxygenation of cyclooctene with 1 atm of molecular oxygen catalyzed by **1** at 356 K. The average carbon balance for six runs was $(100 \pm 8)\%$. Cyclooctene oxide was selectively produced together

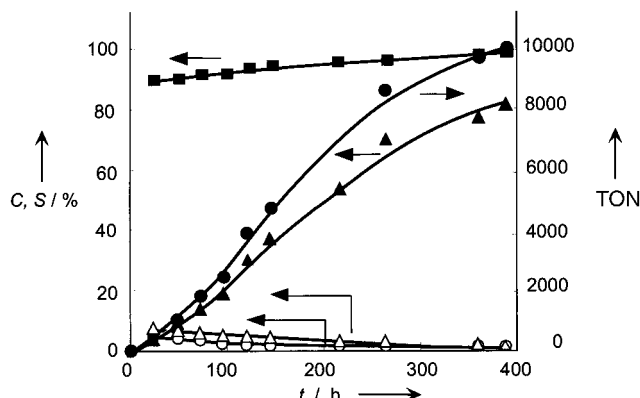


Figure 2. Oxygenation of cyclooctene with molecular oxygen catalyzed by **1** at 356 K. $\blacktriangle$, conversion of cyclooctene; $\bullet$, TON; $\blacksquare$, selectivity for cyclooctene oxide; $\circ$, selectivity for 2-cycloocten-1-ol; $\triangle$, selectivity for 2-cycloocten-1-one. Catalyst, 1.5 μmol ; solvent, 1,2-dichloroethane/acetonitrile 1.5/0.1 mL; substrate, 18.5 mmol; p_{O_2} = 1 atm. C = conversion, S = selectivity.

with small amounts of 2-cycloocten-1-ol and 2-cycloocten-1-one. After 385 h, the conversion and selectivity for cyclooctene oxide reached 82 and 98 %, respectively, and the TON was 10000. The value is more than 100 times higher than those so far reported for the epoxidation of cyclooctene with 1 atm of molecular oxygen alone.^[20]

Oxygenation of various alkenes with 1 atm of molecular oxygen was carried out in the presence of **1** at 356 K. Similarly to the oxygenation of cyclooctene, longer reaction periods increased the TON for each alkene. The results are summarized in Table 1. The main products were the corresponding

Table 1. Oxygenation of various alkenes with molecular oxygen catalyzed by **1** at 356 K.^[a]

Substrate	TON	C [%]	Products	S [%]
cyclododecene	9600	74	cyclododecene oxide	64 ^[b]
			2-cyclododecen-1-ol	31
			2-cyclododecen-1-one	5
cyclooctene	10000	82	cyclooctene oxide	98
			2-cycloocten-1-ol	1
			2-cycloocten-1-one	1
1-octene	2200	17	1,2-octene oxide	93
			1-octen-3-ol	5
			1-octen-3-one	2
2-octene (<i>cis/trans</i> = 8/2)	2500	20	2,3-octene oxide	94
			2-octen-4-ol	5
			2-octen-4-one	1
2-heptene (<i>cis/trans</i> = 8/2)	2900	24	2,3-heptene oxide	91
			2-hepten-4-ol	8
			2-hepten-4-one	1
2-hexene (<i>cis/trans</i> = 4/6)	1300	11	2,3-hexene oxide	79
			2-hexen-4-ol	19
			2-hexen-4-one	2

[a] Reaction conditions: catalyst, 1.5 μmol ; solvent, 1,2-dichloroethane/acetonitrile, 1.5/0.1 mL; substrate, 18.5 mmol; p_{O_2} = 1 atm; reaction time, 385 h. The substrate/ O_2 ratio in the gas phase may lie within the explosion limit. [b] Includes the selectivity for 1,2-cyclododecanediol (6 %).

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epoxides in all oxygenation reactions. This fact and the obtained TONs show that **1** can efficiently catalyze the epoxidation of various kinds of alkenes.

Keggin-type polyoxometalates show characteristic UV/Vis bands, and therefore their structures have often been characterized by UV/Vis spectroscopy. The UV/Vis spectrum of as-prepared **1** showed bands at 275 ($\epsilon = 22\,600$), 334 (10 000), and 470 nm ($68\text{ M}^{-1}\text{ cm}^{-1}$), and after being used for the oxygenation of cyclooctene **1** showed the original absorption bands with almost the same intensities. The IR bands of the original skeletal vibration of **1** changed only slightly (see below). Magnetic susceptibility measurements and recording of Mössbauer and ^{183}W NMR spectra on the reaction solution to investigate the structure of **1** were thwarted by insufficient sensitivity at the low concentration (0.38 mM). After **1** (0.15 M) was treated with 1 atm of molecular oxygen in $[\text{D}_3]\text{acetonitrile}$ for 96 h at 356 K, the ^{183}W NMR spectrum showed two broad signals at $\delta = -1330$ and -1840 with an integral ratio of 2:1, characteristic of the C_{2v} symmetry of the original γ -Keggin structure. This indicates that the two iron atoms occupy the same positions as shown in Figure 1 under the reaction conditions and that the structure of **1** is retained during the reaction. In addition, the fact that **1** is even stable in the presence of hydrogen peroxide,^[21] as demonstrated by ^{183}W NMR spectroscopy, supports this conclusion.

The oxygenation of cyclooctene was not inhibited by the presence of 1–3 equiv (relative to **1**) of alkyl-radical scavengers such as *p*-tert-butylcatechol. For example, the conversion and selectivity for cyclooctene oxide after 96 h in the presence of 1 equiv of *p*-tert-butylcatechol were 20 and 92 %, respectively. These values are in good agreement with those of 18 and 92 %, respectively, in the absence of the radical scavenger. For epoxidation of *trans*- and *cis*-2-octenes, the *trans/cis*-oxide ratios were 10 and 0.2, respectively, that is, the reaction was rather stereospecific. Similarly, epoxidation of *cis*-2-hexene proceeded rather stereospecifically. In contrast, epoxidation via a radical intermediate proceeds nonstereospecifically. In fact, addition of a radical initiator, *N*-hydroxyphthalimide, mainly produced *trans*-2-octene oxide (*trans/cis* = 4) in the epoxidation of *cis*-2-octene. In addition, epoxidations of *cis*-2-octene and *cis*-2-hexene were faster than those of the corresponding *trans*-2-alkenes, as has been observed for epoxidation catalyzed by oxo iron porphyrins, which proceeds differently from epoxidation via a radical pathway.^[22]

The kinetic studies showed zero-order dependence of reaction rates on the concentration of cyclooctene ([cyclooctene]), and first-order dependence on the concentration of **1** (**[1]**) and the partial pressure of molecular oxygen (p_{O_2}). These results indicate that the rate of decrease in [cyclooctene] is expressed by $-\text{d}[\text{cyclooctene}]/\text{d}t = k[\mathbf{1}]p_{\text{O}_2}[\text{cyclooctene}]^0$. Moreover, a maximum rate was obtained for $p_{\text{O}_2} = 1\text{--}2$ atm. The oxygenation of adamantane showed that the ratio of tertiary/secondary C–H bond selectivity on a per bond basis was 11.^[23] Under free-radical conditions, the value is normally three, that is, different from that in the present system. All these results demonstrate that nonradical processes prevail to a major degree in the present system,^[24] although some contribution of free radicals is still a possibility.

Figure 3 shows IR spectra of **1** after oxygenation of cyclooctene with $^{16}\text{O}_2$ and $^{18}\text{O}_2$ at 356 K. As-prepared **1** shows bands at 960 [$\nu(\text{W}=\text{O}_{\text{terminal}})$], 902, 884 [$\nu(\text{SiO})$], 800 ($\nu(\text{W-O-W})$ for corner-sharing octahedra), and 753 cm^{-1} ($\nu(\text{W-O-W})$

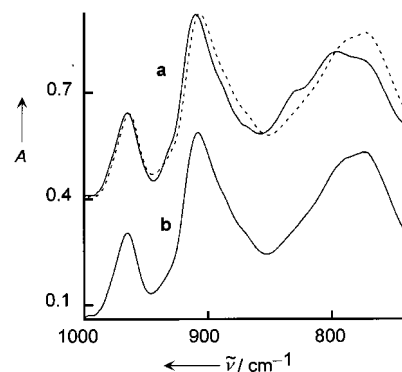


Figure 3. IR spectra of **1** after oxygenation of cyclooctene with $^{16}\text{O}_2$ (a) and $^{18}\text{O}_2$ (b and dotted line in a) for 96 h at 356 K. The spectra were measured by quickly evaporating the reaction solution, washing the resulting solid with diethyl ether, drying and then pressing it into a KBr pellet. A = absorbance.

for edge-sharing octahedra). After **1** being used for the oxygenation of cyclooctene with $^{16}\text{O}_2$, a new band was observed at 832 cm^{-1} (Figure 3a). It is reported that $\text{Fe}=\text{O}$ bands appear in the range of $810\text{--}860\text{ cm}^{-1}$.^[22] After oxygenation with $^{18}\text{O}_2$ a new band was observed at 776 cm^{-1} (Figure 3b). The shift of 56 cm^{-1} is in fair agreement with the expected shift of 48 cm^{-1} . The band disappeared after the reaction with cyclooctene under Ar, and cyclooctene oxide (1.9 equiv) was formed; this shows that the iron–oxygen species is reactive. The amount of H_2^{18}O produced was 2×10^{-4} mol, close to that of 2-cycloocten-1-one, and much less than that of cyclooctene oxide. In addition, the amount of cyclooctene oxide produced was about two times larger than the amount of O_2 consumed.^[25] The above results show that the epoxidation proceeds without co-formation of water, and an intermediate iron–oxygen species is formed.

In conclusion, we have demonstrated that **1** efficiently catalyzes the epoxidation of alkenes with molecular oxygen alone, a green route to epoxides. Detailed investigations on the reaction mechanism are in progress.

Experimental Section

The catalyst precursor **1** was synthesized as its tetrabutylammonium salt by the reported procedure.^[26] A solution of $\text{K}_8[\gamma\text{-SiW}_{10}\text{O}_{36}] \cdot 12\text{H}_2\text{O}$ (3.0 g, 1.0 mmol) in deionized water (30 mL) was quickly adjusted to pH 3.90 with concentrated nitric acid. Then, an aqueous solution of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (0.82 g, 2.0 mmol) in water (5 mL) was added. The color of the solution turned to pale yellow. After the solution had been stirred for 5 min, the addition of an excess of tetra-*n*-butylammonium nitrate (3.1 g, 10 mmol) resulted in a yellow-white precipitate. The precipitate was collected by filtration and purified by twice dissolving it in acetonitrile (15 mL) and adding water (300 mL) to reprecipitate the product. The yield of the purified compound was about 1.5 g (50 %). The polyoxometalate $\gamma\text{-SiW}_{10}[\text{Fe}^{3+}(\text{OH}_2)]_2\text{O}_{38}^{6-}$ (**1**) has a γ -Keggin structure with C_{2v} symmetry, and the two iron centers occupy adjacent, edge-shared octahedra, as shown in Figure 1. UV/Vis, Mössbauer, EPR, and magnetic susceptibility data show that two high-spin Fe^{3+} centers are equivalent and antiferromagnetically coupled.^[26]

Alkenes were distilled and treated with activated alumina to remove impurities and alkyl hydroperoxide. The reaction was carried out in a glass vial or a round-bottomed flask containing a magnetic stir bar under 1 atm of molecular oxygen as described previously.^[21] 2-Cyclohexen-1-one was usually used as an internal standard. The homogeneous reaction solution was periodically sampled and analyzed by gas chromatography on a TC-WAX capillary column and by NMR spectroscopy. The amounts of oxygen consumed were measured with a gas burette. It was confirmed for the oxygenation of cyclooctene that no reaction proceeded without catalysts. Turnover numbers were calculated as moles of products per mole of **1**.

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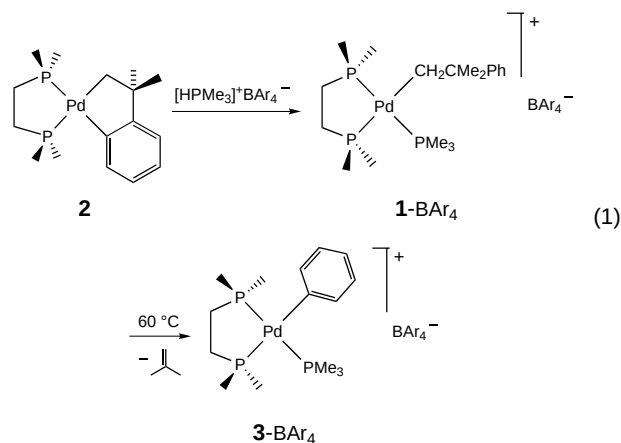
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Cleavage of the C_{alkyl}–C_{aryl} Bond of [Pd–CH₂CMe₂Ph] Complexes**

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The cleavage and functionalization of strong C–C single bonds^[1] by transition metal compounds is an important transformation,^[2–6] which is relevant to Ziegler–Natta catalysis^[7] and to other organometallic processes.^[8, 9] Aryl elimination by activation of a β -C_{alkyl}–C_{aryl} bond^[5] is the microscopic reverse of the migratory insertion of an alkene into a M–C_{aryl} bond, a relevant step of the Heck reaction^[8] and of the SHOP process.^[9] Herein we report on the conversion of a [Pd–CH₂CMe₂Ph]⁺ moiety into the corresponding phenyl derivative, [Pd–Ph]⁺, and the subsequent functionalization of the latter by conventional C₂H₄ migratory insertion chemistry to produce C₆H₅CH=CH₂.

The cationic complex [Pd(CH₂CMe₂Ph)(dmpe)(PMe₃)]⁺ (**1**) (dmpe = Me₂PCH₂CH₂PMe₂) can be generated by reacting the palladacycle [PdCH₂CMe₂-*o*-C₆H₄](dmpe)] (**2**)^[10] with [HPMe₃]⁺BAR₄[–] (Ar = 3,5-C₆H₃(CF₃)₂). At 60° C it under-



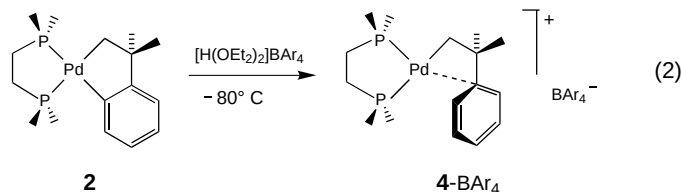
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Supporting information (kinetic data and reaction rates for the transformation **1** → **3** catalyzed by **4**) for this article is available on the WWW under <http://www.angewandte.com> or from the author.

goes very slow thermolysis ([Eq. (1)], $t_{1/2} \approx 60$ h) to give the phenyl derivative **3**-BAR₄^[11] along with isobutene (GC-MS analysis). A formally three-coordinate cationic complex [Pd(CH₂CMe₂Ph)(dmpe)]⁺ (**4**), in which the highly electrophilic metal is stabilized by an auxiliary π, η^1 interaction with the *ipso*-carbon atom of the phenyl group appears as a likely intermediate.^[12] Hence, we have prepared the BAR₄[−] salt of this cation [Eq. (2)] by the low-temperature protonation of



the palladacycle **2** with [H(OEt₂)₂]BAR₄. Similarly to related palladium metallacycles^[12] selective cleavage of the Pd–C_{aryl} bond is observed, leading to **4**-BAR₄ in quantitative yield [Eq. (2)]. Spectroscopic data for **4** (see Experimental Section) are in accord with the proposed structure. In particular, the *ipso*-carbon atom displays a ¹³C{¹H} signal at $\delta = 119.6$ (dd, ²J_{C,P} = 6, 12 Hz). This matches closely the corresponding resonance in the PMe₃ analogue and in the structurally related, X-ray characterized compound [Pd(CH₂CMe₂-Ph)(OTf)(PMe₃)]^[12] ($\delta = 123.5$, dd, ²J_{C,P} = 4, 12 Hz and $\delta = 21.8$, d, ²J_{C,P} = 13 Hz, respectively). The above observation is in agreement with the existence of a Pd–C_{ipso} π, η^1 bonding interaction, which was confirmed by an X-ray structure determination^[13] (Figure 1). Other Pd complexes that display

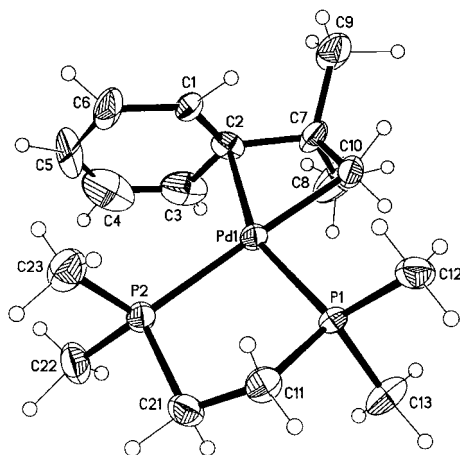
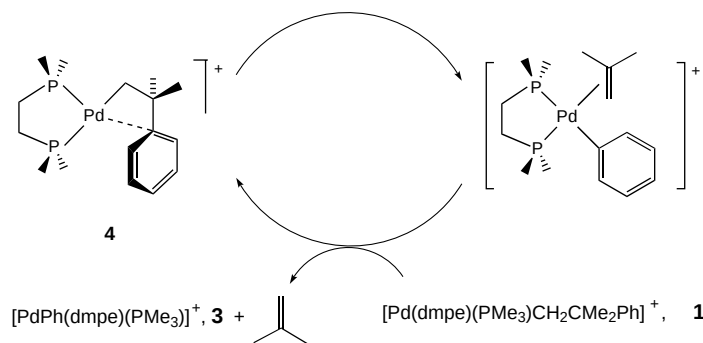


Figure 1. Structure of the cation **4** (ORTEP view; the BAR₄[−] counterion has been omitted for clarity). Selected bond lengths [Å] and angles [°]: Pd1–C10 2.065(7), C7–C10 1.531(11), Pd1–C2 2.343(6), Pd1–P1 2.220(2), Pd1–C1 2.511(8), Pd1–P2 2.363(2), C2–C7 1.530(10); P1–Pd1–P2 86.67(7), Pd1–C10–C7 98.3(5), C2–Pd1–C10 66.2(3), Pd–C2–C7 87.5(4).

similar Pd...aryl interactions (either π, η^1 or π, η^2) have been reported.^[14] It is also worth noting that the structural data obtained for **4** are strikingly similar to those calculated by Rösch et al.^[15] by density functional theory (DFT) methods for [Pd(CH₂CH₂Ph)(C(NH₂)₂)]⁺, which was considered as a model for the insertion step of the Heck reaction.

Complex **4** undergoes intricate thermolysis in CH₂Cl₂, THF, or Et₂O as the solvent to give isobutene, along with C₆H₆,

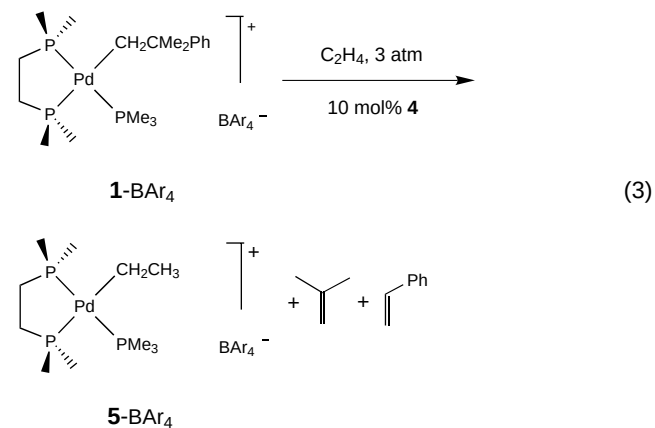
C₆H₅CMe₃, and smaller amounts of other unidentified volatile materials. An uncharacterized mixture of inorganic compounds is also formed. This complexity is, however, foreseeable since the extrusion of isobutene from **4** would generate a highly labile, thermally unstable 14-electron phenyl complex, [PdPh(dmpe)]⁺. Notwithstanding, we have found that the β -Ph elimination reaction of **1** can be made catalytic in the presence of **4** (10 mol %). Thus, a sample of compound **1** converts cleanly under these conditions into [Pd(Ph)(dmpe)(PMe₃)]⁺ (**3**) and CH₂=CMe₂ (Scheme 1). Kinetic measurements show a zero-order dependence on

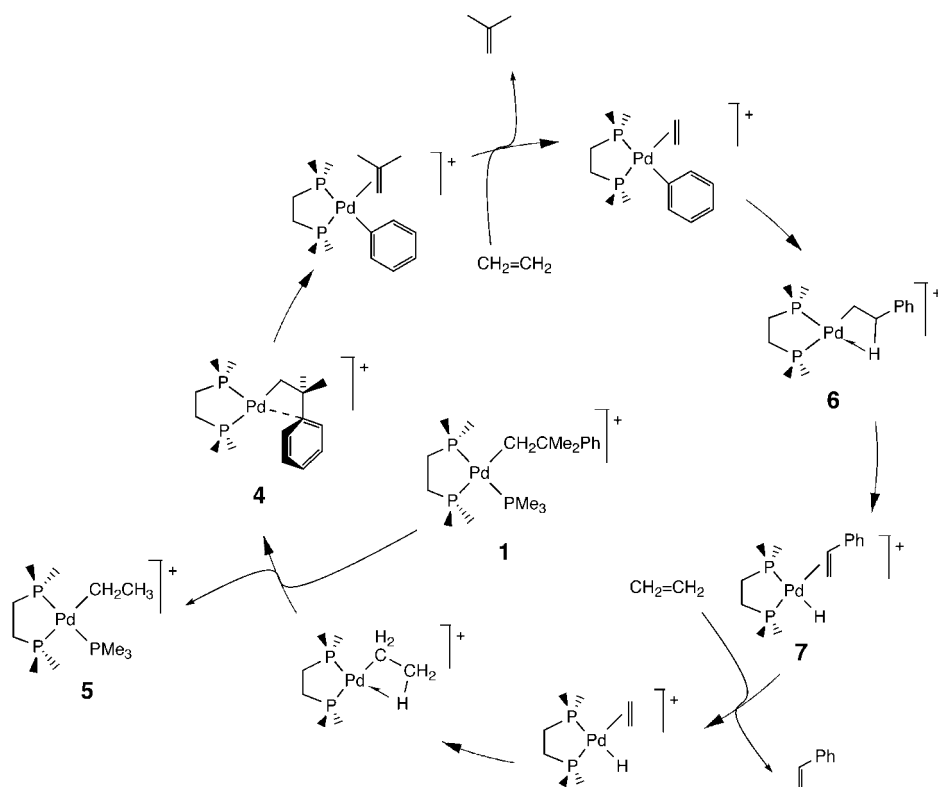


Scheme 1. β -Ph elimination reaction of **1** in the presence of **4**.

1, while the concentration of **4** remains steady during the process. The apparent rate constant exhibits a direct dependency on the concentration of **4**, a value of $2.7 \times 10^{-4} \text{ s}^{-1}$ has been obtained at 60 °C for the overall first-order rate constant. It seems likely that C–C bond cleavage is the rate-determining step.

As already pointed out, the β -Ph elimination can be considered as the microscopic reverse of the olefin insertion step of the Heck reaction. Whereas it is evident that the electrophilicity of the cationic palladium center has a decisive influence in the deinsertion, it seems probable that the irreversibility of this process is a consequence of the steric requirements posed by the insertion of isobutene into the Pd–Ph bond. In accord with these assumptions, C₂H₄ is able to induce the reverse reactivity, and undergoes insertion under the conditions of Equation (3) to produce a mixture of the ethyl derivative **5**, isobutene, and styrene. Scheme 2 depicts a





Scheme 2. Proposed reaction pathway for the overall transformation of **1** to **5**.

likely reaction pathway for the overall transformation. Like in the Heck reaction, the phenethyl intermediate **6**, undergoes facile β -H elimination. In our base-free system, the $[\text{Pd-H}]^+$ complex inserts another molecule of C_2H_4 and gives rise to a $[\text{Pd-Et}]^+$ group which becomes stabilized by the coordination of PMe_3 .^[16] It is interesting to note here the ability of the dmpe ligand to promote the olefin extrusion or insertion as compared to the corresponding PMe_3 system.^[12] This might be rationalized on the basis of the smaller steric hindrance posed by the dmpe ligand to the planar transition state required for the mentioned processes.^[15, 17]

In summary, we have shown that the unstrained $\text{C}_{\text{alkyl}}\text{-C}_{\text{aryl}}$ bond of the neophyl ligand becomes readily activated when bonded to an electrophilic palladium center. Effecting this thermal activation under ethylene allows the coupling of this molecule with the phenyl fragment that results from the cleavage of the $\text{C}_{\text{alkyl}}\text{-C}_{\text{aryl}}$ bond to produce styrene along with isobutene.

Experimental Section

4: $[\text{H}(\text{OEt})_2]\text{BAR}_4$ (0.22 g, 0.25 mmol) was added to a cooled (-30°C) solution of the metallacyclic complex **2**^[10] (0.97 g, 0.25 mmol) in CH_2Cl_2 (20 mL). After the cooling bath had been removed, the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum and the residue was extracted with Et_2O (20 mL). The product was isolated as colorless crystals by partial concentration of the solvent, addition of some petroleum ether, and cooling to -20°C overnight. Yield: 0.28 g, 91%. Elemental analysis (%) calcd for $\text{C}_{48}\text{H}_{41}\text{BF}_4\text{P}_2\text{Pd}$: C 46.01, H 3.30; found: C 46.08, H 3.29; ^1H NMR (CD_2Cl_2 , 20°C): δ = 1.09 (dd, $^3J_{\text{H,P}}$ = 5.5, 8.1 Hz, 2H; CH_2), 1.37 (s, 6H; CMe_2), 7.42 (m, 1H; CH arom.), 7.67 (m, 2H; CH arom.), 7.73 (m, 2H; CH arom.); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C) AX

spin system, $\delta_{\text{A}} = 13.6$, $\delta_{\text{X}} = 32.7$, $J_{\text{AX}} = 29.6$ Hz; $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C): δ = 18.9 (dd, $^2J_{\text{C,P}} = 19$, 34 Hz; CH_2), 32.7 (d, $^4J_{\text{C,P}} = 5$ Hz; CMe_2), 41.6 (d, $^3J_{\text{C,P}} = 3$ Hz; CMe_2), 119.6 (dd, $^2J_{\text{C,P}} = 6$, 12 Hz; C_q arom.), 122.2 (d, $J_{\text{C,P}} = 2$ Hz; CH arom.), 128.6 (s; CH arom.), 133.1 (s; CH arom.).

5: A solution of **1** (0.33 g, 0.25 mmol), **4** (0.030 g, 0.025 mmol), and toluene (50 μL ; internal GC standard) in diethyl ether (20 mL) was transferred to a Fischer–Porter pressure reactor, charged with ethylene (3 bar) and heated at 60°C for 24 h. GC analysis of the resulting yellow solution revealed the formation of styrene (0.25 mmol), isobutene (0.20 mmol), *tert*-butylbenzene (ca. 0.03 mmol), and minor amounts of unidentified volatile products. A $^{31}\text{P}\{^1\text{H}\}$ spectrum of this crude mixture showed full conversion to **5** (ca. 90% purity). The solution was evaporated and the residue extracted with petroleum ether and filtered. Evaporation to dryness left the crude product as an oily solid, which was obtained as pale green crystals by recrystallization from a petroleum ether/ Et_2O (2:1) mixture. Yield: 0.18 g, 60%. Elemental analysis (%) calcd for $\text{C}_{43}\text{H}_{42}\text{BF}_4\text{P}_2\text{Pd}$: C 42.16, H 3.46; found: C 42.21, H 3.27; ^1H ^{31}P NMR (CD_2Cl_2 , 20°C): δ = 1.11 (t, $^3J_{\text{H,H}} = 8.0$ Hz, 3H; CH_3CH_2), 1.41 (q, 2H; CH_3CH_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C): δ = -18.6 (dd, $^2J_{\text{PP}} = 386$, 39 Hz), 16.1 (dd, $^2J_{\text{PP}} = 39$, 26 Hz), 30.1 (dd, $^2J_{\text{PP}} = 386$, 26 Hz);

$^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 20°C): δ = 11.9 (d, $^2J_{\text{C,P}} = 87$ Hz; CH_2), 15.2 (m, partially hidden by dmpe signals, CH_3).

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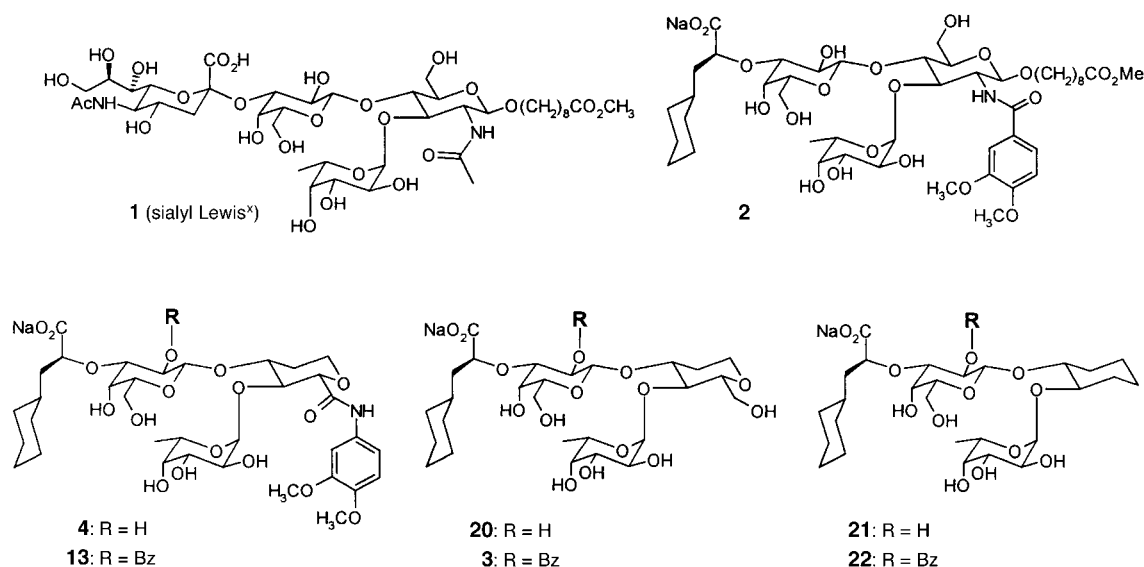
A Readily Available, Highly Potent E-Selectin Antagonist

Gebhard Thoma,* Rolf Bänteli, Wolfgang Jahnke, John L. Magnani, and John T. Patton

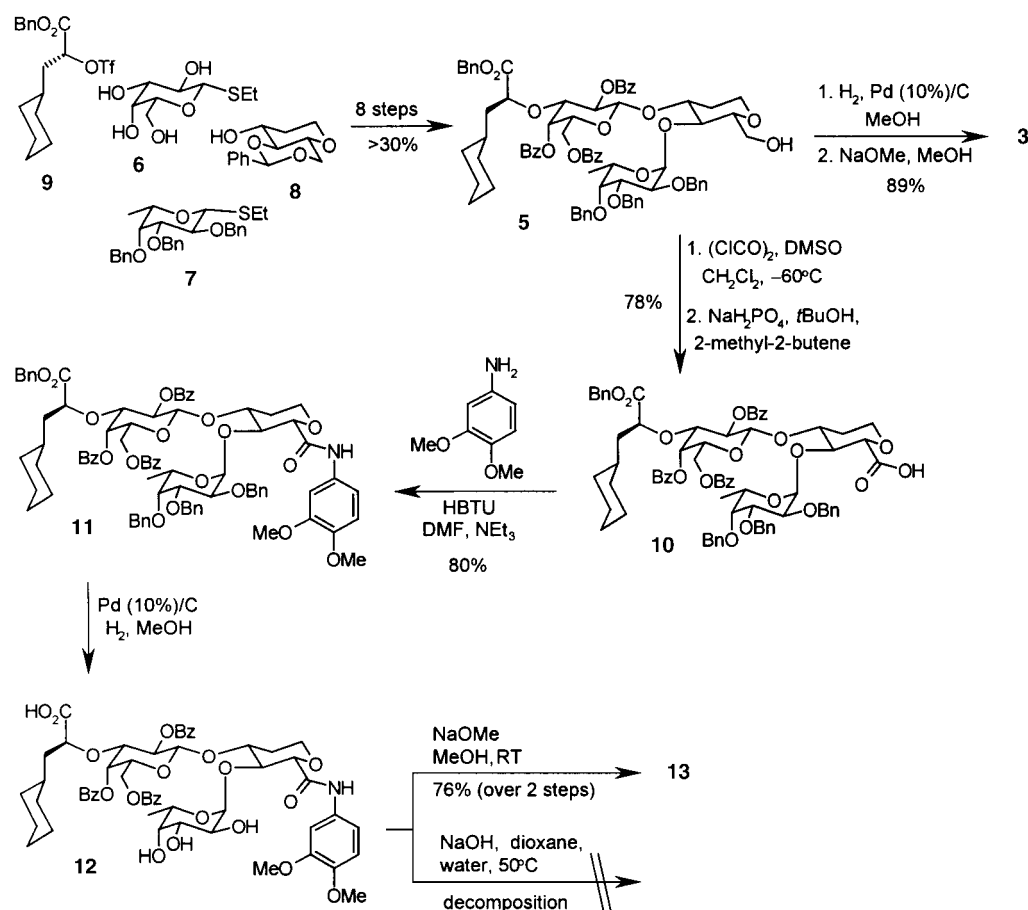
Excessive infiltration of leukocytes from blood vessels into surrounding tissues can cause acute or chronic inflammatory disorders such as reperfusion injuries, stroke, psoriasis, rheumatoid arthritis, or respiratory diseases.^[1] An early step in the cascade of events which finally leads to leukocyte extravasation—their rolling on activated endothelial cells—is mediated by selectin–carbohydrate interactions.^[2] The adverse effects could thus be prevented by selectin blockade. The tetrasaccharide sialyl Lewis^x (**1**, Scheme 1) is a weak^[3] ligand for E-, P- and L-selectin^[4] and became a lead to discover more potent inhibitors.^[5] To assess our E-selectin antagonists we used a static, cell-free ligand-binding assay which measures inhibition under equilibrium conditions.^[6] Sialyl Lewis^x (IC₅₀ = 1000–2000 μM) was tested on each plate to allow direct comparison of data from different test plates. Thus, we obtained relative IC₅₀ values (see Table 1). To further profile our compounds we developed a dynamic in vitro assay which allows to monitor E-selectin-dependent rolling of neutrophils on activated endothelial cells under shear stress and, hence, mimics the nonequilibrium in vivo conditions^[7] (see Table 1). Recently we described the promising E-selectin inhibitor **2** (Scheme 1), which showed good activities in both the static (rel. IC₅₀ = 0.030) and the dynamic (IC₅₀ = 10 μM) assay.^[8] Here we report on our search for simplified analogues of **2** which led to the discovery of **3** (Scheme 1) being the most potent small-molecule E-selectin antagonist to date (IC₅₀ = 1–2 μM in the dynamic flow assay).

To simplify **2** we designed compound **4** (Scheme 1) with a glucal-derived moiety instead of the glucosamine residue. Furthermore, the benzamide in **2** was replaced by the corresponding anilide. We expected compound **4** to be readily available from the earlier described advanced intermediate **5**, which can be assembled from building blocks **6–9** in eight steps in an overall yield of > 30% (Scheme 2).^[9] The primary hydroxyl group of **5** was oxidized to yield the carboxylic acid **10**, which was then coupled with 3,4-dimethoxyaniline to give **11** (Scheme 2). Hydrogenolytic removal of the benzyl protecting groups proceeded smoothly (**12**), but subsequent cleavage of all three benzoyl groups to obtain **4** failed. Transesterification using NaOMe (1.1 equiv) gave clean removal of the gal-4 and the gal-6 benzoyl groups leading to partly protected compound **13**^[10] (Scheme 2). The gal-2 benzoate remained untouched. Harsher conditions (aqueous NaOH; 50 °C) resulted in decomposition, most probably

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Scheme 1. Structures of selected E-selectin inhibitors. Bz = benzoyl.

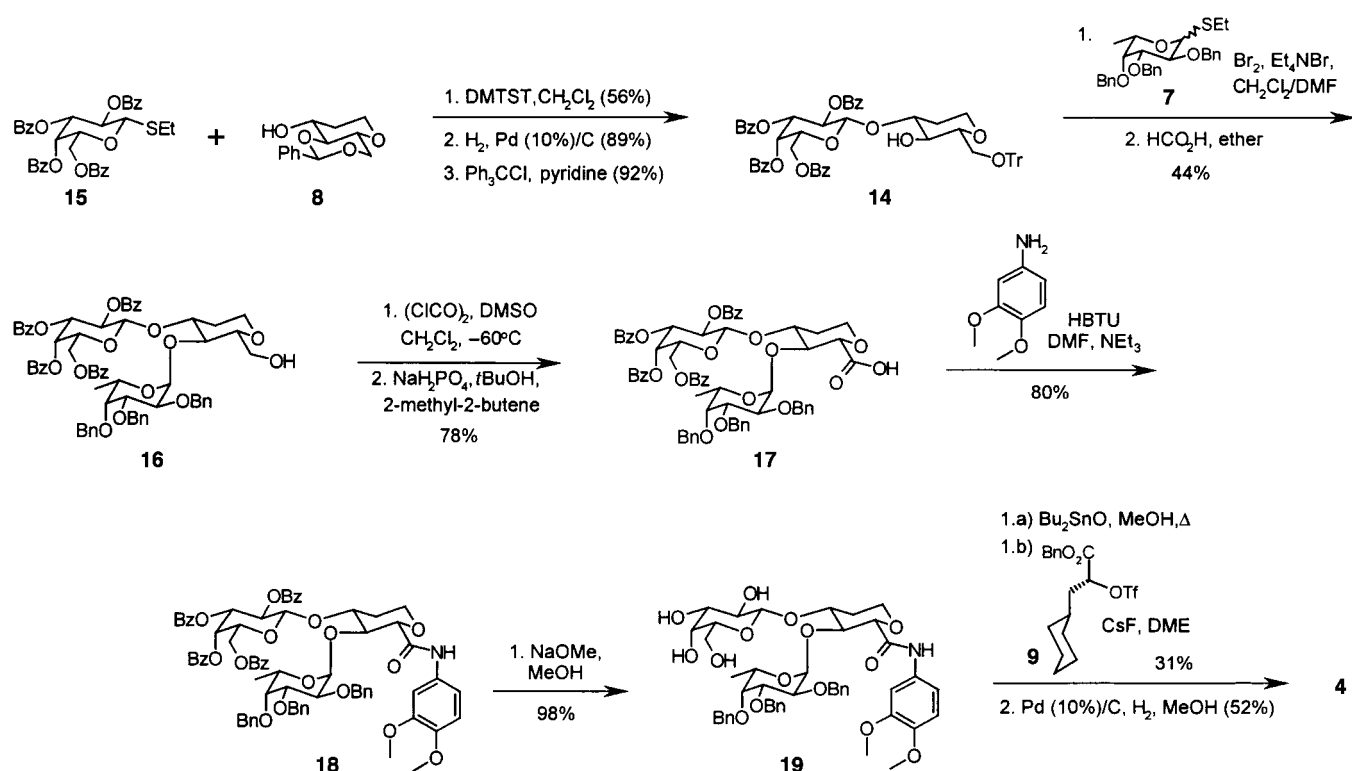


Scheme 2. Synthesis of **13**. Bn = benzyl, DMSO = dimethylsulfoxide, HBTU = benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate.

initiated by deprotonation at the 5-position of the glucal-derived moiety.^[11] Compound **13** was tested in the static assay and, to our surprise, showed >100-fold improved potency compared to sLe^x (rel. IC₅₀ = 0.009). In the flow assay we determined an IC₅₀ value of 1–2 μM which is remarkable for a small-molecule lectin ligand^[3] (see Table 1). Sialyl Lewis^x did

not show any inhibition in this assay at concentrations up to 1000 μM.

To elucidate the effect of the 2-benzoate on the bioactivity we decided to prepare the originally designed compound **4** using a different route (Scheme 3). Disaccharide **14** was assembled in three steps from benzoyl-protected thiogalacto-



Scheme 3. Synthesis of **4**. DMTST = (dimethylsulfanyl)methylsulfonium trifluoromethanesulfonate, DMF = *N,N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

side **15** and the glucal-derived building block **8**.^[12] Fucosylation of **14** using **7** followed by removal of the trityl protecting group gave **16**. A two-step oxidation of the free hydroxyl group yielded the carboxylic acid **17** which was transformed into the anilide **18**. Transesterification using catalytic quantities of NaOMe led to complete removal of all four benzoyl groups giving the tetraol **19**. Tin-mediated selective alkylation of the 3-OH group using the triflate **9**^[12] followed by hydrogenation afforded target molecule **4**.^[10] It was found to be highly active in the static assay (rel. IC₅₀ = 0.025) but significantly less potent than **13** (rel. IC₅₀ = 0.009). Obviously, the gal-2 benzoyl group substantially affects binding to E-selectin.

Recently, we have reported on the readily available E-selectin inhibitor **20** (see Scheme 1; ten linear steps, 18% overall yield, rel. IC₅₀ = 0.031) which is related to **4** and similarly potent.^[12] We decided to prepare compound **3**, the gal-2 benzoyl derivative of **20**.^[11] It was obtained in 89% yield over two steps (see Scheme 2) from **5** by hydrogenation followed by selective transesterification. Compound **3**^[10] was found to be as potent as **13** in both the static (rel. IC₅₀ = 0.010) and the dynamic assay (IC₅₀ = 1–2 μM).

The beneficial effect of the gal-2 benzoate on E-selectin inhibition is not general. Introduction of a benzoate into our first-generation E-selectin antagonist **21**^[13] (rel. IC₅₀ = 0.100) led to **22**^[10, 14] (see Scheme 1) which is slightly less potent (rel. IC₅₀ = 0.140). Thus, it is unlikely that the benzoate group binds to the protein.^[15] Both sLe^x and our inhibitors exhibit decreased fuc–gal distances in the bound form compared to their solution conformations.^[16] Earlier we have demonstrated that the improved bioactivity of **20** compared to **21** is due to an

improved preorganization of the bioactive conformation, caused by intramolecular steric interactions between the CH₂OH substituent of the glucal-derived moiety and the fucose residue, resulting in a decreased fuc–gal distance.^[17] We believe that the gal-2 benzoate and the CH₂OH substituent in **3** (the anilide in **13**) act in concert decreasing the distance between galactose and fucose even more. This is supported by strong NOE's between galactose and fucose observed for **3**. In the static assay compound **3** is 3-fold more potent than our previously described inhibitor **20**. The effect is much more pronounced in the more relevant dynamic flow assay (20-fold) pointing out the importance of the solution conformation of compounds that interfere with dynamic, nonequilibrium processes such as cell–cell recognition

Table 1. In vitro activities of E-selectin antagonists (n.d. = not determined).

	Static rel. IC ₅₀ ^[a]	200 μM	50 μM	Flow ^[b] 10 μM	2 μM	IC ₅₀ [μM]
sLe ^x	1.000					n.d.
2 ^[8]	0.030	97 %	93 %	54 %	n.d.	10
3	0.010	n.d.	92 %	77 %	53 %	1–2
4	0.025	n.d.	n.d.	n.d.	n.d.	n.d.
13	0.009	n.d.	96 %	81 %	56 %	1–2
20 ^[12]	0.031	94 %	60 %	10 % ^[c]	n.d.	30–40
21 ^[13]	0.100	70 %	20 % ^[c]	n.d.	n.d.	n.d.
22	0.140	n.d.	n.d.	n.d.	n.d.	n.d.

[a] Relative IC₅₀ values are defined as rel. IC₅₀ = IC₅₀(test compound)/IC₅₀(sLe^x); compounds were tested at least twice (mean value). [b] Reduction of the number of interacting cells given as percentage. [c] Statistically not significant.

events. The results of all the inhibition tests are found in Table 1.

In conclusion, by a mix of accident, serendipity and rational design, we have discovered compound **3** which is the most potent small-molecule E-selectin inhibitor to date. Compound **3** can be prepared in ten steps in > 25 % overall yield.

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Acids and Bases in One Pot while Avoiding Their Mutual Destruction**

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We have demonstrated recently that separate entrapment in sol-gel matrices of a catalyst and of a reagent which poisons it enables the simultaneous use, in one pot, of these chemicals, which otherwise must be used in consecutive steps.^[1] Here we extend the methodology of changing "chemical hostility" into "chemical friendliness" and compatibility, to the classical family of opposing reagents namely acids and bases.

We routinely teach at elementary-level chemistry that since acids and bases annihilate each other when brought together, one needs to separate acidic steps from basic ones in reaction sequences. We show here that sol-gel entrapment^[2] solves this problem, and makes it possible to place in one-pot acids and bases without their mutual destruction, while still allowing these reagents to activate or participate in desired reactions. In numerous studies it has been shown that molecules entrapped within sol-gel matrices retain their chemical and physical properties^[3] and that external substrate molecules can enter the pore network, react with the dopant, and emerge from the pores as products. Thus, the only

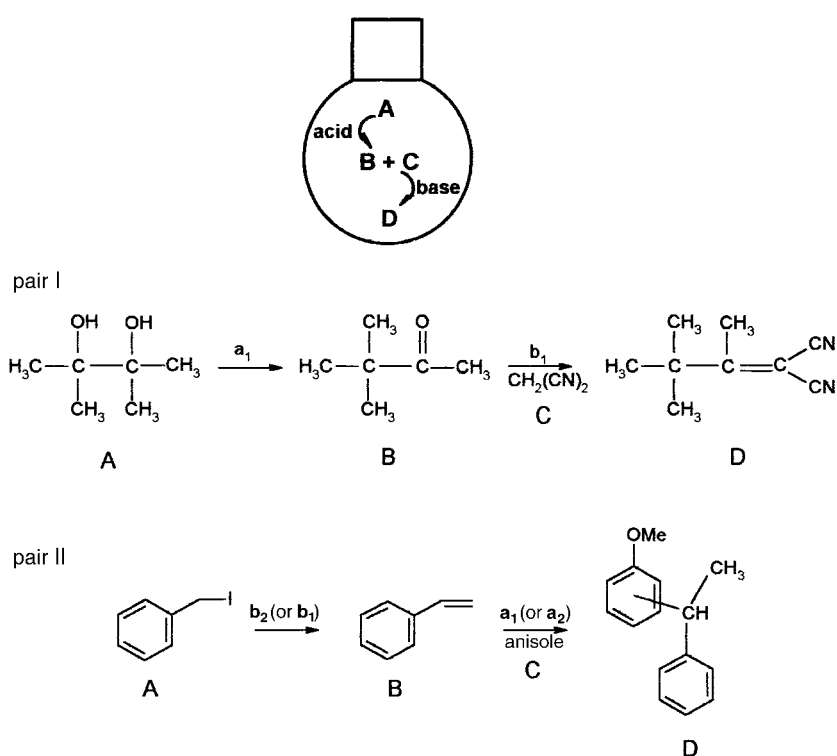
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possible reactivity for the dopant is with *diffusible* substrates. For instance, if an acid is entrapped, it can react with a diffusible base and, indeed, one of the more successful applications of doped sol–gel materials has been in the field of pH sensors:^[4] here, an entrapped (acidic/basic) indicating molecule reacts with external, diffusible hydronium cations or hydroxyl anions. But then, if the acid and the base are entrapped in two *different* materials, they become, on one hand, protected from each other, and on the other hand, still available for useful reactions. Surface adsorption of acids and bases or derivatization of polymers with acidic/basic moieties leave some of the reagent exposed and consequently acid/base syntheses employing solid-state methods are routinely carried out consecutively.^[5] While doped sol–gel materials may contain some of the entrapped molecules at the outer reaches of the particulate or monolithic material, the amount is negligible; there are hundreds of square meters per gram of internal surface area within these porous materials, compared to 1–2 m² g^{−1} of external surface. Of relevance to this report are the elegant studies of Pittman and Smith^[6] on polymeric bicatalytic systems and the solid-state polymeric transfer of functional groups of Rebek, Jr. et al.^[7a] and Cohen et al.;^[7b] and studies with oxides, such as alumina, which contain both acidic and basic sites on their surface.^[8] These oxides lack, however, the versatility of tailoring the acid/base properties by demand as offered by the ability of sol–gel materials to entrap practically any of the thousands of known acids and bases (except, of course, those which destroy the matrix itself). We demonstrate the approach with various combinations of two acids and two bases, on two pairs of reactions.

The *acids* were sol–gel (silica, in all cases) entrapped Nafion (perfluorinated resin sulfonic super acid, **a**₁)^[9] and the sol–gel entrapped molybdic acid MO₃–SiO₂ (**a**₂)^[10a] (H₄SiMo₁₂O₄₀)^[10b]. The *bases* were two Ormosils (organically modified silica sol–gel materials), one carrying H₂N(CH₂)₂NH(CH₂)₃ functional groups (**b**₁)^[11] and the other guanidine base (1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBD) residues (**b**₂).^[12] Thus, three methods for leach-proof entrapments are demonstrated here: the physical entrapment of a polymer, the physical entrapment of an inorganic molecule which strongly associates with the (silanols of the) matrix, and covalent anchoring of small organic molecules. In some reactions the entrapped acids/bases were used as catalysts, while in others as stoichiometric reagents.

The acid/base reaction pairs (Scheme 1) were selected to be corner-stone synthetic steps which are widely used throughout organic and bioorganic chemistry. In pair I (Scheme 1) the first step is a rearrangement reaction catalyzed by an acid, the second step is a carbonyl condensation reaction which requires a base, again as a catalyst. The pinacol–pinacolone rearrangement was used to first convert 2,3-dimethylbutane-2,3-diol into 2,2-dimethylbutan-3-one (Scheme 1) with **a**₁^[13]



Scheme 1. The acids (**a**₁, **a**₂) and bases (**b**₁, **b**₂) are defined in the text.

and the ketone was then condensed with malononitrile in the presence of **b**₁^[14] to (CH₃)₃CC(CH₃)OHCH(CN)₂, which dehydrates spontaneously to (CH₃)₃CC(CH₃)=C(CN)₂ (83 %). Both **a**₁ and **b**₁ are used as catalysts and the ceramic material can be recycled with only minimal loss in activity. We note that consecutive reactions in one pot are possible, naturally in homogeneous systems as well, but with a disadvantage over the heterogeneous procedure we describe herein: in a homogeneous situation, after the first reagent has completed its task, the second reagent has to be added in excess to destroy the first and activate the next step. The sol–gel methodology, on the other hand, allows easy recovery of the reagents or catalysts and their reuse.

With pair II we demonstrated that one can use either the **b**₂/**a**₁ combination or the **b**₁/**a**₂ combination for the same pair of reactions. The first reaction of pair II was a dehydrohalogenation reaction, which requires a base as a reagent, the second was an aromatic alkylation reaction requiring an acidic catalyst. 2-iodoethylbenzene was dehydroiodinated with **b**₂ (or **b**₁)^[1] to styrene (Scheme 1), which then alkylated anisole with **a**₁^[15] (or **a**₂), to 1-(4-methoxyphenyl)ethylbenzene and 1-(2-methoxyphenyl)ethylbenzene in a 5:1 ratio (3.5:1 with **a**₂). Although the product of the first reaction is the starting materials of the second one, one can put together in the same pot the substrates, the reagent, and the catalyst and allow the reactions to proceed simultaneously; any styrene that forms reacts immediately with the anisole.

Blank reactions were carried out to make sure that the double entrapment is needed. Thus, no reaction was observed when anisole and styrene were treated with entrapped Nafion (**a**₁) and dissolved TBD (the homogeneous analogue of **b**₂), which indicates that the base totally quenched the acid. Likewise, the pinacol–pinacolone rearrangement did not

take place when **a**₁ was used with dissolved ethylenediamine (the homogeneous analogue of **b**₁). Additional blank reactions were the treatment of 2-iodoethylbenzene with **a**₁, which resulted in no reaction,^[16] and the treatment of anisole and styrene with undoped silica sol–gel, to ensure that the acidity of the silica does not activate the alkylation reaction (which indeed it does not). Possible leaching was tested by refluxing **a**₁ or **b**₂ in benzene for 2 h, followed by extraction with water; the pH of the water was 7 in both cases which indicates that no leaching of the acid or base occurred.

In conclusion, we have demonstrated a convenient approach for carrying out different reactions which require acids and bases in one pot. It is a general method, as the accumulated experience with doped sol–gel materials shows that *any* acid or base can be used, and this method leads the way to the simultaneous utilization of many other opposing reagents in various combinations.

Experimental Section

Preparation of the entrapped reagents: Nafion was entrapped in silica sol–gel at 13% (by weight) following the procedure in ref. [9].

Sol–gel entrapment of the molibdic acid: Tetramethoxyorthosilicate (TMOS, 13 mmol), H₂O (0.33 mL, 18 mmol), HCl (0.09 mL; 0.04 M), and MeOH (2 mL, 49 mmol) were stirred at 40 °C for 6 h. To this solution was added a mixture of molibdic acid (0.06 g, 0.37 mmol), NH₄OH (0.1 mL, 25%), and H₂O (2 mL). Gelation occurred within a few minutes. The resulting gel was dried at 180 °C for 16 h, then washed with water, sonicated twice in benzene for 20 min, and then dried again at 180 °C for 6 h, resulting in 0.84 g of the ceramic material. Preparation of the covalently entrapped bases was by the procedures in refs. [11, 12], at a 20% molar loading.

Reaction pair I: **a**₁ (1.0 g) and **b**₁ (1.2 g) were suspended in dry benzene (5.0 mL). Pinacol (1.8 g, 1.5 mmol) was added and the mixture was then heated at reflux under N₂ for 30 min. Malononitrile (0.20 g, 3.0 mmol) was then added and the reflux continued for 7 h. Conversion of the pinacol was quantitative (100%), out of which 83% underwent alkylation/dehydration to (CH₃)₃CC(CH₃)=C(CN)₂. A second run with the recovered catalysts resulted in a 76% overall yield.

Reaction pair II, **b**₂/**a**₁ combination: **a**₁ (1.0 g), **b**₂ (0.9 g), 2-iodoethylbenzene (0.35 g, 1.5 mmol), and anisole (0.16 g, 1.5 mmol) of were placed in dry benzene (5.0 mL) and the mixture heated at reflux under N₂. The reaction was stopped after 4 h at 32% conversion yielding 4-MeOC₆H₄CH(CH₃)C₆H₅ and 2-MeOC₆H₄CH(CH₃)C₆H₅ in a 5:1 ratio.

The **b**₁/**a**₂ combination: under similar conditions to those above **a**₂ (0.84 g), **b**₁ (1.2 g), 2-iodoethylbenzene (0.35 g, 1.5 mmol), anisole (0.16 g, 1.5 mmol), 4 h reflux proceeded as well, although at a lower conversion of 21% with a 3.5:1 product ratio. (It seems that the base **b**₂ is superior to **b**₁ because the latter may undergo some competitive N alkylation). All products in this report are known and were identified and characterized by standard techniques (NMR spectroscopy, gas chromatography (GC), and GC-mass spectrometry (GC-MS)).

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Photonic Transduction of a Three-State Electronic Memory and of Electrochemical Sensing of NADH by Using Surface Plasmon Resonance Spectroscopy**

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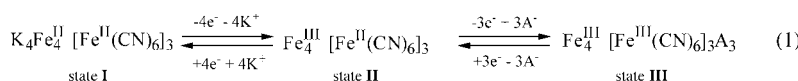
Signal-triggered switching of the functionalities of molecular,^[1,2] macromolecular,^[3] or biomolecular systems^[4,5] has been suggested as a means to develop chemistry-based memory devices. Photonic,^[6] electrochemical,^[7] magnetic,^[8] pH,^[9] or thermal signals^[10] can be used to switch molecular redox or optical functions. Phase transitions or random-coil/helix transformations of polymers are stimulated by temperature,^[11] pH,^[12] chemical,^[13] electrical,^[14] and photonic signals.^[15] Similarly, enzyme transformations,^[16] substrate–receptor complexes,^[17] or double-stranded DNA interactions^[18] are switched by photonic signals. The conversion of “ON” – “OFF” switchable chemical functionalities into memory devices requires, however, the integration of the chemical systems with surfaces such that the triggered functionality and the recorded information are transduced, without erasure of the encoded information. Advances in the field demonstrated the electronic transduction of photonic activated molecular redox functions on electrodes^[19] or light-stimulated bioelectrocatalytic transformations on electrodes,^[20] and also,

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phonic^[21] or mechanical^[22] transduction of the electrochemically triggered redox functions of polymers. Here we report a chemical assembly that acts as a three-state switchable memory device. The electronic information of the three states is photonically transduced using surface plasmon resonance (SPR).^[23] We also demonstrate that the redox-active film acts as an electrocatalyst for the oxidation of 1,4-dihydronicotinamide adenine dinucleotide (NADH). Surface plasmon resonance as well as amperometric measurements allow the quantitative analysis of NADH at the modified surface.

Prussian Blue (PB) is an inorganic, insoluble, three-dimensional polymer that exhibits three redox states [Eq. (1)].^[24] PB-modified electrodes were previously investigated as



electrocatalytic interfaces,^[25] as electrochromic,^[26] and photo-responsive^[27] materials. Usually, electrochemical deposition of PB is performed on a graphite electrode. At neutral pH the cyclic voltammogram of the resulting material has two distinct redox waves.^[28] Direct electrodeposition of PB onto a bare Au-electrode was performed under acidic conditions (pH 1.5), which leads to an unstable redox film with a single quasi-reversible redox wave in the cyclic voltammogram.^[29] Primary functionalization of the Au-electrode with cysteic acid (HS(CH₂)₂CO₂H), followed by the electrodeposition of PB (10 cycles, 100 mVs⁻¹, between -0.2 V and 1.3 V vs. an Ag-quasi-reference electrode in the presence of 0.1 M K₃[Fe(CN)₆] and 0.1 M FeCl₃, pH 7) yields, however, a stable film of PB. The film displays, at neutral conditions (0.1 M KNO₃, pH 7), two redox waves, $E_1^\circ = 0.0$ V and $E_2^\circ = 0.72$ V (Figure 1 A; vs. Ag-quasi-reference electrode), which correspond to the transitions between the states designated II/I and III/II, respectively, in Equation (1). Thus, at a potential of $E = 0.3$ V the film exists in the PB configuration, state II. Switching the potential to $E = -0.2$ V transforms the film to state I, whereas the application of $E = +0.9$ V yields the fully oxidized state III.

The SPR Kretschmann-type spectrometer “BIOSUPPLAR-2” (light-emitted diode light source $\lambda = 670$ nm) and the Au-covered glass slides (20×20 mm) from “Analytical μ -Systems” (Germany) were used in this work. Figure 1 B shows the SPR spectra of the in situ electrochemically generated three redox-states of the film. Substantially different SPR spectra are observed for the three states, and as the thickness of the films is almost unaffected by the redox-state (see below) the different SPR curve may be attributed to changes in the refractive indexes of the polymers in the different redox states. The experimental SPR spectra of the PB film were fitted to the theoretical curves based on five-phase Fresnel calculations using the Neelder–Mid algorithm of minimization.^[30] The computer fitting of the SPR spectra was performed primarily for the state II (curve b, Figure 1 B) using the known refractive index, $n_{\text{re}} = 1.45$, $\lambda = 670$ nm (n_{re} = real component of the refractive index).^[29] The derived thickness of the inorganic film is about 80 nm. The complex refractive indexes of the film in state I ($n_{\text{re}} = 1.435$, $n_{\text{im}} = 0.020$; n_{im} = imaginary component of the refractive index) and state III

($n_{\text{re}}=1.421$, $n_{\text{im}}=0.044$), were calculated by assuming the same PB-film thickness in all three states. Coulometric analysis of the charge associated with the electrodeposition of the film indicates a thickness of approximately 80 nm taking into account the film density 2.6 g cm^{-3} ,^[31] in good agreement with the value obtained from the SPR spectrum.

Figure 2A (panel 1) shows the sequence of multistep chronoamperometric transients applied in situ on the PB film, switching the electrode potential between the semi-oxidized state II, $E = 0.3$ V, and the reduced state I, $E = -0.2$ V. The electrochemical switching is transduced by following the changes in the reflected light intensities in the SPR spectra at a fixed angle of $\theta = 69.5^\circ$, Figure 2A (panel 2).

The reversible change in the SPR signal is observed upon alteration of the potential applied to the electrode. Figure 2B (panel 1) shows the

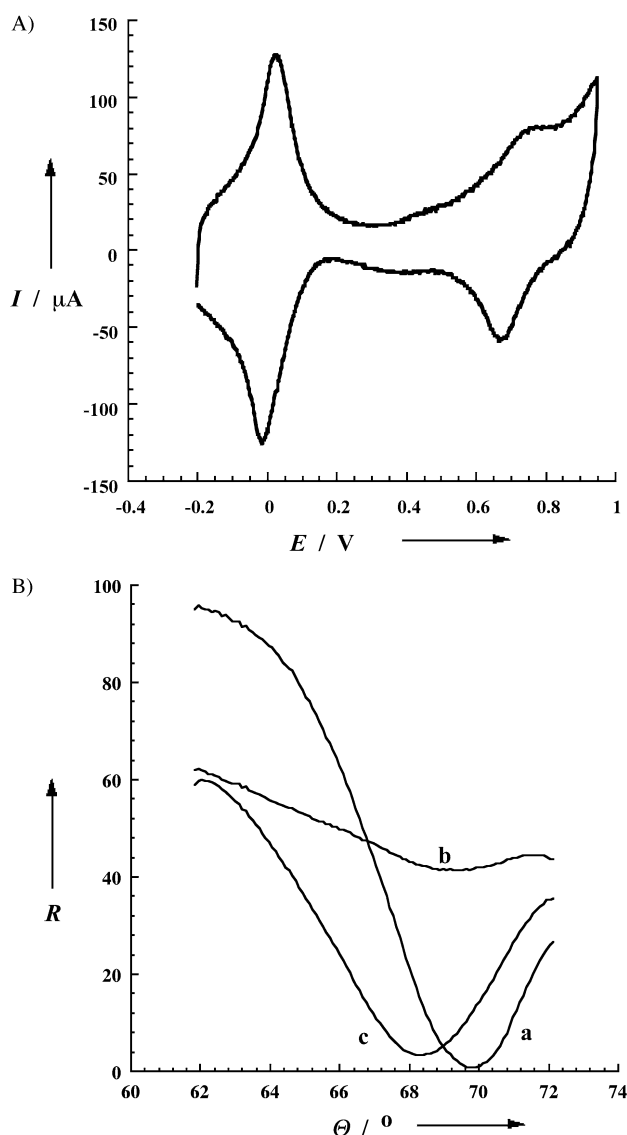


Figure 1. A) The cyclic voltammogram of the PB-functionalized Au-coated SPR slide recorded in 0.1M KNO_3 , pH 7.0, potential scan rate 100 mVs^{-1} . B) SPR spectra measured for the PB-modified Au-surface in the presence of 0.1M KNO_3 , pH 7.0, upon application of different potentials and the generation of the different redox states of the film: a) -0.2 V , state I, b) 0.3 V , state II, c) 0.9 V , state III.

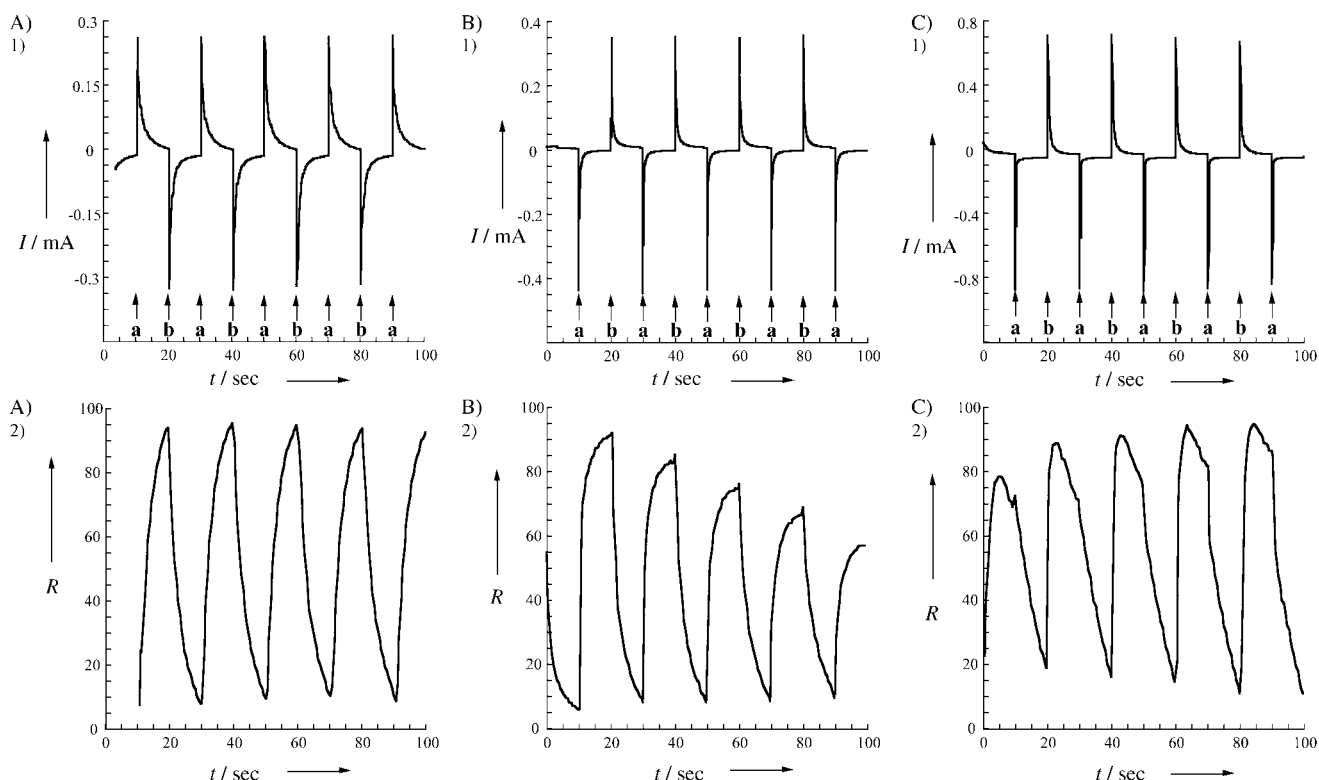


Figure 2. Multipotential step chronoamperometric transients corresponding to the transformations between A) 1) state II and state I, B) 1) state III and state II, and C) 1) state III and state I of the film. The arrows (labeled a and b) show the time of the application of the oxidative and reductive steps. Panels 2) show the time-dependent reflectance changes measured at a fixed angle of incidence at A) 2) $\theta = 69.5^\circ$, B) 2) $\theta = 68^\circ$, C) 2) $\theta = 69.5^\circ$ upon the multipotential step experiment. The measurements were performed in 0.1M KNO_3 , pH 7.0.

sequence of multistep chronoamperometric transients applied in situ on the PB film, switching the electrode potential between the semi-oxidized state II, $E = 0.3$ V, and the fully oxidized state III, $E = 0.9$ V. The signal intensity decreases with the number of cycles implying a partial degradation of the system (Figure 2B, panel 2). The degradation of the system is attributed to the partial oxidation of the base cysteine monolayer and desorption of the redox-active film from the interface. In fact, reduction of the potential-step time interval from 10 s to 1.5 s leads to ten indistinguishable switchable cycles of reflected light intensity. Thus, although the reflected light intensities reveal smaller amplitude because of incomplete oxidation or reduction within the 1.5 s pulse duration, the system reveals higher stability since the film is not desorbed from the electrode. Finally, the system can be electrochemically switched between the two extreme redox-states of the fully reduced state I, $E = -0.2$ V, and the fully oxidized state III, $E = 0.9$ V, Figure 2C.

The SPR transduction of the redox states of the polymer film enables the use of the modified surface as a sensing interface for the in situ electrochemical/SPR detection of NADH. The PB film in state II, $E = 0.3$ V, acts as an electrocatalyst for the oxidation of NADH. In the presence of NADH the PB-functionalized electrode, state II, is reduced to state I. The application of a constant potential, $E = 0.3$ V, on the electrode allows the reoxidation of the film and the regeneration of state II. Assuming that the electrocatalytic oxidation of NADH is fast, compared to the oxidation of

state I to II, the film, subjected to the oxidizing potential of 0.3 V, will exist as a steady-state ratio of states I/II that is controlled by the concentration of NADH. That is, at high NADH concentrations the film will exist mainly in state I, whereas at low concentrations of NADH, the film is mostly in state II. Figure 3A shows the SPR spectra of the PB-modified electrode subjected to the potential of 0.3 V in the presence of variable concentrations of NADH. As the concentration of NADH is higher, the SPR spectrum of the film is shifted and enriched with the state I of the film. Figure 3B, curve a, shows the derived calibration curve corresponding to the changes in the reflected light intensity at variable NADH concentrations measured at $\theta = 68.5^\circ$. For comparison, the in situ amperometric responses of the system, I_{cat} , as a result of the electrocatalyzed oxidation of NADH, are plotted in Figure 3B, curve b. It is evident that NADH can be analyzed in the concentration range of 5×10^{-4} M to 1×10^{-2} M. At NADH concentrations higher than 1×10^{-2} M the electrocatalytic current in the system reaches a constant value of approximately 0.9 mA and the SPR spectrum reaches a constant shape. Under these conditions, the film operates at its highest turnover in respect to the catalytic oxidation of NADH. Note, however, that the SPR spectrum of the film at high concentrations of NADH, curve h, where the film consists of state I, differs substantially from the characteristic SPR spectrum of state I, Figure 3A, curve a. This difference is attributed to the effect of applied potential on the electrode on the resulting SPR spectrum. While state I shown in curve a is formed at a

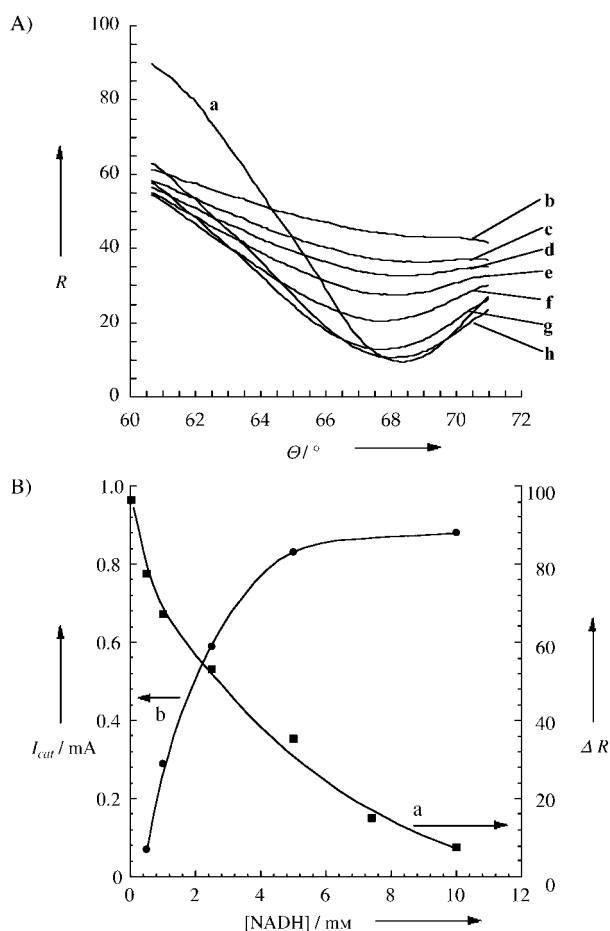


Figure 3. A) SPR spectra of the PB-modified Au-surface measured: a) At an applied potential -0.2 V in the absence of NADH. b–h) At an applied potential 0.3 V and in the presence of variable concentrations of NADH: b) 0 mM, c) 0.5 mM, d) 1.0 mM, e) 2.5 mM, f) 5.0 mM, g) 7.5 mM, h) 10.0 mM. The experiment was performed using 0.1 M KNO_3 as a background electrolyte. B) Calibration plots corresponding to the analysis of NADH by: a) The SPR response. b) The electrocatalytic current measured in situ upon application of 0.3 V to the PB film in the presence of variable concentrations of NADH. The SPR response is defined as the difference of PB-film reflectance measured at $\theta = 68.5^\circ$ in the presence of variable NADH concentrations and in the absence of NADH. All the data were recorded in 0.1 M KNO_3 , pH 7.0 .

potential of -0.2 V, the film in state I shown in curve h is generated under an applied potential of $+0.3$ V (in the presence of NADH).

In conclusion, the present study has integrated a three-state redox-active film with an Au surface to yield a three-state switchable optoelectronic system, where the electrical information stored in the redox states is optically transduced by SPR. In contrast to an electrochemical read-out signal of the redox states that erases the information, the SPR signal does not affect the redox state. In principle, the study implies that complex multistep redox transformations may be used to generate multiswitching optoelectronic systems. Furthermore, the SPR transduction of the electrocatalyzed oxidation of NADH reveals a novel means to develop optoelectronic sensors and to follow electrocatalytic transformations.

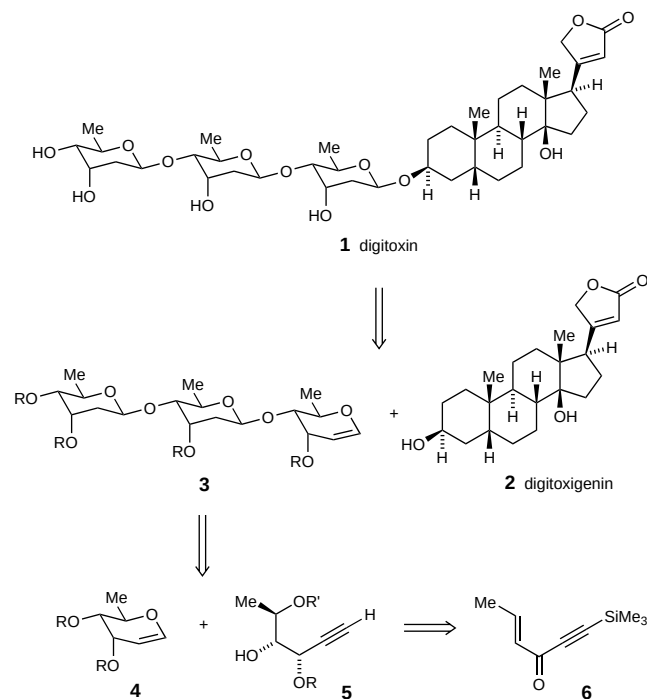
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Convergent Synthesis of Digitoxin: Stereoselective Synthesis and Glycosylation of the Digoxin Trisaccharide Glycal**

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Extracts from the leaves of *Digitalis* (foxglove) plants have long been used to strengthen the force and velocity of heart muscle contraction, and the pure compound digitoxin (**1**, Scheme 1) is widely prescribed for treating congestive heart

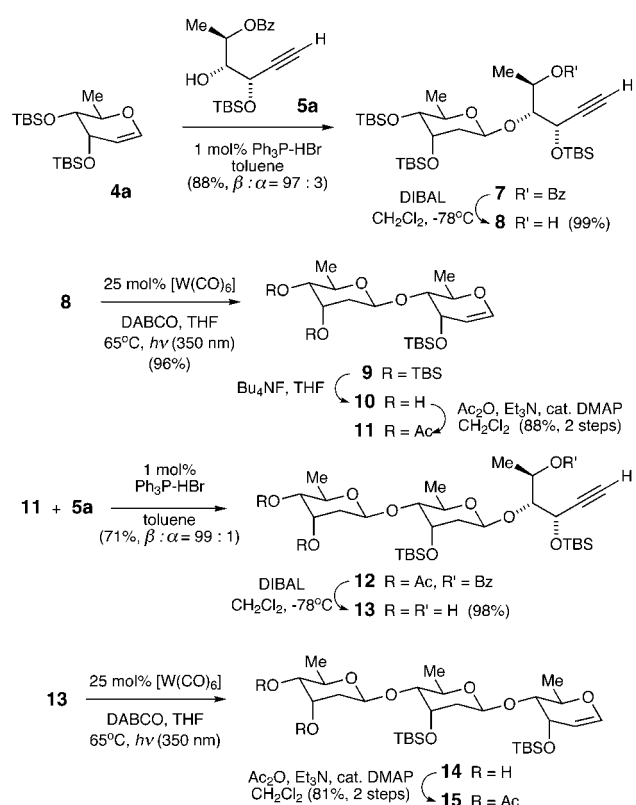


Scheme 1. Retrosynthesis of digitoxin (**1**).

failure and cardiac arrhythmia.^[1] Unfortunately the therapeutic dose for digitoxin (14–26 ng mL⁻¹) is dangerously near the toxic dose (> 35 ng mL⁻¹), thus patients receiving digitalis therapy require careful medical monitoring.^[2] Wiesner and co-workers reported the first and only chemical synthesis of digitoxin.^[3] This landmark synthesis featured construction of the natural product by sequential glycosylations with D-digitoxose monosaccharide glycosyl donors, and suffered from the requirement that the butenolide was masked as a furan derivative for glycosylation and protective group

removal steps. We recognized that a significantly enhanced and convergent synthesis could be accomplished by direct attachment of a preformed trisaccharide to the butenolide-containing digitoxigenin aglycone **2**. In preparation for a study of the structure–activity relationships for the oligosaccharide substructure of digitalis glycosides, we now report the synthesis of trisaccharide glycal **3** by iterative alkynol cycloisomerization^[4] and acid-catalyzed glycosylation to form 2-deoxyglycosides. We also describe herein the first direct coupling of a digitoxose trisaccharide to digitoxigenin aglycone **2**.

Our synthesis begins with protic acid-catalyzed stereoselective glycosylation of monosaccharide 6-deoxy-D-ribo glycal **4a** with alkynyl alcohol **5a** (Scheme 2).^[5] Our initial



Scheme 2. Stereoselective synthesis of digitoxose trisaccharide glycal **15**. TBS = *tert*-butyldimethylsilyl, DIBAL = diisobutylaluminum hydride, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-dimethylaminopyridine.

studies demonstrated that camphorsulfonic acid (CSA) is a suitable catalyst for this transformation, but more extensive studies indicate that Ph₃P–HBr is an even better catalyst with regard to reaction rate (6 h vs. 12–18 h with CSA) and reproducibility at multimillimole scales, as well as providing the 2-deoxyglycoside **7** with excellent anomeric stereoselectivity (Scheme 2). Reductive debenzoylation and tungsten carbonyl catalyzed *endo*-selective cycloisomerization of alkynol substrate **8** gave the disaccharide glycal **9**.

Acid-catalyzed glycosylation of this disaccharide **9** with alkynol alcohol **5a** proceeded with low yield and poor anomeric selectivity (β : α = 76:24, ca. 30% combined yield) relative to glycosylation of the monosaccharide glycal **4a**

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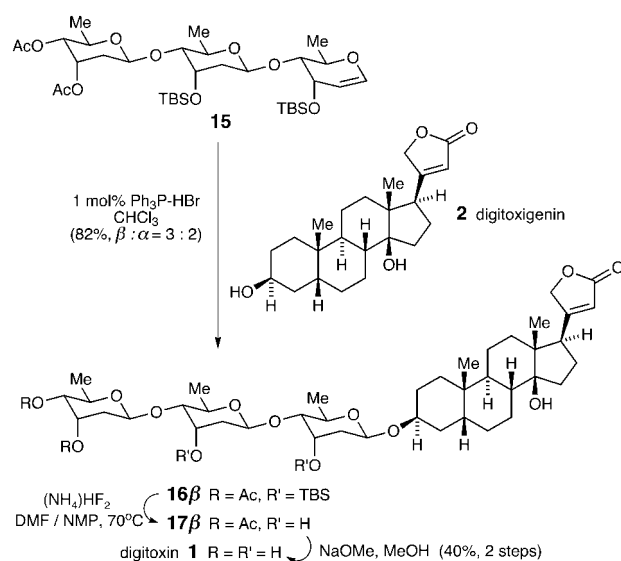
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(β : α = 97:3, 88 % yield of the β -anomer). However, we observed excellent stereocontrol and good yield in the corresponding glycosylation of the disaccharide **11** bearing acetate protective groups at the non-reducing sugar to afford disaccharide glycoside **12** (β : α $\geq$ 99:1, 71 % yield; Scheme 2). These results demonstrate the sensitivity of acid-catalyzed glycosylations to remote substituent effects.^[6] To the best of our knowledge, this represents the first report of acid-catalyzed glycosylations on disaccharide glycals, as all previous reports have been limited to monosaccharide glycal substrates.^[7] In the course of these glycosylations, we observed that better β -selectivity is obtained when toluene is the solvent rather than CH_2Cl_2 or other solvents.

As selective removal of the benzoate at O5 of the alkynyl glycoside would have been difficult, we simply removed all ester protective groups from **12** and explored tungsten carbonyl catalyzed cycloisomerization of the alkynyl triol substrate **13**. This transformation gave trisaccharide glycal **14** without interference from the more distant hydroxy groups. Product **14** was purified after capping the two remaining hydroxy groups as acetate esters to give **15**.

Acid-catalyzed glycosylation of the trisaccharide glycal **15** with digitoxigenin aglycone **2**^[8] was complicated by insolubility of **2** in toluene. $\text{Ph}_3\text{P-HBr}$ -catalyzed glycosylation in CHCl_3 provided a 60:40 mixture of 2'-deoxyglycoconjugate **16 β** along with the α -anomer (Scheme 3; Table 1, entry 2),



Scheme 3. Glycosylation of **15** and synthesis of digitoxin **1**. DMF = *N,N'*-dimethylformamide, NMP = *N*-methylpyrrolidine.

Table 1. Glycosylation of trisaccharide glycal **15** with (+)-digitoxigenin **2**.

Entry	Catalyst ^[a]	Solvent	16β : 16α	Combined yield [%] 16β + 16α
1	CSA	CH_2Cl_2	60:40	68
2	$\text{Ph}_3\text{P-HBr}$	CHCl_3	60:40	82
3	$\text{Ph}_3\text{P-HBr}$	toluene: CHCl_3 (2:1)	64:36	71
4	$\text{Ph}_3\text{P-HBr}$	1,2-dichlorobenzene	73:27	54

[a] In each case 1 mol % of catalyst was used.

and the anomers could be separated by silica gel chromatography. Slightly better anomeric selectivity (β : α = 73:27) was observed with 1,2-dichlorobenzene as solvent (Table 1, entry 4), although in this case the yields of **16** were diminished by poor solubility of the aglycone **2**. Deprotection of the TBS protective groups of **16 β** initially proved challenging, as the cycloisomerization and glycosylation steps placed the O3 silyl ethers of the two central digitoxose sugars in sterically hindered positions.^[9] However, ammonium hydrogen fluoride in dimethylformamide (DMF)/*N*-methylpyrrolidine (NMP) solvent^[10] proved mild enough to remove both TBS ethers from **16 β** in the presence of the fluoride-sensitive butenolide and acid-sensitive 2-deoxyglycoside linkages. The remaining acetate protective groups of **17 β** were then removed by basic methanolysis^[11] to provide digitoxin **1** which was identical in all respects to a commercially available sample (Aldrich Chemical Company, TLC, melting point, ^1H and ^{13}C NMR, and optical rotation).

In conclusion, we have accomplished a highly convergent and stereoselective synthesis of digitoxin **1**. Notable features include iterative application of a tungsten-catalyzed *endo*-selective alkynol cyclomerization methodology, and the first recorded examples of acid-catalyzed glycosylations of disaccharide and trisaccharide glycals. Studies in progress include the synthesis and biological evaluation of additional oligosaccharide stereoisomers of digitoxin.

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Unichemo Protection: A Concept for Chemical Synthesis**

Les P. Miranda and Morten Meldal*

Chemical synthesis is a powerful method for creating complex molecules with tailored biological and physical properties for drug discovery, engineering, nanotechnology, and the investigation of biological processes. However, the applicability of chemical synthesis to peptides, oligosaccharides, and other organic molecules is limited and inherently complicated using the existing functional-group protecting strategies. The differential protection of functional groups of similar reactivity in chemical synthesis is a major challenge with conventional protecting-group strategies, namely orthogonal protection and modulated lability.^[1–3] In particular, the development of effective protective schemes for polyfunctional molecules is not trivial.^[4] The number and type of protecting groups influences the length, efficiency, and complexity of a given synthesis, and is often responsible for its success or failure.

Herein, a new concept, termed unichemo protection (UCP), illustrated in Figure 1, is introduced. This strategy only requires a single chemical process for all deprotection reactions. The UCP protecting groups are derived from a repetitive unit that permits their controlled and efficient stepwise removal. Functional site selectivity is achieved by varying the degree of oligomerization at each site, and, after each deprotection cycle, only the newly liberated functional site is available for derivatization.

In principle, the UCP strategy does not impose a restriction on the possible number of selectively protected sites in a molecule. This method should be particularly useful in areas

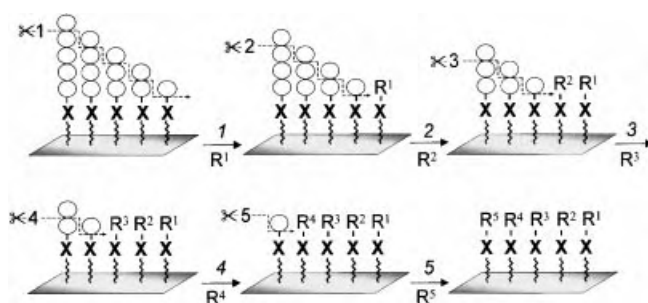


Figure 1. UCP exemplified by the deprotection and selective derivatization of five functional groups (R^1 – R^5). The functional groups (X) are protected with a concatenated set of oligomeric protecting groups (O). The sequential removal of each protecting unit is achieved with a single reaction type. Selective derivatization of each newly unmasked functional group is performed after each deprotection step. This iterative process is repeated until all functional groups are deprotected and derivatized as desired.

including the combinatorial synthesis of highly substituted scaffolds, peptide synthesis, template-assisted synthetic proteins (TASP),^[5, 6] automated oligosaccharide synthesis,^[7] and the general goal of automated organic synthesis.

The effectiveness of the UCP chemistry was demonstrated by the controlled derivatization of a pentyllysine-based amino-functionalized scaffold on the solid support. To facilitate this, a *N*-*sec*-butylglycyl-based protecting-group unit was devised for the protection of amino groups.^[8] With conventional protection strategies, the controlled derivatization of five or more otherwise identical amino groups on the solid-support is a difficult challenge. Here, this problem was solved by using the UCP concept in the form of *N*^ε-oligo(*N*-*sec*-butylglycyl) protected lysine building blocks^[9] for the assembly of scaffold **1** (see Figure 3).^[10]

In its present form the UCP concept takes advantage of large reactivity differences between primary amino functional groups and the otherwise similar protecting groups. The use of oligomeric *N*-*sec*-butylglycyl protecting groups exploits the relatively high degree of steric hindrance around the secondary amino terminus to differentiate between deprotection and derivatization processes. High yields of oligomeric *N*-*sec*-butylglycyl protecting groups are readily obtained using strong activation during amide-bond formation on the solid support.^[11] Importantly, the oligomers were completely inert to less activated carboxylic derivatives, such as readily prepared *para*-nitrophenyl (ONp) and succinimide (OSu) esters (Figure 2).^[12, 13] The inert character of the UCP secondary amine protecting groups under acylation conditions thus allows for the chemoselective derivatization of newly liberated primary amino group with nitrophenyl esters. That is, chemical selectivity against the secondary amino terminus of the protecting groups is employed to distinguish between derivatization and removal steps.

For deprotection cycles, efficient stepwise removal of terminal protecting group units is facilitated by a reliable two-step procedure originally developed by Edman for protein sequencing.^[14] In the first step, phenylisothiocyanate (PITC) reacts quantitatively at pH 8 with the terminal unit of the oligomeric protecting group (Figure 2). In the second step, a quantitative cyclization and elimination reaction occurs at

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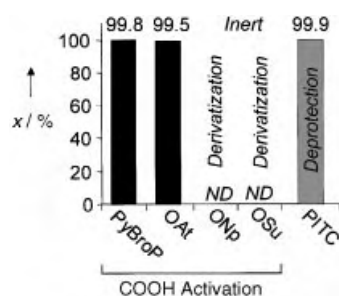


Figure 2. Selective modification of *N*-sec-butylglycyl protecting groups, x = % conversion of *N*-sec-butylglycyl groups. For the assembly of the oligomeric UCP groups, coupling reactions (PyBroP and HOAt active esters^[9]) efficiently acylate the hindered secondary amine in DMF at room temperature in 1 h. Importantly, for the derivatization of liberated primary amines, the protecting group secondary amine is resistant to acylation by less activated ONp and OSu esters at room temperature, such as 0.1 M Boc-Ala-ONp in DMF. For deprotection, PITC reacts in high yield to form the key phenylthiocarbonyl intermediate. The PITC reaction was carried out twice at 55 °C.^[15] Boc = *tert*-butoxycarbonyl.

acidic pH, to give the shortened protecting group by the expulsion of a phenylthiohydantoin derivative.

Accordingly, following assembly of scaffold **1** each of the five primary amino groups on the scaffold was successively liberated with PITC/TFA (TFA = trifluoroacetic acid) deprotection cycles (Figure 3).^[15] Each newly exposed amino group was then acylated with a given carboxylic acid derivative. After five deprotection–derivatization cycles, cleavage from

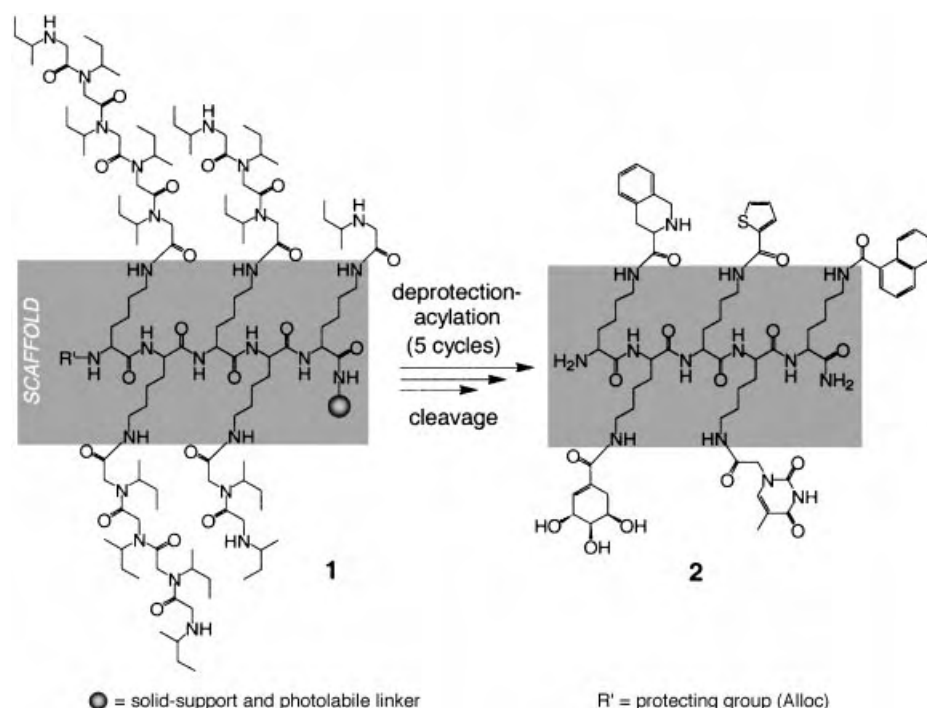


Figure 3. Derivatization of a polyamino scaffold **1** with UCP. The amino group were acylated in the order: β -naphthoic acid, thymine-1-acetic acid, thiophene-2-carboxylic acid, shikimic acid, and Boc-(L)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. The acids (1.05 equiv) were coupled with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU; 1.05 equiv, 0.05 M), *N,N*-diisopropylethylamine (DIEA; 4 equiv) in DMF (25 min). TBTU was initially used, ONp esters may be preferred for routine or combinatorial derivatization because they can be used in large excess while still maintaining selectivity. The target compound **2** was cleaved from the solid support in methanol with UV irradiation (3 h) and then purified by reversed-phase high-pressure liquid chromatography (HPLC).^[16]

the solid support afforded **2**, in good purity and yield.^[16] Molecular dynamics simulations indicate that low-energy conformers of *N*-sec-butylglycyl protecting-group oligomers are generally flexible, extended, and hydrophobic, which agrees well with experimental observations in terms of accessibility and solubility in organic solvents.

The advantage of UCP is its conceptual and practical simplicity. In contrast, orthogonal protection requires the identification, availability, and interplay of a range of sufficiently different orthogonal protecting groups and a multitude of unique chemical conditions for the removal of each individual protecting group in a selective and efficient manner.^[17] This may create a problem particularly in the case of polyfunctional molecules because the cleavage of one protecting group strictly requires not only the stability of all the other protecting groups, but also of the masked molecule itself under a multitude of reaction conditions.^[18–20] At the core of the problem is the limited availability of fully orthogonal protecting groups that work well together.

UCP effectively facilitates an orthogonal process that is not dependent on a range of finely tuned and differently compatible processes. Moreover, since UCP is based on uniform deprotection reactions, the requirement of reaction compatibility with other parts of a molecule only increases linearly with the degree of polyfunctionalization (Figure 4 and 5). That is, after the initial requirement of parent-molecule stability is satisfied, only the sequential requirements towards each newly introduced group is an issue. In contrast, a quadratic increase in complexity with respect to the number of protected functional groups, even in the simplest cases, accompanies existing orthogonal protection strategies.

In the implementation of the strategy described here, a highly efficient PITC/TFA cycloelimination process, which enabled the differential protection of five otherwise identical amino groups, was employed. Differential derivatization of five or more amino groups in a single molecule would be an extraordinary challenge for conventional protection strategies. With UCP chemistry, the number of a given functional group that can be successfully protected and sequentially assessed may exceed twenty. The UCP concept should be amenable to the protection of many other types of functional groups, such as hydroxyls, thiols, and carboxylates. A host of different UCP units may be devised from other sequential cleavage processes. However, several issues need to be considered for their development, these include: 1) the

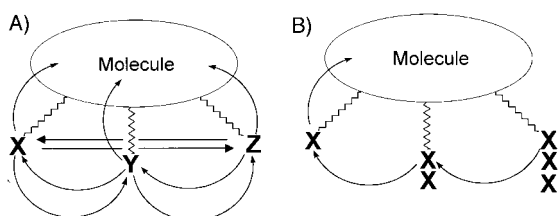


Figure 4. A) 3 orthogonal protection groups gives 9 requirements: 3 for compatible removal of X, Y, and Z with respect to molecule; 2 for compatible X removal with respect to Y and Z; 2 for compatible removal of Y with respect to Z and new X derivative; 2 for compatible removal of Z with respect to new X and Y derivatives. B) 3 UCP protecting groups gives 3 requirements: 1 for compatible removal X units with respect to molecule; 1 for compatible removal of 2nd X unit with respect to new X derivative; 1 for compatible removal of 3rd X with respect to new XX derivatives. Note that the removal of 3rd X with respect to new derivative is redundant with the 2nd X removal.

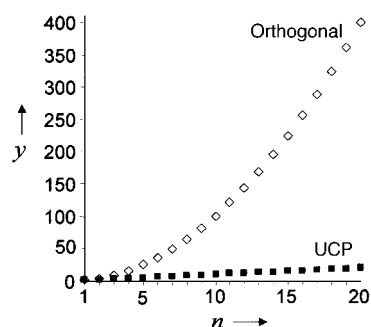


Figure 5. Minimal number of compatibility requirements for the synthesis of polyfunctional molecules with UCP and existing orthogonal protection strategies. y = number of compatibility requirements, n = number of functional groups. In this simple model, orthogonal protection strategies increase quadratically ($y = n^2$) in complexity per functional group (n), whereas UCP strategies only increases linearly ($y = n$).

ease and cost of assembling the protecting group; 2) the practicality, and particularly, the efficiency of the step-wise degradation method; 3) the inertness of the protecting group towards the expected synthesis conditions and reagents for a given application. In this regard, a three-step UCP process in which the UCP protection group is fully protected during derivatization would be advantageous.

UCP complements existing orthogonal protection strategies, and both approaches together will enable the synthesis of more elaborate and novel molecular structures. The experiments reported here show that it is possible to synthesize and derivatize polyfunctional molecules in a simple and effective fashion, without the need for complicated protection chemistry. One outcome of the simplification of both design and chemical requirements is the relative ease of using combinatorial techniques and automating the entire synthesis.

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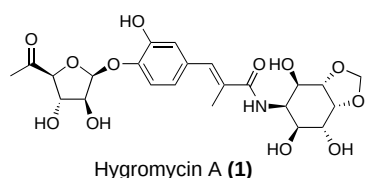
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An Asymmetric Synthesis of C-2-*epi*-Hygromycin A**

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Hygromycin A (**1**) is a fermentation-derived natural product first isolated from *Streptomyces hygroscopicus* in 1953.^[1] The mode of action of hygromycin A is peptidyltransferase inhibition and the compound shares the same binding site on the ribosome as chloramphenicol.^[2] Inhibition through **1** occurs specifically by interfering with peptide bond forma-

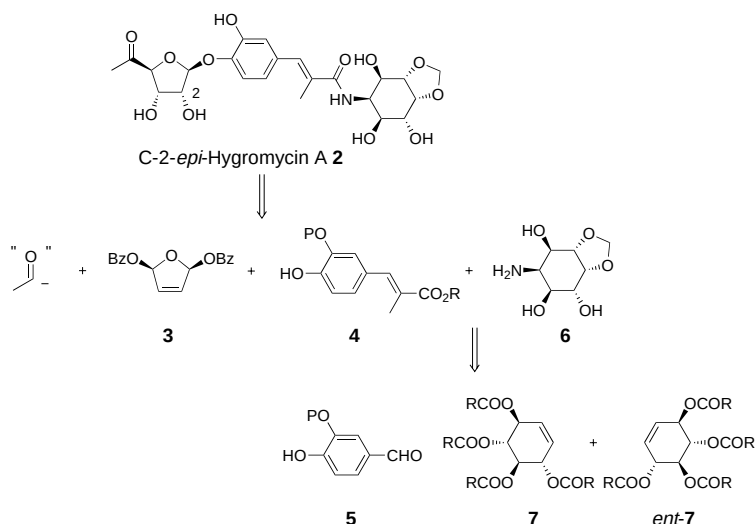


tion, in a way similar to that by chloramphenicol, and is evident by the fact that **1** inhibits the effects of chloramphenicol. It has been reported that **1** has a relative broad spectrum of activity against Gram-positive and Gram-negative bacteria.^[1a,b] Recently, **1** has attracted renewed interest due to the discovery of its hemagglutination inactivation activity^[3] as well as its high antitreponemal activity,^[4] especially as an effective agent for the control of swine dysentery, a mucohemorrhagic disease of economic importance to swine producers. Furthermore the antibiotic also demonstrates efficacy in the treatment of an induced dysentery infection model of swine at a level of 5–20 g ton⁻¹ feed.^[1b]

In spite of the unique structure and interesting biological activity of **1**, only a few reports have appeared on the synthesis of the structural components of **1**,^[5] and only one report of its total synthesis has been described.^[5a] The stereocontrolled synthesis of the β -*cis* glycosidic link between the sugar residue and the central cinnamate unit has not yet been achieved with an anomeric ratio of greater than 2:1. As part of our efforts towards the total synthesis of nucleosides and related structures, we undertook an investigation of the applicability of palladium-catalyzed asymmetric allylic alkylations (AAA)^[6] directed towards a synthesis of hygromycin and analogues. Herein, we report a simple, totally noncarbohy-

drate-based synthetic strategy that culminated in the synthesis of C-2-*epi*-hygromycin A (**2**) which derives from two different mechanisms for the enantiodiscrimination that derives from the AAA reaction.

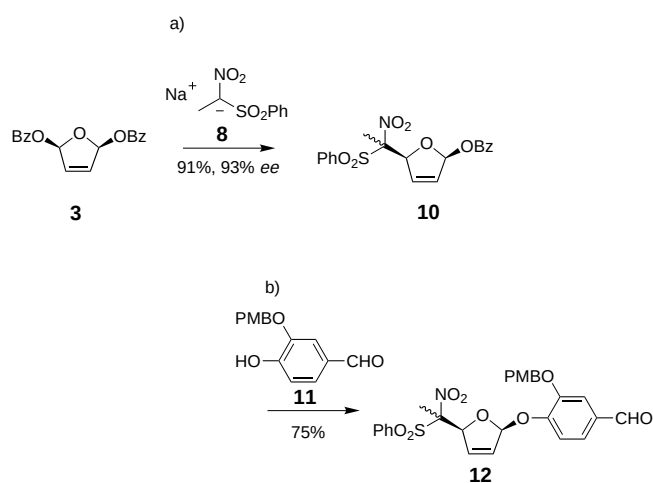
Scheme 1 illustrates the retrosynthetic analysis of **2** in which the furanoside part comes from two AAAs on the bisbenzoate **3**,^[7] one involving an acetyl nucleophile equivalent,



Scheme 1. Retrosynthesis of **2**.

the other involving a phenol, either **4** or **5**, as nucleophile.^[8] Additionally, the aminocyclitol **6** derives from deracemization of the racemic conduritol B tetraester **7**. Its synthesis, which required eight steps from racemic conduritol tetraester **7/ent-7**, employed a *meso*-type of π -allylpalladium intermediate to achieve the enantiodiscrimination and has been recorded elsewhere.^[9]

As an acetyl equivalent, we chose to use the sodium salt of 1-phenylsulfonylethyl-1-nitroethane **8** (Scheme 2) for its soft nucleophilicity and its lack of acidic protons after alkylation.^[10] The insolubility of this salt led us to use phase-transfer



Scheme 2. Stereoselective synthesis of the β -*cis* glycosidic link. a) 4% **9**, 1% [η^3 -C₃H₅PdCl]₂, 10% (*n*-C₆H₁₃)₄NBr, CH₂Cl₂, H₂O, RT; b) 6% *ent*-**9**, 2% [Pd₂(dba)₃] · CHCl₃, (C₂H₅)₃N, THF, 50 °C. dba = *trans,trans*-dibenzylideneacetone.

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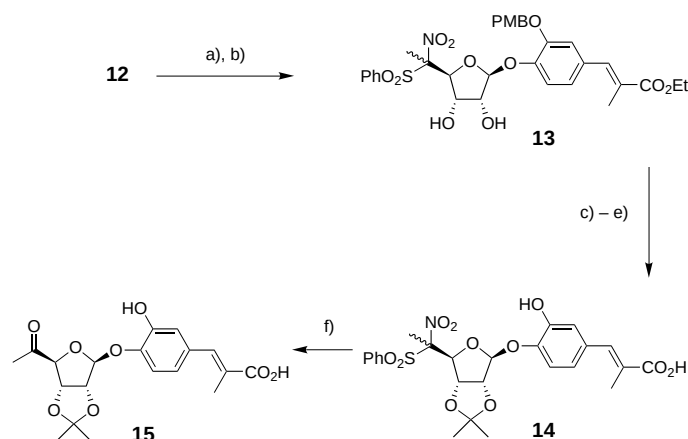
[**] We thank the National Science Foundation and the National Institute of Health, General Medical Sciences, for their generous support of our programs. O.D. thanks the Association pour la Recherche contre le Cancer (ARC) for a postdoctoral fellowship. Mass spectra were kindly provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting information (Experimental and Spectroscopic data of all new compounds) for this article is available on the WWW under <http://www.angewandte.com> or from the author.

conditions, and we were delighted to find that using 4% of ligand **9** with 1% [η^3 -C₃H₅PdCl]₂ and 10% (*n*C₆H₁₃)₄NBr in a 0.2 M mixture of dichloromethane and water afforded the monobenzoate **10**^[11] in 91% yield and 93% *ee*, with respect to the dihydrofuran ring. While inconsequential in the current application, the issue of the diastereoselectivity, with respect to the side chain, in this reaction is interesting. The ratio of diastereoisomers is, on average, 5:1 by ¹H NMR analysis; however, different ratios are observed for each ring enantiomer, as determined by chiral HPLC (4.5:1 for the major ring enantiomer and 8:1 for the minor ring enantiomer). This observation shows not only that the ligand is imparting chirality on the nucleophile, but it exhibits a matched–mismatched behavior.^[12]

The second allylic alkylation reaction does not require the use of a chiral ligand; however, on some occasions, the higher reactivity of the chiral ligands in promoting these alkylations has made them the preferred ligands. Such proved to be the case here. Using *ent*-**9** as ligand and phenol **11** as nucleophile, a low conversion was obtained at room temperature using common concentrations (0.1 M), but an increase of the temperature (50 °C) and concentration (0.5 M) gave our optimized yield of 75%. The palladium source proved to be significant, as switching [Pd₂(dba)₃]·CHCl₃ to [η^3 -C₃H₅PdCl]₂ dropped the yield from 75% to 45%. Direct use of phenol **4** proceeded well but ultimately proved to be unsuccessful because of the wrong chemoselectivity in the subsequent attempts to perform oxidations; that is, the cinnamate-type double bond oxidized faster than the olefin of the dihydrofuran.

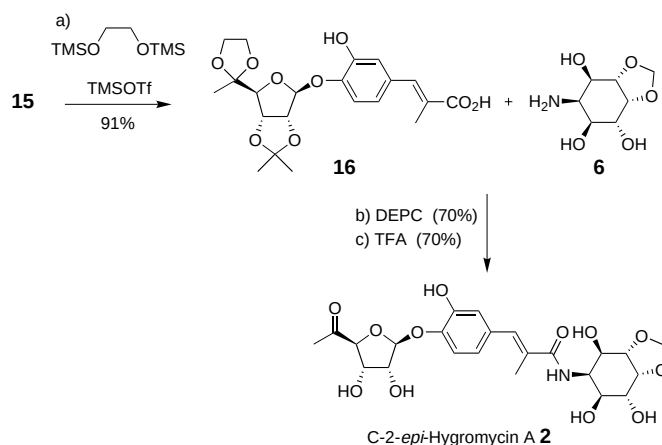
Considerable experimentation revealed the ordering of steps to be highly crucial for the synthesis of the furanoside part of C-2-*epi*-hygromycin A. The sequence commenced with a diastereoselective dihydroxylation^[13, 14] of **12** followed by a stereoselective Wittig reaction to form **13** (Scheme 3).



Scheme 3. Synthesis of the furanoside part. a) OsO₄, NMO, CH₂Cl₂, RT 98% yield; b) Ph₃P=C(Me)CO₂Et, CH₂Cl₂, 45 °C, 99% yield; c) *p*-TsOH, CH₃OH, THF, 50 °C, 100% yield; d) (CH₃)₂C(OCH₃)₂, *p*-TsOH, CH₂Cl₂, RT, 95% yield; e) LiOH, CH₃OH, H₂O, THF, 50 °C, 100% yield; f) THF, RT. NMO = 4-methylmorpholine-*N*-oxide, PMB = *p*-methoxybenzyl.

The PMB protecting group was surprisingly labile under mild acidic conditions, and was efficiently removed by a stoichiometric amount of *p*-toluenesulfonic acid in methanol. The diol was then protected and the ester saponified, leading to **14** in very high yield. The nitrosulfone **14** was then converted into the methyl ketone **15** by using buffered TiCl₃ in water in 80% yield.^[15] Thus, the furanoside unit **15** can be synthesized in eight steps and 50% overall yield from the bis-benzoate **3** with total stereocontrol of the β -*cis* glycosidic link.

All attempts to achieve the coupling of the aminocyclitol (**6**) with **14** followed by the transformation of the nitrosulfone into the methyl ketone failed. The coupling of **15** with the aminocyclitol (**6**) using DEPC in DMF^[16] with different bases, or with no base at all, resulted in amide bond formation, but with complete epimerization at C-4.^[17] A solution to this epimerization problem was found by protecting the ketone. While all the acid-catalyzed methods failed to protect **15**, we were able to achieve this protection using Noyori's conditions in 91% yield (Scheme 4).^[18] The coupling reaction of **16** could now be achieved without epimerization at C-4. A final concomitant deprotection of the ketone and the diol



Scheme 4. Completion of the synthesis. a) CH₂Cl₂, 0 °C; b) (C₂H₅)₃N, DMF, 0 °C; c) H₂O, RT. DEPC = diethylcyanophosphate; TFA = trifluoroacetic acid.

under acidic conditions completed the enantioselective synthesis of C-2-*epi*-hygromycin A **2**.

This synthetic route provides ready access to hygromycin analogues. It develops a new synthon for an acetyl anion equivalent for π -allylpalladium chemistry. Most importantly, it demonstrates the power of asymmetric allylic alkylations (AAAs) for creating effective strategies to complex targets. Desymmetrization of *meso*-diol intermediates provides asymmetric access to the furanose unit and discrimination of enantiotopic termini of a *meso*-type π -allyl intermediate provides asymmetric access to the aminocyclitol moiety. Furthermore, the increased kinetics associated with the chiral ligands are also beneficial for nonenantioselective allylic alkylations. Significantly, this method provides complete diastereoselectivity in the glycosylation step. The shortness of the longest linear sequence (11 steps) and the modular nature make this route a reasonable strategy for access and study of analogues. The shortness of this route derives in part

from the fact that, not employing carbohydrate building blocks at all, minimal use of protecting groups is needed.

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Supramolecular Hydrogen-Bonded Oligo(*p*-phenylene vinylene) Polymers**

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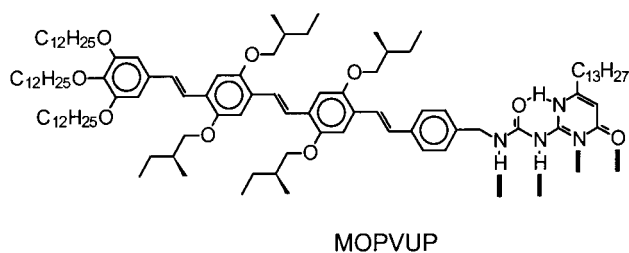
In plastic electronics, π -conjugated oligomers and polymers are applied as advanced materials in a manifold of electro-optical devices such as light-emitting diodes (LEDs),^[1] field-effect transistors (FETs),^[2] and important for the present study, solar cells.^[3] Oligomers possess, due to their well-defined chemical structure, specific electronic and optical properties.^[4] However, the material properties of oligomers are generally secondary to those of their polymeric analogues, since entanglements of macromolecular chains, which are responsible for the typical polymer properties, are lacking. An attractive approach would be to combine the well-defined character of π -conjugated oligomers with the processability of polymers.

Recently, we reported on supramolecular polymers based on the dimerization of strong quadruple hydrogen-bonding self-complementary 2-ureido-4[1*H*]pyrimidinone units ($K_{\text{dim}} = 6 \times 10^7 \text{ M}^{-1}$ in chloroform),^[5] which exhibit real macroscopic polymeric properties such as an increase of viscosity.^[6] Improvement of material properties of low molecular weight telechelic polymers was therefore realized.^[7] These recent developments pave the way to combine the finest properties of conjugated oligomers and polymers by incorporating well-defined π -conjugated moieties in these hydrogen-bonded polymeric assemblies. Furthermore, it provides easy access to multifunctional copolymers by simply mixing the different components containing the quadruple hydrogen-bonded units. A few examples of the combination of π -conjugated oligomers with hydrogen-bonding motifs have been reported. Self-assembled fibers of mono- and bithiophene urea compounds have been described which show efficient charge transport.^[8] More recently, mono- and bifunctional oligo(*p*-vinylene phenylene)s, (OPV)s, functionalized with ureido-s-triazine have been reported that form stacks in dodecane.^[9] In a previous paper we disclosed monofunctionalized ureido-pyrimidinone with OPVs (MOPVUP) and hydrogen-bonded π -conjugated dimers were obtained.^[10]

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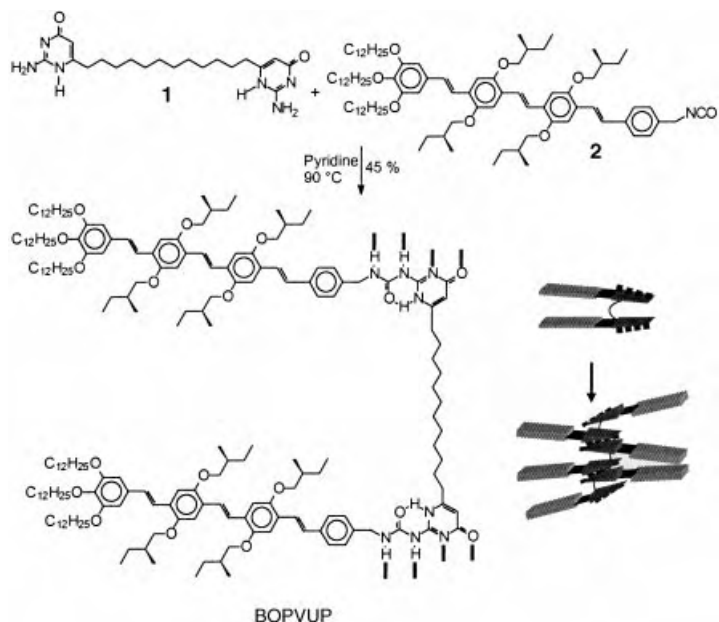
[**] This work was supported by Netherlands Organization for Scientific Research (NWO) and the Royal Netherlands Academy of Arts and Sciences. The authors thank Michel Fransen for the synthesis of the starting materials, Joost van Dongen and Xiamwen Lou for matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) MS measurements, Pascal Jonkheijm for atomic force microscopy (AFM) measurements, and Dr. Rint Sijbesma for fruitful and helpful discussions. Prof. Dr. Jan C. Hummelen is acknowledged for a generous gift of phenyl-[6,6]-C₆₁-butyric acid methyl ester (PCBM).

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Here we report on the synthesis and electronic properties of bifunctional ureido-pyrimidinone BOPVUP, which contains well-defined π -conjugated oligomers (see Scheme 1). The applicability of these processable π -conjugated supramolecular polymers in a photovoltaic device shows for the first time that supramolecular concepts can be used in electronic devices.

Target supramolecular polymer BOPVUP was obtained in 45% yield by reaction of isocyanate **1**^[10] with diisocytosine derivative **2**^[11] in dry pyridine at 90 °C (Scheme 1) and has



Scheme 1. Schematic representation of the synthetic protocol used to prepare the supramolecular polymer BOPVUP.

unequivocally been characterized by ^1H , ^{13}C NMR, FT-IR, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS, and elemental analysis. In this compound, two OPV-ureido-pyrimidinone units are linked through a dodecyl spacer at the 6-position of the isocytosine rings. BOPVUP forms supramolecular polymers in solution by strong association of the hydrogen bonding units. MALDI-TOF MS analysis indicates no contamination with a mono-adduct ($M_r = 3062.62$) m/z 3063.29 (Figure 1 b). The ^1H NMR spectrum in CDCl_3 shows a strong downfield chemical shift of the N–H protons to $\delta = 13.1$, 12.1 and 10.9 (Figure 1 a), in agreement with the keto-tautomer. A dilution experiment shows no change in chemical shift, while no cyclic structures are observed. The association constant, is similar to that of other ureido-pyrimidinones, namely 10^8 M^{-1} . This value deter-

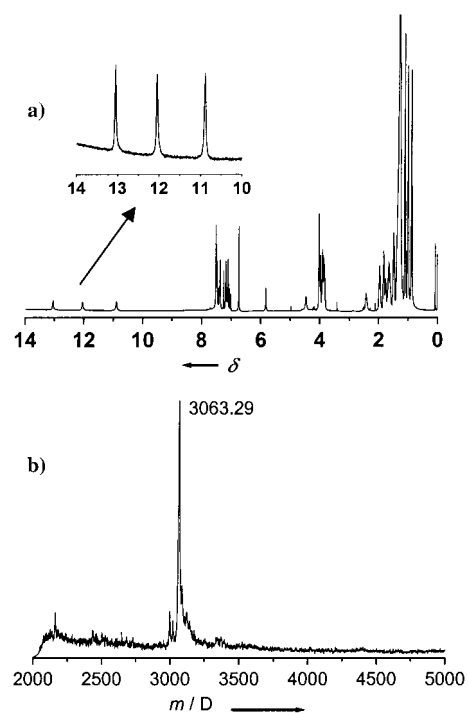


Figure 1. a) ^1H NMR spectra of BOPVUP recorded in CDCl_3 ; b) MALDI-TOF MS spectra of BOPVUP.

mines the virtual degree of polymerization, which is calculated to be about 10000 at a concentration of 1 M .^[5]

UV/Vis and fluorescence spectra were recorded in chloroform and dodecane solutions ($\sim 10^{-4} \text{ M}$) at room temperature (Figure 2). For both solutions, the electronic absorption

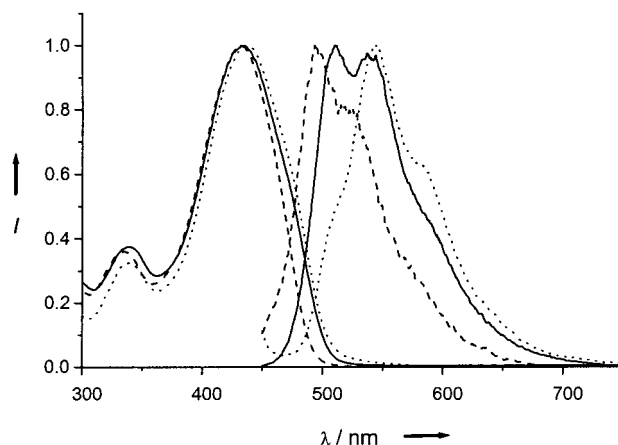


Figure 2. Electronic absorption and emission spectra of BOPVUP; in dodecane (solid line); in chloroform (dashed line) and in a film (dotted line).

maximum is located at $\lambda_{\text{max}} = 432 \text{ nm}$ corresponding to the $\pi - \pi^*$ transition of the OPV units. Fluorescence spectra show an emission maximum at $\lambda_{\text{em,max}} = 494 \text{ nm}$ in chloroform and two emission maxima at 510 and 536 nm in dodecane. Presumably, in chloroform no electronic communication between the two OPV units exists, because the absorption

and emission maxima are similar to that of the monofunctional species MOPVUP in the same solvent.^[10] The red shift in the emission maxima found in dodecane indicates that the OPV units are then aggregated. The Cotton effect (anisotropy factor: $g = 1.86 \times 10^{-4}$) found for BOPVUP in dodecane by using circular dichroism (CD) spectroscopy is relatively weak compared to that for MOPVUP ($g = 6.74 \times 10^{-4}$), indicating that the aggregates for BOPVUP are not highly organized.

Cyclic voltammetry studies of BOPVUP performed in dichloromethane show reversible electrochemical oxidation processes at $E_{1/2} = 0.71$ V versus SCE, which are comparable to those of structurally related tetra(*p*-phenylene vinylene)s.^[12] It is noteworthy that the hydrogen bonds do not participate and are not detrimental for the redox processes.

Photovoltaic devices can be constructed of OPV moieties in combination with C_{60} derivatives in which the π -conjugated oligomers act as electron donors and the fullerenes as acceptors.^[12, 13] To illustrate that this hydrogen-bonded supramolecular π -conjugated polymer can be used in electrooptical devices, the photovoltaic properties were investigated. When BOPVUP was dissolved in toluene, highly viscous solutions were obtained, typical for polymers. These solutions could be spin-coated on glass substrates giving good quality films. Atomic force microscopy (AFM) images show that these supramolecular polymeric films are smooth with height variations in the order of 10 nm, which is similar to those reported for poly(*p*-phenylene vinylene)s (PPVs).^[14] The electronic absorption spectra of these films display a maximum at $\lambda_{\max} = 438$ nm. No CD effect was obtained, which indicated that the films are amorphous resulting in a relative high fluorescence.

Photoinduced absorption (PIA) measurements on spin-coated thin films of BOPVUP ($\lambda_{\text{ex}} = 458$ nm) reveal a band at 1.8 eV that resembles that in the OPV triplet-triplet spectrum. Moreover the photoluminescence of BOPVUP was clearly visible at 2.35 eV. Upon mixing methanofullerene phenyl-[6,6]- C_{61} -butyric acid methyl ester (PCBM, inset Figure 3) as electron acceptor in the spin-coated films of

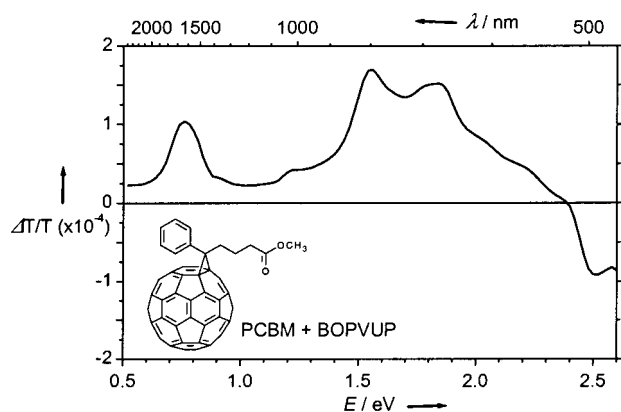


Figure 3. Photoinduced absorption spectra of a mixed BOPVUP:PCBM film (structure of PCBM is shown in the inset).

BOPVUP (BOPVUP:PCBM = 1:2.8 by wt) complete quenching of the OPV fluorescence was observed. PIA measurements revealed the characteristic low energy (LE)

and high energy (HE) absorption bands of the OPV⁺⁺ radical cation at 0.78 and 1.52 eV^[15] and the absorption of the methanofullerene radical anion at 1.24 eV. No photoluminescence for the fullerene moiety was discernable under these conditions, which indicated efficient electron transfer. Varying the modulation frequency from 30 to 3800 Hz revealed that the average lifetime of the charge-separated state is in the order of milliseconds.

Photovoltaic cells were prepared by spin coating a mixture of BOPVUP and PCBM in a ratio of 1:2.8 (by wt) from chlorobenzene onto a transparent ITO front electrode (140 nm) covered with a conducting layer of polyethylenedioxythiophene polystyrenesulfonate (PEDOT:PSS, 90 nm) and depositing an aluminium back electrode (100 nm) in vacuum. The dark current and photocurrent of the device under white-light illumination (88 mW cm⁻², 400–800 nm) reveal promising characteristics (Figure 4). The *I*/*V* curves of

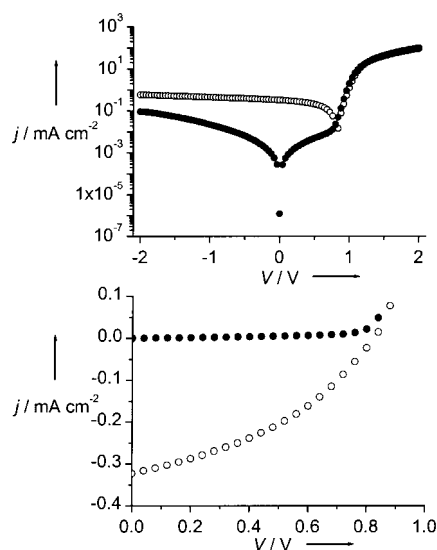


Figure 4. *I*/*V* curves of an ITO/PEDOT:PSS/BOPVUP:PCBM/Al device in the dark (●) and under white-light illumination (○).

the ITO/PEDOT:PSS/BOPVUP:PCBM/Al device show an excellent diode behavior with a rectification ratio (RR) of 1×10^3 at ± 2 V. The high RR shows that the device has no shunts. A short circuit current of $I_{\text{SC}} = 0.32$ mA cm⁻² and an open circuit voltage of $V_{\text{OC}} = 0.82$ V were measured. The fill factor, defined as $(I_{\text{max}} V_{\text{max}})/(I_{\text{SC}} V_{\text{OC}})$, where V_{max} and I_{max} are the voltage and current at maximum power, is 0.39. The values of I_{SC} and V_{OC} are favorable compared to those previously reported for solar cells based on π -conjugated oligomers or polymer and fullerene,^[12, 13, 15] although there has been substantial progress recently by introducing an interfacial layer at the Al electrode.

In conclusion, we have achieved the synthesis of a functional supramolecular hydrogen-bonded π -conjugated polymer that exhibits real macroscopic polymeric properties. A photoinduced charge-separated state was generated within spin-coated blends of the supramolecular polymer with PCBM, and promising photovoltaic devices were obtained. These results create multiple possibilities for using supra-

molecular architectures in electronic devices in which the well-defined character of π -conjugated oligomers is combined with the material properties of polymers

Experimental Section

BOPVUP: Under an argon atmosphere, diisocytosine compound **2** (0.03 g, 0.07 mmol) was dissolved in anhydrous pyridine (5 mL) and heated to 90 °C. A solution of OPV-isocyanate **1** (0.20 g, 0.15 mmol) in anhydrous pyridine (10 mL) was added and the reaction mixture was stirred overnight at 90 °C. The solution was subsequently cooled to room temperature and the pyridine was removed by evaporation under vacuum. The residue was purified by column chromatography (silica gel, ethyl acetate then CH_2Cl_2 to remove impurities and finally $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (97/3, v/v) to collect the desired product) to afford BOPVUP as an orange solid (95 mg; 45 % yield). UV/Vis (CHCl_3): λ_{max} (ϵ) = 432 nm ($258000 \text{ M}^{-1} \text{ cm}^{-1}$); ^1H NMR (400 MHz, $[\text{D}]\text{CHCl}_3$, 25 °C): δ = 13.04 (s, 2H), 12.04 (s, 2H), 10.88 (s, 2H), 7.51–7.36 (m, 14H), 7.18–7.01 (m, 14H), 6.74 (s, 4H), 5.82 (s, 2H), 4.46 (brs, 4H), 4.02–3.85 (m, 32H), 2.42 (br. t, 4H), 2.11–1.27 (m, 160H), 1.10 (s, 24H), 1.00 (s, 24H), 0.87 (brt, 18H); ^{13}C - ^1H NMR (400 MHz, $[\text{D}]\text{CHCl}_3$, 25 °C): δ = 173.4, 157.1, 154.8, 153.5, 152.8, 151.5, 151.4, 151.3, 151.2, 138.3, 137.2, 133.5, 128.8, 128.6, 127.9, 127.8, 127.7, 127.0, 128.9, 123.5, 122.8, 122.7, 11.0, 110.7, 110.1, 109.8, 106.1, 105.3, 74.7, 74.7, 74.4, 74.3, 73.8, 69.3, 43.5, 35.4, 35.3, 35.2, 32.9, 32.2, 32.1, 30.6, 30.0, 29.9, 29.7, 29.6, 29.4, 29.3, 29.2, 27.2, 26.6, 26.4, 22.9, 17.1, 17.0, 14.4, 11.8, 11.7, 11.6; IR (UATR): $\tilde{\nu}$ = 2957 cm^{-1} (m), 2922 (s), 2852 (s), 1695 (m), 1656 (m), 1583 (s), 1503 (s), 1465 (m), 1422 (s), 1386 (w), 1340 (m), 1253 (s), 1200 (s), 1115 (s), 1042 (m), 963 (s), 916 (w), 850 (m); MALDI-TOF MS (M_r = 3062.62) m/z : 3063.29; elemental analysis calcd (%) for $\text{C}_{196}\text{H}_{306}\text{N}_8\text{O}_{18}$ (M_r = 3062.62): C 75.9, H 10.1, N 3.7; found: C 75.1, H 10.0, N 3.3.

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Synthesis of the (+)-C26–C40 Domain of the Azaspiracids by a Novel Double Intramolecular Hetero-Michael Addition Strategy**

Craig J. Forsyth,* Junliang Hao, and Josep Aiguade

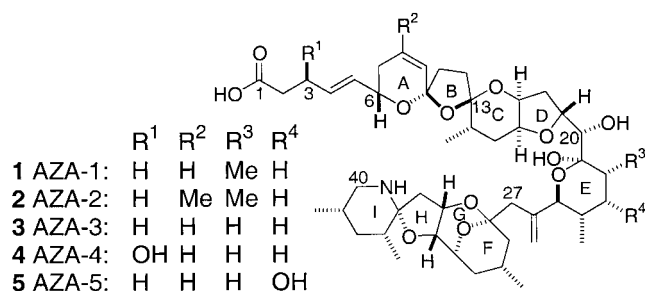
The azaspiracid natural products (AZA **1–5**,) are causative agents of human poisonings associated with the consumption of shellfish that were first recognized in the Netherlands in 1995.^[1] Originally isolated from the mussel *Mytilus edulis* cultivated in Killary Harbor, Ireland, the azaspiracids have since been detected in a growing range of aquatic organisms and geographical locations. Physiological aspects of azaspiracid poisoning (AZP) are distinct from those of other known shellfish intoxications. These include delayed onset and prolonged duration of acute symptoms, and necrosis of the intestine, thymus, and liver. Hence, the azaspiracids represent an emerging new class of environmental toxins with serious economic and human health consequences. As a result there is an urgent need of authentic samples for continued environmental monitoring.

Structurally, the azaspiracids are complex ω -amino acids that contain within their 40-carbon backbone an unprecedented array of polycyclic, spiro-fused ring systems. Among the members of this class reported to date, minor variations in skeletal substitution occur within the C1–C25 domain, but the C26–C40 portion remains constant. The relative stereochemistries within the C6–C25 and C28–C40 domains of the azaspiracids have been assigned, but neither the stereochemical relationship between these two regions, nor the absolute stereochemistry of either has been established. These factors

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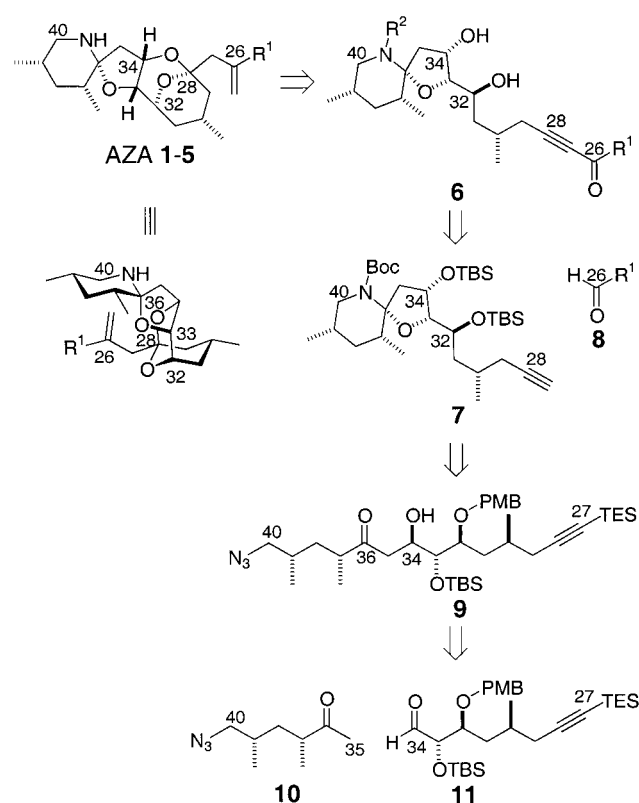
combine to make the azaspiracids premier, yet daunting targets of laboratory synthesis.^[2] Each major domain embodies a wealth of heterocyclic ensembles that transcends the direct application of conventional synthetic methods for their



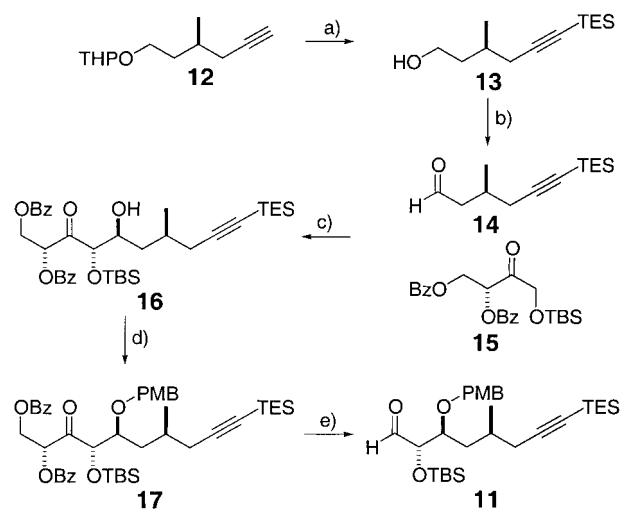
assembly. Of particular challenge is control over the natural products' relative configuration at C13^[2e] of the ABCD polyether and the stereoselective construction of the unprecedented spiroaminal-fused dioxabicyclo[3.3.1]nonane system comprising the FGHI rings. Nicolaou and co-workers recently reported the first successful accomplishment of the latter task.^[2b] Summarized here is an alternative enantioselective assembly of the C26–C40 domain of the azaspiracids that features the implementation of novel heterocycle formation methods recently developed in our laboratories for this purpose.

The synthetic plan for the assembly of the azaspiracid C26–C40 domain involved the sequential formation of the HI and FG ring systems, with an intermediary convergent attachment of the adjacent E ring containing fragment through C26–C27 bond formation (Scheme 1). A novel double intramolecular hetero-Michael addition (DIHMA)^[2f, 3] was designed to form the FG system of the azaspiracids (**1–5**) from dihydroxy ynone **6**. The ynone would be derived from the convergent coupling of a C27–C40 acetylide (**7**) with a C26 aldehyde (**8**). The latter may represent the entire C1–C26 portion of the azaspiracids, or a subfragment thereof. The availability of exceedingly mild and chemoselective methods for acetylide additions to aldehydes^[4] would support a late stage connection of the entire azaspiracid carbon chain through C26–C27 bond formation. Hence, the DIHMA-based heterocycle formation strategy proceeding through a C26–C28 ynone provides a strategic approach for major fragment coupling. To demonstrate the feasibility of this general strategy, access to the HI spiroaminal-containing alkyne **7** was required. This would be obtained from keto-azide **9** by cyclization of a derived primary amino functionality. The β -hydroxy ketone moiety of **9** logically implies an early aldol junction of a C35–C40 methyl ketone (**10**)^[5] and a C27–C34 aldehyde (**11**).

The synthesis of aldehyde **11** began with the known alkyne **12**^[6] bearing the single C30 stereogenic center (Scheme 2). Sequential protection of the alkyne terminus and hydroxyl liberation provided primary alcohol intermediate **13**. The derived aldehyde **14** underwent a substrate controlled boron-mediated *anti*-aldol reaction with chiral ketone **15** to establish the correct relative configurations at C32 and C33.^[7] The newly generated C32 hydroxyl group of **16** was converted into the *p*-methoxybenzyl ether **17**. Thereafter, the dibenzoyl



Scheme 1. Retrosynthesis of **1–5**.

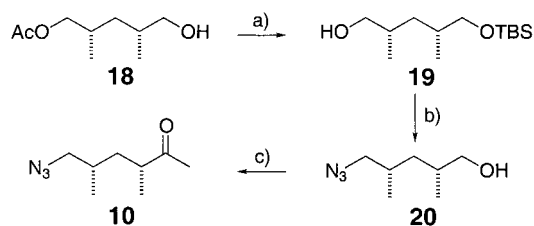


Scheme 2. Synthesis of the C27–C34 aldehyde **11**. a) 1) *n*BuLi, TESCl, THF, –78 °C, 2) PPTS, MeOH, RT, 74 % (two steps); b) TPAP, NMO, 4 Å MS, CH₂Cl₂, RT; c) Cy₂BCl, NEt₃, Et₂O, 72 % (two steps); d) PMBOC(=NH)CCl₃, BF₃·OEt₂, CH₂Cl₂, RT, 87 %; e) 1) NaBH₄, MeOH, RT, 98 %, 2) EtMgBr, THF, 0 °C, 3) NaIO₄, MeOH/H₂O (2:1, v/v), RT, 70 % (two steps). TESCl = chlorotriethylsilane, PPTS = pyridinium *p*-toluenesulfonate, TPAP = tetra-*n*-propylammonium perruthenate-(vii), NMO = 4-methylmorpholine *N*-oxide, Cy = cyclohexyl, PMB = *p*-methoxybenzyl.

ketone was transformed into a triol that was oxidatively cleaved with NaIO₄ to afford aldehyde **11**.

The complementary C35–C40 methyl ketone **10** was obtained conveniently from the known alcohol **18** (Scheme 3).^[2d] Alternative manipulation of the terminally

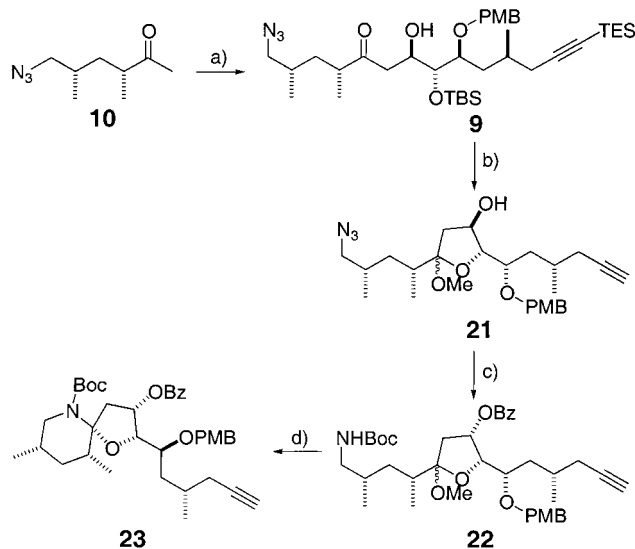
differentiated 1,3-dimethyl building block **18** may allow access to either enantiomer of the C35–C40 methyl ketone. To match the configuration of aldehyde **11**, alcohol **18** was



Scheme 3. Synthesis of the C35–C40 methyl ketone **10**. a) 1) TBSCl, Et₃N, CH₂Cl₂, RT, 2) LiAlH₄, Et₂O, 0 °C; b) 1) Ph₃P, (PhO)₂P(O)N₃, DEAD, THF, RT, 2) TBAF, THF, RT, 69 % (four steps); c) 1) DMSO, CICOCOCI, CH₂Cl₂, –78 °C, Et₃N, RT; 2) MeMgBr, THF, 0 °C, 3) DMSO, CICOCOCI, CH₂Cl₂, –78 °C, Et₃N, RT; 62 % (three steps). TBAF = tetra-*n*-butylammonium fluoride, TBSCl = *tert*-butyldimethylchlorosilane, DEAD = diethyl azodicarboxylate, DMSO = dimethyl sulfoxide.

converted into monosilyl ether **19**. Installation of the latent terminal amino functionality of the azaspiracids was effected by treatment of alcohol **19** with DEAD and (PhO)₂P(O)N₃ to yield the corresponding azide **20**.^[8] The methyl ketone moiety was then incorporated at the opposite terminus to complete the preparation of **10**.

With synthetic access to C27–C34 and C35–C40 aldol partners applicable to either enantiomeric series, construction of the polycyclic F–I system could be thoroughly addressed. The Felkin aldol product **9** was obtained in > 19:1 diastereoselectivity by treatment of ketone **10** with LDA followed by the addition of aldehyde **11** (Scheme 4). The *anti*-selectivity necessitated an inversion of configuration at the newly generated C34 stereogenic center. This was accomplished effectively within the context of the tetrahydrofuran H ring.



Scheme 4. Spiroaminal formation with Yb[OTf]₃. a) 1) LDA, THF, –78 °C, then **11**, 78 %; b) 1) TBAF/AcOH (5:1), THF, RT, 2) PPTS, MeOH, RT, 82 % (two steps); c) 1) Ph₃P, DEAD, BzOH, THF, RT, 62 %, 2) Bu₃P, BocON, toluene, –20 °C to RT, 82 %; d) Yb[OTf]₃, CH₃CN, RT, 72 %. Tf = trifluoromethanesulfonyl, LDA = lithium diisopropylamide, BzOH = benzoic acid, Boc = *tert*-butoxycarbonyl, BocON = 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile.

To this end, desilylation of **9** followed by mixed ketal formation afforded the cyclic intermediate **21**. The C34 configuration was then inverted by a Mitsunobu reaction. Spiroannulation of the terminal piperidine ring upon the H ring was preceded by reduction of the azide and *tert*-butylcarbamate formation using a convenient one-pot procedure.^[9] Upon screening a variety of Lewis acid and solvent combinations to effect spiroaminal formation from the *tert*-butylcarbamate/mixed ketal **22**,^[10] optimal results were achieved by using Yb[OTf]₃ in CH₃CN at room temperature.^[11, 12] This afforded rapid conversion to spiroaminal **23** as essentially a single diastereoisomer. The relative configuration of the newly formed C36 stereogenic center was assigned by NOE studies (Figure 1) to correspond to the azaspiracid natural

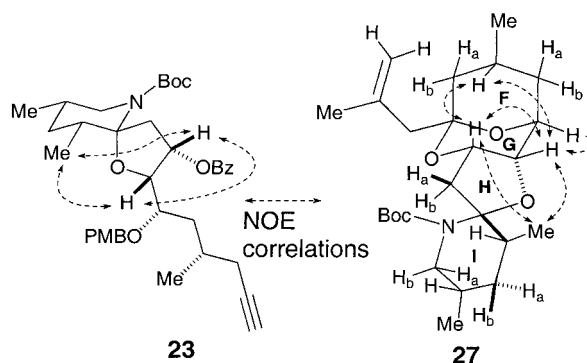


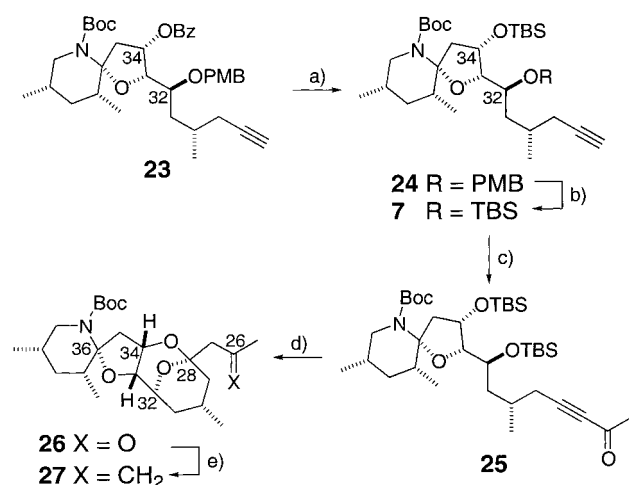
Figure 1. Observed NOEs in **23** and **27**.^[14]

products. As anticipated, this places the C37 and C39 methyl groups equatorially and the C36 oxygen atom axially about the chair of the piperidine I-ring in **23**. The elaborated HI ring system **23** was thus prepared in six steps from aldol partners **10** and **11**.

Spiroaminal **23** bears a terminal alkyne set for coupling with the C1–C26 portion of the azaspiracids, as well as a latent C32,34-diol for formation of the F–G ring system. To facilitate a direct DIHMA process^[2f] for F–G ring formation, the differentially protected C32,34-diol was converted into the corresponding bis-silyl ether prior to C26–C27 bond formation (Scheme 5). The C34 benzoate of **23** was readily cleaved with CsOH and the resulting alcohol was silylated with TBSOTf to provide mono-silyl ether **24**. It was observed that the HI ring spiro[5.4]aminal was susceptible to acid-induced isomerization to the corresponding piperidine–tetrahydropyran spiro[5.5]aminal when the C32 hydroxyl group was free to participate in *trans*-ketalization. Therefore, a pH 9 buffer was used in a DDQ-mediated oxidative cleavage of the C32 *p*-methoxybenzyl ether to attenuate the acidity of the reaction medium. Subsequent silylation gave the bis-TBS ether to complete the preparation of the convergent coupling intermediate **7**. With the intact HI spiroaminal incorporated into **7**, elaboration into the THF-fused dioxabicyclo[3.3.1]nonane ring system could be explored by electrophilic activation of the C28 alkynyl carbon atom by conjugation to a C26 ketone. The viability of this strategy was demonstrated with methyl ketone **25** (Scheme 5). For this, the magnesium

acetylide derived from **7** was added to acetaldehyde and the resultant propargylic alcohol was oxidized with MnO₂ to afford ynone **25**.

Formation of a simple 2,9-dioxabicyclo[3.3.1]nonane system had been accomplished previously from a masked 7,9-



Scheme 5. Formation of the F–G ring system by DIHMA. a) 1) CsOH, MeOH, RT, 2) TBSOTf, 2,6-lutidine, 0 °C, 98 % (two steps); b) 1) DDQ, *t*BuOH, pH 9 buffer, sonication, 2) TBSOTf, 2,6-lutidine, 0 °C, 82 % (two steps); c) 1) EtMgBr, acetaldehyde, THF, –78 °C, 98 %, 2) MnO₂, hexanes, RT, 78 %; d) TBAF, THF, RT, 85 %; e) Ph₃PCH₃Br, *n*BuLi, THF, 0 °C to RT, 72 %. DIHMA = double intramolecular hetero-Michael addition, TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

dihydroxy-ynone under acidic reaction conditions.^[2f] However, the previously noted lability of the HI spiroaminal system towards intramolecular transketalization in the presence of a free C32 hydroxyl group prompted the examination of alternative reaction conditions for the key DIHMA process. In a remarkably facile operation, treatment of ynone **25** with TBAF in THF at room temperature promoted silyl ether cleavage and bis-conjugate addition of the liberated C32 and C34 oxygen atoms upon C28 to provide the targeted FG ring system **26** in high yield (Scheme 5). The relative stereochemistry of the isobutenyl-substituted polycycle **27**^[13] was confirmed by extensive NOE studies (Figure 2)^[14] after methylenation of the residual ketone of **26**. Hence, the complete F–I polycyclic system was formed bearing the complete relative configurations found in the azaspiracid natural products. The C28 configuration obtained in the bis-conjugate addition likely results from initial F ring formation by attack of the proximal C32 oxygen atom upon the β-carbon atom of the ynone followed by a geometrically constrained addition of the C34 oxygen atom upon the resultant enone to close the G ring. By avoiding acidic conditions for the cyclization, the integrity of the piperidine–THF spiroaminal was maintained throughout the TBAF-initiated DIHMA process.

In summary, a stereocontrolled assembly of the substituted FGHI ring system of the azaspiracids that exploits novel methods for heterocycle synthesis has been developed. The sequence featured formation of an alkynyl-substituted H–I ring spiroaminal, generation of a latent 7,9-dihydroxy-ynone,

and bis-heteroconjugate addition to close the F–G rings. The utility of Yb[OTf]₃ for efficient *N*-Boc spiroaminal formation was demonstrated in the formation of the H–I ring system. The C27–C40 alkynyl intermediate **7** containing the intact HI system was designed to allow a highly convergent, chemo-selective, and late-stage fragment coupling with a C26 aldehyde en route to the natural products. The effectiveness of the DIHMA strategy for the synthesis of the fully functionalized 2,9-dioxabicyclo[3.3.1]nonane system representing the substituted F and G rings of the azaspiracids was established by using a TBAF-induced in situ desilylation–bis-conjugate addition sequence. This stereoselective intramolecular dihydroxy-ynone isomerization directly provided a β-keto-ketal that allowed the simple introduction of the C26 alkene of the azaspiracids. Finally, the synthetic sequence is amenable to the generation of either enantiomer of the C28–C40 domain. Hence, this work complements previous studies^[2] to serve as a platform for continued research aimed at the development and application of organic synthesis to meet the needs and opportunities associated with the recent discovery of the azaspiracid class of natural products.

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< 50 % yield at -20°C , whereas $\text{Yb}[\text{OTf}]_3$ provided **23** in 72 % yield at room temperature.

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Total Synthesis of Fostriecin (CI-920)**

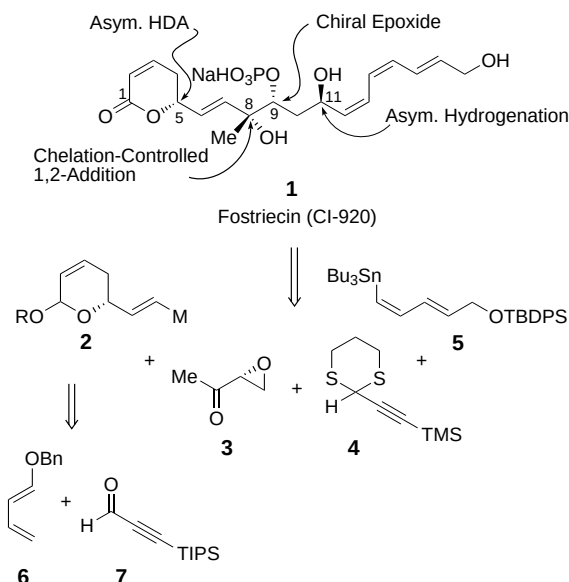
David E. Chavez and Eric N. Jacobsen*

Fostriecin (CI-920, **1**; see Scheme 1) is a structurally interesting antitumor agent that was first isolated in 1983 by scientists at Warner Lambert-Parke Davis.^[1] It displays in vitro activity against a broad range of cancerous cell lines as well as in vivo antitumor activity,^[2] and it appears to operate by a novel mechanism involving inhibition of the mitotic entry checkpoint.^[3] In this context, fostriecin is a potent inhibitor of protein serine/threonine phosphatases, and it is in fact the most selective protein phosphatase inhibitor identified to date (10^4 times greater affinity for the protein phosphatases PP2A and PP4 versus PP1).^[4]

It was not until 1997 that a correct and complete stereochemical assignment of fostriecin was made by Boger and co-workers,^[5] and that was followed very recently by a report of the first total synthesis from the same group.^[6] Certainly, the development of a practical synthetic route to fostriecin is warranted based on its interesting biological properties. In addition, clinical trials carried out at the National Cancer Institute were halted early in Phase I over concerns about the stability and purity of the natural material.^[7] A flexible synthetic route to **1** could serve as a basis for the discovery of analogues with similar biological but more desirable physical properties. In addition, the structure of fostriecin poses an

assortment of interesting challenges to an efficient synthetic design, including the presence of the unsaturated lactone,^[8] the C8–C11 triol monophosphate component, and the conjugated *Z,Z,E*-triene unit. Herein we report a new total synthesis of fostriecin. Our approach integrates highly effective asymmetric catalytic reactions to generate key chiral building blocks, and efficient coupling reactions to enable their convergent assembly.

The synthetic plan involves assembly of four fragments (**2**–**5**) of similar complexity (Scheme 1). Epoxyketone **3** plays a central role in our strategy, serving not only as the source of



Scheme 1. Retrosynthetic analysis of **1**. TBDPS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl

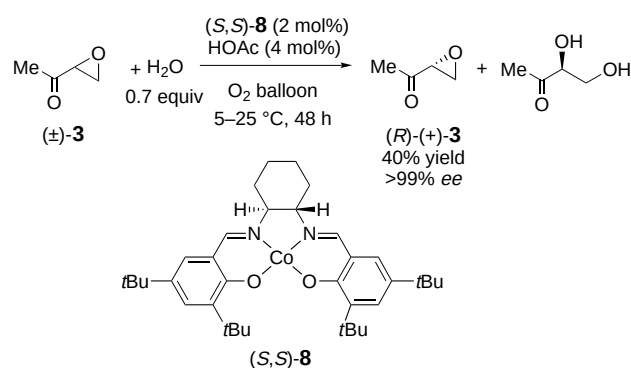
the C9 stereocenter, but also as a lynchpin for joining the left-hand vinyl lactone unit **2** and the right-hand triene diol fragment. We anticipated applying the [(salen)Co]-catalyzed hydrolytic kinetic resolution (HKR) reaction to the preparation of enantioenriched **3**, encouraged by the remarkable generality displayed by this method for the preparation of highly enantioenriched terminal epoxides.^[9] However, while racemic **3** was prepared easily from inexpensive methyl vinyl ketone,^[10] its HKR proved particularly challenging. Under standard conditions ((*S,S*)-**8**, 0.2–2 mol %, 0.55 equiv H_2O), precipitation of catalyst as the reduced [(salen)Co^{II}] complex was observed with low substrate conversion.^[11] Fortunately, this problem proved relatively easy to circumvent. When the reaction was carried out under an atmosphere of O_2 instead of N_2 or air, reduction of catalyst was avoided and the HKR proceeded to completion affording **3** in > 99 % *ee* and 40 % yield (Scheme 2; possible yield = 50 %).

With an effective route to (*R*)-**3** in hand, the next key consideration in the synthesis was the diastereoselective addition of a vinyl organometallic such as **2** to the carbonyl group of **3** to assemble the two left-hand fragments and set the C8 tertiary alcohol stereocenter. While addition of Grignard reagents to **3** proceeded in THF with exclusive reaction at the ketone functionality, only modest diastereoselectivity (ca. 4:1)

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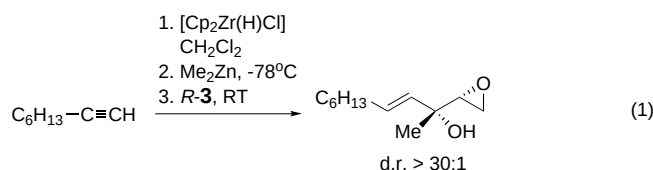
[**] We thank Professor Andrew G. Myers and Scott E. Schaus for helpful discussions, and Dr. Alexandra E. Gould and Isabel K. Reichardt for important preliminary experimental work. We also thank Dr. Robert J. Schultz of the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, for a sample of natural fostriecin. This work was supported by the NIH (GM-59316), and by Beinecke Memorial and NSF predoctoral fellowships to D.E.C.

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

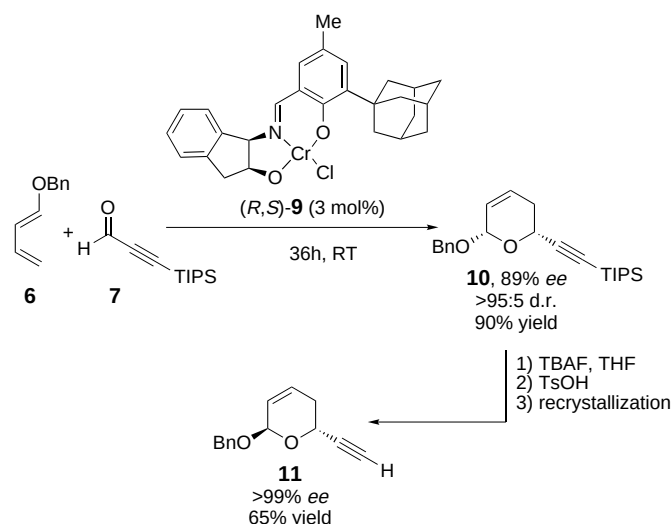


Scheme 2. Hydrolytic kinetic resolution of epoxyketone **3**.

was observed with the desired chelation control product predominating. A variety of alternative methods for addition of vinylorganometallic reagents to **3** was investigated, and the protocol developed by Wipf and co-workers^[12] for the addition of vinyl zinc intermediates to aldehydes proved most effective. For example, hydrozirconation of model substrate 1-octyne, transmetalation with dimethylzinc and addition to **3** led to the isolation of the desired 1,2-addition adduct in good yield (75 %) and with excellent diastereoselectivity (>30:1); the chelation control product was favored [Eq. (1)]. This represents the first extension of the Wipf methodology to ketone vinylation.



Having established a plausible strategy for coupling of fragments **2** and **3**, we sought an efficient enantioselective method for the preparation of alkynyl lactone **10** (Scheme 3).



Scheme 3. Preparation of **11** by means of the asymmetric hetero-Diels–Alder reaction catalyzed by **9**.

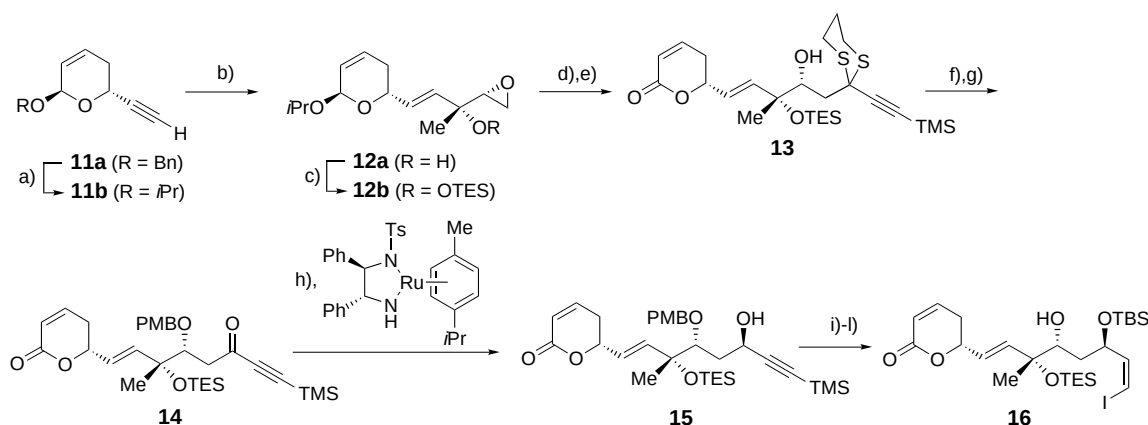
We were particularly intrigued by the possibility of applying the recently developed Cr-catalyzed hetero-Diels–Alder (HDA) reaction to this task, having established in earlier studies that cycloadditions between 1-methoxybutadiene and simple aldehydes are catalyzed by complex **9** with high enantioselectivity.^[13] In the ideal case, it would be possible to establish the entire carbon framework of the left-hand fragment **2** in the HDA reaction, and with that in mind we investigated the reaction of alkoxybutadiene derivatives with ynal **7**. We were pleased to find that **7** was indeed an effective partner in the asymmetric HDA reaction, affording cycloadducts in good yield, diastereoselectivity and enantioselectivity (Scheme 3). Whereas a variety of 1-alkoxybutadiene derivatives underwent reaction with >95 % *de* and >85 % *ee*, benzyloxy derivative **6** led to product with highest yield. Desilylation of **10** with tetrabutylammonium fluoride (TBAF), followed by acidic workup, was accompanied by epimerization of the acetal to the more stable α -anomer **11a**. This intermediate underwent recrystallization to enantiomeric purity in good overall yield.

With the two left-hand chiral building blocks now readily accessible in >99 % *ee*, we investigated their coupling using the Wipf procedure described above. Under carefully optimized conditions,^[14] hydrozirconation/transmetalation of **11b** was followed by reaction with **3** to afford the desired addition product **12a** with excellent diastereoselectivity (>30:1; Scheme 4). Although the yield for this novel vinylation reaction was modest, this coupling enabled introduction of the C8 stereocenter with high selectivity at an early stage in the synthesis and provided advanced intermediate **12a** in only seven steps (five in the longest linear sequence) from commercially available materials.

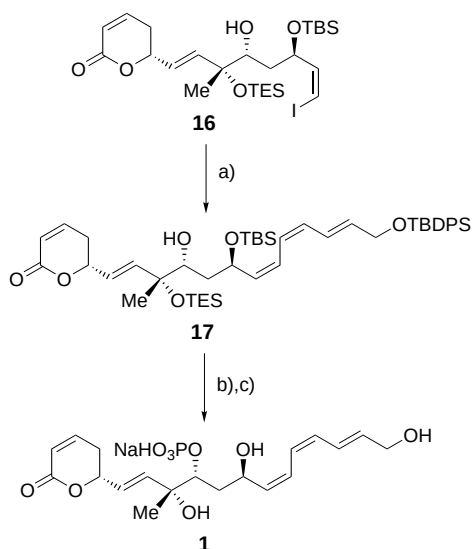
The tertiary alcohol was protected to give silyl ether **12b**, and epoxide ring opening with the anion derived from dithiane **4**^[15] proceeded in excellent yield to accomplish the second fragment coupling. Acetal hydrolysis followed by selective oxidation of the resulting lactol in the presence of the free secondary C9 alcohol provided **13**. Dithiane removal using Stork's protocol,^[16] followed by protection of the secondary alcohol as PMB ether^[17] **14** afforded the C8–C9 diol unit in orthogonally protected form, in anticipation of a later stage selective phosphorylation of the C9 alcohol.

The final stereocenter (C11) was established by using Noyori's transfer hydrogenation methodology.^[18] The catalytic asymmetric reduction allowed us to control the relative stereochemistry of the 1,3-diol unit simply by selection of the appropriate enantiomer of the catalyst.^[19] The reaction proceeded with high selectivity to provide **15** (d.r. >25:1).^[20] Protection of the propargylic alcohol as a silyl ether, one-pot acetylene deprotection and iodination,^[21] followed by PMB deprotection and *cis*-vinyl-iodide formation using a highly selective diimide reduction^[22] provided vinyl iodide **16** (Scheme 4).

The final fragment coupling joined vinyl iodide **16** and the *Z,E*-stannane **5** (Scheme 5).^[23] The cross-coupling was effected under ligand-free Stille coupling conditions^[24] and proceeded with complete retention of olefin stereochemistry. Phosphorylation of the C9 alcohol of **17** was accomplished by using a modification of the protocol developed by Evans.^[25]



Scheme 4. Synthesis of the C₁–C₁₃ fragment. a) TsOH, *i*PrOH, 90%; b) [Cp₂Zr(H)Cl], CH₂Cl₂; then Me₂Zn, –78 °C, 10 min; then **3**, 4 h, RT; c) TESCl, imidazole, DMF; 45%, 2 steps; d) *n*BuLi, **4**, THF, –40 °C; then **12b**; 89%; e) PPTS, acetone/H₂O (4:1); then MnO₂, CH₂Cl₂; 65%, 2 steps; f) bis(trifluoroacetoxyiodobenzene), MeOH/H₂O (9:1); 70%; g) 4-MeO-benzyl trichloroimidate, Ph₃C⁺ BF₄[–], Et₂O; 83%; h) *i*PrOH; 36 h; 93%, >95:5 dr; i) TBSOTf, 2,6-lutidine, CH₂Cl₂; 80%; j) AgNO₃, NIS, acetone; 95%; k) DDQ, CH₂Cl₂; 100%; l) NBSH, THF/*i*PrOH (1:1), TEA; 85%; TES = triethylsilyl; TESCl = chlorotriethylsilane; TsOH = *p*-toluenesulfonic acid; PPTS = pyridinium *p*-toluenesulfonate; PMB = *p*-methoxybenzyl; TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate; NIS = *N*-iodosuccinimide; DDQ = dichlorodicyanoquinone; NBSH = *o*-nitrobenzenesulfonylhydrazide; TEA = triethylamine; PMBOH = *p*-methoxybenzyl alcohol.



Scheme 5. Completion of the synthesis of fostriecin. a) [PdCl₂(CH₃CN)₂], **5**, DMF; 85%; b) PCl₃, pyr; then PMBOH; then *t*BuOOH, CH₂Cl₂; 65%; c) HF, CH₃CN; then pyr; 45%.

Global deprotection of the silyl and *p*-methoxybenzyl groups afforded **1**, with spectroscopic and chromatographic properties identical to those of natural fostriecin.

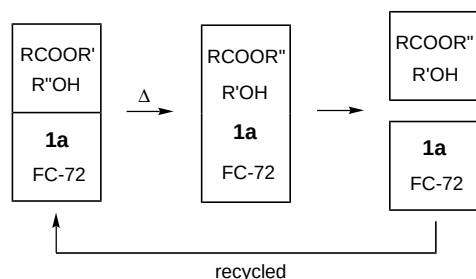
The synthesis of fostriecin was thus completed in 17 steps in the longest linear sequence. Our approach made use of asymmetric catalytic reactions to obtain building blocks **11** and **3** in >99% *ee*. Epoxycetone **3** is now readily accessible using HKR methodology, and holds promise as a versatile chiral building block for asymmetric synthesis. In the context of the fostriecin synthesis, the use of **3** allowed rapid access to advanced intermediate **13** through selective ketone alkylation and subsequent epoxide ring opening. Overall, control of three of the four stereocenters of fostriecin was exerted by means of asymmetric catalytic reactions, while the tertiary C8 allylic alcohol center was installed by using a novel, highly

diastereoselective alkenylation of epoxycetone **3**. This synthesis further illustrates the power of the chiral building block strategy for natural product synthesis, and provides easy access to structural analogues of fostriecin for further study.

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found, except for the transesterification of β -keto esters; but even then the yields were not always satisfactory (50–97%).^[18–21] With this in mind, we used the 1:1 stoichiometry in our reaction in a simple procedure (see Scheme 1 and Experimental Section). No apparatus was needed to remove the alcohol formed. GLC analysis of the organic layer indicated the quantitative conversion and yield, without any sign of residual starting materials, except in one case



Scheme 1. Fluorous biphasic transesterification catalyzed by fluoroalkyldistannoxane **1a**.

Table 1. Fluorous biphasic transesterification catalyzed by fluoroalkyldistannoxane **1a** (ester/alcohol 1:1).^[a]

Entry	RCOOR'	R''OH	Yield of RCOOR'' [%] GLC ^[b]	Isolated
1	Ph(CH ₂) ₂ COOEt	C ₈ H ₁₇ OH	> 99	100
2	Ph(CH ₂) ₂ COOEt	PhCH ₂ OH	> 99	99
3	Ph(CH ₂) ₂ COOEt	PhCH=CHCH ₂ OH	> 99	100
4	Ph(CH ₂) ₂ COOEt	geraniol	> 99	98
5	Ph(CH ₂) ₂ COOEt	THPO(CH ₂) ₈ OH	> 99	99
6	Ph(CH ₂) ₂ COOMe	TBSO(CH ₂) ₈ OH	> 99	100
7	Ph(CH ₂) ₂ COOEt	PhC≡CHCH ₂ OH	> 99	100
8	Ph(CH ₂) ₂ COOEt	2-octanol	98 (2)	96 ^[c]
9		2-octanol ^[d]	> 99 (10) ^[e]	100 ^[c]
10	Ph(CH ₂) ₂ COOEt	cyclohexanol	> 99	99
11	Ph(CH ₂) ₂ COOMe	PhCH=CHCH ₂ OH	> 99	100
12	PhCH=CHCOOEt	PhCH=CHCH ₂ OH	> 99	99
13	PhCOOEt	PhCH=CHCH ₂ OH	> 99	100
14	PhCOOMe	PhCH=CHCH ₂ OH	> 99	100

[a] A mixture of ester (2.0 mmol), alcohol (2.0 mmol), and **1a** (0.10 mmol) in FC-72 (4 mL) was heated at 150 °C for 16 h. [b] In the case of > 99% yield, no starting materials were detected except for entry 8 in which the ethyl ester and 2-octanol (2% each) were detected. The amount of the remaining starting materials is given in parentheses. [c] Isolated by using column chromatography. [d] 2-Octanol (1.1 equiv). [e] Only 2-octanol but no ethyl ester was detected.

(Table 1). Accordingly, pure esters were obtained simply by evaporating the organic layer, as the ethanol or methanol formed was removed during the evaporation. When the reactants were not completely converted (Table 1, entry 8), the product esters could be readily isolated by column chromatography. Alternatively, the use of excess 2-octanol resulted in 100% conversion (Table 1, entry 9).

The catalyst can be quantitatively recovered from the fluorous layer. However, it was more practical to reuse the separated FC-72 solution directly in the next reaction by combining with another mixture of reactants. This manipulation could be repeated more than 20 times^[22] without depression of catalytic activity, even with different combina-

tions of reactants. As a result, all reactions given in Table 1 were carried out with a single catalyst solution.^[23] The fluorous layer was washed simply to remove a small amount of the organic substances that remained on the surface of the FC-72 layer. Hence, washing is no longer necessary if the same reactions are repeated or if the reaction is conducted on a larger scale that allows more efficient phase separation. In such procedures, the pure esters are isolated from the reaction mixture after the ethanol or methanol are pumped off. Hence a process that uses no organic solvents has been established. Of further synthetic significance is the tolerance of labile substrates and functional groups that cannot survive under usual conditions (Table 1, entries 3–7, 11–14).

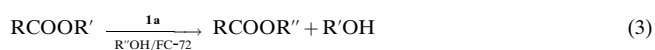
Another simple and practical operation involved the use of alcohols with a low boiling point as the solvent. Accordingly, a mixture of a solution of **1a** in FC-72 and a solution of an ester in the alcohol was heated at 150 °C for 16 h [Eq. (3)]. GLC analysis indicated a > 99% yield of the desired esters,

Table 2. Fluorous biphasic transesterification catalyzed by fluoroalkyldistannoxane **1a** in alcohol solvent.^[a]

Entry	RCOOR'	R''OH	Yield of RCOOR'' [%] GLC	Isolated
1	Ph(CH ₂) ₂ COOEt	CH ₃ OH	> 99	100
2	Ph(CH ₂) ₂ COOEt	2-butanol	> 99	100
3	Ph(CH ₂) ₂ COOMe	C ₂ H ₅ OH	> 99	100
4	Ph(CH ₂) ₂ COOBn	CH ₃ OH	> 99	100 ^[b]
5	Ph(CH ₂) ₂ COOBn	C ₂ H ₅ OH	> 99	100 ^[b]
6	Ph(CH ₂) ₂ COOBn	CH ₂ =CHCH ₂ OH	> 99	100 ^[b]

[a] A mixture of ester (2.0 mmol), alcohol (2.0 mL), and **1a** (0.10 mmol) in FC-72 (4 mL) was heated at 150 °C for 16 h. [b] Isolated by using column chromatography.

concomitant with the complete disappearance of the reactant esters (Table 2). The pure products were isolated in 100% yield, simply by evaporating the organic layer (in the case of ethyl or methyl esters as starting materials) or by column chromatography to remove benzyl alcohol (benzyl ester as starting material). The use of excess alcohol as solvent allows the reactions to occur in the opposite direction to Equation (1), thus allowing even higher alkoxy moieties of the reactants to be replaced under these conditions. The FC-72 solution of the catalyst was reused, as described before.^[24]



In summary, a simple and practical transesterification protocol has been devised on the basis of a novel fluoroalkyldistannoxane catalyst and a fluorous biphasic technique.

Experimental Section

Fluoroalkyldistannoxane 1a: The Grignard reagent derived from C₆F₁₃CH₂CH₂I (30 mmol) and Mg turnings (34 mmol) was coupled with (PhCH₂)₂SnBr₂ (10 mmol) in Et₂O/THF at room temperature for 24 h to afford (C₆F₁₃CH₂CH₂)₂Sn(CH₂Ph)₂ in 81% yield. Treatment of (C₆F₁₃CH₂CH₂)₂Sn(CH₂Ph)₂ (5.4 mmol) with Br₂ (10.8 mmol, 2 equiv) in

CCl_4 at room temperature for 3 h gave $(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_2\text{SnBr}_2$ (96 %), which was hydrolyzed with aqueous NaOH (4 N)/THF at room temperature for 2 h to furnish polymeric $[(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_2\text{SnO}]_n$ (**2**) (93 %). Treatment of **2** (5 mmol) with aqueous HCl (4 N; 6.5 mmol) in acetone at room temperature for 24 h afforded **1a** in 85 % yield: m.p. 90–91 °C (CH_2Cl_2); ^{119}Sn NMR ($[\text{D}_6]\text{acetone}$): $\delta = -178.3, -202.5$; elemental analysis: calcd for $\text{C}_{64}\text{H}_{32}\text{Cl}_4\text{F}_{104}\text{O}_2\text{Sn}_4$: C 22.44, H 0.94; found: C 22.58, H 0.54.

Fluorous biphasic transesterification: A mixture of ethyl 3-phenylpropionate (356 mg, 2.0 mmol), 1-octanol (260 mg, 2.0 mmol), and **1a** (171 mg, 0.1 mmol) in FC-72 (4.0 mL) was added to a test tube. The test tube was placed in a stainless-steel pressure bottle and heated at 150 °C for 16 h. The reaction mixture was then cooled to room temperature and toluene (5 mL) was added. The FC-72 layer was washed with toluene (2×1 mL) and the combined toluene solution was evaporated to afford pure octyl 3-phenylpropionate (525 mg, 2.0 mmol). The FC-72 solution was used in the next reaction.

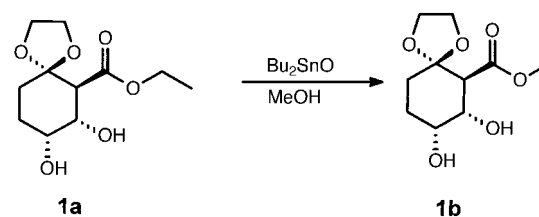
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- [24] The reaction in Table 2, entry 1 was repeated 20 times. The GC yield was constantly >99 % each time, and 91 % of the catalyst was recovered after the 20th run, indicative of virtually no loss and no deactivation of the catalyst during the repetition.

A Mild and Effective Method for the Transesterification of Carboxylic Acid Esters**

Patrick Baumhof, Ralph Mazitschek, and Athanassios Giannis*

Transesterification is one of the most important transformations in organic synthesis.^[1] The most important methods, besides acid or base catalysis, employ titanium tetraalkoxides,^[2] complex tin compounds,^[3] indium iodide,^[4] or enzymes.^[5] During a dibutyltin oxide-mediated selective O-methylation of compound **1a**, we observed the formation of methyl ester **1b** as a side product (Scheme 1). Interestingly,



Scheme 1. Dibutyltin oxide catalyzed transesterification of ethyl ester **1a** into methyl ester **1b**.

neither elimination nor epimerization at the stereogenic center adjacent to the ester moiety was observed. Previous attempts to obtain methyl ester **1b** by using various acids and bases always led either to complete epimerization or to the decomposition of **1a**. Furthermore, $\text{Ti}(\text{OMe})_4$ was not suitable for this purpose owing to its insolubility in methanol.^[2]

The significance of the observed side product encouraged us to optimize this reaction and to investigate the scope and limitations of this method. Several simple as well as highly functionalized aliphatic and aromatic esters were treated with catalytic amounts of dibutyltin oxide (1–10 mol %) in different alcohols as solvents. The isolated derivatives corresponded to the product of transesterification with the alcohol that was used as solvent (Table 1). The reaction conditions are very mild and thus the method is tolerant of several functional groups, for example, acetals, ketals, aliphatic bromides, β -ketoesters, and enol ethers. Most significantly, free hydroxy, phenolic, and even amino groups do not affect the reaction.

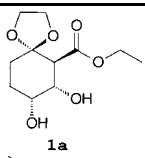
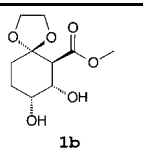
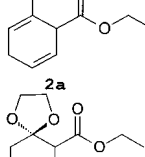
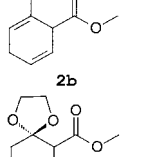
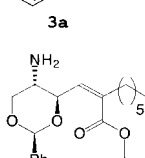
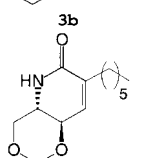
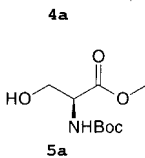
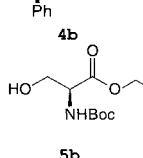
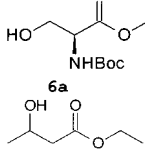
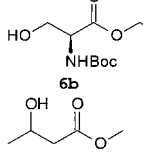
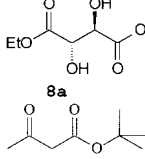
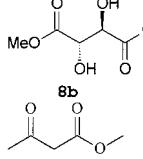
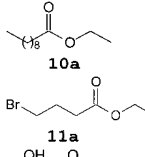
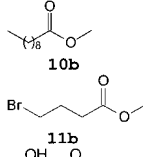
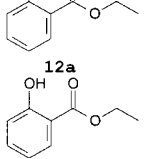
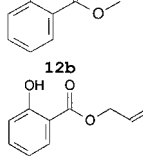
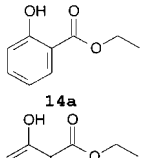
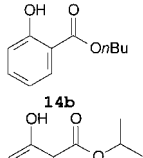
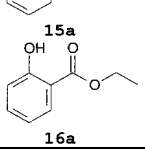
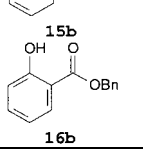
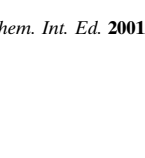
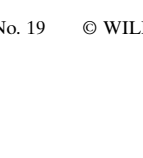
The potential scope of this method was clear from the treatment of **4a** with dibutyltin oxide in methanol to afford the desired derivative **4b** in an excellent yield (Table 1, entry 4).^[6] We suppose that the *tert*-butyl ester moiety in **4a** is first transformed into the methyl ester, which is then attacked intramolecularly by the free amino group to afford the final product **4b**. To exclude the possibility that the amide was

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Table 1. Dibutyltin oxide mediated transesterifications.

Entry	Ester	Product	Alcohol	Time [h]	Yield
1			methanol	12	90
2			methanol	12	88
3			methanol	12	90
4			methanol	24	96
5			allyl alcohol	12	87
6			ethanol	12	85
7			methanol	12	89
8			methanol	12	92
9			methanol	12	90
10			methanol	12	80
11			methanol	12	77
12			methanol	5	96
13			allyl alcohol	5	90
14			n-butanol	5	88
15			isopropyl alcohol	5	91
16			benzyl alcohol	5	86

formed directly under dibutyltin oxide mediation, we treated **4a** with dibutyltin oxide in dioxane in the absence of methanol. After 24 h at 90 °C we did not observe the formation of amide **4b**. The transesterification of N-protected amino acid esters also proceeded smoothly without affecting the urethane group (Table 1, entries 5, 6). In this context it is worth noting that Shapiro et al. reported the O-alkyl transesterification of several urethanes by using $\text{Ti}(\text{O}i\text{Pr})_4$ in the presence of the appropriate alcohols.^[7]

To test the effect of water on the outcome of the reaction we used a mixture of alcohol and water (4:1) as the solvent and obtained the expected transesterification products in high yields; thus strictly dry reaction conditions are not necessary. The highest turnover numbers were observed in the transesterification reactions of salicylic esters with free phenolic groups, which were converted into the corresponding esters in excellent yields in only five hours (Table 1, entries 12–16). By using this method, esters of primary, secondary, and even tertiary alcohols can be transesterified in high yields. Allyl esters and benzyl esters were also prepared by using this method (Table 1, entries 5, 13, 16). However, *tert*-butyl alcohol cannot be used for transesterification.

In 1979 Poller et al. investigated the activity of dialkyl- and diaryltin oxide compounds as catalysts for the conversion of propyl acetate into methyl acetate.^[8] On account of our findings we believe that the use of dibutyltin oxide in transesterification reactions deserves more attention, especially because it is comparable with the complex tin compounds introduced by Otera.^[3] The main advantages of this system are the simple and mild reaction conditions, the inexpensive and commercially available catalyst, the high yields, and especially the compatibility with a variety of functional groups. The method described herein represents a valuable alternative to the known methods and may find a broad application, especially in the field of natural product synthesis.

Experimental Section

General procedure: The carboxylic ester (0.6 mmol) was dissolved in the desired alcohol (5 mL). After the addition of dibutyltin oxide (10 mol%; 15 mg, 0.06 mmol) the mixture was heated at reflux for the time indicated in Table 1 (the reaction was normally complete within 48–72 h when 1 mol% of dibutyltin oxide was used). After completion of the reaction, the mixture was poured into a saturated sodium bicar-

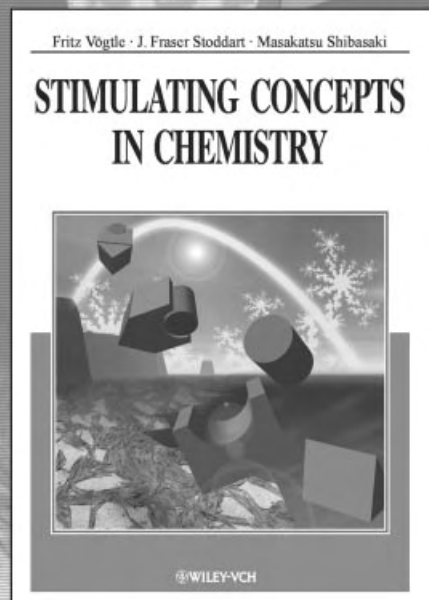
bonate solution (20 mL) and extracted three times with ethyl acetate. The combined organic layers, which contained the dibutyltin oxide as a fine white precipitate, were filtered through celite and dried over sodium sulfate. After removal of the solvent in vacuo, the product was purified by flash chromatography.

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ASPECTS OF MODERN CHEMISTRY



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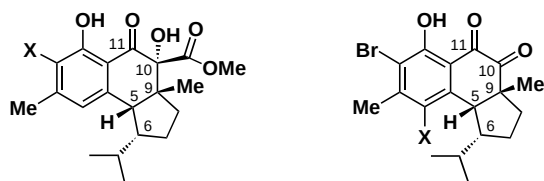
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Total Synthesis of Hamigerans: Part 1. Development of Synthetic Technology for the Construction of Benzannulated Polycyclic Systems by the Intramolecular Trapping of Photogenerated Hydroxy-*o*-quinodimethanes and Synthesis of Key Building Blocks**

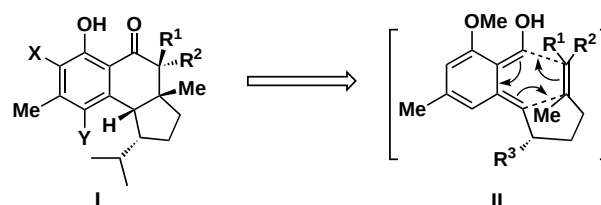
K. C. Nicolaou,* David Gray, and Jinsung Tae

A recent report^[1] disclosed the structures of a series of compounds isolated from the poecilosclerid sponge *Hamigera tarangaensis* BERGQUIST & FROMONT (family Anchinoidae, syn. Phorbasidae) from the Hen and Chicken Islands off the coast of New Zealand. Termed hamigerans (e.g. **1–4**), these natural products contain a unique carbon skeleton in which



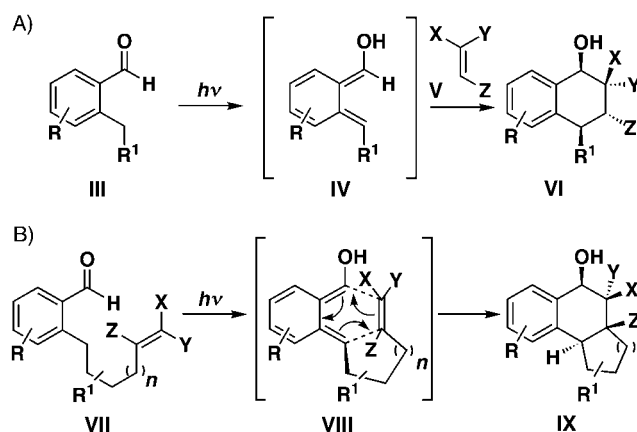
1: X = H: debromohamigeran A **3:** X = H: hamigeran B
2: X = Br: hamigeran A **4:** X = Br: 4-bromohamigeran B

a substituted aromatic nucleus is fused onto a [4.3.0] carbocyclic system that contains three or four stereogenic centers and features an isopropyl group. The biological properties of these compounds range from moderate cytotoxicity (e.g. 4-bromohamigeran B (**4**)) against P-388 leukemia cells to strong antiviral activity (hamigeran B (**3**)) against herpes and polio viruses. Despite their relatively small size, the hamigerans offer both a challenge and an opportunity for the development of new synthetic technologies and chemical biology studies. In contemplating potential synthetic routes to these compounds, we considered the possibility of employing an intramolecular trapping strategy that involves the photochemically generated hydroxy-*o*-quinodimethane species **II** to form the benzannulated system **I** (Scheme 1). With a few notable exceptions,^[2, 3] there are only scant examples of the potential use of this reaction in total synthesis,^[4] despite the early work by Yang and Rivas^[5] on the photo-



Scheme 1. Proposed *o*-enolquinodimethane route to the hamigerans.

chemical enolization of benzophenone. The few reports on this reaction have typically involved mechanistic studies and very simple substrates and/or rather special conditions.^[6] In an effort to develop a streamlined and general method for the synthesis of benzannulated systems such as those found in the hamigerans, we undertook a systematic investigation of this process. In this and the following communication,^[7] we wish to describe the details of our explorations in this area which led to the development of a general and practical entry into such systems (Scheme 2), and its application to the total synthesis of the hamigerans **1–4** and their analogues.



Scheme 2. General strategy for the synthesis of benzannulated systems from substituted benzaldehydes by the photogeneration and trapping of hydroxy-*o*-quinodimethanes. A) Intermolecular variant. B) Intramolecular variant.

With the ultimate goal of applying the developed technology to complex molecule construction, we sought to include in our studies a diverse and polyfunctional collection of substrates for the intended photo-enolization-based reaction (Scheme 2). Thus, it was observed that a wide variety of dienophiles, including vinyl ketones,^[8] acrylate esters,^[9] acrylonitriles, and acroleins^[4b] reacted with the electron-rich *o*-methylbenzaldehyde **7** (Table 1, entries 4–8) to afford a series of benzannulated systems in generally good yields. An initial exploration of the generality of the intermolecular Diels–Alder reaction of the photochemically generated hydroxy-*o*-quinodimethanes (Scheme 2 A) proved to be quite promising, except for the fact that some of the employed dienophiles showed an unacceptable propensity to photo-induced polymerization. We fine-tuned the reaction conditions and found that these reactions could be made quite efficient and practical (Table 1) by employing an excess of the polymerizable dienophiles, by performing the reaction in dilute

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Table 1. Synthesis of benzannulated systems by the intermolecular trapping of hydroxy *o*-quinodimethanes (see Scheme 2A).^[a]

Entry	Aldehyde	Dienophile	Product	<i>t</i> [h]	Yield [%]
1				12	55
2				8	72
3				8	71
4				2	83
5				4	82
6				2	89
7				2	75
8				4	84
9				2	88

[a] *O*-alkyl benzaldehyde (1 mmol) and olefin (5–20 equiv) were dissolved in deoxygenated toluene (0.025 M) in a pyrex flask and irradiated at ambient temperature with a 450-W Hanovia lamp at a distance of 10 cm. Products were obtained as separable mixtures of isomers in the following ratios, by entry number: 1) $\approx$ 4:1; 2) $\approx$ 4:1; 3) $\approx$ 8:1; 4) $\approx$ 3:1; 5) $\approx$ 8:4:1; 6) $\approx$ 6:1; 7) $\approx$ 7:1; 8) $\approx$ 9:3:1; 9) $\approx$ 6:1. The product shown is the major isomer (stereochemistry assigned by NMR spectroscopy).

toluene solution, and by using ordinary pyrex vessels (as opposed to quartz glass). We also noted that in going from the parent 2-methylbenzaldehyde (**5**; Table 1, entry 1) to more substituted substrates, the efficiency of the reaction improved substantially (Table 1, entries 2–9). Interestingly, the more electron-rich benzaldehydes (Table 1, entries 2–8) proved to be excellent substrates in this reaction as did commercially available 3-fluoro-2-methylbenzaldehyde (**8**). The latter reacted with methyl vinyl ketone to afford the corresponding bicyclic fluoride **17** in high yield under the developed photolytic conditions (Table 1, entry 9).

Table 2. Synthesis of benzannulated tricycles by the intramolecular trapping of hydroxy *o*-quinodimethanes (see Scheme 2B).^[a]

Entry	Aldehyde	Product	<i>t</i> [min]	Yield [%]
1			45	95
2			90	83
3			45	95
4			20	90
5			20	90 ^[b]
6			20	88 ^[c]
7			60	75

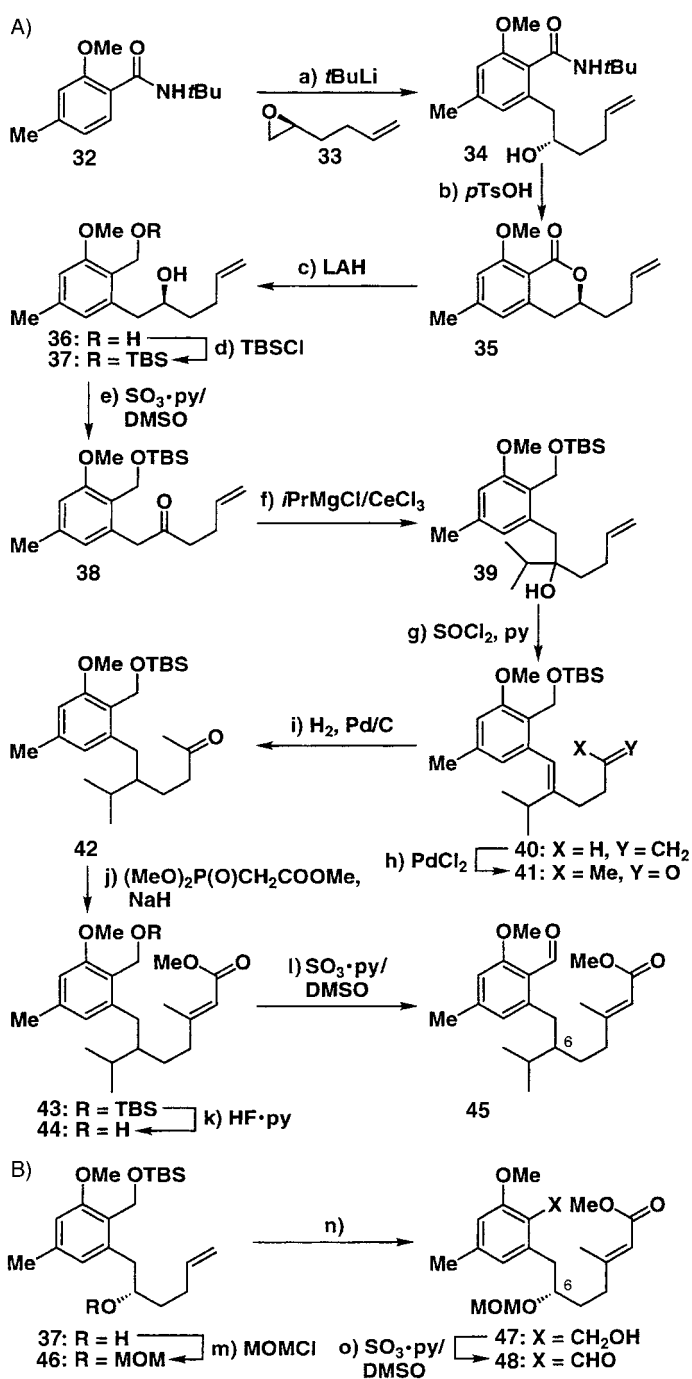
[a] *O*-alkyl benzaldehydes (0.5–1 mmol) were dissolved in deoxygenated toluene or benzene (0.02 M) in a pyrex flask and irradiated at ambient temperature with a 450-W Hanovia lamp at a distance of 5 cm. Products were obtained as separable mixtures of isomers, which reflected the *E*:*Z* ratios of the starting olefins. The starting material and product shown are the major isomers (stereochemistry assigned by NMR spectroscopy). [b] Starting olefin: *E*/*Z* >20:1; product: C10 epimers >20:1. [c] Starting olefin: *Z*/*E* >20:1; product: C10 epimers $\approx$ 3:1.

A powerful extension of this methodology would be its intramolecular variant. This proposition assumed special priority in light of the many foreseeable applications of such synthetic technology. To test this, a rapid entry into a series of *ortho*-alkyl-substituted benzaldehydes was devised and employed to deliver substrates **18–24** (Table 2, entries 1–7). When these aldehydes were exposed to ultraviolet light (450-W Hanovia lamp, pyrex filter) at ambient temperature, a remarkably fast, stereoselective, and high-yielding ring closure took place in each case to furnish the tricycles **25–31** (Table 2, entries 1–7). These examples demonstrate that both [4.4.0] (Table 2, entries 1–3) and [4.3.0] bicyclic systems (Table 2, entries 4–7) can be fused onto the aromatic nucleus, and that the newly generated fusion in the cyclization product

has a *trans*-fused stereochemistry. Furthermore, the three contiguous substituents that extend from the benzylic position (OH, electron-withdrawing group, and H or Me) were found to be *syn* to one another when di- or trisubstituted *E* olefins were employed (Table 2, entries 1–5). Also notable is the ability of this process to deliver quaternary centers (Table 2, entries 3, 5–7), including two such centers in adjacent positions (Table 2, entry 7). Furthermore, some interesting stereochemical aspects of this process are evident (Table 2, entries 5 and 6). When (*E*)-**22** was subjected to the reaction, the product with the *all-syn* stereochemistry at C9, C10, and C11 (**29**; Table 2, entry 5; for selected data, see Table 3) was obtained as the major product together with the isomeric compound **30** in which the ester group is *anti* to the two neighboring substituents (>20:1 ratio). An *endo* approach of the dienophile towards the hydroxy-*o*-quinodimethane accounts for this stereochemical outcome. Surprisingly, however, when pure (*Z*)-**23** was employed, a mixture of the same two products (**29/30** ≈ 1:3) was formed, with stereoisomer **30** now predominating. This observation requires an *exo* mode of approach of the incoming dienophile (to explain the formation of the major product **30** from **23**) and a *Z* to *E* isomerization under the irradiation conditions (to account for the formation of the *all-syn* isomer **29**). Molecular modeling confirms the highly strained nature of both the *exo* approach for the *E* isomer **22** and the *endo* arrangement for the *Z* isomer **23**, thus precluding the formation of the C5–C9 *syn* junction which would require transition states associated with such modes of interaction.

Having established the reaction as a reliable and efficient synthetic process and further defined its scope and generality, we then proceeded to the second phase of the program, which had as its ultimate aim the possible application of the intramolecular version of the developed technology to the total synthesis of the hamigerans. To this end, two cyclization precursors were designed, one in which the isopropyl group at the C6 position of the targeted structure (**45**, Scheme 3 A) was already installed prior to ring closure, and another in which this position was occupied by a protected oxygen functionality (**48**, Scheme 3 B). The latter functionality was chosen so as to serve as a handle to introduce the isopropyl group after cyclization, and to facilitate the desired epimerization at C5 (given the results of the model studies which led to the undesired C5–C9 junction).

The construction of these two substrates is summarized in Scheme 3. Treatment of benzamide **32** with two equivalents of *t*BuLi in the presence of TMEDA (for abbreviations of reagents and protecting groups, see legends in schemes) led to the deep red colored dianion, which opened terminal epoxide **33** to afford secondary alcohol **34** in 69% yield (Scheme 3 A).^[10] For the isopropyl substrate, the commercially available racemic epoxide ($\pm$)-**33** was utilized, whereas for the protected alcohol (Scheme 3 B), enantiomerically enriched (>99% *ee*) epoxide (*S*)-**33**, which was obtained by using the Jacobsen hydrolytic kinetic resolution method with the *S,S* cobalt catalyst,^[11] was used (see below). Acid-induced (*p*TsOH) intramolecular attack of the newly generated alcohol at the amide group of **34** led to δ -lactone **35** in 91% yield.^[10] Compound **35** was then reduced with LiAlH₄, the



Scheme 3. Synthesis of cyclization substrates **45** and **48**. Reagents and conditions: a) *t*BuLi (2.2 equiv), TMEDA (2.0 equiv), –78 → –20 °C, then **33** (1.0 equiv), THF, –78 → 0 °C, 2 h, 69%; b) *p*TsOH (2.0 equiv), toluene, reflux, 2 h, 91%; c) LiAlH₄ (2.0 equiv), THF, 25 °C, 30 min, 91%; d) TBSCl (1.1 equiv), Et₃N (2.0 equiv), 25 °C, 12 h, 89%; e) SO₃·py (3.0 equiv), Et₃N (6.0 equiv), DMSO/CH₂Cl₂ (1:1), 0 °C, 2 h, 94%; f) *i*PrMgCl (2.0 equiv), CeCl₃ (2.0 equiv), –78 → 0 °C, 1 h, 94%; g) SOCl₂, py, CH₂Cl₂, –60 °C, 15 min, 80%; h) PdCl₂ (0.1 equiv), Cu(OAc)₂ (2.0 equiv), DMA/H₂O (10:1), O₂ (1 atm), 25 °C, 12 h, 80%; i) 10% Pd/C, H₂ (1 atm), EtOAc, 25 °C, 2 h, 92%; j) (MeO)₂P(O)CH₂COOMe (3.0 equiv), NaH (3.0 equiv), THF, 60 °C, 3 h, 94% (mixture of *E/Z* isomers, ca. 3:1); k) HF·py (4.0 equiv), THF, 25 °C, 20 min, 91%; l) SO₃·py (3.0 equiv), Et₃N (6.0 equiv), DMSO/CH₂Cl₂ (1:1), 0 °C, 2 h, 86%; m) MOMCl (2.0 equiv), *i*Pr₂NEt (6.0 equiv), CH₂Cl₂, 25 °C, 4 h, 83%; n) same procedure as steps h, j, and k above, similar yields; o) same procedure as step l above, 88%. TMEDA = *N,N,N',N'*-tetramethylethylenediamine. *p*TsOH = *p*-toluenesulfonic acid, TBS = *tert*-butyldimethylsilyl, py = pyridine, DMA = *N,N*-dimethylacetamide, MOM = methoxymethyl.

resulting diol was selectively monosilylated (TBSCl/Et₃N, 89 % yield), and the secondary alcohol was oxidized (SO₃·py/DMSO) to afford ketone **38** in 94 % yield. Reaction of ketone **38** with *i*PrMgCl required prior addition of CeCl₃ to the Grignard reagent to generate the less basic cerium species, which reacted smoothly with the substrate to afford tertiary alcohol **39** in 94 % yield. Elimination of the tertiary hydroxy group from **39** was effected regioselectively towards the aromatic nucleus by the action of SOCl₂/py at –60 °C, leading to olefin **40**, which was subjected to Wacker oxidation (PdCl₂, Cu(OAc)₂, H₂O, O₂) to afford the expected methyl ketone **41** as the major product (80 % yield). Hydrogenation (Pd/C) of the remaining double bond led to compound **42** in 92 % yield. Reaction of ketone **42** with (MeO)₂P(O)CH₂COOMe/NaH furnished the *E*-α,β-unsaturated ester **43** as the major product, together with its *Z* isomer (ca. 3:1) in 94 % total yield. The silyl protecting group was then removed from **43** under carefully controlled conditions to afford the corresponding benzyl alcohol **44** (91 % yield), which was smoothly oxidized to the targeted aldehyde **45** by treatment with SO₃·py/DMSO (86 % yield).

The enantioselective synthesis of the second required aldehyde **48** (Scheme 3B) started with epoxide (*S*)-**33** and proceeded through hydroxy silyl ether **37** (obtained as described above, Scheme 3A). Compound **37** was protected as its MOM ether (MOMCl/*i*Pr₂NEt, 83 % yield) and then carried through the same sequence as described for the preparation of racemic **45** to furnish, in similar yields, benzyl alcohol **47** (for selected data, see Table 3), which was oxidized

hydroxy-*o*-quinodimethane species, which were subsequently trapped by dienophiles in either inter- or intramolecular Diels–Alder fashion. The present technology holds considerable potential in the construction of complex molecules, as demonstrated by the accommodation of a diverse range of functional groups and its application to the total synthesis of the hamigerans described in the following communication.^[7]

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Table 3. Selected data for compounds **29** and **47**.

29: colorless solid; *R*_f = 0.3 (silica gel, hexane/EtOAc 1:1); IR (film): $\tilde{\nu}_{\text{max}}$ = 3386, 2935, 1715, 1453, 1174, 1034 cm^{–1}; ¹H NMR (CDCl₃, 600 MHz): δ = 7.48 (d, *J* = 7.4 Hz, 1H), 7.22–7.12 (m, 3H), 4.98 (t, *J* = 7.0 Hz, 1H), 4.18–4.08 (m, 2H), 3.92 (m, 1H), 3.63 (d, *J* = 7.4 Hz, 1H), 3.59 (m, 1H), 2.94 (d, *J* = 7.0 Hz, 1H), 2.45 (m, 1H), 2.29 (d, *J* = 10.5 Hz, 1H), 2.09 (m, 1H), 1.86 (dd, *J* = 11.6, 8.1 Hz, 1H), 1.68 (m, 1H), 1.58–1.45 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H), 0.55 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz): δ = 173.2, 139.0, 137.3, 127.3, 127.3, 126.4, 124.3, 67.9, 67.2, 60.6, 56.5, 52.0, 44.8, 39.8, 38.0, 21.1, 16.2, 14.2; HR-MS (MALDI): calcd for C₁₈H₂₄O₄ [*M*+Na⁺]: 327.1567; found: 327.1562

47: colorless solid; *R*_f = 0.5 (silica gel, hexane/EtOAc 1:1); [α]_D²⁵ = +5.27 (*c* = 0.168, CHCl₃); IR (film): $\tilde{\nu}_{\text{max}}$ = 3465, 2944, 1716, 1646, 1610, 1581, 1456, 1221, 1149, 1097, 1034 cm^{–1}; ¹H NMR (CDCl₃, 400 MHz): δ = 6.62 (s, 1H), 6.58 (s, 1H), 5.68 (s, 1H), 4.77 (m, 1H), 4.60 (m, 1H), 4.51 (d, *J* = 7.0 Hz, 1H), 4.34 (d, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.78 (m, 1H), 3.67 (s, 3H), 3.06 (s, 3H), 2.94 (m, 2H), 2.74 (m, 1H), 2.30 (s, 3H), 2.24 (m, 1H), 2.14 (s, 3H), 1.74 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ = 167.1, 159.7, 158.0, 138.6, 138.4, 125.3, 123.3, 115.3, 109.7, 95.5, 78.1, 55.9, 55.5, 55.4, 50.8, 39.7, 36.4, 32.3, 29.0, 21.5; HR-MS (MALDI): calcd for C₂₀H₃₀O₆ [*M*+Na⁺]: 389.1934; found: 389.1936

with SO₃·py/DMSO to deliver the targeted intermediate **48** in enantiomerically enriched form.

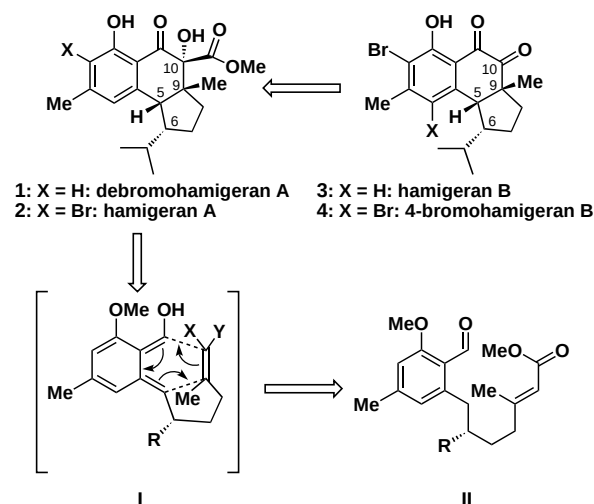
In summary, a highly efficient and direct approach to benzannulated systems has been developed by employing suitable aromatic aldehydes as starting materials and light as a reagent, and proceeding through a cascade reaction sequence that involved initial photo-enolization to afford reactive

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Total Synthesis of Hamigerans: Part 2. Implementation of the Intramolecular Diels–Alder Trapping of Photochemically Generated Hydroxy-*o*-quinodimethanes; Strategy and Completion of the Synthesis**

K. C. Nicolaou,* David Gray, and Jinsung Tae

In the preceding communication,^[1] we detailed the development of a suitable methodology for the expedient construction of the benzannulated carbocyclic frameworks of members of the hamigeran class of natural products^[2] (e.g. **1**–**4**, Scheme 1) as immediate synthetic targets. Based on the



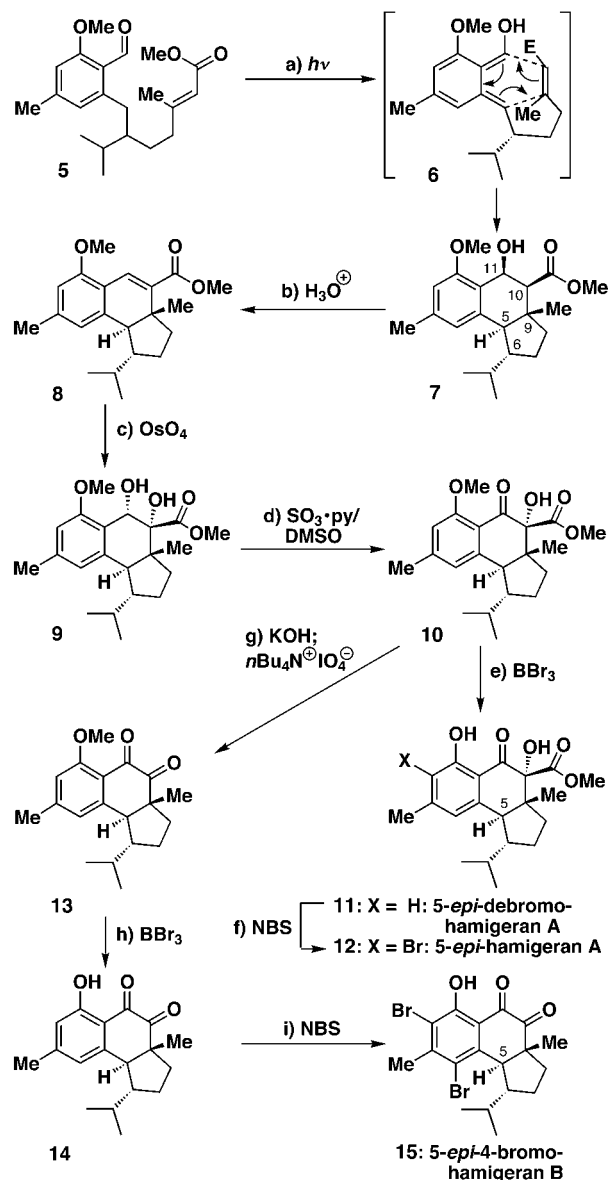
Scheme 1. Molecular structures of the hamigerans **1**–**4** and retrosynthetic analysis through photo-enolization and intramolecular trapping of reactive hydroxy-*o*-quinodimethane species **I**.

photo-induced generation and trapping of hydroxy-*o*-quinodimethanes **I**, this synthetic technology was the centerpiece of our synthetic strategy towards these biologically active compounds as shown retrosynthetically in Scheme 1. In the same article^[1] we also reported the construction of two appropriately functionalized benzaldehydes (e.g. **II**, Scheme 1), which are needed as potential precursors for the total synthesis of the hamigerans. Herein we describe the implementation of this strategy and the completion of the total synthesis of hamigerans A and B (**1**–**4**) and several of their epimers.

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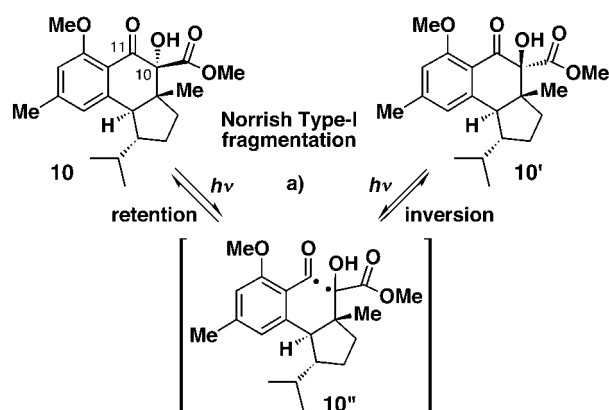
[**] This work was financially supported by the National Institutes of Health (USA) and The Skaggs Institute for Chemical Biology, and grants from Abbott, Amgen, ArrayBiopharma, Boehringer-Ingelheim, Glaxo, Hoffmann-La Roche, DuPont, Merck, Pfizer, and Schering Plough.

A thorny problem in reaching the hamigeran structure was expected to be the establishment of the relative stereochemistry at the four contiguous stereocenters situated at C5, C6, C9, and C10. At the outset, the most direct approach to solve this problem appeared to be the one initiated from benzaldehyde **5** (Scheme 2). Pleasantly, and as predicted from molecular models, when benzaldehyde **5** was irradiated in deoxygenated benzene solution (450-W Hanovia lamp, pyrex filter) the tricyclic system **7** was obtained in 91 % yield, presumably via the transient species **6** (E = COOMe). The relative



Scheme 2. Synthesis of the 5-*epi*-hamigeran series (**11**, **12**, and **15**). Reagents and conditions: a) benzene, $h\nu$ (450-W Hanovia lamp, pyrex filter), 25 °C, 20 min, 91 %; b) 1 % HCl in MeOH, 60 °C, 30 min, 90 %; c) OsO₄ (0.08 equiv), NMO (2.0 equiv), py (2.0 equiv), THF/*t*BuOH/H₂O (10:10:1), 25 °C, 12 h, 93 % (ca. 12:1 mixture of two isomers); d) SO₃·py (3.0 equiv), Et₃N (6.0 equiv), DMSO/CH₂Cl₂ (1:1), 0 °C, 2 h, 88 %; e) BBr₃ (10.0 equiv), CH₂Cl₂, –78 °C, 3 h, 95 %; f) NBS (1.05 equiv), *i*Pr₂NH (0.1 equiv), CH₂Cl₂, 0 °C, 3 h, 95 %; g) KOH, MeOH, 70 °C, 2 h; then *n*Bu₄NIO₄ (2.0 equiv), dioxane, 100 °C, 1 h, 65 %; h) BBr₃ (10.0 equiv), CH₂Cl₂, –78 °C, 3 h, 95 %; i) NBS (2.5 equiv), DMF, 0 °C, 3 h, 95 %. NMO = 4-methylmorpholine *N*-oxide, py = pyridine, NBS = *N*-bromosuccinimide.

configuration of the substituents on the periphery of the newly formed framework is apparently fully controlled by the single C6 stereocenter of the starting substrate **5**. All the stereocenters in **7** were formed with single stereochemistries, except for the one at C10, which was generated as a mixture of isomers (ca. 3:1 ratio), a consequence of the *E*:*Z* mixture (ca. 3:1) in the starting material **5**. The *trans* relationship between the C6 isopropyl group and the C9 methyl moiety in **7** was particularly crucial for the eventual success, as these were the two permanently set centers. In contrast, the wrongly formed stereochemistry at C5 could, in principle, be corrected by epimerization. As seen from the next step (**7**→**8**, HCl/MeOH, 90% yield) the stereochemistry at C10 and C11 was at this stage inconsequential, since it is removed at least temporarily. This elimination step also converged the two C10 epimers obtained in the cyclization reaction. Dihydroxylation of unsaturated ester **8** with NMO/OsO₄ (for abbreviations of reagents and protecting groups, see legends in schemes) in the presence of pyridine resulted in the formation of the α -dihydroxy compound **9** contaminated with small amounts of its isomer in which dihydroxylation occurred from the β -face (ca. 12:1 ratio, 93% total yield). The benzylic alcohol in **9** was then oxidized with SO₃·py/DMSO to give hydroxy ketoester **10** in 88% yield. Demethylation of **10** proceeded smoothly upon exposure to BBr₃ at –78 °C to afford 5-*epi*-debromohamigeran A (**11**) in 95% yield. Attempts to epimerize **11** or any of its precursors **7**–**10** under a variety of conditions failed. Of particular note was the effect of UV irradiation on a benzene solution of hydroxy ketoester **10**: upon irradiation with a UV Hanovia lamp, **10** was converted into an equilibrium mixture of C10 epimers (**10**/**10'** ≈ 1:3; see Scheme 3). A likely mechanism for this equilibration is a



Scheme 3. Photo-induced epimerization of hydroxy ketoester **10** at C10 by means of Norrish Type-I fragmentation–recombination. a) 450-W Hanovia lamp, pyrex filter, benzene, ambient temperature, 20 min, 93%, equilibrium mixture of C10 epimers (**10**/**10'** ≈ 1:3).

Norrish Type-I homolysis^[3, 4] of the C10–C11 bond to form the diradical species **10''**, which then closes with retention of stereochemistry to form **10** again, or with inversion of stereochemistry to form its epimer **10'** (Scheme 3).

With enough quantities of precursor **10** in hand and with future chemical biology studies in mind, we decided to establish procedures for reaching further hamigeran ana-

logues, albeit epimeric at C5. Thus, selective monobromination^[5] *ortho* to the phenolic group of **11** (Scheme 2) was smoothly effected by the action of NBS and catalytic amounts of *i*Pr₂NH in CH₂Cl₂ at 0 °C, to furnish 5-*epi*-hamigeran A (**12**) in 95% yield. It was also found that basic hydrolysis of ester **10** (KOH/MeOH), followed by oxidative 1,2-cleavage promoted by *n*Bu₄NIO₄ in dioxane^[6] offers a practical entry into the hamigeran B series. Thus, diketone **13** was obtained from **10** in 65% overall yield and was subsequently demethylated (BBr₃, –78 °C, 95% yield) to afford phenolic diketone **14**. Aromatic bromination of **14** (NBS, DMF) provided 5-*epi*-4-bromohamigeran B (**15**) in 95% yield (for selected data, see Table 1).

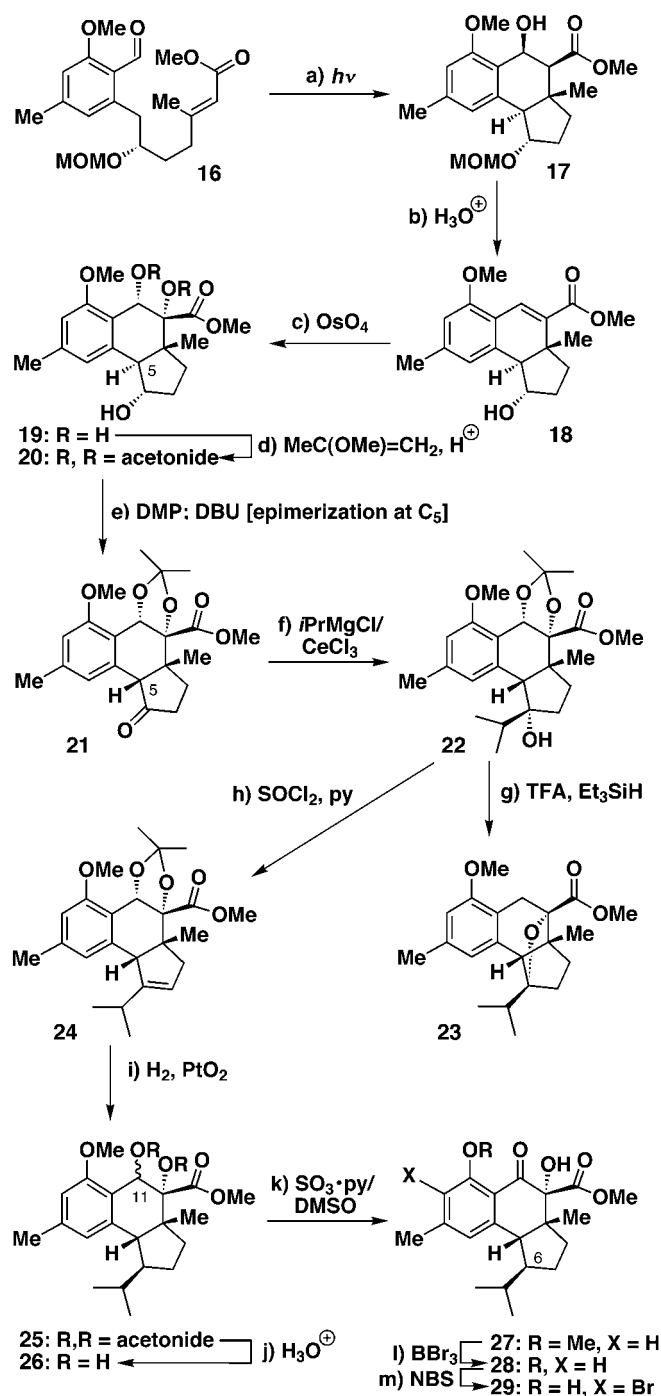
Table 1. Selected data for compounds **15** and **34**.

15: colorless syrup; R_f = 0.5 (silica gel, hexane/EtOAc 4:1); IR (film): $\tilde{\nu}_{\max}$ = 2959, 1734, 1633, 1455, 1376, 1194 cm^{–1}; ¹H NMR (CDCl₃, 500 MHz): δ = 13.1 (s, 1H), 3.29 (d, J = 10.8 Hz, 1H), 2.78 (s, 3H), 2.25 (m, 1H), 1.99 (m, 1H), 1.95–1.85 (m, 2H), 1.67–1.60 (m, 2H), 1.13 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ = 196.9, 185.5, 160.8, 150.8, 141.2, 119.0, 114.3, 114.0, 57.9, 52.6, 41.1, 31.7, 29.8, 27.2, 22.1, 21.1, 19.2, 14.5; HR-MS (MALDI): calcd for C₁₈H₂₀BrO₃ [M +Na⁺]: 464.9671; found: 464.9659

34: colorless solid; R_f = 0.5 (silica gel, hexane/EtOAc 1:1); [α]_D²⁰ = +38.8 (c = 0.100, CHCl₃); IR (film): $\tilde{\nu}_{\max}$ = 3437, 2857, 1738, 1692, 1604, 1460, 1222, 1083, 1026 cm^{–1}; ¹H NMR (CDCl₃, 400 MHz): δ = 6.72 (s, 1H), 6.61 (s, 1H), 4.80 (s, 1H), 3.86 (s, 3H), 3.54 (d, J = 5.9 Hz, 1H), 3.50 (s, 3H), 2.37 (s, 3H), 1.95 (m, 1H), 1.70 (dd, J = 14.8, 8.9 Hz, 1H), 1.58–1.41 (m, 2H), 1.39 (s, 3H), 1.37–1.22 (m, 2H), 1.16 (d, J = 6.2 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 192.1, 169.9, 158.6, 146.1, 145.7, 122.4, 117.3, 109.7, 84.1, 55.9, 53.1, 52.4, 51.3, 46.7, 34.3, 26.9, 26.8, 24.6, 23.5, 22.6, 21.7; HR-MS (MALDI): calcd for C₂₁H₂₈O₅ [M +Na⁺]: 383.1829; found: 383.1817.

Our next attempt at the total synthesis of the hamigerans involved the use of a second benzaldehyde (**16**, Scheme 4), which incorporated an oxygen functionality at C6 in the hope that this additional handle might provide the necessary activation for the obligatory epimerization at C5. Furthermore, since this aldehyde was obtained by asymmetric synthesis, as described in the preceding paper,^[1] this new strategy was expected to provide an enantioselective route to the targeted compounds. Thus, photo-irradiation of **16** (*E*/*Z* ≈ 3:1, inconsequential) under the standard conditions already described for **5** led to the tricyclic hydroxy ester **17** in 92% yield and as a mixture of C10 epimers (ca. 3:1, major product shown, inconsequential). The heating of **17** in methanolic HCl at 60 °C affected both the dehydration and MOM cleavage, leading to hydroxy unsaturated ester **18** in 91% yield. This sequence allowed the multigram synthesis of intermediate **18** with >99% enantiomeric purity as determined by chiral HPLC. The olefin **18** was then stereoselectively dihydroxylated by following the already established protocol (see above) to yield triol **19** as the major product in 91% yield (ca. 12:1 ratio of two separable isomers).

Selective protection of the vicinal hydroxy groups in **19** with 2-methoxypropene and catalytic amounts of PPTS followed by Dess–Martin oxidation of the remaining hydroxy group gave the corresponding ketone acetone **21**. With the

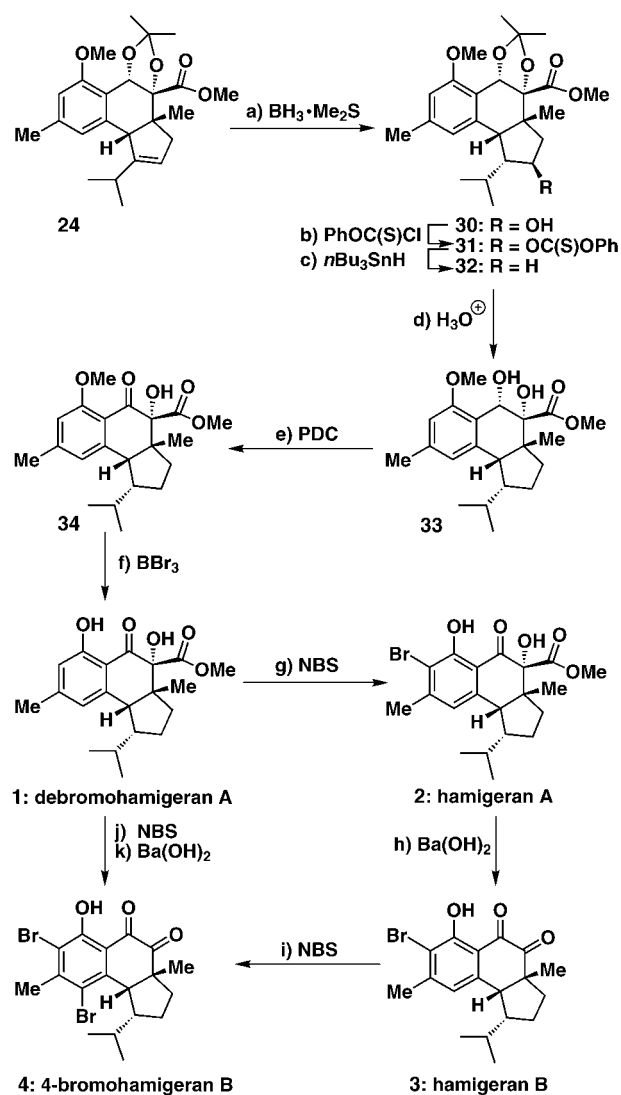


Scheme 4. Synthesis of the 6-*epi*-hamigeran series (**28** and **29**). Reagents and conditions: a) benzene, $h\nu$ (450-W Hanovia lamp, pyrex filter), 25 °C, 20 min, 92%; b) 1% HCl in MeOH, 60 °C, 30 min, 91%; c) OsO₄ (0.08 equiv), NMO (2.0 equiv), py (2.0 equiv), THF/*t*BuOH/H₂O (10:10:1), 25 °C, 12 h, 91% (ca. 12:1 mixture of isomers); d) 2-methoxypropene, PPTS (0.5 equiv), CH₂Cl₂, 0 °C, 30 min, 93%; e) DMP (2.0 equiv), CH₂Cl₂, 0 °C, 1 h; then DBU (0.3 equiv), CH₂Cl₂, 0 °C, 10 min, 92%; f) *i*PrMgCl (2.0 equiv), CeCl₃ (2.0 equiv), –78–0 °C, 1 h, 95%; g) TFA (20 equiv), Et₃SiH (50 equiv), CH₂Cl₂, 25 °C, 1 h, 65%; h) SOCl₂ (8.0 equiv), py, CH₂Cl₂, –60 °C, 15 min, 94% (10:2:1 mixture of three isomers); i) PtO₂ (0.2 equiv), H₂ (3 atm), EtOH, 25 °C, 2 h, 94% (ca. 3:1 mixture of C₆ epimers); j) HCl (3N)/THF (1:1), 80 °C, 4 h, 70% (ca. 1.3:1 mixture of C₁₁ epimers); k) SO₃·py (3.0 equiv), Et₃N (6.0 equiv), DMSO/CH₂Cl₂ (1:1), 0 °C, 2 h, 82%; l) BBr₃ (10.0 equiv), CH₂Cl₂, –78 °C, 3 h, 95%; m) NBS (1.05 equiv), *i*Pr₂NH (0.1 equiv), CH₂Cl₂, 0 °C, 3 h, 95%. PPTS = pyridinium *p*-toluenesulfonate, DMP = Dess–Martin periodinane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFA = trifluoroacetic acid.

neighboring carbonyl group in place, base-induced isomerization at C5 proved extremely facile, requiring only a ten-minute exposure to DBU at 0 °C to afford the desired product **21** with the *cis* 5,6 junction (86% yield over three steps). The carbonyl group also served its second purpose as an electrophile well, allowing the cerium-mediated introduction of the required isopropyl group (**21**→**22**), and thus marking our arrival at intermediate **22** (exclusive attack from the *exo* face, 95% yield). An attempt to reductively remove the tertiary alcohol group from **22** by treatment with TFA/Et₃SiH led, remarkably, to the polycyclic ether **23** (65% yield), presumably formed by trapping the incipient tertiary carbonium ion with the proximal C10 oxygen atom, and reductive cleavage of the benzylic C–O bond.

Having experienced similar side reactions under various other conditions, we opted to proceed through olefin **24**, which was readily obtained from alcohol **22** by the action of SOCl₂/py (–60 °C, 94% yield) as an inseparable mixture with its conjugated (**24'**) and exocyclic (**24''**) double bond isomers (not shown, ≈10:2:1 ratio). However, the intended reduction of this olefin to furnish the correct stereochemistry of the hamigerans at C6 as expected from an *exo* face attack (compare addition of isopropyl group to the carbonyl function, step **21**→**22**) proved elusive. In various reduction experiments, the suspected incorrect C6 stereoisomer **25** was contaminated by unreactive tetrasubstituted olefinic isomers **24'** and **24''**, thus plaguing this approach with further complications. Therefore, it was decided to change course. But before that, and as in the previous case (C5-*epi* compounds), we moved to complete the synthesis of the new series of hamigeran analogues attainable from **24**. Thus, acid-induced hydrolysis of the acetonide group from the reduction product **25** with HCl (3N)/THF (1:1) at 80 °C led to diol **26** (mixture of C₁₁ epimers, ca. 1.3:1 ratio), whose chromatographic purification and spectroscopic characterization now became possible. The mixture of benzylic alcohols **26** was then oxidized with SO₃·py/DMSO to afford hydroxy ketoester **27** in 82% yield and as a single stereoisomer. Demethylation of **27** (BBr₃, –78 °C, 95% yield) led to phenol **28**, whose proton NMR spectroscopic analysis (NOE) confirmed that, indeed, the isopropyl group had the incorrect stereochemistry (C6) and that compound **28** was 6-*epi*-debromohamigeran A. This compound was smoothly converted into 6-*epi*-hamigeran A (**29**) by exposure to stoichiometric amounts of NBS in the presence of *i*Pr₂NH (95% yield).

In the face of this new failure to establish the correct C6 stereochemistry, we began to search for a new branching sequence from one of our readily available intermediates. Such a path was finally found starting with olefin **24** as shown in Scheme 5. The crucial observation for this sequence was made when olefin **24** was hydroborated with BH₃·Me₂S under sonication conditions to give, upon oxidative workup, the desired 6*R*,7*R* alcohol isomer **30** as the major product (*exo* addition, 44% yield) together with its α -stereoisomer (*endo* addition, 24% yield). The chromatographically separated isomer **30** was then sequentially converted (PhOC(S)Cl/py) into the phenylthionocarbonate (**31**, 85% yield) and then into the deoxygenated product **32** by heating with *n*Bu₃SnH/AIBN

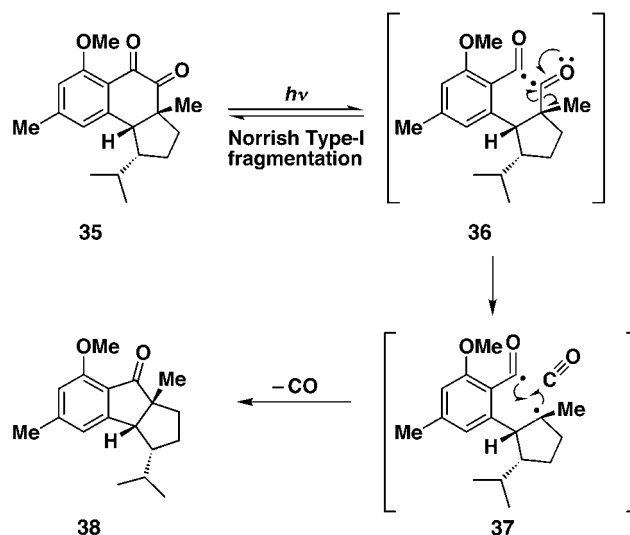


Scheme 5. Total synthesis of hamigerans A (**1,2**) and B (**3,4**). Reagents and conditions: a) $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (40 equiv), THF, sonication, 40°C , 8 h, 68% (ca. 1.8:1 mixture of two isomers); b) PhOC(S)Cl (2.0 equiv), py, 25°C , 2 h, 85%; c) $n\text{Bu}_3\text{SnH}$ (8.0 equiv), AIBN (0.2 equiv), benzene, reflux, 1.5 h, 75%; d) HCl (1N), THF/ H_2O (1:1), 80°C , 1 h, 88%; e) PDC (2.5 equiv), 4 Å molecular sieves, CH_2Cl_2 , 25°C , 3 h, 83%; f) BBr_3 (10.0 equiv), CH_2Cl_2 , -78°C , 3 h, 95%; g) NBS (1.05 equiv), $i\text{Pr}_2\text{NH}$ (0.1 equiv), CH_2Cl_2 , 0°C , 3 h, 95%; h) Ba(OH)_2 (15 equiv), $\text{MeOH}/\text{H}_2\text{O}$ (2:1), air, 25°C , 2 h, 82%; i) NBS (1.5 equiv), DMF, 25°C , 1 h, 95%; j) NBS (3.0 equiv), DMF, 25°C , 1 h, 95%; k) same procedure as step h above, 65%. AIBN = azobisisobutyronitrile, PDC = pyridinium dichromate.

(benzene, reflux, 75% yield). Formation of intermediate **32** paved the way for the completion of the synthesis of all four targeted natural products. Thus, the acetonide protecting group was removed from **32** by heating at 80°C with HCl (1N) in THF (1:1) to afford diol **33** in 88% yield. Although the standard $\text{SO}_3 \cdot \text{py}/\text{DMSO}$ protocol for the oxidation of the benzylic position gave low yields, PDC succeeded admirably in converting **33** into **34** (83% yield; for selected data, see Table 1). The first natural product in this series, debromohamigeran A (**1**), was generated from **34** (95% yield) by the BBr_3 -induced cleavage protocol employed above for the *epi* series, whereas the second product, hamigeran A (**2**), was obtained from the NBS-mediated bromination (95% yield) of

debromohamigeran A (**1**). An expedient conversion of hamigeran A (**2**) into hamigeran B (**3**) was devised based on a cascade reaction initiated by Ba(OH)_2 in $\text{MeOH}/\text{H}_2\text{O}$ (2:1) under aerobic conditions involving: a) saponification; b) decarboxylation; and c) auto-oxidation (82% overall yield). Finally, 4-bromohamigeran B (**4**) was generated from hamigeran B (**3**) by NBS-facilitated introduction of the second bromine atom (95% yield). 4-Bromohamigeran B (**4**) could also be obtained from **1** by dibromination (NBS, DMF) followed by treatment with Ba(OH)_2 (65% overall yield). The spectroscopic data for all four synthetic hamigerans **1–4** matched those reported for the naturally derived compounds.^[2]

An interesting observation made during this study is worth mentioning, particularly since it considerably expands the scope of the developed hydroxy-*o*-quinodimethane based technology. Thus, in our attempts to convert compound **34** (Scheme 5) into the C10,C11-diketone system **35** (Scheme 6) by the two-step protocol used in the conversion of **10** → **13** (Scheme 2; a) KOH ; b) $n\text{Bu}_4\text{NIO}_4$), we observed considerable amounts of a by-product whose structure was determined to be **38** (Scheme 6). It was subsequently confirmed that this ring contraction process could be accelerated by UV irradiation, thus becoming a synthetically useful reaction under these conditions (**35** → **38**, 90% yield, Scheme 6). Presumably the



Scheme 6. Proposed mechanism for the photo-induced decomposition of **35** to form **38**.

Norrish Type-I mechanism shown in Scheme 6 operates in this transformation. The potential of this ring contraction process in organic synthesis is under further investigation.

The chemistry described herein and in the preceding communication^[1] demonstrates the power of the inter- and intramolecular trapping of photochemically generated hydroxy-*o*-quinodimethanes in complex molecule construction. Furthermore, the reported expedient and efficient total syntheses of the hamigerans and their analogues are expected to facilitate chemical biology investigations of these scarce,^[7] and therefore, little-studied marine natural products.

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The Influence of Excess Ammonia on the Mechanism of the Reaction of Boron Trichloride with Ammonia—An Ab Initio Molecular Dynamics Study**

Silke Reinhardt, Christel M. Marian,* and Irmgard Frank

The reaction of boron trichloride with ammonia is well known. Already in 1921, BN was produced by ammonolysis of boron trichloride in liquid ammonia and subsequent heating of the primary products.^[1] Today, the reaction of BCl₃ with NH₃ is used for the preparation of hexagonal and amor-

phous boron nitride by means of chemical vapor deposition (CVD).^[2]

To shine light on the processes during the CVD of BN, Reinhardt et al. recently investigated the energetic course of the gas-phase reaction of BCl₃ with NH₃.^[3] They were able to show that the substitution of the first chlorine atom of BCl₃ in the gas phase is a two-step reaction (Figure 1): the formation of an NH₃·BCl₃ adduct in the first step is followed by the elimination of hydrogen chloride to yield aminodichloroborane. The elimination requires the surmounting of a barrier of 25 kJ mol⁻¹ with respect to the reactants, or 151 kJ mol⁻¹ relative to the adduct. The second and third substitutions follow the same mechanism. The reaction barriers become lower with decreasing chlorine content, and the heats of reaction become smaller. As a result of its high-lying transition state, the first chlorine substitution is the rate-determining step, and the reaction that yields BN is expected to proceed only at elevated temperatures. However, the

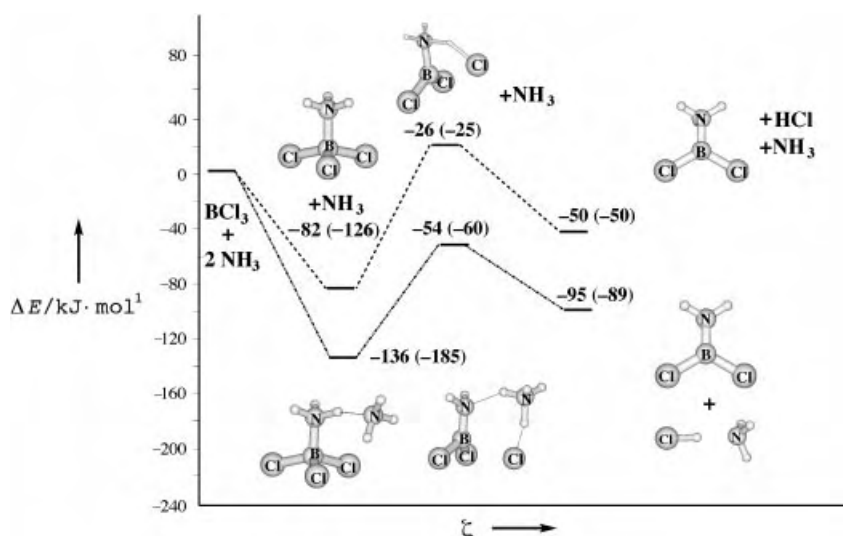


Figure 1. Energy course of the gas-phase reaction of boron trichloride with one ammonia molecule (top curve) and two ammonia molecules (bottom curve), determined at the BLYP level of theory (RI-MP2 values are given in parentheses). ζ = Reaction coordinate.

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ammonolysis of BCl₃ is known to occur spontaneously in the condensed phase even at low temperatures and to be very exothermic.^[1] It can therefore be concluded that additional NH₃ molecules strongly affect the energetic course and the mechanism of the reaction.

The aim of the work herein is to study the influence of additional ammonia molecules on the mechanism and on the energy profile of the first chlorine substitution by an amino group. According to the results of time-independent RI-MP2 calculations (see Calculation Methods), the barrier of the gas phase reaction is lowered in the presence of another NH₃ molecule owing to the formation of a six-centered transition state (Figure 1). However, with respect to the H₃N·BCl₃ adduct the barrier is still rather high (125 kJ mol⁻¹). Furthermore, the product side of the reaction is only slightly stabilized by a single NH₃ molecule. Because solvent molecules participate actively in the reaction, the influence of excess NH₃ cannot be simulated by means of a continuum

model. Instead, the breaking and formation of any of the covalent bonds in the system is modeled by means of a molecular dynamics method that allows a full quantum chemical treatment of solvent molecules. We have employed the Car–Parrinello molecular dynamics (CPMD) method, which uses periodic boundary conditions and represents a numerically very efficient first-principles molecular dynamics approach.^[4–6]

Our simulations point to a reaction mechanism that differs markedly from the two-step gas-phase mechanism. In excess NH_3 , the substitution of a chlorine anion in BCl_3 for an amino group proceeds in three steps (Figure 2): 1) formation of an $\text{H}_3\text{N} \cdot \text{BCl}_3$ adduct, 2) proton transfer to a solvent molecule to yield a salt-like intermediate, and 3) formation of the product

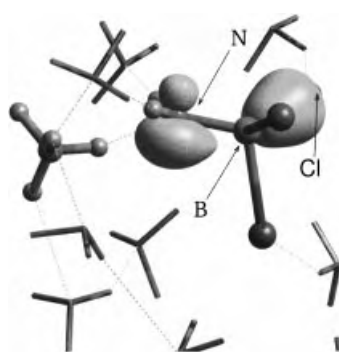


Figure 3. Wannier orbitals of the saltlike intermediate: The electron pair that formed the N–H bond remains at the N atom as a lone pair. The electron pair of the B–Cl bond is polarized towards the Cl atom and leaves the saltlike intermediate together with the Cl atom.

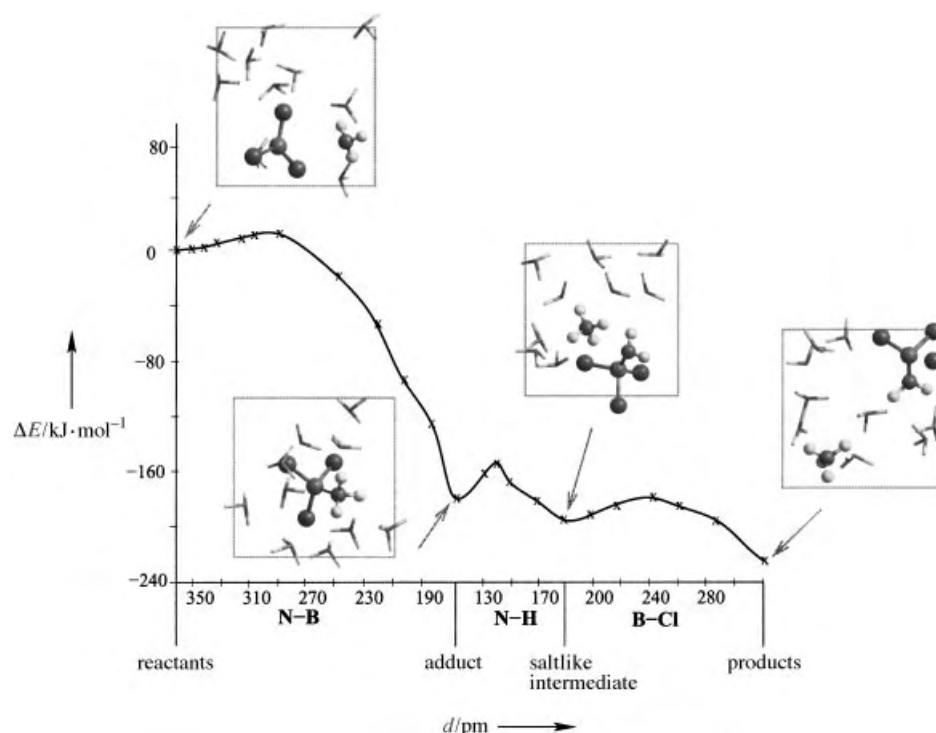


Figure 2. Mechanism and constrained minimum energy path of the reaction of one BCl_3 molecule with eleven NH_3 molecules. The reaction proceeds in three steps: 1) formation of an adduct complex ($\text{H}_3\text{N} \cdot \text{BCl}_3 + 10\text{NH}_3$); 2) elimination of a proton to yield a saltlike intermediate ($[\text{NH}_4^+][\text{BCl}_2\text{NH}_2^-] + 10\text{NH}_3$); 3) formation of the products ($\text{BCl}_2\text{NH}_2 + \text{NH}_4\text{Cl} + 10\text{NH}_3$) by abstraction of a chloride anion.

(BCl_2NH_2) by elimination of a chloride ion. The emerging ammonium chloride is solvated by other NH_3 molecules. The ionic character of the saltlike intermediate was confirmed by analysis of the localized orbitals (Wannier orbitals) (Figure 3): The electron pair that originally connected the N and H atoms has become a lone pair on the nitrogen atom, and H^+ was transferred to an NH_3 molecule. Likewise, the B–Cl bond was cleaved heterolytically to yield a solvated Cl^- ion.

To analyze the energy profile of this reaction, two possibilities are at hand: a) analysis of the reaction times during the simulation or b) extraction of the minimum energy path along the trajectory (reaction coordinate). The first approach yields information about the free-energy barrier that has to be overcome in a real sample, whereas the

minimum energy path can be compared to the results of the static calculations.

We performed CPMD calculations at seven temperatures between 200 and 700 K for three different starting geometries. The reaction mechanism remains the same in all cases. At 200 K the reaction is complete within 10.1 ps, and at 300 K within 8.1 ps. At temperatures of 400 K and above, the total reaction always proceeds in less than 4.4 ps. Although the statistics is not sufficient to produce a meaningful value for the free energy of the reaction, it is clear that the barrier for such an extremely fast reaction (picosecond range) has to be very small.

To compare with previously obtained results in static calculations we have determined a constrained minimum energy path (CMEP) in three steps: 1) stepwise approach of one NH_3 molecule towards the BCl_3 molecule to form the adduct, 2) successive increase of the N–H distance, and 3) stepwise elonga-

tion of the Cl–B bond. The reaction profile is shown in Figure 2. The overall reaction releases 219 kJ mol^{-1} , which is 169 kJ mol^{-1} more than the corresponding gas-phase reaction.^[3] The energy released by the crystallization of NH_4Cl has not been taken into account. The obtained energy values should not be overinterpreted: first, the entropy contribution that is important in solution is neglected in such a calculation, and second, the specification of an internal coordinate as reaction coordinate does not necessarily lead to the optimal pathway. Every single step of the BCl_3 amination is exothermic in excess NH_3 . Contrary to the gas-phase reaction, the adduct formation proceeds via a transition state. It can be assumed that this small barrier is a result of the release of the attacking NH_3 from the ammonia network. Furthermore, the

proton transfer and the chlorine abstraction require the surmounting of small barriers. A comparison of the energy profiles shown in Figures 1 and 2 makes it clear that the three-step mechanism offers a much faster pathway.

To our knowledge, this alternative reaction mechanism has not been discussed before. However, the single steps can easily be interpreted: the Lewis adduct $\text{H}_3\text{N} \cdot \text{BCl}_3$, which contains a fourfold coordinated nitrogen atom, is a Brønsted acid in liquid NH_3 . It loses a proton, which immediately forms an ammonium ion with one of the solvent molecules. The resulting anion is unstable and eliminates a chloride anion to form the neutral and stable BCl_2NH_2 .

Calculation Methods

For all static calculations, a valence-triple-zeta basis set with a polarization function (TZVP) was used. The corresponding auxiliary basis sets were used for the resolution of identity (RI) approximation of the two-electron integrals.^[7–9] The structures and energies were determined by RI-approximated second-order Møller–Plesset perturbation theory (RI-MP2)^[10] by employing the TURBOMOLE 5.1^[11, 12] and ef.x^[13] programs. All simulations were performed by using the Car–Parrinello Molecular Dynamics code, Version 3.0h.^[14] For these calculations, we employed the Becke(88) exchange and Lee–Yang–Parr correlation functionals (BLYP),^[15, 16] The reliability of various nonhybrid density functionals (SVWN, BLYP, HCTH, PBE) was tested by comparing the relative energies of stationary points on the potential energy hypersurface of the gas-phase reaction with results from previous RI-MP2 calculations.^[3] BLYP showed the best performance of these functionals: the relative energies of the transition state and the products with respect to the reactants agree very well ($\pm 1 \text{ kJ mol}^{-1}$). On the other hand, the adduct formation energy is underestimated by 44 kJ mol^{-1} . An error of this size is typical for the description of dative bonds with DFT methods and cannot easily be remedied.^[17] The valence electrons were described with a plane-wave basis set with an energy cutoff of 60 Ry ($\approx 131 \times 10^{-18} \text{ J}$). An extension of the energy cutoff to 70 Ry ($\approx 153 \times 10^{-18} \text{ J}$) has no significant effect on structure and energy. Troullier–Martins pseudopotentials were employed for the representation of the inner electrons.^[18] The simulations at the microcanonical ($\{N, V, E\}$) ensemble were performed with time steps of 4 a.u. (0.0968 fs) and a fictitious electron mass of 400 a.u. ($3.64 \times 10^{-28} \text{ kg}$). One BCl_3 and eleven NH_3 molecules were placed in a cubic box ($(7.94 \text{ Å})^3$). This corresponds to a density of $\approx 1 \text{ g cm}^{-3}$, comparable to the density of liquid BCl_3 at 286 K (1.4 g cm^{-3}) and the density of liquid ammonia at 240 K (0.7 g cm^{-3}). The energies of the arbitrarily chosen starting geometries were optimized ($T = 0 \text{ K}$), that is, they constitute local minima on the potential hypersurface. The initial momenta of the ions were chosen according to a Maxwell–Boltzmann distribution. The delocalized molecular orbitals were transformed into localized Wannier functions to investigate the spatial localization of the electrons.^[19, 20]

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DNA-Directed Functionalization of Colloidal Gold with Proteins**

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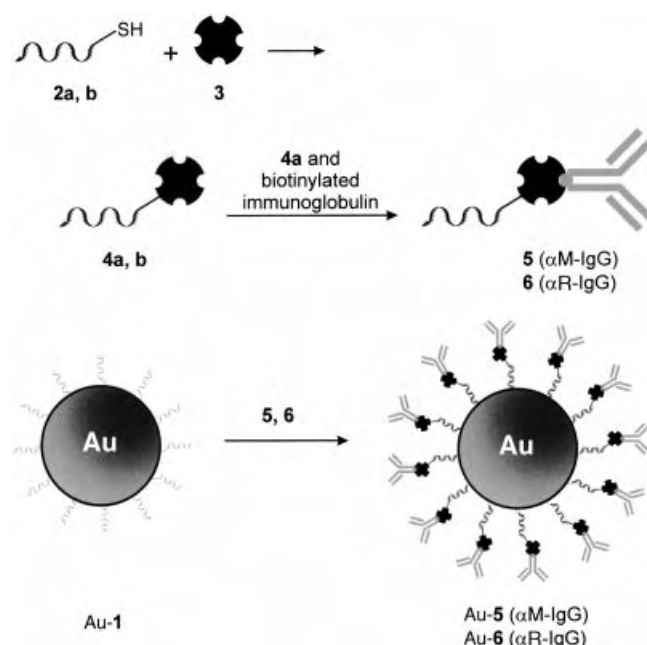
The utilization of nucleic acids and proteins as building blocks in the “bottom-up” self-assembly of nanoscale functional devices is of great current interest.^[1] As an example, DNA has been applied to fabricate nanostructured molecular scaffolding and surface architectures,^[2] and to selectively position proteins^[3] and nanoclusters^[4] on the nanometer scale. In earlier work, we reported the DNA-directed immobilization of proteins,^[5, 6] which concerned the binding of single-stranded DNA-tagged immunoglobulins (IgG) or enzymes to surface-immobilized complementary capture oligonucleotides by means of the highly specific Watson–Crick base pairing. This method not only allows a surprisingly efficient and fully reversible adsorption of the proteins, but also it enables the simultaneous immobilization of many different DNA-tagged components in a single, site-selective process using a DNA microarray as a capture matrix. We here report on the DNA-directed immobilization of proteins at colloidal gold, as well as on applications of the resulting biofunctionalized nanoparticles in immunological detection methods.

To allow the modular functionalization of gold nanoparticles (Au-1) modified with oligonucleotide **1** (see Experimental Section), we chose the covalent DNA–streptavidin (STV) conjugate **4** as a molecular linker. **4** was obtained from the biotin-binding protein STV **3** and 5'-thiol-modified oligonucleotides **2**, using the heterobispecific amino/thiol-reactive

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cross-linker sulfosuccinimidyl-4-(maleimidomethyl)cyclohexane-1-carboxylate (sSMCC).^[5] The oligonucleotide moiety in **4** expands the tetravalent binding capacity of the native STV for biotin by one highly specific binding site for complementary nucleic acids. Thus, **4a** can be used as a biomolecular adapter in the coupling of biotinylated antibodies with Au-**1**, which is modified with the complementary oligonucleotide (Scheme 1).



Scheme 1. DNA-directed immobilization of proteins at gold colloids using the covalent DNA-STV conjugates **4**, obtained from STV **3** and 5'-thiol-modified oligonucleotides **2a, b**. The oligonucleotide **2a** is complementary to the gold colloid bound oligomer **1**. The coupling of **4a** with biotinylated antibodies directed against mouse IgG (αM-IgG) or rabbit IgG (αR-IgG) leads to the DNA-tagged antibody conjugates **5** and **6**, respectively, which bind to Au-**1** by specific nucleic acid hybridization. Complementary DNA strands are drawn as helices. The 3'-ends are indicated by arrow heads.

To experimentally test our concept, we carried out gel electrophoretic measurements (Figure 1) using oligonucleotide **1** covered colloidal gold particles of a mean diameter of 34 nm (Au₃₄-**1**), which were incubated with 100 molar equivalents of the complementary DNA-STV hybrid **4a** at room temperature for 60 min. The comparison of the electrophoretic mobility of Au₃₄-**1** and STV-coated Au₃₄-**4** clearly indicated the coupling of the proteins at the gold particles (lanes 1 and 2, in Figure 1). The specificity of the protein coupling was demonstrated in lane 3, by using a control in which the noncomplementary DNA-STV hybrid **4b** was mixed with Au₃₄-**1**. To immobilize antibodies at the surface of the gold nanoparticles, STV conjugate **4a** was initially coupled with one molar equivalent of an antibody against the mouse IgG antigen (αM-IgG), and without any further purification, the resulting conjugate **5** was incubated with 1 mol% of Au₃₄-**1** at room temperature for 60 min. The electrophoretic mobility of anti-mouse IgG functionalized Au₃₄-**5** was less than that of the STV-modified Au₃₄-**4** (lanes 4

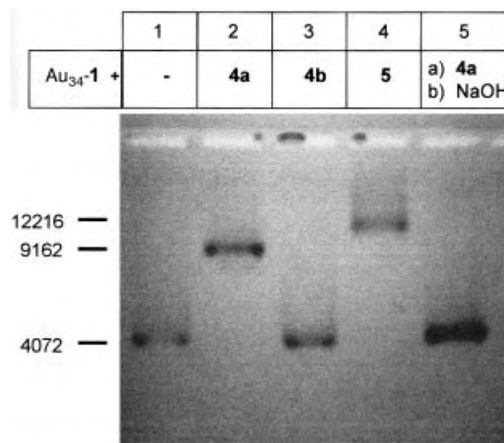
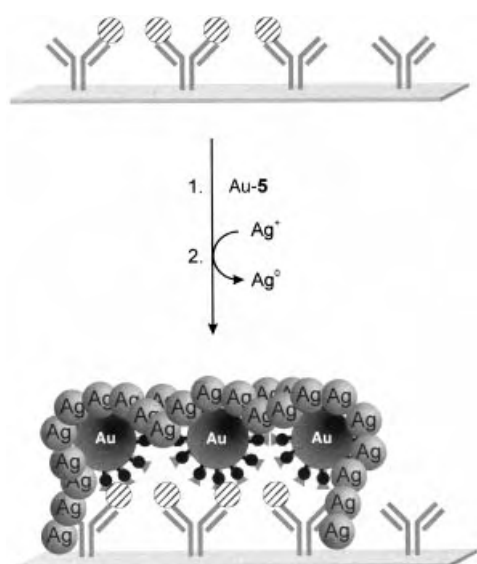


Figure 1. Electrophoretic analysis of the DNA-directed immobilization of proteins at gold nanoparticles. Shown is a grayscale representation of a nondenaturing 1.5% agarose gel (the bands are in fact reddish-purple because of the characteristic absorption of the colloidal gold). The bands indicate the mobility of Au₃₄-**1** (lane 1), Au₃₄-**1** coupled with the complementary DNA-STV hybrid **4a** (lane 2), Au₃₄-**1** mixed with the non-complementary DNA-STV hybrid **4b** (lane 3), Au₃₄-**1** coupled with the complementary antibody conjugate **5** (lane 4), and Au₃₄-**1**, which was initially coupled with the complementary DNA-STV hybrid **4a** and subsequently treated with NaOH to remove the bound proteins (lane 5). The mobility of the DNA fragments of a DNA molecular-weight marker is given in base pairs.

and 2, in Figure 1), which indicates the successful binding of the DNA-tagged antibodies at the gold nanoparticles. Moreover, comparison of the lanes 1, 2, and 5 in Figure 1 indicates that the DNA-bound proteins can be removed from the particles by washing with NaOH and collection of the remaining Au₃₄-**1** by centrifugation. This reversibility of the protein adsorption not only illustrates the remarkable stability of DNA-coated gold nanoparticles, but it can also be utilized for their regeneration on the preparative scale.

The functionality of the antibody-modified nanoparticles **5** was evaluated in a sandwich immunoassay, in which various amounts of the model antigen mouse IgG were specifically immunosorbed through surface-immobilized capture antibodies (Scheme 2). The subsequent coupling Au₃₄-**5** to the antigen led after a short incubation period, to the formation of a characteristic reddish color at the surface, because of the immobilization of the colloidal gold. A silver development was carried out for signal amplification. The chemical reduction of silver ions, which is promoted by gold colloids, is a standard technique in histochemical analyses,^[7] and it has recently been applied in the scanometric detection of nucleic acid hybridization,^[8] as well as in the electrical detection of immuno reactions.^[9] Here, the development of the silver layer was followed by spectrophotometry using a microplate reader, or else by imaging with a flatbed scanner (Figure 2). The signal intensities obtained depended on the amount of antigen present, which indicates that anti-mouse IgG functionalized Au₃₄-**5** allowed the specific detection of the complementary mouse antigen. Controls were carried out using anti-rabbit IgG functionalized Au₃₄-**6**, or else a mixture consisting of Au₃₄-**1** and anti-mouse IgG coupled with the noncomplementary STV conjugate **4b** instead of Au₃₄-**5**. No significant silver development was observed in these controls. The measure-



Scheme 2. Utilization of antibody/DNA-functionalized gold colloids as reagents in a sandwich immunoassay. The model antigen mouse IgG, (striped circles), is bound by surface-attached capture antibodies through specific immunosorption, and the antigen is labeled with anti-mouse functionalized Au-5. For signal generation, a silver development is carried out. The generation of silver is monitored spectrophotometrically or by imaging with a camera or a flatbed scanner.

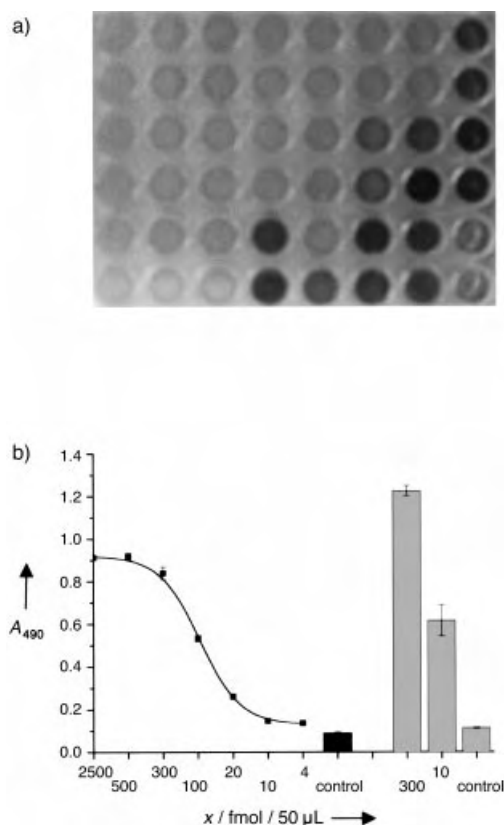


Figure 2. Utilization of the antibody functionalized nanoparticles Au₃₄-5 and Au₁₃-5 as reagents in a sandwich-immunoassay (see Scheme 2). a) Wells of a microplate with silver films developed to a varying extent; b) the absorbance at 490 nm of the silver film depended on the amount x of antigen present in the samples. The data points in the left side of the diagram were obtained for Au₃₄-5, the gray histograms represent signals obtained with Au₁₃-5. The controls were carried out with pure silver-development solution, applied in the absence of other reagents.

ment of a serial dilution indicated that less than 10 fmol of the antigen were detectable. Thus, the detection limit of this assay is similar to that of conventional enzyme-amplified immunoassays.^[10]

Further experiments concerned the influences of the coupling ratio of Au₃₄-1 and DNA-tagged antibody conjugate 5. Maximum signal intensities were obtained at a relative stoichiometry of about 1:100 for Au₃₄-1:5, and a decrease in signal was obtained at the higher coupling ratio of 1:200. This is a result of the competition between Au₃₄-1-bound and unbound 5, and correlates with earlier studies, which indicate that the hybridization efficiency of colloidal gold surfaces is about 6 % of the total number of oligonucleotides attached.^[11] Experiments currently in progress suggest that the optimization of reagents and reaction parameters will further enhance the detection limit of the immunoassay. For instance, the use of smaller 13 nm gold colloids, functionalized with anti-mouse IgG through a DNA bridge (Au₁₃-5), already allowed us to enhance the signal intensities in the sandwich immunoassay (Figure 2). These experiments also clearly indicate that the modular construction approach described here is fully applicable to the functionalization of other colloidal particles.

Herein we reported the convenient and efficient DNA-directed adsorption of proteins at colloidal gold. The biofunctionalized Au nanoparticles not only reveal extraordinary stability and regeneration properties, but they also possess the undisturbed, specific recognition capabilities of the colloid-bound proteins. In an initial application, the biometallic hybrid components were used as reagents in an immunoassay for the detection of proteins. Owing to the gold-particle promoted silver development, low amounts of antigen were detectable. Moreover, because of the lack of diffusion, the development of a silver layer can be used for the site-specific detection of surface-bound antigens.^[12] Thus, the protein/DNA-modified gold colloids are particularly suited for the analysis of protein microarrays, which are increasingly applied in immunological diagnostics^[13] and proteom research.^[14] The biofunctionalized particles should also be suitable for surface-plasmon resonance detection.^[15] Moreover, since the specificity of nucleic acid hybridization allows the simultaneous functionalization of various different DNA-coated Au colloids, particle-bound combinatorial DNA-arrays^[16] might be transformed into corresponding protein arrays for parallel immunoassays. In addition to these bioanalytical applications, the approach described here has also implications for the development of nanostructured hybrid materials.^[17, 18]

Experimental Section

Covalent DNA-STV conjugates 4a,b were prepared from 5'-thiolated oligonucleotides (Interactiva, Ulm) and recombinant STV (IBA, Göttingen) in 10–15 % yields using the heterobispecific cross-linker sSMCC (Pierce).^[5] The nucleotide sequences of the STV-coupled oligomers were: 5'-Thiol-AGCGGATAACAATTTACACAGGA-3' (2a), 5'-Thiol-CCGGGTACCGAGCTCGAATTC-3' (2b), the sequence of the gold colloid bound oligomer 1 was: 5'-Thiol-TCCTGTGTGAAATTGT-TATCCGCT-3'. The preparation of the DNA-coated gold nanoparticles Au-1 was carried out as previously described using 15 nm and 40 nm colloids (ICN Biochemicals, Eschwege) with a diameter of 13.2 ± 0.6 (Au₁₃) or 34.2 ± 2.7 nm (Au₃₄),^[19] as determined by transmission electron microscopy.

To prepare the DNA–STV antibody conjugates **5**: a solution of **4a** (150 μL , 28 nm) in Tris–buffer (10 mM, pH 7.3), containing EDTA (1 mM), and 0.05 % Tween-20 (Tris–EDTA–Tween buffer solution, TETBS) were mixed with solution of biotinylated goat anti-mouse IgG (Sigma, Deisenhofen; 150 μL of a 28 nm) in TETBS, and the mixture was incubated for 10 min at room temperature (Tris = tris(hydroxymethyl)aminomethane, EDTA = ethylenediaminetetraacetic acid, Tween-20 = polyoxyethylenesorbitanmonolaurate). In a similar way, conjugate **6** was prepared from biotinylated goat anti-rabbit IgG (Sigma, Deisenhofen). To couple **5** or **6** with Au-**1**, 275 μL of the above solution were mixed with the same volume of a solution of Au₃₄-**1** (0.14 nm), or else, with the same volume of a solution of Au₁₃-**1** (1.16 nm), and the mixture was incubated for 1 h at room temperature.

To carry out the sandwich immunoassay, microplates were coated with a solution of goat anti-mouse IgG (Sigma, Deisenhofen; 50 μL , 20 nm), and subsequently blocked with milk powder to avoid nonspecific binding.^[20] 50 μL of a solution containing varying amounts of the model antigen mouse IgG were added to each well of the microplate, and subsequent to incubation for 45 min, the plate was washed to remove unbound reagents. Coupling of Au-**5** was achieved by adding a solution of Au₃₄-**5** (50 μL , 0.07 nm), or else, a solution of Au₁₃-**5** (50 μL , 0.58 nm), and incubation for 45 min. Subsequent to washing, 50 μL of a silver enhancement kit (BioRad)^[21] were added to the wells, and the development of silver was monitored spectrophotometrically at 490 nm or by imaging with a flatbed scanner.

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The Unusual Formation of Iron Silicide by Reaction of Iron with SiCl₄**

Michael Binnewies,* Arndt Meyer, and Mike Schütte

Dedicated to Professor Hans Georg von Schnering on the occasion of his 70th birthday

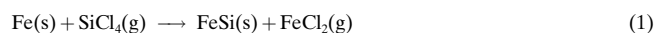
A wide variety of metallic compounds, especially borides, carbides, and silicides^[1] are attractive materials for technical applications due to their hardness and high melting points. As these compounds often are brittle, their preparation and shaping are particularly demanding tasks. Sintering processes require high temperatures and are thus energy- and time-consuming. Herein, we report on a fast chemical reaction of a metal with a nonmetallic compound, in which a metal silicide is generated that surprisingly retains the original shape of the metal. In this way, it is possible, in principle, to produce a material from a tractable, deformable metal, which possesses the shape of the metal employed.

During a chemical reaction of metals with nonmetals or nonmetallic compounds, the outer shape of the utilized metal is completely altered. Regardless of whether the metal is subjected to the reaction as a powder, sheet, or wire, its original shape is unrecognizable after the reaction and the product is formed as a powder. The aim of our experiments was to develop a method for the preparation of refractory alloys, borides, carbides, and silicides that allows these materials to be obtained in a homogeneous phase-pure form and in a short time. Generally, the synthesis of the above-mentioned species from the elements is very inefficient even at high temperatures because the diffusion coefficients are low; therefore, the reaction often leads to nonhomogeneous products. Our idea was to increase the mobility of both components of the synthesis, metal and nonmetal (B, C, Si), to produce a homogeneous metal–nonmetal compound in a

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short period. In this context, in preliminary experiments, which we carried out along the line of those reported in reference [2], we treated iron with silicon tetrachloride with the aim of obtaining FeSi as one of several other iron silicides^[3] according to Equation (1).



Both reactants are mobile in the above-mentioned solid/gas reaction, silicon as the gaseous starting material SiCl_4 and iron through evaporation as FeCl_2 (g). The reaction is highly endothermic ($\Delta H_{298}^\circ = 298.4 \text{ kJ mol}^{-1}$ ^[4]), but proceeds under considerable increase of entropy ($\Delta S_{298}^\circ = 216.8 \text{ J mol}^{-1} \text{ K}^{-1}$ ^[4]). Based on these data (without a correction with regard to the temperature dependence of enthalpy and entropy) the following values can be calculated for the equilibrium constants: $K_p(1000 \text{ K}) = 5.5 \times 10^{-5} \text{ bar}$, $K_p(1200 \text{ K}) = 2.2 \times 10^{-2} \text{ bar}$, and $K_p(1400 \text{ K}) = 1.6 \text{ bar}$.

The reaction should be thermodynamically feasible at temperatures around 1000°C . To avoid side effects resulting from a soiled surface of the metal, we did not use iron powder as the starting material but instead an iron wire with a diameter of about 0.6 mm which was spooled to a spiral.^[5] An argon stream was saturated with SiCl_4 at 25°C ($p(\text{SiCl}_4) = 0.3 \text{ bar}$) and directed over the iron wire for a few hours; during this time the reaction was monitored.^[6]

It was shown by X-ray powder diffraction analyses that the iron wire had been completely converted into phase-pure iron silicide (FeSi) at 1000°C in less than 3 h. However, surprisingly, the morphology of the starting material had not been altered during the reaction, and in fact the spiral form had been completely retained. Therefore, iron of a defined shape can be converted into FeSi of a morphologically identical shape without recognizable change of its outward appearance (Figure 1, top the reaction product, the FeSi spiral, bottom the

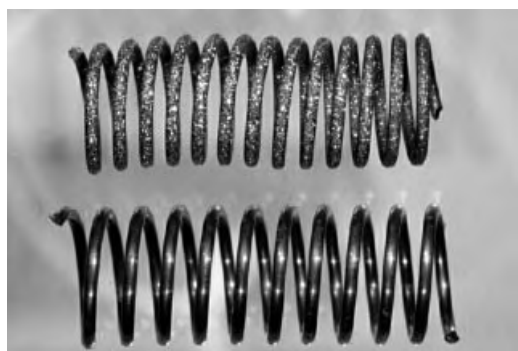


Figure 1. Helical spiral of the reaction product FeSi (top); employed iron spiral (bottom).

starting material, the Fe spiral). This unexpected result contradicts most experiences with reactions of solids with gases and justified further investigation of this reaction. Thus, we have analyzed the course of the reaction as a function of time by interrupting the reaction after different periods of time. At each interruption the changes of weight were determined and the product was analyzed by using wavelength-dispersive X-ray spectroscopy.

If the reaction proceeds according to the defined Equation (1), a weight loss of about 49.9% is expected. In Figure 2, the experimentally determined weight loss is shown as a

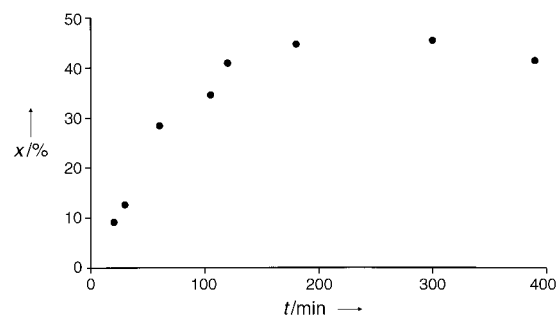


Figure 2. Experimentally determined weight loss x as a function of the reaction time t .

function of the reaction time. It can clearly be seen that the reaction starts quickly and the expected loss of weight is achieved in less than 180 minutes. Further losses in weight were not observed for longer reaction times.

The X-ray analyses were carried out on polished surfaces from the products. The spirals were embedded in synthetic resin, sanded and polished, and the composition was determined.^[7] Figure 3a shows the electron backscattering film of

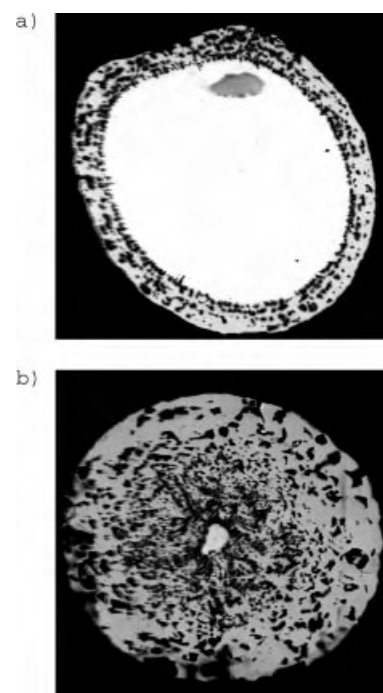


Figure 3. Electron backscattering images of polished surfaces of an iron silicide wire at 1000°C after a reaction time of a) 30 min and b) 120 min.

an iron silicide wire after a reaction time of 30 min. The outer zone consists of FeSi, and measures about 0.1 mm in thickness. After a reaction time of about 120 min, only part of the iron inner core was left (Figure 3b). The electron microprobe analysis, which shows the formation of FeSi, correlates with the measured weight loss of the reaction product.

The investigated solid-state reaction is highly unusual and remarkable in two ways: First, the conversion of the starting material proceeds quickly and second, its morphology is unmodified. Taking into account the massive weight loss during the reaction, it is remarkable that not only the length but also the diameter of the iron wire used as starting material remained unaltered. Considering the densities of iron and iron silicide, and taking into account the weight loss of the product, a 34.5% loss of volume could be calculated for the product according to Equation (1). This is not reflected in the outer shape, diameter, or length of the product in any way. In this case, the loss of volume must be accounted for by the formation of pores in the inner core of the material. The black areas in the electron backscattering images (Figure 3) are indicative of such pores. In our opinion, the formation of hollows and channels in the center of the wire is necessary for the reaction to proceed quickly. Through these channels, transport of material is made possible from the gaseous to the solid phase and back. In this way, the formation of a completely coated surface of the starting material, which would hinder further reaction, is avoided.

The iron core present at the beginning of the reaction allows the formed iron silicide to remain on the surface of the wire at first, then intergrow, and after completion of the reaction, the iron is converted into iron silicide while maintaining its original shape.

In general, it should be possible to transform solids into other solids while maintaining the starting material's morphology by employing reactions such as that we have reported here. Our ongoing research shows that this reaction is not a particular case but widely applicable. We have repeated this experiment with nickel and found that it reacts in an analogous way to iron. At 1000 °C it reacts with silicon chloride under the conditions employed for the synthesis of FeSi to form the γ -phase ($\text{Ni}_{31}\text{Si}_{12}$) with retention of the morphology. Also, chromium reacts with silicon tetrachloride to give the compound Cr_3Si . However, molybdenum and tungsten do not form gaseous dichlorides under these conditions. Accordingly, no particular gain in entropy occurs during the strongly endothermic reaction; thus, the reaction equilibrium favors silicon tetrachloride and the reaction does not proceed. In the future, it will be interesting to direct research towards the synthesis of micro- and nanostructured materials. In this context, the major problems that arose during the preparation of wires from high-temperature superconducting materials should be remembered.

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Gold Pentafluoride: Structure and Fluoride Ion Affinity**

In-Chul Hwang and Konrad Seppelt*

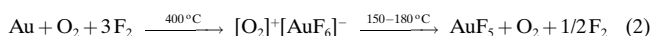
Our knowledge about binary gold fluorides is still limited. AuF can be detected as a molecule,^[1] and according to recent calculations has a dissociation energy of 73 kcal mol^{-1} .^[2] All attempts to isolate it in the condensed phase have failed so far. $\text{F}_3\text{As}-\text{Au} \cdots \text{F} \cdots \text{SbF}_5$ is evidently the only fully characterized compound having a $\text{Au}^{\text{I}}-\text{F}$ interaction.^[3]

AuF_2 has not been isolated at all, although calculations predict it should be a linear molecule.^[4] An Au^{II} ion surrounded only by fluorine atoms is observed in $\text{Au}(\text{SbF}_6)_2$; however, attempts to convert this into AuF_2 have failed.^[5]

AuF_3 , however, has been known for a long time.^[6] Its helix structure with *cis*-fluorine bridges between almost square AuF_4 units is remarkable and is observed for a second time only in AgF_3 .^[7, 8] Salts with the $[\text{AuF}_4]^-$ ion are possibly the most stable gold fluorides.^[6, 9] Thus, mixed-valent Au_3F_8 should evidently be formulated as $\text{Au}(\text{AuF}_4)_2$.^[10]

The existence of AuF_4 , prepared by the reaction between Au and F_2 in a nickel reactor at 500°C ,^[11] however, is highly questionable. Reproduction of this synthesis under similar conditions yields NiF_2 ^[12] and $\text{Ni}(\text{AuF}_4)_2$,^[13] as shown by X-ray powder measurements.^[12]

Gold pentafluoride was obtained shortly after the first isolation of hexafluoroaurates(V) $[\text{Xe}_2\text{F}_{11}]^+[\text{AuF}_6]^-$,^[11] $\text{Cs}^+[\text{AuF}_6]^-$,^[14] $[\text{O}_2]^+[\text{AuF}_6]^-$,^[14, 15] and $[\text{KrF}]^+[\text{AuF}_6]^-$.^[16] It is prepared by thermal decomposition of $[\text{O}_2]^+[\text{AuF}_6]^-$ or $[\text{KrF}]^+[\text{AuF}_6]^-$ [Eq. (1) and Eq. (2), respectively].^[16, 17]



Finally, according to our *ab initio* and density functional theory (DFT) calculations, AuF_6 should not exist, either as an octahedral or as a nonoctahedral molecule.

AuF_5 is an extreme oxidant and fluorination agent which makes its manipulation difficult. In contrast, salts with $[\text{AuF}_6]^-$ ions are quite stable. $[\text{O}_2]^+[\text{AuF}_6]^-$ can be recrystallized from anhydrous HF, and it does not react with HF/SbF₅ solutions. This is a first indication of the high acidity of the HF/AuF₅ system. The single-crystal structure determination (Figure 1) shows ordered $[\text{O}_2]^+$ and octahedral $[\text{AuF}_6]^-$ ions in an almost regular rhombohedral unit cell.^[18]

The high-temperature phase of $[\text{O}_2]^+[\text{AuF}_6]^-$ is regular rhombohedral, which results inevitably in a threefold disorder of the $[\text{O}_2]^+$ ions around their center of gravity, as has

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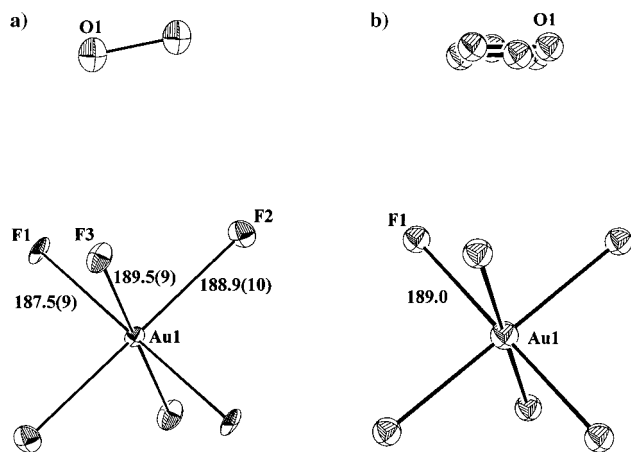


Figure 1. ORTEP representations of an $[\text{O}_2]^+[\text{AuF}_6]^-$ unit in the triclinic (a) and in the rhombohedrally disordered (b)^[15] crystal structure (vibrational ellipsoids indicate 50% probability). One molecular unit is shown with the shortest interionic distance [pm]. Atoms without labels are generated by the center of symmetry.

been found earlier.^[15] This rhombohedral–triclinic phase change is a very simple ordering process, since it affects only the cation. The determination of the O–O distance in $[\text{O}_2]^+$ salts is often difficult because of partial or complete disorder, and values between 95.0 and 121.6 pm are given in the literature.^[15, 19–21] Here a value of 107.9(27) pm is obtained, which still has a large uncertainty but is at least fairly close to the value for the gaseous $[\text{O}_2]^+$ ion (112.3 pm).^[22]

We have prepared AuF_5 according to route outlined in Equation (2) and have obtained single crystals by sublimation. The crystal structure determination reveals that AuF_5 exists as a dimer in the solid state (Figure 2).^[23] AuF_5 is

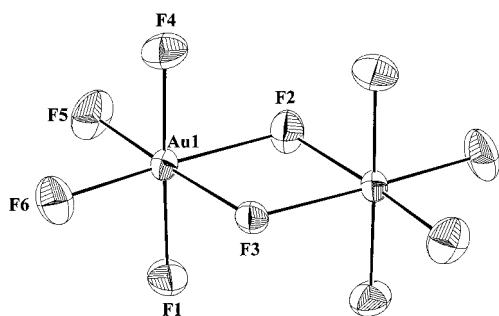


Figure 2. ORTEP representation of the dimer $(\text{AuF}_5)_2$ in the crystal (vibrational ellipsoids indicate 50% probability). Atoms without labels are generated by a mirror plane. Distances and angles, see Table 1.

evidently the only pentafluoride that is dimeric. Other pentafluorides are monomeric (P ,^[24] As ,^[25] Cl ,^[26] Br ,^[27] I ^[27, 28]), tetrameric^[29, 30] (Nb ,^[31] Ta ,^[31] Cr ,^[32] Mo ,^[33] W ,^[34] Tc ,^[35] Re ,^[36] Ru ,^[37] Os ,^[38] Rh ,^[39, 40] Ir ,^[41] Pt ^[42, 43]), or polymeric (Bi ,^[44] V ,^[36] $\alpha\text{-UF}_5$,^[45] $\beta\text{-UF}_5$ ^[46]).

In the gas phase AuF_5 is evidently also strongly associated.^[47] A structure determination from electron diffraction data revealed a mixture of dimer and trimer in the ratio 82:18.^[48] The structure data of the gaseous dimer agree well with our crystal structure data (Table 1). In this double fluorine-bridged structure the gold atoms get quite close to

Table 1. Distances [pm] and angles $^\circ$ in the $(\text{AuF}_5)_2$ molecule according to the crystal structure analysis, in comparison to the values for the gas structure (electron diffraction), and the results of ab initio calculations.

	Crystal structure	Electron diffraction ^[a]	Ab initio calculation
Au–F1, Au–F4	189.1(6), 190.1(5)	188.9(9)	196.5
Au–F2, Au–F3	201.3(5), 203.1(5)	203.0(7)	207.7
Au–F5, Au–F6	185.4(6), 187.5(6)	182.2(8)	192.5
F2–Au–F3	78.4(2)	80.1(5)	79.0
F1–Au–F4 ^[b]	178.5(3)	181.0(11)	179.3
F5–Au–F6	87.0(3)	92.3(17)	96.2

[a] See ref. [48]. [b] Measured over center of ring.

each other (313.5 pm). According to our calculations there is no gold...gold interaction that is frequently found among lower valent gold compounds. An earlier attempt to solve the crystal structure of AuF_5 from X-ray powder data gave a hexagonal cell with completely different metrics, and a spiral polymeric AuF_6 chain structure was suggested. Since the Au...Au distances of 424 pm are extremely large even for linear Au–F–Au bridges, this structure model appears questionable.^[49] The surprisingly simple and temperature-independent Raman spectrum does not support the existence of several solid-state modifications (see Experimental Section and references [17, 49]).

The enthalpy of dimerization of two AuF_5 molecules, which are predicted to be square pyramidal, is calculated to be $-70.1 \text{ kcal mol}^{-1}$.^[50] This already indicates a very high fluoride ion affinity for AuF_5 . Christe et al. have recently established a quantitative Lewis acid scale based on fluoride ion affinities which have been calculated by simplified ab initio methods.^[51] Typical values are 83.1 (BF_3), 94.9 (PF_5), 105.9 (AsF_5), 114.6 (AlCl_3), 115.0 (AlF_3), 120.3 kcal mol^{-1} (SbF_5). The record of SbF_5 on this scale is broken by AuF_5 with 141.2 kcal mol^{-1} and $(\text{AuF}_5)_2$ with 128.8 kcal mol^{-1} . To describe the competition between AuF_5 and SbF_5 for an F^- ion we calculated the structure of the so far unknown dinuclear anion $[\text{F}_5\text{Au} \cdots \text{F} \cdots \text{SbF}_5]^-$ (Figure 3). It turns out that the bridging fluorine atom is closer to the gold than to the antimony atom, in spite of the larger ionic radius of gold. Thus, the structure is best described as $[\text{AuF}_6]^- \cdot \text{SbF}_5$.

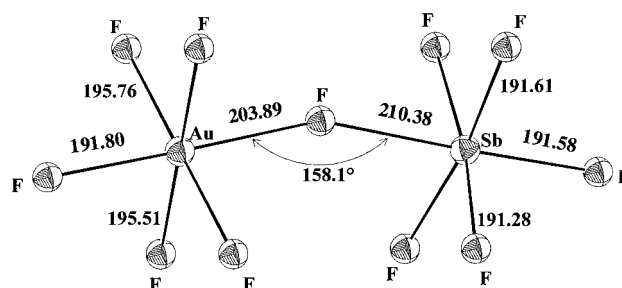


Figure 3. Calculated structure of the $[\text{AuSbF}_{11}]^-$ ion. Distances are given in pm.

It can therefore be assumed HF/AuF_5 solutions are stronger Brønsted acids than the so far strongest acid HF/SbF_5 .^[52] But the extreme acidity of such a HF/AuF_5 solution is also the

reason why AuF_5 dissolved in HF decomposes to AuF_3 and F_2 . It is well known that the highest oxidation states are destabilized in acidic solutions.^[5] Were it not such an unstable system, HF/AuF_5 could be used for protonation reactions that otherwise are not even possible with HF/SbF_5 .

Experimental Section

$[\text{O}_2]^+[\text{AuF}_6]^-$ was prepared as described in reference [14, 15] After the autoclave had been cooled (0.05 K min^{-1}) from 400°C to room temperature, and the pressure of excess O_2/F_2 had been relieved, $[\text{O}_2]^+[\text{AuF}_6]^-$ was obtained as cubic, light yellow crystals, which had formed by sublimation in the upper part of the monel autoclave. Single crystals of $[\text{O}_2]^+[\text{AuF}_6]^-$ were obtained by recrystallization from anhydrous HF on cooling from 50 to $+20^\circ\text{C}$, or from HF/SbF_5 on cooling from 20 to -18°C . Raman spectra (1064 nm , 200 mW , RT, crystals): $\tilde{\nu} = 1833, 595, 228 \text{ cm}^{-1}$. Crystal structure analysis:^[18] With the help of a special device^[53] a suitable crystal was mounted on a Bruker-SMART-CCD-1000-TM-diffractometer and measured. The SHELX programs were used for structure solution and refinement.^[54, 55]

$(\text{AuF}_5)_2: [\text{O}_2]^+[\text{AuF}_6]^-$ (1 g) was placed into an 80 cm long perfluoroethylene (FEP) pyrolysis tube. This tube was connected to a metal vacuum line and cooled to -20°C by external cooling. The solid was then pyrolyzed at 180°C in high vacuum for 15 h . In the cooled zone at 60°C a yellow solid, at $+25^\circ\text{C}$ a red viscous liquid phase, and at 0°C brown-red crystalline platelets were formed. After complete pyrolysis the tube was sealed. Raman spectra identified the yellow solid as $[\text{O}_2]^+[\text{AuF}_6]^-$, the red viscous liquid and the brown-red crystals were identified as AuF_5 . AuF_5 is insoluble in anhydrous HF below 0°C , above 0°C it decomposes to AuF_3 and F_2 . Raman spectrum (-100°C , 1064 nm , 70 mW), (rel. intensities in parentheses): $\tilde{\nu} = 654(60), 596(100), 501(5), 279(3), 254(2), 239(7), 228(3), 220(7), 213(1), 178(1) \text{ cm}^{-1}$. Crystal structure analysis:^[23] Measurement as described above.

Further details on the crystal structure investigations 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-411864 ($[\text{O}_2]^+[\text{AuF}_6]^-$) and CSD-411877 ($(\text{AuF}_5)_2$).

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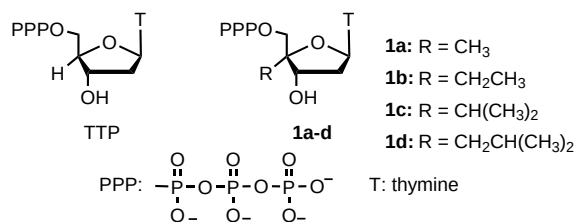
DNA Polymerase Selectivity: Sugar Interactions Monitored with High-Fidelity Nucleotides**

Daniel Summerer and Andreas Marx*

The essential prerequisite of any organism is to keep its genome intact and to accurately duplicate it before cell division. All DNA synthesis required for DNA repair, recombination, and replication depends on the ability of DNA polymerases to recognize the template and correctly insert the complementary nucleotide. In a current model, fidelity is achieved by the ability of DNA polymerases to edit nucleobase pair shape and size.^[1] This model is supported by crystal structures of DNA polymerases that suggest the formation of nucleotide binding pockets, which exclusively accommodate Watson–Crick base pairs.^[2] Nevertheless, structural data of DNA polymerases complexed with the DNA substrates and a noncanonical triphosphate, which would be very helpful for gaining insights into the causes of error-prone DNA synthesis, have at present not been reported. Thus, functional studies of DNA polymerases with nucleotide analogues have been shown to be extremely valuable.^[1] Since most functional studies have focused on nucleobase recognition processes,^[1] little is known about the

impact of DNA polymerase interactions with the 2'-deoxyribose moiety and the participation of these interactions in processes which contribute to fidelity. Crystal structures of DNA polymerases together with enzyme mutation studies suggest that the sugar moiety of the incoming triphosphate is fully embedded in the nucleotide binding pocket and undergoes essential interactions with the enzyme.^[1a, 2] Here we report a functional strategy to monitor steric constraints in DNA polymerases that act on the sugar moiety of an incoming nucleoside triphosphate within the nucleotide binding pocket. We found that novel modified nucleotide probes are substrates for a DNA polymerase with significantly increased selectivity compared to their natural counterpart. Through use of these high-fidelity nucleotides in functional investigations we could show that enzyme–sugar interactions are involved in DNA-polymerase fidelity mechanisms.

In order to sense interactions of DNA polymerases with the sugar moiety of incoming triphosphates we introduced alkyl labels at the 4'-position in the 2'-deoxyribose moiety in such a way that they do not interfere with hydrogen bonding, nucleobase pairing, and stacking. We designed steric probes **1a–d** by substituting the hydrogen atom at the 4'-position of thymidine triphosphate (TTP) with alkyl groups of different size (Scheme 1).



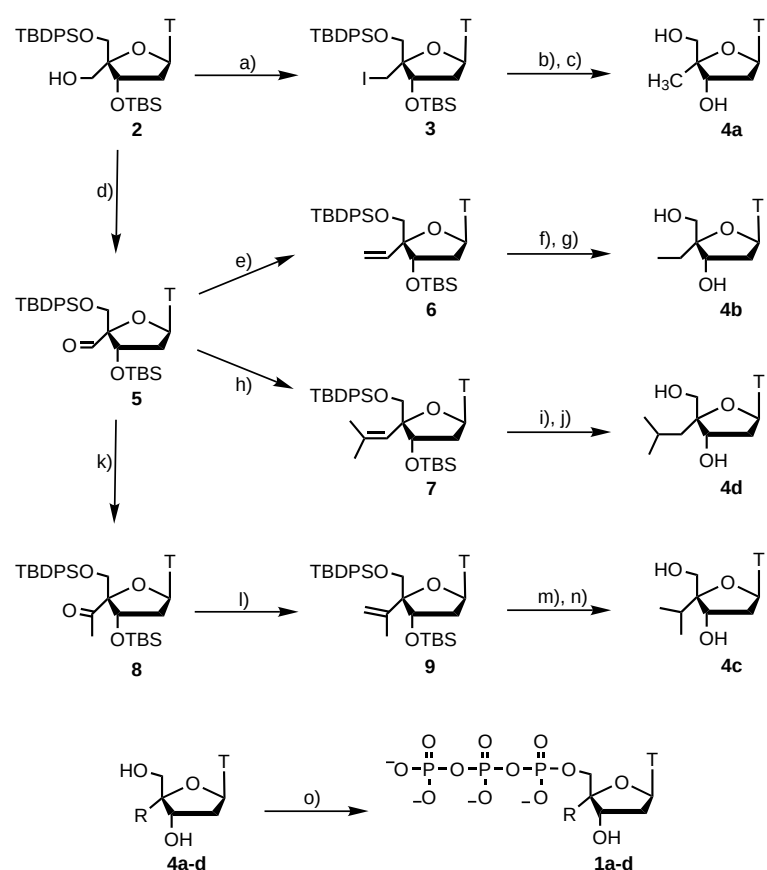
Scheme 1. Thymidine-5'-triphosphate (TTP) and the steric probes **1a–d**.

The synthesis of nucleosides **4a** and **4b** with different synthetic strategies (see Scheme 2) has been reported previously.^[3, 4] However, these methods are not suitable for the synthesis of all the targeted compounds and the formation of undesired by-products was observed in the synthesis of **4a**.^[3] Thus, we developed a more suitable access to the target compounds. Our synthesis started with the known alcohol **2**, which is easily accessible as described recently.^[5] Compound **2** was converted into the methylated thymidine **4a** by functional-group interconversions (Scheme 2). Alkylated nucleosides **4b–d** were synthesized from known compounds^[5] by employing Wittig reaction, desilylation, and subsequent reduction of the aliphatic double bond. Next, nucleosides **4a–d** were converted into the desired triphosphates **1a–d** following standard procedures.^[6] In order to gain insights into potential effects of the modifications on the sugar conformation we performed conformation analysis based on coupling constants deduced from the ¹H NMR data by employing described methods.^[7] We found only small differences in **1a–d** compared to natural TTP, which indicates that similar sugar conformations are present in solution (see Supporting Information).

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



Scheme 2. Syntheses of **1a-d**. a) Ph_3P , I_2 , imidazole, C_6H_6 , 50°C , 85%; b) Pd/C , H_2 , EtOH , EtOAc , NEt_3 ; c) TBAF, THF, 79% (two steps); d) oxidation;^[5] e) $\text{CH}_3\text{PPh}_3\text{Br}$, $n\text{BuLi}$, THF, -78 to 25°C , 99%; f) TBAF, THF; g) Pd/C , H_2 , CH_3OH , 88% (two steps); h) $(\text{CH}_3)_2\text{CHPPh}_3\text{I}$, $n\text{BuLi}$, THF, -78 to 25°C , 83%; i) TBAF, THF; j) Pd/C , H_2 , CH_3OH , 94% (two steps); k) alkylation and oxidation;^[5] l) $\text{CH}_3\text{PPh}_3\text{Br}$, $t\text{BuOK}$, THF, 25°C , 91%; m) TBAF, THF; n) Pd/C , H_2 , CH_3OH , 84% (two steps); o) POCl_3 , 1,8-bis(dimethylamino)naphthalene, $(\text{CH}_3\text{O})_3\text{PO}$, 0°C , then $(n\text{Bu}_3\text{N})_2\text{H}_2\text{P}_2\text{O}_7$, $n\text{Bu}_3\text{N}$, DMF, then 0.1 M aqueous $(\text{Et}_3\text{NH})\text{HCO}_3$, 23–68%. TBDPS = *tert*-butyldiphenylsilyl, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran, DMF = *N,N*-dimethylformamide.

We tested the effect of probes **1a-d** on the Klenow fragment (KF^-) of *E. coli* DNA polymerase I (*exo*⁻-mutant), an enzyme extensively used as a model for investigations into intrinsic DNA-polymerase mechanisms and function.^[1] We used a gel-based single nucleotide insertion assay,^[8] where an adenine in the template strand codes for the insertion of a

thymidine analogue adjacent at the primer 3'-end,^[9] to monitor polymerase function. Figure 1A shows the pattern of insertion of thymidine-5'-triphosphate (TTP) and **1a-d** catalyzed by KF^- . The results obtained reveal that **1a-d** are functionally competent, although with varied efficiencies.

In order to quantify these observations we determined the insertion efficiencies (v_{max}/K_M ; v_{max} = the maximum rate of the enzyme reaction, K_M = the Michaelis constant) of the thymidine analogues by investigation of single-nucleotide insertion at various nucleotide concentrations under single completed hit and steady-state conditions as recently described.^[8, 10–12] The quantitative analyses revealed that KF^- incorporates **1a** and **1b** with virtually the same efficiency as unmodified TTP (Table 1). Thus,

Table 1. Steady-state analyses for canonical nucleoside triphosphate insertion. The data presented are averages of duplicate or triplicate experiments. Further experimental details are described in Supporting Information.

Nucleoside triphosphate	K_M [μM]	v_{max} [$\text{min}^{-1} \times 10^{-3}$]	v_{max}/K_M [$\text{M}^{-1} \text{min}^{-1}$]
TTP	0.11 ± 0.05	20 ± 3	180 000
1a	0.40 ± 0.01	58 ± 4	150 000
1b	0.21 ± 0.01	29 ± 5	140 000
1c	47 ± 4	85 ± 5	1 800
1d	241 ± 22	76 ± 1	320

it appears that 4'-methyl and -ethyl groups are nicely accommodated within the nucleotide binding pocket of KF^- . Further increase in the bulk of the probes caused a marked decrease in the insertion efficiency of **1c** and **1d**, presumably due to a steric clash since the modifications do not cause significant perturbation of the sugar pucker conformation.

Since the ratio of nucleotide-insertion efficiencies opposite a complementary to a noncomplementary nucleobase is a measurement of DNA-polymerase fidelity,^[8, 10, 11] we next investigated the ability of KF^- to catalyze non-Watson–Crick nucleobase pair formation. We focused on **1a** and **1b**, since only these are inserted as efficiently as TTP by KF^- in

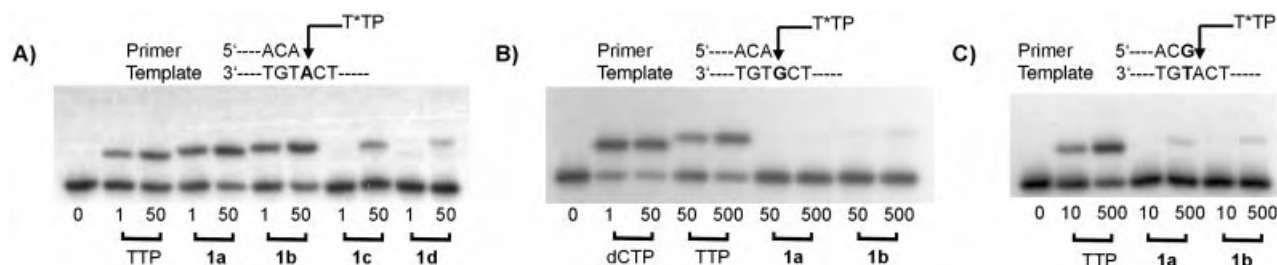


Figure 1. Nucleoside triphosphate insertion catalyzed by KF^- . A) Insertion encoded by adenine (A) in the template strand. Conditions: Primer/template complex (50 nM), KF^- (2 nM), 37°C , 5 min. B) Nucleoside triphosphate insertion encoded by guanine (G) in the template strand. Conditions: Primer/template complex (50 nM), KF^- (4 nM), 37°C , 5 min. C) Mismatch extension. Conditions: Primer/template complex (50 nM), KF^- (2 nM), 37°C , 20 min. In each case, the nucleotide concentrations [μM] are shown in the figure. dCTP = 2'-deoxycytidine-5'-triphosphate, T*TP = TTP analogues. Further experimental details and the DNA sequences employed are described in the Supporting Information.

canonical base pair formation and thus they should be ideally suited for use in the monitoring of differential enzyme interactions between insertion and misinsertion events. Assays of nucleotide incorporation opposite G, T, and C revealed that KF^- misinserts TTP and **1a**, **b** opposite G with the highest efficiency.^[9, 13] Strikingly, as is already apparent from the results shown in Figure 1B, **1a** and **1b** exhibit dramatically decreased misinsertion efficiency. Steady-state kinetic analyses revealed an approximately 100-fold decrease in misinsertion efficiency using the 4'-alkylated probes **1a**, **b** compared to TTP (Table 2).

Table 2. Steady-state analyses for nucleoside triphosphate misinsertion and mismatch extension. The data presented are averages of duplicate or triplicate experiments. Further experimental details are described in Supporting Information.

Nucleoside triphosphate	K_M [μM]	v_{max} [$\text{min}^{-1} \times 10^{-3}$]	v_{max}/K_M [$\text{M}^{-1} \text{min}^{-1}$]
<i>misinsertion:</i>			
TTP	22 $\pm$ 0.2	16 $\pm$ 1	730
1a	65 $\pm$ 5	0.34 $\pm$ 0.02	5
1b	228 $\pm$ 5	1.7 $\pm$ 0.1	7
<i>mismatch extension:</i>			
TTP	19 $\pm$ 1	36 $\pm$ 2	1900
1a	80 $\pm$ 17	2.9 $\pm$ 0.1	40
1b	40 $\pm$ 5	4.0 $\pm$ 0.3	100

Further experiments also showed that the analogues **1a** and **1b** were not as well inserted opposite T or C as unmodified TTP was (see Supporting Information). These results clearly show that nucleotide-insertion selectivity is increased by substitution of the hydrogen atom at the 4'-position of the sugar with bulkier alkyl groups.

The second critical determinant of intrinsic DNA-polymerase fidelity is the capacity to extend from mismatched primer/template ends.^[1a, 8, 11] Here again, **1a** and **1b** should be ideally suited to monitor differential DNA-polymerase interactions with the sugar moiety in mismatch extension events. We investigated extension from template-T/primer-G, T/T, and T/C by using KF^- to extend from a mismatched base at the primer 3'-end by incorporation of TTP or **1a**, **b**. The most efficient extension was from T/G for all thymidine triphosphate derivatives (data shown for T/G in Figure 1C).^[9, 13] The results of quantitative analyses of T/G extensions are presented in Table 2. KF^- extends a T/G mismatched primer end with probes **1a**, **b** significantly less efficiently than with TTP. Again, this is in contrast to the results in Table 1 where TTP and **1a**, **b** extension of a perfectly matched primer were equivalent. Our results indicate that nucleobase pair mismatches at the 3'-end of a primer/template complex trigger unfavorable enzyme interactions with the sugar moiety of an incoming nucleoside triphosphate and prevent inadvertent sealing of a base substitution in the nascent DNA strand. Indeed, this mechanism may be considered essential for proofreading, and may allow a pause for other functions such as intrinsic exonuclease activity or dissociation of the DNA-replication complex.

In conclusion, the selectivity of nucleotide insertion by a DNA polymerase can be significantly increased by modified sugar moieties. Our results strongly implicate the involvement of differential DNA-polymerase interactions with the sugar in processes that contribute to the fidelity of DNA synthesis. Furthermore, our studies provide a new functional and general method to monitor steric constraints in nucleotide binding pockets of DNA polymerases. Further analyses with such steric probes, both at the functional and structural level should reveal more insights into mechanisms of DNA polymerase selectivity.

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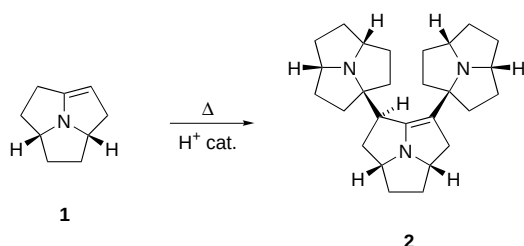
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The Azatriquinenamine Trimer—A Novel Proton Chelate**

Mark Mascal,* Manuel Lera, Alexander J. Blake, Malgorzata Czaja, Anna Kozak, Mariusz Makowski, and Lech Chmurzynski

Proton sponges and neutral organic superbases are molecules of both theoretical and practical interest.^[1, 2] Their extraordinary basicity is attributed in the former to the relief of lone pair repulsion between basic sites in enforced proximity and the establishment of a high quality H-bond on protonation, and in the latter to extensive resonance stabilization of the HB⁺ ion.

In the course of our synthetic studies in the azatriquinane series, we prepared *cis*-10-azatricyclo[5.2.1.0^{1,10}]dec-1-ene (azatriquinenamine **1**),^[3] as a pivotal intermediate in the syntheses of azatriquinane, azatriquinadiene, and azatriquinacene.^[4] This compound is a distillable liquid which is stable under ambient conditions. However, heating **1** at > 100 °C in the presence of a proton source leads to solidification of the reaction mixture, the principle component of which was assigned the trimeric structure **2** (Scheme 1) on the basis of spectroscopic data.



Scheme 1. Formation of **2**.

We believe this type of enamine trimerization to be unique. Although the $\Delta^{1,8}$ -dehydropyrrolizidine enamine dimerizes in an analogous manner, it does not proceed to give a trimer.^[5] The *N*-methyl- Δ^2 -pyrroline enamine has also been observed to both dimerize and trimerize,^[6] but in the latter case the

central ring functions first as an enamine nucleophile and then as an imine electrophile, unlike in **2** where the central azatriquinenamine reacts as a nucleophile, tautomerizes, and then reacts a second time as a nucleophile.

It was not, however, until an X-ray crystal structure of the hydrochloride salt of **2** was carried out that a remarkable feature of this unusual nonacycle was recognized, that is that the two terminal azatriquinane rings were situated face-to-face, chelating the H⁺ with an N...N distance of 2.75 Å and an N–H...N angle of 177° (Figure 1a).^[7] The bis-trialkyl-

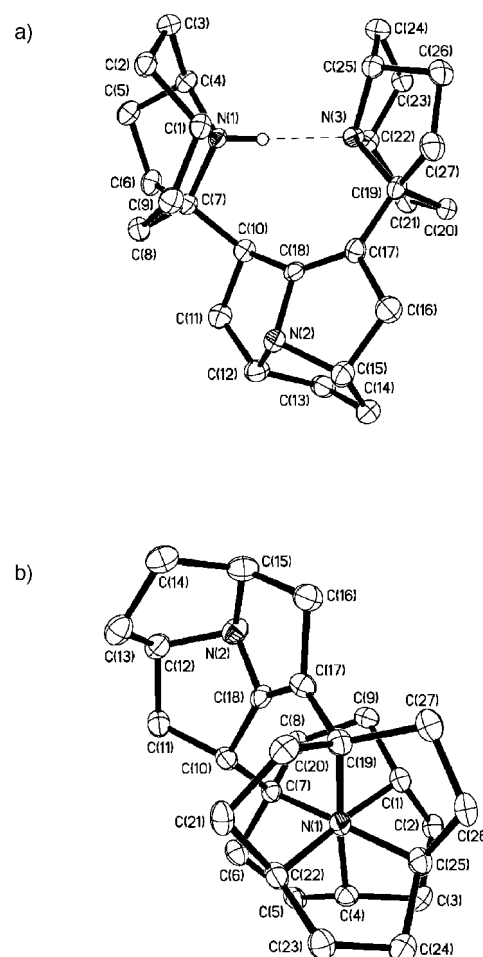


Figure 1. a) View of the X-ray crystal structure of the **2H**⁺ ion normal to the N–H...N axis. b) View of the X-ray crystal structure of the **2H**⁺ ion down the N–H...N axis.

amino environment around the acidic proton is reminiscent of the 1,6-diazabicyclo[4.4.4]tetradecane H⁺ cryptate of Alder, et al.,^[8] except that in **2H**⁺ the conformation down the R₃N–H...NR₃ axis is nearly perfectly staggered (Figure 1b). Interestingly, we had previously noted the enhanced basicity of the azatriquinane molecule relative to other trialkylamines due to the acute and enforced pyramidalization of the apical nitrogen atom in this rigid tricycle,^[3] and so the high intrinsic basicity of the subunits of **2** in combination with its overall tweezerlike structure led us to consider whether this might render the molecule particularly basic.

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[**] Azatriquinanes, Part 3. This work was financially supported by the University of Nottingham and the Polish State Committee for Scientific Research (grant DS/8231-4-0097-1). We also thank the EPSRC National Crystallography Service, University of Southampton, for data collection. Part 2: Ref [4].

We thus undertook an investigation of the basicity of **2** using both chemical and computational approaches. A standard experimental protocol for deriving the pK_a values of strong, neutral bases is potentiometric titration in acetonitrile solution.^[9] By this method, the dissociation constants of several well known amines have been measured and are available for comparison. Substantial work has also been published on the computational determination of gas-phase proton affinities and their correlation to solution basicity.^[10] The overall results for **2** are presented in Table 1, and show

Table 1. Calculated protonation energies (ΔE_{prot} , kcal mol⁻¹) and conjugate acid dissociation constants (pK_a) of known organic superbases and **2**.

Amine	ΔE_{prot}	$pK_{a(\text{theory})}$	$pK_{a(\text{MeCN})}$
DMAP ^[a]	243.4	18.2	18.2 ^[16]
"proton sponge" ^[b]	243.8 ^[2d]	18.3	18.5 ^[17]
PhTMG ^[c]	252.6	21.5	20.6 ^[18]
DBU ^[d]	256.9	23.0	23.9 ^[18]
2	265.3	26.0	25.1
(Me ₂ N) ₃ P=NtBu	265.8	26.2	26.9 ^[2a]

[a] 4-Dimethylaminopyridine. [b] "Proton sponge", 1,8-bis(dimethylamino)naphthalene, is a registered trademark of Sigma-Aldrich, Milwaukee, WI, USA. [c] *N*-Phenyltetramethyl guanidine. [d] 1,8-Diazabicyclo[5.4.0]undec-7-ene.

that the molecule is in fact highly basic; about seven orders of magnitude more so than 1,8-bis(dimethylamino)naphthalene ("proton sponge") and 4-dimethylaminopyridine (DMAP). Indeed, it was our experience in the isolation of **2** that its handling in dichloromethane led directly to the hydrochloride salt, presumably by α -dehydrohalogenation of the solvent. The free base could not be liberated by shaking with aqueous NaOH solution, but was obtained by treatment of **2**·HCl with potassium hexamethyldisilazide, and was observed to quickly reprotonate on exposure to atmospheric moisture.

A computational study of the proton affinity of **2** supports the experimental determination of its high pK_a . Monte Carlo molecular mechanics simulations with the MM2* and MM3* force fields^[11] suggested that the lowest energy conformer of the free base **2** was unexpectedly similar to that of the protonated form, that is the convex surfaces of the terminal azatriquinanes, although offset relative to **2**·HCl, still faced each other, in spite of the fact that a number of alternative structures with completely divergent nitrogens are possible. The protonation energy (ΔE_{prot})^[12] of **2** was calculated to be -265.3 kcal mol⁻¹ using the HF/6-31G(d)//HF/6-31G(d) theoretical model. This could be correlated to a solution pK_a of about 26.0 by the linear relationship $pK_{a(\text{theory})} = -0.357(\Delta E_{\text{prot}}) - 68.8$, derived by plotting ΔE_{prot} against experimental pK_a values in acetonitrile for the bases in Table 1 (regression coefficient 0.98). The agreement with the measured pK_a value of **2**H⁺ (25.1) is remarkably good considering the modest level of theory applied and the different classes of bases to which it was compared.

It is noteworthy that a base such as **2** benefiting neither from conjugation nor the proton sponge effect competes nonetheless in terms of proton affinity with the likes of DBU

and the P1-polyaminophosphazine base,^[2a] although it is considerably less basic than Schwesinger's remarkable higher generation phosphazene^[2a] and vinamidine^[13] superbases. We also note that **2** is an unusual example of a chiral neutral superbase. Further investigations of the properties of **2**, as well as its resolution into enantiomers, will be reported elsewhere.

Experimental Section

2: Dichloromethane (1 mL) was added to the freshly distilled enamine **1** (0.781 g, 5.78 mmol) and the mixture was heated at 140 °C with stirring for 12 h. The reaction was then cooled to room temperature and the resulting brown solid dissolved in dichloromethane and applied to the top of a silica gel column. Elution with dichloromethane/methanol 10:1 gave the mono-hydrochloride salt of **2** (0.254 g, 30 %) as a hygroscopic, pink crystalline solid, m.p. 127–130 °C, ¹H NMR (400 MHz, CDCl₃): δ = 4.05 (m, 1 H), 3.98 (m, 1 H), 3.72 (m, 1 H), 3.61–3.53 (m, 2 H), 3.45–3.40 (m, 1 H), 2.98 (dd, J = 15.0, 7.6 Hz, 1 H), 2.85 (dd, J = 7.9, 3.9 Hz, 1 H), 2.39 (d, J = 15.1 Hz, 1 H), 2.34–1.63 (m, 25 H), 1.60–1.47 (m, 3 H), 1.32–1.22 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃): δ = 147.5, 112.8, 81.7, 76.0, 67.6, 67.1, 66.7, 66.6, 62.2, 60.3, 43.0, 42.5, 36.8, 36.7, 36.3, 32.7, 32.1, 31.7, 31.0, 30.3, 30.1, 29.9, 29.7, 25 (C), 29.6 (2 C), 28.6; MS (FAB): m/z (%): 406 ([*M* + *H*], 53), 307 (26), 155 (32), 154 (100), 138 (36), 137 (67), 136 (86), 107 (26), 91 (29), 73 (68), 57 (32), 55 (29); HRMS (FAB): m/z calcd for C₂₇H₄₀N₃ [*M* + *H*]: 406.3222; found: 406.3223.

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Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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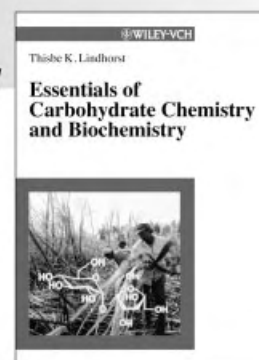
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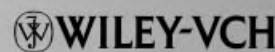
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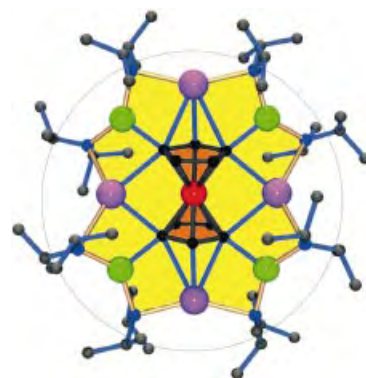
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COVER PICTURE

The cover picture shows the molecular structure of the first ferrocene inverse crown complex. Ferrocene, located in the core, has been fourfold deprotonated at the 1,1',3,3'-positions by the encapsulating action of the 16-membered tetrasodium–tetramagnesium amide cationic ring which surrounds it. The perimeter of this ring is highlighted in yellow, the sodium and magnesium atoms are shown in violet and green, respectively. More details on the fascinating structure of this inverse crown complex are described by R. Mulvey et al. on pages 3902 ff.



REVIEWS

Contents

Asymmetric catalysis is almost synonymous with the use of metals in a chiral environment. Are metals really indispensable for these catalytic processes? Or, can some of their functions be emulated by an organic system? The last few years have witnessed a spectacular advancement in new catalytic methods based on organic molecules. In many cases, extremely high enantioselectivities were achieved with these small organic compounds.

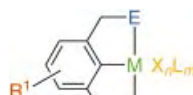
Angew. Chem. **2001**, *113*, 3840–3864

P. I. Dalko,* L. Moisan 3726–3748

Enantioselective Organocatalysis

Keywords: asymmetric catalysis •
chiral auxiliaries • synthetic methods

Pincer ligands are excellent candidates for regulating the reactivity of a metal center through selective ligand substitution (ligand tuning), without affecting the binding mode, particularly in chelation-reinforced metal–carbon bonding (see picture). The implementation of this approach has provided a large variety of platinum group metal complexes that display unprecedented properties. Besides their synthesis, their significance as functional units for the construction of materials is illustrated.



Angew. Chem. **2001**, *113*, 3866–3898

M. Albrecht,
G. van Koten* 3750–3781

Platinum Group Organometallics Based on “Pincer” Complexes: Sensors, Switches, and Catalysts

Keywords: homogeneous catalysis • cyclometalation • materials science • pincer ligands • platinum group metals

ESSAY

The first Nobel Prize in Chemistry was awarded to the Dutch physical chemist Jacobus Henricus van’t Hoff in 1901, exactly hundred years ago. His impact on the chemical sciences is unparalleled with concepts ranging from tetrahedra to thermodynamics. He reshaped the discipline of chemistry at a very young age. Through the years, Van’t Hoff has inspired many Dutch scientists to perform research on novel stereochemical concepts. The picture shows stereochemical models, which Van’t Hoff produced himself.



Angew. Chem. **2001**, *113*, 3899–3905

E. W. Meijer* 3783–3789

Jacobus Henricus van’t Hoff; Hundred Years of Impact on Stereochemistry in the Netherlands

Keywords: biography • kinetics • stereochemistry • supramolecular chemistry • thermodynamics

VIPs

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

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F. Cacace,* G. de Petris,
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Y. Tobe,* R. Furukawa,
M. Sonoda, T. Wakabayashi ◆

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Origin of Ferromagnetism in Cyano-Bridged Compounds Containing d^1 Octacyanommetallates

L. F. Chibotaru,* V. S. Mironov,
A. Ceulemans

Lewis Acid/Base-Stabilized Phosphanylalane and -gallane

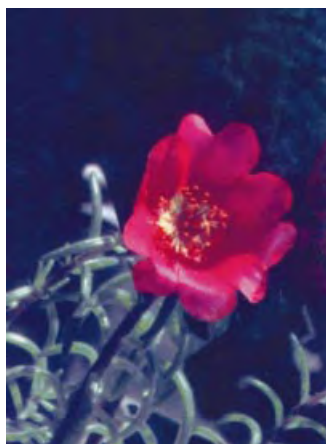
U. Vogel, A. Y. Timshkin,
M. Scheer*

Towards the Understanding of Solid-State Structures: From Cubic to Chain-like Arrangements in Group 11 Halides

T. Söhnel, H. Hermann,
P. Schwerdtfeger*

Enzymes in search of a function, for polyphenol oxidases (PPOs), described as such, this situation has changed recently. A tyrosinase is involved in betacyanin biosynthesis in common portulaca (see picture) and red beet, and a chalcone-specific PPO is responsible for the formation of aurones in yellow snapdragon flowers.

Angew. Chem. **2001**, *113*, 3907–3911



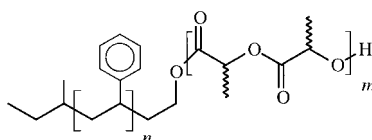
D. Strack,* W. Schliemann* . 3791–3794

Bifunctional Polyphenol Oxidases: Novel Functions in Plant Pigment Biosynthesis

Keywords: aurones • biosynthesis • flower pigments • natural products • oxidases • tyrosinases

Defined porosity in the low-nanometer range is exhibited by easy-to-modify template materials, which can be prepared from mesoporous polystyrene monoliths. These are readily accessible by a mild hydrolysis reaction of a poly(styrene-*b*-lactic acid) precursor (see picture)

Angew. Chem. **2001**, *113*, 3911–3913



M. R. Buchmeiser* 3795–3797

New Ways to Porous Monolithic Materials with Uniform Pore Size Distribution

Keywords: membranes • mesoporous materials • nanostructures • polymers

COMMUNICATIONS

Coordinated water molecules induce the aggregation and self-assembly of the lyotropic liquid crystalline phase formed from non-ionic surfactants $C_nH_{2n+1}(CH_2CH_2O)_mOH$ and transition metal aqua complexes ($[Ni(H_2O)_6](NO_3)_2$, $[Co(H_2O)_6](NO_3)_2$, $[Zn(H_2O)_6](NO_3)_2$, $[Cd(H_2O)_4](NO_3)_2$, and $[Co(H_2O)_6]Cl_2$) into hexagonal (see schematic representation) and/or cubic structures. While the Ni^{II} and Co^{II} complexes undergo recrystallization and phase separation at high complex concentrations, the Zn^{II} and Cd^{II} complexes form cubic phases above metal/surfactant molar ratios of 3.2/1 at room temperature.

Angew. Chem. **2001**, *113*, 3916–3919



Ö. Çelik, Ö. Dag* 3800–3803

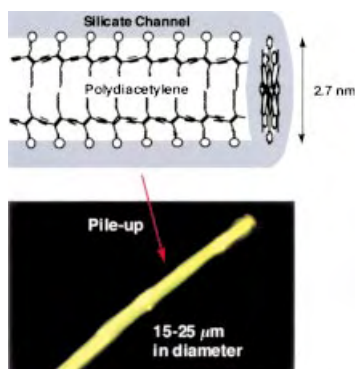
A New Lyotropic Liquid Crystalline System: Oligo(ethylene oxide) Surfactants with $[M(H_2O)_n]X_m$ Transition Metal Complexes

Keywords: liquid crystals • mesophases • nanostructures • surfactants • transition metals



Sticklike silicate materials containing aligned nanodomains of conjugated polymers (see picture) were synthesized by sol–gel-based in situ polymerization of ammonium ion terminated diacetylenic surfactant monomers. Upon photoexcitation at 450 nm, the silicate microsticks emit a yellowish green luminescence centered at 550 nm.

Angew. Chem. **2001**, *113*, 3919–3922



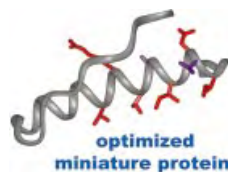
T. Aida,* K. Tajima 3803–3806

Photoluminescent Silicate Microsticks Containing Aligned Nanodomains of Conjugated Polymers by Sol–Gel-Based In Situ Polymerization

Keywords: luminescence • nanostructures • organic-inorganic hybrid composites • polymerization • sol–gel processes



A major challenge for chemical biologists lies in the design of potent and selective ligands for protein surfaces. Here a protein grafting and evolution strategy is used to discover highly potent and specific miniature protein ligands (see picture) for human Bcl-2 and Bcl-X_L. Miniature proteins could be used to dissect, modulate, or analyze a single protein function, irrespective of the other functions the protein may regulate within the proteome.



J. W. Chin, A. Schepartz* ... 3806–3809

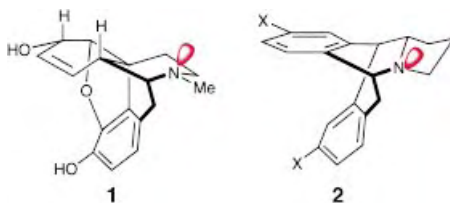
Design and Evolution of a Miniature Bcl-2 Binding Protein

Keywords: apoptosis • protein design • protein–protein interactions • proteins

Angew. Chem. **2001**, *113*, 3922–3925



The power of visual imagery can reach Daliesque proportions in the mind's eye of the synthetic chemist. The topologically interesting isopavine nucleus, with an orthogonal orientation of two aryl groups, can be obtained as two diastereomeric structures, depending on the course of a [1,2]-Stevens rearrangement. When viewed as a constrained piperidine, a close spatial relationship with morphine (**1**) becomes apparent. Indeed, tetracyclic isopavine **2** exhibits morphine-like activity toward the human μ -opioid receptor.



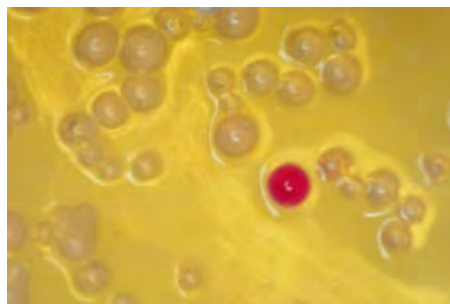
S. Hanessian,* M. Mauduit .. 3810–3813

Highly Diastereoselective Intramolecular [1,2]-Stevens Rearrangements—Asymmetric Syntheses of Functionalized Isopavines as Morphinomimetics

Keywords: alkaloids • medicinal chemistry • morphine mimetics • rearrangement • synthetic methods

Angew. Chem. **2001**, *113*, 3926–3929

Catalytic beads are readily distinguished from inactive controls in a method which exploits the localizing potential of a gel. A useful variant employs an acid/base indicator to detect the pH change on ester hydrolysis (see picture). Precipitation of the acidified indicator (red) creates an especially strong contrast between active and inactive beads.



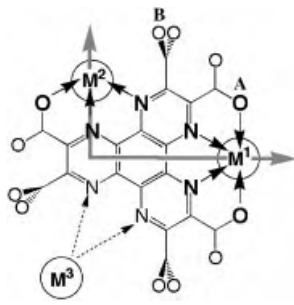
M. Müller, T. W. Mathers, A. P. Davis* 3813–3815

A New Screen for Combinatorial Catalysis; On-Bead Testing in Agarose Gel

Keywords: combinatorial chemistry • enzyme catalysis • high-throughput screening • hydrolysis • supported catalysts

Angew. Chem. **2001**, *113*, 3929–3931

The construction of nanostructured polynuclear metal complexes with cyclic topologies, particularly those containing multifunctional ligands containing π -electronic structures, is of great interest since they can potentially lead to compounds with unusual electrochemical properties. A novel cyclic module with a hexacarboxylate derivative (see picture) is described. The results show that the peripheral substituents not only control the electronic structure, but also influence its mode of coordination.



S. Masaoka, S. Furukawa, H.-C. Chang, T. Mizutani, S. Kitagawa* ... 3817–3819

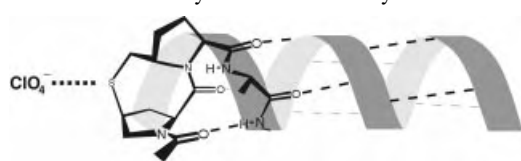
A New Class of Cyclic Hexamer: [Co₆L₆]²⁴⁻ (H₆L = hexaazatriphenylene hexacarboxylic acid)

Keywords: carboxylate ligands • crystal engineering • nanostructures • transition metals

Angew. Chem. **2001**, *113*, 3933–3935



Regiospecific binding of perchlorate ions to the N-terminus of short-chained template-substituted polyalanine sequences (see schematic representation) in water dramatically increases helicity.



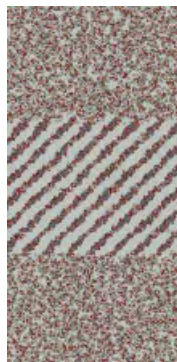
W. Maison, R. J. Kennedy, D. S. Kemp* 3819–3821

Chaotropic Anions Strongly Stabilize Short, N-Capped Uncharged Peptide Helices: A New Look at the Perchlorate Effect

Keywords: chaotropic anions • circular dichroism • helical structures • peptides

Angew. Chem. **2001**, *113*, 3936–3938

Detailed hydrophobicity and lipophilicity charts of the surfaces of crystalline cellulose $I\beta$ are produced by using atomistic molecular dynamics simulations. They reveal patterns of possible sites for the adsorption of hydrophilic and apolar groups of organic adsorbents. The picture shows the simulated distribution of water molecules over a chain of a crystalline 110 surface of cellulose (center; above and below this range lies the bulk water).



O. Biermann, E. Hädicke, S. Koltzenburg, F. Müller-Plathe* 3822–3825

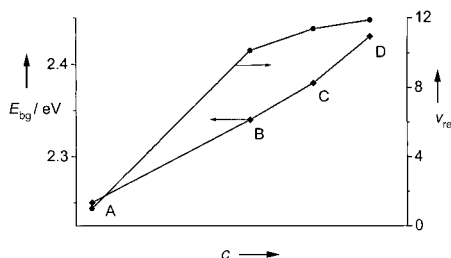
Hydrophilicity and Lipophilicity of Cellulose Crystal Surfaces

Keywords: cellulose • hydration • hydrophobic effect • molecular dynamics • surface chemistry

Angew. Chem. **2001**, *113*, 3938–3942



The bandgap of CdS increases with decreasing coverage when CdS is supported on silica (see plot of E_{bg} against CdS concentration c). Likewise the photocatalytic activity of these heterogeneous photocatalysts increases, as illustrated by the relative rate (v_{rel}) of an organic addition reaction. CdS (A, $v_{rel} = 1$), CdS-50/SiO₂ (B), CdS-30/SiO₂ (C), and CdS-12/SiO₂ (D).



H. Weiss, A. Fernandez, H. Kisch* 3825–3827

Electronic Semiconductor–Support Interaction—A Novel Effect in Semiconductor Photocatalysis

Keywords: cadmium sulfide • photocatalysis • photoelectrochemistry • semiconductors

Angew. Chem. **2001**, *113*, 3942–3945

Indications of the occurrence of mutations can be gained from accurate mass measurements by electrospray ionization mass spectrometry. On-line coupling to liquid chromatography is essential for the application to real samples. By utilizing the coupled method, insertions, deletions, and point mutations are rapidly discovered in DNA restriction fragments and PCR products (see image).



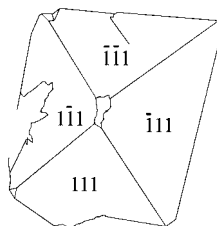
H. Oberacher, P. J. Oefner, W. Parson, C. G. Huber* 3828–3830

On-Line Liquid Chromatography Mass Spectrometry: A Useful Tool for the Detection of DNA Sequence Variation

Keywords: liquid chromatography • mass spectrometry • mutation detection • nucleic acids

Angew. Chem. **2001**, *113*, 3945–3948

Mimicking recommended! The natural formation conditions of zeolites can be mimicked by treating water-free glass precursors with the composition of the natural zeolite under high-pressure hydrothermal conditions. The picture shows the indexing of the surface of a faujasite crystal obtained in this way. This process can be adapted for the tailored synthesis of zeolites with new properties.



H. Ghobarkar, O. Schäf,* P. Knauth* 3831–3833

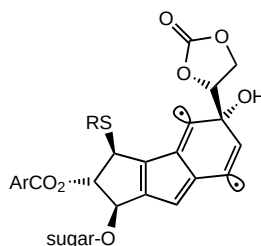
Zeolite Synthesis by the High-Pressure Hydrothermal Method: Synthesis of Natural 6-Ring Zeolites with Different Void Systems

Keywords: crystal growth • high-pressure chemistry • hydrothermal synthesis • zeolites

Angew. Chem. **2001**, *113*, 3948–3951



While the general course of the mode of action of the antitumor agent neocarzinostatin (NCS) is clarified, it is still unclear which structural elements are relevant for the high efficacy of NCS. This question and the role of alternatively possible biradicals (see picture) are addressed.



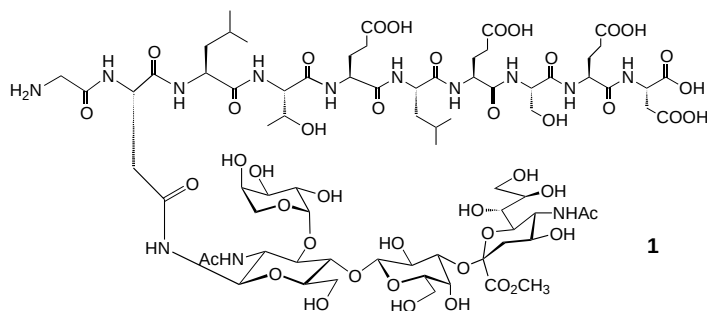
P. W. Musch, B. Engels* 3833–3836

Which Structural Elements Are Relevant for the Efficacy of Neocarzinostatin?

Keywords: ab initio calculations • antibiotics • density functional calculations • DNA cleavage • solvent effects

Angew. Chem. **2001**, *113*, 3951–3954

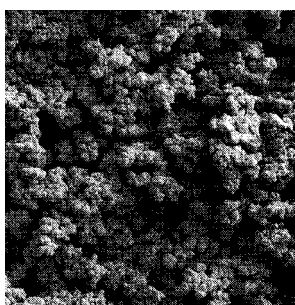
Particularly selective methods are required for the synthesis of arabino sialyl Lewis^x glycopeptides owing to the acid-labile β -arabinopyranoside bond. It is important for the inhibition of cell adhesion that the arabino sialyl Lewis^x glycopeptide **1**, which contains the Gly⁶⁷²–Asp⁶⁸¹ sequence of the E-selectin Ligand 1 (ESL-1), binds ten times more strongly than sialyl Lewis^x to E-selectin, although it is monovalent and does not contain L-fucose, which is considered essential.



Angew. Chem. **2001**, *113*, 3954–3957



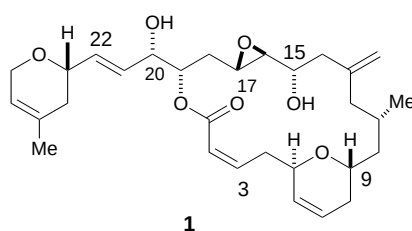
Back to the roots: Ring-opening metathesis polymerization allows the synthesis of monolithic materials, which may be subject to an in situ derivatization with dihydroimidazolium salts through metathesis graft polymerization. This method offers an attractive route to highly reactive, permanently immobilized metathesis initiators. The picture shows an electron microscope image of the microstructure of the monolithic support.



Angew. Chem. **2001**, *113*, 3957–3960



The microtubule-stabilizing anti-tumor agent laulimalide (**1**) has been obtained in by new synthetic route. The carbon skeleton was assembled by means of Julia–Kocienski (C16–C17) and Horner–Wadsworth–Emmons (C21–C22) olefinations. Still–Gennari olefination was used for the C2–C3 ring closure. The key step of the synthesis was a regioselective C16–C17 matched Sharpless asymmetric epoxidation.



Angew. Chem. **2001**, *113*, 3961–3964

Through isoelectronic replacement of the oxygen atoms in SO_4^{2-} ions by one CH_2 and three NtBu groups one arrives formally at the dianion $\text{H}_2\text{CS}(\text{NtBu})_3^{2-}$, which has been isolated for the first time in the form of the sulfur(vi) ylide complex $[(\text{tmeda})_2\text{Li}_2\{\text{CH}_2\text{S}(\text{NtBu})_3\}]$ (see structure). Deprotonation of the S-bonded methyl group in the triimidosulfonate $\text{MeS}(\text{NtBu})_3^-$ ion provides facile access in good yields. Hydrolysis favors the formation of the triimidosulfate $[(\text{tmeda})\text{Li}_2\{\text{OS}(\text{NtBu})_3\}]_3$ and methane, and not, as one might expect, diimidomethylenesulfate and the amine. tmeda = $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$.



Angew. Chem. **2001**, *113*, 3965–3968

M. Rösch, H. Herzner, W. Dippold,
M. Wild, D. Vestweber,
H. Kunz* 3836–3839

Synthetic Inhibitors of Cell Adhesion: A Glycopeptide from E-Selectin Ligand 1 (ESL-1) with the Arabino Sialyl Lewis^x Structure

Keywords: allyl anchor • E-selectin ligand • glycopeptides • sialyl Lewis^x mimetica • solid-phase synthesis

M. Mayr, B. Mayr,
M. R. Buchmeiser* 3839–3842

Monolithic Materials: New High-Performance Supports for Permanently Immobilized Metathesis Catalysts

Keywords: heterogeneous catalysis • metathesis • nanostructures • ring-opening polymerization • ruthenium

J. Mulzer,* E. Öhler* 3842–3846

An Intramolecular Case of Sharpless Kinetic Resolution: Total Synthesis of Laulimalide

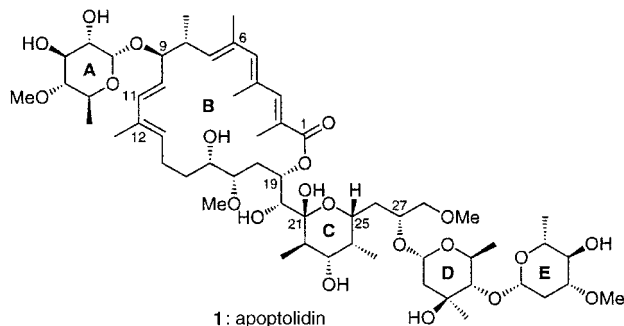
Keywords: asymmetric synthesis • chiral pool • epoxidation • macrolides • olefination

B. Walfort, D. Stalke* 3846–3849

Methylenetriimidosulfate $\text{H}_2\text{CS}(\text{NtBu})_3^{2-}$ —The First Dianionic Sulfur(vi) Ylide

Keywords: bond theory • carbanions • lithium • S ligands • ylides

No less than 30 stereogenic elements, a highly unsaturated 20-membered macrocyclic system, four carbohydrate units, and unique biological activity, make the natural occurring apoptolidin (**1**) a challenging synthetic target. The retrosynthetic analysis revealed five key building blocks—three for the construction of the macrolide ring **B** and two prospective pendant saccharide units—which were synthesized in a highly convergent manner and then connected. Apoptolidin's rather labile nature proved particularly challenging in the final deprotection, purification, and characterization procedures.



Angew. Chem. **2001**, *113*, 3968–3972

Angew. Chem. **2001**, *113*, 3972–3976

K. C. Nicolaou,* Y. Li,
K. C. Fylaktakidou, H. J. Mitchell,
H.-X. Wei, B. Weyershausen 3849–3854

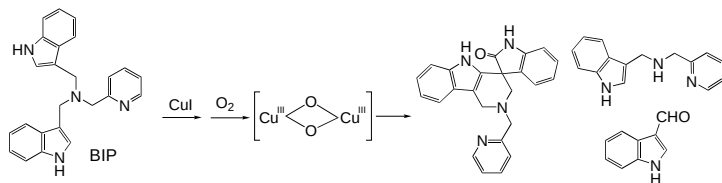
Total Synthesis of Apoptolidin-Part 1:
Retrosynthetic Analysis and
Construction of Building Blocks

K. C. Nicolaou,* Y. Li,
K. C. Fylaktakidou, H. J. Mitchell,
K. Sugita 3854–3857

Total Synthesis of Apoptolidin-Part 2:
Coupling of Key Building Blocks and
Completion of the Synthesis

Keywords: apoptolidin • macrolides •
natural products • total synthesis

Stabilization of the bis(μ -oxo)dicopper(III) intermediate is achieved by using a bidentate N-donor ligand with pendent indole rings: *N,N*-bis[(3-indolyl)methyl]-*N*-(2'-pyridyl)methylamine (BIP). The intermediate decomposes to give products arising from N-dealkylation and a product with a spiro ring composed of two indole rings (see scheme). This latter product probably results from a radical-coupling reaction.



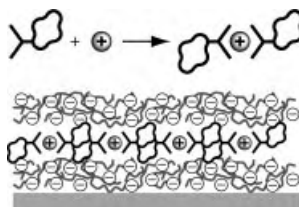
Angew. Chem. **2001**, *113*, 3977–3980

Y. Shimazaki, T. Nogami, F. Tani,
A. Odani, O. Yamauchi* ... 3859–3862

Effects of a Side Chain Aromatic Ring on
the Reactivity of Copper(I) Complexes
with Dioxygen

Keywords: copper • N ligands •
oxidation • radical reactions • structure
elucidation

Layer-by-layer deposition of π -assembled arrays of discrete metallo units with aryl tails and polystyrenesulfonate gives structurally well-defined thin films (see schematic representation). The formation of these films, which is controlled by π - π interactions, metal–ion coordination, and electrostatic interactions, bridges the gap between supramolecular crystal engineering and design of layered materials.



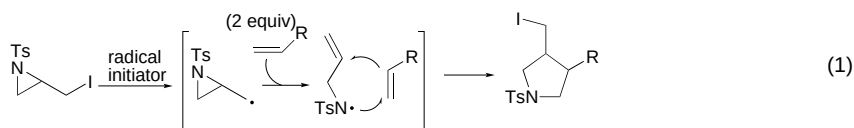
Angew. Chem. **2001**, *113*, 3980–3983

H. Krass, E. A. Plummer, J. M. Haider,
P. R. Barker, N. W. Alcock,
Z. Pikramenou,* M. J. Hannon,*
D. G. Kurth* 3862–3865

Immobilization of π -Assembled Metallo-
Supramolecular Arrays in Thin Films:
From Crystal-Engineered Structures to
Processable Materials

Keywords: crystal engineering • N
ligands • π interactions • supramolecular
chemistry • thin films

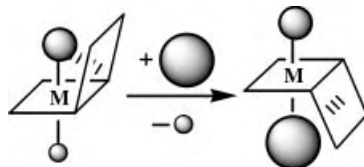
Functionalized pyrrolidine derivatives are accessible in good yields by radical iodine-transfer [3+2] cycloaddition of electron-rich alkenes with azahomoallyl radicals [Eq. (1)], which were generated by treating iodoaziridine derivatives with radical initiators. Ts = tosyl; 4-methylphenyl sulfonyl



Angew. Chem. **2001**, *113*, 3983–3985

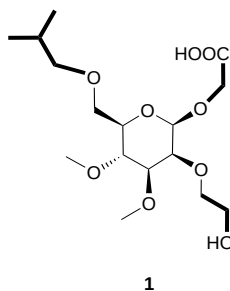


Control of the conformation of the fluorenylidene moiety is achieved through an intramolecular interaction between the fluorenylidene moiety and the axial ligand during the oxidative addition and successive substitution of $[\text{Pt}^{\text{II}}(\text{fm})]$ to give $[\text{Pt}^{\text{IV}}(\text{X})(\text{X}')(\text{fm})]$ (fm = 9-fluorenylidene-malonate; see scheme). The conformation of the fm moiety can be effectively induced by the fluorenylidene-philicity of the axial X/X' ligands, $\text{OOCCH}_3 > \text{OCH}_3 > \text{OH}$.



Angew. Chem. **2001**, *113*, 3986–3988

A cyclic peptide role model was used for the design and synthesis of a new class of biologically active and α_4 -selective integrin antagonists (e.g. **1**) based on β -D-mannose. These carbohydrate-based peptidomimetics were synthesized to include the functional groups of their cyclic peptide precursors without the redundant amide backbone.

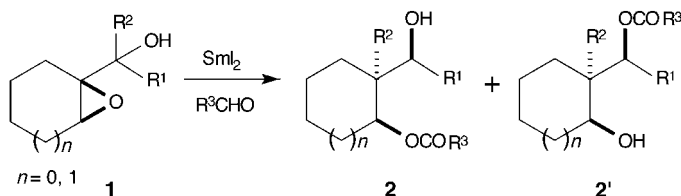


Angew. Chem. **2001**, *113*, 3988–3991

The solvent plays a pivotal role in controlling the selectivity of the catalytic hydrogenation of alkenes and alkynes by $[\text{Ru}_3(\text{CO})_{12-x}(\text{PPh}_3)_x]$ ($x = 1$ or 2) with the mechanism varying with the solvent polarity. In polar solvents the reaction proceeds via H_2 addition products based on $[\text{Ru}_3(\text{H})(\mu\text{-H})(\text{CO})_9(\text{PPh}_3)_2]$, as demonstrated by parahydrogen-induced polarization (PHIP). In nonpolar solvents catalysis by $[\text{RuH}_2(\text{CO})_2(\text{PPh}_3)(\text{substrate})]$, resulting from fragmentation, competes with that by the intact cluster.

Angew. Chem. **2001**, *113*, 3992–3995

Three contiguous stereocenters are constructed with high diastereoselectivity in a novel samarium-catalyzed tandem reaction of α -hydroxy epoxides **1** to give exclusively the C1,C2-*anti* isomers of **2** and **2'**. This could lead to the development of a general procedure for the diastereoselective construction of 2-quaternary 1,3-diol units.



R^1, R^2 : alkyl, aryl; R^3 : phenyl, *p*-chlorophenyl

Angew. Chem. **2001**, *113*, 3995–3998

O. Kitagawa, Y. Yamada, H. Fujiwara, T. Taguchi* 3865–3867

Iodoaziridine Derivatives as Novel Azahomoallyl Radical Precursors for [3+2] Cycloaddition Reactions with Alkenes

Keywords: cycloaddition • nitrogen heterocycles • radical reactions • synthetic methods

Y.-A. Lee, O.-S. Jung* 3868–3870

Unusual Fluorenylidene-philic Interactions for Effective Conformational Induction

Keywords: arene ligands • conformation analysis • noncovalent interactions • oxidative addition • platinum

J. Boer, D. Gottschling, A. Schuster, B. Holzmänn, H. Kessler* .. 3870–3873

Design, Synthesis, and Biological Evaluation of $\alpha_4\beta_1$ Integrin Antagonists Based on β -D-Mannose as Rigid Scaffold

Keywords: carbohydrates • drug research • integrins • peptidomimetics

D. Blazina, S. B. Duckett,* P. J. Dyson,* J. A. B. Lohman 3874–3877

Direct Comparison of Hydrogenation Catalysis by Intact versus Fragmented Triruthenium Clusters

Keywords: catalysts • cluster compounds • hydrogenation • parahydrogen • ruthenium

C.-A. Fan, B.-M. Wang, Y.-Q. Tu,* Z.-L. Song 3877–3880

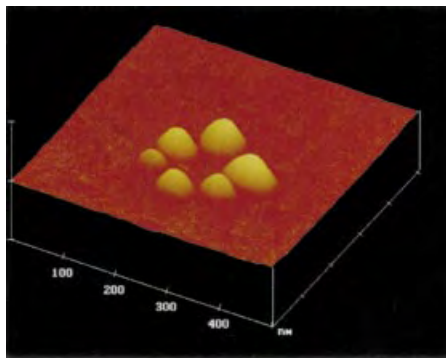
Samarium-Catalyzed Tandem Semipinacol Rearrangement/Tishchenko Reaction of α -Hydroxy Epoxides: A Novel Approach to Highly Stereoselective Construction of 2-Quaternary 1,3-Diol Units

Keywords: alcohols • diastereoselectivity • rearrangement • samarium



A “grafting” method for creating new polymer/V₂O₅/carbon structures with nanodimensions results in materials that are chemically tailored to exhibit fast ion/electron transport. The rate responses are high enough to be of interest in applications such as lithium batteries and supercapacitors, and the concept is applicable to a variety of materials. The picture shows the atomic force microscopy image of V₂O₅/C-PEG nanoparticles on a mica surface. C-PEG = polyethylene glycol functionalized carbon.

Angew. Chem. **2001**, *113*, 3998–4002



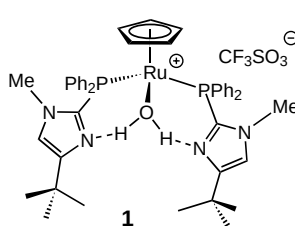
H. Huang, L. F. Nazar* 3880–3884

Grafted Metal Oxide/Polymer/Carbon Nanostructures Exhibiting Fast Transport Properties

Keywords: carbon • conducting materials • nanostructures • organic-inorganic hybrid composites • scanning probe microscopy



A binding pocket for water is created in **1** by the imidazolyl phosphane ligands and the Ru^{II} center. Compound **1** proves to be an excellent catalyst for a highly selective anti-Markovnikov hydration of terminal alkynes to give aldehydes rather than isomeric ketones under near-neutral conditions (aldehyde-to-ketone ratio up to 1000:1).



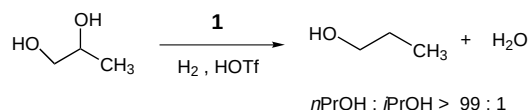
D. B. Grotjahn,* C. D. Incarvito, A. L. Rheingold 3884–3887

Combined Effects of Metal and Ligand Capable of Accepting a Proton or Hydrogen Bond Catalyze Anti-Markovnikov Hydration of Terminal Alkynes

Keywords: aldehydes • alkynes • homogeneous catalysis • N,P ligands • ruthenium

Angew. Chem. **2001**, *113*, 4002–4005

The internal OH group of 1,2-propanediol is selectively removed in the deoxygenation catalyzed by [(Cp*₂Ru(CO)₂(μ-H))⁺OTf[−]] (**1**, Cp* = C₅Me₅, OTf = trifluoromethanesulfonate; see scheme). This reaction provides a model for deoxygenation of polyols derived from carbohydrates, for use in alternative, biomass-based feedstock applications. An ionic mechanism is proposed that involves the dihydrogen complex [Cp*₂Ru(CO)₂(η²-H₂)⁺].



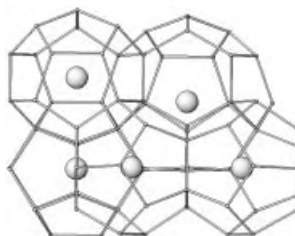
Angew. Chem. **2001**, *113*, 4005–4008

M. Schlaf, P. Ghosh, P. J. Fagan, E. Hauptman, R. M. Bullock* 3887–3890

Metal-Catalyzed Selective Deoxygenation of Diols to Alcohols

Keywords: alcohols • deoxygenation • homogeneous catalysis • hydrido complexes • hydrogenation

When hyperpolarized xenon is placed in contact with a structure II hydrate of THF, Xe NMR spectroscopy shows that a metastable structure II hydrate of Xe (see picture) forms that decomposes to a structure I Xe hydrate and a mixed structure II hydrate of xenon and THF.



I. L. Moudrakovski, C. I. Ratcliffe, J. A. Ripmeester* 3890–3892

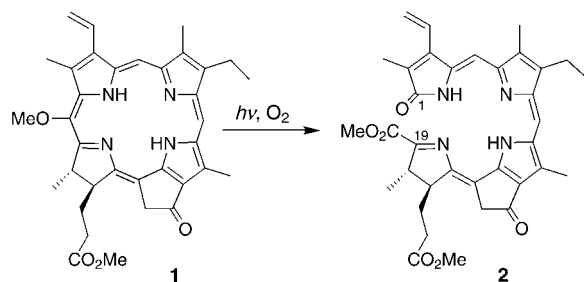
Probing Transient Hydrate Structures with Hyperpolarized ¹²⁹Xe NMR Spectroscopy: A Metastable Structure II Hydrate of Xe

Keywords: clathrates • host–guest systems • NMR spectroscopy • phase transitions • xenon

Angew. Chem. **2001**, *113*, 4008–4010



Remarkable selectivity is exhibited in the photooxidation of 20-methoxychlorin methyl ester (**1**) to exclusively yield the C1–C20 bond cleaved product **2**. This selectivity lends strong support to the hypothesis that a hydroxy or equivalent group at C20 directs the C1–C20 bond cleavage that transforms chlorophylls into krill and dinoflagellate luciferins.



Angew. Chem. **2001**, *113*, 4010–4012

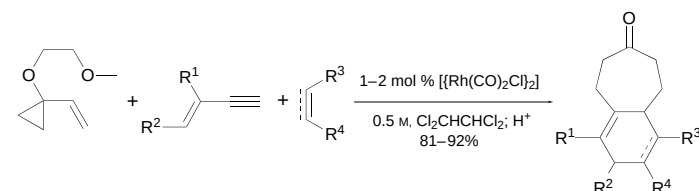
G. Topalov, Y. Kishi* 3892–3894

Chlorophyll Catabolism Leading to the Skeleton of Dinoflagellate and Krill Luciferins: Hypothesis and Model Studies

Keywords: chemoselectivity • chlorophyll catabolism • cleavage reactions • photooxidation • porphyrinoids



Four new bonds and up to four new stereocenters are formed in the title reactions which allow the conversion of readily available starting materials into complex bicyclo[5.4.0]undecane derivatives (see scheme). The reactions are performed in a single, simple operation that can be conducted on a preparative scale (100 mmol thus far).



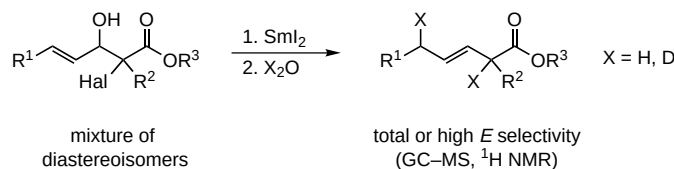
Angew. Chem. **2001**, *113*, 4013–4015

P. A. Wender,* G. G. Gamber, M. J. C. Scanio 3895–3897

Serial [5+2]/[4+2] Cycloadditions: Facile, Preparative, Multi-Component Syntheses of Polycyclic Compounds from Simple, Readily Available Starting Materials

Keywords: chemoselectivity • cycloaddition • enynes • rhodium • tandem reactions

A simple, efficient, highly diastereoselective method for preparing (*E*)- α,δ -dideuterio- β,γ -unsaturated esters: SmI_2 -promoted reduction/elimination of α -halo- β -hydroxy- γ,δ -unsaturated esters in the presence of D_2O (see scheme). This provides the desired products in which the C–C double bond is generated with total or high diastereoselectivity.



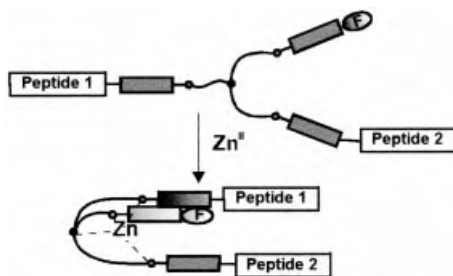
Angew. Chem. **2001**, *113*, 4015–4017

J. M. Concellón,* P. L. Bernad, H. Rodríguez-Solla 3897–3899

Synthesis of Isotopically Labeled (*E*)- β,γ -Unsaturated Esters with Total or High Diastereoselectivity by Using Samarium Diiodide

Keywords: asymmetric synthesis • deuterium • elimination • reduction • samarium

A sevenfold increase in the ability to bind to the dimerization interface of HIV-1 protease is observed by adding a Zn^{II} ion to a tris(aminoethyl)-amine (TREN) templating unit, which bears two peptides with similar sequences as those at the C and N termini of each monomer of the dimeric enzyme (see picture). It is suggested that the metal ion changes the conformation of the putative inhibitor.



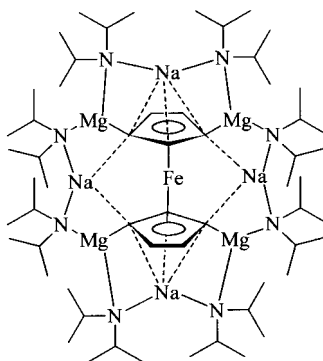
Angew. Chem. **2001**, *113*, 4017–4020

S. Valente, M. Gobbo, G. Licini,* A. Scarso, P. Scrimin* 3899–3902

Allosteric Regulation of an HIV-1 Protease Inhibitor by Zn^{II} Ions

Keywords: allosterism • enzyme inhibitors • peptides • zinc

Remarkably, four hydrogen atoms have been regioselectively removed from the 1,1',3,3'-positions of ferrocene in a single reaction leading to the formation of the new macrocyclic host–guest complex $[\{\text{Fe}(\text{C}_5\text{H}_3)_2\}\text{Na}_4\text{Mg}_4\{\text{iPr}_2\text{N}\}_8]$ (see picture). This novel addition to the s-block metal inverse crown family possesses a tetrasodium–tetramagnesium amido $(\text{Na}_4\text{Mg}_4\text{N}_8)^{4+}$ ring to complete a series of 8, 12, 16, and 24-membered rings.



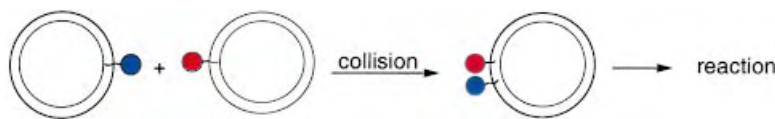
W. Clegg, K. W. Henderson,
A. R. Kennedy, R. E. Mulvey,*
C. T. O'Hara, R. B. Rowlings,
D. M. Tooke 3902–3905

Regioselective Tetrametalation of
Ferrocene in a Single Reaction: Extension
of s-Block Inverse Crown Chemistry to
the d-Block

Keywords: alkali metals • alkaline earth
metals • amides • crown compounds •
ferrocene • host–guest systems

Angew. Chem. **2001**, *113*, 4020–4023

An organic reaction between two populations of vesicles, one containing a nucleophile (blue) and the other an electrophile (red), was examined kinetically (see scheme). By comparing the rates with those of suitable controls, it was demonstrated that the electrophile is transferred during vesicle collisions, and a fast intra-vesicular reaction ensues.



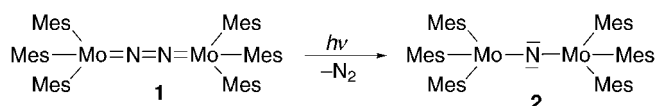
Angew. Chem. **2001**, *113*, 4023–4025

F. M. Menger,* K. L. Caran,
V. A. Seredyuk 3905–3907

Chemical Reaction between Colliding
Vesicles

Keywords: colloids • homogeneous
catalysis • reaction kinetics • vesicles

Photoinduced cleavage of the residual N–N bond in the dimetallahydrazone **1** (Mes = 2,4,6-Me₃C₆H₂) led to a transient monomeric nitrido complex, which reacts further with **1** to form **2**. Compound **1** was synthesized by the reductive arylation of MoCl₄·DME by MesMgBr under an N₂ atmosphere.



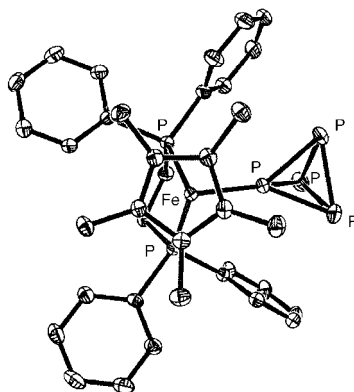
Angew. Chem. **2001**, *113*, 4025–4027

E. Solari, C. Da Silva, B. Iacono,
J. Heschelbrouck, C. Rizzoli,
R. Scopelliti, C. Floriani* .. 3907–3909

Photochemical Activation of the N≡N
Bond in a Dimolybdenum–Dinitrogen
Complex: Formation of a Molybdenum
Nitride

Keywords: dinitrogen • molybdenum •
nitrides • photochemistry

At variance with white phosphorus, the most reactive allotrope of the element, which is unstable and ignites spontaneously in air, the new η^1 -tetrahedro-tetraphosphorus complexes $[\text{Cp}^*\text{M}(\text{PR}_3)_2(\eta^1\text{-P}_4)]\text{Y}$ (M = Fe, Ru; Y = Cl, PF₆, BPh₄, BAr₄; Cp* = C₅Me₅) the structure of the $[\text{Cp}^*\text{Fe}(\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2)(\eta^1\text{-P}_4)]^+$ ion is depicted) exhibit a surprising and unprecedented thermal stability and an astonishing reluctance to react with oxygen and other oxidants.



Angew. Chem. **2001**, *113*, 4028–4030

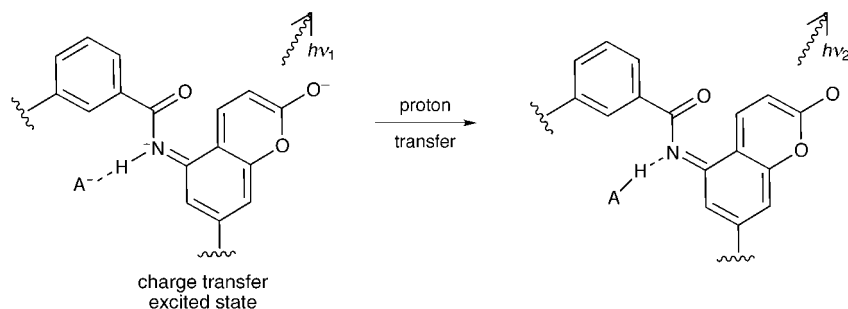
I. de los Rios, J.-R. Hamon, P. Hamon,
C. Lapinte,* L. Toupet, A. Romerosa,
M. Peruzzini* 3910–3912

Synthesis of Exceptionally Stable Iron
and Ruthenium η^1 -tetrahedro-
Tetraphosphorus Complexes: Evidence
for a Strong Temperature Dependence of
M–P₄ π Back Donation

Keywords: cyclopentadienyl ligands •
iron • phosphorus • ruthenium •
structure elucidation



A macrocycle containing an aminocoumarin fluorophore showed two different fluorescence emission bands on binding with certain anions. Proton transfer from the fluorophore excited state occurred depending on the basicity of the bound anion (see scheme, A⁻: anion) and this new pathway makes more-sensitive anion sensing possible.



Angew. Chem. **2001**, *113*, 4030–4033



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

K. Choi, A. D. Hamilton* .. 3912–3915

A Dual Channel Fluorescence
Chemosensor for Anions Involving
Intermolecular Excited State Proton
Transfer

Keywords: anions • host–guest systems •
molecular recognition • sensors

* Author to whom correspondence should be addressed



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The picture shows the delicate white blooms of the giant Saguaro, a cactus found in the deserts of Arizona. The flowers first appear only when the plant is about 50 years old. An attractive parallel can be seen between this slowly maturing beauty and the development of asymmetric organocatalysis, the origin of which goes back to the emergence of the efficient homogeneous asymmetric catalysis.



Enantioselective Organocatalysis

Peter I. Dalko* and Lionel Moisan

Dedicated to Prof. Henry B. Kagan on the occasion of his 70th birthday

The last few years have witnessed a spectacular advancement in new catalytic methods based on metal-free organic molecules. In many cases, these small compounds give rise to extremely high enantioselectivities. Preparative advantages are notable: usually the reactions can be performed under an aerobic atmosphere with wet solvents. The catalysts are inexpensive and they are often more stable than enzymes or other bioorganic catalysts. Also, these small organic molecules can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues, and show promising adaptability to high-throughput screening and process chemistry. Herein we focus on four

different domains in which organocatalysis has made major advances: 1) The activation of the reaction based on the nucleophilic/electrophilic properties of the catalysts. This type of catalysis has much in common with conventional Lewis acid/base activation by metal complexes. 2) Transformations in which the organic catalyst forms a reactive intermediate: the chiral catalyst is consumed in the reaction and requires regeneration in a parallel catalytic cycle. 3) Phase-transfer reactions: The chiral catalyst forms a host–guest complex with the substrate and shuttles between the standard organic solvent and the second phase (i.e. a solid, aqueous, or fluorous phase in which the organic

transformation takes place). 4) Molecular-cavity-accelerated asymmetric transformations: the catalyst can select between competing substrates, depending on size and structure criteria. The rate acceleration of a given reaction is similar to the Lewis acid/base activation and is the consequence of the simultaneous action of different polar functions. Herein it is shown that organocatalysis complements rather than competes with current methods. It offers something conceptually novel and opens new horizons in synthesis.

Keywords: asymmetric catalysis • chiral auxiliaries • synthetic methods

1. Introduction

Since the importance of the spatial arrangement within molecules to the fundamental properties of the substances was recognized, chemists have become increasingly interested in enantioselective synthesis. In the course of time, the field of enantioselective synthesis has outgrown the academic environment. The chiral drug industry has become a rapidly growing segment of the drug market and represents close to one third of all drug sales worldwide.^[1] This has been driven by the increased regulatory control of enantiomeric composition of drug candidates, and the potential of isomerically pure drugs to provide improvements over the previously available racemates.

Undoubtedly, the more elegant and economically most attractive way to introduce chirality into a molecule is by using a catalytic amount of chiral controller to induce the chiral transformation. Enantioselective reactions have had the most significant impact on the development of synthetic organic chemistry in the last 30 years. Among them, methods based exclusively on metal-free chiral organic catalysts have become more significant. Helped by intuition, persistence, and good fortune, these new reactions are becoming powerful tools in the construction of complex molecular skeletons.

Chiral organic molecules have been used from the early days of chemistry to promote reactions. The emergence of homogeneous enantioselective organometallic catalysis has had a decisive effect on the development of enantioselective organocatalytic reactions. With the advent of the first powerful ligands (4,5-bis[(diphenylphosphanyl)methyl]-2,2-dimethyl-1,3-dioxolane-4,5-diol, DIOP), rhodium complexes served as the basis for the development of enantioselective catalytic hydrogenation reactions (reduction of α -acylamino acrylic

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E-mail: peter.dalko@espci.fr

acids, L-DOPA synthesis at Monsanto)^[2b] and thus became the general precursors of enantioselective catalytic reactions. Thus the concept of asymmetric catalysis has become almost synonymous with the use of metals in a chiral environment.^[3] But are metals really indispensable in these catalytic processes? Or can some of their functions be emulated by an organic system? In contrast to most synthetic methods, nature provides a subtle balance between metal-free and metal-mediated conditions. Metals certainly have considerable advantages over organic substances, for example, molecular and structural diversity and a large array of reactivity patterns that can easily be tuned by varying ligands. As well as the tremendous benefits that metal derivatives offer they are also the source of increasing problems such as high price, toxicity, pollution, waste treatment, and product contamination.^[4] A large number of asymmetric transformations are based exclusively on organic reagents: there is an increasing tendency to devise reaction conditions that allow the regeneration of the chiral reagents. This concept will certainly help the development of a number of new organocatalytic reactions in the near future. On the other hand, roles that are typically associated with metals, for example, as Lewis acids/bases and as redox agents^[5] can be emulated fairly well by organic compounds.

The last few years have witnessed a spectacular advancement in new catalytic methods based on organic molecules. In many cases, these small compounds result in extremely high enantioselectivities. Preparative advantages are notable: usually the reactions can be performed under an aerobic atmosphere with wet solvents. The catalysts are inexpensive and they are often more stable than enzymes or other bioorganic catalysts. Also, these small organic molecules can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues, and show promising adaptability to high-throughput screening and process chemistry.

There is a dichotomy between organic and organometallic/bioorganic catalysis, particularly with respect to their reactivity and applications. On one hand, organocatalytic reactions have evolved essentially from the ligand chemistry of

organometallic reactions. A large array of ligands were developed for metal-mediated enantioselective catalytic reactions and are still among the most effective organocatalysts. It is thus not surprising that there are metal-catalyzed reactions in which the metal-free ligand is known to be active by itself, even in the same enantioselective transformations.^[6] On the other hand, organocatalytic reactions can be more closely related to enzyme- or antibody-catalyzed reactions than to organometallic processes. Indeed, these small organic molecules, which are often also known as artificial enzymes^[7] or enzyme mimetics, show some characteristic features of bioorganic reactions. They often follow saturation or Michaelis–Menten kinetics reminiscent of a mechanism that involves the reversible formation of an enzyme–substrate complex. However, this apparent similarity hides major differences, especially in the mode of action. Enzymes act essentially by stabilizing the transition state of the reaction by the subtle orchestration of a number of functions, whereas organic molecules promote the reactions as simple reagents. Enzymes are more than just highly evolved catalysts^[8]—catalytic efficiency, selectivity, and high turnover are only part of the peculiar characteristics of the sophisticated system, which involves built-in feedback mechanisms and subtle intra- and intermolecular cooperation. Herein we show that organocatalysis complements rather than competes with current methods.^[9] It offers something conceptually novel and opens new horizons in synthesis.

Organic molecules can catalyze chemical reactions through four different mechanisms:

- Activation of the reaction based on the nucleophilic/electrophilic properties of the catalysts. The chiral catalyst is not consumed in the reaction and does not require parallel regeneration. This type of activation is reminiscent of conventional Lewis acid/base activation.
- Organic molecules that form reactive intermediates. The chiral catalyst is consumed in the reaction and requires regeneration in a parallel catalytic cycle.
- Phase-transfer reactions. The chiral catalyst forms a host–guest complex with the substrate and shuttles between the standard organic solvent and a second phase (i.e. the solid,

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Lionel Moisan was born in Annemasse (France) in 1975. He studied chemistry at the Ecole Supérieure de Physique et de Chimie Industrielles, Paris and obtained his Diplôme d'Etudes Approfondies in organic and bioorganic chemistry at the Pierre et Marie Curie University, Paris. He is currently working at the Commissariat à l'Energie Atomique as a scientific fellow.



P. I. Dalko



L. Moisan

aqueous or fluorous phase in which the reaction takes place).

- Molecular-cavity-accelerated asymmetric transformations, in which the catalyst may select between the competing substrates, depending on size and structure criteria. The rate acceleration of the given reaction is similar to the Lewis acid/base activation and is a consequence of the simultaneous action of different polar functions.

2. Principal Factors That Govern the Stereoselectivity of the Organocatalytic Reactions

In metal-mediated enantioselective catalytic reactions, the metal plays an organizational role by translating chiral information and activating the reagents. In the absence of the metal, the well-organized transition state, which is required for the enantioselective transformation, can be formed either by passive or dynamic interactions, as is the case in biological systems. Passive binding refers to ordinary molecular recognition through hydrophobic, van der Waals, and electrostatic interactions. Dynamic binding refers to interactions between catalysts and substrates at the reaction centers. Hydrogen bonding plays a crucial role in the determination of the stereoselectivity of the reaction. Although this represents an energy contribution of only 1–6 kcal mol⁻¹ to the interactions, hydrogen bonding influences the conformational preferences by forming rigid three-dimensional structures and contributes to the affinity and selectivity of molecular recognition. Hydrogen bonding also plays an important role in stabilizing the reactive intermediates and in modulating the reactivity,^[10] in a very similar way to enzyme catalysis. More and more evidence is being gathered on the complexity of the enantioselective transformation caused by the formation of aggregates (dimers) between substrates and catalysts in the most enantioselective path. These new findings challenge our traditional view, which is based essentially on the consideration of monomers.

3. Enantioselective Catalytic Transformations Based on the Nucleophilic/Electrophilic Properties of the Catalyst

3.1. Principal Catalyst Classes

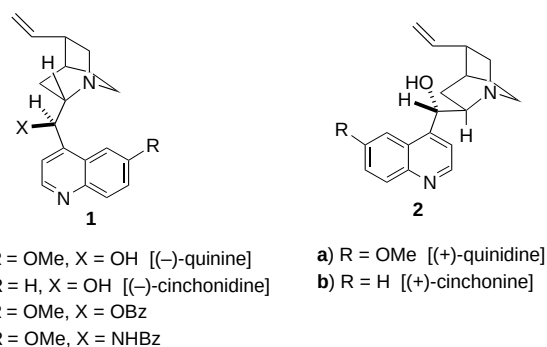
The Lewis acid/base function of organometallic reagents can be emulated by organic systems and applied to enantioselective catalytic processes. A particularity of organocatalysts is the facile equilibrium between the relatively electron-rich and electron-deficient states (i.e. the acidic and basic forms) of the same center. It is easy to conceive this equilibrium simply by considering protonation–deprotonation, which on one hand can activate the reagent and on other hand can contribute to the kinetic lability of the ligand. As a result of this equilibrium the same center can act as a Lewis acid or as a Lewis base, depending on the reaction conditions. Although in any given reaction one can have a clear idea of the role of the organic catalyst as an acid or a base, the

classification based on the electron-donating or electron-accepting ability of the molecules can be ambiguous. This acid–base dichotomy is well known in biological systems. In ribonuclease A, one imidazole unit acts as a general base and the protonated form of the other imidazole unit acts as a general acid.^[11] In the mechanism that is widely proposed for aspartic proteases such as pepsin, penicillopepsin, renin, and HIV protease, one carboxy group acts as a general acid and the ionized form of the other carboxy group acts as a general base or as a nucleophile.^[12] Moreover, the acid/base classification of the catalysts is hampered by the fact that a number of organocatalysts, for example, amino acids, possess both acidic and basic functions and arguably mediate the reaction by a push–pull mechanism.

Most organic catalysts are well known to organic and organometallic chemists. These are either natural or synthetic chiral ligands that were developed for organometallic reactions.^[13] Some natural products and catalysts derived from diversity-driven research by using, for example, combinatorial chemistry and biological screening, have been added to this pool of compounds. These techniques, which generate a large number of potential candidates and select those that perform best, is particularly useful for preparing peptide-based catalysts.

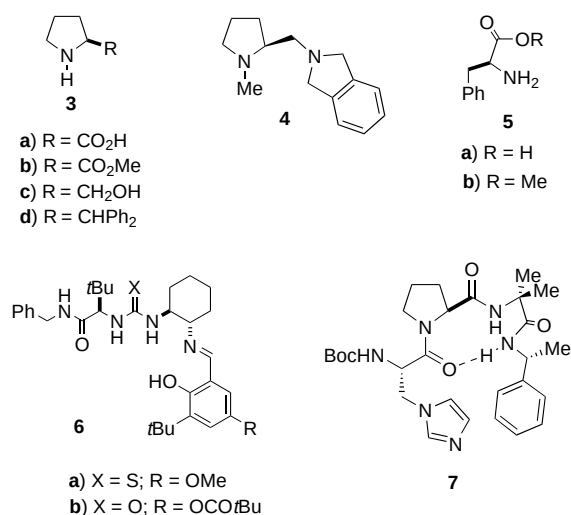
3.1.1. Catalysts Derived from Natural Products

Not many of the alkaloids that have been tested in organocatalytic reactions have been selected for further studies. Only a few possess a naturally occurring enantiomeric counterpart that would allow their convenient use in enantioselective synthesis. An exception is the readily available and inexpensive cinchona alkaloids, which have pseudoenantiomeric forms such as quinine **1a** and quinidine **2a** (Scheme 1). Both forms of this natural product and their derivatives produced impressive results in enantioselective catalytic reactions.



Scheme 1. Cinchona alkaloids and some cinchona-derived chiral catalysts. Bz = benzoyl.

Although amino acids such as proline (**3a**) and phenylalanine (**5a**) and derivatives have been used for a long time in enantioselective catalytic reactions, the use of peptide-like enzyme mimics such as **6** or **7** is a recent development (Scheme 2). The “oligopeptide approach” has some advan-

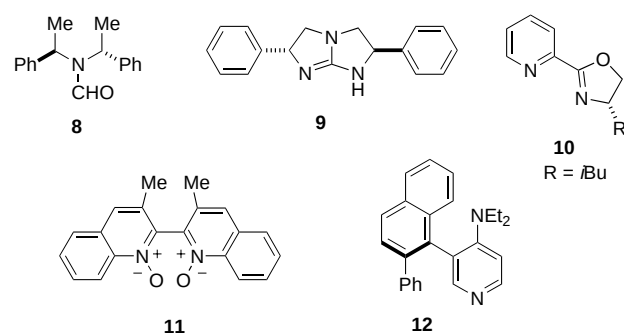


Scheme 2. Some catalysts derived from amino acids and peptides. Boc = *tert*-butoxycarbonyl.

tages. Firstly, the efficiency of the catalyst can be improved by varying the nature of the amino acids by using combinatorial synthetic methods. Secondly, the structural simplicity of the oligopeptides contrasts with the complexity of the enzymes and thus renders the mechanistic investigations easier. Thirdly, the flexibility of the method is of great use: it is easy to prepare the peptide sequence that can produce the opposite enantiomer or its epimer; this is not often possible with enzymes.

3.1.2. Synthetic Molecules

The main advantages of synthetic over natural molecules are that both enantiomers are readily available, and that the structure can be easily modified. Many synthetic molecules are known to be efficient organic catalysts: most originate from ligand chemistry. Among them, C₂-symmetrical molecules such as **8** and **9** (Scheme 3) attracted much interest.

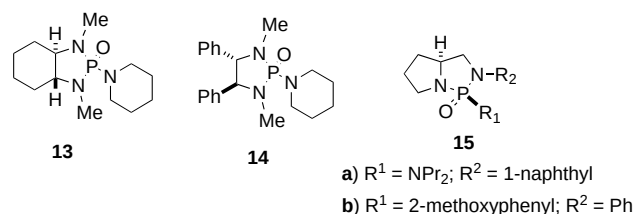


Scheme 3. Some N-containing catalysts.

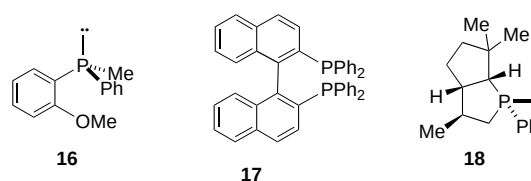
Symmetry, however, is not a structural requirement for a good catalyst (**10**). Also, atropisomerism (e.g. **11** and **12**) remains an efficient means of inducing chirality. Although there is no naturally occurring source of phosphorus-containing chiral compounds for enantioselective catalytic use, there is under-

standably intense synthetic activity to complete the gap.^[14] Besides the potential complexation ability of the phosphorus atom, a particular advantage of this type of compound is its ability to act both as a nucleophilic site as well as a stereogenic center. Scheme 4 illustrates some of the principal phosphorus-containing organic molecules that are used as Lewis bases in enantioselective catalytic transformations.

Phosphoramides:



Phosphanes:



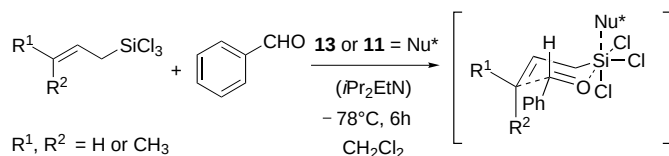
Scheme 4. Selected P-based catalysts used in enantioselective catalytic transformations.

3.2. Reactions and Applications

3.2.1. Allylation Reactions^[15]

Chiral Lewis bases such as phosphoramides,^[16, 17] formamide,^[18] urea,^[19] oxazolidine,^[20] and amine *N*-oxide,^[21] have been used in the enantioselective allylation of aldehydes. The work relies on the observation that hexamethyl phosphoramide (HMPA) considerably accelerates the addition of “activated” allylsilanes to aldehydes. The activation involves a decrease in the electron density at the silicon atom by using halogen substituents, which in turn increases the electrophilicity of this center. Trichlorosilanes were selected to facilitate the coordination of the Lewis base and to increase the coordination ability of the silicon center to the carbonyl group of the substrate. The asymmetric activation relies on the formation of a tightly bound chiral complex between the HMPA analogues and the silicon compounds. According to the postulated mechanism, the allyl transfer occurs via a well-defined six-membered transition state (TS). In the postulated TS, the octahedral hexacoordinated silicon center effects a rate acceleration and provides a chiral environment.^[22] *Anti* and *syn* addition products can be prepared by using *E* or *Z* allyl silanes, respectively. This selectivity is undoubtedly an advantage over the metal-mediated Lewis acid activation in allylation, which provides the optically active *syn* homoallylic alcohols from either stereoisomer of crotyltrialkylsilanes and -stannanes.^[23] The reaction gives good results with aromatic aldehydes, but most reactions with aliphatic analogues fail. When monodentate phosphoramidate catalysts are used, the enantioselectivity of the allylation/crotylation reaction is

sensitive to the amount of catalyst. For example, in the transformation depicted in Scheme 5, a large amount (1 equivalent) of catalyst **13** resulted in *ee* values of up to 66%, but a decrease in the catalyst to 10% afforded product



13 (1.0 equiv) 68–81% (60–66% *ee*)
11 (0.1 equiv) 52–85% (49–88% *ee*)

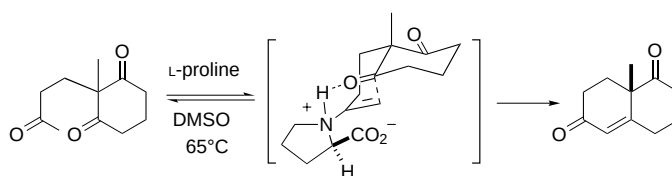
Scheme 5. Enantioselective catalytic allylation of benzaldehyde.

with 53% *ee*. This is the consequence of two parallel competing reaction paths: the less selective route involves the complex with a single bound base, and the more selective route involves the complex with two bound chiral bases.^[24] The observed nonlinear effect and higher-order dependence on the concentration of phosphoramidate accommodates the bis-ligated mechanistic picture well.^[24] Tethered bis-phosphoramides result in better *ee* values and allow the concentration of the catalyst to be decreased to 5–10% without a significant loss of selectivity. The reaction can be accelerated by the addition of diisopropylethylamine. The best enantioselectivity to date (*ee* up to 92% with 10% catalyst) was obtained in the simple alkylation reaction with bisquinoline *N,N'*-dioxide **11**.

3.2.2. Aldol Condensations^[25]

Aldol condensations under organocatalytic conditions have been the focus of extensive studies. Among them, chiral amine-catalyzed (Knoevenagel or Mannich) condensations and a novel, Lewis base mediated aldol reaction deserve particular interest. The enantioselective catalytic two-phase aldol reaction will be discussed in Section 5.2.3.

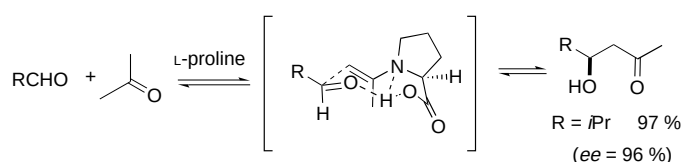
Since its discovery, the amino-acid catalyzed asymmetric Robinson annulation received a considerable amount of synthetic and mechanistic interest.^[26] The reaction is mediated by a number of other natural and unnatural amino acids.^[25a,b, 27] Amongst these, L-proline (**3a**) was shown to be the most general and L-phenylalanine (**5a**) the most efficient catalyst for the preparation of substituted enones.^[28] In the original L-proline-catalyzed intramolecular version, the reaction is a desymmetrization reaction that discriminates between two enantiotopic carbonyl groups (Scheme 6). The reaction most probably proceeds via an enamine intermediate, at least in the proline-catalyzed version, in which a hydrogen bond between the protonated nitrogen atom of the proline moiety and a carbonyl group is a prerequisite for the



Scheme 6. The synthesis of the Wieland–Miescher ketone by using L-proline-mediated asymmetric Robinson annulation. DMSO = dimethyl sulfoxide.

asymmetric induction (Scheme 6). The length of the hydrogen bond is one of the criteria that allow selection between the diastereotopic carbonyl groups.

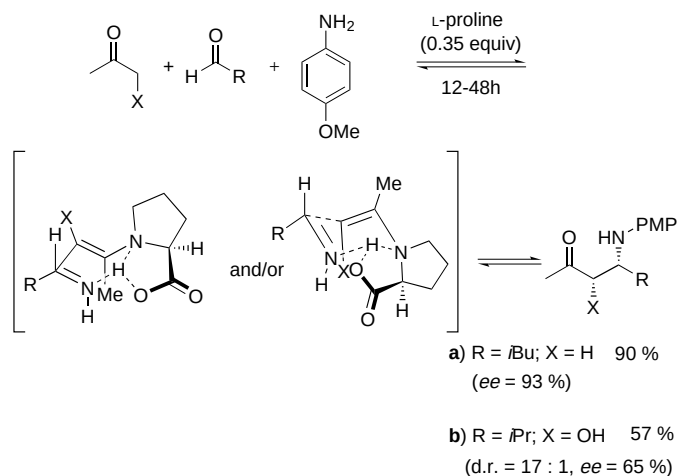
Interestingly, it proved difficult to develop an intermolecular version of this aldol reaction. Only recently was the reaction of acetone and selected aldehydes reported, with *ee* values of up to 96% (Scheme 7).^[29] A limitation of the process



Scheme 7. The intermolecular asymmetric aldol reaction mediated by L-proline.

arises, however, from the selfcondensation of the ketone and the aldehyde, which results in a low yield of the desired crosscondensation product. These side reactions can be minimized by using α -unsubstituted aldehydes.^[30] It was pointed out that the catalyst functions as a micro-aldolase, reminiscent of natural class I aldolases. These enzymes work through an enamine-based mechanism and do not require a metal cofactor.

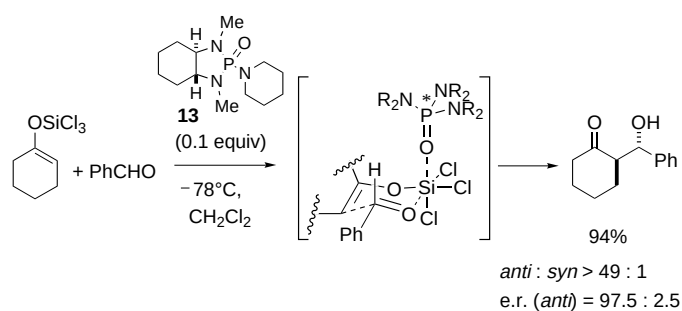
For a high selectivity in the enantioselective catalytic three-component (Mannich) coupling reaction, two conditions must be fulfilled: 1) the nucleophilic addition of the proline enamine (Scheme 8) must be faster to an imine than to an



Scheme 8. The L-proline-catalyzed three-component Mannich reaction. PMP = *p*-methoxyphenyl.

aldehyde; 2) the imine formation with a primary amine must be faster than the competitive aldol reaction.^[31, 32] These conditions are not always true in practice and the side product of the reaction is the corresponding aldol product. Both α -substituted and α -unsubstituted aldehydes can be used and afford the corresponding β -amino ketones in good yields and enantiomeric excesses. However, the ketone component does not allow as much variation. Interestingly, despite the fact that both the previously discussed aldol reaction and the Mannich reaction proceed through an enamine mechanism, the opposite enantiofacial selectivity is observed in the reactions when L-proline or L-penicillamine derivatives^[33] are used as catalysts.

The Lewis base activation of the reacting silyl enol ether is a conceptually novel approach in catalytic aldol reactions (Scheme 9).^[34] The required trichlorosilyl enolates, which

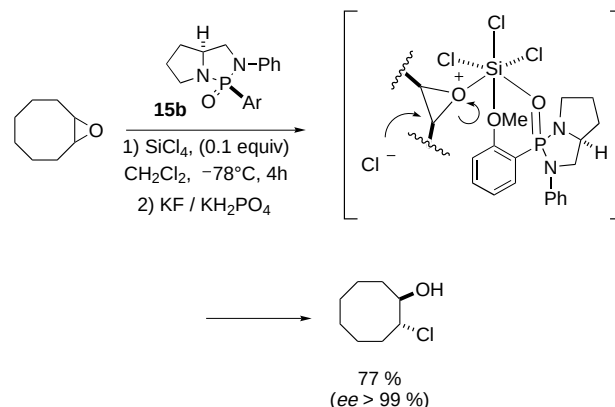


Scheme 9. Chiral-phosphoramidate-mediated asymmetric aldol reaction.

can be prepared in situ from the corresponding trimethylsilyl (TMS) ether by a mercury(II)-catalyzed transsilylation reaction, are reactive intermediates in the absence of any additives and react with aldehydes at ambient temperature or even below. This uncatalyzed reaction provides the aldol adducts in high yields, albeit with low diastereoselectivity. The aldol reactions are dramatically accelerated by the addition of a catalytic amount (10%) of HMPA or its asymmetric analogues, such as **13** or **14** (Scheme 4). The enantioselectivity of the process is sensitive to the enolate structure, with larger groups resulting in lower enantioselectivities. The structure of the aldehyde has a marked effect on the rate of the reaction: aliphatic and sterically hindered aldehydes are less reactive. Also, the reaction of the methyl ketone enolates that bear α substituents or the use of chiral aldehydes give rise preferentially to the *anti* product with predictable albeit lower enantioselectivity. As in the allylation reaction, the asymmetric activation relies on the formation of a tightly bound chiral complex between the HMPA analogues and the silicon compounds, which increases the rate of the reaction (Scheme 9). A careful analysis of the kinetic data supports a dual reaction path as was the case in the chiral phosphoramidate mediated allylation reaction (Section 3.2.1). The complexity of the system makes it difficult to draw transition structures that could explain the steric differentiation and thus the origin of the enantioselectivity is not currently well understood.

3.2.3. Nucleophilic Ring Opening of Epoxides^[35]

Chiral organophosphorus Lewis bases such as **15a**, **b** are known to mediate the enantioselective ring opening of *meso*-epoxides.^[36] Cyclic phosphonic amides such as **15b** with *ortho*-alkoxy substituents on the arylphosphane oxide moiety are superior catalysts in the desymmetrization of *meso*-epoxides than the compounds without alkoxy substituents (Scheme 10).^[37] These compounds have been shown to mediate



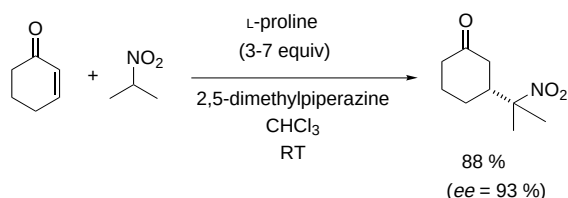
Scheme 10. Desymmetrization of *meso* epoxides by ring opening with a chiral phosphoramidate catalyst.

the asymmetric ring opening of *meso*-epoxides by SiCl_4 with 10% of catalyst loading with up to 99% *ee*. A decrease in the amount of catalyst from 10 to 5% considerably decreases the enantioselectivity. The catalyst and the substrate are organized around a hypervalent silicon intermediate in the putative mechanism, as is the case in the previously described aldol condensation. The required chloride anion is believed to be generated from the binding of the phosphoramidate to the SiCl_4 . The chlorohydrin is formed by the enantioselective ring opening of the activated oxirane ring by a chloride anion.

3.2.4. Asymmetric Conjugate Additions to α,β -Unsaturated Carbonyl Compounds^[38]

Cinchona alkaloids **1a**, **1b**, **2a**, and **2b** as well as L-proline (**3a**) were shown to mediate enantioselective alkylation reactions either under homogenous or biphasic (phase-transfer) conditions. The relatively low basicity of amines restricts the range of potential Michael donors and acceptors. Nitroalkanes were used, either with or without basic additives, in enantioselective catalytic reactions and under homogenous conditions.^[39] Thiols,^[40, 41] thioglycolic acids,^[42] or azides^[43] were used as heteroatom-containing nucleophiles.

Catalytic asymmetric additions of nitroalkanes to cyclic enones afford poor enantiomeric excesses when chiral metal complexes are used. These reactions can be mediated efficiently with L-proline in the presence of *trans*-2,5-dimethylpiperazine. Under these conditions, secondary nitroalkanes were added to cyclopentenone, cyclohexenone and cycloheptenone with 75–93% *ee* (Scheme 11).^[44] Somewhat less selective results were observed when primary nitroalkanes were tested. The structure and the basicity of the



Scheme 11. Asymmetric L-proline-catalyzed conjugate addition of an α,β -unsaturated carbonyl compound.

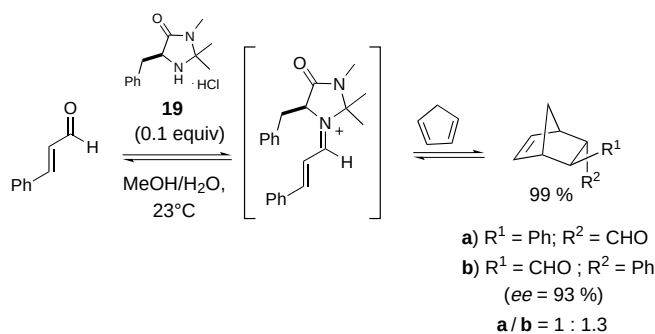
additive plays a major role in the stereodifferentiation step. An interesting nonlinear effect was observed when either the piperazine, quinine, or piperidine additives were used. Although no attempt was made to develop a mechanistic picture, the pronounced nonlinear effect indicates a complex multicomponent chiral catalytic system.

3.2.5. Cycloaddition Reactions

3.2.5.1 Diels–Alder Reactions^[45]

Organic systems, like metal-derived Lewis acids, can mediate Diels–Alder reactions by lowering the lowest-unoccupied molecular orbital (LUMO) of the dienophile. Chiral amines such as cinchona alkaloids, ephedrine, and prolinol derivatives have been known for more than a decade to catalyze [4+2] cycloadditions although with modest selectivities.^[46, 47]

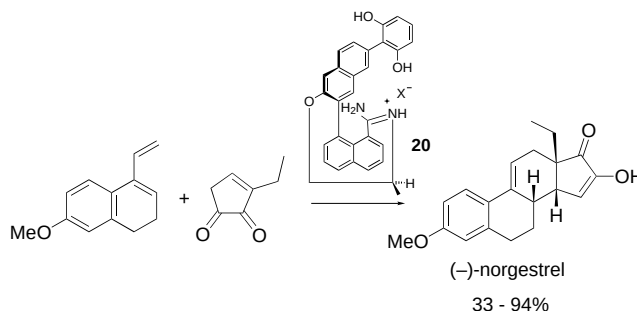
The reversible formation of iminium ions (Scheme 12), from α,β -unsaturated aldehydes and amines shows the characteristics of Lewis acid catalysis.^[48] Naturally occurring



Scheme 12. Asymmetric Diels–Alder reaction mediated by a cyclic L-phenylalanine derivative.

amines (e.g. L-proline- and abrine (*N*-methyltryptophan) methyl ester) as well as synthetic linear and cyclic derivatives (e.g. **19**) were tested in this reaction and were shown to be efficient catalysts. Interestingly, the presence of water results in increased rates and enantioselectivities, which indicates that the iminium ion is hydrolyzed in the catalytic cycle.

Chiral amidinium ions such as **20** may act as mild Lewis acids in the activation of α -diketones in Diels–Alder reactions.^[49] Both the stoichiometric “host–guest” activation and the reaction with substoichiometric amounts of catalysts (as little as 0.1 equivalents) were tested in the construction of the (–)-norgestrel skeleton (Scheme 13). A considerable rate

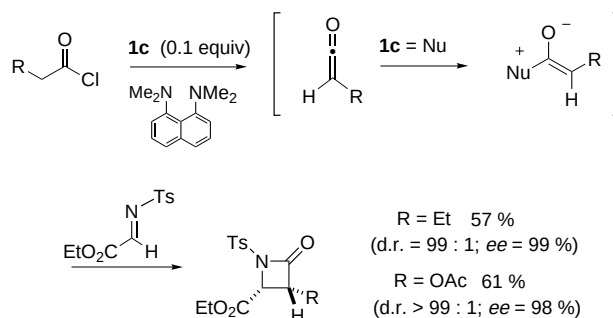


Scheme 13. Enantioselective synthesis of (–)-norgestrel by means of an asymmetric Diels–Alder reaction mediated by a chiral immonium salt.

acceleration was observed in the presence of different substituted amidinium catalysts relative to the uncatalyzed reaction, although both the regio- and enantioselectivity remained low ($\leq 3.8:1$ and $\leq 2.5:1$, respectively).

3.2.5.2. [2+2] Cycloaddition Reactions^[50]

The cinchona alkaloid catalyzed asymmetric [2+2] cycloaddition reaction between ketenes and aldehydes has been known for almost two decades.^[51] The product of this transformation is the corresponding β -lactone. Recently it was shown that the reaction can also be extended to the enantioselective preparation of β -lactams by using cinchona alkaloid derivatives (Scheme 14).^[52] The reaction requires



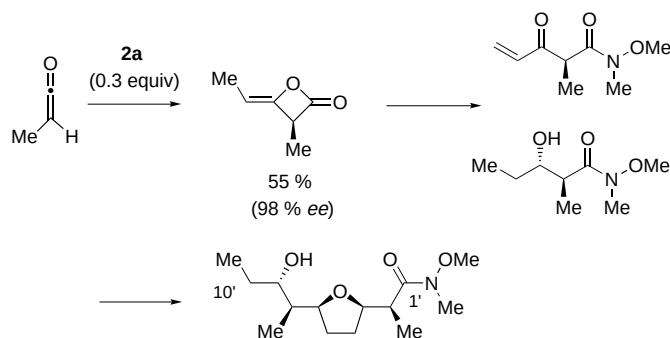
Scheme 14. Enantioselective catalytic cycloaddition of imines to ketenes catalyzed by cinchona derivatives. Ts = *p*-toluenesulfonyl.

high dilution to obtain a high degree of asymmetric induction. The benzoylquinine catalyst **1c** plays two distinct catalytic roles and acts as a dehydrohalogenation agent and as a nucleophilic catalyst. The reaction is driven by a strong non-nucleophilic organic base “proton sponge” that regenerates the catalyst, thus forming a salt that precipitates from the toluene solution (Scheme 14).

Cinchona derivatives also mediate the enantioselective dimerization of ketenes (Scheme 15).^[53] This reaction was used to prepare the C_{17} – $C_{10'}$ segment of the macrocyclic antibiotic pamamycin 621A.^[54]

3.2.5.3. [3+2] Cycloaddition Reactions

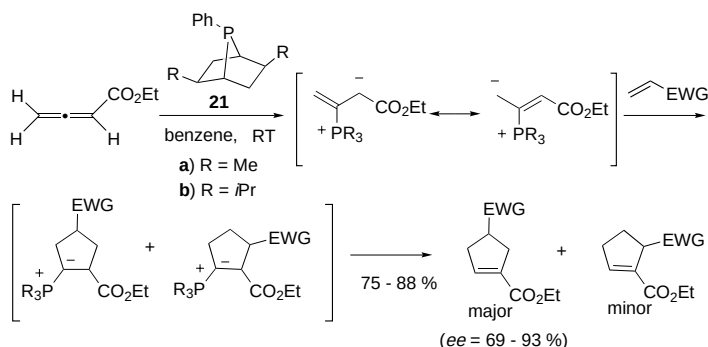
α,β -Unsaturated aldehydes are usually poor substrates for metal-catalyzed nitron cycloadditions owing to the prefer-



Scheme 15. Synthesis of the C_{1'}–C_{10'} fragment of the pamamycin 621A by using quinidine-mediated enantioselective catalytic dimerization of methyl ketenes.

ential coordination of Lewis acids to nitron oxides. This reaction is amenable by using chiral amines such as **19**.^[55]

Activated alkenes undergo a formal asymmetric [3+2] cycloaddition in the presence of allenic esters and a catalytic amount of chiral phosphane catalyst **21**.^[56] The proposed mechanism of this transformation is depicted in Scheme 16.

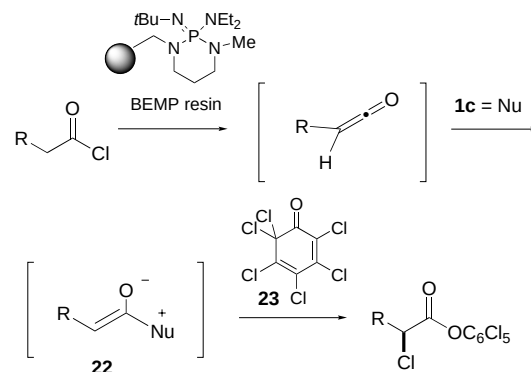


Scheme 16. The phosphane-catalyzed [3+2] cycloaddition reaction. EWG = electron-withdrawing group.

Although a mixture of both regioisomers were generally obtained, a pronounced selectivity in favor of the β -substituted cyclopentene derivative was observed.

3.2.6. α -Halogenation of Carbonyl Compounds

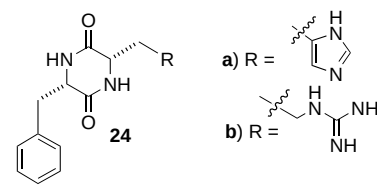
Ketenes derived from acyl halides may undergo asymmetric α -halogenation/esterification in the presence of halogenating agents such as **23** and cinchona alkaloids.^[57] The reaction is based on the reversible addition of the chiral amine to the ketene to form the zwitterionic enolate **22**. An electrophilic halogenating reagent then reacts at the α -position of the enolate to afford an acylammonium salt, which is then transacylated to regenerate the chiral nucleophile and to give rise to an α -halo ester in yields of 50 to 81 % and with 80 to 99 % *ee* (Scheme 17). Interestingly, cinchona alkaloids such as **1c** are significantly more catalytically active than typical tertiary amines. The best yields were obtained when the ketene was preformed by using a solid-phase-supported base such as triaminophosphonamide imine on 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorin (BEMP) resin.



Scheme 17. Asymmetric α -halogenation of ketenes derived from carboxylic acids.

3.2.7. Hydrocyanation Reactions^[58]

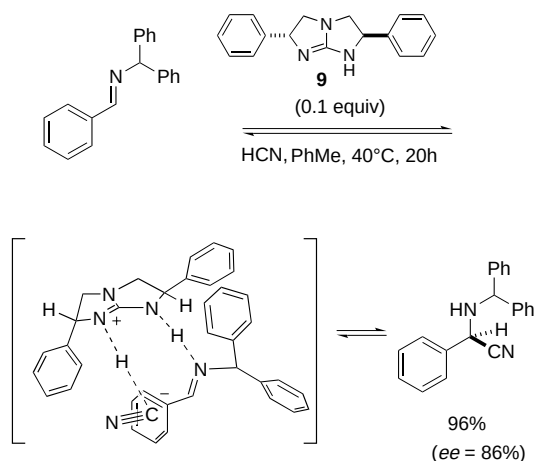
The hydrocyanation reaction of carbonyl compounds by using optically active alkaloids as catalysts was among the first organocatalytic reactions to be discovered.^[59] The low enantioselectivity of the early systems were considerably improved. Synthetically useful asymmetric inductions have been obtained by using cyclic dipeptides such as **24a** (Scheme 18).^[60, 64] It was postulated at this time that linear peptides



Scheme 18. Cyclic dipeptides as catalysts for asymmetric hydrocyanation.

are unsuitable for asymmetric catalysis because of their flexible structure and variable conformation. The mechanism of this reaction, however, remains confusing because of the complex experimental conditions required to obtain good asymmetric induction.^[61]

The organocatalytic variant of the asymmetric aminoalkylation reaction (the Strecker reaction) was the logical extension of the cyanohydrin synthesis.^[62] The first catalyst employed was a cyclic dipeptide^[63] **24b** which is structurally related to **24a**.^[64] Interestingly, **24a** does not result in any asymmetric induction in the mechanistically similar aminoalkylation reaction. The replacement of the imidazole moiety with a more basic guanidine side chain provides a solution. Although efficient catalytic reactions give rise to α -amino nitriles from benzaldehyde derivatives with high enantioselectivities, a low selectivity was observed in the reactions of aldimines derived from aliphatic and heterocyclic aldehydes. The structurally related although more simple chiral guanidine **9** efficiently mediates the addition of HCN to achiral *N*-benzhydrylimines^[65] (Scheme 19). The catalytic action of the bicyclic guanidine can be rationalized by the formation of a guanidium cyanide complex, which activates the Schiff base (aldimine) substrate by hydrogen bonding. The mechanism suggests an insight into the efficacy of the guanidine-bearing diketopiperazine catalyst **24b**.

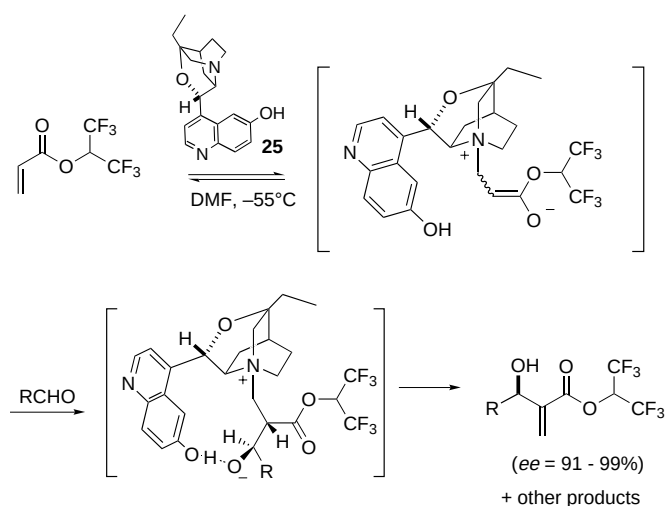


Scheme 19. The asymmetric hydrocyanation with the chiral guanidine catalyst **9**.

One of the most notable advantages of organic catalysts over organometallic reagents is that the former can be used in solid-phase reactions. High-throughput screening of resin-supported catalyst candidates was used to prepare oligopeptide-like catalysts and to select the most enantioselective library members for the Strecker reaction.^[66] The selected compounds were validated by the preparation of soluble analogues such as **6a, b**. These small, acyclic, peptide-like molecules showed remarkable selectivity with aryl imine and selected cycloalkyl imine derivatives. Consistent with the notion that these catalysts emulate enzymes, the reaction follows a Michaelis–Menten kinetic profile, which indicates the reversible binding of the imine followed by the rate-limiting addition of HCN.

3.2.8. The Enantioselective Catalytic Baylis–Hillman Reaction^[67]

The reaction of aldehydes with activated alkenes such as acrylates (the Baylis–Hillman reaction) is typically catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) or tertiary phosphanes. Under asymmetric conditions both N- and P-based catalysts have been used. The asymmetric Baylis–Hillman reaction can be mediated efficiently by hydroxylated chiral amines derived from cinchona alkaloids such as **25** (Scheme 20).^[68] The reaction is applicable either to aromatic or aliphatic aldehydes and results in high enantioselectivities. The selectivity can be rationalized by the formation of a betaine intermediate, which is stabilized by intramolecular hydrogen bonding between the oxy anion and the phenolic hydroxy group. This structure provides rigidity to the postulated activated complex and thus allows a higher selectivity.^[69] In this arrangement the conformation is nearly ideal for the subsequent elimination process that is necessary for the regeneration of the catalyst. Phosphorus-based chiral molecules also mediate the asymmetric Baylis–Hillman transformation efficiently. Catalytic amounts of 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP; **17**) were shown to catalyze the reaction with selected aldehydes with *ee* values of up to 44%.^[70] The enantiomerically enriched chiral

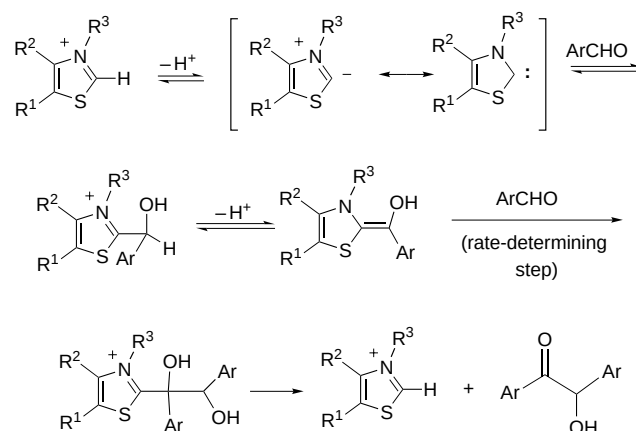


Scheme 20. The asymmetric Baylis–Hillman reaction catalyzed with cinchona-derived **25**.

phosphane (–)-CAMP **16** has been shown to mediate the intramolecular reaction although in low enantiomeric excesses.^[71] The low selectivity was attributed to the reversibility of the cyclization. The major drawbacks of the organocatalytic Baylis–Hillman reaction are its slow reaction rate and the limited scope of substrates. These shortcomings can be partly overcome by using metal-derived Lewis acids.^[72]

3.2.9. Asymmetric Synthesis with Chiral Heteroazolium Catalysts^[73]

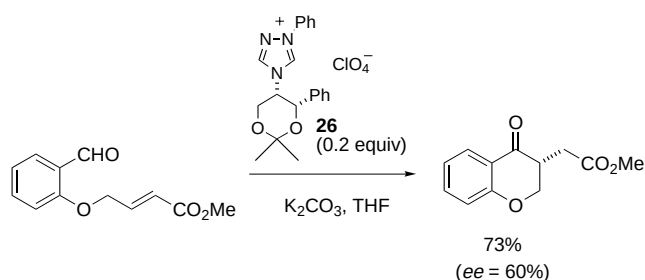
Thiazolium, 1*H*-imidazolium, and triazolium derivatives catalyze reactions such as the benzoin condensation and nucleophilic acylation reactions (the Stetter reaction) with a mode of action reminiscent of that of thiamine (vitamin B₁) under biochemical conditions. The mechanistic foundation of the condensation reaction was laid down more than four decades ago (Scheme 21).^[74] Accordingly, the C(2) proton of the heteroazolium derivative is ionized and the resulting anion (a resonance-stabilized carbene) adds to the electro-



Scheme 21. The mechanism of the thiazolium-catalyzed benzoin condensation.

phile, which is usually benzaldehyde or formaldehyde. Subsequent deprotonation leads to the formation of the corresponding enol which is stabilized by conjugation. This intermediate adds to the second electrophile, for example, an aldehyde, conjugated olefin, or enoate and finally affords the product and reforms the catalyst.

Although the achiral reaction proceeds well with a wide range of substrates and catalysts,^[75] the asymmetric version is often limited by a low level of stereinduction and low substrate compatibility. In most of the cases the stereocontrol is induced by a freely rotating chiral side chain. Some conformationally restricted analogues were also prepared and tested in benzoin condensation, with moderate success (20–30% *ee*).^[76, 77] Significant synthetic results were obtained in the intramolecular Stetter reaction with triazolium catalyst **26** (Scheme 22).^[78]



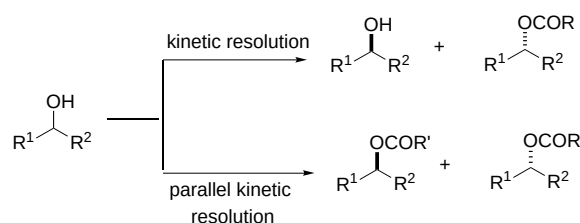
Scheme 22. The intramolecular Stetter reaction catalyzed by chiral triazolium salt **26**.

3.2.10. Enantioselective Acylation^[79]

Probably the most thoroughly studied organocatalytic reaction is the kinetic resolution of secondary alcohols by means of enantioselective acylation. The origin of this transformation goes back to the late 1920's when Vavon and Peignier and then in the early 1930's Wegler showed that optically active alkaloids such as brucine and strychnine could induce enantiomeric enrichment either in the esterification of *meso* dicarboxylic acids or in the acylation of secondary alcohols.^[80] Over the years the performances of the earlier systems were improved to become useful synthetic methods. The principle of the reaction remained the same: a nucleophilic chiral Lewis base and the acylating agent (usually anhydride) form a chiral activated complex which adds to the alcohol. However, much less is known about factors that play a role in the stereodiscriminating step, that is, the transition state preferences associated with different catalysts, which leads to questions about the 3D structure and the location of the carboxylate anion within the activated complex which may be involved as a general base in the proton-transfer step.

A considerable difficulty in overcoming the kinetic resolution is that during the progression of the reaction, the starting material becomes continuously enriched with the isomer that reacts more slowly. To obtain a synthetically useful *ee*, an exceptionally large difference in the rate is required between the enantiomers.^[81a] Nevertheless, the enantioselectivity is sensitive to the progression of the

reaction: one can optimize either the formation of the acylated product (low conversion) or the amount of recovered starting material (high conversion), and one is at the expense of the other. A solution to this problem is to run two reactions of approximately same rate, but of opposite sense and selectivity in the same pot; this affords two different products from each of enantiomers (parallel kinetic resolution, PKR) (Scheme 23).^[81]



Scheme 23. Enantioselective acylation of prochiral secondary alcohols.

To improve the selectivity in the fully catalytic version of PKR, a three-phase system that uses an immobilized acylation catalyst and a polymer-supported reagent ("phase isolation") has been developed.^[82] By using this system, a good enantiomeric purity (*ee* > 90%) was obtained for both products with a high conversion ($\geq 85\%$), even though the enantioselectivities of the two catalysts were not closely matched. Although most of the initial efforts were directed at the kinetic resolution of aryl alkyl carbinols, considerable progress has been made with substrates that contain more versatile functions such as allylic alcohols, cyclic 1,2-diols, amino-alcohols, and bromohydrins. Whereas the use of a chiral nitrogen catalyst is almost trivial in the acylation reaction, the first example of chiral phosphanes as catalysts is recent.^[81b] A particular advantage of this atom is its dual function as a stereogenic center and as a nucleophilic site towards the transferable acyl function. Although lipase resolution is still more efficient, it was the first time that the selectivity factor *s*^[83] reached 12 or 15 for a nonenzymatic system with an achiral acyl donor.

In the rational design of a chiral catalyst, the eternal dilemma arises from the relative positions of the active center and the chiral environment, that is, selectivity versus reactivity. If the reaction center cannot be rendered chiral, the most straightforward approach is to introduce the stereogenic center near to the active site. This steric hindrance of the chiral handle unfortunately often reduces the reactivity of the nucleophilic site of the catalyst. Another approach relies much more on enzyme-like structures. The strategy consists of building a simplified version of a complex chiral environment around the catalytic site, very much like in enzymes, in which the chiral handle is distant from the active site (as in **7**). Such artificial enzymes may consist of a short oligopeptide sequence with an active site (imidazole), and a basic secondary structure, for example, a β -turn or a β -hairpin. Hydrogen bonding plays a dominant role in the stabilization of the secondary structure of the catalyst and the substrate–reagent complex (see Section 2).

3.2.10.1. Nitrogen-Based Catalysts

The main body of work is related to the variation of the 4-dimethylaminopyridine (DMAP) structure in a chiral environment.^[84–86] One of these approaches consists of placing the stereogenic center at the *meta* position of the pyridine ring, as in **12**, whereas such a center at the *ortho* position is known to be deleterious to catalytic activity.^[86] Another approach consists of introducing the stereogenic center far from the active site of the DMAP analogue.^[84] This modification allows the catalytic activity of the achiral molecule to be preserved. The asymmetric induction occurs in a similar way to the induced-fit mechanism in enzymes.

The proline-derived chiral catalyst **4** was shown to be very efficient in the kinetic resolution of both cyclic and acyclic *meso*-1,2-diols with benzoyl halides as the acylating agent.^[87, 88] Alcohols were recovered with up to 97% *ee*. High enantioselectivities ($s > 100$) were also found in the kinetic resolution of several bromohydrins.^[89] This class of ligands has been utilized in other applications, such as in the asymmetric Mukaiyama-aldol reaction^[90] and in the asymmetric rearrangement of allylic imidates to form allylic amides.^[91] Recently, the catalyst was immobilized on a polymer support and used for the kinetic resolution of racemic mixtures of secondary alcohols.^[92]

Small peptide catalysts that contain modified histidine residues are efficient catalysts in enantioselective acylation reactions.^[93] In particular, tetrapeptide β -hairpins such as **7** exhibit result in selectivities.^[93a] Some recently prepared octapeptide catalysts perform even better than the earlier tetrapeptide β -turns.^[93b] Catalyst rigidity and structural complexity contribute to the enantioselectivity. Good enantiomeric excesses were obtained with substrates that allow hydrogen bonding to the peptide (i.e. *trans* aminocyclohexanols) under conditions that favor hydrogen bonding (non-polar solvents, aprotic conditions). Substrates that are not subject to hydrogen bonding have lower selectivities. Kinetic studies indicate that the enantioselectivity is the consequence of a specific acceleration of reaction for one substrate enantiomer rather than the deceleration of the reaction for the other. The enantioselective acylation reaction can also be used for the desymmetrization of cyclic *meso*-anhydrides.^[94] A variety of chiral amines such as ephedrine and cinchona alkaloids efficiently mediate the enantioselective ring-opening of different symmetrical anhydrides. The product of the reaction is the corresponding *hemi*-ester. The reaction can be rendered catalytic by using stoichiometric amounts of sterically hindered bases that liberate the alkaloid. The catalytic protocol affords products in high yields and up to 98% *ee*.

3.2.10.2. Chiral Phosphorus-Based Acylation Catalysts

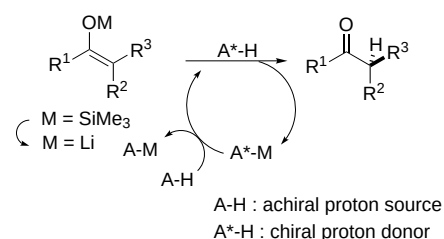
Chiral phosphane catalysts may promote the enantioselective acyl transfer reaction of bulky and slowly reacting anhydrides such as *m*-chlorobenzoic or isobutyric anhydride. Among the tested catalysts, the 2-phosphabicyclo[3.3.0]octane derivatives such as **18** were particularly selective in the kinetic resolution of racemic aryl or alkyl carbinols.^[95] Notably, **18** performs well over a broad range of temperatures and substrates. Either the esters were obtained ($ee \leq 98.7\%$,

44.4% conversion, $s = 369$) or the alcohols were recovered ($ee \leq 95.3\%$, 50.1% conversion, $s = 145$). The enantioselectivity of the reaction is very sensitive to the optical purity of the phosphane catalysts.

4. Organic Molecules Forming Reactive Intermediates

4.1. Catalytic Enantioselective Protonation^[96]

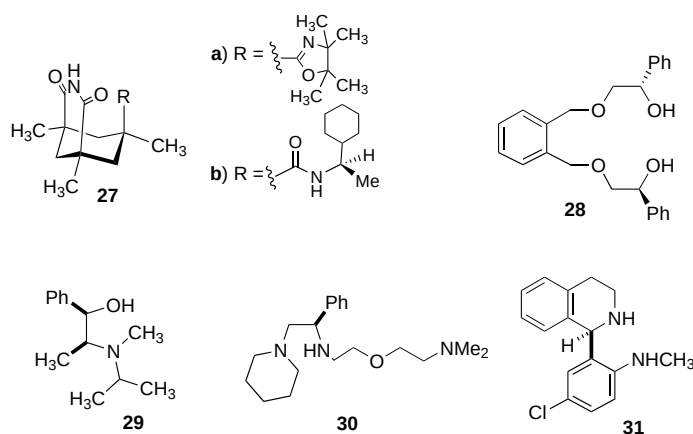
The rational design of catalytic systems for enantioselective protonation remains largely empirical, although important advances have been made. The role of chiral additives in the reaction has not been fully elucidated. Besides their primary functions as chiral proton sources, they can also act as ligands for the metal. The asymmetric protonation of metal enolates fundamentally takes place catalytically if a coexisting achiral proton source ($A-H$) reacts with the deprotonated chiral proton source (A^*-M) faster than with the metal enolate (Scheme 24).^[97] The consumed chiral proton source is regen-



Scheme 24. Enantioselective catalytic protonation of prochiral lithium enolates.

erated by subsequent protonation with the achiral proton source. Thus a higher reactivity of A^*-M toward $A-H$ than toward the metal enolate is the key to the success of the catalytic cycle. If proton transfer from the achiral proton source ($A-H$) to the enolate occurs quickly at low temperature, the selective deprotonation of one enantiomer of the resulting racemic ketone by A^*-M is a possible alternative catalytic mechanism. To diminish the competing reaction between the achiral and the chiral proton source with the enolate, the chiral catalyst was added before the achiral proton source.

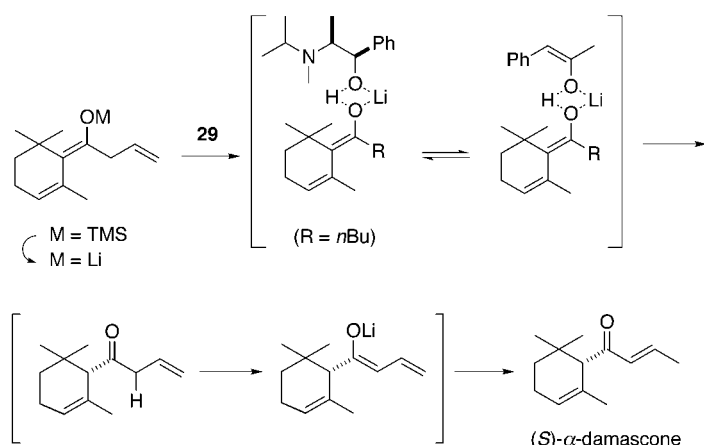
Numerous chiral proton sources such as imides, amides (e.g. **27** derived from Kemp's triacid), phenols, alcohols such as **28**, amino alcohols such as **29**, and amines such as **30**, **31** have been developed (Scheme 25). Among the achiral proton sources, moderately acidic rigid and sterically hindered proton donors usually result in high *ee* values. For this purpose, cyclic imides (such as succinimide, glutarimide, and phthalimide), nonactivated phenol derivatives (such as catechols), dipivaloylmethane, or moderately acidic carbonyl compounds (such as phenyl-2-propanone) were selected. Prochiral substrates are often metal enolates, such as lithium or samarium enolates (generated either from preformed silyl enol ethers or enol acetates, with an excess of organometallic reagents), or they are the products of an organometallic



Scheme 25. Selected organic molecules used in enantioselective catalytic protonation.

coupling reaction. In some cases, transient enolates or enols can be used as substrates that are generated under the reaction conditions and protonated enantioselectively *in situ*.^[98] Although 0.01 equivalents of chiral catalyst may result in acceptable *ee* values, the enantioselectivity increases with a higher concentration of the catalyst.^[99]

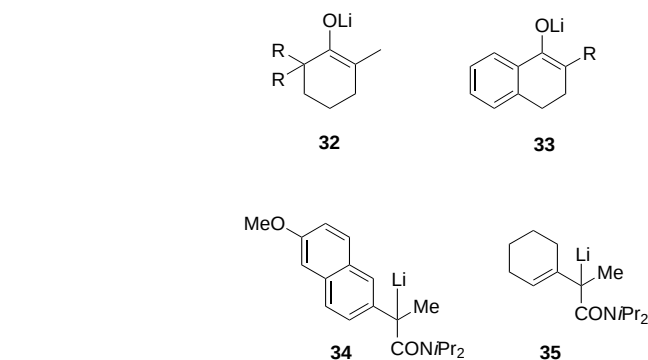
The basis of the enantioselective catalytic protonation was laid out in a series of papers on the synthesis of enantiomerically pure (*S*)- α -damascone without the addition of any external achiral proton source (Scheme 26).^[100] This autocat-



Scheme 26. Synthesis of (*S*)- α -damascone by means of enantioselective catalytic protonation. TMS = trimethylsilyl.

alytic system is based on the presence of an acidic proton on the protonated intermediate which allows the regeneration of the chiral catalyst **29**. To rationalize the results, a transition-state-like complex was postulated in dynamic exchange with the achiral complex (Scheme 26). According to this hypothesis, the chiral complex affords the product faster than the achiral one.

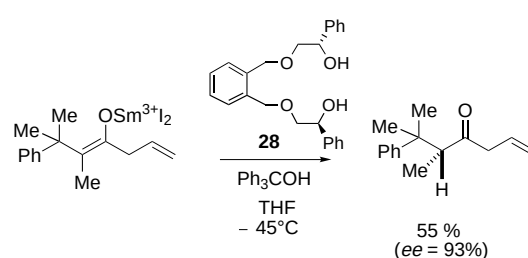
Chiral amides such as **27a** and **27b**, which are derived from Kemp's triacid, may serve as catalysts in the asymmetric protonation of lithium enolates such as **32** (Scheme 27).^[101] A chiral tetradentate amine such as **30** is another example of a catalyst for enantioselective protonation.^[102] In the presence



Scheme 27. Some selected substrates used in enantioselective catalytic protonations.

of a stoichiometric amount of an achiral proton source (succinimide) and a catalytic amount (0.2 equiv) of a chiral amine **30**, the protonation of tetralone-derived lithium enolate **33** afforded the desired product with 15–83% *ee*. The LiBr which is present in the reaction mixture, may be part of the structure of the active intermediate. The slow addition of the achiral proton source required for the good *ee* was effected by solid–liquid heterogeneous reaction conditions: the succinimide is weakly soluble in toluene at -78°C , and thus slowly liberates the achiral H^+ . Asymmetric protonation is not limited to enolates derived from ketones. The catalytic protonation of lithium enolates of amides such as **34** or **35** by using 10 mol % of **31** as the catalyst results in poor to good *ee* values, depending on the nature of the achiral proton source.^[103] The best *ee* values were obtained when $\text{PhCH}_2\text{CO}_2\text{Et}$ and $\text{PhCH}_2\text{CO}_2t\text{Bu}$ were used as achiral proton sources (92 and 94%, respectively). On decreasing the amount of catalyst from 10 mol % to 5 mol %, a high *ee* ($\leq 92\%$) could be maintained.

The enantioselective catalytic protonation of samarium enolates requires more drastic conditions than those of lithium enolates (Scheme 28). The reaction can be catalyzed



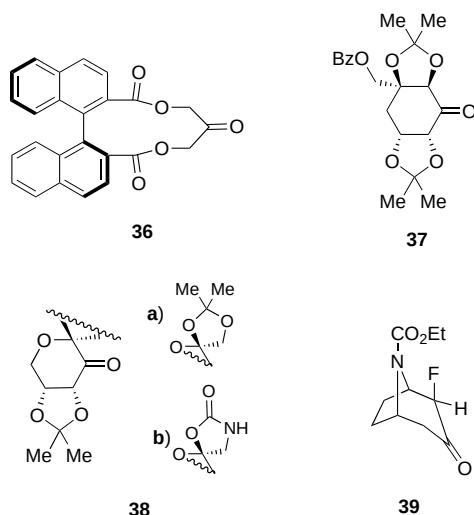
Scheme 28. Enantioselective protonation of samarium enolates.

with **28** as the chiral proton donor.^[104] The best result is obtained when the achiral proton source (trityl alcohol) is added very slowly to the reaction mixture. The relatively high temperature (-45°C) and the longer reaction time required is a consequence of the stronger coordination of the oxygen anion to the samarium ion than to the lithium ion. The use of a fluororous biphasic system^[105] ensures the very slow diffusion of the achiral proton source into the reaction phase and results in a somewhat higher *ee* than the single-phase reaction.

4.2. Oxidations^[106]

4.2.1. Epoxide formation^[107]

The first powerful highly enantioselective oxidation method of isolated olefins is based on osmium. This reaction remains one of the most general methods in the asymmetric epoxidation and hydroxylation of alkenes. The category of nonmetal-catalyzed, asymmetric epoxidation has only recently emerged as a viable method. New methods are based on the use of chiral ketones,^[111] iminium salts,^[108a–d] α -amido ketones,^[108e,f] and simple imines,^[109] as well as a co-oxidant such as H_2O_2 or Oxone, which generates the chiral oxidizing agent in situ (Scheme 29).^[109, 110]

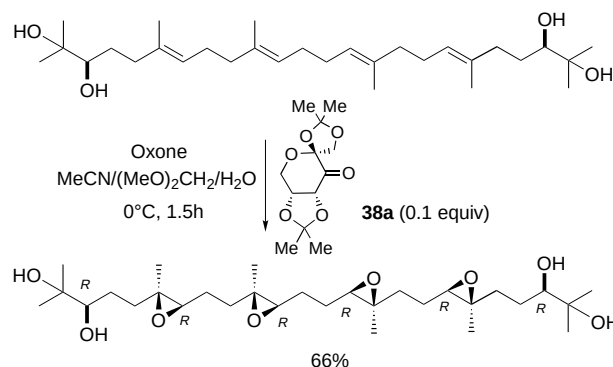


Scheme 29. Some selected catalysts for enantioselective catalytic oxidations. Bz = benzoyl.

Chiral ketones that form dioxiranes under the condition of the reaction are probably the most versatile oxidation catalysts with remarkable potential in asymmetric synthesis.^[107d, 112] Recent developments in enantioselective catalytic oxidation concern the use of C_2 -symmetrical ketones such as **36**,^[111] (–)-quinic acid derived cyclitols such as **37**,^[112b] and sugar derivatives such as **38**.^[112a] Both the structures of the catalysts and the reaction conditions were optimized to minimize the competing Baeyer–Villiger side reaction of the ketone catalyst. These compounds show a great structural diversity (Scheme 29). A strong electron-withdrawing substituent such as fluorine, immonium, or ammonium near the carbonyl group is often a common structural element (Scheme 29). This functionality increases the reactivity of the carbonyl towards the co-oxidant and diminishes the propensity of the catalyst toward Baeyer–Villiger oxidation.

C_2 -Symmetrical cyclic ketones such as α,α' -diacyloxyketone **36** provide *ee* values of up to 87% in the epoxidation of nonfunctionalized alkenes that bear large aromatic substituents.^[107c] Fructose-derived ketones such as **38a** can epoxidize a large number of *trans*-olefins and trisubstituted alkenes with high *ee*.^[113, 107d] However, epoxidation of *cis*-olefins using this ketone led to rather poor enantioselectivity. On the other hand, the spiro-oxazolidine derivative **38b** gave good results for both *cis*- and *trans*-olefins.^[114] To minimize the catalyst

degradation, a high pH value (pH 10.5 in the case of D-fructose-derived catalyst **38a**) is required.^[115] These catalysts must be soluble in water as the reactions are usually performed in a homogeneous CH_3CN/H_2O solvent system to dissolve the co-oxidant. Additional studies have been carried out in a biphasic solvent system. Optimization of the reaction conditions has extended the field of asymmetric epoxidation to dienes, enynes, 2,2-disubstituted vinylsilanes, enol silyl ethers, and esters. A structurally related ketone derived from (–)-quinic acid **37** is also an efficient catalyst for the epoxidation of alkenes.^[116] Likewise, the tropinone-derived chiral ketone **39** was described as a good catalyst for the enantioselective epoxidation of alkenes substituted with aromatic groups (33–100% yield, 29–83% *ee*).^[117] A recent application in the synthesis of (–)-glabrescol illustrates the scope of this method (Scheme 30).^[118]



Scheme 30. Synthesis of a key intermediate in the synthesis of (–)-glabrescol by means of an enantioselective catalytic epoxidation. Oxone = $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

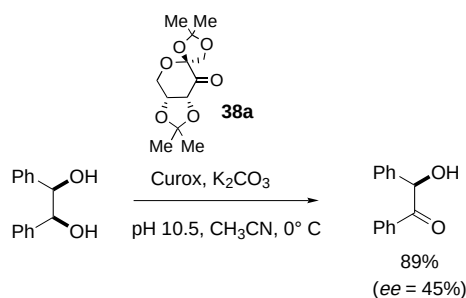
The epoxidation reaction with imine catalysts and Oxone co-oxidant is less developed than the chiral ketone mediated variant.^[109] This reaction is believed to proceed via a radical cation intermediate. The side-product found with the desired epoxide is the corresponding diol. The asymmetric induction is usually low when 2-diphenylmethylpyrrolidine **3d** is used as catalyst.^[109]

4.2.2. Desymmetrization of Vicinal Diols by Oxidation

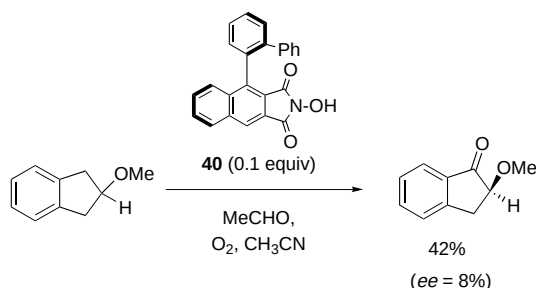
The scope of the oxidation reaction that uses chiral dioxiranes, which are generated in situ, extends beyond the asymmetric epoxidation of isolated olefins. For example, this catalytic system can be used to oxidize vicinal diols into α -hydroxyketones (Scheme 31).^[119] The *meso*-hydrobenzoin were desymmetrized at a high pH value (pH 10.5) by using 3 equivalents of fructose-derived ketones such as **38a** (17–60% *ee*).

4.2.3. Oxidation at Benzylic Positions

A conceptually different approach in oxidation allows the use of molecular oxygen as co-oxidant (Scheme 32).^[120] A mixture of chiral *N*-hydroxyphthalimide (NHPI; **40**) and acetaldehyde in the presence of O_2 was used to oxidize indane. The yield and selectivity of this transformation is nevertheless



Scheme 31. Desymmetrization of *meso* diols by means of enantioselective oxidation. Curox = potassium monoperoxysulfate.



Scheme 32. Enantioselective oxidation at benzylic positions.

low. The phthalimide *N*-oxyl radical, which is formed by the one-electron oxidation of, was proposed as a key intermediate in the reaction.

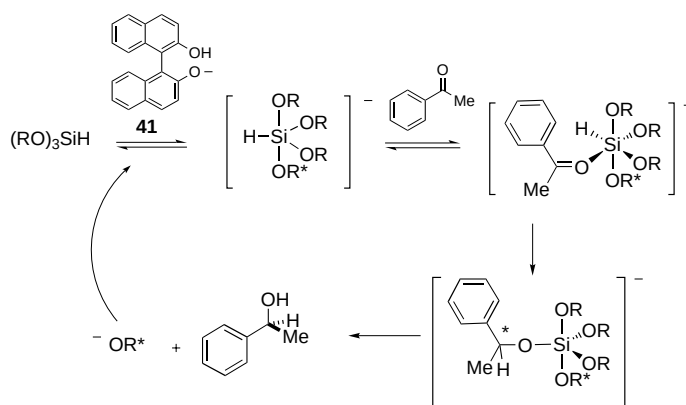
4.2.4. Asymmetric Oxidation of Sulfides to Sulfoxides^[121]

The asymmetric oxidation of sulfides to sulfoxides can be realized by using a catalytic amount (10–20%) of chiral sulfonylimines, with potassium percarbonate as co-oxidant.^[121c] Yields are high (95–100%) although *ee* values are low (14%).

4.3. Asymmetric Catalytic Reduction

The asymmetric reduction of ketones by using transient hypervalent silicon hydrides is on the borderline of organo-catalytic reactions, since the reaction requires the presence of alkoxide anions.^[122] However, it is argued that the metal center does not participate in the reaction mechanism (Scheme 33).

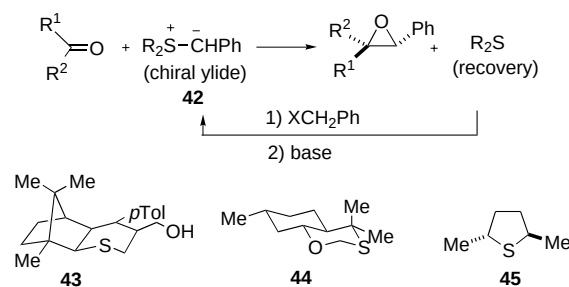
The reaction is based on the activation of trialkoxysilanes by a small amount of a chiral nucleophile (alkoxide). This activated complex undergoes addition to the carbonyl group to form the corresponding silyl-protected alcohols, and liberates the chiral nucleophile. Since the aggregation of organolithium compounds has a strong effect on their reactivity, the use of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as co-solvent not only increases the yield but also enhances the enantioselectivity. Among the tested alcohols, the monolithium salt of 2,2'-dihydroxy-1,1'-binaphthyl (BINOL; **41**) resulted in *ee* values of up to 93%.



Scheme 33. Enantioselective reduction of aromatic ketones by using BINOL-activated silanes.

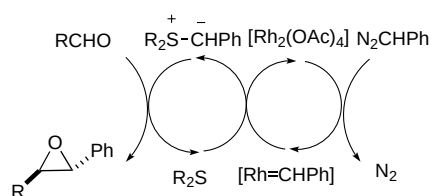
4.4. Asymmetric Ylide Reactions: Epoxidation, Cyclopropanation, Aziridination

Since its discovery, the reaction of sulfur ylides with aldehydes or ketones to give epoxides has received considerable attention and has been extensively developed.^[123] Enantiomerically enriched epoxides were prepared either under biphasic/phase-transfer conditions or in homogenous solution by using either alkylation/deprotonation or direct carbene coupling procedures. In the enantioselective catalytic process, the chiral ylide precursor is recovered and is converted back into the ylide reagent **42** under the reaction conditions. The general mechanism of the reaction is depicted in Scheme 34. Among the tested catalysts, conformationally restricted sulfides derived from camphor,^[124] **43**, pulegone,^[125] **44**, or *C*₂-symmetrical thiolane,^[126] **45**, afforded *trans* stilbene oxide derivatives with high *ee*.



Scheme 34. Some chiral sulfides used in enantioselective catalytic epoxidation reaction. *p*Tol = *p*-tolyl, X = halogen.

It is considered that the formation of the sulfonium salt is the rate-determining step in the catalytic cycle. To assure the required reaction rate, additives such as AgClO₄ or AgBF₄ salts have been used. An alternative method for the ylide formation is the generation of the sulfonium ylide by carbenes or carbenoids. In this procedure, the sulfonium ylide is formed in a second catalytic cycle from a diazo compound and [Rh₂(OAc)₄] or [Cu(acac)₂] (acac = acetylacetonate; Scheme 35) or by using Simmons–Smith reagents.^[127] This variant also allows the preparation of chiral cyclopropanes and aziridines.



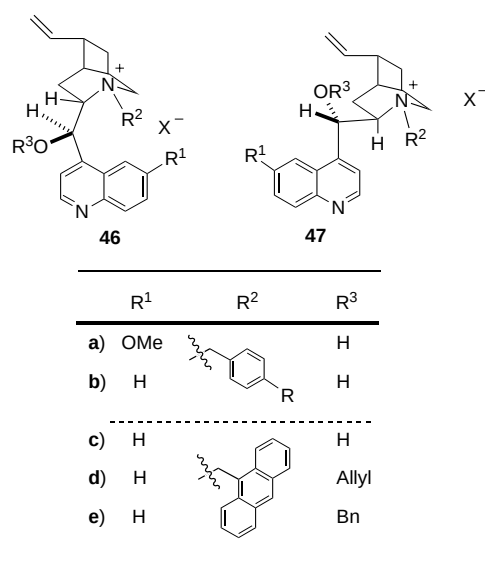
Scheme 35. Enantioselective catalytic epoxidation mediated by chiral sulfides. The catalyst is regenerated by using a metallocarbene in an auxiliary catalytic cycle.

5. Asymmetric Phase-Transfer Catalysis^[128]

5.1. The Catalysts

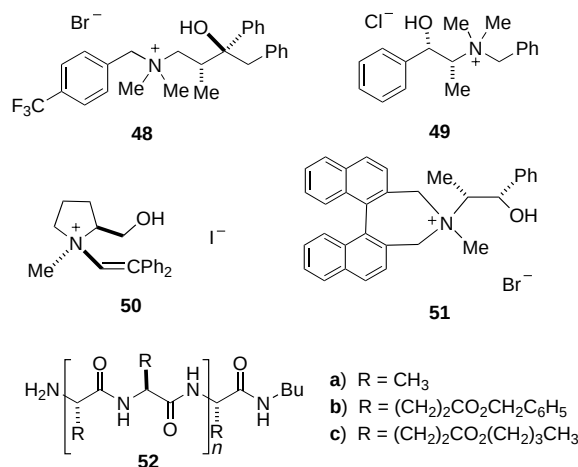
Phase-transfer catalysis (PTC) mediated by chiral quaternary ammonium salts represents a unique ion-pair-mediated reaction.^[129] The mechanism was determined in 1986, and three main steps were proposed:^[130] 1) deprotonation of the active methylene compound with the base generally occurs at the interface of the two layers (either liquid–liquid or liquid–solid phases); 2) extraction of the anion into the bulk organic phase by ion exchange with the cation of the chiral quaternary ammonium salt by forming a lipophilic ion pair; and 3) alkylation of the ion pair with the reagent as well as the concomitant regeneration of the catalyst. Highly enantioselective PTC reactions have been known for many years^[131] although some high-induction results were revealed to be erroneous as a result of the high optical rotation of trace impurities.^[135b] Among the quaternary ammonium salt catalysts, cinchonium derivatives have been shown to be particularly efficient (Scheme 36).^[132]

A number of other chiral ammonium salts that contain the key β -hydroxyammonium structure of the cinchonium derivatives have also been used. The ephedra alkaloid catalysts, for example, **48**, **49**, and **51**, were particularly successful in many



Scheme 36. Selected cinchona-derived quaternary ammonium salts used in the enantioselective catalytic phase-transfer reaction. Bn = benzyl.

reactions. Moreover, oligopeptides such as **52a–c** and polymer catalysts were also used (Scheme 37).^[133] The substitution pattern plays a crucial role in the control of the stereoselectivity of the cinchona-catalyzed reactions. A major



Scheme 37. Selected catalysts for enantioselective catalytic phase-transfer reactions.

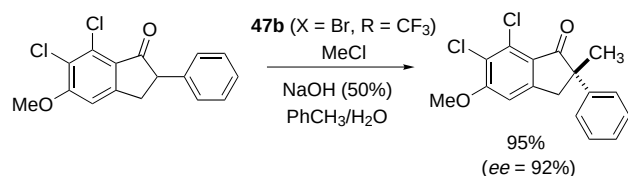
improvement in the *ee* values was observed by changing the alkyl or benzyl substituent of the quaternary ammonium for the bulkier anthracen-9-ylmethyl (anth) group either in solid–organic or aqueous–organic biphasic systems. This modification resulted in a decisive breakthrough in the application of the enantioselective phase-transfer reactions. The efficiency of the “third generation” catalysts is being exploited increasingly in the synthesis of biologically relevant molecules.

Arguably the catalyst forms a well-ordered contact ion pair with the substrate in the organic phase for enantioselective reactions. This mechanistic model is based on the X-ray structure analysis of the catalyst–substrate complex in which the anionic oxygen atom of the enolate and the cationic nitrogen atom form a well-ordered rigid structure. The predominant forces that hold the complexes together are coulombic, and the charges are highly dispersed.^[134] The combination of electrostatic and van der Waals interactions results in a tight ion pair in which only one face of the complex is accessible for reaction.^[135] The solvents have important effects on the selectivity: nonpolar solvents resulted in higher *ee* values than polar solvents.

5.2. Reactions

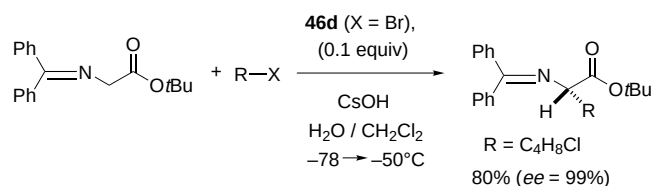
5.2.1. Enantioselective Alkylation

The enantioselective alkylation reaction under biphasic conditions was one of the first examples of chiral PTC transformations.^[136] This methodology was already used in the early 1980's when the uricosuric indanone derivative was prepared in an almost quantitative yield and with a remarkably good selectivity (Scheme 38).^[137] The “first generation” catalysts with an unsubstituted hydroxy function usually



Scheme 38. Enantioselective alkylation under phase-transfer conditions with a cinchonine-derived catalyst.

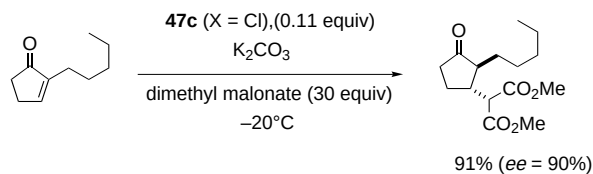
resulted in moderate enantioselectivity even with optimized substrates. Although the free hydroxy function of the catalyst was thought to be indispensable for a high *ee*, it was proposed later that the active catalyst is the *O*-alkyl cinchona salt formed during the alkylation reaction.^[138] The “second generation” (*N*-benzyl-*O*-allyl or -alkyl salts) and then the “third generation” (*N*-anth) showed very significant improvements in *ee* values.^[139] Furthermore, it was demonstrated that substrates with stronger electron-withdrawing substituents on the adjacent position increase the catalyst selectivity.^[140] In particular, the alkylation of the *tert*-butylglycinatebenzophenone Schiff base,^[143] which is considered to form a tight catalyst–substrate complex, gave impressive results. A series of natural and unnatural α -amino acid derivatives were prepared with enantioselectivities of up to 400:1 by using catalyst **46d** (Scheme 39).^[141]



Scheme 39. The enantioselective alkylation of the *tert*-butylglycinate benzophenone under phase-transfer conditions.

5.2.2. Michael Additions

N-Alkylated cinchoninium derivatives mediate the enantioselective conjugate addition of carbanions to α,β -unsaturated ketones.^[142] However, the addition of thiols and nitroalkanes to similar substrates resulted in low *ee* values using catalyst **46a, b** ($R = H$ or NO_2 ; $X = Cl$). The use of **47a, b** ($R = CF_3$; $X = Br$) as catalysts in the enantioselective alkylation reaction was shown to be particularly efficient in the construction of quaternary carbons.^[143] The therapeutically useful GABA_B receptor agonist (*R*)-baclofen·HCl was prepared by using the enantioselective Michael addition of nitromethane to the chalcone-derived α,β -unsaturated ketone.^[144] Also, 9-anthracenylmethyl-substituted cinchonidium chloride **47c** ($X = Cl$) mediated the addition of the dimethyl malonate anion to a cyclopentanone derivative in the enantioselective synthesis of methyl-dihydrojasmonate (Scheme 40).^[145] The key enantioselective step in the synthesis involves a new system of asymmetric solid–liquid phase-transfer catalysis that uses solvent-free conditions. Vinyloxysilanes can also be used as nucleophiles in the enantioselective Michael addition of cinchona-derived quaternary ammonium salts.^[146] The advan-



Scheme 40. Application of a chiral quaternary ammonium salt in an asymmetric Michael reaction towards the synthesis of (–)-methyl dihydrojasmonate.

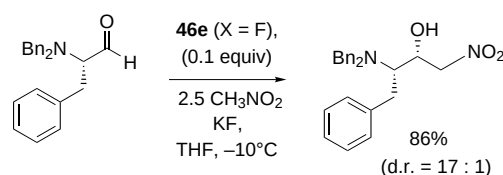
tages of using enol ethers instead of ketones include faster reactions, higher enantioselectivities and chemical yields, and minimization of the aldol side reaction.

5.2.3. Aldol and Related Condensations

As a logical extension of the PTC alkylation, “first generation” catalysts **46b** and **47b** ($R = H$; $X = Cl$) were tested in inter- and intramolecular aldol and nitroaldol reactions. A variety of β -hydroxy- α -amino acids were synthesized enantioselectively by using cinchona-derived catalysts.^[147] Although the observed enantioselectivities were in the range of 70–90 % when simple substrates were used, the *syn/anti* ratio varied substantially (from 1:1 to 13:1).^[147b]

Catalysts **47b** ($R = H$) with a fluoride counterion ($X = F$) were used in the aldol reactions of the enolates of silyl-enol ethers (Mukaiyama–Kuwajima aldol reaction).^[148] The advantage of this method is that the use of additional base for the aldol reaction is avoided. Although the diastereoselectivity of the reaction was modest, *ee* values of up to 72 % was obtained.

The catalytic asymmetric nitroaldol reaction (Henry reaction) under PT conditions was for a long time compared with the more selective metal complex mediated versions.^[149] In a recent variant under solid–liquid PT conditions the reaction of aldehyde with nitromethane catalyzed by **46e** ($X = F$) afforded the key intermediate of the second generation HIV protease inhibitor amprenavir in good yield and with remarkable stereoselectivity (Scheme 41).^[150] The *Re*-face selectivity of the reaction follows mechanistic model discussed in Section 5.1.



Scheme 41. Application of a nitroaldol reaction promoted by a chiral quaternary ammonium salt in the synthesis of amprenavir.

5.2.4. (1,2)-Addition Reactions

The nucleophilic trifluoromethylation of carbonyl compounds was realized by using trifluoromethyltrimethylsilane ($TMS-CF_3$) under PT conditions.^[151] The *N*-benzylcinchoninium fluoride catalyst **47b** ($R = H$; $X = F$) mediates the reaction, and enantioselectivities in the range of 15–51 % are observed for simple ketones.

5.2.5. Olefination Reactions

The desymmetrization of ketones was mediated by cinchonium salts under PT conditions in catalytic asymmetric Horner–Wadsworth–Emmons reactions.^[152] The reaction results in *ee* values of up to 57% when *tert*-butylcyclohexanone was used as a substrate.

5.2.6. Darzen Reaction

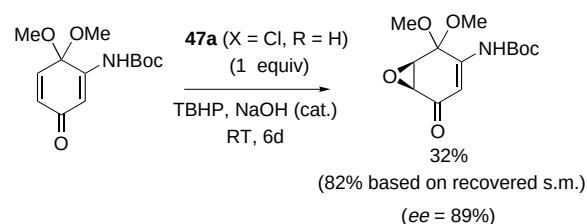
It is difficult to design a catalytic cycle for the metal-promoted Darzen reaction because of the formation of the stable inorganic salt (a metal halide) in the reaction. Therefore a stoichiometric amount of a chiral organometallic reagent is needed. Phase transfer conditions with cinchona-derived catalysts may allow the reaction to be rendered catalytic.^[153] Enantiomerically enriched α,β -epoxysulfones were prepared from chloromethyl phenylsulfone with various aromatic aldehydes in the presence of 10 mol% of quinine-derived salt **47b** ($R = CF_3$; $X = Br$). In the optimized case the reaction afforded the *trans* aryl epoxysulfone in up to 81% *ee*.^[154] Chiral sulfides can also catalyze the asymmetric Darzen-type epoxidation.^[155] The reaction is suitable for the coupling of benzyl halides with aromatic aldehydes. However, this reaction is limited to the formation of stilbene oxides.

5.2.7. Oxidations

5.2.7.1. Epoxide formation

The enantioselective oxidation of enones with polyamino or resin-supported polyamino acids under tri- and biphasic conditions has been known since the early 1980's.^[156] Both the catalyst recycling and the reactivity have been improved considerably over the years. Although the mechanism of the reaction is not well understood, it performs well with remarkable selectivity in a number of cases. Excellent enantioselectivities were obtained on acyclic, and more recently, on cyclic enones.^[157] The poly-L-leucine variant epoxidation has been scaled up by SmithKline Beecham in the synthesis of the leukotriene antagonist SK&F 104353.^[158]

Additionally, cinchona-derived quaternary ammonium salts are efficient in mediating epoxidation under phase-transfer conditions.^[159] This reaction was used in the synthesis of different members of the manumycin family (Scheme 42).^[160] The use of one equivalent of *N*-benzylchinidinium chloride



Scheme 42. Enantioselective phase-transfer epoxidation in the synthesis of a key intermediate of (+)-manumycine A. TBHP = *tert*-butylhydroperoxide.

47a ($R = H$; $X = Cl$), and *tert*-butyl hydroperoxide (TBHP) with a catalytic amount of sodium hydroxide gave the desired epoxide with 89% *ee* (Scheme 42). The reaction conditions were also optimized for the oxidation of some chalcone derivatives. Under these conditions 1% of catalyst ($X = Br$) was enough to mediate the epoxidation of α,β -unsaturated ketones in a solution of NaOCl in high dia- and enantioselectivity and in high chemical yields.^[161] Likewise, face-selective conjugate additions of ion-paired hypochlorite to an α,β -enone have been realized by using **46e** ($X = Br$) as catalyst.^[162] The reaction affords the corresponding epoxide with a remarkably good (up to 130:1) enantioselectivity.

5.2.7.2. Asymmetric Oxidation of Sulfides to Sulfoxides

Sulfides can be asymmetrically oxidized to form sulfoxides by using hypervalent iodine compounds in reversed micellar systems that contain a chiral source.^[163] Accordingly, $PhIO_2$ (0.5 equiv), in the presence of a catalytic amount of cetyltrimethylammonium bromide (CTAB) as the surfactant, and a catalytic amount of diacyltartaric acid as the chiral source, oxidizes the substrates with moderate to good enantioselectivities (up to 72% *ee*).

5.2.8. Asymmetric Reductions

An enantioselective reduction that uses chiral ammonium fluoride catalysts under phase-transfer conditions was described.^[164] The reaction is based on silanes such as trialkyloxysilanes, tris(trimethylsiloxy)silane, and polymethylhydrosiloxane, which undergo a hydride-transfer reaction in the presence of F^- . High enantioselectivities were obtained in the reduction of simple ketones such as acetophenone.^[164]

5.2.9. Enantioselective Protonation under Phase-Transfer Conditions

Enantioselective protonation can be carried out in a fluoruous/organic biphasic system (FBS).^[105] The reaction conditions were developed in a way to assure the very slow diffusion of the achiral proton source into the reacting phase. In this system, both the chiral and achiral proton sources have a long fluoruous chain. Whereas the achiral proton source remains essentially in the fluoruous solvent (FC-72), the chiral proton source shuttles between the standard organic solvent and the fluoruous phase.

6. Chiral-Cavity-Accelerated Asymmetric Transformations

The selective recognition of substrates followed by chemical transformation with the help of a molecular cavity is a largely documented field in organic chemistry.^[165, 166] Although chiral host–guest chemistry is an increasingly important field in asymmetric synthesis, there are few examples in which an enantioselective catalytic transformation occurs. The reason is that the formed host–guest complex is often too stable to allow efficient catalytic turnover. Nevertheless, the

chiral-cavity-accelerated asymmetric transformation probably offers the closest analogy to enzyme catalysis. This analogy goes further than it does with simple organic molecules: not only the recognition process but the mode of action, that is, in creation of the transition state analogues, are reminiscent of enzyme activity. Catalytically active chiral cavities were devised either by using polyfunctionalized cyclic molecules such as cyclodextrins, or by using molecular imprinting. For the latter, the term “plastic enzymes” was coined to indicate the use of polymers as supports and the mode of action, which is reminiscent of enzymes.

6.1. Cyclodextrins in Enantioselective Catalytic Synthesis^[167]

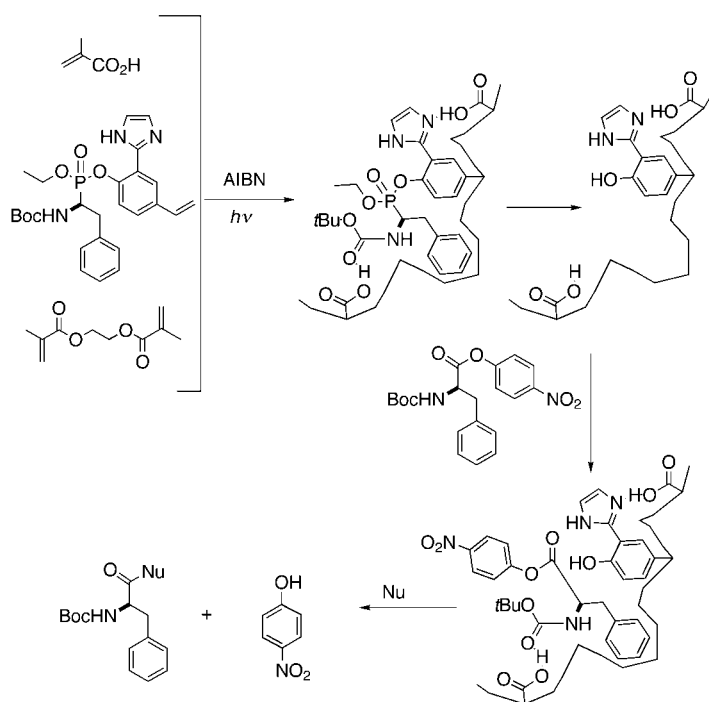
Cyclodextrins form inclusion complexes with a variety of hydrophobic guests based on size, structure, and polarity. Although enantioselective reactions are known, relatively few are amenable to enantioselective catalytic turnover. There are examples of optical induction in the cyanohydrin formation from benzaldehyde, in the asymmetric reduction of ketones, and in the transamination of α -keto acids.^[7, 167, 168]

6.2. Molecular Imprinting^[169]

When a highly crosslinked network polymer is made in the presence of a template molecule and the template is then liberated, a polymer that contains selective binding sites can be obtained. This technique is called molecular imprinting. This polymer is able to distinguish between a variety of structures in a similar manner to bioorganic catalysts such as enzymes or antibodies. The molecular cavity selectively binds substrates that have similar structures to those of the original template. The molecular recognition arises from a combination of covalent, ion-pairing, and hydrogen bonds. This simple and appealing concept has for more than 50 years attracted chemists from several disciplines and is a promising and important breakthrough in enantioselective catalysis. Highly crosslinked network polymers were developed and exhibit excellent recognition properties for enantiomers of a highly interesting range of substances such as carbohydrates, esters, amino acids and peptides, steroids, and nucleotide bases. Beyond the host–guest complexation ability, some of the bioorganic functions can be mimicked notably by using the binding force energies for chemical reactions and by stabilizing the transition state of the reaction in question (cf. antibodies with enzyme properties, abzymes).

6.2.1. Enantioselective Ester Hydrolysis

Predictable enantioselectivities were obtained in the hydrolysis of different esters by using template-imprinted polymers.^[170] The polymeric matrix contained similar catalytic elements that are believed to be responsible for the catalytic action of chymotrypsin (Scheme 43). The esterase site was modeled by mimicking the transition state structure of the hydrolysis reaction by using a template with a similar



Scheme 43. Enantioselective ester hydrolysis with an imprinted polymer. AIBN = azobisisobutyronitrile.

structure in the ground state. The mechanism of the ester hydrolysis or transesterification is believed to involve a high-energy tetrahedral oxanion transition-state-like intermediate. Rate enhancements caused by esterase enzymes can, to a large extent, be ascribed to the electrostatic stabilization of this structure.^[171]

As stable transition state analogues, phosphonates have been selected as templates. The hydrolytic molecular machinery was modeled around a nucleophilic center in the proximity of the reactive carbonyl group as well as an imidazole and carboxy group within hydrogen bonding distance of the nucleophile. The imidazole group is apparently required for the catalytic activity since only small rate enhancements and no template-induced catalysis were seen when this group was absent. The polymeric catalyst was found to be catalytically active and retains the enantioselectivity over a period of 10 years. Although the reported rate enhancement was modest it can be considered as a first step in the development of imprinted polymers for enantioselective catalysis.

7. Summary

The enantioselective organocatalysis in which the reaction is mediated by a catalytic amount of chiral organic molecule is an emerging powerful tool in organic synthesis. The interest in this field has increased spectacularly in the last few years and more reactions are expected in the near future. Owing to the sensitive substrate dependency of many of the discussed reactions, only a partial solution has been provided for their practical use. In some cases, the catalyst is very toxic (e.g. the HMPA analogues) and is at odds with potential advantages

over metal-catalyzed reactions outlined in the introduction. Although there are important gaps in the understanding of basic factors that control the reactivity and selectivity of the reactions, parallel analyses of the mechanisms help in the rational design of the next generation of catalysts. Despite the fact that the field is in its relative infancy, it offers new perspectives for academic, industrial, economic, and ecological benefit. The scope of reactions is currently restricted, but newly emerging domains pave the way for further developments. Good fortune, intuition, and persistence, as well as the traditional trial and error methods may help in the development of enantioselective catalytic reactions from the almost infinite number of stoichiometric chiral organic transformations.

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Crystalline-state transformations have led to the development of a crystalline switch, which represents one of the many applications realized with materials based on pincer complexes.



Absorbance

Pincer

1200

1100

$\leftarrow \tilde{\nu} / \text{cm}^{-1}$

Fe	Co	Ni
Ru	Rh	Pd
Os	Ir	Pt

Platinum Group Organometallics Based on “Pincer” Complexes: Sensors, Switches, and Catalysts**

Martin Albrecht and Gerard van Koten*

Since the first reports in the late 1970s on transition metal complexes containing pincer-type ligands—named after the particular coordination mode of these ligands—these systems have attracted increasing interest owing to the unusual properties of the metal centers imparted by the pincer ligand. Typically, such a ligand comprises an anionic aryl ring which is *ortho,ortho*-disubstituted with heteroatom substituents, for example, CH_2NR_2 , CH_2PR_2 or CH_2SR , which generally coordinate to the metal center, and therefore support the M–C σ bond. This commonly results in a terdentate and meridional coordination mode consisting of two metalla-

cycles which share the M–C bond. Detailed studies of the formation and the properties of a large variety of pincers containing platinum group metal complexes have provided direct access to both a fundamental understanding of a variety of reactions in organometallic chemistry and to a range of new applications of these complexes. The discovery of alkane dehydrogenation catalysts, the mechanistic elucidation of fundamental transformations (for example, C–C bond activation), the construction of the first metallodendrimers for sustainable homogeneous catalysis, and the engineering of crystalline switches for

materials processing represent only a few of the many highlights which have emanated from these numerous investigations. This review discusses the synthetic methodologies that are currently available for the preparation of platinum group metal complexes containing pincer ligands and especially emphasizes different applications that have been realized in materials science such as the development and engineering of sensors, switches, and catalysts.

Keywords: catalysis • cyclometalation • materials science • pincer ligands • platinum group metals

1. Introduction

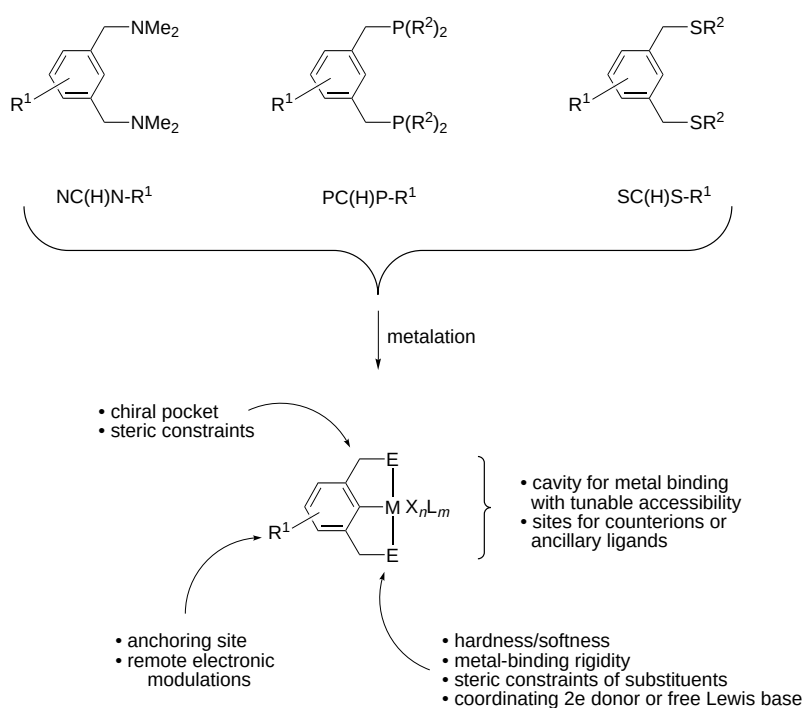
The control of the properties of metal centers by a well-defined ligand system is an ultimate goal of inorganic and organometallic chemistry. Chelation, that is, the binding of a ligand to a metal through two or more bonds, is a versatile method to realize this. In organometallic complexes containing a direct (transition) metal–carbon bond, chelation leads to the formation of metallacycles, which provide additional stabilization of the M–C bond.^[1] The first organometallic complexes containing terdentate monoanionic ligands were reported in the late 1970s.^[2] These so-called “pincer”^[3] ligands have the general formula $[\text{2,6-(ECH}_2)_2\text{C}_6\text{H}_3]^-$ (ECE) and comprise a potentially *E,C,E* terdentate coordinating, mono-

anionic array, where E is a neutral two-electron donor such as $\text{N(R}^2)_2$, $\text{P(R}^2)_2$, $\text{As(R}^2)_2$, OR^2 , or SR^2 , while C represents the anionic aryl carbon atom of the 2,6-disubstituted phenyl ring (Scheme 1, further examples are shown in Tables 1 and 2).^[4] R^1 is a substituent on the aryl ring, most frequently in the 4-position, and is in this review $\text{R}^1 = \text{H}$, unless otherwise stated.

This review is restricted to an overview of the pincer chemistry of platinum group metals (Ru, Os, Rh, Ir, Pd, Pt), but includes some aspects of the chemistry of nickel complexes as representatives of the first row metals.^[5] Metal complexation with pincer ligands usually occurs with formation of two five-membered metallacycles to afford complexes $[\text{MX}_n(\text{ECE})\text{L}_m]$ (Scheme 1). A few examples are known that contain a two-carbon linkage between the aryl-carbon and the E-donor atoms, which results in the formation of six-membered metallacycles. These systems are included in the discussion where appropriate. A large variety of binding modes has been observed for the complexation of (transition) metals to NCN pincer ligands, ranging from $\eta^1\text{-C}$ monodentate to $\eta^3\text{-N,C,N}$ terdentate bonding as shown in Figure 1, together with one of the metals, for which a particular NCN –

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[**] In memory of Prof. Dr. Luigi M. Venanzi and his pioneering work in organometallic chemistry, particularly in PCP pincer chemistry.



Scheme 1. Potential modification sites in pincer ligands and their effects on the properties of the metal center.

metal binding mode has been found.^[6] It seems that this versatility in ECE binding is a unique feature of the NCN system, since until now neither in related PCP nor SCS pincer chemistry has such a diversity been encountered.

By far the most frequently observed is the meridional η^3 -*E,C,E*-coordination mode, in which the ligand bonds to the metal center in a terdentate manner as a six-electron donor with *trans*-positioned neutral donors E. This bonding mode forces the aryl ring of the pincer ligand into a conformation which is approximately coplanar with the coordination plane

of d^8 square-planar metal centers (Rh^I , Ir^I , Ni^{II} , Pd^{II} , Pt^{II}) or with the basal plane of d^6 square-pyramidal metal geometries (Ru^{II} , Rh^{III} , Ir^{III}). Modification of various ligand parameters allows for a refined adjustment of the steric and electronic properties of the complexed metal center without changing its bonding pattern significantly. In such pincer systems, the correlation of modifications in the ligand with the properties of the metal center is exceptionally high (see Scheme 1). These facts have been essential for the realization of most of the concepts and applications described herein.^[7] For example, steric influences may be varied by altering the size of the donor substituents or by introducing functional groups in the benzylic positions. Clearly, some of these modifications will also have electronic consequences. Strong electronic effects are attributed to the type of donor atoms E and the electron-withdrawing or -releasing character of their substituents. Fine-tuning of electronic properties can also be achieved by further substitution of the aromatic ring. Sites which do not exhibit significant or undesirable influences on the metal center

may be used for other purposes, for example, for the introduction of molecular recognition sites or for the anchoring of the ECE–metal group to a support (see Sections 3 and 5).

Thus far, the majority of investigations have been carried out with pincer ligands containing nitrogen, phosphorus, or sulfur donor groups (that is, $E = N(R^2)_2$, $P(R^2)_2$, or SR^2).^[8] Related OCO-type pincer ligands have not been used as frequently,^[9] and no applications have been reported for these complexes thus far.

Gerard van Koten has been Professor of Organic Synthesis at the Debye Institute of the Utrecht University since 1986. He is Scientific Director of the Netherlands Institute for Catalysis Research (NIOK). His research interests comprise the study of fundamental processes in organometallic chemistry, the application of organometallic complexes as homogeneous catalysts (in particular for fine-chemical synthesis), and as materials with special physicochemical properties (molecular wires and switches). The preparation and use of the first examples of homogeneous metallodendrimer catalysts demonstrate his interest in supramolecular systems with (organometallic) catalytically active functionalities.



G. van Koten



M. Albrecht

Martin Albrecht was born in Geneva, Switzerland, in 1971. After obtaining his M.S. in Chemistry from the University of Bern, Switzerland, in 1996, he carried out Ph.D. research under the guidance of Professor G. van Koten. These studies focused on platinum group metals containing pincer ligands and included fundamental aspects of C–H and C–C bond activation as well as the application of organoplatinum complexes as functional devices in materials, which led to new sensors and the first crystalline switches. He was the recipient of the Backer prize for the best Ph.D. thesis in the Netherlands in 2000. Currently, he is a postdoctoral fellow with Professor R. H. Crabtree at Yale University.

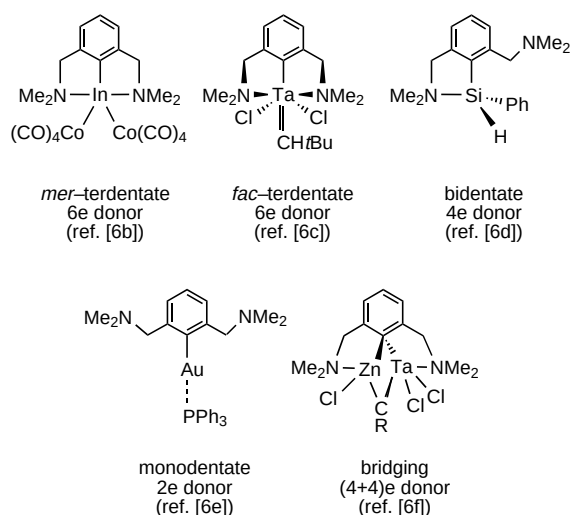


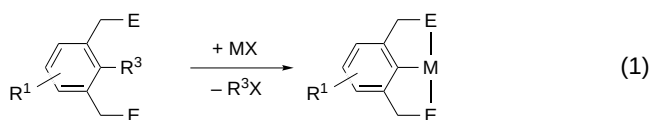
Figure 1. Observed coordination modes for NCN pincer ligands.

2. Strategies for the Metalation of Pincer Ligands

Various methods have been developed for the metalation of pincer ligands and the creation of a new transition metal–carbon σ bond. The applicability of any of these methods is strongly dependent on the transition metal M and the donor sites E of the pincer ligand.

2.1. Direct Cyclometalation by C– R^3 Bond Activation

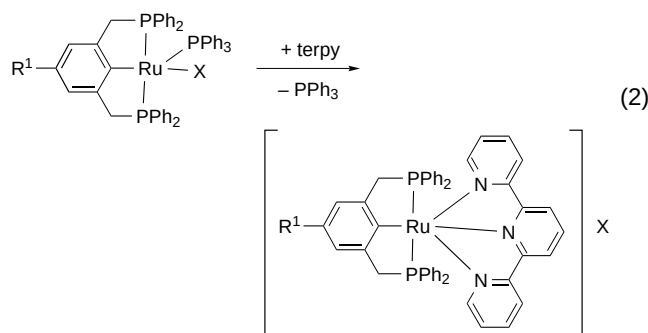
Direct cyclometalation [Eq. (1), $R^3 = H, CR_3, SiR_3$] is a particularly attractive method for the formation of a new $M-C$ bond, since it does not require prefunctionalization of



the pincer ligand in order to achieve regioselective metalation.^[7b, 10] C–H bond activation and subsequent biscyclometalation was successfully used as early as 1976 for the complexation of various Group IX (Rh, Ir) and Group X metal centers (Ni, Pd, Pt) with PCP ligands ($E = P(tBu)_2$).^[2a] Long reaction times and high temperatures were usually necessary. Milder reaction conditions in terms of reaction time and temperature could be used when the electron-releasing *tert*-butyl substituents on the phosphorus donors were replaced by weakly electron-withdrawing phenyl substituents ($E = PPh_2$).^[11] Since then, a wide variety of phosphanes $P(R^2)_2$ ($R^2 = iPr, tBu, Ph, Bn$, for example) and metal precursors (predominantly Pd and Pt) were successfully used for direct cyclometalation.^[12] However, some metal precursors failed to induce C–H bond activation even after prolonged heating, and coordination complexes containing a

η^2 -*P,P* bidentate coordinating pincer ligand were formed.^[13] Such species have been suggested to be intermediates preceding the cyclometalation.

PCP pincer complexes of ruthenium have only recently been prepared by direct cyclometalation.^[12d, 14] The ruthenium complexes $[RuX(PCP)L]$ ($L = PPh_3$, $X = Cl, OTf$ ($Tf = \text{trifluoromethanesulfonyl}$)) are highly oxygen sensitive, but can be significantly stabilized by conversion into the cationic terpyridine (terpy) complex $[Ru(PCP)L'](X)$ ($L' = 2,2':6',2''$ -terpyridine) according to Equation (2). Remarkably, modification of the phosphane donors from PPh_2 to the more bulky



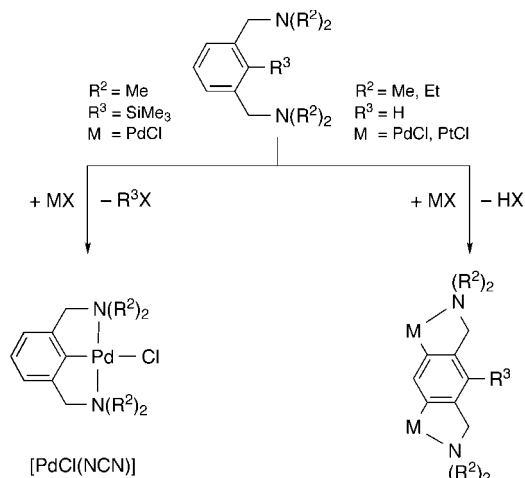
$P(tBu)_2$ reduces the oxygen sensitivity of the neutral complexes dramatically. Moreover, this change of phosphane donors allowed for the borohydride-mediated preparation of various hydride complexes $[RuH(PCP)L]$ ($L = CO, \mu-N_2$).^[15]

The corresponding PCP–osmium complexes are very rare, and suitable protocols for the direct metalation of PCP ligands with osmium(II)^[16a] and -(IV)^[16b] precursors appeared only recently. The lower valent complexes $[OsX(PCP)L]$ have been found to readily react with terminal acetylenes to form vinylidenes and carbynes.

Direct cyclometalation of PCP pincer ligands with rhodium has been extensively studied by Kaska and more recently by Milstein and co-workers, and has resulted in the isolation and characterization of a series of rhodium(I) complexes $[Rh(PCP)L]$ ($L = C_2H_4, H_2, CO, PPh_3, N_2$, carbene, for example).^[17] Remarkably, appropriate reaction conditions promoted a direct cyclometalation involving $C_{aryl}-C_{alkyl}$ bond activation [$R^3 = Me, Et$ in Eq. (1); see also Section 4.1], thus providing an elegant access to rhodium(III) complexes of the type $[RhX(R^3)(PCP)]$.^[18] Similarly, PCP–iridium complexes can be prepared by direct cyclometalation through C–H or C–C bond activation.^[17a, 19]

Direct cyclometalation of NCN pincer ligands is less common, and the topic was reviewed in 1998.^[7b] The reduced tendency for cyclometalation with these ligands may be explained by the relatively low bond strength of the $M-N$ bond. Therefore, initial coordination of the NCN pincer ligand to the metal precursor, which is an essential prerequisite for cyclometalation, is less favored than with the corresponding PCP and SCS pincer ligands. Moreover, this situation results in kinetically rather than thermodynamically controlled reaction pathways, and consequently, *ortho,para* doubly metalated products rather than *ortho,ortho*-biscyclo-

metalated species are obtained (Scheme 2).^[20, 21] Insertion of a Me_3Si substituent as a directing group on the aromatic system ($\text{R}^3 = \text{Me}_3\text{Si}$) successfully suppresses undesired *ortho,para*-metalation.^[22]

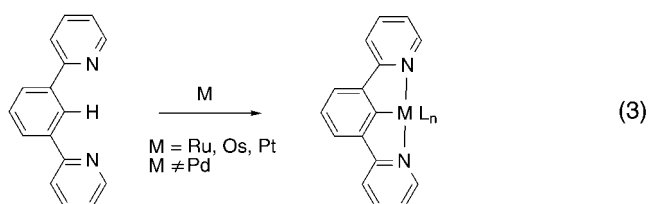


ortho,ortho-palladation

ortho,para-metalation

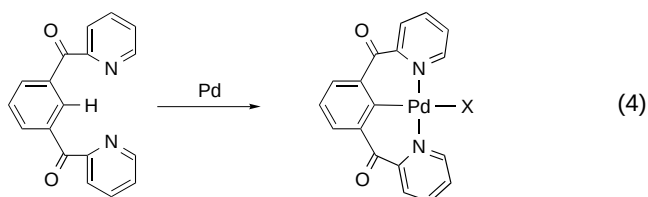
Scheme 2. Site-selective cyclometalation of NCN pincer ligands as a function of the ligand substitution pattern.

In contrast to NCN pincer ligands with amine groups, their pyridine analogues undergo facile cyclometalation with ruthenium, osmium,^[23] and platinum^[24] precursors to give the corresponding biscyclometalated products [Eq. (3)]. It is



noteworthy that the analogous reaction with palladium precursors did not give *ortho,ortho*-biscyclometalation, but resulted in metal insertion into the *ortho,para*-positions instead. This reactivity pattern is similar to that observed for NC(H)N ligands with palladium or platinum precursors (Scheme 2). Remarkably, introduction of a C_1 spacer between the central aryl ring and the pyridine unit (either C(=O) or CHMe) facilitated the biscyclopalladation considerably and afforded six-membered metallacycles [Eq. (4)].^[25]

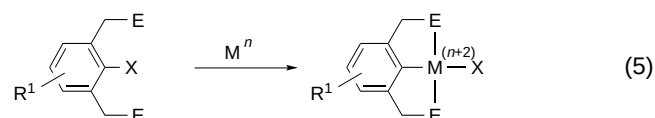
Palladation was reported for sulfur-type SC(H)S pincer ligands as early as 1980.^[26] Studies using a variety of SC(H)S arene ligands have revealed that the electronic configuration



of the sulfur atom and the cavity size of the SCS unit, imposed by the substituents on the donor atoms, are key factors in the promotion of cyclometalation.^[27] Benzyl and aryl substituents on the sulfur donor atoms were found to enhance the rate of cyclometalation, whereas sterically demanding *t*Bu groups required prolonged reaction times to achieve comparable yields. Experiments using SC(H)S pincer ligands containing small alkyl groups (for example, $\text{R}^2 = \text{Me}$) on the sulfur atom gave the cyclometalated product in low yields only (typically 10%). These results clearly demonstrate the potential of selective and controlled ligand tuning as a means of tailoring the properties of the metal center in such pincer complexes (see Scheme 1). Remarkably, the organometallic chemistry of SCS-type pincer ligands with platinum group metals other than palladium has thus far been virtually unexplored.^[28]

2.2. Oxidative Addition with Low-Valent Metal Precursors

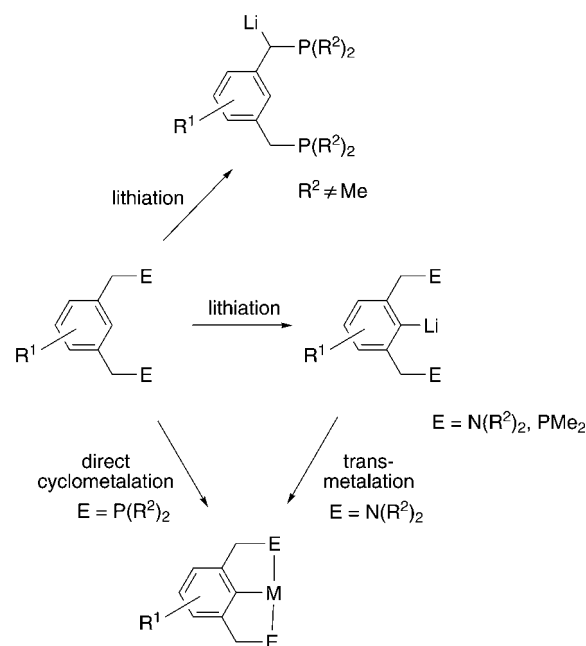
In contrast to direct cyclometalation, oxidative addition to carbon–halogen bonds [Eq. (5)] has hardly been explored in PCP chemistry, presumably because C–H activation has been



a successful method for complexation with all platinum group metals. The method might become more important when further functionalization on the pincer ligand is required, for example, with acid-labile or thermally unstable substituents, since direct cyclometalation by C–H bond activation formally releases HX as the by-product [$\text{X} = \text{Cl}, \text{Br}, \text{I}$; see Eq. (1)]. For NC(X)N ligands, which are much more resistant to direct cyclometalation, extensive studies on the oxidative addition of an aryl halide as a means of metalation have been carried out. Synthetic protocols for the preparation of suitable ligand precursors ($\text{X} = \text{Br}, \text{I}$) have been developed which tolerate a large diversity of functional groups R^1 on the pincer ligand ($\text{R}^1 = \text{NR}_2, \text{OR}, \text{I}, \text{CHO}$, for example).^[29] Successful approaches have included the oxidative addition to nickel (as $[\text{Ni}(\text{cod})_2]$ or $[\text{Ni}(\text{PPh}_3)_4]$),^[30] palladium (as $[\text{Pd}_2(\text{dba})_3]$), and recently also to platinum (as $[\text{Pt}(\text{4-tol})_2(\text{SET}_2)_2]$; dba = dibenzylideneacetone, cod = cycloocta-1,5-diene, 4-tol = 4-methylphenyl).^[29c] The reaction with the bis(tolyl)platinum precursor probably involves the formation of a platinum(IV) intermediate, which reductively eliminates 4,4'-bitolyl to give the desired complex $[\text{PtX}(\text{NCN})]$.^[31]

2.3. Transmetalation

Lithiation of PC(H)P ligands generally does not occur on the arene, but predominantly yields products arising from lithiation at the benzylic position of the PC(H)P ligand (Scheme 3). The use of an aryl halide precursor improves the



Scheme 3. Reactivity of PC(H)P and NC(H)N pincers towards lithiating agents.

selectivity, since Li/halide exchange is quantitative. However, the aryllithium species is generally not stable and isomerizes to the benzyllithium complex. This migration has been efficiently suppressed only when methyl substituents were used on the phosphorus atom ($E = \text{PMe}_2$).^[32] In this case, lithiation takes place at the arene and solid-state analyses (X-ray) have shown the presence of a dimeric $[\text{Li}_2(\text{PCP})_2]$ species with two Li-C-Li three-center, two-electron (3c-2e) bonds interconnecting the two PCP residues. This structure is closely related to those that have been isolated earlier with NCN pincer ligands (see Figure 2). Transmetalation of the lithium dimer with anhydrous MgCl_2 afforded the corresponding magnesium compound $[\text{Mg}(\text{PCP})_2]$ as a thermally stable complex, which has been characterized by single-crystal X-ray diffraction studies. Thus far, however, none of these complexes have been used as a precursor for transmetalation reactions.

Lithiation of the NC(X)N ligand precursors has been extensively applied to the preparation of suitable substrates for transmetalation. Early studies showed that the choice of solvent was crucial for the regioselectivity of the reactions.^[2c] In hexane, the lithiation ($X = \text{H}$) is an intramolecular, heteroatom-assisted process and favors C-H bond activation in the *ortho,ortho*-position. However, in ethereal solvents or using pincer ligands with oxo substituents ($R^1 = \text{OR}$), the oxygen-centered lone pairs exert a stronger directional influence than the amine donors and lithiation in the *ortho,para*-position is competitive or even dominant.^[2c, 33] Selective lithiation of such ligand precursors in the *ortho,ortho*-position by Li/halide exchange requires appropriate prefunctionalization of the pincer ligand. Various studies have revealed that the aryllithium species are generally^[34] dimers in solution as well as in the solid state (Figure 2).^[35] Transmetalation of these aryllithium species is straightforward and has been applied to the synthesis of iridium, nickel,

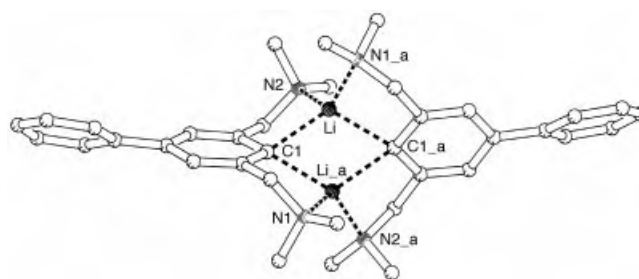
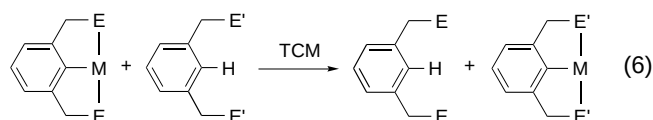


Figure 2. Molecular structure of dimeric $[\text{Li}(4\text{-Ph-NCN})_2]$ containing a phenyl-substituted NCN pincer ligand as a representative of $[\text{Li}(\text{NCN})]$ -type structures.^[35a,e]

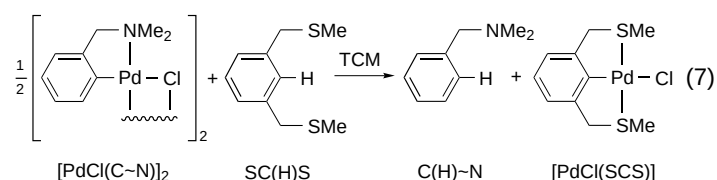
palladium, platinum, and ruthenium complexes.^[36] Significantly, transmetalation is thus far the only available method for the coordination of amine NCN pincer ligands with ruthenium.

2.4. Transcyclometalation

Recently, transcyclometalation (TCM) has been introduced as a novel method for the preparation of cyclometalated pincer compounds [Eq. (6)].^[37] The term is adapted from

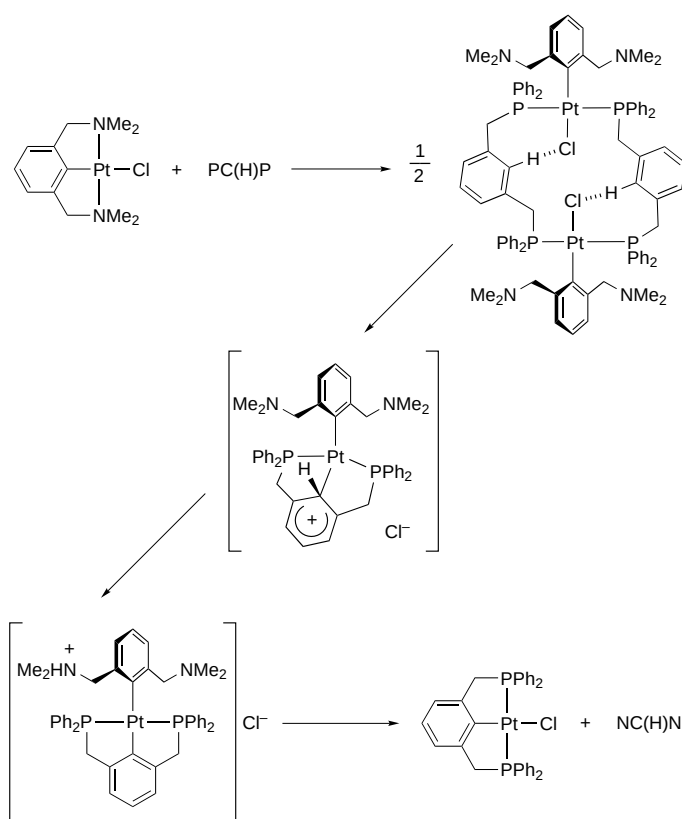


organic chemistry and is analogous to, for example, the term transesterification.^[38] The latter describes the replacement of one ester group by another one without formation of a stable cleavage or addition product (for example, an acid). Accordingly, transcyclometalation describes the substitution of one cyclometalated ligand by another one without the formation of significant and detectable amounts of purely inorganic compounds (dissociated metal salts). TCM reactions were initially investigated with bidentate coordinating ligands,^[39] but the concept has subsequently been extended also to terdentate-binding pincer ligands. Preliminary results included the reaction of the pincer ligand precursor SC(H)S with half an equivalent of the biscyclometalated dimer $[\text{PdCl}(\text{C} \sim \text{N})_2]$ (where $\text{C} \sim \text{N}$ is the $\eta^2\text{-C,N}$ bidentate coordinating ligand $[2\text{-C}_6\text{H}_4\text{CH}_2\text{NMe}_2]^-$), which afforded the biscyclometalated palladium complex $[\text{PdCl}(\text{SCS})]$ along with two equivalents of the protonated ligand $\text{C(H)} \sim \text{N}$ [Eq. (7)].^[39] The product



yield was markedly improved when instead of direct cyclometalation conditions ($[\text{Pd}(\text{OAc})_3]$, < 10% yield) the TCM reaction was applied (> 90%). Recently, the doubly cyclo-

metalated starting materials $[\text{PtCl}(\text{NCN})]$ and $[\text{RuCl}(\text{NCN})(\text{PPh}_3)]$ have been successfully used as starting materials for the preparation of the corresponding PCP-type complexes by a TCM protocol.^[37] The driving force in these reactions is most probably the higher M–E bond strength of $\text{E} = \text{PPh}_2$ (or SMe) than for $\text{E} = \text{NMe}_2$.^[40] This result shows that complexes containing the NCN pincer ligand are particularly suitable starting materials for TCM reactions. In the case of platinum, this method has been studied in detail and various intermediates have been isolated and characterized.^[37b] A mechanism of transcyclometalation has been suggested from these results that involves C–H bond activation through formation of an initial $\text{C}_{\text{aryl}}\text{--H}\cdots\text{Cl--Pt}$ hydrogen bonding and formation of a self-assembled dimer (Scheme 4).



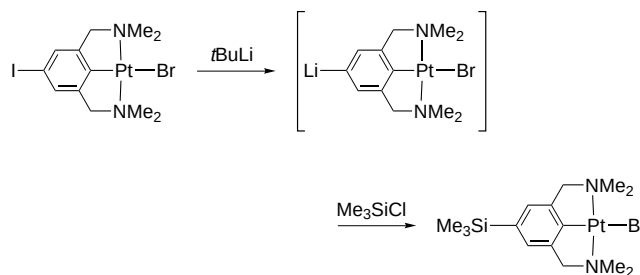
Scheme 4. Proposed reaction trajectory for the formation of a PCP-platinum complex by transcyclometalation.

Subsequent arenium formation and acid-mediated cleavage of the NCN ligand by M– C_{aryl} bond fission finally leads to the formation of $[\text{PtCl}(\text{PCP})]$ and $\text{NC}(\text{H})\text{N}$. Preliminary investigations in analogous ruthenium chemistry have indicated a different mechanism, however.^[41] It is thus clear that various mechanisms exist for the TCM reaction which are dependent on the ligand array and the metal center. Remarkably, the TCM reaction has enabled the metalation of polyfunctional cartwheel ligands (see Section 5.3), which could not be cyclometalated by any of the three methods described above, which clearly indicates that the TCM reaction presents a different and, in certain cases, superior methodology for metal insertion.^[42]

3. New Materials Properties

3.1. Stability—The Key to New Materials

The rigid terdentate binding mode of the pincer ligands provides the metal complexes having a substantially stabilized M–C σ bond. This is best illustrated by the advances achieved in the functionalization of the pincer ligand by aryl substitution ($\text{R}^1 \neq \text{H}$). The classical protocol uses ligand modification prior to metal insertion.^[24] Recent results with NCN complexes have shown that functionalization of the 4-position is possible even on the platinated complex.^[43] Related palladium complexes are slightly more sensitive but also tolerate a large variety of functionalizations. For example, esterification and etherification reactions of the hydroxy group ($\text{R}^1 = \text{OH}$)^[44] or amidation of a remote acid functionality ($\text{R}^1 = \text{linker with a COOH end group}$)^[45] have been shown not to affect the organometallic site of the complex. Most interestingly, the platinum complex $[\text{PtBr}(\text{I-NCN})]$ was lithiated selectively at the aryl position without inducing any detectable decomposition, and the heterobimetallic complex was subsequently quenched with Me_3SiCl , which acted as a model substrate for a reactive silyl chloride periphery on carbosilane dendrimers (Scheme 5).^[29c]

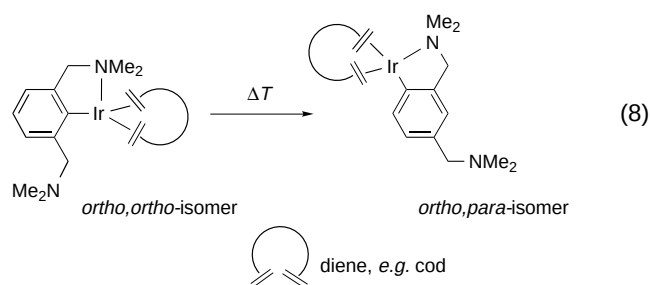


Scheme 5. Lithiation of NCN-platinum complexes without affecting the organoplatinum site, thus demonstrating the high stability of the Pt–C bond.

The successful performance of these reactions implies there is rigid coordination of the nitrogen atom to the metal center which efficiently protects the M–C σ bond from being cleaved. These $[\text{M}(\text{NCN})]^+$ units ($\text{M} = \text{Pt}, \text{Pd}$) can therefore be envisaged as organometallic synthons for organic synthesis. Notably, strongly nucleophilic bases (for example, NaOMe , $n\text{BuLi}$) are not compatible with this synthon, but instead promote M–C bond cleavage and the formation of decomposition products, presumably by hydrogen elimination pathways. These limitations can be avoided, however, by using protecting group strategies, a concept originally developed for organic synthesis. For example, the halide X in $[\text{PtX}(\text{NCN})]$ has been quantitatively replaced by an acetylide anion ($\text{X}' = \text{C}\equiv\text{CR}$).^[46] Removal of the protecting group and formation of the halide complex $[\text{PtX}(\text{NCN})]$ again was achieved by the addition of molecular iodine, a CuX_2 salt, or ammonium halides R_4NX ($\text{X} = \text{Cl}, \text{Br}, \text{I}$). These latter results illustrate the high stability of the *trans*-C–M–X arrangement in these complexes, which has also been encountered in other applications (see Sections 3.3 and 4.1). Strong evidence for

this remarkable stability came from detailed kinetic investigations on exchange reactions in $[\text{PtX}(\text{NCN})]$ complexes and comparison with data obtained from related *cis*- $[\text{PtX}(\text{CNN})]$ species (X = halide, solvent molecule; CNN = pincer ligand containing mutually *cis*-coordinating nitrogen donor atoms).^[47]

In contrast to the robustness of the palladium and platinum species, the related iridium complexes $[\text{Ir}(\text{NCN})(\text{diene})]$ (diene = cod, norbornadiene) are configurationally unstable. A thermal isomerization process has been observed in which the metal migrates from the *ortho,ortho*- to the *ortho,para*-position of the aryl ring by sequential intramolecular C-H bond-making and -breaking processes [Eq. (8)].^[36b] Isotopic



labeling revealed that the process is intramolecular and probably not solvent-assisted. A similar rearrangement was observed with analogous ruthenium complexes $[\text{RuX}(\text{NCN})(\text{diene})]$ and $[\text{Ru}(\text{C}_3\text{H}_5)(\text{NCN})(\text{PPh}_3)]$.^[48] The fluxional behavior of the CH_2NMe_2 donor groups in related rhodium(i) complexes^[49] suggested that the coordination of the nitrogen atom in these complexes is much less rigid than in the corresponding platinum and palladium species. Moreover, it also demonstrates that the free CH_2NMe_2 groups represent *ortho* substituents with considerable steric bulk which make the *ortho,ortho* to *ortho,para* rearrangement an irreversible process in the complexes $[\text{Ir}(\text{NCN})(\text{diene})]$ [Eq. (8)].

One aspect common to all pincer metal complexes is the high electron density on the metal center, which provides the metal with Lewis base properties.^[50] The pronounced nucleophilic character is a direct consequence of the monoanionic *E,C,E* donor motif of the pincer ligand, especially of NCN ligands containing hard electron-donating amine nitrogen atoms that coordinate in a *trans* arrangement. Moreover, the rigid terdentate binding mode forces the anionic aryl ring into an orientation which is almost coplanar with the d^8 -metal coordination plane. This is a significantly different situation than the one observed in classical Vaska compounds,^[50c] since it enables unusual orbital overlap of the metal-centered (filled) d_{xz} orbital and antibonding π^* -aryl orbitals.^[51] Nucleophilic behavior is well-documented (for example, data from UV-photoelectron spectroscopy) for the platinum(II) and palladium(II) species $[\text{PtX}(\text{NCN})]$ and $[\text{PdX}(\text{SCS})]$, respectively,^[52] both of which have a filled d_z orbital as the HOMO. These Lewis bases are known to coordinate AgX or HgX_2 . Confirmation of a direct metal–metal donor bond in the adducts was obtained by X-ray diffraction studies (for a platinum–mercury bond, see Figure 3),^[53] and also for

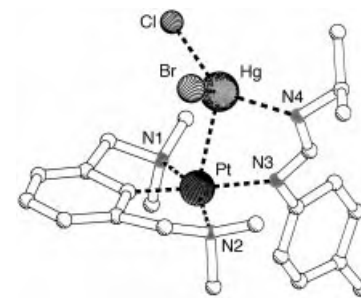
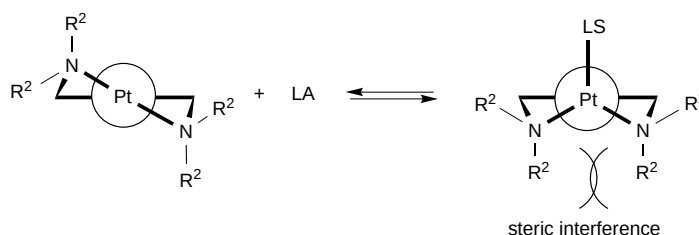


Figure 3. Molecular structure of a heterobimetallic pincer complex containing a direct platinum–mercury bond.^[53a]

platinum...silver interactions by a series of early ^{107}Ag and ^{109}Ag NMR spectroscopic measurements.^[54]

Another example of Lewis acid–base interaction was found between SO_2 and platinum(II) and nickel(II) (but remarkably not palladium) complexes containing NCN pincer ligands, which resulted in the reversible formation of penta-coordinate adducts.^[55] Importantly, the Lewis basic character of NCN pincer complexes is strongly dependent on the functional groups on the donor sites. An increase in the steric bulk from $\text{E} = \text{NMe}_2$ to NEt_2 is sufficient to induce an efficient shielding of the metal z -axis and therefore prevents the formation of these Lewis acid–base complexes even though NEt_2 is more basic than NMe_2 (Scheme 6).^[30b, 56]



Scheme 6. Repulsive interactions of large substituents on the heteroatom would cause steric congestion in Lewis acid/base adducts and therefore prevent the binding of Lewis acids (LA) by the nucleophilic metal center.

Unambiguous evidence for the Lewis basicity of the platinum centers in pincer complexes was deduced from their intriguing ability to bind a proton through a $\text{Pt}\cdots\text{H}^+$ interaction.^[57] Complexes containing a η^2 -*P,C,P*-coordinating PCP pincer ligand and a η^1 -*C*-coordinating NCN pincer ligand created a coordination pocket for reversible bidentate proton fixation through interaction with a lone pair on a noncoordinating nitrogen donor atom and the nucleophilic platinum center [Eq. (9)].^[37b] Solid-state and solution measurements on the protonated analogues provided evidence for a η^2 - Pt,N -chelated proton rather than a $\text{Pt}^{\text{IV}}\text{-H}$ hydride species ($\delta_{\text{H}} = 11.8$, $J_{\text{Pt,H}}$ not observed, $\text{Pt}\cdots\text{H}$ 2.82 Å; Figure 4).^[37b] Related studies using either PCP- or NCN-ligated platinum complexes containing *N*-acetyl-8-aminoquinoline at the fourth coordination site, that is, a pyridine-type ligand with an amino substituent as a potential proton receptor, confirmed this

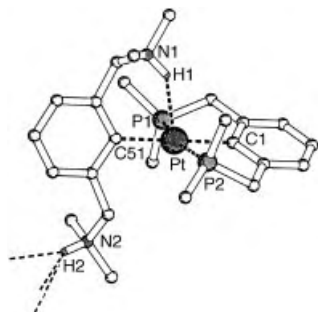
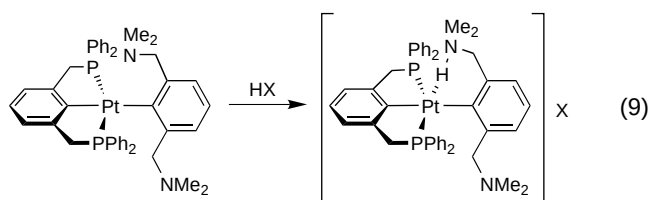
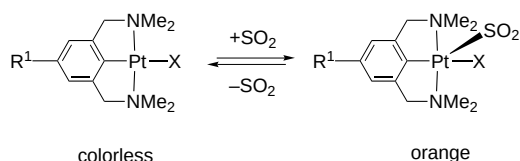


Figure 4. Molecular structure of the protonated form of an organometallic proton sponge comprising a platinum(II) center bound to a η^3 -*P,C,P*-coordinating PCP ligand and an η^1 -*C*-coordinating NCN ligand. The hydrogen atom is sequestered by *N,Pt* bidentate chelation.^[37b]

binding mode. Proton chelation through η^2 -*Pt,N* bidentate bonding was identified in the presence of an acid by extensive NMR spectroscopic analyses ($\delta_{\text{H}} = 13.02$, $^1J_{\text{Pt,H}} = 55$ Hz for the NCN analogue).^[58] These complexes therefore represent a rare type of organometallic proton sponge.^[59]

3.2. Gas Sensors

Exposure of square-planar platinum or nickel complexes containing an NCN pincer ligand to an atmosphere of SO_2 results in the instantaneous and reversible formation of the pentacoordinate adduct $[\text{MX}(\text{NCN})(\text{SO}_2)]$ (Scheme 7).^[54, 60] This reaction occurs in the solid state as well as in solution and



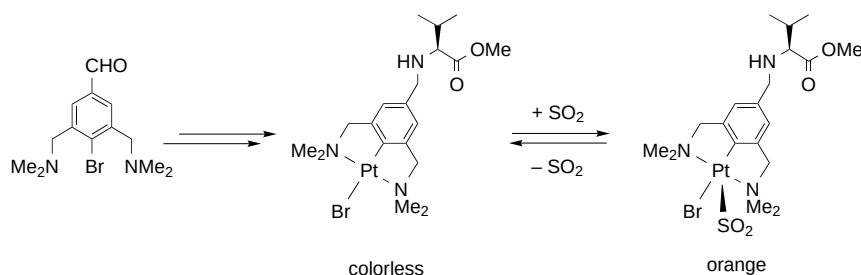
Scheme 7. Reversible binding of SO_2 on NCN-platinum complexes with formation of five-coordinate adducts.

is fully reversible for the platinum complexes, while the corresponding nickel complexes gradually decompose—probably because of the low stability of the pentacoordinate nickel adduct. Upon binding of SO_2 , the organoplatinum material undergoes a reversible color change from colorless to bright orange, which is diagnostic for the presence (or absence) of this gas. This property suggests the use

of the $\text{Pt}(\text{NCN})$ unit as an active site for the construction of novel sensor materials for the detection of SO_2 gas. Titration measurements have shown that concentrations of SO_2 in the ppm range may be detected qualitatively and quantitatively.^[60b] The threshold limit is very sensitive to steric modifications in the pincer ligand. An increase in the bulk on the nitrogen donor substituents from $\text{E} = \text{NMe}_2$ to NMeEt significantly lowered the sensor response (see Section 3.1), and a further increase to $\text{E} = \text{NEt}_2$ resulted in a complete deactivation of the sensor. On the basis of solid-state (X-ray) and solution (NMR) studies, this behavior was attributed to an efficient shielding of the d_{z^2} orbital of the metal center which is involved in the most relevant interactions with the SO_2 frontier orbitals.^[61]

Remarkably, the molecular recognition process between the platinum center and SO_2 is very selective and is not disturbed by the presence of other atmospheric gases (including CO and HCl) or humidity (H_2O). The reversible binding of SO_2 is an extremely fast process at ambient temperature and reaction rates in the order of nanoseconds were established ($k = 2 \times 10^8 \text{ s}^{-1}$).^[62] Detailed kinetic investigations using low-temperature NMR spectroscopy and ab initio calculations have indicated that SO_2 bonding occurs directly at the metal site and that the metal-bound halide exerts only secondary influences on the reaction.

The high stability of platinum complexes containing the NCN pincer ligand combined with the specific NMR activity of the ^{195}Pt nucleus ($I = 1/2$)^[63] suggested the use of these $[\text{Pt}(\text{NCN})]$ units for labeling purposes in biochemical and medicinal applications. For example, they are thermally inert in the presence of bases or strong acids (for example, 2 N HCl, 60°C), conditions which otherwise cause rapid denaturation of proteins. A high stability of the organometallic labeling sequence under physiological conditions is essential for potential biochemical and medical applications, since heavy metal release must be strictly avoided in in vivo applications. For this purpose, the covalent anchoring of organoplatinum sites to the N-terminus of amino acids has been performed (Scheme 8).^[64] These organoplatinum-labeled peptide mimics indeed showed a diagnostic NMR signal, whose chemical shift values are strongly dependent on the chemical environment of the biomarker. Hence these biomarkers provide a probe for the localization of the labeled sequence in a complex system. Additionally, they display attractive (bio)sensor properties, since such complexes detect SO_2 reversibly, which is indicated, for example, by a characteristic downfield shift of the ^{195}Pt NMR signal ($\Delta\delta_{\text{Pt}} = 1200$, compared to SO_2 -free solutions).



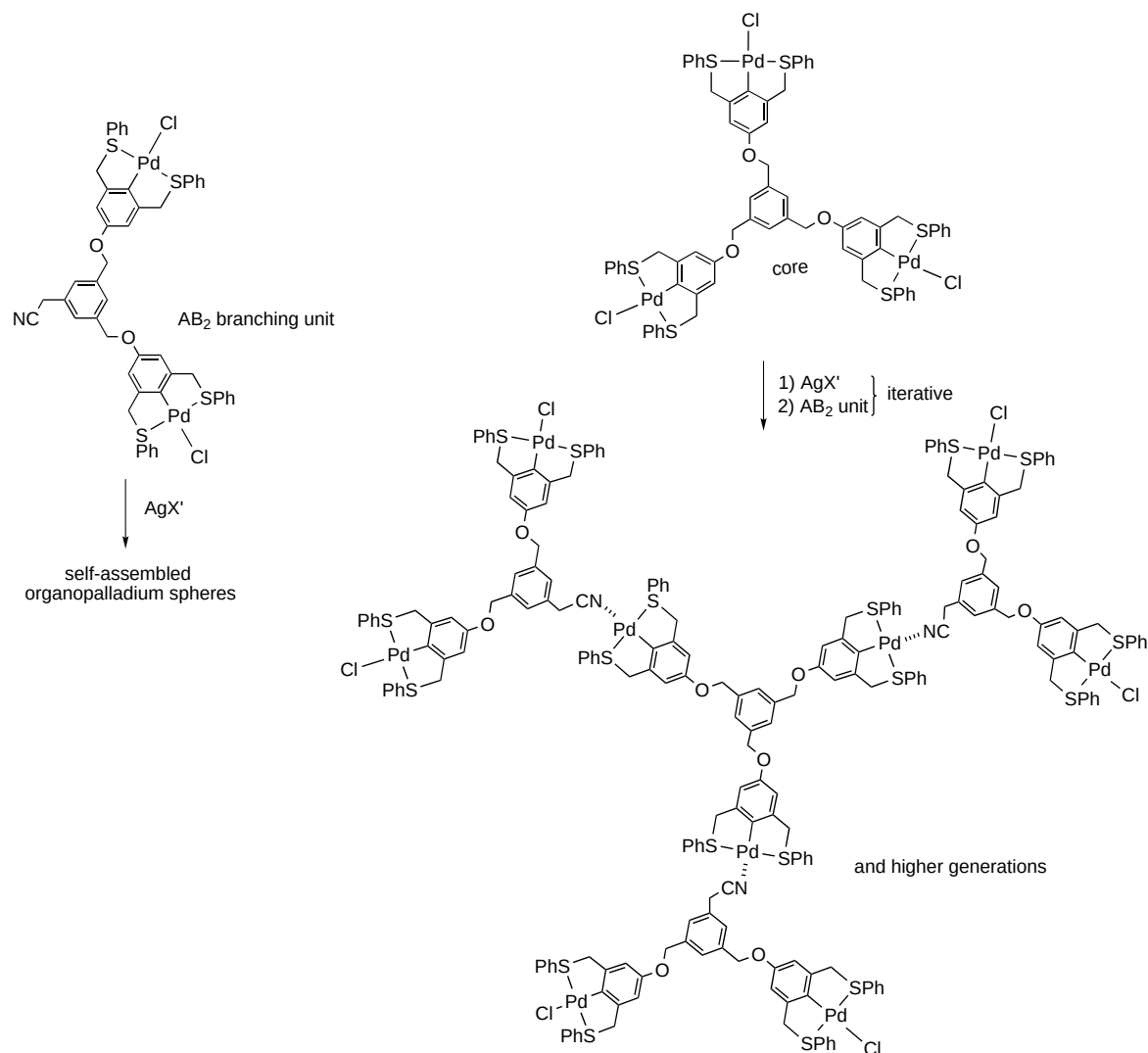
Scheme 8. Biosensors and markers obtained by covalent functionalization of the N-terminus of an α -amino acid with a diagnostic NCN-platinum site.

3.3. Self-Assembled Systems

The excellent stability of the palladium and platinum pincer complexes suggests their potential use as novel building blocks in materials science. In such square-planar d^8 complexes, only one coordination site *trans* to the M–C σ bond is left open, which can be occupied by a variety of neutral or ionic ligands. Interesting possibilities emerge from functionalization of the pincer ligand prior to metalation, for example, by aryl substitution ($R^1 \neq H$). For example, the introduction of coordinating nitrile sites into the aryl system of SCS ligands (R^1 is a linker with a CH_2CN end group) afforded a bifunctional ligand that can bind to a metal center through terdentate ECE coordination and also through weak monodentate nitrile binding. On the basis of these ideas, a bimetallic Pd_2 -CN synthon and a trimetallic Pd_3 complex were prepared, which represent an AB_2 building block and a core unit, respectively, for noncovalent metallodendrimer synthesis (Scheme 9).^[65] A divergent synthesis (including repetitive halide abstraction in the core molecule and subsequent addition of an AB_2 branching point) provided dendritic structures up to the 5th generation that were

fabricated by controlled self-assembly. Substitution of the sulfur donors by phosphanes facilitated the incorporation of different metals and resulted in the construction of homometallic ($M = Pd$) and heterometallic metallodendrimers ($M = Ni, Pd, Pt$).^[66]

A similar convergent dendrimer synthesis is difficult because of the competitive coordination strength of the focal point of the dendrons and the added branching point. Second generation dendrimers have been prepared convergently, however, by modifying the coordination site from a nitrile to a pyridine-type site.^[67] Large self-assembled organopalladium spheres have been generated by halide abstraction and subsequent removal of the coordinating solvent (Scheme 9).^[68] Light-scattering techniques and microscopy (TEM, AFM) have revealed self-assembled particles in the submicrometer range (estimated diameter roughly 200 nm). The noncoordinating anions were assumed to play a key role during surface congestion—a process that determines the end-point of the self-assembly and hence the particle size. Moreover, branching of the building blocks seems to be essential for spherical self-assembly. Notably, the noncovalent (that is, coordinating) interactions between the building blocks are formed rever-



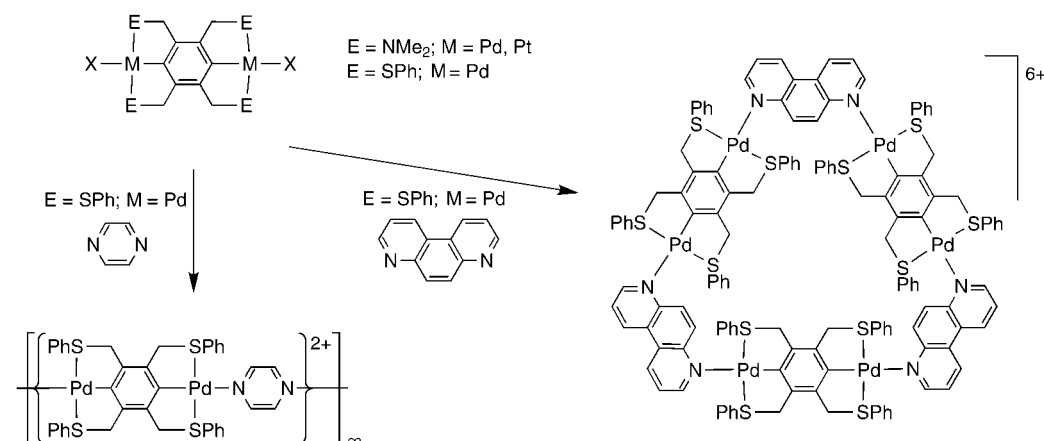
Scheme 9. Palladium complexes containing functionalized SCS pincer ligands self-assemble into infinite (left) and finite (right) supramolecular structures.

sibly and are highly sensitive towards the presence of small coordinating molecules (for example, H_2O , Cl^-), which disrupt the self-assembled structures within a few minutes.

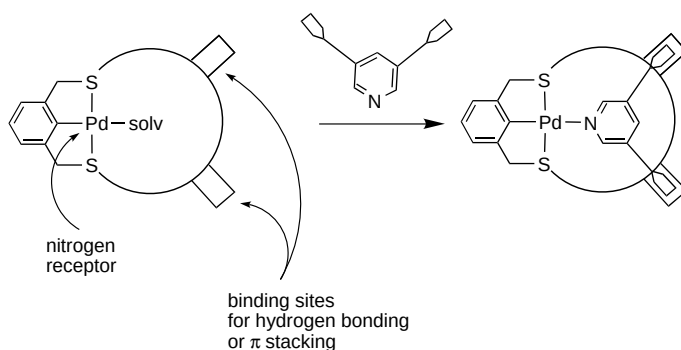
Similar coordination chemistry has been employed for the construction of supramolecular assemblies from bimetallic synthons (Scheme 10).^[69] Depending on the pyridine-type ligand occupying the fourth coordination site (pyrazine or 4,4'-bipyridine),^[70] either linear polymeric structures or molecular macrocycles can be obtained. The latter result from a [3+3] self-assembly of the bimetallic building block and 4,7-phenanthroline.^[71]

On a supramolecular level, these assemblies correspond to host–guest interactions, where the $[\text{Pd}(\text{SCS})]$ moiety serves as a host (receptor) for nitrile and pyridine guests. Loeb and co-workers have refined the host system in order to achieve more-selective binding sites for specific guest molecules.^[72] For this purpose, the sulfur donors were functionalized with bridging polyether or calixarene substituents that were to act as receptors for secondary host–guest interactions. As a result, $\text{Pd}\cdots\text{N}$ coordination is assisted by secondary hydrogen bonding of guest protons to crown ether oxygen atoms or π -stacking interactions with calixarenes (Scheme 11). Modification of the ring size and oxygen distribution in the dithia-macrocycle allowed for the optimization of the binding pockets of these metalloreceptors. Various host–guest complexes have been prepared with amines, imines, and water. In most cases, secondary hydrogen-bonding interactions have been established in the solid state. However, competition studies have revealed that selectivity in these reactions is generally low. The most promising results have been obtained for the selective recognition of purine bases. The complexation of cytosine was preferred in these systems, and thymine was efficiently discriminated against, provided that the solvent and macrocyclic ligand system were appropriately chosen.^[73] The employment of two sequential extraction steps has also allowed for the differentiation between guanine and adenine, and hence for the specific detection of all DNA nucleobases.

Similar macrocyclic NCN ligands without additional recognition sites have been metalated with rhodium, palladium, and platinum.^[74] Detailed NMR and X-ray studies revealed a high flexibility of the macrocycle and indicated that the metal coordination site *trans* to the metal–carbon bond is significantly shielded.^[74b,c]

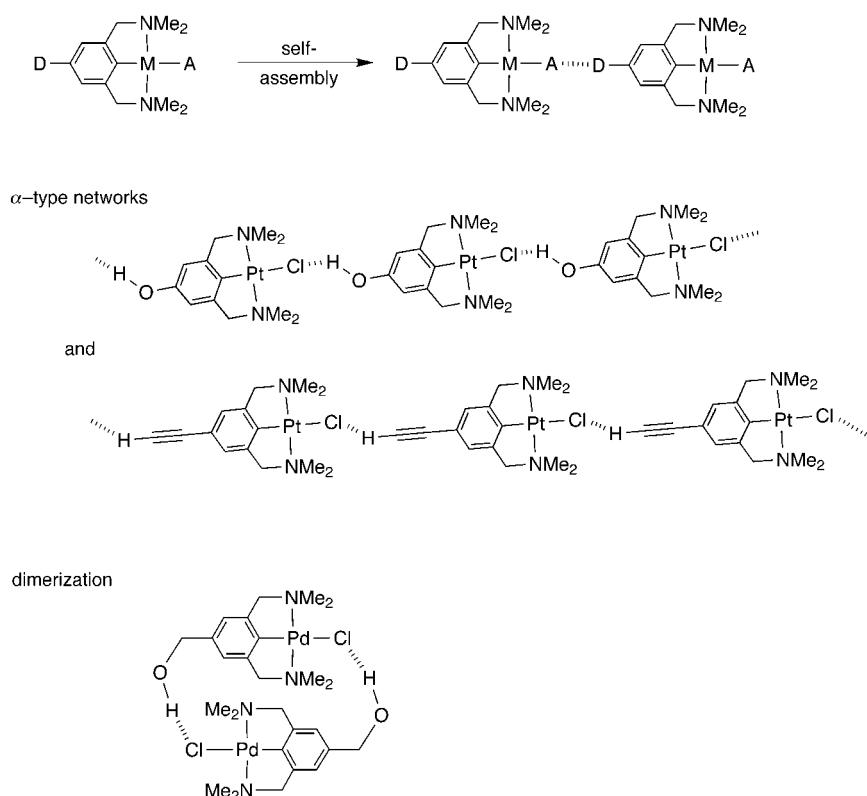


Scheme 10. Pyridine derivatives control the self-assembly of bimetallic SCS–palladium building blocks into hexametallacycles and polymetallic chains.

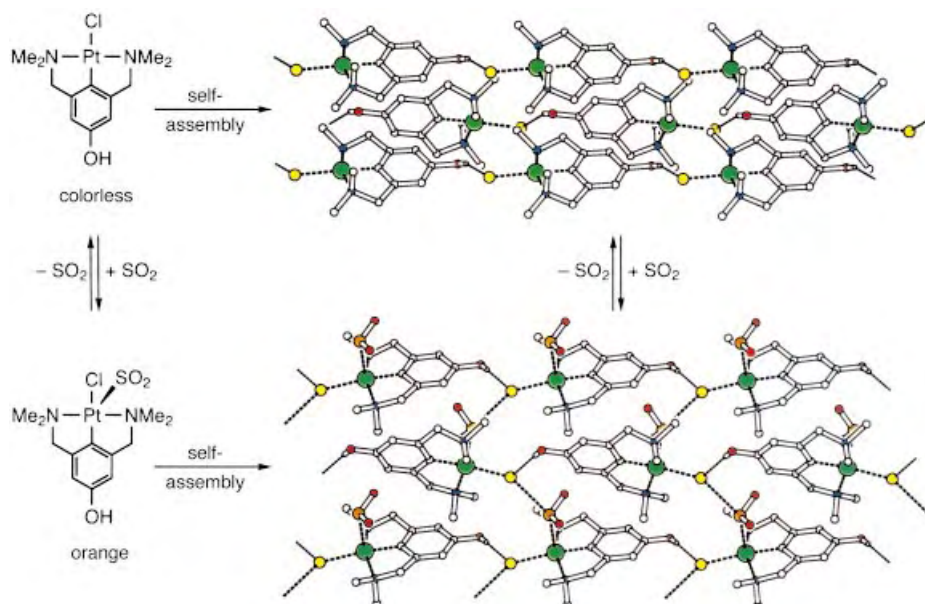


Scheme 11. Schematic representation of palladium complexes containing SCS pincer ligands that are functionalized with secondary recognition sites for substrate discrimination.

A different supramolecular synthon, which proved to be suitable for crystal engineering, has been prepared by incorporating directional hydrogen bond donor (D) and acceptor (A) sites on the metal–pincer complex. One suitable design has involved the introduction of hydroxyl or acetylene substituents onto the aryl unit of the NCN pincer ligand ($\text{D} = \text{OH}$, $\text{C}\equiv\text{CH}$, or CH_2OH , Scheme 12) as hydrogen donor groups and a platinum-bound chloride ion as the hydrogen acceptor.^[75] This configuration promoted the hydrogen-bond-mediated self-assembly of these building blocks through $\text{O}-\text{H}\cdots\text{Cl}-\text{M}$ or $\text{C}\equiv\text{C}-\text{H}\cdots\text{Cl}-\text{M}$ interactions ($\text{M} = \text{Pd}$, Pt). The specific architectures that are formed by this self-assembly are strongly dependent on the flexibility of the hydrogen bond donor and acceptor sites. For example, the CH_2OH donor promoted the formation of discrete dimers, whereas hydroxy or acetylene donors induced the formation of infinite linear, α -type networks. Interestingly, these networks are present in the solid state as well as in solution, as has been demonstrated by IR spectroscopy.^[75a] The addition of gaseous SO_2 to the hydroxyl complex resulted in the formation of the corresponding adducts. The $\text{O}-\text{H}\cdots\text{Cl}-\text{Pt}$ hydrogen-bonding motif is also conserved in the adduct in the solid state. In addition, these chains are superimposed by orthogonal $\text{Pt}-\text{S}(\text{O})_2\cdots\text{Cl}$ interactions.^[60a] Hence, the addition of SO_2 interconnects the self-assembled hydrogen-bond chains and results in the formation of β -type networks (Scheme 13).



Scheme 12. Appropriate ligand functionalization with donors (D) or acceptors (A) promotes the self-assembly of palladium and platinum complexes through formation of $M-Cl \cdots H$ hydrogen bonds.



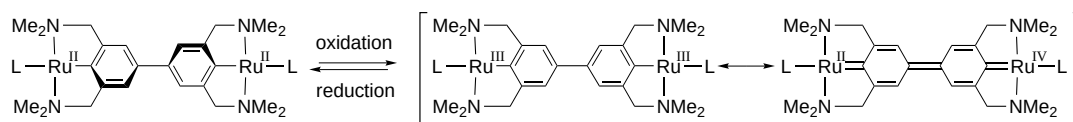
Scheme 13. A SO_2 -triggered switch that operates in the crystalline phase.

3.4. Switches

Since the bonding of gaseous SO_2 to the platinum complexes $[PtX(R^1-NCN)]$ occurs both in solution and in the solid state, the gas fixation process was further explored by using crystalline material. Remarkably, exposure of the crystalline material to an atmosphere of SO_2 resulted in adduct formation without destruction of the crystalline organization

($R^1 = H, OH$).^[76] Removal of the SO_2 atmosphere promoted the reverse crystalline transformation and the crystalline starting material was recovered in quantitative yield. Spectroscopic (IR) and X-ray diffraction studies have provided unambiguous evidence that the molecular structure of the crystalline material changes significantly on SO_2 addition. Moreover, gas bonding and release are accompanied by an expansion and shrinkage, respectively, of the unit cell by more than 15 %, without affecting the materials crystallinity. Importantly, the presence of a supramolecular hydrogen-bonding network which is conserved during the crystalline transformations opens interesting applications for crystal engineering, but is not essential for the observed crystalline transformations.^[77] The binding and release of SO_2 in the crystalline material of the complexes $[PtX(NCN)]$ ($R^1 = H$; $X = Cl, Br, I$) also occurs with full conservation of crystallinity. Hence, these materials represent gas-triggered crystalline switches that are based on the self-assembly of single $[PtX(R^1-NCN)]$ building blocks in the solid state. The color and the characteristic IR absorption bands serve as diagnostic signals to indicate the “on” and “off” positions of the switch. The development of such devices is a unique combination of crystal engineering and sensor properties of the platinum complexes $[PtX(R^1-NCN)]$. Such switches, which are triggered by environmentally relevant gases, have been suggested as functional devices for (opto-)electronic applications.

A different type of molecular switch is based on the redox activity of ruthenium centers that are complexed to NCN pincer dimers ($R^1 = NCN$; Scheme 14). Such bimetallic complexes have been prepared successfully through a $C_{aryl}-C_{aryl}$ bond coupling of pincer ruthenium–terpyridine complexes.^[78] Remarkably, these bimetallic Ru_2 complexes change their color and molecular conformation in response to the oxidation state of the metal centers (Scheme 14).^[78b] For example in a reducing environment, the ruthenium centers are present in the blue Ru^{II}/Ru^{II} oxidation state and the aryl rings of the two pincer ligands are tilted by more than 20° . In the green, oxidized Ru^{III}/Ru^{III} state, however, these aryl rings are virtually coplanar and allow for metal–metal π -electron

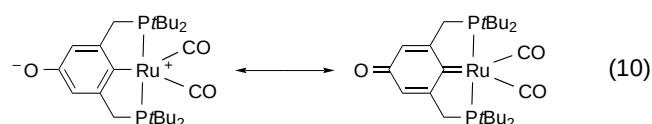


Scheme 14. Redox-active molecular switch that reversibly changes its color and conformation. L = terpy.

conjugation. This latter state is illustrated by a resonance structure comprising a C=C bond between the two aryl rings (emphasizing their coplanarity) and a mixed-valence Ru^{II}/Ru^{IV} species (Scheme 14). Importantly, the slow reduction enabled the characterization of a Ru^{II}/Ru^{III} complex in solution (cyclic voltammetry), which indicated that the oxidation and reduction are stepwise processes and that the ruthenium centers are not independent.

This latter property has been addressed by Sauvage and co-workers.^[23, 79] They used homobimetallic ruthenium and osmium complexes containing dimeric NCN ligands with pyridine donors, [M₂(NCN-NCN)(terpy)₂]ⁿ⁺ [see Eq. (3)], in which the two biphenyl-bridged metal centers were able to “communicate” with each other. Huge molecular extinction coefficients resulted from the stabilization of the mixed-valence M^{II}/M^{III} complexes, which points to particularly strong inter-metallic interactions. Such bimetallic systems, in which the metal–metal communication may be turned on and off by applying an oxidizing or reducing environment, have a high potential for application in molecular electronics, for example, as redox-sensitive gates in conducting molecular wires.

A solvent-triggered molecular switch based on monometallic PCP–ruthenium complexes has been developed recently.^[80] The prefuctionalization of the arene moiety of the PCP ligand with an acidic hydroxy group is essential for the remarkable properties of these complexes. Abstraction of the phenolic proton by an appropriate base afforded a ruthenium(II) complex which displays two limiting resonance structures [Eq. (10)]. Analysis by UV/Vis and multinuclear NMR



spectroscopy clearly indicated that the preferred resonance form is highly solvent dependent. In polar solvents, such as MeOH and acetone, the complex is yellow, and formulated as a zwitterionic species, whereas in less polar solvents (for example, THF, benzene) it is red, and formulated as a metallaquinone with a ruthenium–carbene unit.

4. Slow and Fast Catalysts

4.1. Trapping of Intermediates

The particular electronic and steric configuration of pincer ligands has been used in several studies to tune the properties of a metal center. A particular consequence emanating from this approach is that complexes with a restricted reactivity

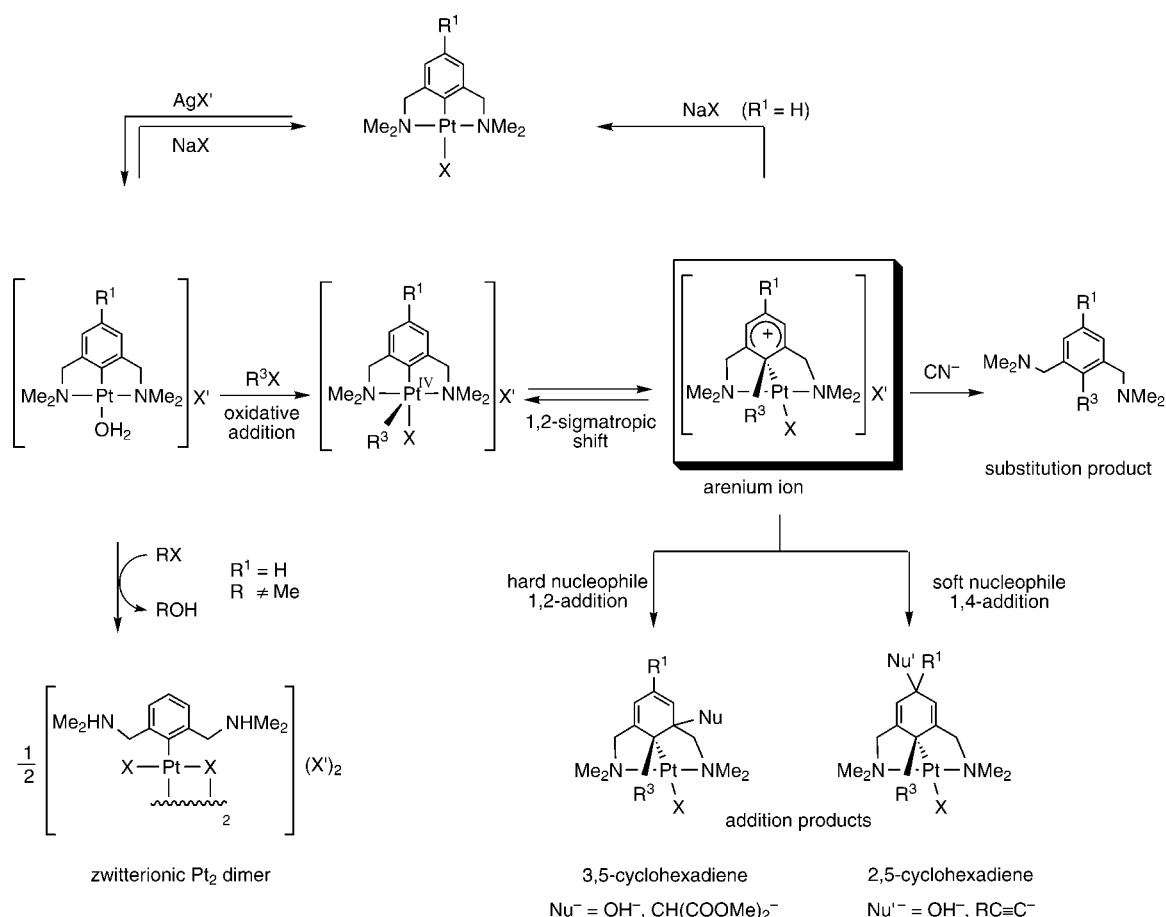
have been generated. These complexes have resulted in reactions that were markedly slowed and sometimes even halted at a certain stage, thus providing valuable information about the mechanistic details of the reaction coordinate and about the precise configuration of key intermediates.

4.1.1. C–C Bond Activation

Major efforts have been directed towards the elucidation of the mechanistic aspects of metal-mediated C_{aryl}–C_{alkyl} bond formation and cleavage. Milstein and co-workers have focused predominantly on C–C bond cleavage (by using alkylated PC(R³)P pincer ligands; R³ = alkyl), whereas we have concentrated on the reverse process, namely, C–C bond formation with NCN-ligated complexes and alkyl halides. Despite these different approaches, the resultant conclusions are generally congruent and indicate a uniform process that is essentially independent of the metal center and ligand system.

Upon treatment of the aqua complex [Pt(NCN)(OH₂)](X') with methyl iodide (Scheme 15), the platinum-stabilized arenium complex [Pt(1-Me-NCN)](X') was isolated and characterized (Figure 5).^[2b, 36d, 81] As expected for arenium structures, the *ipso*-carbon atom was considerably rehybridized with sp³ rather than sp² character. Consequently, the platinum coordination plane was significantly tilted with respect to the aryl plane (by more than 80°). This complex was thus proposed as a key intermediate of a C_{aryl}–C_{methyl} bond-forming process, and furthermore represents a frozen Wheland-type intermediate in electrophilic aromatic substitution. Theoretical considerations have suggested that the oxidative addition of MeI to the metal center and formation of an (alkyl)(aryl)platinum complex occurs prior to a 1,2-sigmatropic shift of the alkyl group to form the arenium product (Scheme 15).^[51] These arenium compounds are stable towards air and water, as a result of the intramolecular stabilization of the platinum center by nitrogen atoms, and their reactivity could be investigated in full detail.^[82] Selective bond cleavage of either the newly formed C_{aryl}–C_{alkyl} bond or the Pt–C_{aryl} bond can be triggered by a careful choice of reagents (Scheme 15). Alternatively, neutral cyclohexadiene derivatives with conserved C_{aryl}–C_{alkyl} and the Pt–C_{aryl} σ bonds can be generated by trapping the arenium intermediate with a nucleophile. The hardness of the nucleophile determines whether 1,2- or 1,4-addition products are obtained, that is, 3,5- or 2,5-cyclohexadiene pincer ligands with an sp³ hybridized metal-bound carbon.

This reactivity pattern of platinum-stabilized arenium ions shows remarkable analogies to that of Wheland-type intermediates, which suggests there is a similar mechanism for the formation of these species. However, arenium formation was initially restricted to reactions with methyl halides, which



Scheme 15. Intermediates and product variation in platinum-mediated C–C bond-making and -breaking processes.

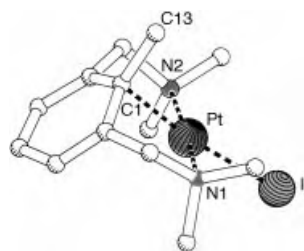
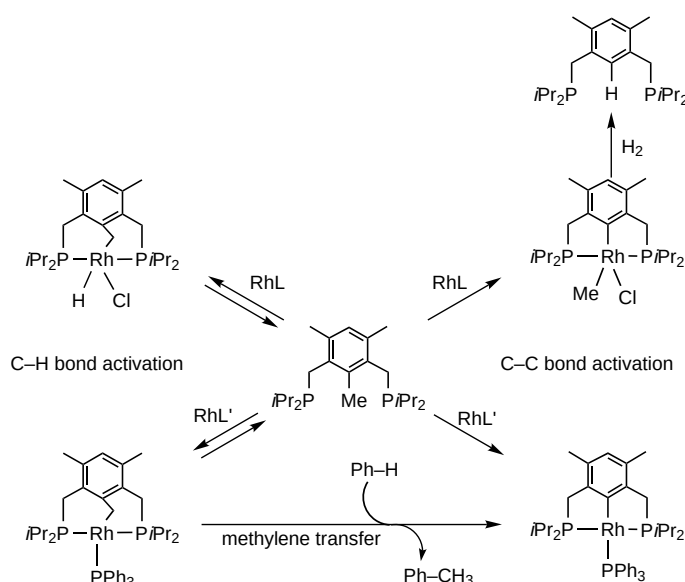


Figure 5. Molecular structure of the cationic methyl arenium complex $[PtI(1-Me-NCN)]^+$ with a newly formed C1–C13 bond as a key intermediate in platinum-mediated C_{aryl} – C_{alkyl} bond formation (the anion $X' = BF_4$ is omitted for clarity).^[2b, 36]

precluded extensive analyses that would allow a generalization of this reaction.^[83] These reactivity limitations have only recently been successfully overcome by the introduction of electron-releasing groups on the aryl ring of the pincer ligand, a concept which is deduced from electrophilic aromatic substitution theory.^[84] Arenium formation took place with various alkyl halides when platinum complexes containing oxo-functionalized pincer ligands were used $[Pt(R^1-NCN)(OH_2)]^+$ ($R^1 = OH, OMe$). Moreover, the kinetic and thermodynamic effects of these aromatic substituents, namely, activation of the aromatic ring and stabilization of positive charges, has also allowed for the spectroscopic detection and characterization of the proposed (alkyl)(aryl)-

platinum(IV) intermediates, which indeed precede arenium formation. Direct evidence has been provided for a reversible 1,2-sigmatropic alkyl shift along the Pt– C_{aryl} bond for the final transformation to the arenium species.

Activation of unstrained C_{aryl} – C_{alkyl} bonds, the microscopic reverse process of the reaction sequence described above, has been induced in the presence of a rhodium(I) precursor on an alkyl-functionalized $PC(R^3)P$ pincer ligand ($R^3 = Me, Et$; Scheme 16).^[7a, 18] Surprisingly, the reaction with $[RhCl(coe)_2]_2$ ($coe = cyclooctene$) and under mild H_2 pressure has been performed catalytically. A respectable 106 turnovers were obtained within 72 h when the methyl-functionalized PCP pincer ligand precursor was used.^[85] A series of mechanistic investigations^[17c, 19, 86] and a theoretical study^[87] revealed that C_{alkyl} –H bond activation and formation of a benzylic Rh–C bond may be a competitive reaction, but not an intermediate of the C_{aryl} – C_{alkyl} bond-activation process (Scheme 16). The kinetic preference for one of the two products is strongly dependent on the reaction conditions and can be altered by an appropriate choice of, for example, phosphane substituents, rhodium precursor, solvent, or reaction temperature. In all cases, the thermodynamic product was found to be the five-membered metallacycle resulting from C–C bond cleavage, which, in contrast to C–H bond activation, is irreversible. Hence, the benzylic rhodium complexes obtained from C–H bond activation were transformed to the arylrhodium com-

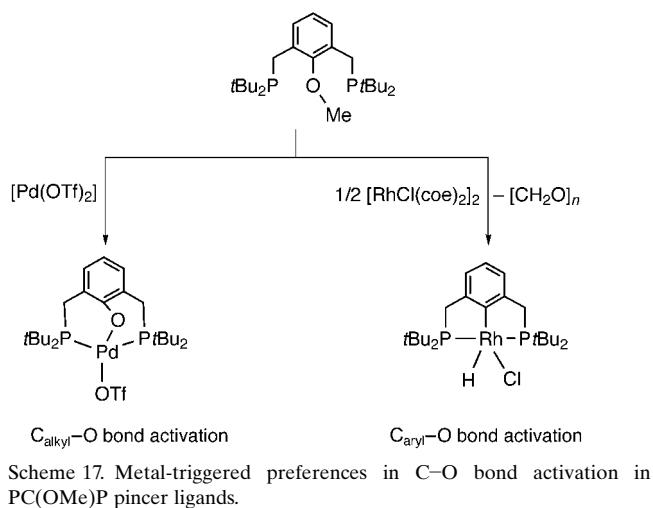


Scheme 16. Selective C-H or C-C bond activation in PC(Me)P ligands as a function of the applied reaction conditions. RhL = [RhCl(coe)₂]₂, RhL' = [RhH(PPh₃)₄].

plexes, a process which can be induced either thermally or by the addition of H₂. This process is presumed to reverse the C-H bond activation and results in the formal release of a CH₂ fragment (for R³ = Me).^[88] Remarkably, this CH₂ group can be selectively delivered to an organic substrate under certain reaction conditions, thus giving, for example, toluene from benzene (Scheme 16).^[89] This is an interesting application of a reaction system in which the thermodynamic and kinetic preferences of product formation diverge.

Similar reaction patterns were observed upon changing the active metal center to ruthenium or platinum.^[12d] In the latter system, the activation barrier for C-C bond activation is apparently too high and the benzylic complex resulting from C-H bond activation is the exclusive product. The addition of HCl induces the formation of the Pt-C_{aryl} bond, which corresponds to the net transfer of a CH₂ group of the PC(Me)P ligand to HCl. Similar product discrimination was obtained in the reaction of the methoxy-functionalized pincer ligand PC(OMe)P with different metal precursors. Palladation results in the selective formation of six-membered metallacycles by the activation of the O-CH₃ bond, whereas rhodium(I) insertion occurred exclusively into the O-C_{aryl} bond (Scheme 17).^[17b, 90]

Detailed analysis of the C-C bond-activation process revealed that the reaction already occurs at low temperature (−40 °C).^[91] Coordination of the phosphane donors to the rhodium ion has been established as the first reaction sequence, which results in the formation of a monomeric, or alternatively a dimeric,^[13, 37b] coordination compound. No further intermediates have been observed at low temperatures, which clearly shows that the rate-determining step is the activation of this coordination compound, and that subsequent intermediates, if present, would be only weakly stabilized. A cyclopropane-type metallacycle seems to be the most probable transition state on the reaction coordinate of C-C bond activation (Figure 6a). Various structures that



Scheme 17. Metal-triggered preferences in C-O bond activation in PC(OMe)P pincer ligands.

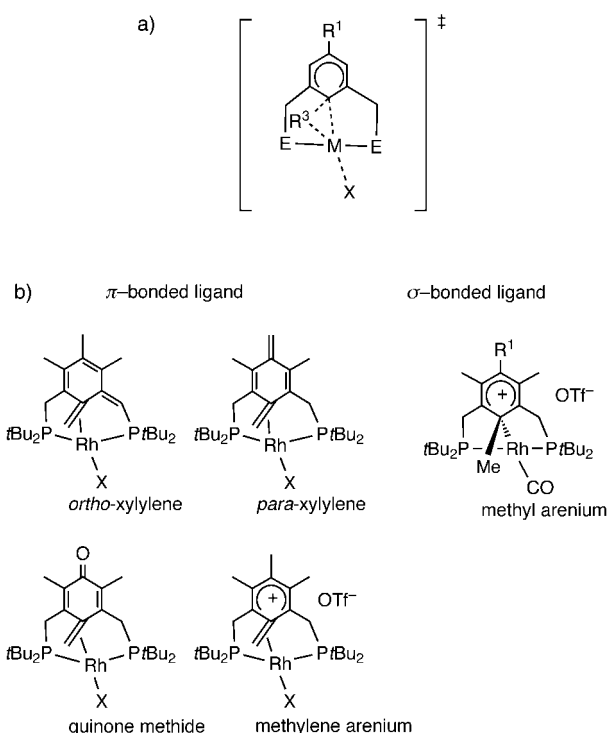


Figure 6. a) Proposed transition state in metal-mediated C-C bond activation. Depending on the substitution pattern on the pincer ligand (E, R¹) and the metal center, one or more of the weak interactions (indicated by dashed lines) is more pronounced, thus giving agostic, methyl, or methylene arenium species with more or less localized π electrons. b) Potential mimics of the proposed transition state: isolated and characterized structures containing a π - or σ -bonded PCP ligand.^[92]

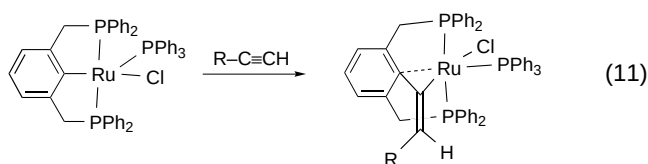
could mimic such a transition state have been prepared by independent routes and include rhodium-stabilized quinone methides, xylylenes, and methylene arenium complexes (Figure 6b). In all of these complexes the rhodium center is π bonded to one exocyclic double bond of the arene moiety of the PCP pincer ligand.^[92]

Another potential class of intermediates comprises alkyl arenium structures containing a Rh-C σ bond. Such intermediates have been thoroughly analyzed in related platinum chemistry directed towards the mechanism of C-C bond-

forming reactions, but they are apparently less stabilized by rhodium. The addition of CO is essential to promote the formation of rhodium–arenium σ complexes from the corresponding π -coordinated methylene arenium complexes.^[92c,d] Presumably, the high affinity of the rhodium(I) ion to coordinate to a π acceptor prevents a spontaneous ($\pi \rightarrow \sigma$) rearrangement in the absence of a CO ligand. Notably, the rhodium-stabilized alkyl arenium complexes do not exhibit the typical reactivity patterns of arenium species, as established, for example, for the platinum analogues. This different behavior has been explained by a relatively strong tendency of the arene to aromatize when coordinated to a rhodium center.

Although the approaches chosen to detail the metal-mediated $C_{\text{aryl}}-C_{\text{alkyl}}$ bond-making and -breaking process diverge considerably, for example, with respect to the metal center (Rh/Pt), the ligand array (PCP/NCN), and the overall process (C–C bond activation/formation), the results obtained display significant qualitative overlap. In both systems arenium complexes (alkyl)(aryl)metal species have been characterized, the latter only spectroscopically in NCN–platinum complexes. Moreover, the equilibrium established in the platinum-mediated process directly relates these two species to each other and corresponds to the microscopic C–C bond-making and -breaking sequence. These results suggest that C–C bond formation and cleavage have a common reaction coordinate, clearly with opposite directionality, and, depending on the metal used to mediate the reaction, have different preferences for stabilizing certain intermediates along this reaction coordinate.^[84b] Therefore, the combination of the recent achievements provides a considerably refined version of a previously suggested mechanism for metal-mediated $C_{\text{aryl}}-C_{\text{alkyl}}$ bond formation and cleavage (Scheme 15 and Figure 6).^[93] Most importantly, coordination of the free ligand to the metal precursor by M–E bond formation is essential for initiating C–C bond activation. Formation of such products has been accomplished with PCP pincer ligands ($E = PR_2$), but it has not been possible so far with nitrogen donors, because of the lower bond strength of the M–NMe₂ bond.

A related C–C bond-forming reaction has been observed when PCP–ruthenium complexes were treated with terminal acetylenes.^[94] Unusual addition products containing a bridging carbene ligand were obtained instead of vinylidene compounds [Eq. (11)]. Remarkably, these products seem



strongly related to the proposed intermediate in rhodium-mediated C–C bond activation (see Figure 6a), and may result from an incomplete insertion of the vinylidene unit into the Ru–C bond. Clearly, the orbital situation at the intermediate carbene stabilizes the bridging conformation and, assisted by the chelating phosphane donors, prevents dissociation of the ruthenium atom.

4.1.2. C–H and C–Si Bond Activation

Studies directed towards mechanistic elucidation of the C–H bond activation process by using pincer ligands have resulted in the isolation of various intermediates. A compound containing an activated C–H bond was isolated as an intermediate in the transcyclometalation reaction of [PtCl(NCN)] with PC(H)P ligand precursors. The first stable intermediate in this reaction comprised a dimeric structure with two bridging $\eta^2:\mu^2$ -*P,P* bidentate coordinating PC(H)P ligands (see Scheme 4).^[37b] Solid-state and solution studies have indicated that the PCHP proton was activated by $C_{\text{aryl}}-H \cdots Cl-Pt$ hydrogen bonding. Moreover, the $Pt \cdots ipso-C$ distance was shown to be relatively short, which suggested an aromatic substitution of the activated proton by the platinum metal center as a consequent reaction step. Indeed, cyclometalation was observed upon heating this complex and the mechanism is likely to include intermediates with agostic metal $\cdots$ ligand interactions.^[95] The cationic ruthenium(II) complex [Ru(PCP)(PCHP)](OTf) comprising two PCP ligands represents a potential model of such an intermediate (Figure 7).^[41] This complex was characterized by

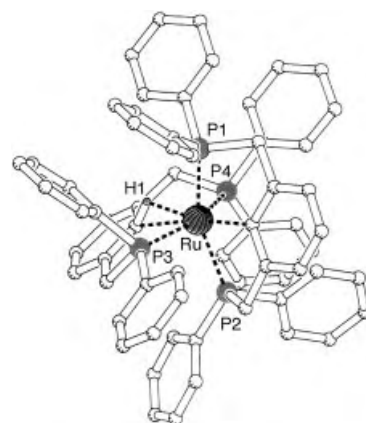
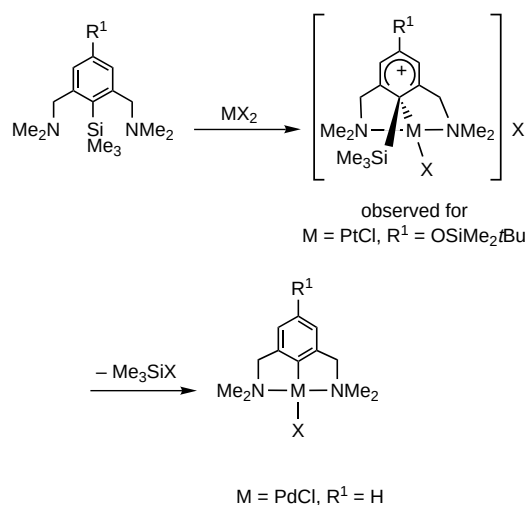


Figure 7. Agostic $C-H1 \cdots Ru$ interactions in the cation [Ru(PCP)(PCHP)] (the anion and phosphor-bound phenyl groups are omitted for clarity).^[41a]

X-ray analysis and extensively by NMR spectroscopy; the latter thus provided additional information about its nature in solution. Deuterium labeling of the PCP ligands has enabled the cyclometalated PCP ligand to be differentiated from the *P,P* bidentate coordinating ligand. Interestingly, these studies pointed to a flexible coordination mode of the ligands, and evidence was obtained for a fluxional behavior of the agostic $C_{\text{aryl}}-H$ proton which resulted from a reversible migration from the coordinated PCP ligand to the cyclometalated one.

These observations for $C_{\text{aryl}}-H$ bond activation are in good agreement with the mechanistic features established for $C_{\text{aryl}}-C_{\text{alkyl}}$ bond activation, which suggests that the two processes are mechanistically closely related. The similarities were further underlined by the identification of hydrogen–arenium structures, which were obtained as the products after treatment of the activated platinum aqua complex [Pt(RO–NCN)(OH₂)]⁺ with anhydrous HCl.^[84b]

Similar results were obtained when the alkyl group was replaced by a silyl substituent ($R = \text{SiMe}_3$). Cyclometalation with a palladium(II) precursor involved selective C–Si bond activation and formation of the complex $[\text{PdCl}(\text{NCN})]$ (Scheme 18). This reaction was also proposed to proceed

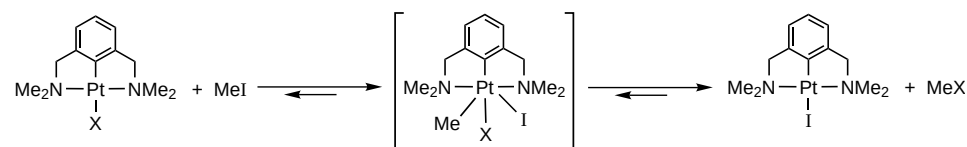


Scheme 18. Metal-mediated $\text{C}_{\text{aryl}}\text{--Si}$ bond activation involving an arenium ion as a key intermediate.

through an arenium intermediate. The kinetic reactivity of the palladium center meant that such structures could not, however, be isolated.^[22] In contrast, treatment of the platinum complex $[\text{PtI}(\text{tBuMe}_2\text{SiO-NCN})]$, containing a silyl-protected oxo-group as an activator, with Me_3SiOTf resulted in the formation of highly air- and moisture-sensitive silyl arenium species.^[84b] This result shows that the silyl arenium ions are reasonably stable and that such species may also represent key intermediates in silyl-directed cyclopalladation.

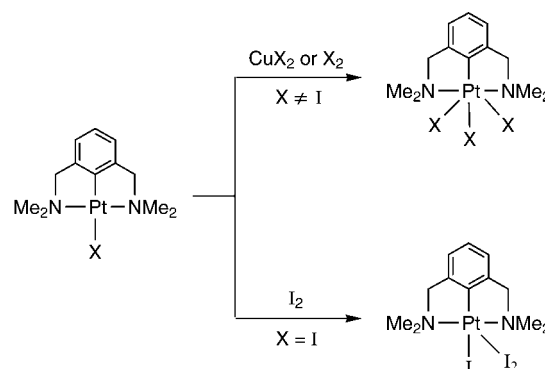
4.1.3. Oxidative Addition

As pointed out in the previous section, the addition of MeX to platinum(II) complexes containing the NCN pincer ligand does not lead to oxidative addition products that can be isolated. However, the fact that neutral platinum complexes $[\text{PtX}(\text{NCN})]$ ($X = \text{Cl}, \text{Br}, \text{I}$) react with MeI to give the complex $[\text{PtI}(\text{NCN})]$ along with MeX suggests the transient formation of a platinum(IV) species (Scheme 19).^[81] Apparently, the subsequent reductive elimination process is faster than the corresponding oxidative addition, and hence the proposed platinum(IV) intermediate has not been observed thus far for these reactions. This situation contrasts with the reactivity of related platinum(II) complexes containing a $\text{C}_2\text{N}_2\text{X}$ ligand array, since those complexes readily form stable oxidative addition products in the presence of RX .^[96]



Scheme 19. Halide exchange on NCN-platinum complexes through oxidative addition of an alkyl halide.

Platinum(IV) complexes containing the NCN pincer ligand were only accessible when stronger oxidizing agents such as CuX_2 or X_2 were used.^[97] The latter method is restricted to platinum(II) complexes $[\text{PtX}(\text{NCN})]$ that are treated with molecular chlorine or bromine. Surprisingly, the addition of iodine afforded a pentacoordinate platinum(II) adduct $[\text{PtI}(\text{NCN})(\text{I}_2)]$ which contains the iodine molecule bound in an η^1 (end-on) fashion to the metal center (Scheme 20).^[98] An X-ray structure analysis on this adduct revealed a considerably stretched I–I bond length in the neutral I_2 ligand compared to that in free I_2 (Figure 8a).



Scheme 20. Reactivity of NCN-platinum complexes towards different oxidizing agents: oxidative addition versus adduct formation.

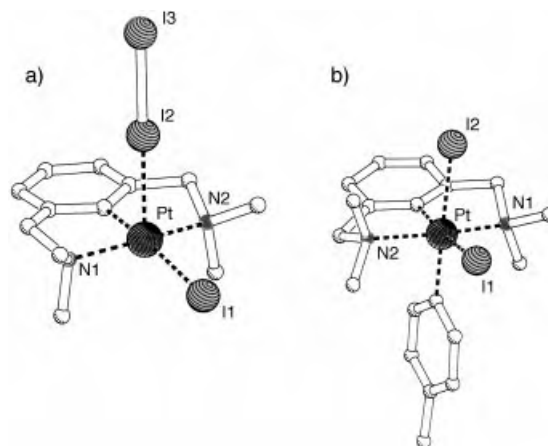
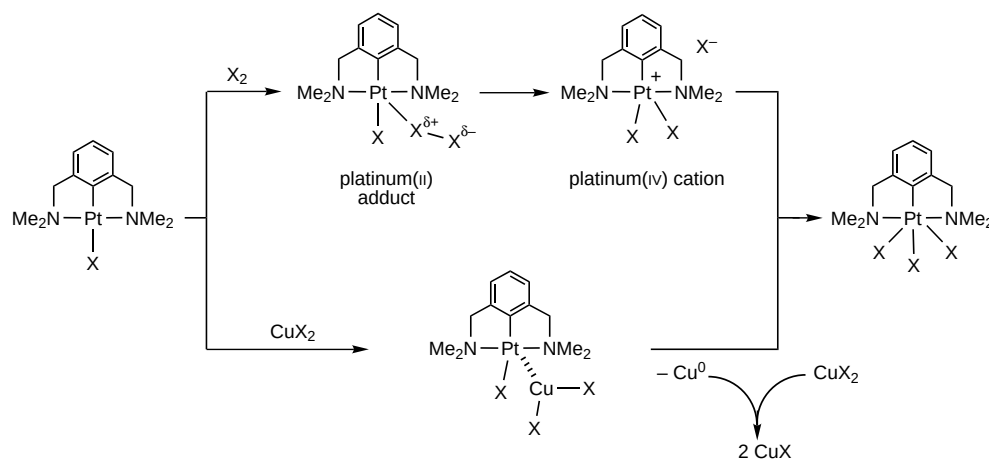


Figure 8. a) End-on (η^1) bound I_2 in the pincer platinum complex $[\text{PtI}(\text{NCN})(\text{I}_2)]$ as a model species for the initial stage of oxidative addition of dihalogen molecules to a square-planar d^8 metal center.^[98] b) The platinum(IV) complex $[\text{Pt}(\text{I}_2)(\text{NCN})(4\text{-tolyl})]$ obtained from oxidative addition of I_2 to $[\text{Pt}(\text{NCN})(4\text{-tolyl})]$.^[97]

Similar adduct formation with I_2 occurs with platinum complexes containing modified nitrogen substituents on the pincer ligand (for example, $\text{E} = \text{NMe}_2\text{tBu}$).^[99] Two iodine molecules bind to the platinum complex on exposure to I_2 : one through η^1 coordination to the platinum center as described above and a second to the platinum-bound iodide ion to form an I_3^- ion. The presence of an

iodide ligand in the starting material $[\text{PtX}(\text{NCN})]$ ($\text{X} = \text{I}$) is important for adduct formation. In the case of the corresponding chloride and bromide complexes or if ICl or IBr is used as the oxidizing agent, halide scrambling takes place to give the oxidative addition product $[\text{PtX}_3(\text{NCN})]$ along with the platinum(II) adduct $[\text{PtI}(\text{NCN})(\text{I}_2)]$.^[98] The relevance of the metal-bound iodide is further underlined by the results from the reaction of the halide-free platinum(II) complex $[\text{Pt}(\text{NCN})(4\text{-tol})]$ with I_2 , which afforded the oxidative addition product $[\text{Pt}(\text{I})_2(\text{NCN})(4\text{-tol})]$ exclusively (Figure 8b).^[97]

Complexes containing end-on-bound iodine have therefore been suggested as representatives of the initial stage of dihalogen oxidative addition to a (late) transition metal center.^[100] Subsequent two-electron oxidation of the metal and concomitant heterolytic cleavage of the $\text{I}-\text{I}$ bond is anticipated to lead to the platinum(IV) intermediate $[\text{PtI}_2(\text{NCN})]^+$ and I^- (Scheme 21). A rapid trapping of the



Scheme 21. Distinct reaction pathways for the oxidative addition of dihalogen and CuX_2 to NCN-platinum complexes.

released iodide ion finally results in the neutral oxidative addition product. In the case of I_2 , this process is probably halted at the first stage because of the soft character of I_2 as an oxidizing agent (relative to other dihalogen reagents), paired with the special electronic configuration of the platinum(II) center imposed by the NCN pincer ligand (the aryl plane of the pincer ligand coincides with the platinum coordination plane, thus allowing unusual overlap between the aryl π^* orbitals and the metal d_{xz} orbitals, see Section 3.1).

Metal oxidation by means of CuX_2 (Scheme 21) is supposed to follow a different reaction pathway, which probably involves Pt–Cu interactions.^[100] The dimetallic Pt–Hg structure shown in Figure 3 may be considered as a model intermediate in such a process. Subsequent transfer of two halide ions from copper to platinum (either stepwise or concerted) would then result in the formal oxidative addition ($\text{Pt}^{\text{II}} \rightarrow \text{Pt}^{\text{IV}}$) and reductive elimination ($\text{Cu}^{\text{II}} \rightarrow \text{Cu}^0$; Scheme 21). A fast comproportionation reaction between the formed Cu^0 species and residual CuX_2 salts is assumed to occur as the last step of this platinum oxidation process.

4.2. Catalytic Applications

Complexes containing biscyclometalated pincer ligands offer particularly attractive possibilities for catalytic applications, since the tailoring of catalytic properties is readily achieved (see also Scheme 1): First, the terdentate binding mode and the covalent $\text{M}-\text{C}$ σ bond stabilize the catalytically active (metal) site. This stabilization is assumed to efficiently prevent metal leaching, and hence circumvents a problem common to most catalysts containing exclusively heteroatom-coordinated metals. Second, the electronic properties of the metal center are highly sensitive towards modifications in the donor array (substitution patterns and hybridization of the donor atom E, element alteration). Electronic fine-tuning through variation of the aromatic substituent R^1 represents an additional option in some cases. Third, the steric requirements around the catalytic site may be modified to discriminate against some substrates or to create a chiral pocket for asymmetric catalysis.

When these aspects are taken into account, the availability of a broad range of powerful catalysts containing pincer ligands is no surprise. Table 1 summarizes the reactions promoted by these catalysts.

4.2.1. C–C Bond-Forming Reactions

In line with recent trends in catalysis research, the activity of various palladacycles was explored extensively and successfully.^[101] Particularly impressive conversions were obtained with PCP-palladium catalysts in the arylation of alkenes, which is commonly referred to as the Heck reaction.^[102] The complex $[\text{PdCl}(\text{PCP})]$ with $\text{R}^2 = i\text{Pr}$ has a remarkable effectiveness, with turnover numbers (TON) exceeding 5×10^5 (Table 1, entry 1).^[103] However, 1,4-dienes were observed to poison the catalytic activity of these PCP-palladium complexes, thus limiting their application for intramolecular Heck coupling in complex systems.^[104] The use of phosphite rather than phosphane donors, that is, replacement of the methylene spacer between the aryl ring and the phosphorus donor by oxygen, and introduction of aryloxy substituents on phosphorus, $\text{E} = \text{P}(\text{OAr})_2$, had a dramatic effect on catalyst performance (Table 1, entry 2).^[105] A minimal catalyst loading (0.1 ppm) resulted in unprecedentedly high rates being obtained for the Heck reaction (TON 8.9×10^6 , TOF 4×10^5), that is, more than 100 coupling reactions per second.^[105a] A PCP-palladium complex with $\text{R}^2 = i\text{Pr}$ provided one of the most active catalysts known so far for the olefination of aryl chlorides (entry 3).^[105b] In addition, similar phosphinite catalysts proved highly efficient in the Suzuki coupling of aryl boronic acids with aryl

Table 1. Catalytic activity of pincer complexes.^[a]

Entry	Catalyst	Catalyzed reaction	TON	Ref.	
1		$\text{ArI} + \text{CH}_2=\text{CH-R} \longrightarrow \text{Ar-CH=CH-R}$	520 000	[103a]	$\text{R}^2 = i\text{Pr}$
2		$\text{ArI} + \text{CH}_2=\text{CH-R} \longrightarrow \text{Ar-CH=CH-R}$	8 900 000	[105a]	$\text{Ar} = 4\text{-MeOC}_6\text{H}_4$
3		$\text{ArCl} + \text{CH}_2=\text{CH-R} \longrightarrow \text{Ar-CH=CH-R}$	150	[105b]	
4		$\text{ArBr} + \text{C}_6\text{H}_5\text{-B(OH)}_2 \longrightarrow \text{Ar-C}_6\text{H}_5$	190 000	[105d]	
5 a		$\text{ArI} + \text{CH}_2=\text{CH-R} \longrightarrow \text{Ar-CH=CH-R}$	48 500	[108]	$\text{R}^2 = t\text{Bu}$
5 b		$\text{ArI} + \text{CH}_2=\text{CH-R} \longrightarrow \text{Ar-CH=CH-R}$	1 000	[45]	$\text{R}^2 = \text{Ph}$
6		$\text{R-CHO} + \text{NC-COOMe} \longrightarrow \text{R-CH(OH)-COOMe}$	100	[109]	
7		$\text{R-CO-R'} + \text{CH}_3\text{-CH(OH)-CH}_3 \longrightarrow \text{R-CH(OH)-CH}_3 + \text{CH}_3\text{-CO-CH}_3$	1 000	[115]	
8		$\text{R-CO-R'} + \text{CH}_3\text{-CH(OH)-CH}_3 \longrightarrow \text{R-CH(OH)-CH}_3 + \text{CH}_3\text{-CO-CH}_3$	10 000	[115]	$\text{X} = \text{Cl, OTf}$
9		$\text{R-CH}_2\text{-CH}_2\text{-R'} \longrightarrow \text{R-CH=CH-R'}$	400	[117]	$\text{R}^2 = t\text{Bu, } i\text{Pr}$
10		$\text{CH}_2=\text{C(OMe)-CO}_2\text{R} + \text{CCl}_4 \longrightarrow \text{CH}_3\text{-C(OMe)-CO}_2\text{R}$	310	[120]	
11		$\text{CH}_2=\text{C(OMe)-CO}_2\text{R} \longrightarrow \text{polymer}$	–	[123]	

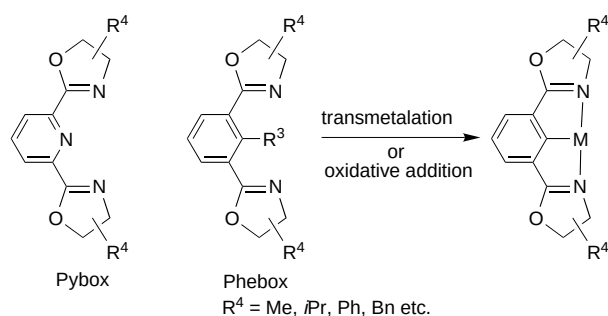
[a] tfa = CF₃COO[−]; OTf = CF₃SO₃[−].

bromides, and—to a lesser extent—also with activated aryl chlorides (entry 4).^[105d]

No colloidal palladium was observed and the catalyst precursor was recovered, irrespective of whether phosphane or phosphinite donors were used. Therefore, it indicated that the Pd–C bond was conserved throughout the reaction and a catalytic cycle involving palladium(0) intermediates was discarded, since metal reduction was supposed to induce Pd–C bond fission. The absence of any evidence for Pd–C bond cleavage and concomitant Pd⁰ formation is a strong indication, but clearly does not yet prove, the formation of a Pd^{II}–Pd^{IV}–Pd^{II} cycle, since other intermediate structures (for example, molecular ensembles with cluster-type configurations, or palladates such as [Pd(PCP)][−] that may or may not have one phosphane donor dissociated^[106]) must also be considered as potential, highly reactive palladium(0) sources.^[106, 107] Catalytic activity in the Heck reaction has also been

observed with palladium(II) catalysts containing SCS pincer ligands (Table 1, entry 5).^[45, 108] In these cases, catalyst performance is considerably lower than with PCP ligands. Comparative studies further demonstrated that the terdentate ligands were inferior to the corresponding *S,C* bidentate coordinating analogues. Palladium complexes of the NCN pincer ligand were used for the aldol condensation (entry 6).^[109]

As a consequence of the excellent catalytic performance of related complexes containing *N,N,N* terdentate coordinating Pybox ligands,^[110] their organometallic (Phebox) counterparts were explored in detail for catalytic applications (Scheme 22). The introduction of a covalent M–C σ bond was anticipated to suppress metal leaching, which is an issue in the corresponding Pybox complexes because of the coordinative and more labile M–N bonds. However, the steric modifications were only marginal and, therefore, a similar catalytic activity was



Scheme 22. Metalation of Phebox ligands by transmetalation ($R^3 = \text{Li}$) or oxidative addition ($R^3 = \text{Br}$).

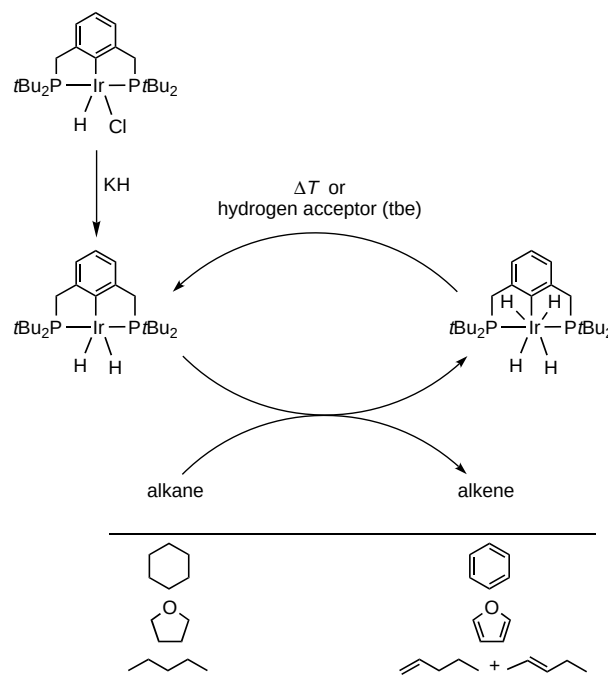
expected. Metalation of Phebox ligands was achieved by lithiation of the ligand precursor with LDA followed by transmetalation with a suitable rhodium(III),^[111] palladium(II),^[112] or platinum(II)^[113] salt. The palladium complex with $M = \text{PdBr}$, $R^4 = \text{Bn}$, $i\text{Bu}$ (Scheme 22) was also obtained by oxidative addition of the Phebox ligand with $R^3 = \text{Br}$ to $[\text{Pd}(\text{dba})_2]$.^[114] These complexes have been successfully used as catalysts for various C–C bond-forming reactions (see Table 2). Direct cyclometalation of Phebox ligands by C–H bond activation has been reported for rhodium(III) precursors.^[111]

4.2.2. Transfer Hydrogenation

Ruthenium(II) complexes containing either NCN or PCP pincer ligands are effective catalysts in the transfer hydrogenation reaction of ketones (Table 1, entries 7 and 8).^[115] The complex $[\text{RuCl}(\text{PCP})(\text{OTf})]$, which contains a weakly bound triflate ligand, has been shown to be the most active catalyst system. Both aryl and alkyl ketones have been transformed into the corresponding alcohols.

4.2.3. Alkane Dehydrogenation

Iridium complexes of the type $[\text{IrCl}(\text{H})(\text{PCP})]$ have been identified as precursors for efficient dehydrogenation catalysts (Table 1, entry 9). The corresponding rhodium complexes are thermally less stable and displayed low activity as dehydrogenation catalysts (TON for the formation of cyclooctene from cyclooctane was 0.8). The formal abstraction of HCl (mediated by $\text{NaN}(\text{SiMe}_3)_2$ or KH, for example) in the presence of a hydrogen atmosphere provides the dihydride complex $[\text{Ir}(\text{H})_2(\text{PCP})]$ as the active catalyst.^[17a] A similar reactivity pattern towards molecular hydrogen has also been observed with $[\text{Ir}(\text{NCN})(\text{cod})]$ at low temperatures, and afforded the thermally unstable complex $[\text{Ir}(\text{H})_2(\text{NCN})(\text{cod})]$.^[116] These iridium pincer complexes thus represent novel organometallic devices for reversible H_2 storage. More remarkably, catalytic C–H bond activation of alkanes has been accomplished with the complex $[\text{Ir}(\text{H})_2(\text{PCP})]$. A variety of unstrained substrates can be dehydrogenated using this catalyst in the presence of a sacrificing alkene, for example, cycloalkanes to cycloalkenes, cyclohexanes to arenes, THF to furan, and alkanes to α -alkenes, which slowly isomerize to internal alkenes (Scheme 23).^[117]



Scheme 23. Catalytic functionalization of nonactivated alkanes by metal-mediated dehydrogenation using PCP–iridium catalysts.

A hydrogen acceptor substrate (*tert*-butylethene, tbe) was initially used to reduce the intermediate $[\text{Ir}(\text{H})_2(\text{PCP})]$, but good performances have also been achieved without a hydrogen acceptor; a reflux temperature promotes the loss of H_2 from solution, thus regenerating the catalytically active iridium complex.^[118] Remarkably, an “inert” nitrogen atmosphere was shown to inhibit the reaction, and catalysis must be performed under argon. Investigations in the presence of an N_2 atmosphere have revealed the formation of $[\text{Ir}(\text{PCP})]_2(\mu\text{-N}_2)$, an $\text{Ir}(\text{PCP})$ dimer containing N_2 as a bridging ligand.^[119] Deuterium labeling experiments further indicated that the bulky alkyl groups of the phosphane substituents assist in the catalytic cycle, particularly by promoting the dissociation of the converted hydrogen acceptor (namely, *tert*-butylethane formed from tbe).

4.2.4. Divalent Catalysts for C–C Bond Formation and Polymerization

Another intriguing system is the nickel(II) complex $[\text{NiX}(\text{NCN})]$, since two different reactions are catalyzed by the same complex (Table 1, entries 10 and 11). The reactivity can be regulated by the ratio of the substrate concentrations. These species were initially reported to be catalysts for the Kharasch atom-transfer radical-addition (ATRA) reaction of a polyhalogenated alkane (for example, CCl_4) to a terminal olefin (entry 10).^[120] Detailed investigations have revealed that the mechanism follows a radical pathway and includes the formation of the nickel(III) complex $[\text{NiX}_2(\text{NCN})]$ as a persistent radical,^[121] and $\cdot\text{CCl}_3$ as the reactive species for the addition to the olefin to form products containing a novel C– CCl_3 bond.^[122] However, the prerequisite for the reaction is that both substrates (CCl_4 and olefin) are available in approximately equal ratios. In the presence of a large excess

of alkene (for example, methyl methacrylate) and only catalytic amounts of CCl_4 , atom-transfer radical polymerization (ATRP) is induced and poly(methyl methacrylate) is formed (entry 11).^[123] CCl_4 is essential for the generation of the persistent Ni^{III} and CCl_3 radicals which initiate the polymerization. An intrinsic property of ATRP catalyst systems is that the radicals are slowly but irreversibly consumed (predominantly by polymer-chain recombination), which results in the gradual deactivation of the catalyst. In this case this is identified by isolation of the catalytically inactive nickel(III) complex $[\text{NiX}_2(\text{NCN})]$ at the end of the reaction.^[124]

4.2.5. Catalysts Containing Chiral Pincer Ligands

Chiral analogues of some of the above-mentioned catalysts were also prepared from C_2 -symmetric pincer ligands for asymmetric catalysis (Table 2). The earliest achievements in this area were the syntheses of nickel complexes with NCN ligands containing substituents derived from chiral pyrrolidine derivatives on the amine nitrogen atom (entry 1).^[125] The absence of any significant asymmetric induction in the Kharasch addition provided the most substantial motivation at that time for postulating a radical mechanism.

Table 2. Asymmetric catalysis using enantiopure pincer complexes as catalysts.

Entry	Catalyst	Catalyzed reaction	ee [%]	Ref.
1			17	[125]
2			65	[126]
3			77	[127]
4			< 10	[33]
5			14	[33]
6			79	[128]
7			34	[112]
8			< 2	[114]
9			80	[129]

At the same time, Venanzi and co-workers reported chiral PCP ligands which were functionalized on the benzylic positions with acetals that were generated by enantioselective Sharpless epoxidations. The corresponding platinum complexes were probed as catalysts for the asymmetric aldol condensation of methyl isocyanoacetate and aldehydes and produced substituted oxazolines with up to 65 % *ee* (entry 2).^[126] Recently, related C_2 -symmetric ligands containing alkyl groups on the benzylic positions of PCP ligands were prepared by enantioselective reduction of the ketone precursors and subsequent nucleophilic substitution of the resulting hydroxy groups by phosphanes.^[127] The catalytic activity and enantioselectivity of the corresponding palladium(II) complexes in the aldol condensation (entry 3) were slightly higher than the data obtained by Venanzi and co-workers with a platinum(II) catalyst precursor.^[126] Remarkably, catalysis with palladium complexes containing the corresponding C_2 -symmetric NCN ligands resulted in a marked drop of asymmetric induction and the product distribution was nearly racemic (*ee* < 10 %, entry 4).^[33] Clearly, methyl groups on the benzylic positions of either PCP or NCN pincer ligands do not induce sufficiently pronounced chiral pockets for distinct substrate recognition by the metal center. However, studies on the influence of methyl and ethyl substituents on these ligands demonstrated a strong influence of this functionalization on the accessibility of the *ipso*-carbon atom, and hence provided a methodology for adjusting the metal-binding cavity (see Scheme 1).^[33] These conclusions were independently confirmed by the results from experiments using ruthenium complexes containing a similarly alkylated C_2 -symmetric PCP ligand as catalysts for the asymmetric transfer hydrogenation reaction (entry 5).^[33, 37a] The activities and rates (TON, TOF) of the chiral catalysts were identical to those observed with the achiral complex, and the enantioselectivity was low (14 % *ee*).

Better asymmetric induction was observed by using palladium complexes of the same ligand as catalysts for allylic alkylation (entry 6).^[128] Products were obtained in up to 79 % *ee* depending on the reaction conditions. It should be noted, however, that in these experiments the catalyst is not a well-defined species since it has been prepared *in situ* by mixing the ligand and the metal salt. Consequently, the catalytically active species may consist of coordination compounds in which the ligand actually behaves as a chiral diphosphane rather than a *P,C,P* terdentate-bonding pincer ligand.

A different synthetic strategy for the formation of chiral pincer ligands has used α -amino acids as a chiral pool. The corresponding β -amino alcohols were suitable building blocks for the synthesis of C_2 -symmetric Phebox ligands. Complexation to palladium has been reported to provide catalysts for the asymmetric Michael addition and for the synthesis of chiral cyclopropanes. Whereas the former reaction proceeded with some enantioselectivity (up to 34 % *ee*; entry 7),^[112] the latter produced only racemic product mixtures, regardless of ligand modifications, reaction conditions, and additives used (entry 8).^[114]

The corresponding rhodium(III) complexes have recently been used in the asymmetric allylation of aldehydes (maximum 80 % *ee*).^[129] Stoichiometric amounts of the cationic

platinum complex $[\text{Pt}(\text{Phebox})(\text{OH}_2)]^+$ have also been described as efficient chiral auxiliaries in the asymmetric alkylation of aldimines.^[113]

5. Recycling of Functional Pincer–Metal Units by Immobilization

5.1. Identification of Suitable Anchoring Points

One of the most challenging issues of catalysis represents the successful combination of the advantages of homogeneous (selectivity, rate control) and heterogeneous catalysis (product/catalyst separation, recycling). Straightforward methods for convenient and quick catalyst recovery and recycling of (precious) metal systems are highly desirable, both from an environmental and from an economic point of view, in processes involving toxic and/or expensive catalysts. A few different approaches have been pursued during the last few years to achieve this combination of beneficial aspects of homogeneous and heterogeneous catalyst systems. Common to most of these attempts is that they aim to immobilize the homogeneous catalyst through a covalent linker to a soluble or heterogeneous support without influencing its homogeneous mode of action.^[130]

Suitable linker positions on the reactive pincer metal complexes ideally exert no influence on the desired application. They are readily identified as such while optimizing the properties of the metal center by ligand tuning. In many cases it has been shown that functionalization of a selected *para* substituent of the aryl unit of these pincer ligands ($R^1 = \text{OCR}_3, \text{OSiR}_3, \text{NCOR}$) had only marginal direct influence on the electronic configuration of the metal center and on the stability of the M–C bond.^[60, 84] Consequently, this position has predominantly been used as the anchoring point for the introduction of suitable linkers.

5.2. Heterogeneous and Polymeric Supports

Gold surfaces have been suggested as heterogeneous supports because of their strong interaction with thiols, thioethers, and other sulfur-containing organic molecules. For these purposes, SCS pincer ligands were functionalized with a thioether tail and, after cyclopalladation, were self-assembled on gold to provide organometallic monolayers.^[131] These surface-confined organopalladium units have been used as new cores for the construction of self-assembled metallodendrimers. A strict control of the degree of functionalization and hence the number of immobilized units could be achieved by monitoring the adsorption by atomic force microscopy.

Carbon nanotubes are increasingly attractive supports for catalysts and other functional molecules. Selective monoaddition of NCN pincer ligands to fullerene C_{60} (as a representative model for carbon nanotubes in many respects) and subsequent metalation by nickel or palladium provided catalysts containing a backbone with a particular electronic configuration (Figure 9).^[132] These fullerene-containing cata-

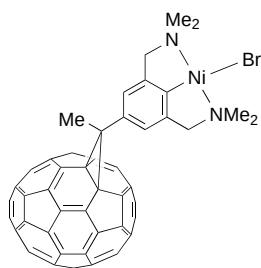


Figure 9. The $[\text{NiBr}(\text{NCN})]$ catalyst immobilized on fullerene as a model for functionalized carbon nanotubes.^[132]

lysts are easily traced by spectroscopic techniques as a consequence of their strong color.

Silica represents an alternative, cheap, and ubiquitous support. Direct immobilization of the pincer ligand on commercially available silica has been achieved with urea-type linkers containing protected silanol end groups.^[133] The grafting of these substituted pincer ligands on silica colloids occurs by covalent Si-O-Si bond formation (Figure 10, left).

A model system, which allowed a more detailed investigation of the influence of this specific support on the catalyst, was provided by soluble siloxane polymers, on which pincer ligands were attached by using an amide linker (Figure 10, right).^[134] Nickel insertion was achieved by oxidative addition to give homogeneous, polymer-supported catalysts. The performance of this immobilized system compared

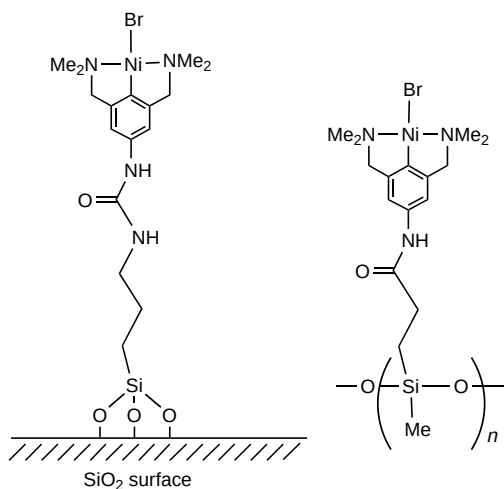


Figure 10. Catalytically active $[\text{NiBr}(\text{NCN})]$ sites confined on different silica supports.^[133, 134]

well with the monomeric material, and retrieval of the catalyst (in its irreversibly deactivated Ni^{III} form) was conveniently achieved by precipitation and filtration.

In a similar approach, a soluble ethylene glycol polymer containing hydroxide side-chain functionalities was used for the attachment of SCS pincer ligands.^[45] Subsequent palladation resulted in the formation of multisite catalysts for the Heck reaction, which were successfully recycled by precipitation/filtration procedures. Repetitive catalytic cycles did not show any loss of activity, which is in accordance with a rigid immobilization of the palladium center which prevents catalyst leaching and metal dissociation. An elegant improvement of this procedure, which avoids the precipitation of the polymeric catalyst but guarantees its recovery, has recently been presented by performing the catalyzed reaction under thermomorph conditions.^[135] A careful choice of solvents (for example, dimethylacetamide and heptane) provides a

mixture that is homogeneous at the elevated temperatures required for catalysis, but biphasic at room temperature. This difference allows the facile separation of the organic products (soluble in heptane) from the polymeric catalyst, which remains in the dimethylacetamide phase (Figure 11).

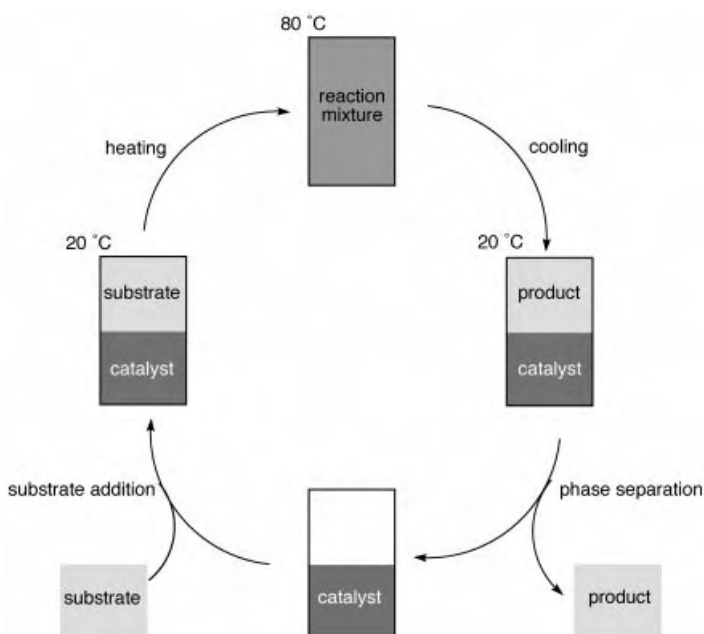
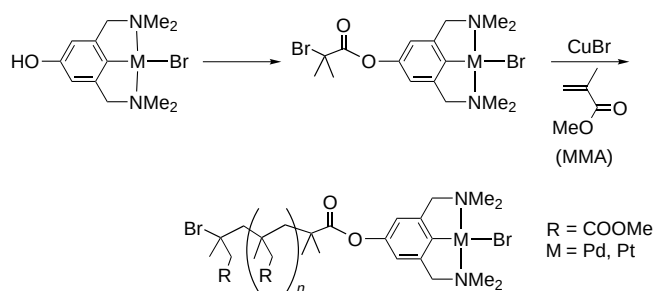


Figure 11. Heck catalysis mediated by a SCS–palladium complex under thermomorph conditions.^[135] At room temperature (left), the polymer-supported catalyst dissolves in dimethylacetamide, whereas the substrates (for example, ArI and methyl methacrylate) are soluble in heptane. At elevated temperatures (top), the system becomes homogeneous, which allows for homogeneous catalysis. Upon cooling, the biphasic system is regenerated (right) and the products are easily separated from the catalyst by phase separation (bottom). The addition of a fresh substrate-containing solution allows for repetitive use of the catalyst.

A valuable synthetic modification of this immobilization approach on polymers was demonstrated by using *metalated* pincer systems as monomer substrates for polymerization. This method eliminates difficulties associated with metal insertion in the polymer-supported pincer sites—insertion may be incomplete or may be accompanied by the formation of undesirable side products (for example, from interactions of the metal center with the polymer support). Clearly, for this latter method there must be no dissociation of the metal–ligand bond (C or N) during the polymerization. The strong M–N and M–C bonds in platinum and palladium complexes containing the NCN pincer ligand have thus far been shown to fulfill these requirements. Functionalization of the aromatic *para* position of these complexes $[\text{MBr}(4\text{-R}^1\text{-NCN})]$ ($\text{M} = \text{Pd}, \text{Pt}$) with an initiator group ($\text{R}^1 = \text{OC}(\text{O})\text{CMe}_2\text{Br}$) and subsequent ATRP in the presence of methyl methacrylate gave end-group functionalized poly(methyl methacrylate) containing functional end groups (Scheme 24) for either repetitive catalytic applications ($\text{M} = \text{Pd}$) or for reversible gas detection ($\text{M} = \text{Pt}$).^[43] The diagnostic color of the platinum complex in the presence of SO_2 displays a novel probe for the fast assessment of the average molecular weight M_w of the polymer produced.



Scheme 24. Transition metal labeled poly(methyl methacrylate) polymers obtained from radical polymerization with an initiator containing a NCN–metal functionality.

Improved separation methods by filtration techniques are expected for polymers that have a spherical rather than a linear shape. Such a polymer constitution has been achieved by the polymerization of branching monomers to give so-called hyperbranched polymers.^[136] For steric reasons, not all the polymeric chains propagate in every possible direction, thus leaving unreacted functional groups at the periphery and in the inner sphere of the hyperbranched polymer. These groups have been employed for the attachment of NCN pincer ligands through a direct C_{aryl}–Si bond (R¹ = hyperbranched carbosilane polymer).^[109] Interestingly, low molecular weight fractions can be conveniently separated by dialysis experiments; this caused a significant narrowing of the polydispersity of the material. Lithiation and subsequent transpalladation afforded polymetalated spheres containing active catalysts for the aldol condensation (Figure 12). Preliminary catalytic runs revealed the immobilized catalyst had only a slightly lower activity compared to that of a mononuclear model species. The reduced performance was attributed to steric constraints imposed by the hyperbranched support, which is likely to shield some palladium centers and thus prevent substrate binding to these sites. Alternatively, the

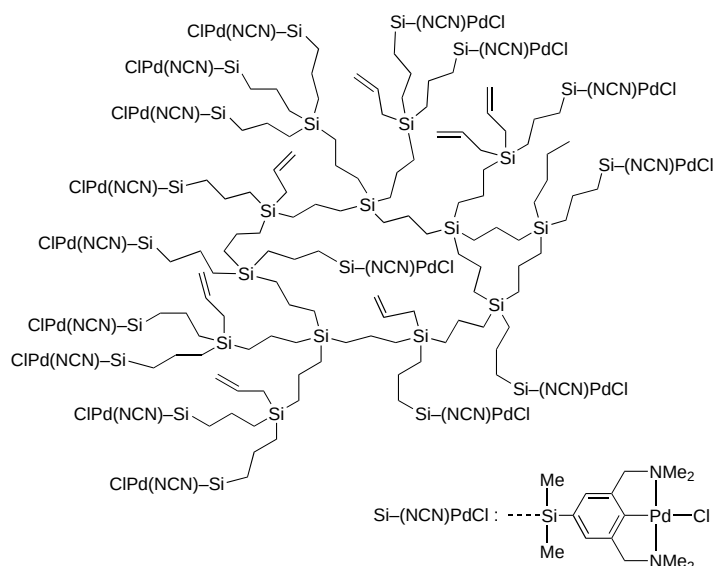


Figure 12. Hyperbranched polymer containing catalytically active pincer palladium sites at the periphery. Note that some of the metal centers are encapsulated and have therefore a different environment from those at peripheral sites.^[109]

microenvironment of some catalytic sites may be defined entirely by the polymeric support and not by the solvent. This leads to locally modified solubility effects, which may influence the reactivity and product selectivity of these metal centers.

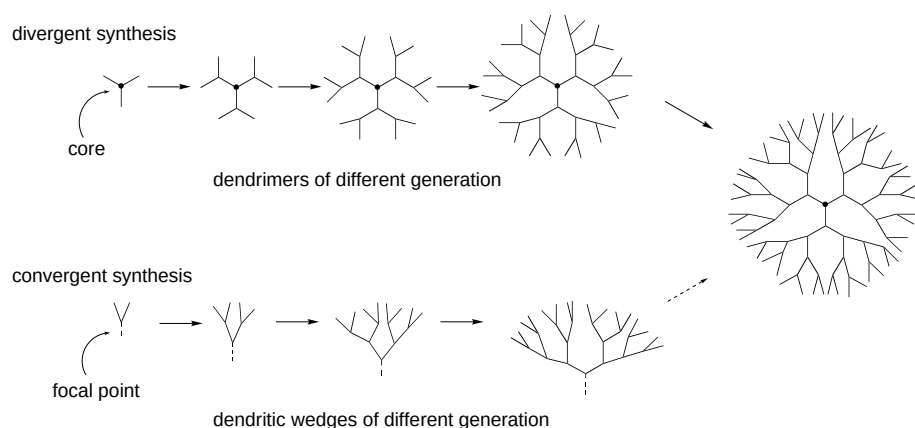
5.3. Homogeneous Dendritic Supports

Improvement of such undesired effects can be achieved when dendrimers are used as macromolecular supports.^[137] These treelike macromolecules are prepared by a regular and stepwise growth using repetitive synthesis sequences. Consequently, they are characterized by a well-defined connectivity pattern and a precise number of functional sites, which are located at the periphery and/or in the core. A consequence of this highly regular architecture is that the polydispersity of dendrimers ideally equals 1.^[138] Variations in the generation number and/or interconnection of dendrimers or dendritic wedges are appropriate methodologies to tailor the size of these materials. This has been illustrated by the engineering of such macromolecules into nanometer-sized spheres and cylinders.^[139] It was therefore assumed that nanofiltration techniques would provide a facile methodology for the separation of these nanodimensional structures from reaction solutions, and that these properties would hence enable the use of heterogeneous separation techniques for homogeneously operating catalysts.^[140]

Two principally different concepts are available for the preparation of periphery-functionalized organometallic dendrimers (Scheme 25):^[141]

1. A divergent synthetic approach consisting of repeated functionalization of a dendrimer core with branching units,^[137a] subsequent anchoring of the pincer ligand precursor at the periphery, and finally metal insertion.
2. A convergent synthesis^[137c] starting with the functionalized (and metalated) pincer ligands as zero-generation dendritic wedges and branching units, which are repetitively attached at the focal site of the dendrons. The synthesis is then completed by the coupling of the dendrons to a core unit.

The divergent strategy is the method of choice for the preparation of polyfunctionalized dendrimers containing active (metal) centers which are highly sensitive (for example, towards air or water). Probably the most significant drawback of this method is that the number of reactive (peripheral) sites increases with every repetitive step, and therefore the difficulties in quantitative transformation of the end groups also increases. Consequently, metal insertion by periphery functionalization of higher generation dendrimers is often incomplete and tedious. These difficulties are effectively circumvented by a convergent strategy, where the number of reactive centers is constant in each growing step (independent of the generation number). A high stability of the metal site towards the reaction conditions of the dendrimer synthesis is essential, particularly for the preparation of periphery-functionalized metallodendrimers, since these groups have to be inert to the conditions used for the coupling of the wedges to branching points and to the core.



Scheme 25. Schematic representation of divergent and convergent routes for dendrimer synthesis.

Initial efforts were directed toward divergent metallodendrimer synthesis using relatively inert carbosilane dendrimers. Covalent attachment of the pincer ligand to the dendritic silyl end groups was achieved either directly or using a carbamate linker.^[36c, 142] Catalytically active nickel centers were inserted by oxidative addition or a lithiation/transmetalation protocol to afford a model catalyst system (Figure 13) for the ATRA reaction. Nanosize architectures with a diameter of 2–3 nm were fabricated by careful choice of the generation number and the type of branching points on the carbosilane dendritic support employed. Up to 36 nickel centers can be incorporated into the largest of these structures. Complete functionalization of the periphery is difficult to achieve and an average loading of approximately 80% was determined by analytical methods (elemental analysis, integration of NMR signals). Incomplete metalation of the dendritic surface with nickel was rationalized to be a consequence of a subquantitative transmetalation sequence paired with partial decomposition of the highly sensitive polyolithiated precursor (for example, by

hydrolysis). Nevertheless, the dendrimer-immobilized species were useful catalysts. More importantly, these confined catalysts were efficiently separated from product solutions at the end of the reaction by using nanofiltration membranes. The suitability of this technique was strongly dependent upon the molecular dimension of the dendrimers, which is a direct consequence of the dendrimer generation and of the spacers used to interconnect the branching points (see Scheme 25). Importantly, an increase in the dendrimer generation was paralleled by a drop in catalytic

activity, and dendritic catalysts containing 36 nickel centers were deactivated after only one hour and 10% conversion.^[143] This dendritic effect may be understood by considering the reduced intramolecular Ni...Ni distance in these macromolecules which favors, in a kinetic sense, the interaction of the activated substrates (for example, $\cdot\text{CCl}_3$ radicals in the Kharasch addition reaction) with each other. This interaction promotes the pre-assembly of $\cdot\text{CCl}_3$ radicals on the dendritic surface for the formation of, for example, C_2Cl_6 (Scheme 26). This recombination process is competitive with the reaction of the radical with methyl methacrylate, and also lowers the radical concentration, thus preventing the essentially important reduction of the persistent nickel(III) radical to the catalytically active nickel(II) species. This interrupts the catalytic cycle and ultimately leads to a complete deactivation of the catalyst, a feature which is stimulated by surface congestion.

Undesired metal–metal interactions can be avoided by using shape-persistent core units, which force the pincer metal

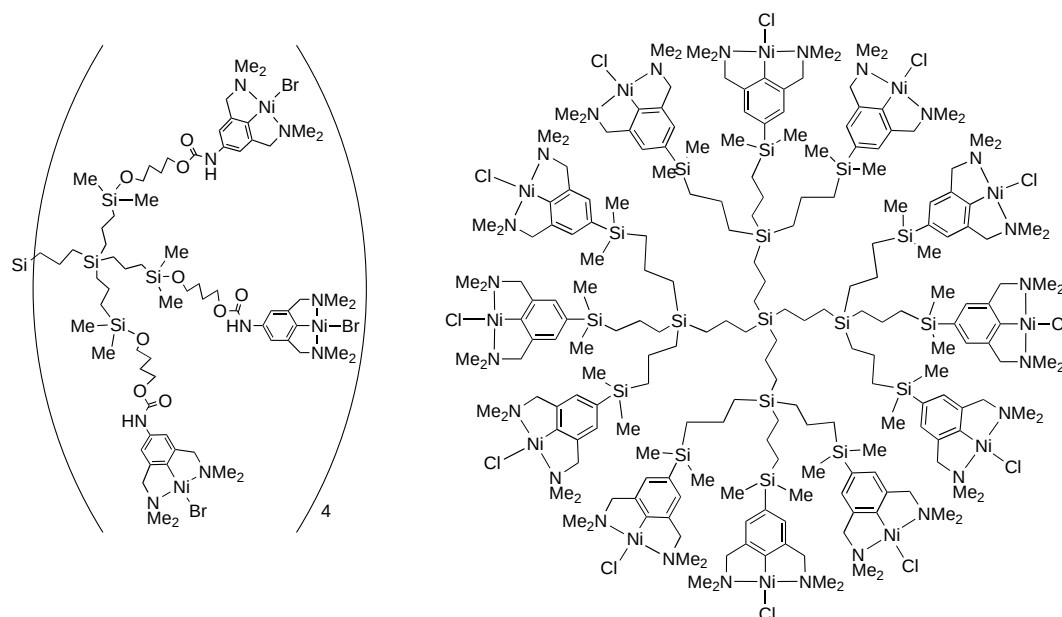
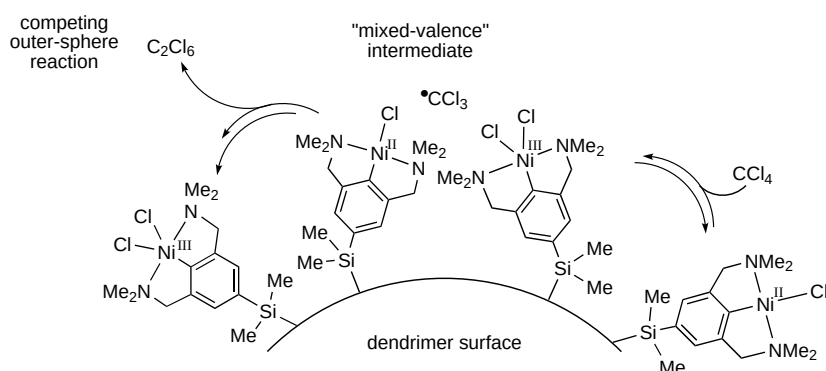


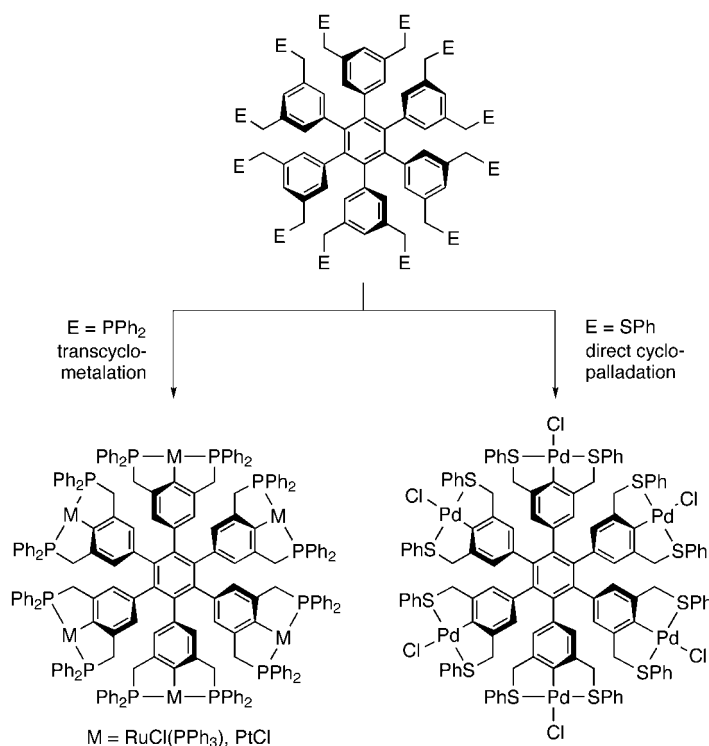
Figure 13. The immobilization of nickel catalysts at the periphery of carbosilane dendrimers affords soluble macromolecular catalysts which operate homogeneously and which can be recovered by nanofiltration techniques.^[36c, 142]



Scheme 26. Deactivation pathways in the nickel-catalyzed Kharasch addition reaction that occur provided that the catalytically active sites are in close proximity, such as at the periphery of high-generation dendrimers.

unit into a specific relative orientation. Another advantage of such cores is that metallodendrimers of considerable size are already available at a low generation number. This reduces the laborious multistep preparation of higher generation dendrimers to a few repetitive sequences without losing the required retention properties for nanofiltration membrane applications. Following these lines, a “cartwheel”-like molecule was constructed containing six pincer ligands each connected by a $C_{\text{aryl}}-C_{\text{aryl}}$ bond to a central benzene core.^[144] A synthetic protocol was chosen which allowed the introduction of a variety of donor groups E into the ligand framework.

Complete metalation of all six pincer sites with platinum or ruthenium centers (for $E = PPh_2$) was only successful by transcyclometalation reactions^[37] of the corresponding monomeric $[M(NCN)]$ -type precursor (Scheme 27). Direct cyclo-

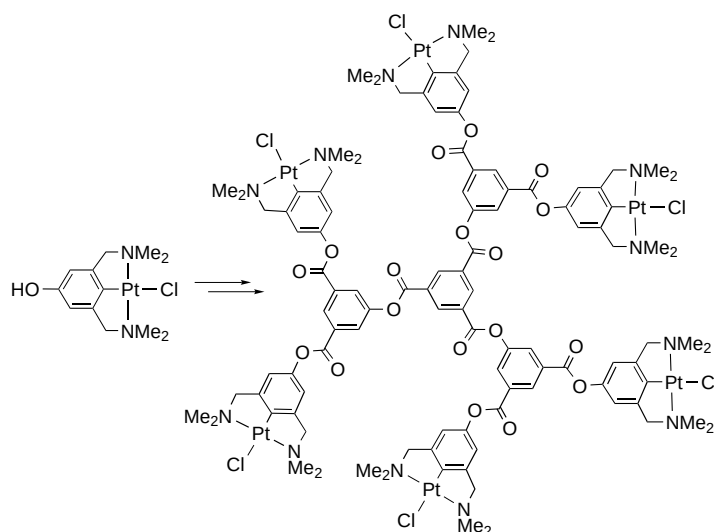


Scheme 27. Different routes for the preparation of hexametalated cartwheel-type macromolecules.

metalation or transmetalation procedures failed to give the hexametalated product, probably because of the high local phosphane concentration at the dendritic periphery. By way of contrast, direct palladation was observed for the sulfur analogue ($E = SPh$, Scheme 27). A single-crystal structure determination of the hexapalladated complex revealed a diameter of 2.1 nm and a torsion angle of approximately 22° between the pincer aryl rings and the core benzene ring, which resulted in a cartwheel-type structure. Modification of the dendritic dimension was demonstrated by the introduction of rigid acetylene spacers, which did not affect the macromolecular shape-persistence.^[145] Thus

far, however, the low solubility of these hexametallic systems have hampered their application as homogeneous catalysts considerably.

A well-defined connectivity pattern and a strict control of the metal loading is essential for homogeneous sensor applications, since quantitative detection of a substrate requires sensor devices with a precise number of recognition sites.^[146] Such materials are available for the reversible detection of SO_2 gas^[60] through the selective grafting of dendrimers with sensor-active organoplatinum units, for example, by immobilizing platinum complexes $[PtX(HO-NCN)]$ containing a phenolic functionality onto these macromolecules. The excellent stability properties of this organometallic synthon meant that a fully convergent synthetic strategy could be applied: first the pincer ligand was platinated and then subsequently deprotected/esterified, either to branching points or to a core (Scheme 28). This



Scheme 28. Convergent synthesis of periphery-functionalized platinum dendrimers starting from robust platinated building blocks.

sequence afforded polymetallic aryl ester dendrimers containing fully functionalized end groups.^[44, 60a] All the peripheral arylplatinum sites in these metallodendrimers were shown to be independent sensor sites, which is in accordance

with a conformationally rigid skeleton of the aryl ester dendrimer and negligible intermetallic interactions. The very low solubility of these macromolecular sensors in common organic solvents is a serious disadvantage for homogeneous applications and parallels the solubility properties of other periphery-functionalized metallodendrimers (for example, “cartwheel”-type structures).^[144]

Particular physical properties (surface behavior, size, solubility) of metallodendrimers can be engineered by using core-functionalized dendritic wedges. In such macromolecules, these properties are generally defined by the peripheral constitution and are therefore virtually isolated from the chemical activity since the functional site (sensor, catalyst) is located at the focal point.^[147] These unique characteristics allow for the independent tailoring of the physical and chemical properties. This concept was exploited by the core-functionalization of Fréchet-type dendritic wedges with a pincer metal site (Scheme 29).^[148] These metallodendritic

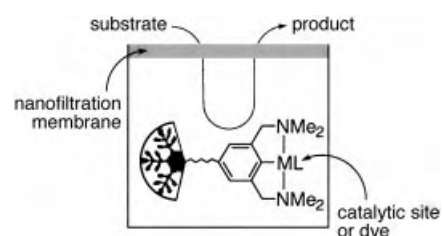


Figure 14. Application of metallodendritic materials that are compartmentalized in a membrane-covered vial, for example, as nanosized dyes or as multiple-use catalysts working at ambient pressure.^[148]

are conveniently recovered, regenerated, and stored. These applications do not require dendritic supports of exceedingly high generation.

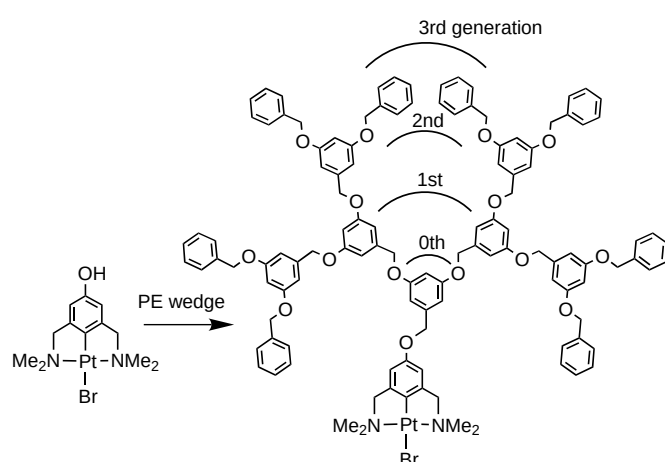
6. Perspectives

Early studies directed toward the synthesis of chiral triorganotin halides with a stable configuration led us to use the concept of intramolecular stabilization. The NCN pincer was used for the first time in an attempt to make water-soluble triorganotin compounds.^[2b,c] The observed rigid *N,C,N* terdentate coordination mode in this complex suggested that this presumed property (see, however, the different bonding modes in Figure 1) could be exploited to control oxidative addition/reductive elimination cycles in transition metal chemistry and homogeneous catalysis. The first experiments concentrated on the oxidative addition of platinum–pincer complexes [PtX(NCN)], which for X=OTf led to the discovery of the novel arenium–platinum compound (see Figure 5). This was the start of the research described in this review.

After 20 years, many experiments, and surprising results, we may conclude that the transition metal chemistry with pincer ligands has addressed various interesting aspects:

1. Comparative studies of the organometallic chemistry of complexes containing a single M–C_{aryl} bond and some additional ligands versus complexes containing a M–C_{aryl} σ bond which is supported intramolecularly by two neutral ligands.
2. New types and mechanistic details of metal-mediated reactions such as rearrangements of M–C_{aryl} units, C–C bond couplings and selective cleavage, the reactivity of arenium ions, and the stabilization of various proposed intermediates, for example, in oxidative addition.
3. Unprecedented organometallic properties imparted by the presence of well-defined pincer–metal units were used to explore new ideas for the immobilization of homogeneous catalysts, labeling of dendrimers and hyperbranched polymers, the reverse binding of H₂ (H₂ storage), and the sensing of small molecules such as SO₂.
4. New catalytic behaviors, for example, for NCN–nickel complexes acting as redox catalysts which are in many respects superior to alternative systems for similar reactions.

Finally, it should be noted that the concepts described in this review do not apply only for platinum group metals but



Scheme 29. Core-functionalized metallodendrimers, whose size and retention properties in nanofiltration membranes can be tailored by modification of the generation of the dendritic wedge. PE = polyether.

wedges displayed markedly improved solubility properties relative to the corresponding periphery-functionalized metallodendrimers and were, therefore, appropriate for homogeneous applications in membrane reactors. This scenario was realized by first assessing the permeability of a given membrane by monitoring the diffusion of platinum complexes functionalized with dendritic wedges of different generations through it. These materials are orange colored in the presence of excess SO₂, which facilitates their detection. The retention properties of the dendrimers correlated with their size and molecular weight and allowed for the identification of dendritic wedges that are appropriate for nanofiltration techniques. Substitution of the platinum center at the core by nickel provided dendritic catalysts with defined retention properties. When a solution of metallodendrimers of suitable size is loaded in a membrane-covered vial, a compartmentalized catalyst system is obtained which operates fully homogeneously and which is separated from the product solution simply by removing the vial (Figure 14). Such catalyst compartmentalization was shown to provide a suitable approach for the development of multiple-use catalysts which

have also found successful application in the chemistry of early transition metals,^[149] lanthanides,^[150] and main group metals.^[151]

The development and optimization of functional materials, certainly a key challenge in modern chemistry, requires well-defined and tunable systems, namely, functional units that can be specifically tailored on a chemical level. Metal complexes containing the pincer ligand were shown to be outstanding candidates for these purposes. Future research has to concentrate ever increasingly on the incorporation of these functional materials (for example, catalysts, light-harvesting antennas, or sensors) into macroscopic devices for routine applications. Clearly, this requires strong interdisciplinary cooperations with various fields such as physics, biology, engineering, or medicine. A particular issue consists of the appropriate translation of customer needs (that is, physical properties) into (supra)molecular modifications of promising materials. A balanced combination of profound chemical understanding and of serendipity will remain essential to achieve this ambitious aim.

7. Addendum

The continuous interest in pincer chemistry with platinum group metals is manifested by a number of noteworthy articles which have appeared since the submission of this manuscript. Contributions to this research area include the synthesis of new pincer-containing PCP–osmium^[152] and NCN–rhodium(II) complexes (Section 2).^[153] The diverse coordination chemistry of (immobilized) SCS–palladium units has been used for the construction of self-assembled supramolecular structures (Section 3.3).^[154] The mechanism of C_{aryl}–C_{alkyl} bond activation with PCN–rhodium complexes has recently been studied theoretically (Section 4.1).^[155] Moreover, pincer-type palladium complexes have been disclosed as novel catalysts for C–C bond-forming reactions (Section 4.2).^[156, 157] Finally, chiral Phebox–rhodium(III) species functioned as active catalyst precursors for the asymmetric hetero-Diels–Alder reaction of Danishefsky's dienes and glyoxylates.^[158]

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Jacobus Henricus van't Hoff; Hundred Years of Impact on Stereochemistry in the Netherlands**

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The First Nobel Prize for Chemistry

There is no award in science that can compete with the Nobel Prize; an award announced in a call from Stockholm in the month of October. At this very moment a selected number of eminent and highly respected chemists are hopefully and wishfully waiting to have their name added to the impressive list of previous laureates. All other chemists are eager to know who will be honored for his or her outstanding contributions to chemistry this year. How different it was exactly a hundred years ago, when in October 1901, at the age of 48, the Dutch physical chemist Jacobus Henricus van't Hoff (Figure 1) was named the first recipient of the Nobel Prize in chemistry in recognition of his discovery of the laws of chemical kinetics and the laws governing the osmotic pressure of solutions. Since awards gain significance in time, and that is certainly the case for the Nobel Prize, the first recipient certainly felt different from the laureate(s) of this year. Unfortunately, the feelings of Van't Hoff in October of 1901, as compared to those of this year's recipient(s), will remain within the realm of imagination.

Jacobus Henricus van't Hoff^[1] at that time Professor in Berlin, was highly respected within the chemical community for bringing physics and chemistry together (physicam chemiae adiunxit). However, this was only two decades after he was highly criticized for his ideas on stereochemistry and only one decade after his colleagues disagreed with him on the theory of dilute solutions. At the time he introduced the concept of tetrahedral carbon he was a 22-year-old physical chemist at Utrecht, and the major opposition to the three-dimensional arrangements of atoms in a molecule came from organic chemists from Germany. In 1895, he moved from the Netherlands to Germany, initiated by Max Planck. Without doubt every modern chemist agrees that Van't Hoff fully deserved the Nobel Prize, although many of them will connect Van't Hoff's name more to stereochemistry than to



Figure 1. Jacobus Henricus van't Hoff (1852–1911) (with permission of the Boerhaave Museum, Leiden).

the awarded science on chemical kinetics or osmotic pressure, despite the existence of the Van't Hoff factor i for the osmotic pressure of electrolytes.

In this essay, a short description of the first chemistry Nobel laureate and his chemistry is given.^[2] Although Van't Hoff is one of those unique scientists who inspired almost all chemists, his impact on the stereochemistry as performed at universities in the Netherlands is unparalleled. Therefore, this essay will also highlight some of the other achievements in stereochemistry following the hundred years after Van't Hoff's Nobel Prize and will conclude by showing some prospects for future stereochemical research within supramolecular chemistry; an area of intense research in the Netherlands. It is with the deepest respect that I take the liberty of addressing parts of the work of Van't Hoff and its impact on the stereochemistry in the Netherlands;^[3] the more I read about his achievements, the more I am impressed by the brilliance of his ideas and the more I realize the insignificance of our own small contributions in comparison.

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Jacobus Henricus van't Hoff (1852–1911)

Jacobus Henricus van't Hoff was born in Rotterdam on August 30, 1852 as the third child of Alida Jacoba Kolff and Jacobus Henricus van't Hoff. He was one of the first students that attended a new type of high school (HBS: Hoogere Burger School; Figure 2) that was initiated to educate young



Figure 2. A statue of van't Hoff in front of his former high school the Hoogere Burger School in Rotterdam, where he received his degree in 1869 (with permission of the KNCV).

people to become businessmen of small enterprises. Strangely, he did not go to the Gymnasium, which prepared students for study at a university. His teachers at the HBS stimulated his interest in chemistry, and consequently he started his study of chemical technology in Delft; however, he was much more interested in chemistry than in technology. Therefore, he moved to the University of Leiden for which he needed special permission from the Minister of Domestic Affairs. It is probably fair to say that he received his true training and passion for science in the laboratories of August Kekulé in

Jacobus Henricus van't Hoff

1852	born in Rotterdam
1869–1871	studied engineering at Technical Highschool of Delft
1871–1872	studied chemistry (Bachelor) at the University of Leiden
1872–1873	student with August Kekulé in Bonn
1873	studied chemistry (Masters) at the University of Utrecht
1874	worked with Adolphe Wurtz in Paris wrote his essay on stereochemistry received his PhD degree at the University of Utrecht
1874–1876	private teacher doing laboratory experiments in his free time
1876–1877	assistant at the Veterinary College in Utrecht
1877–1878	Lecturer at the University of Amsterdam
1878–1895	Professor of Chemistry at the University of Amsterdam
1895–1911	Professor at the University of Berlin
1901	Nobel Prize for Chemistry
1911	died of lung tuberculosis

Germany and Adolphe Wurtz in France. His stay in Paris, where he met Joseph-Achille le Bel and where the ideas of Louis Pasteur on optical activity were all around, should have given him the ideal opportunity to get his creative ideas on stereochemistry and the tetrahedral arrangement of carbon to explain the experiments of Pasteur (Figure 3). The results were disclosed in “*La Chimie dans l'Espace*” in 1875 (Figure 4).^[4] The same environment brought le Bel almost simultaneously to similar ideas.



Figure 3. Ten models of asymmetric molecules made by van't Hoff for his friend G. J. W. Bremer. The latter used these in his thesis in 1875. The original models are at the Boerhaave Museum in Leiden (with permission of the Boerhaave Museum).

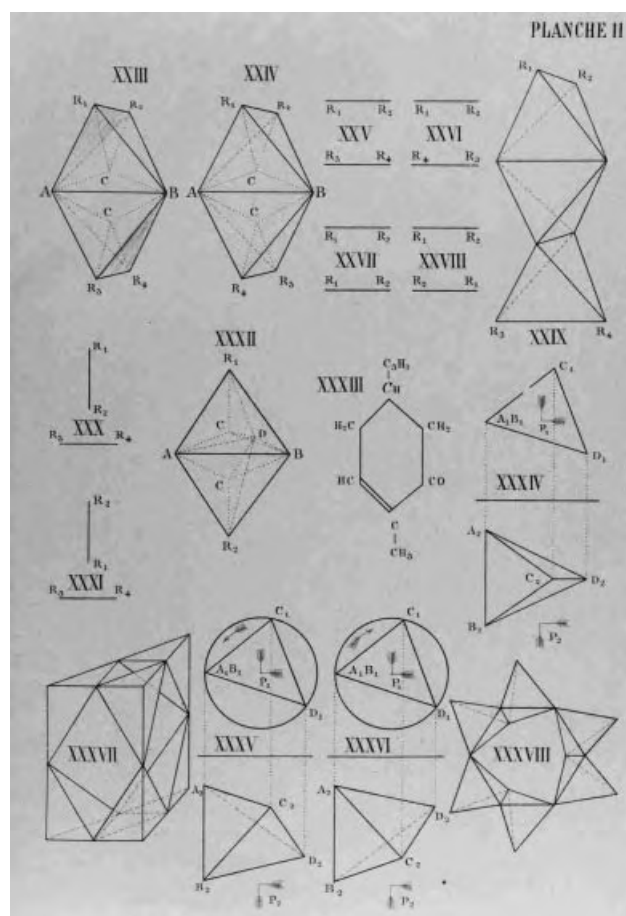


Figure 4. Van't Hoff's theories as published in *La chimie dans l'espace* (with permission of the Boerhaave Museum).

Van't Hoff received his PhD at the University of Utrecht in 1874 for a thesis on cyanoacetic acid and malonic acid. After defending his thesis, he unsuccessfully tried to get a job as a high-school teacher and thus gave lessons on a private basis to earn some money. In 1876 he was appointed as an assistant at the Veterinary College in Utrecht, the place that became famous due to Kolbe's attacks on him (see box).

Young versus Established

The stereochemical ideas about the three-dimensional arrangements of atoms within molecules were made by a 22-year-old Van't Hoff. With this concept, he could explain the experiments of, the also very young, Pasteur on tartaric acid. Not everyone, and especially the established chemists, agreed with the proposal of Van't Hoff on stereochemistry, as was expressed by the famous German professor Hermann Kolbe in 1877.^[26]

*In his opinion the lack of general education and of thorough training in chemistry was one of the causes of the deterioration of chemical research in Germany. He then went on to add that if anyone felt his worries were exaggerated then they should read, if they could, a recent memoir by Van't Hoff on *The Arrangements of Atoms in Space*, a document that he felt was crammed to the hilt with the outpourings of a childish fantasy. He went on point out that this dr. J. H. van't Hoff, who was employed at the Veterinary College at Utrecht, had, it seemed, no taste for accurate chemical research and found it more convenient to mount his Pegasus (evidently taken from the stables of the Veterinary College) and to announce how, on his bold flight to Mount Parnassus, he saw the atoms arranged in space.*

When in 1877 the Amsterdam Athenaeum became the University of Amsterdam, he was asked by J. W. Gunning to become a lecturer in theoretical and physical chemistry. Not long thereafter, he accepted the full chair of chemistry, mineralogy, and geology at the same university on October 11, 1878 with his inaugural lecture that was entitled: "De Verbeeldingskracht in de Wetenschap", meaning "The imagination in Science", a title that is still relevant today. In this lecture he discussed in detail the many attacks by the German chemist Hermann Kolbe and stressed the importance of imagination together with observation. The Amsterdam period, was by far his most original period in terms of the chemistry, for which he later won the Nobel Prize, and for which he became world famous. An offer from the University of Leipzig in 1887 was rejected, and as a result the city of Amsterdam built a new laboratory for him at the Roetersstraat. The University of Amsterdam later honored their former professor by naming the Physical Chemistry Department the "Van't Hoff Laboratories". However, at that time Van't Hoff often mentioned the problem of his many duties as teacher and organizer of the laboratories. In 1895, he was visited by Max Planck and accepted an offer to become a member of the "Königlich Preußische Akademie der Wissenschaften" in Berlin. In 1896 he also became a professor at the University of Berlin. He received his own laboratory and had only one hour of teaching duties a week. He dedicated his

time fully to science and in 1901 he received the first Nobel Prize for Chemistry. Van't Hoff died of lung tuberculosis on March 1, 1911.

Physicam Chemiae Adiunxit

Although science progresses with an ever-increasing speed, some issues are time insensitive and the early introduction of those issues is given to the true masters of science only. Connecting physics and chemistry (Physicam Chemiae Adiunxit) was the inscription on a sculpture given to J. H. van't Hoff by his (former) students from the University of Amsterdam in 1889. It not only nicely shows their appreciation for his elegant way of bringing physical theories within the realm of chemistry; it also illustrates the scientific time insensitivity. It is less than two years ago that Angewandte Chemie launched successfully the new Journal ChemPhysChem, which has grown to become a highly appreciated forum for publishing science that brings physics and chemistry together. The title "De Verbeeldingskracht in de Wetenschap", meaning "The imagination in Science", of Van't Hoff's inaugural lecture at the same University, offers another way to learn about the modern ideas from Van't Hoff at that time. He was arguing, as a defence against the attacks of Kolbe, that next to observations it is useful to use your imagination. The third and last example of time insensitivity based on studying the history of Van't Hoff, can be found in his struggle with the board of the city of Amsterdam. He was not only asking for more money to get a perfect infrastructure for science, he also argued that there should be places at Universities where scientists could dedicate most of their time to science and where they were not fully occupied by teaching and administrative duties. This passion brought him to Germany in 1895.

The award-winning chemistry (1872–1901)

Although every textbook on organic chemistry will highlight Van't Hoff's contributions to the understanding of stereochemistry, the Nobel committee honored Van't Hoff's work in the area of physical chemistry in general. Details of the work for which the award was received can be found in three seminal contributions, from which I would like to highlight only a few aspects. In 1884 the dynamics of chemical reactions were disclosed in a remarkable book entitled "*Etudes de dynamique chimique*", published in Amsterdam.^[5] He was interested in linking the chemical constitution of molecules to their properties and in giving organic chemistry a physical and/or mathematical foundation. He describes the notion that molecules with oxygen atoms react faster than molecules without oxygen, for example the oxidation of methanol is faster than that of methane. The serendipitous finding that 2,3-dibromosuccinic acid decomposes at 100 °C into hydrogen bromide and bromomaleic acid was used to follow the formation of hydrogen bromide with time. With these kinetic measurements he found that the reaction was unimolecular. As an example of a bimolecular reaction he studied the hydrolysis of the sodium salt of chloroacetic acid. Based on the temperature dependency of both reactions, he

deduced the now well-known thermodynamic relationship between the absolute temperature T and the rate constant k in which A and B are temperature independent factors [Eq. (1)].

$$\mathrm{d} \ln k / \mathrm{d} T = A / T^2 + B \quad (1)$$

A is that which later was denoted to as E_a/R , the quotient from the activation energy and the gas constant. In the second part of his *Etudes*, he discussed the issue of chemical equilibrium and introduced the double arrow to denote an equilibrium. In the last part of the *Etudes*, he discussed the affinity of chemical compounds. All in all, the *Etudes* were fundamental for a completely new field at that time: chemical dynamics.

After the completion of the *Etudes de dynamique chimique*, he studied the theory of dilute solution. As Professor Snelders mentioned in his book on the history of science in the Netherlands,^[2] he used his 1884 summer vacation with his wife and three children in Hilversum for performing this study. The results were disclosed in three articles that were published in 1886. The full text can be found in “*Kongliga Svenska Vetenskaps-Akademiens Handlingar*”;^[6] please remember that at that time there was no reason what so ever to show your qualities as a scientist to the Swedisch Academy. However, again according to Professor Snelders’ analysis, he thought that the Norwegian scientists Guldberg and Waage, who did earlier seminal work in the field, were from Sweden and to honor them he submitted its manuscripts to Sweden. It is an interesting question whether this mistake helped him to receive the first Nobel Prize for Chemistry. Anyhow, the major contribution mentioned in the articles relates to the, as it is known now, Van’t Hoff factor i . Since the osmotic pressures of electrolytes were always higher than predicted by the equations used to that time, sometimes with a factor of two or three, he modified the equation as shown in Equation (2).

$$\Pi = i c R T \quad (2)$$

With the correction factor i Van’t Hoff was able to get theoretical and experimental results to agree. Using four different techniques, he started to establish the value of the factor; all of the measurements are important ingredients for fundamental studies of osmotic pressures.

Finally, Van’t Hoff was actively involved in explaining the findings made by Arrhenius on the conductivities of electrolytes in water.^[7] The anomalies found in Arrhenius’ experiments were attributable to electrolytic dissociation. Together with Wilhelm Ostwald he founded the “*Zeitschrift für Physikalische Chemie*” in 1887 and the work describing the reason for the fact that not all species contributed to the conductivity at high concentrations was published there in the first year of issue.^[8] Together with the theories of Arrhenius, his work initiated another way of thinking about chemical reactivities. Both theories were in contrast with the general ideas at that time and it took some years before the scientific community accepted them.

Chemistry in the Netherlands (1901–1945)

The move made by Van’t Hoff from Amsterdam to Berlin was logical for that period of time and was illustrative for the leading position of Germany in science. In the Netherlands, chemistry became a subject taken seriously at Universities and in 1903 the Royal Dutch Chemical Society was founded. Most, if not all, of the important work that was performed in the Netherlands was published in the *Recueil des travaux chimiques des Pays-Bas*. Major activities at the time were related to synthetic organic chemistry, primarily due to the industrial relevance of the work, and stereochemistry was not an issue of serious investigation. However, the pioneering work of Professor Jacob Böeseken (1868–1949) in Delft, on what was later called conformational analysis, is worth mentioning in connection with Van’t Hoff’s stereochemical interest.^[9] Böeseken also studied *cis*- and *trans*-cyclopentane-diol; the latter could be resolved in its two enantiomers in contrast to the *cis*-isomer. During World War II the scientific activities slowed down considerably at Dutch universities and for those interested in details, I would like to refer you to an excellent report published 1947.^[10]

The Dutch stereochemistry schools (1945–1985)

Owing to the high impact of scientific and technological findings for the outcome of World War II, an immense expansion of academic activities was observed throughout the world in the period after 1945. A similar trend was observed within the Netherlands and in addition major Dutch industrial laboratories started fundamental research projects. This was the start of an active collaboration between academia and industry as well as an exchange of scientists; a relationship that remained fruitful through the years and probably was the basis for the current status of Dutch chemistry. The impact of Van’t Hoff for Dutch science is illustrated below with a short description of three selected examples from the period 1945–1985 with stereochemical topics as a lead.

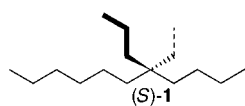
To honor the contributions to science by one of their former students, the University of Utrecht also named their Laboratory for Physical Chemistry after Van’t Hoff. In the period after the war Professor Johannes Martinus Bijvoet (1892–1980) was the director of this laboratory. He performed with his co-workers Peereboom and Van Bommel one of the most critical experiments in the field of stereochemistry.^[11] Using anomalous scattering in X-ray diffraction they were able to determine the absolute configuration of sodium rubidium tartrate, and thereby show that M. A. Rosanoff of New York University in 1906 made the correct choice, or better guess, for the assignment of the configuration of (+)-glyceraldehyde. As a result it was not necessary to change the assignments of all stereoisomers published prior to that date. This landmark experiment was published in 1951, exactly 50 years ago, and will be the topic of an upcoming essay in *Angewandte Chemie* by Professor Jack Dunitz.^[12] The Van’t Hoff Laboratories still exists at Utrecht.

In Leiden, Professor Egbert Havinga (1909–1988) was appointed as Professor of Organic Chemistry in 1945. He excelled in many aspects of physical organic chemistry,

including photochemistry and stereochemistry. He created the Leiden school of Organic Chemistry, and for many reasons it is appropriate to see him as one of the successors in the Van't Hoff tradition. His many contributions have attracted high international recognition. His work started with the conformational analysis of cyclohexane derivatives, and inspired by the photochemical synthesis of vitamin D he explored the many theoretical issues of the stereochemistry of the electrocyclic ring closures of 6π -electron systems. He formed a very successful partnership with Professor L. J. Oosterhoff (1907–1974), a theoretical organic chemist. One of the most intriguing results of their collaboration was published in *Tetrahedron* in 1961.^[13] In a study on the specificities of the photochemical and thermal transformations in the vitamin D field, they discussed the difference in pathways observed. In addition to a number of possible causes, they mention the thoughts of Professor Oosterhoff: "As Prof. Oosterhoff pointed out, another factor that possibly contributes to the stereochemical difference between the thermal and photo induced ring closure may be found in the symmetry characteristics of the highest occupied π -orbital of the conjugated hexatriene system. In the photo-excited state, the highest occupied orbital is antisymmetric with regard to the plane that is perpendicular to the bond 6,7 making "syn" approach less favourable." This conservation of orbital symmetry approach was later followed by the well-known work of Woodward and Hoffmann, who in their first article on this topic in 1965 note the important role of Havinga and Oosterhoff: "Professor Oosterhoff (Leiden) clearly deserves credit for having first put forward the suggestion that orbital symmetries might play a role in determining the course of the stereochemical phenomena attendant upon triene cyclization (private communication to prof. Havinga). The suggestion was described so succinctly that it has received no currency, and it has been not generalized to include other cases".^[14] Why the Leiden team did not give their initial thoughts more attention remains unclear, although it is argued that Oosterhoff did not like the approximations made in the one-electron model and was pursuing a more general explanation using valence bond theory.

Professor Havinga was able to organize a Fulbright fellowship to get Hans Wynberg back to the Netherlands as a visiting scientist in Leiden in 1959. In 1961 Wynberg was appointed as Professor of Organic Chemistry in Groningen where he established one of the most successful schools of modern stereochemistry in the Netherlands. He continued the Van't Hoff style of combining careful observations with sparkling imagination. Hans Wynberg was the first scientist who used chiral phase-transfer reagents based on quinine to perform catalytic asymmetric synthesis, while he also studied the optical activity in bio- and chemiluminescence in collaboration with students from the Leiden school.

One of Wynberg's benchmark experiments, being part of many textbooks of organic chemistry, concerned the optical inactivity of an enantiomerically pure branched alkane (*S*)-



1.^[15] The lack of optical transitions in the UV/Vis region and the high degree of flexibility of (*S*)-**1** was argued to be the reason for this

unconventional behavior. This experiment was obviously connected with the seminal work of Van't Hoff. In recent years, and long-after his formal retirement, Professor Wynberg and his co-workers of his contract research company Syncom introduced the Dutch resolution technique; a methodology in which combinatorial approaches are used to speed up the discovery of successful combinations in the selective crystallization of diastereoisomers, leading to a quick access to enantiomerically pure compounds.^[16] Moreover, many students from Hans Wynberg have taken up academic positions and continued his tradition in modern stereochemistry.

The present and future of Dutch stereochemistry (from 1985)

For a variety of reasons Dutch chemists love to work on issues related to stereochemistry. Obviously, most of these reasons are similar to those well known to all of us, but the tradition set by Van't Hoff and the excellent teachers in stereochemistry in the period after Van't Hoff have provided great inspiration to study stereochemical topics in the Netherlands. In the final section of this Essay, I would like to show some of the many possibilities of stereochemistry in combination with supramolecular chemistry, a topic of great interest at present within the Netherlands. With the increasing complexity of molecular structures and supramolecular assemblies, the intriguing issues of the origin of life and the importance of the interaction of light with matter, it is highly attractive to introduce stereochemical subtleties within supramolecular research topics.

Professor David N. Reinhoudt (University of Twente) initiated activities into Supramolecular chemistry in the Low Countries, these were followed by major activities in Nijmegen, Groningen, and Eindhoven. Directly after the discovery of the crown ethers and their ability to complex cations, David Reinhoudt, at the time at the Royal Shell Laboratories in Amsterdam, started the exploration of this class of new compounds. After his move to Twente, he extended his activities to a large variety of systems, from which building blocks for nanotechnology have now been developed.^[17] Recently his group showed that it is possible to make enantiomerically pure supramolecular objects of nanometer dimensions without using chiral molecules using a so-called memory effect.^[18] With the successful application of surface chemistry and micro/nano-manipulation techniques, the work from his group is of prime importance for the progress in the area of nanotechnology in general and hopefully that of chiral nanotechnology in particular.

Roeland J. M. Nolte made his entrée in stereochemistry, after obtaining a PhD degree from Utrecht with Professor Wiendelt Drent, with the synthesis and characterization of chiral polyisocyanides.^[19] The synthesis of polymers with one handedness, the study of their stability with respect to atropisomerization, and a postdoctoral stay with the late Professor Donald Cram (Los Angeles), inspired Roeland Nolte to start his own group in supramolecular chemistry at the University of Nijmegen. Seminal contributions to supramolecular catalysis, chiral supramolecular assemblies based on phthalocyanines (Figure 5),^[20] and more recently chiral superamphiphilic structures have made him one of the leading

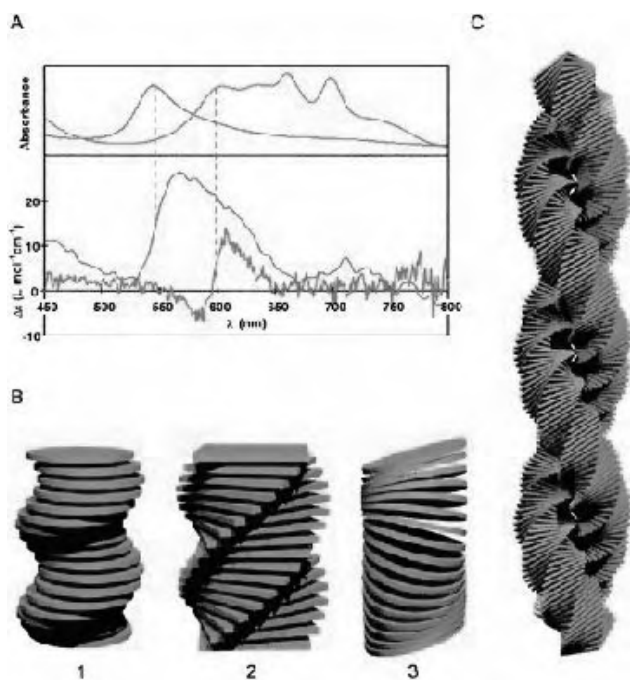


Figure 5. Supramolecular chirality by the self-assembly of chiral phthalocyanines (with permission from ref. [20]).

scientists in the field of supramolecular chemistry.^[21] His physical organic background has enabled him to make detailed studies of the aggregation of self-assembling molecules and by using a variety of microscopic techniques the Nolte group have been able to visualize the structures proposed.^[22] His recent work is now directed to the incorporation of biomacromolecules in supramolecular systems, leading to an area of hybrid systems with unexplored chemistry.

Ben L. Feringa moved after his PhD with Hans Wynberg to the Royal Shell Laboratories and returned to his alma mater as a professor. As the successor of Wynberg, he not only continued the tradition of stereochemistry in Groningen, but he also broadened the scope of the research significantly. Seminal experiments were performed with chiroptical switches and molecular rotors, based on chiral twisted olefins. As a result of the photochemical isomerization of this twisted double bond, the Feringa group has been able to bias the induced chirality of a liquid crystalline matrix, leading to a molecular switch.^[23] The same isomerization, followed by an irreversible ring flip leads to a light-driven monodirectional rotary motion.^[24] The group of Feringa is also actively involved in asymmetric synthesis using a variety of new chiral catalytic systems and, therefore, he is successfully combining advanced synthesis with novel stereochemical concepts.^[25] In the future developments of molecular motors, switches, and machines, his group will certainly be at the forefront of this discipline.

It is now tempting to end this Essay with a short resume of my own activities in stereochemical issues; an interest that was initiated during my PhD research with Hans Wynberg. However, it is more appropriate to end with the lessons learned from Van't Hoff.

What can we learn from Van't Hoff

It is without doubt that many of the ideas of the current and future generation of chemists in the world are and will be guided by the seminal science of the first Nobel laureate in chemistry, who received this accolade exactly one hundred years ago. Jacobus Henricus van't Hoff was one of the greatest chemical thinkers of his generation and he showed us that imagination is as important in science as observation. It is also not necessary that your scientific community directly agrees with your ideas. This is nicely illustrated with the only other Dutch winner of the Nobel Prize in Chemistry (1995), Professor Paul Crutzen, who likewise was also employed in Germany at the time he received his call from Stockholm. The impact of his research on the chemistry and its effects to the ozone layer was not recognized from the beginning.

Finally, for all of us who believe that it was much easier to establish breakthroughs in chemistry hundred years ago, they should just use their own imagination and focus on the many challenges given to us by the progress in the experimental techniques. In front of us, we can foresee a successful merging of physics, chemistry, and biology leading to a complete understanding of natural processes and to the challenge of the production of artificial systems that can perform complex tasks. If I could have a look in the future for just one second, I would love to see for what scientific breakthrough the Nobel Prizes in sciences were awarded for in the year 2101; a hundred years from now.

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Bifunctional Polyphenol Oxidases: Novel Functions in Plant Pigment Biosynthesis

Dieter Strack* and Willibald Schliemann*

Anyone who has observed a cut apple or a damaged banana notices the appearance of brown and black pigmentation from the formation of complex polyphenols. This color change is caused by a group of copper proteins, polyphenol oxidases (PPOs), in plants often described as latent thylakoid membrane-located enzymes.^[1]

PPOs can be divided into tyrosinases, catechol oxidases, and laccases, all belonging to the copper type-3 proteins containing binuclear copper centers.^[2] Tyrosinases are bifunctional PPOs, which catalyze hydroxylation of phenols to *o*-diphenols (EC1.14.18.1; monophenol: monooxygenase) and their subsequent oxidation to *o*-quinones (EC1.10.3.1; *o*-diphenol: oxygen oxidoreductase). Catechol oxidases catalyze only the latter reaction.^[3] In contrast, laccases (EC1.10.3.2; *p*-diphenol: oxygen oxidoreductase) accept preferentially *p*-diphenols and a laccase-like enzyme is proposed to be involved in lignin biosynthesis.^[4]

Tyrosinases play a pivotal role in the formation of complex polyphenols in bacteria, fungi, plants, and animals including humans. For example, in insects they are involved in cuticular melanization and sclerotization of the exoskeleton as well as in the defense against other organisms by encapsulating them in melanin. Tyrosinases are also active in the formation of the black colorant sepia in *Sepia officinalis* (octopus). In animals (including humans), these enzymes are responsible for skin and hair coloration (eumelanins, pheomelanins); in plants they might have a role in defense reactions against insects and microbial pathogens, however, this has not yet been proven.

With the amino acid tyrosine as substrate, the activity of the enzyme tyrosinase leads from tyrosine via 3,4-dihydroxyphenylalanine (dopa) to dopaquinone. Dopaquinone then undergoes a spontaneous cyclization by Michael addition to form *cyclo*-dopa, which polymerizes following oxidation to dopachrome to form melanin. On the other hand the formation of dopa as an endproduct in various plant tissues by the hydroxylation activity of tyrosinase^[5] or as an intermediate metabolite, for example, via dopamine in the

biosynthesis of benzyltetrahydroisoquinoline alkaloids,^[6] has been shown. However, with regard to their bifunctional properties, the plant PPOs are among those enzymes to which a function has not yet been assigned.^[7] This situation has, however, recently changed. The involvement of both reactions, hydroxylation and oxidation, in the biosynthesis of low molecular weight products has been proven in two different pathways of plant pigment biosynthesis. A tyrosinase is involved in betalain biosynthesis^[8] and a chalcone-specific PPO participates in aurone biosynthesis.^[9]

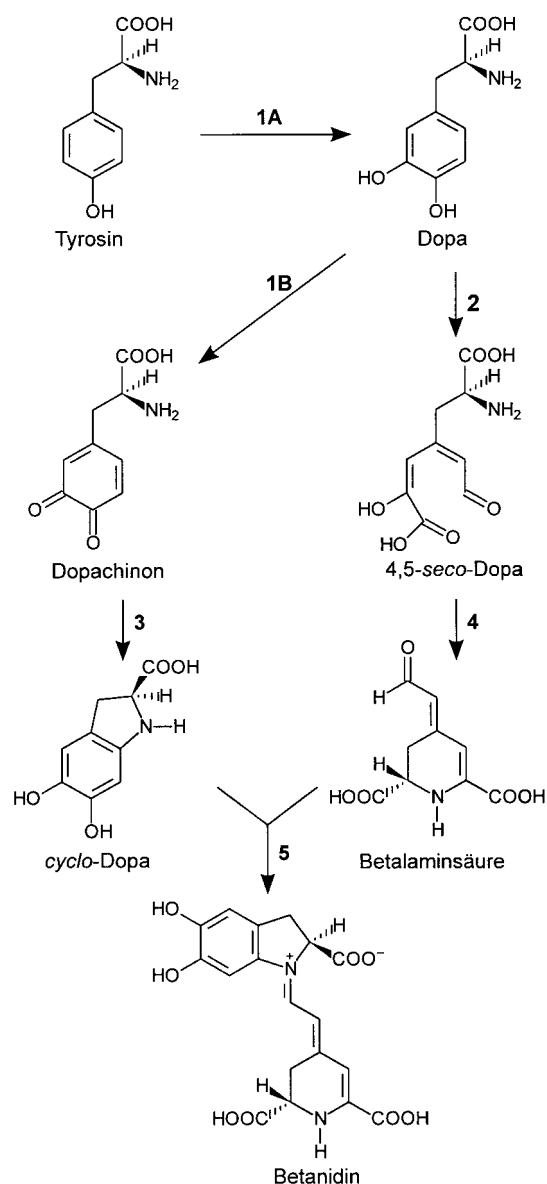
The tyrosinase involved in betalain biosynthesis has been found in common portulaca (*Portulaca grandiflora*) and red beet (*Beta vulgaris*). Figure 1 shows a flowering common



Figure 1. A betacyanin-accumulating common portulaca plant and a corresponding callus culture, (photographs kindly provided by U. Steiner, University Freiburg, Germany).

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portulaca plant and a corresponding callus culture, which accumulate betacyanins, a class of red-violet betalains. Along with the yellow betaxanthins, betalains are characteristic water-soluble, nitrogen-containing pigments accumulating in flowers, fruits, and occasionally in vegetative tissues of plants of most families of the Caryophyllales.^[10] These pigments take the place of the anthocyanins, a class of flavonoids, which occur in all other families of flowering plants. Scheme 1 shows



Scheme 1. Betacyanin biosynthesis involving two enzymes, the bifunctional tyrosinase (reaction **1A**, hydroxylation; reaction **1B**, oxidation) and the dopa 4,5-dioxygenase (reaction **2**). The tyrosinase acts bifunctionally as well as monofunctionally in the biosyntheses of *cyclo*-dopa and dopa, respectively. Reactions **3**, **4**, and **5** are considered to proceed non-enzymatically. The product is betanidin, the basic structure of glycosyl and acylglycosyl conjugates (pigments) in most families of the Caryophyllales.

the pathway of betacyanin biosynthesis in which only two enzymes, a tyrosinase and a dopa 4,5-dioxygenase are required. The bifunctional tyrosinase catalyzes the sequential

formation of dopa and dopaquinone. The *cyclo*-dopa, spontaneously formed from dopaquinone, is protected in vivo against further oxidation and polymerization by an unknown mechanism. In vitro this protection can be achieved by the addition of reducing agents (e.g. ascorbic acid) in the tyrosinase assay mixture.^[8]

Another unknown mechanism is how a significant portion of the tyrosine hydroxylation product, dopa, is protected against the second tyrosinase activity, the oxidation. This is absolutely essential, since dopa must be available as a substrate for the dopa 4,5-dioxygenase in betalain biosynthesis. The enzyme catalyzes the 4,5-extradiol cleavage of dopa to give 4,5-*seco*-dopa that recycles to betalamic acid, part of the betacyanin chromophore. Betalamic acid and *cyclo*-dopa enter a spontaneous condensation reaction. The product betanidin is the basic structure of various glycosyl and acylglycosyl conjugates.^[10]

The betalain-specific tyrosinase was partially purified and characterized from common portulaca callus cultures^[8] (Figure 1). The presence of a high salt concentration (500 mM NaCl), ascorbic acid, and CuCl₂ turned out to be essential for enzyme extraction. The highest hydroxylation activity was observed when ascorbic acid and catalase were added and the assay mixture saturated with O₂. The hydroxylation activity at a pH optimum of 5.7 was specific for L-tyrosine, the reaction rates with L-tyrosine and D-tyrosine are in a ratio of 1:0.2. Other monophenols tested were not accepted as substrates. The highest dopa oxidase activity was determined to be at pH 7.0. The enzyme appeared to be a monomer with an apparent molecular mass of around 53 kDa. Tyrosinase activity correlated with betacyanin accumulation in hypocotyls of developing red beet seedlings. These results showed for the first time that both tyrosinase reactions (hydroxylation and oxidation) are involved in the formation of low molecular weight plant products, the betacyanins.

A recent report on the involvement of a bifunctional PPO in the biosynthesis of another class of plant pigments, the aurones, is a true highlight.^[9] The authors were able to demonstrate the role of this enzyme in the biosynthesis of aurones in snapdragon (*Antirrhinum majus*) flowers (Figure 2). Besides chalcones, flavanones, and dihydroflavonols, aurones belong to the group of "minor flavonoids".^[11] Based upon 2-benzylidene-coumaran-3-one^[12] their structures lack the typical flavonoid skeleton, but they are biosynthetically directly derived from chalcones, the pivotal precursor of all flavonoids.^[13] Aurones are gold-colored (latin aurum = gold) pigments occurring as glycosides in petals of some members of the Asteraceae (e.g. *Cosmos*, *Coreopsis*), Scrophulariaceae (e.g. snapdragon), Cyperaceae, and Fabaceae. The 6-*O*-glucosides of aureusidin and bracteatin are the main pigments in snapdragon petals.

For almost 30 years an oxidative cyclization of chalcones catalyzed by a peroxidase and a subsequent spontaneous dehydration of the intermediate was postulated.^[14] Contrary to this, it has been demonstrated^[9] with an enzyme from snapdragon buds that both the hydroxylation and the oxidative cyclization of chalcones are catalyzed by a single enzyme (called aureusidin synthase), a PPO. The purified enzyme catalyzes at a pH optimum of 5.4, in the presence of



Figure 2. Aurone-accumulating snapdragon flowers, (photograph kindly provided by T. Nakayama, Tohoku University, Sendai, Japan).

H_2O_2 , the 3-hydroxylation and oxidative cyclization of 4,2',4',6'-tetrahydroxy-chalcone (THC) to yield aureusidin as the only product (Scheme 2). The enzyme was found to be monomeric with an apparent molecular mass of 39 kDa. Aureusidin formation proceeds with the equimolar consumption of oxygen, but not of H_2O_2 , which may work as an enzyme activator.^[15] 3,4,2',4',6'-Pentahydroxychalcone (PHC) was a much better substrate than THC (relative activity 2210%) for the enzyme to produce aureusidin and bracteatin in a molar ratio of 6:1. In this case, H_2O_2 was also not required for enzyme activity but rather inhibited the reaction. These results suggest that aureusidin can be produced either from THC or PHC. Bracteatin is not produced through the 5'-hydroxylation of aureusidin but arises solely from PHC. Not only the free chalcones (THC, PHC) were good substrates in vitro, but also the corresponding 4'-*O*-glucosides, with relative activities of 220 and 2490%, respectively.

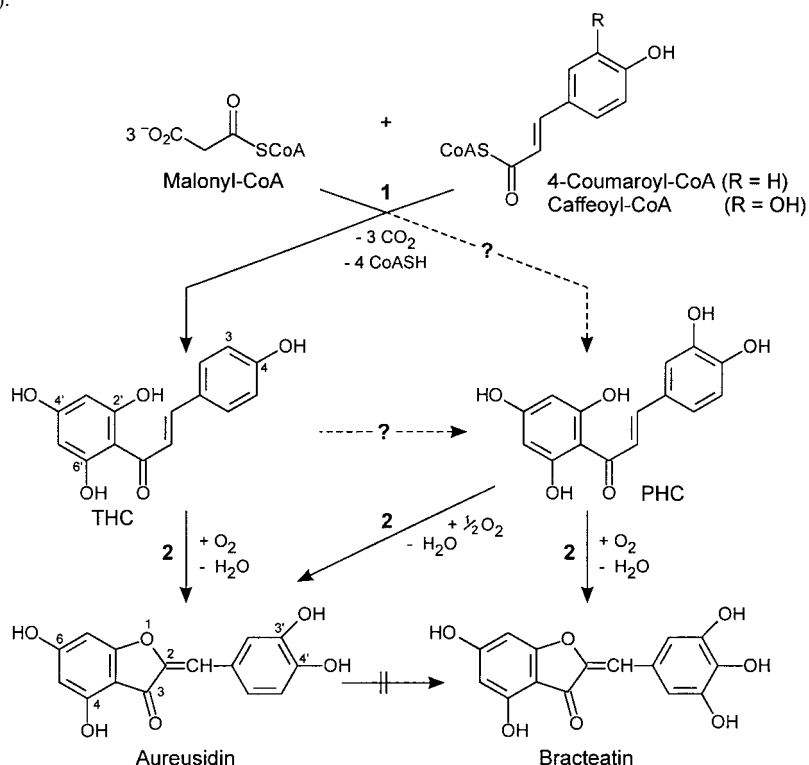
With regard to the mechanism of the chalcone-specific PPO activity, it has been proposed^[16] that both THC and PHC are converted into a 3,4-*o*-quinone derivative which cyclizes by nucleophilic attack of the activated double bond by the 2'-hydroxyl group leading, after subse-

quent hydrogen transfer, to the final aureusidin (Scheme 3). However, for naturally occurring aurones lacking a 3,4-dihydroxy substitution pattern, clearly a different reaction mechanism has to be postulated.

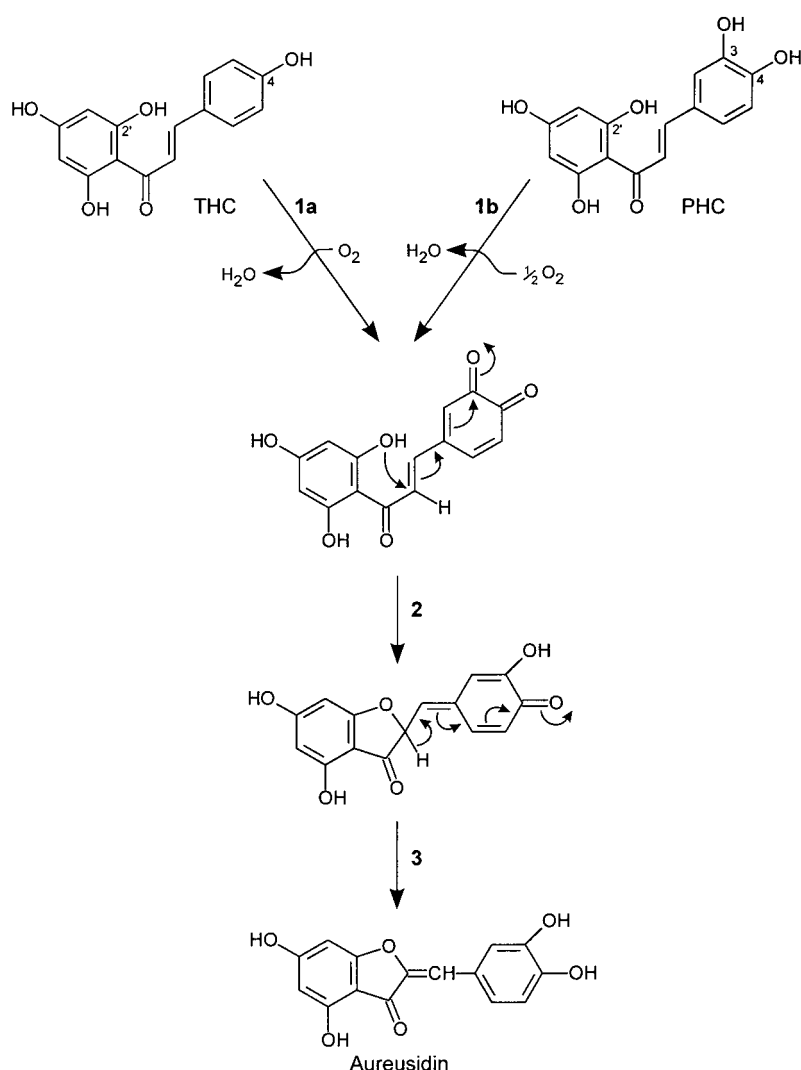
The amino acid sequences of proteolytic fragments of aureusidin synthase were found to be identical to stretches of the deduced amino acid sequence of a clone that was specifically expressed in the pigment-containing snapdragon petals and obtained by subtractive hybridization. A cDNA (*AmAS1*) was isolated from a petal cDNA library using this clone as a probe. The cDNA encoding the precursor of aureusidin synthase contained an open reading frame of 1686 base pairs encoding 562 amino acids. That the AmAS1 protein is a binuclear copper enzyme, expected for a bifunctional PPO, was demonstrated by identification of two histidin-rich Cu-binding domains and by atomic absorption spectroscopic analysis.

The AmAS1 protein showed significant sequence similarity to other plant PPOs, such as those from apple fruit (*Malus x domestica*) (identity, 51%), grape berry (*Vitis vinifera*) (47%) as well as to two PPO cDNAs from pokeberry (*Phytolacca americana*) (48 and 49%). Increase of the transcript levels of the pokeberry PPOs correlated with the betacyanin formation in the fruits.^[17]

The identification of aureusidin synthase as a PPO homologue gave a reason to test *Neurospora crassa* tyrosinase for aureusidin synthase activity,^[9] and indeed, aureusidin was



Scheme 2. Aurone biosynthesis in snapdragon flowers. The chalcone-specific PPO (reactions 2) catalyzes the hydroxylation and/or oxidation of the chalcones THC and PHC in the formation of aureusidin and bracteatin. It is unknown whether PHC derives from chalcone synthase (reaction 1) acting towards caffeoyl-CoA^[19, 20] or alternatively from a putative B-ring hydroxylase^[19] accepting THC. On the other hand, the hydroxylation activity of the aureusidin synthase towards THC to yield PHC (in a reducing milieu) is conceivable, analogous to the role of the betalain-specific tyrosinase (see Scheme 1).



Scheme 3. Proposed mechanism (redrawn from ref.[16]) of aureusidin-synthase-catalyzed aurone formation from THC (reaction 1a) or PHC (reaction 1b). Hydroxylation and oxidation is followed by a two-step non-enzymatical cyclization (reactions 2 and 3).

formed from THC, thus establishing the general ability of PPO to catalyze aurone synthesis from chalcones. In contrast to other PPOs, the aureusidin synthase showed virtually no 3',4'-dehydrogenation activity towards aureusidin and very low L-dopa-oxidizing activity.^[16] Finally, the spatial and temporal expression of the *AmASI* gene analyzed by RNA gel blots revealed a strict correlation with the aurone formation during flower development.

In the light of these topical results, which demonstrate novel and surprising functions of bifunctional PPOs in the biosynthesis of low molecular weight plant products, it is now a priority to address the question of the molecular mechanism of these enzyme activities, a question that has been raised recently in this journal by Decker et al.^[18]

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New Ways to Porous Monolithic Materials with Uniform Pore Size Distribution

Michael R. Buchmeiser*

Basics of porous monolithic materials

Porosity represents an important structural feature of many inorganic and organic materials. It may be used to vary important material properties such as electrical and thermal conductivity, refractive index, density, mechanical strength, and toughness. Additionally, porosity may be used for any kind of transport process as well as for molecular recognition. Both inorganic and organic porous materials, for example in the form of membranes,^[1] find broad application in many areas of separation science such as membrane filtration for the clean up of biologically relevant compounds and fluids, (haemodialysis),^[2] for the clean up of gases,^[3, 4] and as ion-selective membranes.^[5] Membranes for these applications usually consist of either isolated polymer networks or porous polymer films.^[6] With the exception of materials for gas separation, there are comparably low demands on the pore size distribution. Organic, porous monolithic materials are of particular interest because of their intriguing properties in many areas of materials research.^[7] The term “monolith” refers to unibody structures composed of interconnected repeating cells or channels.^[8]

Compared to their mesoporous analogues, macroporous monoliths are easily accessible by copolymerization of different monomers such as glycidyl methacrylate and ethylene dimethacrylates. Derivatization is accomplished by a polymer transformation, for example, of the epoxide group. Such surface compatibilizations are of particular importance in various bioapplications, since they reduce or even prevent nonspecific surface adsorption. Monolithic media are used mainly as separation media in particular for macromolecules and biopolymers, but also as bioreactors.^[9] In particular, systems based on polymers (PS-DVB or (meth)acrylates) mainly developed by Fréchet et al.^[10] as well as those based on rigid rods composed of silica represent new benchmarks in separation science. Generally, the microstructure of such materials is characterized by a comparably broad distribution of micro- and macropores. It is generated by means of solvent-induced phase separation. Access to a broad range of functionalization was achieved by imprinting techniques,^[11] a more generally applicable route was established by a transition metal catalyzed monolith synthesis which entailed a subsequent surface graft-polymerization.^[12, 13]

Materials with defined porosity

Compared to the synthesis of materials with a continuous pore size distribution, the synthesis of mesoporous analogues with a *uniform pore size distribution* is definitely not trivial. If such a *defined* porosity could be generated within materials with dimensions of at least a few micrometers, these would possess enormous potential as “advanced materials” for many high-tech applications such as (parallel-)microelectrophoresis.^[14–19] Additionally, because of their (thermal) degradability, defined organic pore structures may be used in the template-assisted syntheses of metals, semiconductors, etc. with nano- and mesoscopic dimensions.^[20, 21] On the other hand, because of their high-temperature resistance, inorganic supports with defined porosity are already used in catalysis.^[22–25] They may be accessed in a comparably easy way by template-assisted syntheses. Thus, inorganic metal oxides with a large variety of mesoscopic morphologies such as hexagonally packed cylinders may be prepared.^[26, 27] Organic polymers, which can be removed thermally, serve as templates. Mesoporous structures based on carbon may be prepared in an analogous way.^[28]

In contrast, for organic materials the inorganic domains were introduced in the system either in the form of uniform inorganic particles or by sol–gel techniques.^[29] Unfortunately, volume contraction of the polymer as well as “chemical defects” within the remaining polymer domain after template removal (e.g. silica) may cause problems, which severely impede a uniform porosity.^[30] In addition, insufficient amounts of template surrounding the polymer may result in coagulation of the template, thus leading to the formation of large pores. Consequently, synthetic strategies are applied that are based on the pore generation by the selective chemical destruction and removal of single organic polymer domains. For this purpose, low polydispersity block copolymers with well-defined blocks were synthesized, which were, for example, (spin-)coated onto a support and annealed to allow self-organization. In the course of this process, prepositioning of the pore precursors (one polymer block) and consequently of the pores is accomplished. Poly(methylmethacrylate-*b*-styrene), poly(isoprene-*b*-pentamethyldisilylstyrene-*b*-isoprene), poly(styrene-*b*-isoprene), poly(styrene-*b*-butadiene), and poly(*tert*-butylacrylate-*b*-2-cinnamoylmethylmethacrylate) have been applied as di- and triblock copolymers.^[31–34]

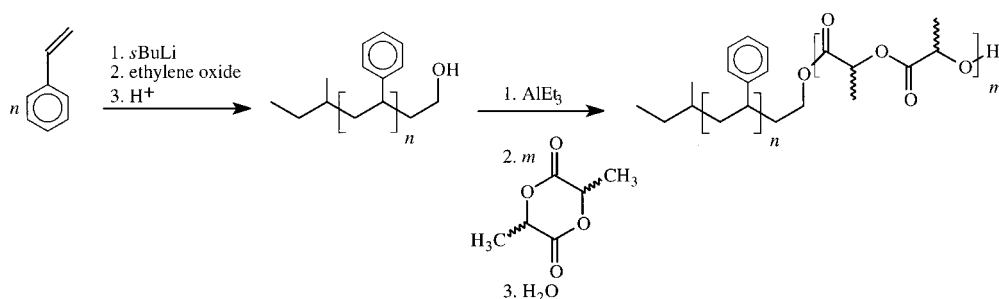
In this context, the ability to undergo phase separation represents a crucial requirement. During pore generation, generally, the larger polymer block undergoes cross-linking, while the smaller one is destroyed (thermally or chemically) and removed. Among other methods, the use of MeOH/OsO₄ has application, in particular with poly(butadiene)- and poly(isoprenes) respectively.^[35–37] This method may be applied

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to the synthesis of thin porous polymeric layers, yet is not applicable to the generation of a defined bulk porosity within thicker materials. These problems must be attributed mainly to the oxidation process which is hard to control within the interior of highly cross-linked material. Furthermore, a controlled and broad functionalization of the surface is generally difficult to achieve by this method.

A Breakthrough?

Recently, an interesting approach to the synthesis of mesoporous monoliths from poly(styrene-*b*-lactic acid) (P(S-*b*-LA)) precursors has been described.^[38] The synthesis of these block copolymers is based on an anionically initiated styrene polymerization. The living polymerization is terminated with ethylene oxide. Work-up of the hydroxy telechelic polystyrene (PS) and subsequent reaction with AlEt₃ allows the ring-opening polymerization (ROP) of lactic acid (Scheme 1).



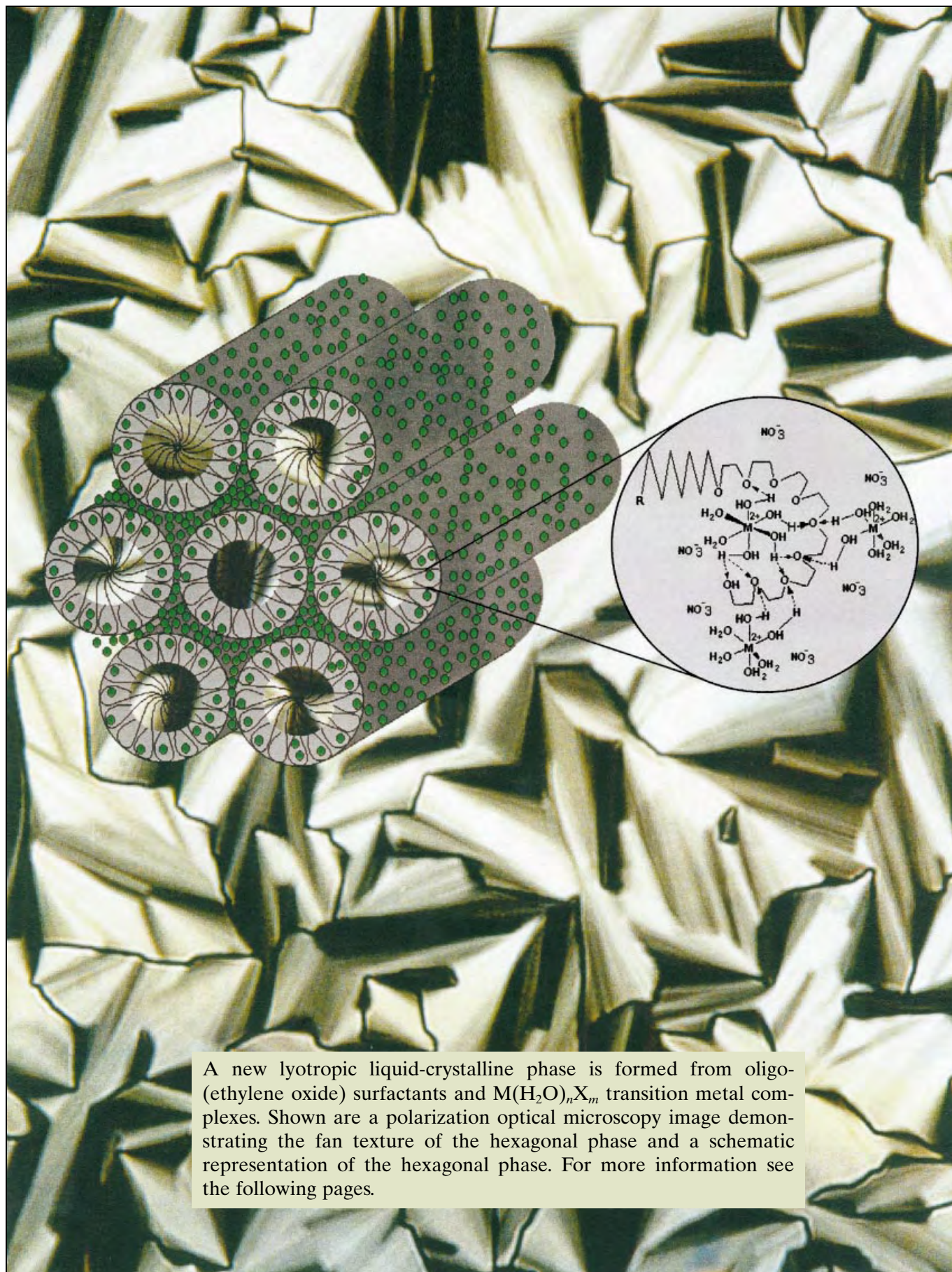
Scheme 1. Synthesis of P(S-*b*-LA).

The excellent control over block size in terms of average degree of polymerization and polydispersity are prerequisites for the subsequent use as a monolith building matrix. The polylactic acid (PLA) segments form cylindrical domains which are rearranged into an (almost) perfect parallel arrangement. Basic hydrolysis of the PLA units above the glass temperature (T_g) of the PLA segments, yet below the T_g of the PS segment ($T_{\text{hydrolysis}} = 65^\circ\text{C}$) results in the formation of a PS monolith with defined porosity. The careful choice of the degradation temperature avoids softening of the PS segments, which would result in matrix deformation. On the other hand, a sufficient softness of the PLA segments is achieved and provides sufficient flexibility of the PLA segments to facilitate hydrolysis.

Despite a few structural defects, the comparably mild conditions used for the pore-generating step as well as the high uniformity of the surface functional groups generated in course of this process (primary hydroxyl groups) make this approach highly attractive. These advantages justify the fact that the concept is a priori subject to the same restrictions as found in standard leaching procedures and that the pore size is predetermined to a large extent by the block size of the PLA segment. The efficient transversal penetration of the monolith by (colored) solvent such as methanol suggests a sufficient porosity. Nevertheless, in view of the mechanical and chemical instability of non-cross-linked polymer structures, *cross-linking* appears highly favorable to gain access to some of the

above-mentioned applications. Since the authors underline the advantages of the non-cross-linked matrix, which may be removed easily, applications of these materials can be expected mainly in the area of template synthesis.

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A new lyotropic liquid-crystalline phase is formed from oligo-(ethylene oxide) surfactants and $M(H_2O)_nX_m$ transition metal complexes. Shown are a polarization optical microscopy image demonstrating the fan texture of the hexagonal phase and a schematic representation of the hexagonal phase. For more information see the following pages.

A New Lyotropic Liquid Crystalline System: Oligo(ethylene oxide) Surfactants with $[M(H_2O)_n]X_m$ Transition Metal Complexes**

Özgür Çelik and Ömer Dag*

The realization of self-assembling liquid crystalline templating (SLCT) for the synthesis of *meso*-structured materials has attracted great attention from the materials community over the past decade.^[1–16] The SLCT approach has also made the materials community realize new approaches to the synthesis of materials in the form of powders,^[5] thin films,^[6] fibers,^[7] and even photonic band-gap materials.^[8] The lyotropic liquid crystalline (LLC) properties and the phase diagrams of many oligo(ethylene oxide)-type surfactants, which are the main focus of our work, have been established in water^[17] and in the presence of alkali metal salts which complex with the oxyethylene oxide chains.^[18] The non-ionic oligo(ethylene oxide) surfactants have also been used as templates for the synthesis of mesoporous materials.^[9–15] Attard et al^[9] first introduced the synthesis of the oriented monolithic mesoporous silica by using the LC phase-templating approach. Since its introduction, this approach has been applied to the synthesis of nanostructured and mesoporous CdS, CdSe,^[10] ZnS,^[10, 11] Pt mesh,^[12] and CaPO₄.^[13] The approach has also been applied to the introduction of LiCF₃SO₃ and AgNO₃ into mesoporous silica materials.^[14, 15] However, in all these procedures, the LC phase was first achieved by using the lyotropic property of the oligo(ethylene oxide) in water (typically, 50 % w/w water/surfactant mixture and with a low concentration of the additives, such as H₂[PtCl₆] (the phase diagrams have also been constructed),^[16] LiCF₃SO₃, AgNO₃, CdX_n (X = Cl[–], SO₄^{2–}, NO₃[–], and CH₃COO[–]), and Zn(NO₃)₂).^[10–16] In the majority of these studies it was established that the metal salt concentration must be low to maintain the LC phase during further processing of the mixtures.^[10–15]

Here we report that the assemblies formed between non-ionic oligo(ethylene oxides) surfactants C₁₂H₂₅-(CH₂CH₂O)₁₀OH (N^o) with transition metal aqua complex salts (such as [Co(H₂O)₆](NO₃)₂, [Ni(H₂O)₆](NO₃)₂, [Zn(H₂O)₆](NO₃)₂, and [Cd(H₂O)₄](NO₃)₂ (MX₂)) have LC behavior at various MX₂/N^o mole ratios. The transition metal aqua complexes, which induce the oligo(ethylene oxide) surfactants to undergo self-assembly into a LC phase, act as the second component of the LLC. The concentration range for various MX₂ salts, the isotropization temperatures (ITs), and the effect of the counterion on the IT in these mixtures were determined.

Various MX₂/N^o mixtures were prepared in order to study the behavior of the LC phase of non-ionic surfactants in the

presence of NO₃[–] salts of [Ni(H₂O)₆]²⁺, [Co(H₂O)₆]²⁺, [Zn(H₂O)₆]²⁺, and [Cd(H₂O)₄]²⁺ ions. The Cl[–] and SO₄^{2–} salts of these transition metal aqua complexes do not dissolve in this surfactant and therefore no LC phase could be observed. However, [Co(H₂O)₆]Cl₂, which is the only exception, behaves in a similar way to that of NO₃[–] salts. Interestingly, we found that [Co(H₂O)₆]Cl₂ undergoes exchange reactions to form the CoCl₄^{2–} ion in the [Co(H₂O)₆]Cl₂/N^o mixture. A color change from reddish pink to sharp blue, which is the typical color of the CoCl₄^{2–} ion, is observed upon mixing the [Co(H₂O)₆]Cl₂ complex with the non-ionic surfactant.^[19] The formation of the CoCl₄^{2–} ion has also been investigated by UV/Vis-Near IR spectroscopy and will be discussed elsewhere.

A typical polarized-light optical microscopy (POM) image between the crossed polars is shown in Figure 1a. The POM image, which is representative of the hexagonal LC phase of

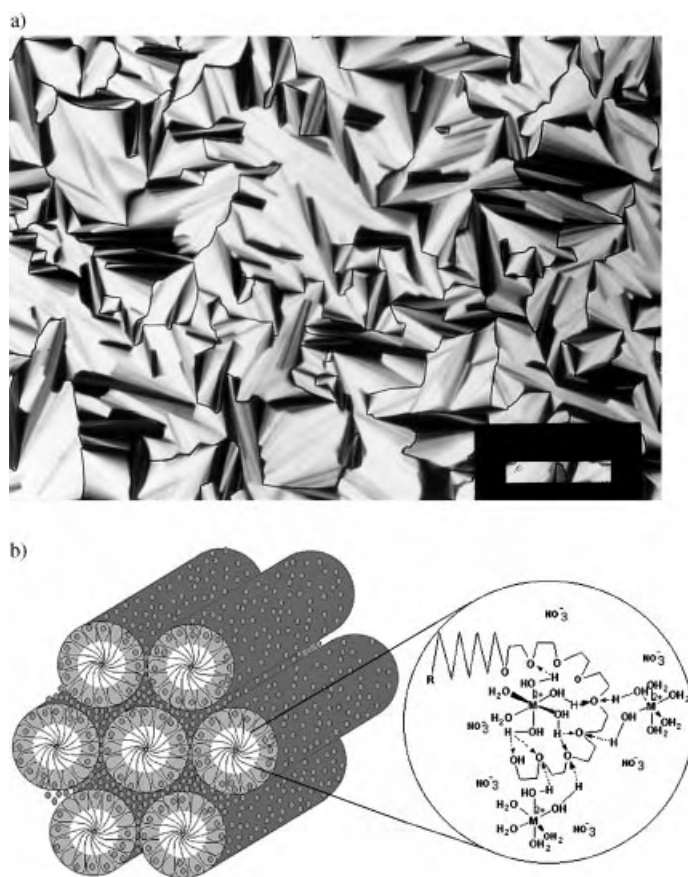


Figure 1. a) A representative POM image of [Cd(H₂O)₄](NO₃)₂ in C₁₂H₂₅(CH₂CH₂O)₁₀OH with a MX₂/N^o mole ratio of 2.0/1 (the scale bar is 200 μm). b) A schematic representation of a hexagonal LC MX₂/N^o structure, the small circles represent $[M(H_2O)_n]^{2+}$ and NO₃[–] ions.

oligo(ethylene oxide)-type surfactants, displays a fan texture within the MX₂/N^o mole ratio range 1.2/1–3.2/1 (which corresponds to 22.2–43.2 % w/w for [Co(H₂O)₆]Cl₂/N^o and 27.0–49.7 % w/w for [Cd(H₂O)₄](NO₃)₂/N^o) at RT. A schematic representation of the hexagonal structure is shown in Figure 1b. The thermal properties were studied and the IT values for a broad range of MX₂/N^o mole ratios were

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determined (Figure 2). Interestingly, the LC phase of the mixture becomes more stable upon increasing the $\text{MX}_2/\text{N}^\circ$ mole ratio (Figure 2). Above a critical mole ratio, the IT does not change much from sample to sample for Ni^{II} and Co^{II} complexes. The mixtures of these two complexes are liquid

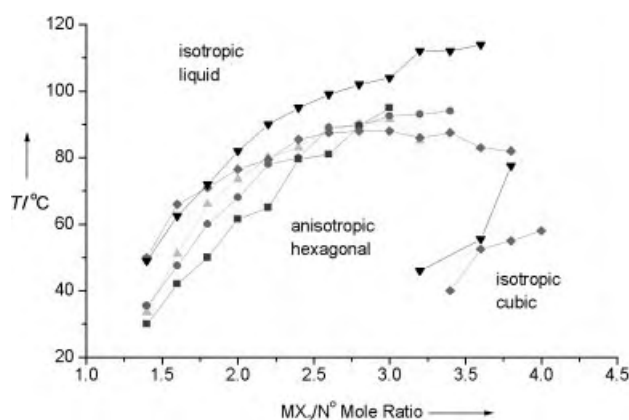


Figure 2. A plot of the isotropization temperatures of the mixtures of MX_2 and $\text{C}_{12}\text{H}_{25}(\text{CH}_2\text{CH}_2\text{O})_{10}\text{OH}$ versus the $\text{MX}_2/\text{N}^\circ$ mole ratios: ∇ $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2$, $\blacklozenge$ $[\text{Zn}(\text{H}_2\text{O})_6](\text{NO}_3)_2$, $\blacktriangle$ $[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2$, $\bullet$ $[\text{Co}(\text{H}_2\text{O})_6](\text{NO}_3)_2$, $\blacksquare$ $[\text{Co}(\text{H}_2\text{O})_6]\text{Cl}_2$ (mole ratio axis corresponds to 23.6–58.1% w/w for $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ and 19.1–51.7% w/w for $[\text{Co}(\text{H}_2\text{O})_6]\text{Cl}_2/\text{N}^\circ$).

crystalline and stable up to a $\text{MX}_2/\text{N}^\circ$ mole ratio of 3.5/1 (ca. 50.5% w/w), and have a fan texture when observed between cross polars. However, the samples with high mole ratios (2.5 and above) undergo slow recrystallization to yield the Ni^{II} and Co^{II} salts.

The $\text{MX}_2/\text{N}^\circ$ mixtures (where MX_2 is $[\text{Zn}(\text{H}_2\text{O})_6](\text{NO}_3)_2$ or $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2$) are even more stable: it is possible to increase the $\text{MX}_2/\text{N}^\circ$ mole ratio up to 5/1 and 6.5/1 (ca. 59.8 and 62.8% w/w), respectively. The POM images of the $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ systems above a 3.2/1 mole ratio do not show the hexagonal fan texture at room temperature (RT). Even at a 6.5/1 mole ratio, the $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ sample is still in a gel phase (highly viscous and transparent, with no fluidity), optically isotropic, and there is no recrystallization of the $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2$ salt in the mixture if the mixture is kept in a closed container. A sample with a $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ mole ratio of 3.2/1 (ca. 49.7% w/w) has two phases, the highly viscous (most likely cubic) phase (between RT and 42.5 °C) and the anisotropic phase (with a fan-shaped focal conic texture, which is representative of a columnar hexagonal phase, in the POM image obtained between 42.5 to 113 °C). The cubic to columnar hexagonal phase transition temperature increases with increasing $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ mole ratios, and reaches approximately 78 °C at a 3.8/1 mole ratio. The $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ samples decompose over 115 °C above this mole ratio (Figure 2). The samples at higher $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ mole ratios (above 3.2) display one diffraction line around 50 Å d spacing. However, this optically isotropic phase does not show any anisotropy upon shearing under POM and the samples are highly viscous; these properties are good indications for the existence of a cubic phase.^[20]

The $[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2$ and $[\text{Co}(\text{H}_2\text{O})_6](\text{NO}_3)_2$ samples with a $\text{MX}_2/\text{N}^\circ$ mole ratio above 3.0/1 undergo recrystallization and there is no sample of these two metal complexes with a cubic phase at RT. The POM images of samples at higher $\text{MX}_2/\text{N}^\circ$ mole ratios always show the characteristic fan texture and the MX_2 salt crystals. The $\text{MX}_2/\text{N}^\circ$ mole ratio of 3.0/1 (ca. 46.5% w/w) is most likely the saturation point. Above this ratio, crystallization of the MX_2 salt complexes ($[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2$ and $[\text{Co}(\text{H}_2\text{O})_6](\text{NO}_3)_2$) takes place. Even at a lower concentration, such as below a 3.0/1 mole ratio, the $[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2$ and $[\text{Co}(\text{H}_2\text{O})_6](\text{NO}_3)_2$ crystals have been observed after several months of the sample being rested in a closed container. However, heating the crystallized samples to their ITs recovers the LC phase without any MX_2 crystals.

A set of XRD patterns were recorded on both oriented and unoriented samples (Figure 3) to establish the existence of the *meso*-phase and the structure type. The XRD pattern of the mixtures usually displays the first three lines at around 48, 28,

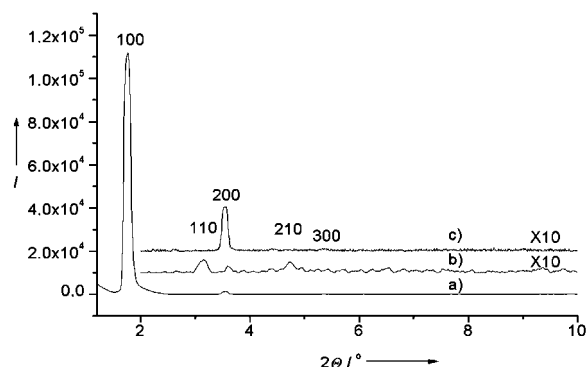


Figure 3. Typical XRD patterns of the oriented $[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2/\text{C}_{12}\text{H}_{15}(\text{CH}_2\text{CH}_2\text{O})_{10}\text{OH}$ sample with a $\text{MX}_2/\text{N}^\circ$ mole ratio of 1.8/1 (a and c) and an unoriented sample of the same composition (b).

and 24 Å d spacings, which correspond to the (100), (110), and (200) planes of a 2D-hexagonal phase (with a lattice parameter a of 55.4 Å). Some samples display up to five diffraction lines corresponding to (100), (110), (200), (210), and (300) planes of the 2D-hexagonal phase (Figure 3). The samples were run in a 0.5-mm deep glass powder X-ray diffraction (PXRD) sample holder by making 0.5-mm-thick films. Heating and cooling the samples several times between the IT and RT, respectively, enabled preparation of the film samples. However, the heating/cooling cycle makes the samples highly oriented. As a result, the (100), (200), and (300) diffraction lines are intense and in general the other lines are invisible. The samples packed without heating/cooling cycles (unoriented samples) display a strong (100) line with relatively weak (110), (200), and (210) lines, but the intensity of the (100) line of the unoriented samples is much weaker than that of the oriented samples. Ozin and co-workers as well as Miyata and Kuroda also observed a similar behavior in their oriented mesoporous silica film samples.^[21] They observed that while the film samples (oriented) display (100) and (200) diffraction lines, their crushed (powdered) samples show the (100), (110), and (200) diffraction lines corresponding to the hexagonal symmetry.^[21]

The Vis/Near-IR absorption spectra of a series of $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ and $[\text{Co}(\text{H}_2\text{O})_6]^{2+}$ complex ions proves that there is no ligand substitution reaction taking place between the surfactant molecules and the aqua complexes. The spectra were recorded in the 400–1400 nm region for $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ and $[\text{Co}(\text{H}_2\text{O})_6]^{2+}$ at various concentrations in the LC phase and in pure water. The characteristic d–d transitions of these two complexes show no changes in the Vis/Near-IR region other than an increasing intensity with increasing metal aqua complex concentration. This observation indicates that there is no chemical interaction between the surfactant ethylene oxide (EO) groups and the metal center of the aqua complexes (that is, water molecules stay in the coordination sphere).

FT-IR spectroscopy has been used extensively to elucidate the local structural changes in LC mixtures with increasing $\text{MX}_2/\text{N}^\circ$ mole ratios. The general trend is that the FT-IR spectra of $[\text{M}(\text{H}_2\text{O})_n]\text{X}_m$ in surfactants display drastic changes around 1200–1500 cm^{-1} and 900–1100 cm^{-1} , the ν -CO stretching region (Figure 4). The peaks at around 1000–1100 cm^{-1} , which corresponds to the C–O stretching region

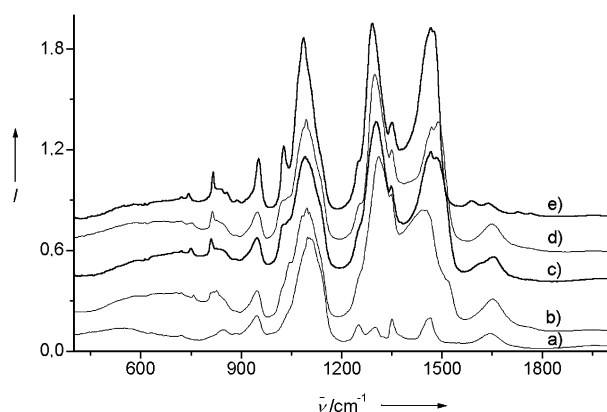


Figure 4. FT-IR spectra in the 500–2000 cm^{-1} region of the samples with a $\text{MX}_2/\text{N}^\circ$ mole ratio of 2.00/1 and free surfactant: a) free surfactant, b) $[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2$, c) $[\text{Co}(\text{H}_2\text{O})_6](\text{NO}_3)_2$, d) $[\text{Zn}(\text{H}_2\text{O})_6](\text{NO}_3)_2$, and e) $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2$.

of the surfactant, show a shift to a lower energy upon the formation of hydrogen bonds between the EO units of the non-ionic surfactant and the metal aqua complexes. Another reason for the shift to lower energy is likely a result of the symmetric stretching of the NO_3^- counterion^[22] which also absorbs in this region of the spectrum. The doubly degenerate NO_3^- asymmetric stretching, which splits into two peaks at around 1300 cm^{-1} and 1460 cm^{-1} , displays visible changes from complex to complex. These two peaks show variation in their frequencies from metal to metal and are most likely a result of the NO_3^- ion interacting with the surfactant and metal aqua complexes. Note that the FT-IR spectra of the $[\text{M}(\text{H}_2\text{O})_n](\text{NO}_3)_2$ salts display a characteristic single peak at around 1385 cm^{-1} , and the free nitrate ion displays a very broad peak at around 1400 cm^{-1} . It is clear from our observations that upon introducing these salts into the surfactant both the dissociated NO_3^- (free nitrate ion) and associated NO_3^- ions (ion-pair) coexist with the metal aqua complex. The peak at around 945 cm^{-1} and the broad feature

at around 930 cm^{-1} are characteristic of the *gauche* and *trans* forms, respectively, of the ethylene oxide (EO) units of the surfactant.^[23] [18]crown-6 is one of the molecules in which all of the EO groups are in a *gauche* form and which displays a very sharp peak^[24] at 945 cm^{-1} . However, disordered poly-(ethylene oxide)- and oligo(ethylene oxide)-type surfactants mostly display the peak corresponding to the *trans* form.^[23] The *gauche* form, we believe, is the major structural type, which organizes the surfactant molecules into the hexagonal and/or cubic LC phases. The characteristic peak at 945 cm^{-1} , which is attributed to the *gauche* form of the EO units, is more intense for the Cd(II) system (Figure 4). This result is also consistent with the observed thermal properties that show the $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2/\text{N}^\circ$ systems to be thermally more stable than the Co, Ni, and Zn systems.

In conclusion, we have shown that oligo(ethylene oxide)-type surfactants show LC behavior in the presence of $[\text{M}(\text{H}_2\text{O})_n](\text{NO}_3)_m$ -type transition metal aqua complexes which function as the second component of the LLC phase. Here, the coordinated water molecules of the transition metal aqua complexes induce the aggregation and self-assembly of the surfactant molecules into hexagonal and/or cubic structures and allow the transition metal ions to be distributed into these structures uniformly in the form of free ions and ion pairs with the NO_3^- counterion.

Experimental Section

The samples were prepared by mixing the surfactant and the salts of metal complexes in a solid phase. 10-lauryl ether (1 g, ca. 1.6×10^{-3} mol) was mixed with the metal salts in the $\text{MX}_2/\text{N}^\circ$ mole ratios of 0.1/1–7.0/1. The mixtures were homogenized by heating over their IT and cooling with constant shaking. These heating and cooling cycles were repeated several times to achieve homogeneity. Finally, the samples were kept under their ITs for several to 24 h. This is a crucial step to ensure that the metal ions are homogeneously distributed; otherwise one may obtain different isotropization temperatures for different measurements on the same sample. However, over-heating, especially in the case of $[\text{Cd}(\text{H}_2\text{O})_4](\text{NO}_3)_2$ samples, may destroy the desired LC phase. The new phases, obtained upon homogenizing, are transparent and have the color of the complex ion. They display optical-fan textures between the cross polars under POM.

The POM images were recorded in transmittance mode on a stereo microscope Stemi 2000 from Carl Zeiss Jena GmbH and on a Meije Techno ML9400 series polarizing microscope with transmitted light illumination, by using convergent white light between parallel and crossed polarizers. The thermal properties of the mixtures were studied using a Leica Microscope Heating Stage 350 attached to the above microscope. The X-ray diffraction (XRD) patterns were obtained on a Rigaku Miniflex diffractometer using a high-power $\text{Cu}_{\text{K}\alpha}$ source operating at 30 kV/15 mA. FT-IR spectra were recorded from thin films deposited between two Si(100) wafers on a BOMEM 102 FT-IR spectrometer in transmittance mode. UV/Vis absorption spectra were recorded from film samples prepared on quartz windows by using a Varian Cary 5 double-beam spectrophotometer.

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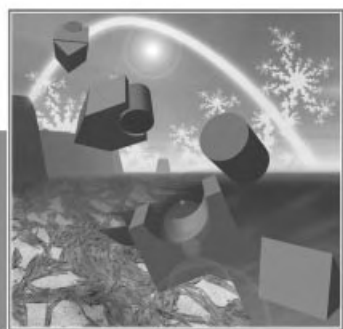
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Photoluminescent Silicate Microsticks Containing Aligned Nanodomains of Conjugated Polymers by Sol–Gel-Based In Situ Polymerization**

Takuzo Aida* and Keisuke Tajima

Polymeric materials with unidirectionally aligned nanodomains of conjugated polymers are expected to have potential for novel electroconductive and optoelectronic devices.^[1] In this respect, template-assisted polymerizations in organized media have attracted much attention.^[2, 3] An attractive approach is to utilize mesoporous inorganic materials with ordered hexagonal arrays of uniformly sized nanoscale channels.^[4] Bein et al. reported the synthesis of a graphite-type conducting carbon nanowire by free-radical polymerization of acrylonitrile within the silicate channels of MCM-41, followed by pyrolysis of the resulting polymer.^[5] More recently, Cardin et al. reported Ni^{II}-catalyzed polymerization of alkynes inside the silicate channels of MCM-41 to give polyyne/silica hybrid composites.^[6] On the other hand, Tolbert et al. reported the synthesis of photoluminescent polymer/silica hybrids by loading poly(phenylene vinylene) derivatives into pre-formed mesoporous silicate channels.^[7] However, because of adsorption, such post-loading approaches may not always guarantee complete filling of the nanoscopic channels with functional guests. Hence, new strategies are required for the synthesis of well-defined composite materials from conjugated polymers and nanostructured silicates.

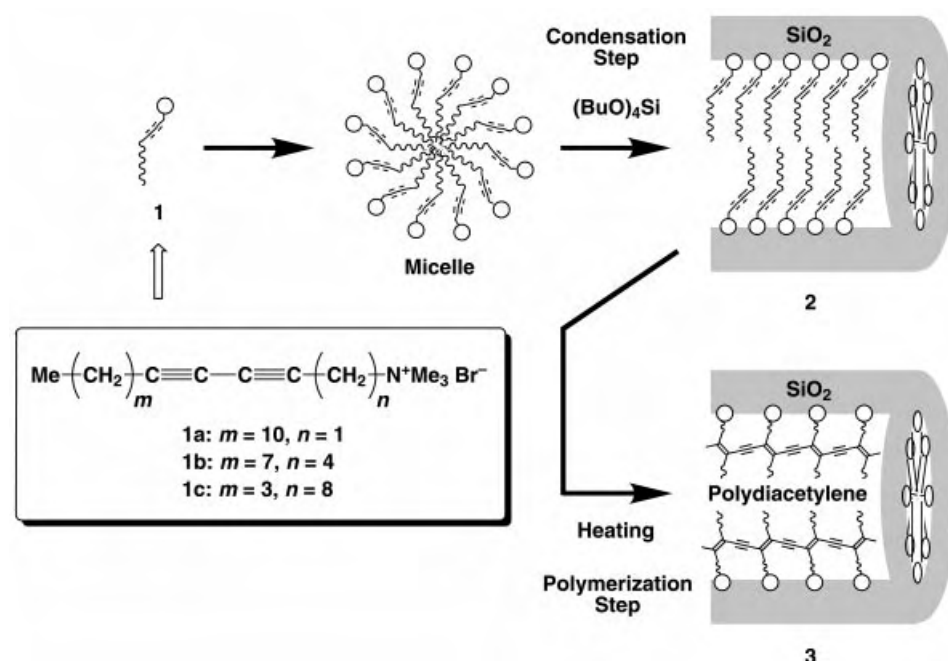
We have reported some unique approaches toward controlled macromolecular synthesis using mesoporous silicate materials.^[8–10] Here we report on the fabrication of novel micrometer-scale photoluminescent silicate sticks with segregated nanodomains of conjugated polymers by sol–gel-based in situ polymerization of diacetylenic surfactant monomers **1**, which were then used as templates for the formation of mesostructured silicates (Scheme 1). This method is expected to allow complete filling of the silicate channels with ordered diacetylenic monomers **2**. Such a dense packing of the monomer is essential for the polymerization of **1** within the silicate channel, since diacetylene derivatives can only be polymerized topochemically in condensed crystalline and semi-crystalline phases.^[11]

The template surfactant monomers 2,4-, 5,7-, and 9,11-hexadecadiynyltrimethylammonium bromides **1a–1c** were synthesized by a Cadiot–Chodkiewicz coupling reaction of

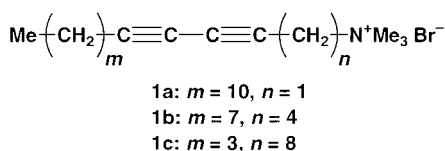
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Scheme 1.



the corresponding 1-bromo-1-alkynes with alkynic alcohols, followed by subsequent transformation of the terminal hydroxy groups of the products into ammonium salts. Mesostructured silicates **2a** and **2b** were synthesized by a method reported by Stucky et al. for the preparation of mesoporous silica fiber.^[12] Typically, **1** (0.5 g) and tetrabutyl orthosilicate (0.98 g) were successively added to aqueous hydrochloric acid (6 wt %) with stirring, and the resulting phase-separated system was allowed to stand for 5 d at 20 °C. When **1a** and **1b** were used as templates, white fibrous precipitates were formed, which were collected by filtration and dried in vacuo. In contrast, when **1c** was used which has eight methylene units between the diacetylenic moiety and the ammonium ion, no precipitation resulted.

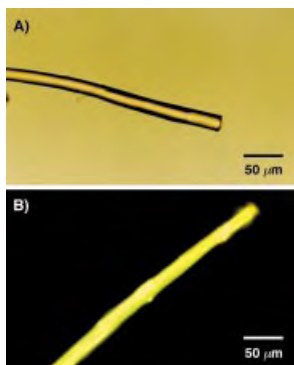


Figure 1. A) Optical micrograph of **2a** and B) fluorescence micrograph of **3a**.

Optical microscopy showed that precipitates **2a** (Figure 1 A) and **2b** both have a sticklike morphology with a diameter of approximately 15–25 μm.^[12] The IR spectrum of **2a** showed a stretching band due to C≡C at 2260 cm⁻¹, and the electronic absorption spectrum showed a band at 260 nm and essentially no absorption bands in the visible region (Figure 2A). These spectral profiles indi-

cate that the fibrous silica contains template surfactant monomer **1a**. X-ray diffraction (XRD) on **2a** showed a peak with a d spacing of 37.7 Å, which is characteristic of a (100) diffraction originating from the hexagonal structure of the silicate.^[12, 13] Fibrous silicate **2b**, prepared from surfactant monomer **1b**, showed a smaller d spacing of 34.9 Å (Figure 3). Compared with the d spacing of 39.9 Å for a fibrous mesostructured silica prepared with a saturated template such as hexadecyltrimethylammonium bromide,^[12] these d spacings are clearly smaller and suggest a tilted orientation of the diacetylenic moiety of the monomer in the nanoscale silicate channel (Scheme 1). Thermogravimetric analysis (TGA) of **2b** showed a content of surfactant monomer of 41 wt %, which is as high as those reported for conventional mesoporous silicates con-

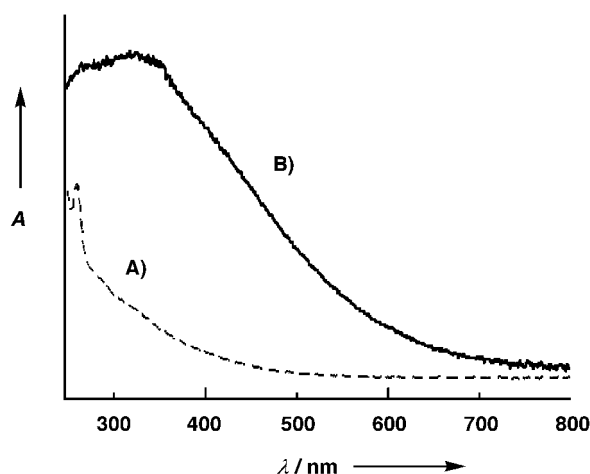


Figure 2. Electronic absorption spectra of A) **2a** and B) **3a**.

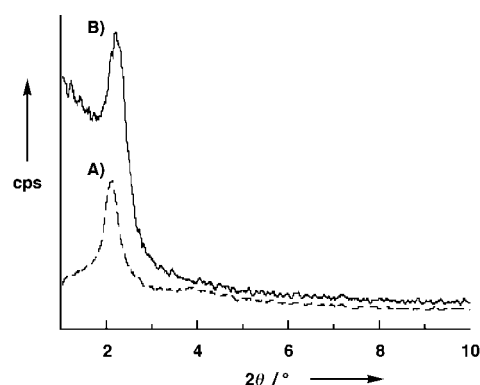


Figure 3. X-ray diffraction (XRD) patterns of A) **2b** and B) **3b**.

taining template surfactants.^[4a, 6] Therefore, the silicate channels of **2b** are likely filled with densely packed **1b**.

Exposure of **2a** and **2b** to UV light ($\lambda_{\text{max}} = 254 \text{ nm}$) from a high-pressure mercury lamp for 2 h did not result in any color change associated with the polymerization of the included monomers. In contrast, upon heating at 170°C for 2 h under N_2 ,^[14] **2a** and **2b** both showed a marked color change from white to orange. Infrared spectroscopy on the colored material formed from **2a**, for example, showed a complete disappearance of the $\text{C}\equiv\text{C}$ vibrational band at 2260 cm^{-1} , which indicates that included monomer **1a** has polymerized to form an IR-silent $-\text{C}=\text{C}-\text{C}\equiv\text{C}-\text{C}=\text{C}-$ sequence (**3a**). Electronic absorption spectroscopy on **3a** in the solid state showed a broad band centered at 350 nm with an upper threshold around 650 nm (Figure 2B), assignable to a $\pi-\pi^*$ electronic transition of the conjugated polymer backbone. Differential scanning calorimetry (DSC) on **2b** showed a broad exothermic peak at $150-280^\circ\text{C}$, originating from the polymerization of included **1b**, while no exothermic peak was observed for a mesoporous silica reference prepared with hexadecyltrimethylammonium bromide as a nonpolymerizable template.^[13] Colored material **3b** was found to retain essentially the same XRD characteristics as those of **2b**, although the diffraction peaks were slightly less intense (Figure 3). Transmission electron microscopy (TEM) on **3b** indicated that the honeycomb array of the hexagonal silicate channels is maintained during the thermally induced polymerization of included **1b**.^[13] Fluorescence microscopy on **3a** and **3b** (Figure 1B) showed that the entire silicate sticks emit a yellowish green fluorescence. The emission spectrum of **3a** showed a broad fluorescence band centered at 550 nm , while the excitation spectrum, monitored at 550 nm , displayed a band centered at 450 nm ,^[13] which corresponds to the long-wavelength part of the absorption band of **3a** (Figure 2). Absorption and emission profiles of polydiacetylene derivatives are known to be influenced by the effective conjugation length along the polymer chain.^[15-17] In general, polymerization of diacetylenes in highly ordered, crystalline states gives nonemissive, blue polymeric materials having a long conjugation length. At lower degrees of molecular ordering, red, photoluminescent materials with a relatively short conjugation length are usually formed.

Interestingly, when the conjugated polymer was isolated from **3b**, by destroying the silicate framework with HF, and cast on a quartz plate, the emission spectrum showed two fluorescence maxima at 470 and 510 nm (Figure 4B), which are considerably blue-shifted from that of **3b** at 550 nm (Figure 4A). Similarly, the excitation spectrum of the cast film, monitored at 510 nm , also showed a peak (400 nm) with a notable blue shift relative to that of **3b** (470 nm). For comparison, when microcrystalline **1b** was thermally polymerized, the resulting polymeric material, cast on a quartz plate, showed quite similar emission (Figure 4C) and excitation spectral profiles to those of the cast film of the polymer extracted from **3b** (Figure 4B). Since these two polymers showed almost identical emission profiles in CHCl_3 ($\lambda_{\text{em}} = 470$ and 500 nm), the red-shifted spectral profiles of **3b** indicate a possible effect of confinement in the nanoscale silicate channel on the effective conjugation length of the polymer

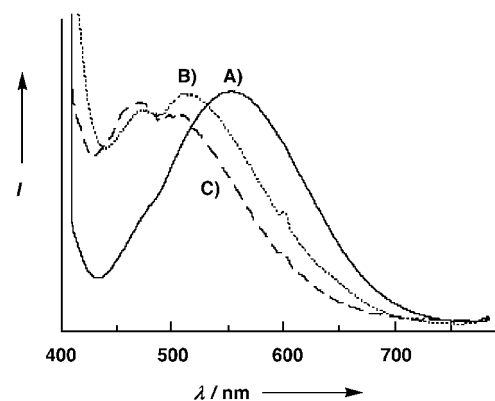


Figure 4. Fluorescence spectra upon excitation at 400 nm of A) **3b**, B) a cast film of the polymer extracted from **3b**, and C) a cast film of a polymer obtained by thermally induced polymerization of **1b**.

chain. To investigate whether the polymer extracted from **3b** can be reloaded into the nanoscale silicate channels, calcined mesoporous silica fibers^[12] were dispersed in a solution of the extracted polymer in CHCl_3 , and the resulting suspension was subjected to several freeze–pump–thaw cycles and allowed to stand overnight. Filtration of the suspension left a yellow powder, whose emission profile did not reproduce that of **3b** but was quite similar to that of the cast film of the extracted polymer. Therefore, **3b** can not be prepared by post-loading.

In conclusion, template-assisted in situ polymerization gave the first micrometer-scale photoluminescent silicate sticks with nanodomains of conjugated polymers segregated by ordered silicate channels. These silicate microsticks with a diameter of $15-25 \mu\text{m}$ are easily manipulated under the optical microscope to give a particular alignment for investigating optical and electronic properties. The present sol–gel-based approach could possibly be useful for the development of nanostructured optoelectronic and electroconductive materials.^[18]

Experimental Section

Propargyl alcohol (0.84 g, 15.0 mmol) was added at room temperature to a mixture of CuCl (90 mg), MeOH (6 mL), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.6 g), water (2.1 mL), and a 70 wt % aqueous solution of EtNH_2 (4.8 mL) under N_2 to give a yellow suspension. 1-Bromotridecyne (3.0 g, 11.6 mmol) was then added dropwise at 35°C , and the mixture was heated at 40°C for 1 h. The reaction mixture was extracted three times with diethyl ether, and the combined extract was dried over MgSO_4 and subjected to column chromatography with hexane/ethyl acetate (10/1) as eluent. The second fraction was collected and the solvent evaporated to give 2,4-hexadecadiynol in 68 % yield. 2,4-Hexadecadiynol (0.6 g, 2.6 mmol) was treated with CBr_4 (1.1 g, 3.3 mmol) in the presence of Ph_3P (1 g, 3.8 mmol) in CH_2Cl_2 (20 mL) at 0°C for 5 min, and the reaction mixture was subjected to chromatography on silica gel with hexane as eluent. The second fraction was collected and the solvent evaporated to give 1-bromo-2,4-hexadecadiyne in 92 % yield. 1-Bromo-2,4-hexadecadiyne (0.25 g, 0.83 mmol) was then treated with an excess of Me_3N (28 % aqueous solution, 5 mL) at room temperature overnight, and the reaction mixture was evaporated to dryness and freeze-dried to give **1a** in quantitative yield. $^1\text{H NMR}$ (270 Hz, CDCl_3): $\delta = 0.90$ (t, 3H, CH_3), 1.28 (16H, CH_2), 1.57 (2H, CH_2), 2.30 (t, 2H, CH_2), 3.56 (s, 9H, NCH_3), 4.94 (s, 2H, CH_2); FAB-MS: m/z : 277 [$M^+ - \text{Br}$] (calcd: 276), 633 [$2M^+ - \text{Br}$] (calcd: 633). Surfactant monomers **1b** and **1c** were obtained in comparable yields in a manner similar to that for the preparation of **1a**. **1b**: $^1\text{H NMR}$ (CDCl_3): $\delta = 0.90$ (t, 3H, CH_3), 1.27 (10H, CH_2), 1.52 (2H, CH_2), 1.65 (2H, CH_2), 1.96 (2H, CH_2), 2.26 (t, 2H,

CH₂), 2.42 (t, 2H, CH₂), 3.48 (s, 9H, NCH₃), 3.72 (2H, NCH₂); FAB-MS: 276 ([M – Br]⁺ calcd 276). **1c**: ¹H NMR (CDCl₃): δ = 0.90 (t, 3H, CH₃), 1.37 (14H, CH₂), 1.77 (2H, CH₂), 2.26 (4H, CH₂), 3.48 (s, 9H, NCH₃), 3.60 (2H, NCH₂); FAB-MS: 276 [M⁺ – Br] (calcd 276), 634 [2M⁺ – Br] (calcd 633).

Thermally induced polymerization of **1b**, **2a**, and **2b** was carried out by heating a N₂-purged glass tube containing a powder sample in a Kugelrohr apparatus at 170 °C for 2 h. For extraction of the included polymer from **3b**, the composite powder was suspended in aqueous hydrofluoric acid (55 wt %) at room temperature for 1 h, and N₂ was bubbled into the resulting clear solution to flush out volatile fractions.

Absorption and fluorescence spectra were recorded in reflection mode on JASCO U-best V-560 and FL-777W spectrophotometers, respectively, with attachments for powder samples. Infrared spectra of KBr pellet samples were recorded on a JASCO FTIR-610 spectrophotometer. X-ray diffraction patterns were recorded on a Rigaku RINT 2400 diffractometer with CuK_α radiation (20 kV, 50 mA) and a step size of 0.004° at a scan speed of 1° min^{–1}. Optical and fluorescence micrographs were taken by an Olympus VANOX AH2-FL microscope, and excitation (395–415 nm) and emission filters (>455 nm) were used for fluorescence microscopy. Thermogravimetric analysis (TGA) was carried out on a Shimadzu TGA-50 at a heating rate of 10 °C min^{–1}. Transmission electron microscopy (TEM) was performed on a Hitachi H-9000UHR electron microscope operated at 300 kV.

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Design and Evolution of a Miniature Bcl-2 Binding Protein**

Jason W. Chin and Alanna Schepartz*

The design of molecules that bind protein surfaces with nanomolar affinity and high specificity presents a major challenge for chemical biologists.^[1] Molecules that possess these properties have potential as therapeutic leads for protein targets^[2] and new tools for proteome research.^[3] We have described a general strategy for the design of miniature α -helical proteins^[4] that bind DNA with high affinity and selectivity.^[5] This protein grafting strategy involves identifying the α -helical residues used for DNA recognition by a natural DNA-binding protein and substituting them on the small, stable protein scaffold avian pancreatic polypeptide (aPP).^[6] Grafting of the DNA contact residues of the bZIP protein GCN4^[7] followed by functional selection generated a folded miniature protein that bound DNA with exceptional affinity and specificity.^[8] Here we demonstrate the versatility of protein grafting for the design of selective miniature protein-binding proteins (Figure 1) and report highly potent and specific ligands for human Bcl-2 and Bcl-X_L.^[9]

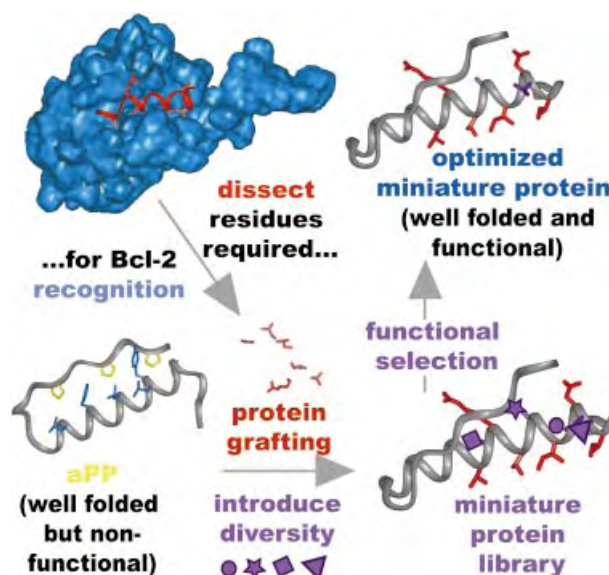


Figure 1. Protein grafting and evolution of high affinity miniature protein ligands for Bcl-2 and Bcl-X_L.

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Bcl-2 and Bcl-X_L are central antagonists of programmed cell death (apoptosis).^[10] Bak,^[11] and other members of the Bcl-2 protein family, are death agonists. The pro-apoptotic activity of Bak can be localized to a 16-residue sequence known as a BH3 domain (Bcl-2 homology domain 3).^[12] The BH3 domain of Bak binds Bcl-2^[13] and Bcl-X_L,^[14] and these interactions can induce apoptosis in both cell-free *Xenopus* extracts^[15] and HeLa cells.^[12] High Bcl-2 levels are found in 80% of B-cell lymphomas as well as certain other cancers,^[16] and can protect malignant cells from apoptosis induced by gamma irradiation and clinically used anticancer drugs.^[17] Inhibition of the anti-apoptotic function of Bcl-2 in tumors is an attractive strategy for restoring apoptosis in cancer cells and increasing their susceptibility to chemo- or radiotherapy.^[18]

Our design of a miniature protein that binds Bcl-2 and Bcl-X_L began with the structure of the Bak_{72–87}·Bcl-X_L complex.^[14] This structure shows Bak_{72–87} bound as a three-turn α -helix to an irregularly shaped hydrophobic cleft on Bcl-X_L. Several observations suggest that the complexes of Bak_{72–87} with Bcl-X_L and Bcl-2 are structurally homologous. First, the backbones of free Bcl-2 and Bcl-X_L superimpose with a root mean square deviation (RMSD) of 1.91 Å.^[13] Second, nine of ten residues within Bcl-X_L that contact Bak are also found in Bcl-2. The lone exception is L112 in Bcl-X_L, which is mutated conservatively to M115 in Bcl-2. Two other differences are notable in the primary sequence that forms the hydrophobic groove of Bcl-2. A108 of Bcl-X_L is mutated to D111 in Bcl-2 and S126 of Bcl-X_L is mutated to R129 in Bcl-2. These mutations alter the charge distribution in the binding pocket on Bcl-2 with respect to the binding pocket on Bcl-X_L.^[13] Finally, Bak binds both Bcl-2 and Bcl-X_L, although with somewhat different affinities.^[13]

We considered all possible alignments of the primary sequences of Bak_{72–87} and the aPP α -helix and assessed their relative merits in three ways. First, each alignment was scored for conflicts, positions where a residue important for maintaining aPP structure was aligned with a residue important for binding Bcl-X_L. Alignments with multiple conflicts were

disfavored as we believed they would produce miniature proteins that were either well folded or had high affinity for Bcl-X_L, but not *both* these properties. Second, each alignment was scored on the basis of unfavorable steric clashes in a model of each miniature protein·Bcl-X_L complex created by using INSIGHT II (Figure 2). Alignments were ranked on the basis of overlap between the van der Waals surfaces of Bcl-X_L and the miniature protein. Finally, we considered the backbone RMSD of each alignment.

Our scoring procedure favored alignment III, in which residues 21–34 of aPP aligned with residues 74–87 of Bak (Figure 2) and a library of 1×10^5 miniature proteins (20^4) was designed (Figure 3a).^[19] All library members contained six

a)

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Bak (72–87) .....GQVGRQLAIIIGDDINR
aPP      GFSQITYPGDDAPVEDLIRFYNDLQQYLNVTTRHY
PPBH3LIB GFSQITYPGDDAPVEDLIRFVXRLLXYTLKDKINR
  
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b)

	#	K_d (nM)
Bak (72–87) GQVGRQLAIIIGDDINR	–	4933 ± 450
20 25 30 34		
PPBH3-2.....FVGRLLRYFGDEINR	6	80 ± 12
PPBH3-3.....FVGRLLAYFGDDINR	2	120 ± 20
PPBH3-1.....FVGRLLAYFGDTINR	3	52 ± 5
PPBH3-4.....FVSRL-RYIADLINR	2	N.D.
.....FVRRLLGYIIDIINR	1	
.....FVLRLLMYITPDGINR	1	
.....FVRRLLVYITWDDINR	1	

Figure 3. a) Alignment of Bak_{72–87}, aPP and the miniature protein library. Color coding is described in the legend for Figure 2. Positions varied in PPBH3LIB are in purple. b) Selected miniature proteins. The number of times (#) each sequence was represented among 16 clones is shown. PPBH3-1–4 were synthesized to carry a C-terminal cysteine and labeled with acetamidofluorescein^[22] to facilitate fluorescence polarization analysis. The K_d shown^[24] represents the stability of each PPBH3-Flu·Bcl-2 complex ± the standard error of at least three trials. PPBH3-4 underwent a time-dependent polarization change in the absence of Bcl-2 and its affinity for Bcl-2 could not be measured (no other peptide tested exhibited this property).

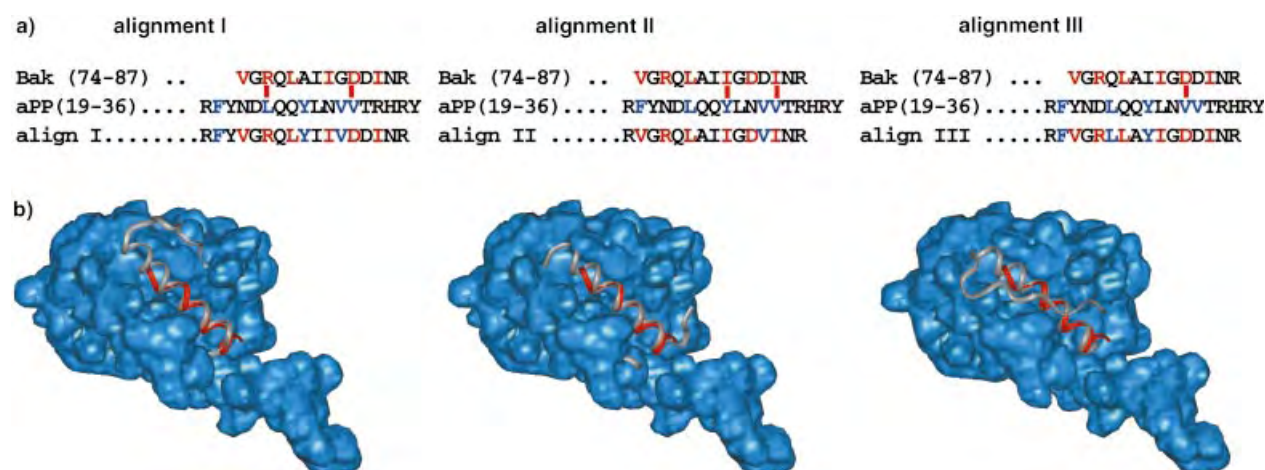


Figure 2. Alignment of aPP and Bak used to guide protein design. a) The three highest scoring alignments of aPP with residues 72–87 of Bak (Bak_{72–87}). Residues in red contribute to Bcl-X_L binding by Bak; residues in blue contribute to folding of aPP. Conflicts between the two are indicated with a red bar. b) Models of miniature proteins resulting from each alignment (gray) superimposed on the Bak_{72–87} backbone (red) when in complex with Bcl-X_L (blue). The conflict in alignment III (between D83 of Bak and V30 of aPP) was expected to be insignificant as residues 30 and 31 are used interchangeably by PP-fold proteins for hydrophobic core formation.^[6, 19]

Bak₇₂₋₈₇ residues (V74, R76, L78, I81, D83, and I85) that contribute significantly to Bcl-X_L affinity^[14] and four aPP residues (V14, F20, L24, Y27) that comprise the aPP hydrophobic core.^[6] The four remaining residues between V21 and I34 were varied across all 20 amino acids. The library of M13 phage produced was sufficient to examine greater than 97 % of all potential DNA sequences.^[20]

Phage were sorted for five rounds on the basis of their affinity for GST-Bcl-2. Seven distinct sequences were represented in the sixteen clones sequenced after round 5 (Figure 3b). Analysis of the four sequences represented multiple times indicated a strong preference for amino acids similar to those in Bak and other BH3 domains at all four randomized positions.^[21] Surprisingly, PPBH3-1, PPBH3-2 and PPBH3-3 each contained phenylalanine at position 28, although this position was not randomized and was encoded as isoleucine. We believe this mutation is functionally significant for two reasons. First, isoleucine was present at position 28 in all 10 independent clones sequenced from the library prior to selection and in all 15 independent clones sequenced after two selection rounds. Second, a clone containing isoleucine at position 28 in addition to G₂₂, A₂₆, G₂₉, and E₃₁ was identified in round 2. This clone differs from Bak₇₂₋₈₇ at only one selected position, but was out-competed in later rounds by sequences containing F₂₈.

The four sequences represented multiple times in round 5, as well as Bak₇₂₋₈₇, were labeled with iodoacetamidofluorescein^[22] and their affinities for Bcl-2 determined by fluorescence polarization analysis.^[23, 24] Under the conditions of our assay the Bak₇₂₋₈₇·Bcl-2 complex was characterized by an equilibrium dissociation constant (K_d) of $4.9 \pm 0.5 \mu\text{M}$. Miniature proteins PPBH3-2 and PPBH3-3 bound Bcl-2 with 40- and 60-fold higher affinity than Bak₇₂₋₈₇, respectively (Figure 3b). PPBH3-1, however, bound Bcl-2 with 100-fold higher affinity to form a complex with a K_d of $52 \pm 5 \text{ nM}$. Comparison of the Bcl-2 affinities of Bak₇₂₋₈₇ and PPBH3-1 suggests that the polyproline helix in PPBH3-1 contributes as much as $\Delta\Delta G = 2.5 \text{ kcal mol}^{-1}$ to PPBH3-1·Bcl-2 complex stability (Figure 3b).

Circular dichroism (CD) spectroscopy was used to examine the secondary structures of PPBH3-1 and Bak₇₂₋₈₇ and explore the structural basis for the enhanced affinity of PPBH3-1 for Bcl-2. The CD spectrum of free PPBH3-1 at 4 °C was concentration independent between 1 and 7 μM and exhibited minima at 208 and 222 nm, as expected for a protein containing one or more α -helices. The mean residue ellipticity (Θ_{mre}) at 222 nm of $-20000 \text{ deg cm}^2 \text{ dmol}^{-1}$ suggested that approximately 60 % of PPBH3-1 possessed an α -helical conformation.^[25] The stability of the fold was examined by monitoring the temperature-dependence of Θ_{mre} at 222 nm. PPBH3-1 underwent a cooperative melting transition with a T_m of 65 °C. These data suggest that PPBH3-1 adopts a stable, well-folded, monomeric, aPP-like structure containing an extended, contiguous α -helix. By contrast, the CD spectrum of Bak₇₂₋₈₇ showed little α -helix ($\Theta_{\text{mre}} = -2000 \text{ deg cm}^2 \text{ dmol}^{-1}$). We conclude that the increased affinity of PPBH3-1 for Bcl-2 relative to Bak₇₂₋₈₇ ($\Delta\Delta G = 2.5 \text{ kcal mol}^{-1}$) reflects preorganization of the otherwise unstructured Bak₇₂₋₈₇ functional epitope.

One advantage of molecules that bind proteins in the nanomolar concentration range may be their ability to discriminate effectively among numerous protein surfaces in a biological milieu. To evaluate the specificity of the interaction between PPBH3-1 and Bcl-2, we monitored the affinity of PPBH3-1 for several proteins that themselves bind hydrophobic peptides or small molecules. PPBH3-1 bound calmodulin, a protein notorious for its ability to bind many α -helical peptides and proteins,^[26] with $K_d > 100 \mu\text{M}$, and bound carbonic anhydrase II^[27] and protein kinase A^[28] with K_d values between 30 and 40 μM (Figure 4b). The large differ-

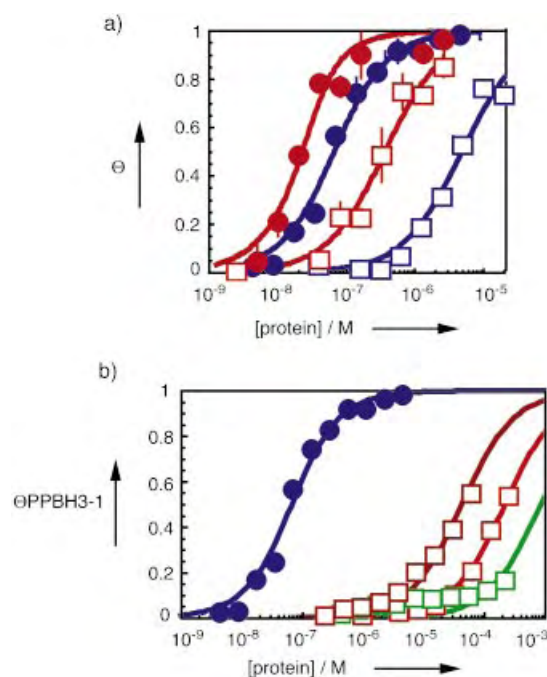


Figure 4. Fluorescence polarization analysis of affinity and specificity. a) Binding isotherms illustrating the affinity of PPBH3-1 (●) and Bak₇₂₋₈₇ (□) for Bcl-2 (blue) and Bcl-X_L (red) at 4 °C in PBS. Θ represents the fraction bound. Data was fit as previously described.^[24] Error bars represent the standard error of at least three trials. b) Binding isotherms illustrating the affinity of the PPBH3-1 for Bcl-2 (●), calmodulin (green), PKA (brown), and carbonic anhydrase II (pink). $\Theta_{\text{PPBH3-1}}$ represents the fraction of PPBH3-1 bound.

ences between the stabilities of these complexes and PPBH3-1·Bcl-2 suggest that the latter is stabilized by a highly stereospecific set of van der Waals contacts. By comparison, Bak₇₂₋₈₇ bound carbonic anhydrase II and calmodulin with K_d values greater than 100 μM and protein kinase A with a K_d value greater than 10 μM .

A critical test of how well protein grafting reproduces the Bak₇₂₋₈₇ epitope is how well PPBH3-1 discriminates between related Bcl-2 proteins. Bak₇₂₋₈₇ itself prefers Bcl-X_L; the Bak₇₂₋₈₇·Bcl-X_L complex ($K_d = 0.35 \pm 0.04 \mu\text{M}$) was 14-fold more stable than the Bak₇₂₋₈₇·Bcl-2 complex ($K_d = 4.9 \pm 0.5 \mu\text{M}$; $\Delta\Delta G = 1.4 \pm 0.1 \text{ kcal mol}^{-1}$) (Figure 4a). Indeed, PPBH3-1 displays a similar preference ($\Delta\Delta G = 1.1 \pm 0.2 \text{ kcal mol}^{-1}$). The PPBH3-1·Bcl-X_L complex ($K_d = 7 \pm 2 \text{ nM}$) was 7-fold more stable than the PPBH3-1·Bcl-2 complex ($K_d = 52 \pm 5 \text{ nM}$). Thus the prefolded recognition

helix in PPBH3-1 differentiates the molecular surfaces of Bcl-2 and Bcl-X_L as well as Bak_{72–87} although it does so in the nM concentration range. It remains to be seen whether PPBH3-1 can evolve further to discriminate more effectively the subtle differences in the Bcl-2 and Bcl-X_L binding pockets.

In summary, here we extend the utility of protein grafting and evolution^[5, 8] to produce miniature protein ligands for protein surfaces. The combined features of high affinity, high specificity, and a compact fold imply that miniature proteins could be used to dissect, modulate, or analyze a single protein function, irrespective of the other functions the protein may regulate within the proteome. In this regard, miniature proteins may possess significant advantages over molecules that down-regulate transcription or those that possess micro-molar affinities and poor or uncharacterized specificities.

Experimental Section

Phage display selection:^[29] The phage display library, PPBH3LIB, was created by cloning an insert encoding the α -helix of library residues 18–35 into the vector pJC20 between unique BglII and NotI restriction sites.^[8] M13 Phage were produced, propagated, and purified as previously described,^[8] except that XL1-blue cells were used in place of TG-1 cells in rounds 3–5. To select for Bcl-2 binding proteins, approximately 10¹⁰ phage were incubated for 2 h in TBST (150 mM NaCl, 50 mM Tris-HCl, pH 7.5, 0.1% (v/v) Tween-20) with human GST-Bcl-2 (Sc4096, Santa Cruz Biotechnology) which had been immobilized on glutathione-coated 96-well microtiter plates (Pierce #15140). Rounds 1 and 2 were performed at 4 °C and rounds 3–5 at 25 °C. Wells were then washed 10 times with TBST for 1 min at 1 min intervals in round 1 and for 5 min at 5 min intervals in rounds 2 through 5. Bound phage were eluted with 0.1N HCl–glycine (pH 2.2) and neutralized with 2M Tris (pH 9.5) before infecting log-phase *E. coli*.

Peptide purification and analysis: All peptides were synthesized by solid-phase methods,^[30] purified to homogeneity by HPLC, labeled with acetamidofluorescein^[22] if necessary, and characterized by MALDI-TOF mass spectrometry and amino acid analysis. CD spectra were recorded on an Aviv 202 CD spectrometer at 4 °C in phosphate-buffered saline (PBS) and were background corrected but not smoothed. PPBH3–1 and Bak_{72–87} were used at 7 and 24 μ M respectively. Binding analyses were performed by using a Photon Technologies 814 fluorimeter at 4 °C in PBS buffer^[22] except for experiments with calmodulin which were measured in buffer containing 20 mM HEPES (pH 7.2), 130 mM KCl, 1 mM CaCl₂.

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Highly Diastereoselective Intramolecular [1,2]-Stevens Rearrangements—Asymmetric Syntheses of Functionalized Isopavines as Morphinomimetics**

Stephen Hanessian* and Marc Mauduit

This paper is dedicated to Professor A. I. Meyers in recognition of his seminal contributions to organic synthesis

The isopavine alkaloids of the Papaveraceae family were first recognized as a novel heterocyclic framework following intensive studies on their isolation and structure elucidation four decades ago.^[1] Isopavines and pavines have been associated with varying pharmacological properties^[2, 3] pertaining to Alzheimer's disease, Parkinson's disease, and Down's syndrome. The traditional syntheses of the isopavines^[4] have relied on intramolecular cyclizations of α -aryl- α -benzylamino acetaldehydes, proceeding first to 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines, followed by a second cyclization. Syntheses of enantiomerically pure or enriched isopavine alkaloids have traditionally resorted to optical resolution, or starting with naturally occurring compounds.^[5] Other syntheses of racemic isopavines are also known.^[6] Natural *O*-methylthalisopavine was first prepared by Meyers and co-workers,^[7] by utilizing chiral nonracemic formamides as substrates in an asymmetric synthesis. Dominguez and co-workers^[8] relied on β -amino alcohols as chiral auxiliaries in their synthesis of the same alkaloid.

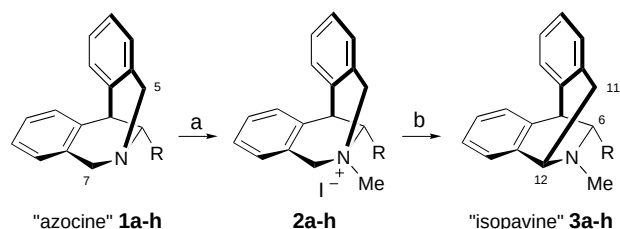
In view of the pharmacological importance of the isopavines, and the paucity of methods to access enantiopure analogues that would be useful to study selective interactions with designated receptors, we investigated various routes to their stereocontrolled synthesis. We report herein examples of highly stereocontrolled, diastereoselective [1,2]-Stevens rearrangements^[9, 10] of 13-substituted dihydro methanodiarlylazocines, which are readily available from α -amino acids,^[11] to give 6-substituted enantiopure isopavines.

Scheme 1 illustrates the sequence and the generality of the [1,2]-Stevens rearrangement. Methylation of the individual azocine analogues **1a–h** afforded the corresponding quaternary ammonium salts **2a–h**. Treatment with a solution of potassium *tert*-butoxide in 1,4-dioxane^[2b] at 80 °C for 1 h, and chromatographic purification gave the corresponding 6-substituted isopavines **3a–h** in excellent yields. The

structures of **3a** and **3e** were ascertained by means of single-crystal X-ray analysis (Figure 1)

The facile construction of the 6*R*-methyl-*O*-methylthalisopavine **6** skeleton from the *N,N*-dibenzylamino alcohol **4** via the azocine **5** is shown in Scheme 2.

The highly stereoselective [1,2]-Stevens rearrangement in this series is unprecedented^[12, 13] and can be rationalized by considering two reaction pathways (Scheme 3). Abstraction of a C-7 benzylic proton in the azocinium ion intermediate (pathway a) leads to ylide A, which fragments to the iminium



Scheme 1. Reagents and conditions: a) MeI, acetone, reflux; b) *t*BuOK, 1,4-dioxane, 80 °C, 1 h; **a**: R = Me, 85 %; **b**: R = *i*Pr, 88 %; **c**: CH₂CH(CH₃)₂, 78 %; **d**: R = benzyl, 75 %; **e**: R = CH₂OH, 55 %; **f**: R = CH₂CH₂OH, 57 %; **g**: R = CH₂CH₂CH₂OH, 65 %; **h**: R = 3-indolyl, 28 % (yields over two steps).

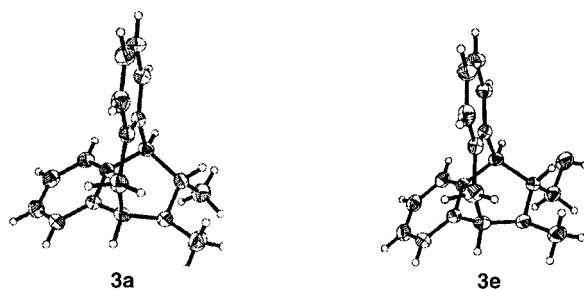
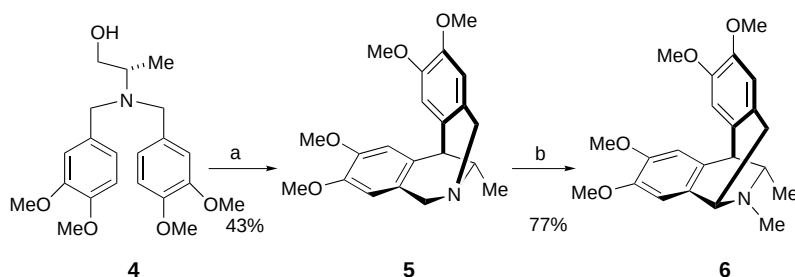


Figure 1. X-ray crystal structure of isopavines **3a** and **3e**.



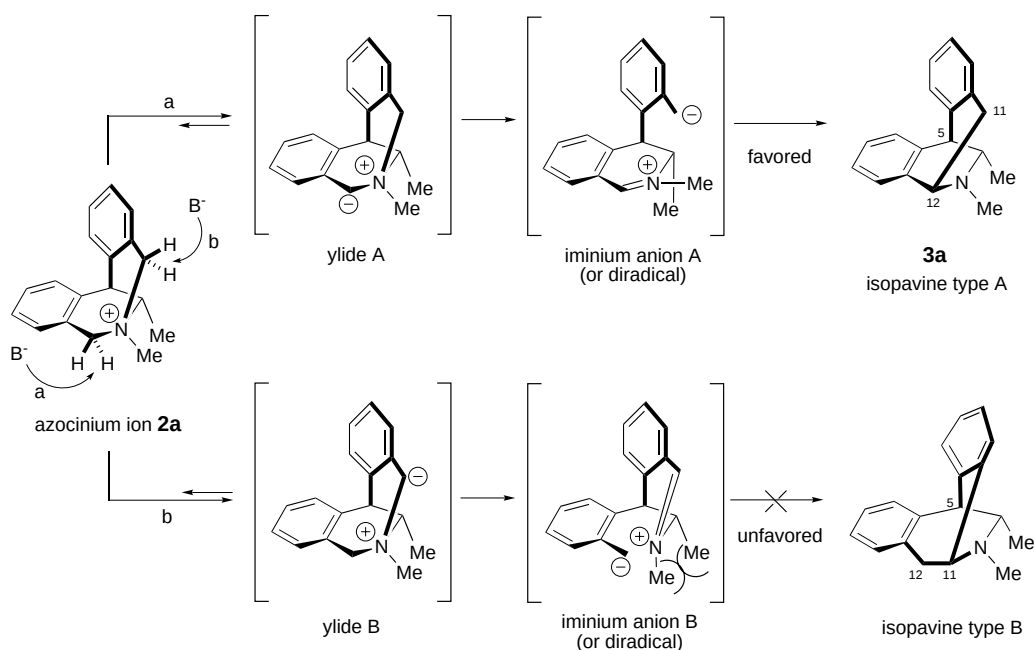
Scheme 2. Reagents and conditions: a) 1. Swern oxidation; 2. AlCl₃ (3 equiv.), CH₂Cl₂, 0 °C, 30 min; b) 1. MeI, acetone, reflux; 2. *t*BuOK (1.5 equiv.), 1,4-dioxane, 80 °C, 1 h. **6**: [α]_D²⁵ = –98.2 (*c* = 1, CHCl₃); (–)-*O*-methylthalisopavine: [α]_D²⁵ = –103 (*c* = 1, EtOH).^[8]

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anion A or its diradical equivalent.^[10] This is in a favorable alignment for an intramolecular attack (recombination), which leads to the observed isopavine **3a**. On the other hand, abstraction of the C-5 benzylic proton generates ylide B, which upon fragmentation results in an anion or diradical that is destabilized by allylic 1,2-strain in the incipient iminium ion B. These highly diastereoselective [1,2]-Stevens rearrangements are general throughout the series of 13-substituted azocines **1a–h**, and none of the isomeric isopavines of type B were detected.



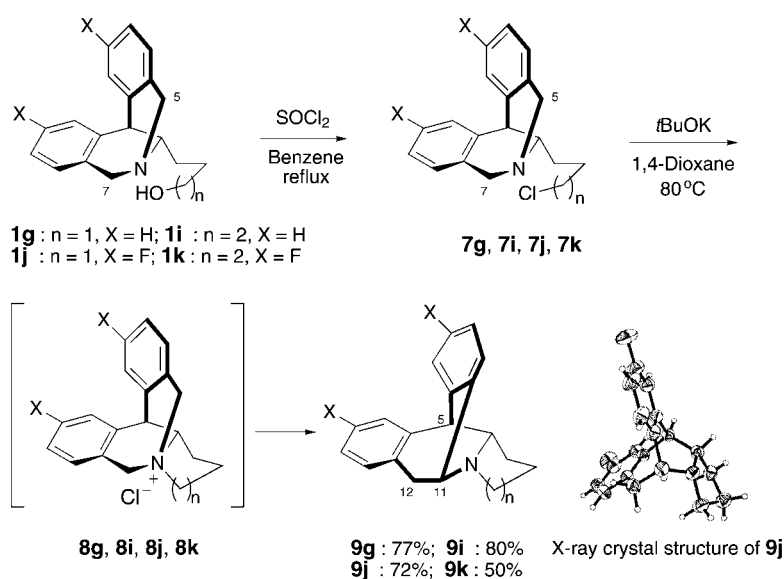
Scheme 3. [1,2]-Stevens rearrangement, which leads to isopavine type A via dianion (or diradical) intermediates.

The isopavines A and B have interesting topologies, particularly when viewed in the context of constrained piperidine analogues. As such, they are closely related to morphine,^[14] with a quasi-ideal convergence of their carbon skeleton and the strategic location of the tertiary nitrogen atom. The prospects of developing a morphinomimetic^[15] would hinge, among other factors, on the proper orientation of the lone pair of electrons on the nitrogen atom.^[16] Inspection of the X-ray crystal structure of 6-alkyl isopavines **3a** and **3e**^[17] clearly shows that the orientation of the lone pair of electrons on the nitrogen atom is opposite to that found in morphine.^[18] It became evident that the desired stereoelectronic effects could occur in a tetracyclic analogue related to

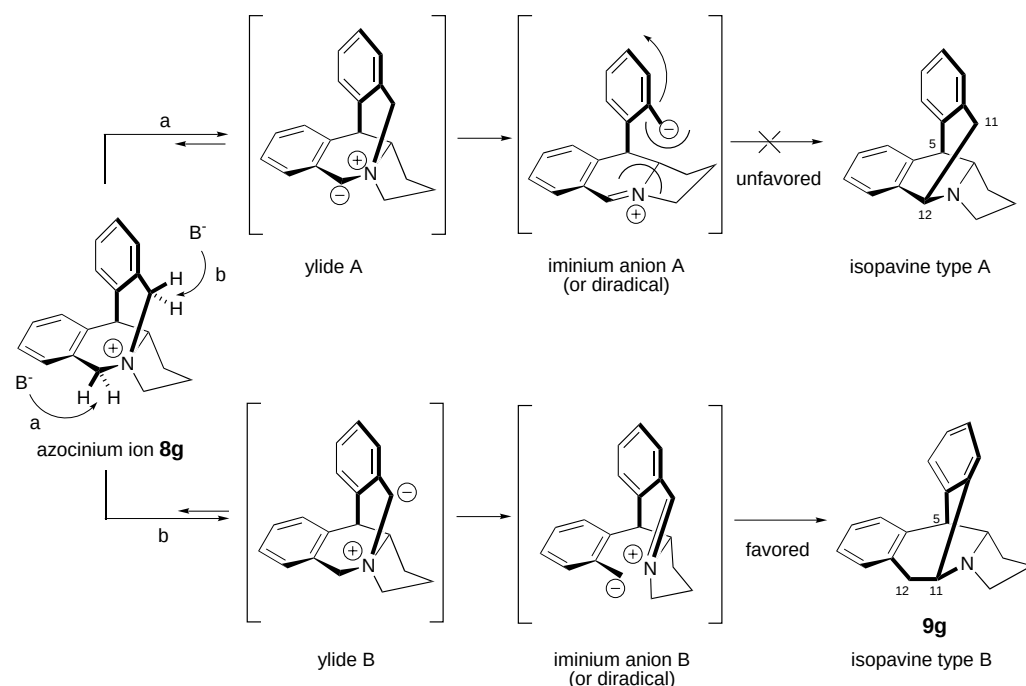
the isopavine B skeleton (Scheme 4). Thus, chlorination of **1g** afforded the primary chloride **7g**, which upon treatment with *t*BuOK in refluxing dioxane gave the tetracyclic isopavine **9g** by means of a highly diastereoselective [1,2]-Stevens rearrangement of the azocinium ion **8g**.

The X-ray crystal structure^[19] of the corresponding 3,8-difluoro analogue **9j** confirmed the expected course of the [1,2]-Stevens rearrangement and the correct “morphine-like” orientation of the lone pair of electrons on the nitrogen atom. The corresponding six-membered analogues **9i** and **9k** were also prepared. Contrary to the results observed with the 13-alkyl azocines (**1a–h**), the rearrangement of the tetracyclic analogues **1g–k** afforded only the products that correspond to the isopavine B skeleton (Scheme 5). In these cases, the most favorable trajectory for recombination involves the C-5 benzylic anion or radical following pathway b, rather than the C-7 counterpart (pathway a).

Our optimism in the quest towards a novel morphinomimetic was rewarded by the realization that the prototypical analogue **9g** showed an IC_{50} value of 60–66 nM against the human μ -opioid receptor (morphine, IC_{50} = 0.6–1 nM), with interesting selectivity (IC_{50} = 6113 nM for κ and 8226 nM for δ , compared to morphine, IC_{50} = 169 and 146 nM, respectively).^[20] Figure 2 illustrates the spatial relationship between morphine and the tetracyclic type B isopavines **9g** and **9j**, including the orientation of the lone pair of electrons on the nitrogen atom. The piperidine analogue **9i** (Scheme 4) showed an IC_{50} value of 264 (μ receptor). The type A isopavine **3a** (IC_{50} = 635 nM) is, in fact, spatially related to the enantiomer of morphine (IC_{50} = >100 nM). Clearly, further elaboration of the type B isopavine struc-



Scheme 4. Synthesis of tetracyclic isopavine analogues of type B.



Scheme 5. [1,2]-Stevens rearrangement, which leads to isopavine type B via dianion (or diradical) intermediates.

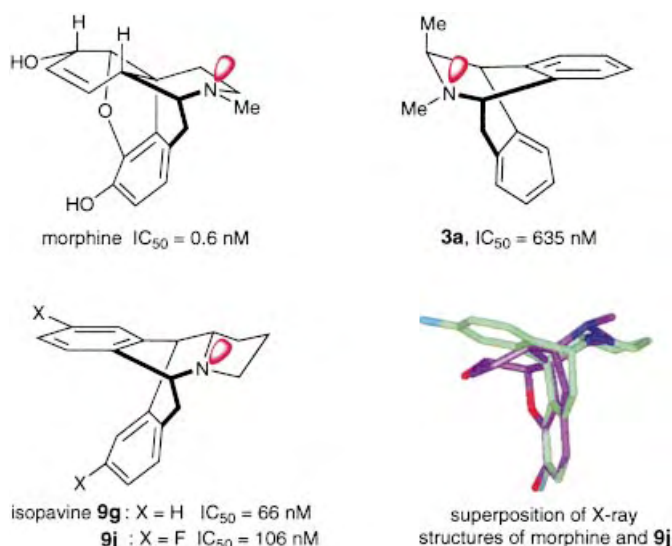


Figure 2. Relationship of isopavine **9g**, **9j**, and **3a** to morphine, and IC_{50} values for the human μ -opioid receptor.

ture by introducing anionic sites of interaction as in morphine, augurs well for increased morphinomimetic activity and selectivity.

The highly diastereoselective [1,2]-Stevens rearrangements outlined in this paper represent rare examples of applications of this venerable reaction to the synthesis of pharmacologically interesting compounds.^[13] The discovery of promising morphine-like activity against the opioid receptor was achieved through an appreciation of the unique topologies of isopavines A and B, and the consequences of structure-based chemical design.

Experimental Section

Iodomethane (0.280 mL, 4.5 mmol, 15 equiv) was added to a solution of azocine **1a** (70.5 mg, 0.3 mmol, 1 equiv) in dry acetone (2 mL) at room temperature. The mixture was stirred at reflux for 1 h. Evaporation of solvent and excess iodomethane gave the desired azocinium salt. The crude azocinium salt was diluted in dry 1,4-dioxane (7 mL) and potassium *tert*-butoxide (101 mg, 0.9 mmol, 3 equiv) was added. The mixture was heated at 80 °C for 1 h. After diluting with water, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified by chromatography to give the desired isopavine **3a** in 85% yield. M.p. 103–104 °C (ethyl acetate); $[\alpha]_D^{20} = -119$ ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.15$ (d, $^3J(H,H) = 6.3$ Hz, 3 H; CH_3), 2.68 (s, 3 H; CH_3), 2.94 (dd, $^3J(H,H) = 3.3$ and 18.1 Hz, 1 H; CH), 3.21 (q, $^3J(H,H) = 6.3$ Hz, 1 H; CH), 3.59 (s, 1 H; CH), 3.80 (dd, $^3J(H,H) = 3.3$ and 18.1 Hz, 1 H; CH), 4.10 (t, $^3J(H,H) = 3.3$ Hz, 1 H; CH), 7.05–7.25 (m, 8 H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 22.6$, 31.7, 40.1, 54.0, 61.6, 62.7, 124.7, 125.6, 126.2, 126.3, 126.4, 127.1, 127.4, 131.0, 134.8, 138.8, 140.2, 143.7; HR-MS (peak matching, MAB (metastable atom bombardment)), calcd for $[M^+]$: 249.15175, found: 249.15059.

Thionyl chloride (0.073 mL, 1 mmol, 2 equiv) was added to a solution of the azocine **1g** (139.5 mg, 0.5 mmol, 1 equiv) in dry benzene (5 mL), and the mixture was heated at reflux for 1 h. Evaporation of the solvent gave the corresponding chloride in quantitative yield as an amorphous solid. The chloride was dissolved in dry 1,4-dioxane (10 mL), potassium *tert*-butoxide (168 mg, 1.5 mmol, 3 equiv) was added, and the mixture was heated at 80 °C for 1 h. Water was then added, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash chromatography (chloroform/methanol 85:15) to give the desired isopavine **9g** in 77% yield. $[\alpha]_D^{20} = +180$ ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6 , 25 °C, TMS): $\delta = 1.22$ (m, 1 H; CH), 1.50 (m, 1 H; CH), 1.62 (m, 1 H; CH), 1.73 (m, 1 H; CH), 2.64 (d, $^3J(H,H) = 17.8$ Hz, 1 H; CH), 2.70 (ddd, $^3J(H,H) = 5.5$; 8.1 and 10.6 Hz, 1 H; CH), 2.82 (dd, $^3J(H,H) = 7.2$ and 11.2 Hz, 1 H; CH), 3.47 (dd, $^3J(H,H) = 4.6$ and 17.8 Hz, 1 H; CH), 3.52 (d, $^3J(H,H) = 3$ Hz, 1 H; CH), 3.72 (ddd, $^3J(H,H) = 3.0$; 6.3 and 9.5 Hz, 1 H; CH), 4.20 (dd, $^3J(H,H) = 1.7$ and 4.6 Hz, 1 H; CH), 6.80 (m, 1 H; CH), 6.82–7.05 (m, 7 H; CH); ^{13}C NMR (100 MHz, C_6D_6 , 25 °C): $\delta = 24.1$, 26.8, 33.3, 46.2, 50.5, 55.4, 61.7, 122.7, 122.7, 123.1, 124.0, 124.1, 124.3, 127.6, 128.7, 132.9, 136.9, 138.7, 140.1; HR-MS (peak matching, MAB), calcd for $[M^+]$: 261.15175, found: 261.15216.

Experimental details for the synthesis of **1a**, **1g**, **3b–h**, **6**, **9j**, **9i**, and **9k** are found in the Supporting Information.

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A New Screen for Combinatorial Catalysis; On-Bead Testing in Agarose Gel**

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Catalyst discovery through combinatorial chemistry is under study in many laboratories.^[1] Much of this work involves small- to medium-sized libraries, synthesized in parallel and tested in compartmentalized apparatus.^[2] There are still rather few methods for screening the very large, bead-bound libraries accessible through “split-and-mix” synthesis.^[3] Realistically, such libraries must be screened visually under conditions that allow picking of active beads. Visual screening for catalysis is nontrivial, given that starting materials and products can diffuse freely between beads. Published solutions rely on a) thermographic screening,^[4] b) test reactions that give insoluble, colored products,^[5] c) bead-bound indicators,^[6] or d) screening for reactivity, as an indicator of potential catalytic properties.^[7] A very recent method developed by Miller et al. employs a gel, covalently bonded to a fluorescent indicator, formed by polymerization around the library beads.^[8]

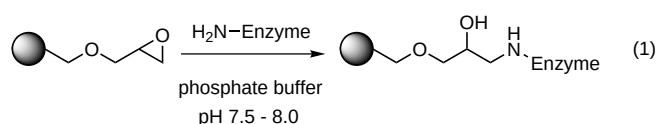
Herein we report an alternative gel-based protocol for screening for bead-bound catalytic activity in aqueous media.

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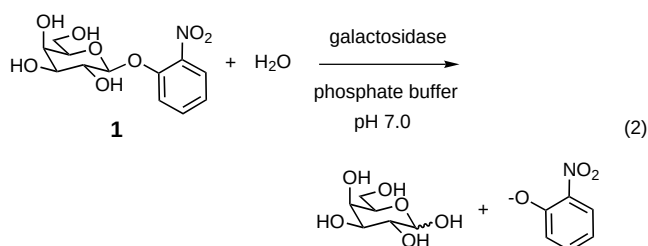
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Like the method of Miller et al., it relies on the gel to limit diffusion of reaction products, allowing a visual indication of reaction (e.g. a color change) to be associated with a particular bead. However, the present method requires no preparation of specialist materials, and no special equipment other than a low-power optical microscope.

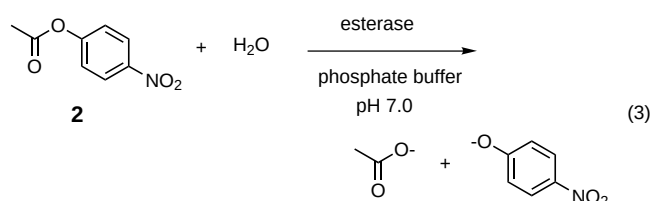
The new screen employs “low-melting agarose”, a gel which is widely used in electrophoresis.^[9] The gel phase can be prepared simply by dissolving the powdered agarose in hot water, cooling below a critical temperature, and waiting for a few minutes. The gel can be remelted and recast as necessary. To test its potential as a medium for catalysis screening, we used enzymes immobilized by reaction with oxirane acrylic beads [Eq. (1)].^[10] Inactive control beads were produced by



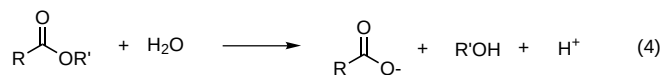
reaction of the oxirane beads with benzylamine. Early experiments employed β -D-galactosidase with the standard test substrate *o*-nitrophenyl- β -D-galactopyranoside (**1**) [Eq. (2)], the reaction being signalled by the yellow color of



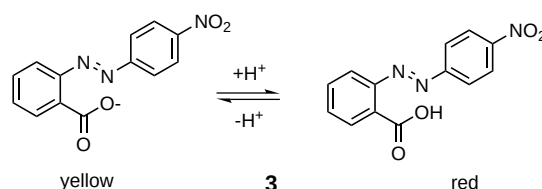
o-nitrophenolate. Samples of the agarose gel were placed in Petri dishes and remelted. Small quantities of **1** were dissolved in the molten gel, which was then allowed to cool and set. Mixtures of immobilized enzyme beads (3–5 %) and inactive control beads (97–95 %) were spread on the gel surfaces. Active beads were clearly identifiable, acquiring a yellow color within a few minutes (Figure 1 a). Control experiments established that the gel was indeed necessary; in the absence of agarose, the nitrophenolate products diffused rapidly throughout the mixture (Figure 1 b). Similar results were obtained with pig liver esterase, for which *p*-nitrophenyl acetate **2** was employed as substrate [Eq. (3); Figure 1 c].



The reactions in Equations (2) and (3) involve specific substrates which may not be good models for compounds of interest. Screens with broader scope are clearly desirable. Ester hydrolysis may be monitored simply by the change in pH [Eq. (4)]. Color pH indicators may therefore provide a



general visual screen for esterase activity.^[11] We looked particularly for indicators which would change color at moderate pH, and which showed the stronger color when protonated. Methyl Red (**3**), which is yellow at pH 6.2 and red at pH 4.2, seemed a good candidate. The esterase/inactive



bead mixture was tested as above with gels containing ethyl acetate and a small quantity of methyl red sodium salt. Within 5 minutes the few active beads acquired an intense red color, clearly visible against the yellow background (Figure 2 a,b). Closer examination revealed that the red (protonated) indicator was insoluble, precipitating on the surface of the beads (Figure 2 c). Presumably this assists the experiment, increasing the contrast between beads and background, and providing a further barrier to diffusion. The gel is still necessary, however. In control experiments omitting agarose, all the beads acquired the red color of protonated indicator (Figure 2 d). We also investigated a second procedure, in which the beads are suspended in the molten gel just before it sets. In this case the inactive beads acquired a faint pink color,



Figure 1. Micrographs from experiments employing nitrophenolate substrates [Eqs. (2), (3)]. a) Galactosidase bead + controls, on agarose + **1**, after 5 min. b) Galactosidase beads + controls (2:98) + **1** in aqueous solution, after 5 min. Nitrophenolate disperses through active and inactive beads. c) Esterase beads + controls, on agarose + **2**, after 5 min. Despite the uniform yellow background, due to spontaneous hydrolysis of **2**, the two active beads are still distinguishable.

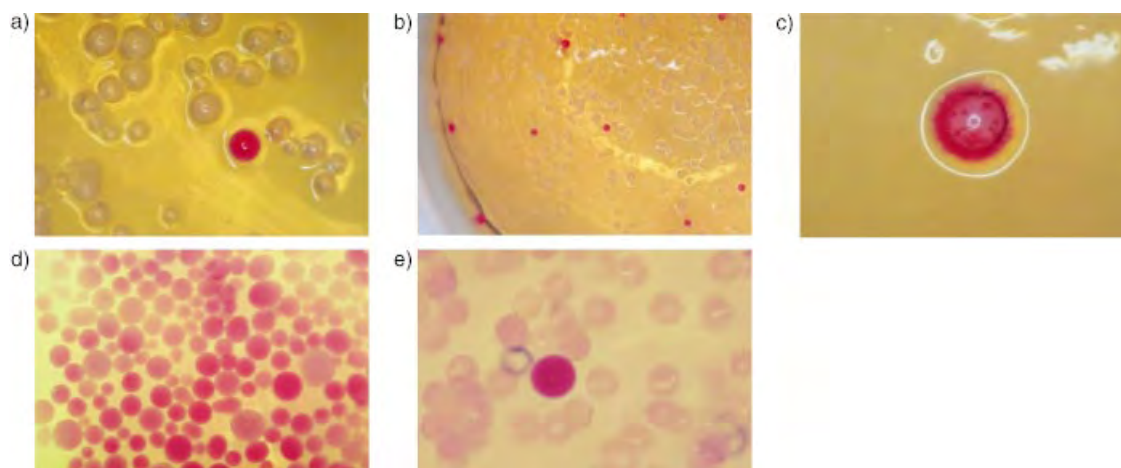


Figure 2. Micrographs from the hydrolysis of ethyl acetate in the presence of **3**. a) Esterase bead + controls, on agarose + EtOAc + **3**, after 4 min. b) As in a), at lower magnification. c) Esterase bead on agarose + EtOAc + **3**, after 15 min. Precipitated **3** forms a filamentous halo around the bead. d) Esterase beads + controls (5:95) + EtOAc + **3** in aqueous solution, after 4 min. e) Esterase bead + controls suspended in agarose + EtOAc + **3**, after 4 min.

but the contrast between active and inactive beads was still perfectly clear (Figure 2e).

In conclusion, we have used immobilized enzymes to demonstrate a protocol potentially usable for catalysis screening in “split-and-mix” combinatorial libraries.^[12] Although it has been used just for two reaction types, both in aqueous media, it should be generalizable to other transformations and also to organic solvents (given an appropriate gelator). The examples include a pH-based screen for ester hydrolysis, which avoids the use of elaborate, specific substrates. In future work we hope to exploit this method to detect “synthetic esterase” activity in steroidal podand libraries.^[7]

Experimental Section

Materials: Agarose gel was prepared by dissolving low-melting agarose (0.5 g; Life Technologies, GibcoBRL, 15517-014) in boiling water (50 mL), then allowing to cool and set. β -D-Galactosidase (Sigma, G 2513) and porcine liver esterase (Sigma, E 2884) were immobilized on oxirane acrylic beads (Sigma, O 7628) following the procedure of Laumen et al.^[10]

Galactosidase screen (Figure 1a): Agarose gel (0.5 mL) was melted in a small Petri dish in a drying oven. Phosphate buffer (pH 7.0, 0.02 M, 2 drops) and *o*-nitrophenyl- β -D-galactopyranoside (5 mg) were stirred into the gel, which was then filtered through cotton wool to remove undissolved substrate and allowed to set in a second Petri dish. A mixture of galactosidase and control beads (ca. 5:95) was spread onto the surface of the gel. The active beads became perceptibly yellow after about one minute.

Esterase/Methyl Red screen (Figure 2a,b,e): Agarose gel (0.5 mL) was melted in a small Petri dish in a drying oven. An aqueous solution of Methyl Red, sodium salt (Acros 41484-0100, $\sim 1 \text{ mg mL}^{-1}$) was added dropwise to give the solution a moderate yellow color (final concentration between 0.1 and 0.2 mM). Ethyl acetate (two drops) was added with stirring and the gel was allowed to set. A mixture of esterase and control beads (ca. 2:98) was spread onto the surface of the gel. The active beads became perceptibly red within 1 min, and acquired a visible halo of precipitated indicator after about 20 min. Alternatively, the mixture of esterase and control beads was stirred into the cooling gel at just above the setting temperature (ca. 40 °C). Again, the active beads became red within 1 min.

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- [12] There is potential concern that a screen developed by using true enzymes may not be capable of detecting the lower activities expected for artificial enzymes. However a rough estimate suggests that the indicator-based esterase screen, at least, should be usefully sensitive. Titration of aqueous AcOH into a solution of Methyl Red sodium salt in deionized water ($1.4 \times 10^{-4} \text{ M}$, as used in the screen) established that about five equivalents of the acid are required for complete conversion to the red precipitate. Therefore, a bead capable of generating $[\text{AcOH}]_{\text{local}} = 0.7 \text{ mM}$ should certainly be detected. A potential catalyst synthesized on Tentagel would be present at about 10 mM within the bead. While the effective concentration of the catalyst may be less, it seems likely that catalysts would be detectable after one turnover at most.

A New Class of Cyclic Hexamer: $[\text{Co}_6\text{L}_6]^{24-}$ (H_6L = hexaazatriphenylene hexacarboxylic acid)

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The design and construction of nano-sized polynuclear metal complexes with cyclic topologies are of great current interest as a result of their potential applications, such as molecular inclusion,^[1, 2] as well as their electrochemical,^[3] magnetic,^[4] and/or photophysical properties.^[5] Of particular interest are molecular modules containing multifunctional ligands with π -electronic structures which could provide unique electronic properties. Hexaazatriphenylene (hat) and its derivatives, which are multifunctional ligands with π -electronic structures, have been studied in the fields of supramolecular chemistry, photochemistry, and crystal engineering.^[1, 6] Recently we have synthesized a trinuclear copper(I) complex containing the stable radical anion $[\text{hat}(\text{CN})_6]^{1-}$ which indicates that the peripheral substituents influence the electronic structure, in particular, the low-lying π^* orbitals of the hat moiety.^[7] Herein we report the synthesis of a novel cyclic molecular module containing a hat derivative which indicates that the peripheral substituents can control not only the electronic structure but also its coordination modes.

The key feature of this successful synthesis is the design of a hat derivative whose coordination topology is controlled by carboxylate groups, in this case hexaazatriphenylene hexacarboxylic acid (H_6L). L^{6-} , the deprotonated form of H_6L , functions as a quadridentate chelate ligand (two aromatic nitrogen atoms and two carboxylate oxygen atoms). The carboxylate groups involved in the chelate coordination (A in Figure 1 a) lie on the same plane of the aromatic moiety of the L^{6-} unit. The nearest-neighbor carboxylate group (B in Figure 1 a) sits perpendicularly to the plane because of the steric hindrance. Therefore, each carboxylate group is arranged in an ABABBA fashion. In this way the three donor atoms participate in the coordination of a second metal cation, to form a tridentate chelate coordination. The coordination of the two metal cations cause a marked decrease in the basicity of the other remaining nitrogen donors, which could be a principal reason for the coordination of no further cobalt cations. Consequently L^{6-} acts as a

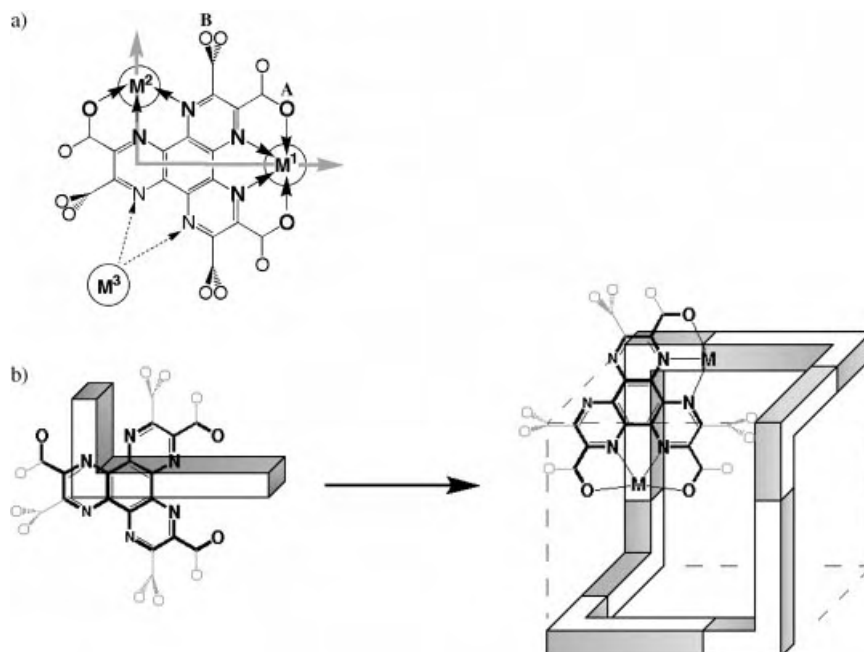


Figure 1. a) Coordination mode of L^{6-} . b) Schematic representation of the design and self-assembly of a cyclic nanostructure.

building block with a right angle, which is useful for constructing a cyclic nanostructure^[8] (Figure 1 b). The spontaneous assembly of these subunits is shown schematically in Figure 1 b. Since L^{6-} acts as a building block with a right angle and the metal center links two L^{6-} ligands perpendicularly, the formation of the unique nano-sized cyclic hexamer is expected through a molecular self-assemble process. In the resulting cyclic structure six out of the eight corners of a cube are connected (Figure 1 b).

The reaction of $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ with Na_6L in acetonitrile/ H_2O results in the novel cyclic hexamer $[\{\text{Co}(\text{H}_2\text{O})_6\}_{10}[\text{Co}_6\{\text{Co}(\text{H}_2\text{O})_3\}_2\{\mu_3\text{-L}\}_6] \cdot 74\text{H}_2\text{O}\}_n$ (**1**), which was characterized by X-ray crystallography. The structure of **1** has four unique features:

1. distorted pentagonal-bipyramidal cobalt(II) centers,
2. nano-sized (ca. 2 nm) cyclic units,
3. a cobalt complex encapsulated in the central cavity of the cyclic unit,
4. a two-dimensional honeycomb layer.

As regards point 1, the coordination geometry around the Co center which constructs the cyclic units is shown in Figure 2. The four aromatic nitrogen atoms and three carboxylic oxygen atoms form a distorted pentagonal bipyramid around the Co^{II} center; the N(3) and O(5) atoms are in the axial positions and the N(3)-Co-O(5) angle is $152.7(3)^\circ$. Two oxygen atoms, O(1) and O(3), coordinate weakly (Co-O(1): 2.458(8), Co-O(3): 2.347(7) Å) compared with the others (bond lengths: Co-O(5): 2.138(7), Co-N(1): 2.151(8), Co-N(2): 2.120(7), Co-N(3): 2.281(7), and Co-N(4): 2.030(8) Å). There have been to date several examples of seven-coordinate pentagonal-bipyramidal cobalt(II) complexes which have the equatorial plane made up of the five coordination atoms of a quinquedentate ligand,^[9] except for examples of nitrate anions functioning as chelate

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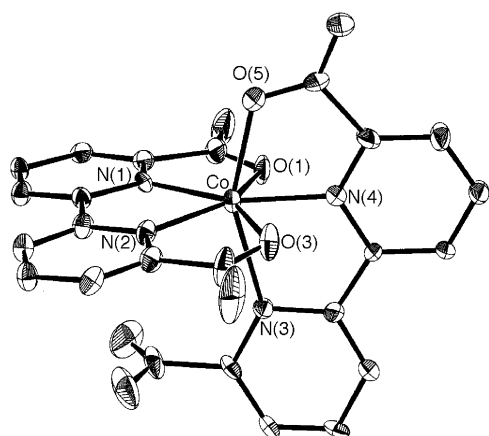


Figure 2. Coordination geometry around the Co center that constructs the cyclic unit.

ligands.^[10] To the best of our knowledge, the complex reported here is the first example of a seven-coordinate pentagonal-bipyramidal cobalt(II) complex comprised of quadridentate and tridentate ligands.

The structure of the nano-sized cyclic hexamer (see point 2) formed by six Co^{II} ions and six L⁶⁻ ligands is illustrated in Figures 3 and 4. Figure 3 highlights the cyclic framework,

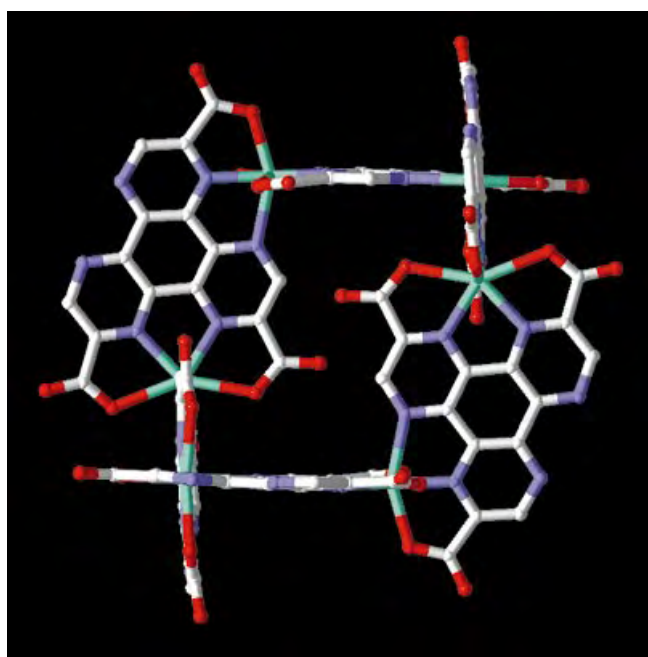


Figure 3. Structure of the cyclic hexamer in the solid state. Carboxylate groups which do not join in the formation of the cycle are omitted for clarity. Color code: C: white, N: blue, O: red, Co: green.

which is consistent with our design shown in Figure 1b. The cyclic module (Figure 4) has an S_6 -symmetrical screwlike structure. The distance between the opposite cobalt atoms of the unit is 13.68 Å. When the van der Waals radii are taken into consideration, the diameter of the ring is about 2 nm and that of the cavity is approximately 1 nm.

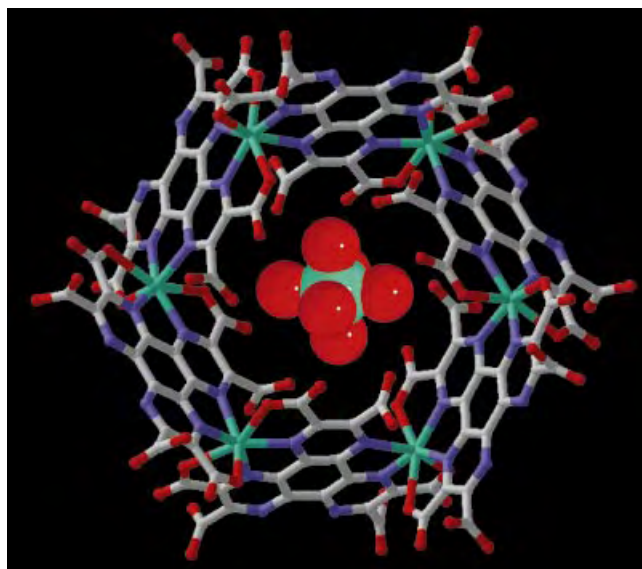


Figure 4. Structure of the cyclic module along the *c* axis. A hexaaquacobalt(II) cation is encapsulated in the central cavity of the cyclic module.

In the construction of cyclic nanostructures (point 3) it is very important to control not only the angles of the subunits but also the templating effect. In the case of **1**, a hexaaquacobalt(II) cation ($[\text{Co}(\text{H}_2\text{O})_6]^{2+}$) is encapsulated in the central cavity of the cyclic hexamer. The water molecules of the guest complex are hydrogen-bonded to carboxylate groups from the cyclic hexamer, and acts in a supporting role for the formation of the cyclic framework.

The three residual carboxylate groups which do not participate in the formation of the cycle are involved in the module-link framework (see point 4). One of them acts as the secondary interaction site to link the cyclic units. The coordination of the carboxylate groups to another cobalt(II) ion leads to a facial-type coordination geometry with the six oxygen atoms (three from the water molecules and three from the carboxylate groups) to form a two-dimensional honeycomb layer in the *ab* plane (Figure 5). The L⁶⁻ ligand has three different coordination sites: quadridentate and tridentate chelate coordination sites to form the cyclic unit and a monodentate coordination site to form the honeycomb layer.

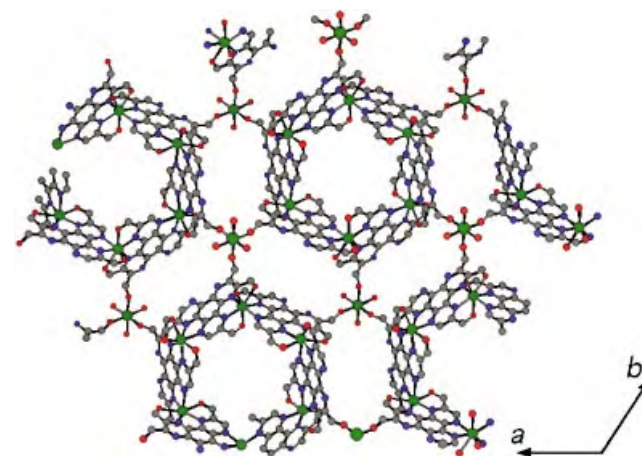


Figure 5. Honeycomb layer structure of **1** in the *ab* plane.

The crystal structure of **1** shows there are three hexaaquacobalt(II) complexes per cyclic unit that are located between the cyclic units in the honeycomb layer and act as counteranions, and a further six complexes that are located between the honeycomb layers. The anionic honeycomb layers and the cationic layers composed of hexaaquacobalt(II) cations lie alternately along the *c* axis and results in a canceling out of their electrical charge.

The electronic absorption spectrum of **1** in the solid state has an intense band centered at 383 nm, which is dissimilar to that of the ligand alone with two $\pi\text{-}\pi^*$ transition bands centered at 293 and 336 nm, and is therefore attributed to the metal-to-ligand charge-transfer transition in the cyclic core. The magnetic susceptibilities of **1** over the temperature range 2–300 K show a monotonous decrease in the $\chi_{\text{m}}T$ value (from 7.07 emu K mol⁻¹ at room temperature) with decreasing temperature.

In this work we have succeeded in the design and synthesis of a novel cyclic module with a hexacarboxylate derivative. These results have important implications for the design of nano-scaled materials.

Experimental Section

1: H₆L (prepared from a literature procedure^[11]) was added to an aqueous NaOH solution. An acetonitrile solution of Co(NO₃)₂ · 6 H₂O was carefully layered on top of the aqueous solution and the mixture allowed to stand for one month. The red prismatic crystals obtained were collected by filtration (65% yield). Elemental analysis calcd for C₁₈H₂₂Co₃N₆O₂₃ · 4 H₂O: C 23.02, H 3.22, N 8.95; found: C 22.70, H 2.80, N, 9.27.

X-ray structure determination of **1**: All data were measured on a Rigaku/MSD Mercury CCD diffractometer with graphite-monochromated MoK α radiation. The structure was solved by Patterson methods (DIRDIF92 PATTY). The water molecules of the [Co(H₂O)₆]²⁺ ion encapsulated in the central cavity of the cyclic hexamer were disordered, and were modeled as oxygen atoms with 33.33% occupancy factors. Non-hydrogen atoms which were not disordered were refined anisotropically, except for the solvent water molecules. All the water molecules were modeled as oxygen atoms. Refinement was carried out with full-matrix least-squares on *F*². All calculations were performed with the TEXSAN crystallographic software package. Crystal data for C₁₈H₂₂Co₃N₆O₂₃ · 12.33 H₂O: *M*_r = 1089.34, crystal size 0.20 × 0.20 × 0.20 mm, trigonal, space group *R*3̄ (No. 148), *a* = 22.632(3), *c* = 39.794(3) Å, *V* = 17 652(3) Å³, *Z* = 18, ρ_{calcd} = 1.844 g cm⁻³, $\lambda(\text{MoK}\alpha)$ = 0.71069 Å, *F*(000) = 10 085.58, $\mu(\text{MoK}\alpha)$ = 13.80 cm⁻¹, *T* = 25 °C, $2\theta_{\text{max}}$ = 54.2°. Of the 32 745 reflections collected, 8580 were unique (*R*_{int} = 0.043). For 4373 reflections with *I* > 4.00σ(*I*), 518 parameters; *R*(*R*_w) = 0.087(0.238). Min./max. residual electron density −0.88/1.10 e⁻ Å⁻³.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-161830. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Chaotropic Anions Strongly Stabilize Short, N-Capped Uncharged Peptide Helices: A New Look at the Perchlorate Effect**

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In the course of an analysis of the pH-dependent helicity of short alanine peptides N-capped with helix-initiating templates of the Ac-Hel family,^[1] we noted a remarkable helix stabilization caused by binding of anions with low hydration volumes, the so-called chaotropic anions.^[2] These are well-known to bind both to pH-denatured proteins^[3] and to helically disposed polycationic peptides,^[4] electrostatically shielding and thereby stabilizing partially folded conformations such as helices. We now demonstrate efficient anion-induced helix stabilization for short N-capped polyanilines that lack charged groups. In addition to the helix-inducing N-cap these polyaniline peptides also contain recently reported N- or C-caps that solubilize the polyaniline se-

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quence and isolate it from potential helix-modifying effects of the K₄ solubilizing region and the UV reporter group tryptophane (Trp; W). For example, the cap *t*LInp₂K₄W contains the isolating element *t*LInp₂, derived from the α -amino acid *tert*-leucine (*t*L, *tert*-butylglycine) and the γ -amino acid isonipecotic acid (Inp, 4-carboxypiperidine). We have previously shown^[5] that regions of a peptide that are separated by *t*LInp₂ contribute independently to the circular dichroism (CD) spectrum and that under the conditions of this study, the reporting, solubilizing, spacing region *t*LInp₂K₄W contributes insignificantly to the molar ellipticity per residue at 222 nm ($[\theta]_{222}$), used in this study as a helicity monitor.

Direct 1:1 binding of a chaotropic anion with the helix molecule must be invoked to explain the observed effects, such as the dependence of $[\theta]_{222}$ on the perchloric acid concentration for WK₄Inp₂LGHel-A₈-NH₂ (**3**) displayed in Figure 1. Acid- and aggregation-induced helix stabilization

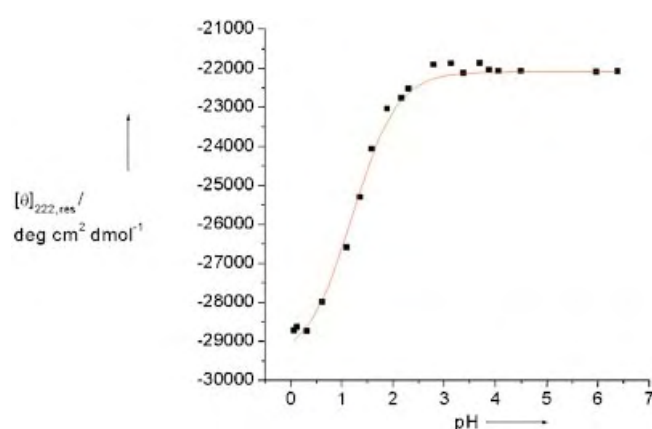


Figure 1. CD spectroscopic investigation of the titration of peptide **3** with perchloric acid at 2 °C. The squares represent experimental values and the red line the best fit obtained by least-square fit analysis.

were excluded by the absence of a detectable change of $[\theta]_{222}$ on the addition of HCl and by the invariance of $[\theta]_{222}$ over a 100-fold dilution (see Supporting Information).

As seen in Figure 2, replacement of perchloric acid HClO₄ by sodium perchlorate gives a comparable helix stabilization

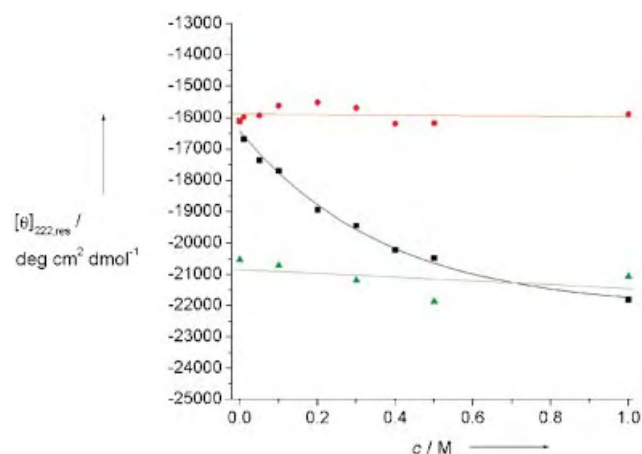


Figure 2. CD spectroscopic investigations of the salt titrations of peptides **5** and **9** at 2 °C. ■ NaClO₄ (entry 5a in Table 1); ● NaCl (entry 5c), ▲ NaClO₄ (entry 9).

but other common salts do not. An anomalous salt dependence of $[\theta]_{222}$ that is unrelated to helicity was ruled out by measuring ¹³C NMR chemical shift changes for ¹³C=O labeled peptides,^[6] which parallel the changes in $[\theta]_{222}$, as do changes in the *s-trans/s-cis* ratio of the NMR helix reporter property of our N-terminal cap Ac-Hel^[7] (see Supporting Information). Thus, three independent methods confirm that the ClO₄[−] ion induces a strong helix-stabilizing effect in alanine-rich peptides.

Table 1 summarizes the results of titrations of other peptide sequences. These peptides were constructed from a short core alanine-rich sequence, N-capped by Ac-Hel or X-Gly-Hel,

Table 1. Summary of salt and acid titration data derived from CD spectroscopic analysis of a series of polyalanines at 2 °C.

Entry	Sequence ^[a]	Additive	$\Delta[\theta]_{222, \text{res}}^{[b]}$ [%]	$c_{1/2}^{[c]}$ [M]
1	WK ₄ Inp ₂ LGHelA ₄ -NH ₂ 1	HClO ₄	84	0.13 ± 0.01
2	WK ₄ Inp ₂ LGHelA ₆ -NH ₂ 2	HClO ₄	78	0.09 ± 0.01
3	WK ₄ Inp ₂ LGHelA ₈ -NH ₂ 3	HClO ₄	30	0.06 ± 0.01
4	WK ₄ Inp ₂ LGHelA ₁₂ -NH ₂ 4	HClO ₄	9	0.07 ± 0.01
5a	AcHelA ₈ tLInp ₂ K ₄ W-NH ₂ 5	NaClO ₄	35	0.24 ± 0.04
5b	AcHelA ₈ tLInp ₂ K ₄ W-NH ₂ 5	NaBF ₄	22	— ^[d]
5c	AcHelA ₈ tLInp ₂ K ₄ W-NH ₂ 5	NaCl	—	—
5d	AcHelA ₈ tLInp ₂ K ₄ W-NH ₂ 5	NaHSO ₄	—	—
5e	AcHelA ₈ tLInp ₂ K ₄ W-NH ₂ 5	NaH ₂ PO ₄	—	—
5f	AcHelA ₈ tLInp ₂ K ₄ W-NH ₂ 5	NaPF ₆	39	— ^[d]
6	AcHelA ₄ K ₃ tLInp ₂ K ₄ W-NH ₂ 6	NaClO ₄	49	0.20 ± 0.01
7	AcHelA ₇ KtLInp ₂ K ₄ W-NH ₂ 7	NaClO ₄	23	0.21 ± 0.02
8	AcHelA ₇ βtLInp ₂ K ₄ W-NH ₂ 8	NaClO ₄	29	0.12 ± 0.01
9	Ac ^D DHelA ₇ βtLInp ₂ K ₄ W-NH ₂ 9	NaClO ₄	—	—

[a] *t*L: *tert*-leucine, Inp: 4-carboxypiperidine, β: β-aminoalanine, Ac^DD: *N*-acetyl-β-aspartate. [b] Difference between observed $[\theta]_{222, \text{min}}$ and $[\theta]_{222, \text{max}}$ in salt titrations. [c] Salt concentration at half saturation of the peptide binding site obtained from a least-squares analysis of experimental ellipticities. Note that $1/c_{1/2} = K$ (binding constant). [d] Data does not fit a 1:1 binding model of anion to peptide.

which have comparable helix-inducing propensities. Each peptide contains a solubilizing polylysine region, a UV reporting tryptophane (Trp) residue, and the spacing element *t*LInp₂ which shields the polyalanine core from helicity effects of the solubilizer and reporter.^[5] Entries 3 and 5a of Table 1 show that the position of the solubilizing spacer does not influence the sensitivity of the CD ellipticity to perchlorate concentration. It should be noted that the CD spectra of peptides **1–9** at high salt concentrations show the typical features of a classical spectrum for a helical peptide, that is minima at 208 and 222 nm and a maximum at short wavelength (see Supporting Information).

The curve of Figure 1 was calculated by assuming stoichiometric 1:1 binding of peptide and anion; the analysis assigns $[\theta]_{222, \text{max}}$ the limiting value at high [ClO₄[−]] and a binding constant *K*. As seen in Table 1, an average value for *K* corresponds to half saturation of a peptide binding site at a ClO₄[−] concentration of 0.1–0.2 M. The % change in $-\theta]_{222, \text{max}}$ is largest for short peptides and for peptides that exhibit a low value for $-\theta]_{222}$ in water alone. For the tetraalanine sequence **1**, for example, the value for $-\theta]_{222}$ nearly doubles at high [ClO₄[−]], while for the dodecaalanine sequence **4**, only a 9 % increase is seen.

Although none show the complete set of features seen with our short uncharged helices, certain peptides and proteins exhibit perchlorate-induced helicity changes.^[8] Certain denatured proteins that form molten globules at low pH values can show increased helicity in the presence of chaotropic anions such as perchlorate. Goto, Takahashi, and Fink observed this effect for β -lactamase, cytochrome c, and apomyoglobin.^[9] To further probe the helix-inducing effects of chaotropes Goto and Aimoto constructed a cationic peptide that folds to a double-helical conformation containing a solvent-shielded hydrophobic core.^[10] All these examples exhibited titration curves and formed compact, folded, highly helical conformations in the presence of low concentrations of a range of chaotropic anions. These positively charged proteins undergo complex conformational changes in the presence of chaotropes at lower concentrations than those reported in Table 1. The exceptional sensitivity of these polycationic proteins and peptides to chaotropic anions probably reflects their greater capacity to undergo subsequent folding to hydrophobically stabilized compact structures, once salt-induced helices have formed. Our uncharged polyalanine substrates appear to be unique in undergoing a single, simple conformational change to form hydrated helices.

Our use of CD spectroscopic analysis to measure helicity is restricted to those anions that lack significant UV absorption in the 195–220 nm region and thus excludes the most efficient chaotropic anions studied by Goto et al. As seen in Table 1, salts formed from anions with normal hydration volumes, such as chloride and sulfate, induce insignificant changes in the value of $-\theta_{222}$. Only the chaotropic anions BF_4^- , PF_6^- , and ClO_4^- induce large changes in $-\theta_{222}$ that implies anion binding. Our findings underline the difficulties of conducting salt-dependent CD studies of polypeptides at low pH values in water, since no UV transparent noninteracting anion appears to be available.

How does a chaotropic anion change the helicity of our uncharged polyalanine systems? Where does perchlorate bind to the peptide? The CD spectroscopic investigation of the peptide **9**, which bears a negatively charged N-terminal cap, provides the first answers to these questions. Addition of perchlorate to **9** has no noticeable influence on the CD ellipticity $[\theta]_{222}$ (Figure 2). Helical conformations are stabilized by the presence of terminal charges, positive charges at the C-termini and negative at the N-termini, and modeling suggests a natural anion binding site for a chaotropic anion in a cleft in the Hel function, proximate to the NH group of the first amino acid of the peptide sequence. This hypothesis is supported by the fact that, among the anions we studied, only the titration behavior of perchlorate fits a simple 1:1 binding model. This suggests that not only the chaotropic nature of the anion but also its size is of vital importance for efficient binding to the peptide.

X-ray crystallographic data for binding of anions to helix N-termini of globular proteins have recently been reviewed and suggest precedents for our hypothesis.^[11] We have shown that an anion bound in the vicinity of the N-terminus of a potentially helical peptide can strongly stabilize it. With our template-substituted model peptides, the binding effect was found to be specific for chaotropic anions of a certain size. The

perchlorate ion was found to be strongly favored over other chaotropic anions. In addition to the strongly helix-stabilizing effect of perchlorate for short uncharged peptides, our findings may be of significant importance for folding pathways of partially helical intermediates. These intermediates may be sensitive to the presence of locally bound anions, which also may play a tuning role in complex protein-dependent signal transfer pathways.

Experimental Section

Peptides were prepared as previously described^[7] and purified by repeated reverse-phase high performance liquid chromatography (RP-HPLC), and characterized by EI-MS (electrospray ionization mass spectrometry). The purity of all compounds is estimated to be higher than 95%. CD spectra were recorded on a thermostated Aviv 62DS circular dichroism spectrometer calibrated according to literature methods.^[12] pH values were measured at 20 °C with a PHM240 pH-meter from Radiometer Copenhagen.

The Supporting Information contains the salt and acid titration curves for all compounds as well as ^1H NMR and ^{13}C NMR spectroscopic data for compounds **1** and **5**, as well as the CD spectrum of **3**.

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Hydrophilicity and Lipophilicity of Cellulose Crystal Surfaces

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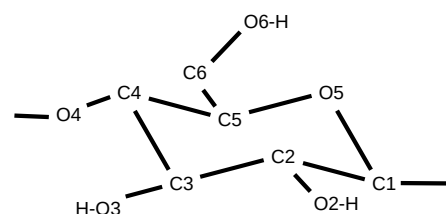
Cellulose is one of the most abundant biopolymers and a basis for many industrial derivatives and products. Its surface physics and chemistry are important for the understanding of adhesion to other materials (e.g. in nanocomposites of cellulose fiber reinforced thermoplastics),^[1] adsorption processes from solution (e.g. in paper production),^[2] and of industrial processes that start from a cellulose slurry (e.g. the preparation of cellulose derivatives, where often counter-intuitive substitution preferences are found).^[3] Although applications cover many areas of chemistry, biology and technology, the cellulose surface is still not well understood. The situation is complicated by the simultaneous presence of several phases in natural and processed cellulose fibers: There are three principal crystalline phases, triclinic (type I α) and monoclinic (type I β), and type II, with two likely surfaces each, as well as varying contents of amorphous material. Not even the behaviour of the crystalline surfaces towards water and hydrophobic organics has been fully characterized on a molecular level.

Molecular dynamics (MD) simulations with empirical force fields provide a detailed description of molecular systems. Provided the force field is realistic, the system is large enough to avoid finite-size effects, and the simulations last long enough to explore the relevant phase space, MD can deliver information complementary to experiments.^[4] We have undertaken MD simulations to better understand the cellulose surface. In particular, we attempt to characterize the cellulose in its behavior towards water (hydrophilicity/hydrophobicity) and towards apolar parts of organic molecules (lipophilicity/lipohobicity). We use simulation techniques that yield spatially resolved adsorption free energies for the respective moiety, to obtain charts of hydrophilicity and lipophilicity. While a comparative study of all possible cellulose surfaces would be desirable from a scientific and technological viewpoint, we have to restrict the simulations to the two surfaces of crystalline cellulose I β because of the computational cost.

Experimentally, the surface of crystalline cellulose has been visualized by atomic force microscopy (AFM). One important result is that it preserves the underlying crystal structure, as can be seen from unit cell parameters obtained by AFM, which compare well with those from X-ray diffraction.^[5–7] Computational studies have mainly investigated the bulk behavior of crystalline cellulose.^[8–12] The MD simulations of

Heiner and Teleman^[13, 14] explored the interface between triclinic (I α) and monoclinic (I β) cellulose and water.

We simulated the 110 (“wide”) and 1 $\bar{1}$ 0 (“narrow”) surfaces of monoclinic (I β) cellulose in contact with water. Except for the in-plane distance between parallel chains (0.614 (110), 0.540 nm (1 $\bar{1}$ 0), room temperature values corrected to 333 K using the experimental thermal expansion coefficient^[15]), they are very similar: The chains run parallel to the surface and the cellobiose units tilt out of the surface plane by about 45°. The cellulose was modelled as a slab of 6 $\times$ 8 (deep $\times$ wide) parallel chains of three cellobiose units each, cut from the crystal structure at the respective crystal face.^[16] In both cases, eight parallel chains run along the surface in the *x* direction. Neighboring chains are shifted along *x* by half an anhydroglucose unit (quarter of a cellobiose unit). The C6 groups point in the direction of the crystal and the water alternatingly (Scheme 1 shows the atomic numbering). The *z*



Scheme 1. Atom labeling in the anhydroglucose unit of cellulose.

direction is the surface normal, *z* = 0 being the point where the densities of water and cellulose are equal. Orthorhombic periodic boundary conditions were applied (this necessitated a small distortion of the unit cell by 1.2° with respect to the monoclinic crystal structure but gained substantial simulation speed). In the *z* direction, there is a gap between the upper surface of the cellulose slab and the nearest periodic image of its lower surface of 4.495 and 5.107 nm for the 110 and 1 $\bar{1}$ 0 surface, respectively; this gap is filled with 2197 water molecules. Three independent simulations were conducted for each surface. Each was equilibrated for about 1 ns and then sampled for about 1.0–1.3 ns with a time step of 0.002 ps. Coordinates were written out for analysis every 0.6 ps. The temperature *T* was maintained at 333 K using the Berendsen thermostat^[17] with a coupling time of 0.5 ps. We used the GROMOS96^[18] united-atom force field for cellulose and the simple point-charge model^[18] for water, both with bond constraints. Coulomb interactions were truncated at 1 nm with a reaction-field correction (dielectric constant 78.5).^[19]

The hydrophilicity/hydrophobicity at a point *r* was quantified by the local value of the chemical potential of water $\mu_{\text{H}_2\text{O}}(\mathbf{r})$ relative to that of bulk water $\mu_{\text{H}_2\text{O}}(\text{bulk})$. This difference in chemical potential is given by the ratio of the local water density $\rho_{\text{H}_2\text{O}}(\mathbf{r})$ and the bulk density $\rho_{\text{H}_2\text{O}}(\text{bulk})$, Equation (1) ($R = 8.3145 \text{ J mol}^{-1} \text{ K}^{-1}$).

$$\Delta\mu_{\text{H}_2\text{O}}(\mathbf{r}) = \mu_{\text{H}_2\text{O}}(\mathbf{r}) - \mu_{\text{H}_2\text{O}}(\text{bulk}) = -RT \ln \frac{\rho_{\text{H}_2\text{O}}(\mathbf{r})}{\rho_{\text{H}_2\text{O}}(\text{bulk})} \quad (1)$$

A value of $\Delta\mu_{\text{H}_2\text{O}}(\mathbf{r}) < 0$ indicates hydrophilicity and $\Delta\mu_{\text{H}_2\text{O}}(\mathbf{r}) > 0$ hydrophobicity at *r*. Figure 1 shows $\Delta\mu_{\text{H}_2\text{O}}$ as a function of the distance *z* from the cellulose surface, that is,

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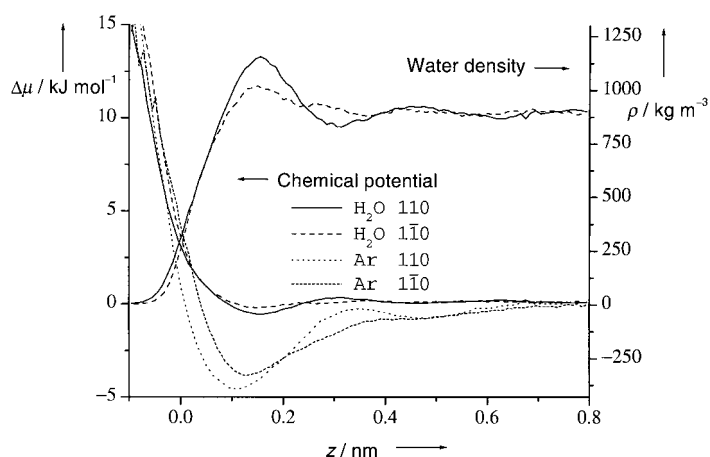


Figure 1. Local chemical potential μ [kJ mol⁻¹] (left scale) of water $\Delta\mu_{\text{H}_2\text{O}}(z)$ and argon $\Delta\mu_{\text{Ar}}(z)$ as a function of the distance z [nm] from the cellulose I β 110 and 11 $\bar{0}$ surfaces, respectively. Also given are the water density profiles [kg m⁻³] (right scale) above both surfaces.

averaged over x and y . The enrichment of water near both surfaces is minute and the basins of negative chemical potential at $z \sim 0.15$ nm are shallow (-0.56 (110), -0.21 kJ mol⁻¹ (11 $\bar{0}$)). Hence, both surfaces are in essence nonhydrophilic. This is also evident in the water-density profile normal to the surface, which lacks the sharp first peak characteristic for hydrophilic surfaces.^[20] The 110 surface has a second, even shallower, chemical potential minimum (at $z \sim 0.47$ nm), which we attribute to its wider lateral spacing between the cellulose chains.

Lipophilicity is not necessarily the opposite of hydrophilicity, but must be similarly quantified by the chemical potential difference of an appropriately chosen “lipophile”. Since our interest is in the adsorption of small lipophilic moieties (present in low concentrations in the water phase) rather than entire molecules, we chose as the lipophile a model argon atom,^[21] which is similar in size and cohesion to a methylene group. Moreover, its size is comparable to that of a water molecule, so probes of similar diameter are used for both hydrophilicity and lipophilicity. Its local excess chemical potential $\mu_{\text{Ar}}^{\text{ex}}(\mathbf{r})$ is obtained by spatially resolved test-particle insertion,^[22] Equation (2), where the angle brackets denote ensemble averaging and $E(\mathbf{r})$ is the change in potential energy on insertion of an argon atom into the cellulose–water system at position $\mathbf{r}$.

$$\mu_{\text{Ar}}^{\text{ex}}(\mathbf{r}) = -RT \ln(\exp(-E(\mathbf{r})/RT)) \quad (2)$$

The excess chemical potential of argon in bulk water $\mu_{\text{Ar}}^{\text{ex}}(\text{bulk}) = +6.0$ kJ mol⁻¹ (experiment: $\sim +10$ kJ mol⁻¹)^[23] is calculated in a similar way. Figure 1 shows $\Delta\mu_{\text{Ar}}(z) = \mu_{\text{Ar}}^{\text{ex}}(z) - \mu_{\text{Ar}}^{\text{ex}}(\text{bulk})$. Both surfaces exhibit clear minima of -4.5 (110) and -3.8 kJ mol⁻¹ (11 $\bar{0}$). As RT at 333 K equals 2.8 kJ mol⁻¹, both would attract small lipophiles from aqueous solution. More obvious than in the corresponding $\Delta\mu_{\text{H}_2\text{O}}(z)$

curves, the $\Delta\mu_{\text{Ar}}(z)$ curve of 110 has two minima, that for 11 $\bar{0}$ has one. The intervening maximum (at $z \sim 0.32$ nm) of the 110 curve is a shoulder for 11 $\bar{0}$.

Hydrophilicity and lipophilicity can also be resolved laterally to study the distribution of hydrophilic/phobic and lipophilic/phobic spots on the surface. We use a mesh of 0.095×0.102 (110, Figure 2) and 0.095×0.090 nm² (11 $\bar{0}$, Figure 3) resolution in x and y over a layer 0.2 nm thick (z) above the surface. The effect of the crystal structure on hydrophilicity and lipophilicity patterns is clearly visible (Figures 2 and 3), with only some variation due to a small disorder. Note that the atoms shown in the figures are a guide to the eye only, as the surface atoms have substantial positional fluctuations during the course of an MD simulation. In most cases, the lipophilic and hydrophobic areas (both dark red) coincide for both surfaces, the lipophilic areas being somewhat larger. Although surprising at first, this is easily explained, as the exclusion is steric for both water and argon. There is, however, a qualitative difference between the hydrophilic and lipophilic regions: Lipophilic patches (dark blue) are nearly equal in size to the lipophilic ones. In contrast, there are only small hydrophilic spots, as most of the nonhydrophobic surface is “neutral” (green: $\Delta\mu_{\text{H}_2\text{O}} \sim 0$ kJ mol⁻¹) with the same water density as bulk water. The differences between the patterns of the two surfaces are small for both hydrophilicity and lipophilicity.

Local hydrophilicity and lipophilicity are related to the functional groups presented to the water phase. Figure 4 shows hydrophilicity and lipophilicity above a single cellobiose unit on the 110 surface. (The patterns on the 11 $\bar{0}$ surface are qualitatively very similar, therefore they are not shown and only major differences between the two surfaces are mentioned below.) They have been obtained by averaging over all corresponding repeat units and, thus, include static

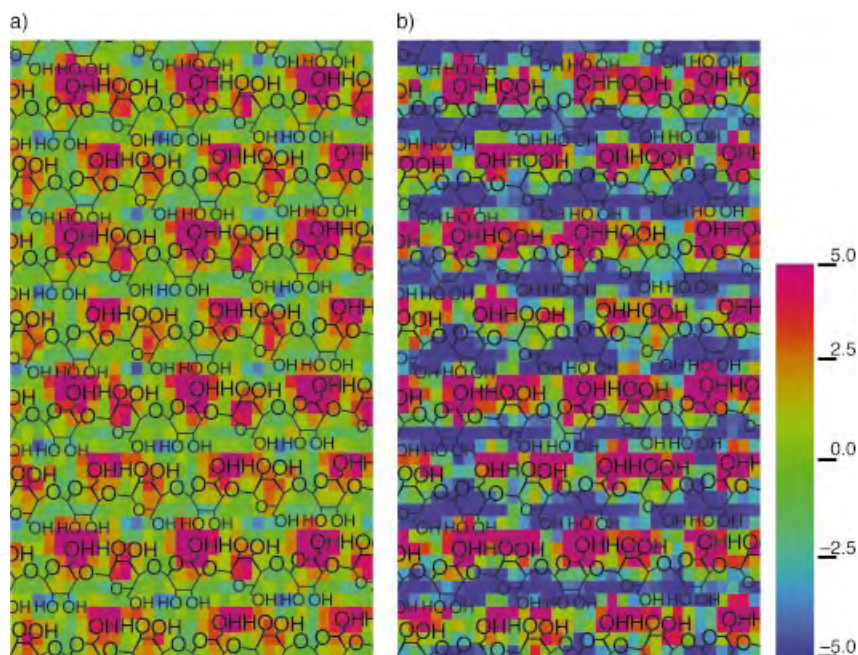


Figure 2. Hydrophilicity and lipophilicity charts of the cellulose I β 110 surface in a layer between $z = 0$ and 0.2 nm. The surface cellulose chains are shown to provide a rough indication of the positions of chemical groups. The lateral grid spacing is approximately 0.1 nm, see text. a) $\Delta\mu_{\text{H}_2\text{O}}(x,y)$ [kJ mol⁻¹]; b) $\Delta\mu_{\text{Ar}}(x,y)$ [kJ mol⁻¹].

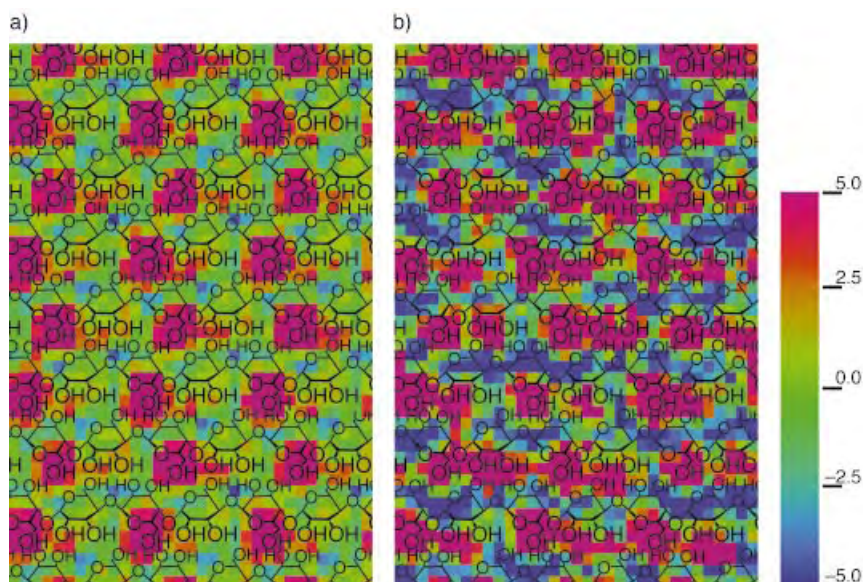


Figure 3. Hydrophilicity and lipophilicity chart of the cellulose $I\beta$ $1\bar{1}0$ surface in a layer between $z = 0$ and 0.2 nm. The plot details are the same as in Figure 2. a) $\Delta\mu_{\text{H}_2\text{O}}(x,y)$ [kJ mol^{-1}]; b) $\Delta\mu_{\text{Ar}}(x,y)$ [kJ mol^{-1}].

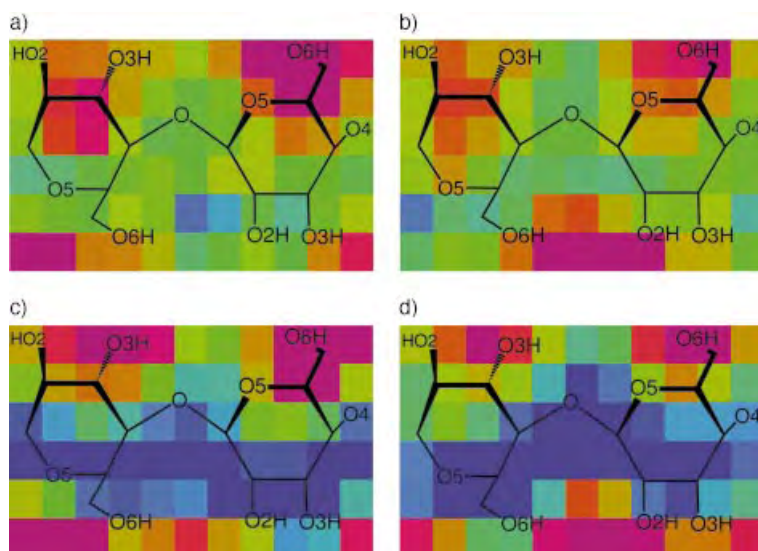


Figure 4. Averaged hydrophilicity $\Delta\mu_{\text{H}_2\text{O}}(x,y)$ [kJ mol^{-1}] and lipophilicity $\Delta\mu_{\text{Ar}}(x,y)$ [kJ mol^{-1}] above a single cellobiose unit on the cellulose $I\beta$ 110 (wide) surface. a) $\Delta\mu_{\text{H}_2\text{O}}(x,y)$ for even-numbered cellulose chains; b) $\Delta\mu_{\text{H}_2\text{O}}(x,y)$ for odd-numbered chains; c) $\Delta\mu_{\text{Ar}}(x,y)$ for even-numbered chains; d) $\Delta\mu_{\text{Ar}}(x,y)$ for odd-numbered chains. The color code is the same as in Figures 2 and 3. Averaging was performed over all 12 crystallographically equivalent cellobiose units of the even or odd chains, respectively, in a layer above the surface between $z = 0$ and 0.2 nm. The structural formulae reflect average atomic positions and are meant as an aid to orientation only.

and dynamic disorder. There are two crystallographically different types of chains, denoted even (Figures 4a and 4c) and odd (Figures 4b and 4d), which have been averaged separately. Even and odd refers to the sequence number of the cellulose chains on the surface counted from the top in Figure 2. For both types of cellulose chains (Figures 4a and 4b), the protruding C6/O6 units and, to a lesser extent, the C2/O2 moieties create hydrophobic areas (high chemical potential towards water). This is due to their space requirements. The effect is slightly more pronounced for the narrow $1\bar{1}0$

surface due to the stronger tilt of the glucose rings. The chain packing in the two surfaces also has an effect on the type of contacts a water molecule has with the surface groups (Table 1). They are obtained by integrating the appropriate partial radial distribution functions (not shown) between water oxygen atoms and different surface groups.^[24] For both surfaces, half of the water contacts are, on average, “hydrophilic” OH groups. On the wider 110 surface, the remaining contacts are equally divided between “hydrophobic” groups and “intermediate” groups. This distribution is shifted from the hydrophobic to the intermediate groups in case of the narrower $1\bar{1}0$ surface.

The lipophobicity (high chemical potential towards argon, dark red) follows qualitatively the hydrophobicity, since it is also mainly due to excluded volume (Figures 4c and 4d). However, the spatial variation of $\Delta\mu_{\text{Ar}}(x,y)$ is larger than that of $\Delta\mu_{\text{H}_2\text{O}}(x,y)$, and there are attractive (dark blue) sites as well. For the 110 surface, they form continuous grooves (Figures 4c and 4d), whereas on the narrow $1\bar{1}0$ surface the attractive patches are not connected, probably due to the lack of space. The lipophilic areas are generally located in depressions on the surface and are lined by hydrophobic atoms such as ether oxygen atoms (O4 and O5) and apolar carbon atoms (C1, C4, and C5). This is also reflected in the surface contacts of argon (Table 1): On the $1\bar{1}0$ surface, the distribution of argon contacts closely resembles that of water contacts, steric accessibility being the criterion for both interactions. In contrast, on the wider 110 surface, the hydrophobic groups are more exposed, and more interactions with them are found.

In summary, both interfaces of cellulose $I\beta$ share common features. Both are stable with respect to surface reconstruction and water penetration, at least on the nanosecond time scale and in the absence of defects. Both show essentially the crystal structure of cellulose $I\beta$, also in the adsorption patterns for water and argon. In

Table 1. Types of surface contacts and their distribution (in percent of all surface contacts) for a water molecule and an argon atom as the prototype lipophile.

Surface groups	H_2O		Ar	
	110	$1\bar{1}0$	110	$1\bar{1}0$
hydrophilic: O2, O3, O6	49.0	51.6	36.8	47.4
intermediate: C2, C3, C6	25.6	29.3	22.9	31.4
hydrophobic: C1, C4, C5, O4, O5	25.4	19.1	40.3	21.2

spite of the presence of OH groups, both surfaces are nonhydrophilic and lipophilic: Water molecules are not attracted to the surface, as they are equally happy in bulk water. On the other hand, the presence of the surface perturbs the water structure sufficiently to create free volume, in which an argon atom (and, hence, a small lipophilic moiety of an organic adsorbent) can dissolve more easily than in the denser bulk water. The wider spacing of cellulose chains allows the 110 surface to expose more of the hydrophobic grooves where lipophilic adsorption takes place. In contrast, the protruding OH groups are less affected by chain packing, so the behavior towards water is similar for both surfaces.

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Electronic Semiconductor–Support Interaction—A Novel Effect in Semiconductor Photocatalysis**

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*Dedicated to Professor Yasuo Wakatsuki
on the occasion of his 60th birthday*

The growing field of semiconductor photocatalysis has moved from basic research to practical applications. Typical examples are the detoxification of air and water^[1] and novel organic syntheses^[2] photocatalyzed by titania and cadmium sulfide. The photonic efficiency of these transformations largely depends on the ratio of the rate of interfacial electron transfer (IFET) to the rate of recombination of the photo-generated electron-hole pair. It is generally assumed that only substrates adsorbed at the semiconductor surface can participate in the IFET. Therefore in many cases the reaction rate increases when substrate adsorption is improved. A better adsorption was also invoked to rationalize the higher detoxification rates induced by supporting semiconductors like titania onto silica or alumina.^[3]

During our work on addition reactions photocatalyzed by semiconductors (semiconductor photocatalysis type B) we observed that precipitation of cadmium sulfide onto silica afforded a much better photocatalyst than the unsupported material. Herein we report on experimental evidence that this enhanced photocatalytic activity does not stem from improved adsorption but rather from an electronic semiconductor–support interaction (SEMSI), which alters the bandgap energy and flatband potential. Whereas electronic catalyst–support interactions are well documented in thermal heterogeneous catalysis, they have been unknown in the field of semiconductor photocatalysis.

Thus, whereas the reaction between cyclopentene (RH) and the Schiff base **1** (Scheme 1)^[2d,e] is quite slow in the presence of CdS it becomes about 10 times faster when silica covered with 50% CdS (CdS-50/SiO₂) is used as the photocatalyst. According to the proposed mechanism, the intermediate aminobenzyl and allyl radicals are formed through proton-coupled IFET reactions of the substrates with reactive electrons and holes (e⁻, h⁺). Their C–C hetero- and homocoupling lead to **2** and **3** as the major and by-product, respectively.^[2d,e]

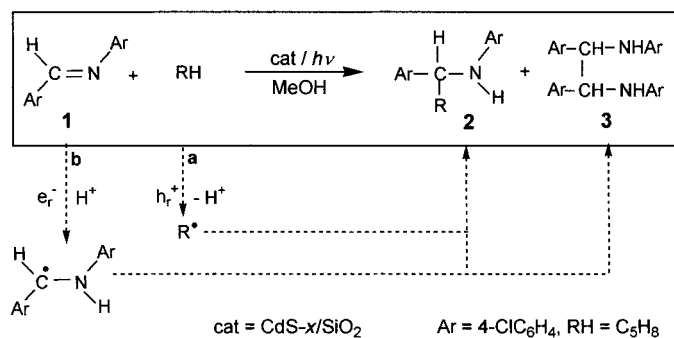
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Scheme 1. Photoaddition of cyclopentene (RH) to the Schiff base 1.

Silica-supported photocatalysts CdS-*x*/SiO₂ containing 50, 30, and 12 wt % of CdS were prepared by impregnating SiO₂ with cadmium sulfate and successive precipitation with sodium sulfide. Specific surface areas of the resulting materials were in the range of 157–270 m²g^{−1}. To obtain the bandgap energy, diffuse reflectance spectra were measured and the modified Kubelka–Munk function $[F(R_{\infty})/hv]^2$ was plotted against hv .^[4] Surprisingly, the bandgap of CdS employed (2.25 eV) increases to 2.34, 2.38, and 2.43 eV when the coverage varies from 50 to 30 and 12 %, respectively (Figure 1, Table 1).^[5] The effect does not arise from a quantum size effect, as indicated by the following.

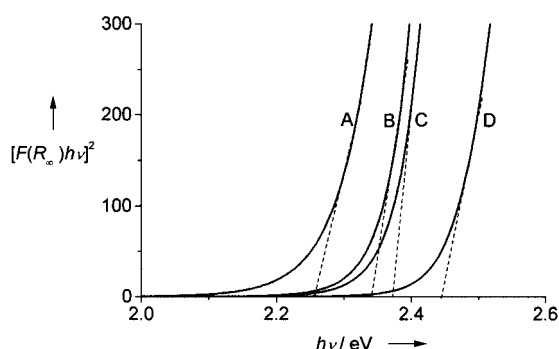


Figure 1. Transformed diffuse reflectance spectra of CdS (A), CdS-50/SiO₂ (B), CdS-30/SiO₂ (C), and CdS-12/SiO₂ (D).

Table 1. Photoelectrochemical data^[a] and bandgap energies.

	pH ₀	<i>U</i> _{fb} [V, NHE] ^[b]	<i>E</i> _{bg} [eV] ^[c]
CdS	9.0	−0.38	2.25
CdS-50	9.0	−0.38	2.34
CdS-30	8.5	−0.41	2.38
CdS-12	3.0	−0.59	2.43

[a] Measured according to ref. [9]. [b,c] Reproducibility was better than ±0.01 V and ±0.02 eV, respectively.

All samples contain micrometer-sized aggregates composed of cubic and amorphous CdS nanoparticles of 6–10 nm.^[6] In general, transmission electron microscopy in various regions of the powders reveals that with decreasing coverage the aggregates become smaller and more homogeneously dispersed on the silica surface. Representative high-resolution transmission electron micrographs of CdS and CdS-12/SiO₂

are displayed in Figure 2. They clearly reveal the presence of CdS nanocrystals having the same average diameter of 6–10 nm both for the unsupported and the lowest coverage photocatalyst. This independence of particle size on coverage

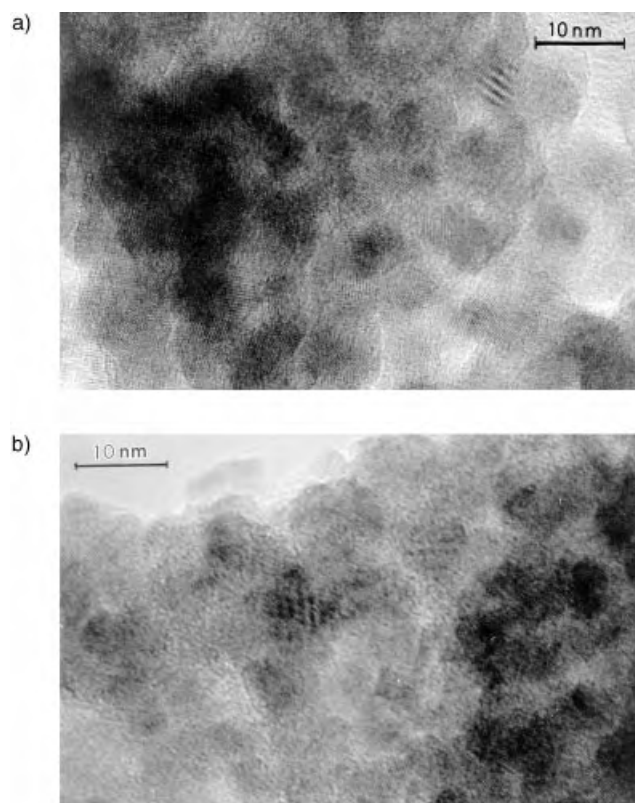


Figure 2. High-resolution transmission electron micrographs of CdS (a) and CdS-12/SiO₂ (b).

is also seen in the X-ray powder diffractograms. For all four samples the peak width is the same.

The bandgap energy does not change when silica and CdS are ground in a mortar or when silica is first silylated with Me₃SiCl before impregnation with cadmium ions. In both cases the photocatalytic activity corresponds to that of unmodified CdS. From this it is evident that the observed bandgap shifts originate from an electronic interaction between CdS and SiO₂, which is induced by formation of [Si]–O–Cd bonds through reaction of surface OH groups with cadmium ions. The presence of these bonds is indicated by the disappearance of the broad IR absorption band of silica at 1190 cm^{−1}, when the silica is loaded with CdS.^[7] Accordingly, it is expected that upon addition of sulfide, growth of the CdS particles starts at these surface-bound cadmium ions. Of the resulting aggregate only the non surface-bound part is sensitive to the diffuse reflectance measurement and it is assumed that the electronic influence of the surface-bound CdS layer on this part should be stronger for the smaller aggregate. As expected, the strongest blue-shift is measured for CdS-12/SiO₂.

To test whether the larger bandgap is caused by a shift of the valence or conduction band edges, the position of the flatband potential (*U*_{fb}) of the photocatalysts was determined

by the methods of Bard^[8] and Roy^[9] through measuring photocurrent and photovoltage as a function of the pH value. The values obtained by the latter method are summarized in Figure 3 and Table 1. From the corresponding inflection

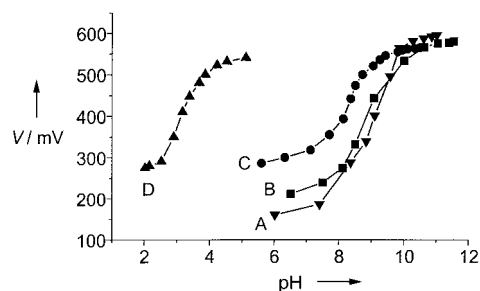


Figure 3. Dependence of photovoltage (vs. NHE) on the pH value of the electrolyte. CdS (A), CdS-50/SiO₂ (B), CdS-30/SiO₂ (C), and CdS-12/SiO₂ (D).

points (pH₀) the U_{fb} values are easily obtained and converted to the value at pH 7.^[10] A lower pH₀ value corresponds to a more negative flatband potential.

Whereas the flatband potential of -0.38 V measured for CdS-50/SiO₂ does not differ from that of unsupported CdS, it is shifted to -0.41 and -0.59 V in the case of CdS-30/SiO₂ and CdS-12/SiO₂, respectively. In the same sequence the relative initial rate^[11] increases from 1.0 through 10 and 11 to 12 (Figure 4). Since the tenfold rate increase found for CdS-50/-

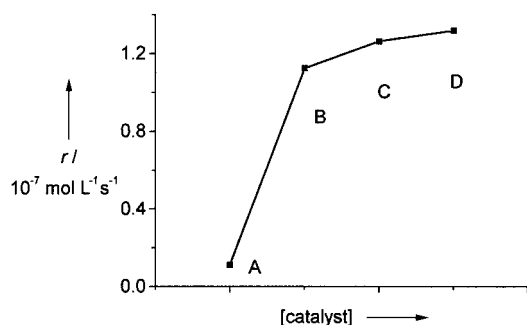


Figure 4. Dependence of reaction rate for formation of **2** on the coverage. CdS (A), CdS-50/SiO₂ (B), CdS-30/SiO₂ (C), and CdS-12/SiO₂ (D).

SiO₂ cannot be caused by a change of the position of the flatband potential, which is the same as for unmodified CdS, it may originate from an anodic shift of the valence band edge, which would result in an acceleration of the oxidative IFET reaction (path a, Scheme 1).

Another possibility is that the silica support may increase the rate through inducing a better substrate adsorption. To test this hypothesis the adsorption of **1** and cyclopentene onto CdS and CdS-50/SiO₂, suspended in methanol, was measured. Since no significant differences were found, it is unlikely that the observed rate increase arises from an improved adsorption. More likely, it is a consequence of an anodic shift of the valence band edge, which should render the reactive hole a better oxidizing agent and therefore accelerate the oxidative IFET reaction. Since the valence band has predominantly sulfur character, this shift should increase the binding energy

of the sulfur 2p electrons. In fact, values of 162.7, 162.9, and 163.2 eV were measured for CdS, CdS-50/SiO₂, and CdS-30/SiO₂, respectively. As in the case of the bandgap shift, the SEMSI effect is stronger for the sample with a better dispersion of CdS onto the support surface.

Based on these experimental data, it is concluded that the enhanced photocatalytic activity of silica-supported CdS is attributed to an electronic semiconductor–support interaction mediated through surface [Si]–O–Cd–S bonds.

Experimental Section

Cadmium sulfide was prepared as described in reference [2e]. Neutral SiO₂ of specific surface area of 360 m² g^{−1} was obtained commercially. Supported samples were prepared by stirring SiO₂ with an aqueous CdSO₄ solution of appropriate concentration overnight, followed by addition of dissolved sodium sulfide.^[2e] Transmission electron microscopy measurements were carried out with a PHILIPS CM200 microscope working at 200 kV. The samples were dispersed in ethanol by ultrasound and cast on a copper grid coated with a carbon film. XPS spectra were recorded by using a VG-Escalab 210 Spectrometer ($\Delta E = cte$ mode, pass energy of 50 eV, MgK α radiation). The binding energy (BE) reference was taken as the C1s peak from carbon contamination of the samples at 284.6 eV. Rates of this pseudo zero-order reaction were obtained by irradiating a suspension of 4.2 g L^{−1} of CdS or 8.4–35 g L^{−1} of CdS-*x*/SiO₂ in methanol, containing the same total amount of CdS, in the presence of 0.01 M of the imine **1** and 0.47 M of cyclopentene; product formation was measured by HPLC.^[2d]

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On-Line Liquid Chromatography Mass Spectrometry: A Useful Tool for the Detection of DNA Sequence Variation**

Herbert Oberacher, Peter J. Oefner, Walther Parson, and Christian G. Huber*

After completion of the human genome sequence by the end of the year 2001,^[1] the discovery of small dissimilarities in the DNA sequences of different individuals, so-called polymorphisms, will gain increasing significance.^[2] Information about genetic diversity facilitates valuable insights into inherited disposal to disease as well as into human origin and gene migration. The standard technique for the determination of DNA sequences is the fully automated Sanger sequencing method employing multiplexed capillary electrophoretic analysis.^[1] In Sanger sequencing the whole sequence is determined, since polymorphisms between two randomly chosen chromosomes occur only at a frequency of one in 800–62000 base pairs (bp), their discovery by Sanger sequencing would require a lot of time and experimental effort simply for the determination of already known sequences. As a consequence, the development of novel and rapid screening methods for the discovery of variations in DNA sequences is of utmost importance, because they will enable a considerable reduction in the sequencing required and an increase in sample throughput.^[3] Moreover, such methods are also mandatory for the quality control of complete genes, prepared by total chemical synthesis, that are gaining importance.^[4]

The application of mass spectrometry (MS) to the investigation of high molecular nucleic acids was not feasible before the ionization techniques of matrix-assisted laser desorption/ionization (MALDI) and electrospray ionization (ESI) were developed.^[5] ESI-MS was applied successfully to the characterization of intact plasmids,^[6] polymerase chain reaction (PCR) products,^[7, 8] RNA,^[9] and synthetic oligonucleotides^[10] as well as to the genotyping of single nucleotide polymorphisms (SNPs)^[8] and short tandem repeats (STRs).^[11, 12] Nevertheless, the success of mass spectrometric assays largely depends on the amount and purity of the nucleic acids samples introduced into the mass spectrometer. Substantial drawbacks of the available purification methods, such as precipitation,^[13] solid-phase extraction,^[14] and liquid chro-

matography^[9, 15] are the high amounts of sample required and the low recovery. Consequently, these methods are frequently not appropriate for the characterization of real samples or quantitative analysis. Recently, we demonstrated the applicability of ion-pair reversed-phase high-performance liquid chromatography (IP-RP-HPLC) utilizing monolithic, 200 μm internal-diameter capillary columns for the separation and subsequent mass-spectrometric characterization of 180 fmol of DNA restriction fragments up to a length of 267 bp.^[16] Nonetheless, sample preparation by PCR typically supplies amounts of nucleic acids merely in the upper amol to lower fmol range. Moreover, the separation column had to be overloaded because of the relatively high detection limit of ESI-MS, which results in poor separation and insufficient characterization of the longer DNA fragments.

Significant improvements in the chromatographic conditions now enable for the first time the separation and subsequent on-line mass-spectrometric investigation of upper amol amounts of DNA. Figure 1 illustrates the total ion

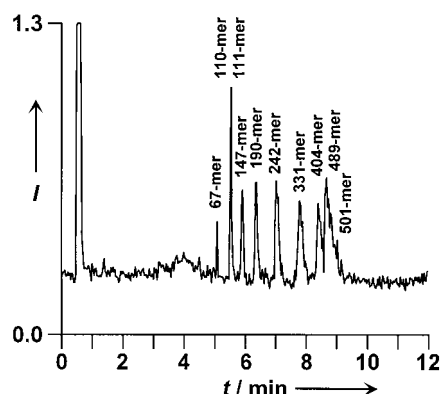


Figure 1. Chromatographic separation and mass analysis of the restriction fragments of a pUC19 MspI digest. Column: PS/DVB monolith, 60×0.2 mm internal diameter; mobile phase: A) 25 mM butyldimethylammonium bicarbonate, pH 8.4, B) 25 mM butyldimethylammonium bicarbonate, pH 8.4, 40% acetonitrile; linear gradient: 10–40% B in 3 min, 40–50% B in 12 min; flow rate: $3.0 \mu\text{L min}^{-1}$; temperature: 25°C ; scan: 1000–3000 amu; electrospray voltage: 3.40 kV; sheath gas: nitrogen; sheath liquid: acetonitrile, $3.0 \mu\text{L min}^{-1}$; sample: 753 amol digest; I = signal intensity $\times 10^{-6}$ /counts.

matogram of 753 amol of a digest of the cloning vector pUC19 with the restriction enzyme MspI. Because of the high separation efficiency and the avoidance of overloading the ten fragments of the digest, ranging in size from 67–501 bp, could be resolved into eight peaks. Only the 110- and 111-mer as well as the 489- and 501-mer fragments coeluted, a consequence of the small difference in their lengths. Mass spectra were extracted from the total ion chromatogram and deconvoluted by means of a computer-aided algorithm,^[17] which yielded the molecular masses of the DNA fragments with high accuracy. As indicated in Table 1, mass spectra were obtained for all the fragments upon analyzing 15 fmol of material, from which the molecular masses were measured with an average accuracy of $\pm 0.025\%$. This value correlates well with the mass accuracy reported for an ion-trap mass spectrometer (0.02% for a single-stranded 81-mer PCR product).^[18] Even the coeluting DNA fragments were unambiguously identified

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Table 1. Masses of the DNA restriction fragments from the pUC19 cloning vector digested with MspI; n.d. = not detected.

Length [bp]	M_{calcd}	M_{found} (753 amol)	Relative deviation [%]	M_{found} (15 fmol)	Relative deviation [%]
67	41438.1	41413	−0.061	41423	−0.036
110	68005.6	67986	−0.029	67977	−0.042
111	68623.0	68664	0.060	68623	0.000
147	90883.4	90841	−0.047	90862	−0.024
190	117438.0	117413	−0.021	117424	−0.012
242	149566.0	149583	0.011	149596	0.020
331	204588.8	204520	−0.034	204611	0.011
404	249643.9	n.d.	n.d.	249750	0.043
489	302222.7	n.d.	n.d.	302391	0.056
501	309574.2	n.d.	n.d.	309567	−0.002

in the extracted mass spectra on the basis of their different masses (Table 1). After a reduction in the amount of sample to 753 amol, molecular masses were still obtained with equivalent mass accuracy for fragments ranging in size up to 331 bp (Table 1).

The attainment of low detection limits was made possible by the use of butyldimethylammonium bicarbonate as the ion-pair reagent instead of triethylammonium bicarbonate. A direct comparison of 25 mM butyldimethylammonium bicarbonate and 25 mM triethylammonium bicarbonate in 80:20 (v/v) water:acetonitrile as solvents for the ESI-MS of nucleic acids in direct-infusion experiments revealed an improvement in signal-to-noise ratio by a factor of 1.5 with butyldimethylammonium bicarbonate. This tendency correlates well with the observation that spectrum quality is enhanced by the use of less basic amines^[19] (pK_a of triethylamine: 10.72, pK_a of butyldimethylamine: 10.06). Moreover, the concentration of acetonitrile necessary to elute the nucleic acids from the column is higher with butyldimethylammonium ions (16.0–17.6%) compared to triethylammonium ions (6.5–7.9% acetonitrile), a result of the higher affinity of the former to the stationary phase. The concomitant decrease in surface tension and the increase in volatility of the eluent cause an additional improvement in electrospray ionization efficiency.^[20]

The applicability of IP-RP-HPLC-ESI-MS to the detection of insertions and deletions was evaluated through the characterization of restriction fragments of the pUC18 cloning vector. After digestion with HaeIII, all fragment masses were determined with a maximum mass deviation of $\pm 0.09\%$. The only exception was the 257 bp fragment showing a mass deviation of -0.39% , which differed significantly from the average value for the mass deviation given above ($\pm 0.025\%$). The measured mass difference of 620 mass units (found: 158220, calcd: 158840.1, Figure 2) corresponded almost exactly to the mass of one base pair. In fact, Sanger sequencing revealed the deletion of a C–G base pair at position 184 proving that the fragment is actually a 256-mer (calcd mass: 158221.7, Figure 2). Assuming that for the detection of an insertion or deletion the mass has to be measured to ± 200 mass units and that the maximum mass deviation is 0.09%, the method is generally applicable for nucleic acid fragments up to a mass of approximately 222000 (360 bp).

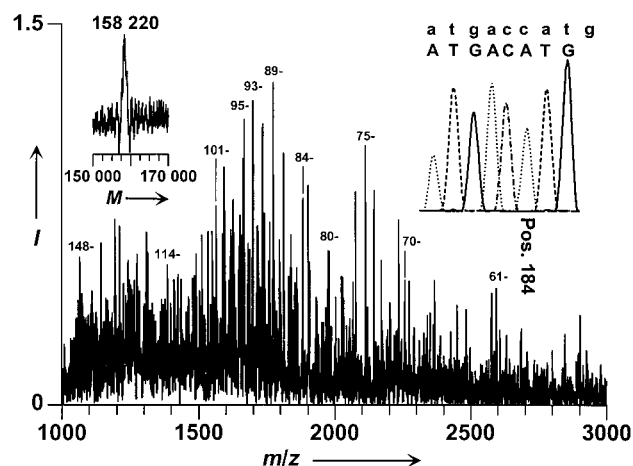


Figure 2. Mass spectrum for the detection of a deletion in a double-stranded DNA fragment from the cloning vector pUC18 by means of IP-RP-HPLC-ESI-MS. Mobile phase: A) 25 mM triethylammonium bicarbonate, pH 8.4, B) 25 mM triethylammonium bicarbonate, pH 8.4, 20% acetonitrile; linear gradient: 5–16% B in 3 min, 16–25% B in 12 min; flow rate: 3.0 $\mu\text{L min}^{-1}$; sample: 12 fmol pUC18 DNA HaeIII digest; other conditions as in Figure 1. The inset on the left side shows the deconvoluted mass spectrum, the one on the right side the sequence determined by Sanger DNA sequencing (in uppercase letters), which confirms the deletion suspected by mass spectrometry as a missing G–C base pair at position 184 in the published sequence (in lowercase letters); I = signal intensity $\times 10^{-3}$ /counts.

IP-RP-HPLC-ESI-MS analysis is also suitable for the characterization of SNPs. The distinction of the two alleles of an SNP both in homozygous and heterozygous individuals is possible by means of completely denaturing HPLC.^[21] For this method short DNA double strands (<100 bp) are amplified by PCR, then completely denatured into single strands, chromatographically separated by IP-RP-HPLC, and finally detected by UV-absorbance. The retention behavior of the single strands is characteristic for each allele. However, differences in retention are typically rather subtle, and thus, unequivocal identification of the alleles can sometimes be difficult or even impossible, especially in the case of a G/C polymorphism.^[21] Detection by means of ESI-MS can substantially alleviate the problem, since coeluting fragments having different masses are readily distinguished. An example for the recognition of an A/C polymorphism in a heterozygous individual is illustrated in Figure 3. Although all four single strands coeluted because of the application of a steep gradient (Figure 3a), the presence of the alleles A and C both in the forward and reverse strand (identified by the indices f and r) was effortlessly deduced from the mass spectrum (Figure 3b). Based on the high accuracy of mass measurements and a comparison of the measured and theoretical masses it is evident from Table 2 that from the four possible alleles only the alleles A and C fit the experimental data. As expected, the masses of the forward strands were shifted by 312 mass units to higher mass, a result of the non-template addition of an additional deoxyadenosine unit by Taq-polymerase.

The possibility to genotype an SNP in the form of a deletion was examined by means of a T/–T polymorphism in an 82 and 81 bp PCR product. Both alleles were unambiguously identified by the molecular masses of the single strands

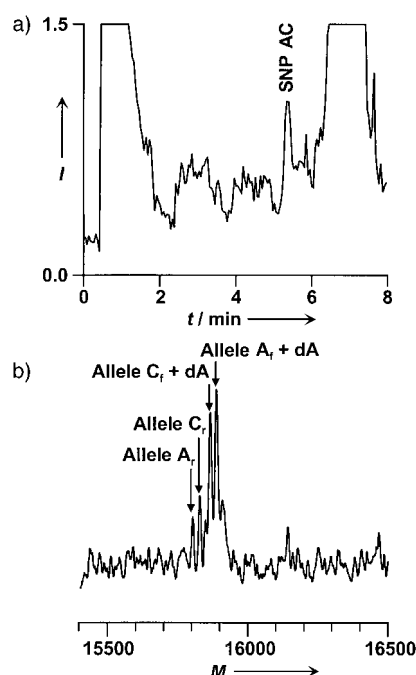


Figure 3. Identification of a single nucleotide polymorphism by IP-RP-HPLC-ESI-MS. Mobile phase: A) 25 mM triethylammonium bicarbonate, pH 8.4, B) 25 mM triethylammonium bicarbonate, pH 8.4, 20% acetonitrile; linear gradient: 10–60% B in 10 min; flow rate: 3.0 $\mu\text{L min}^{-1}$; temperature: 70 °C; scan: 500–2000 amu; sample: 500 nL PCR-amplicon; other conditions as in Figure 2; I = signal intensity $\times 10^{-6}$ /counts.

Table 2. Allele identification through comparison of the eight theoretically possible masses with the measured masses.

Allele	M_{calcd}	M_{found}
A + dA _f	15893.54	15890
A _r	15806.42	15806
T + dA _f	15884.52	–
T _r	15797.40	–
G + dA _f	15909.54	–
G _r	15871.47	–
C + dA _f	15869.51	15869
C _r	15831.44	15831

(found/calcd T_f: 25277/25278.55; T_r: 25261/25262.75; –T_f: 24973/24974.36; –T_r: 24945/24949.54).

The on-line coupling to liquid chromatography represents an important step towards the application of electrospray ionization mass spectrometry for the detection of variations in DNA sequences in real molecular biological and biochemical samples. Highly accurate mass measurements enable the characterization of nucleic acids by their molecular mass as an intrinsic property of these molecules. Future developments will focus on the possibility of nucleic acid sequencing by means of fragment ion mass spectra, and it must be emphasized that the on-line separation and purification using liquid chromatography will be essential to obtain mass spectra of high quality and information content.

Experimental Section

All DNA separations were performed in monolithic, divinylbenzene cross-linked polystyrene (PS/DVD) polymer-based capillary columns (60 $\times$

0.2 mm internal diameter).^[16] Separation of nucleic acids was accomplished by IP-RP-HPLC using 25 mM triethylammonium bicarbonate or butyldimethylammonium bicarbonate as the ion-pair reagent. Reproducible gradients at a flow rate of 1–2 $\mu\text{L min}^{-1}$ were formed upon splitting a primary flow of 100–200 $\mu\text{L min}^{-1}$ by means of a fused silica capillary (1 m length, 375 μm external diameter, 50 μm internal diameter) and a tee-piece. Separated nucleic acids were detected by ESI-MS in an ion trap mass spectrometer (LCQ, Finnigan, San Jose, CA). A mixture of caffeine, methionyl–argininyl–phenylalanyl–alanine and Ultramark 1621 was used for external mass calibration according to the manufacturer's protocol. Subsequently, the parameters of the ion optics were tuned at m/z 1808.7 for maximum ion transmission in the negative ion mode with a solution of 20 pmol μL^{-1} (dT)₂₄ and 25 mM triethylammonium bicarbonate in 80:20 (v/v) water:acetonitrile. Acetonitrile at a flow rate of 3 $\mu\text{L min}^{-1}$ was added as sheath liquid to improve detection sensitivity.^[22] The digests of the cloning vectors were purchased from Sigma (St. Louis, MO). The sequence and PCR amplification of the 51 bp biallelic A/C polymorphism is described in ref.[21] that of the 82/81 bp T/T – T polymorphism in the SNP database of the NCBI at <http://www.ncbi.nlm.nih.gov/SNP>, No. rs769382.

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Zeolite Synthesis by the High-Pressure Hydrothermal Method: Synthesis of Natural 6-Ring Zeolites with Different Void Systems

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Their unique properties make zeolites interesting for scientific research as well as for industrial applications—for example they are used as sorbing materials for gaseous and liquid components, as ion exchangers in aqueous systems with a wide variety of applications, and as shape-selective catalysts in the petrochemical industry.

Zeolites are conventionally produced by hydrothermal processing at relatively moderate temperatures.^[1] By this method only an empirical correlation exists between the precursor material and the zeolite product. Although several industrially important zeolites can be synthesized by applying such an empirical correlation, the conventional hydrothermal synthesis process is steered in a certain range by using structure-directing agents (templates) to obtain zeolites with the desired channel system and structure type. All known zeolites with 6-ring structural building units have already been synthesized in this way.^[2] The empirical character of the zeolite synthesis process remains, however, at least unsatisfactory in the search of new zeolite structure types for advanced specific applications. Furthermore, the removal of the template materials from the zeolite cavity systems may cause problems that have often not been solved satisfactorily: residual template materials in the cavity system reduce the zeolite activity, or these agents are cracked during application processes leading to poisoning. Besides this, some zeolites, such as stilbite or laumontite, that are very common in nature have not yet been obtained by any conventional hydrothermal synthesis process.^[3] Consequently, only relatively few zeolite structure types are applied industrially.

Davis and co-workers have developed a synthesis process in which conventional hydrothermal zeolites are modified by ion exchange and the desired zeolite is obtained by using seed material of the zeolite structure type to be produced.^[4]

A direct, alternative method for zeolite synthesis is presented here, in which the hydrothermal natural formation conditions of this class of materials are simulated. In this process artificial, water-free glasses of identical composition to those of the respective natural zeolite are used as starting materials, and distilled water is applied as pressure and reaction medium. In general, the pressure range for this kind of synthesis lies between 500 bar and 4 kbar, the temperatures between 30 and 450 °C, and the reaction times between 12 h

and 60 days.^[5] Neither organic templates nor reactive solutions are necessary to obtain zeolite products of the desired channel size and structure type (Table 1).

Based on the experience of former zeolite syntheses, a water pressure of 1 kbar and a reaction time of 60 days were

Table 1. Channel diameters [Å] of synthesized 6-ring aluminosilicate zeolites (data from ref. [5]).

Code	Zeolite phase	Channel system	
		in the first crystallographic direction	in the second
FAU	faujasite	$\langle 111 \rangle$ 12 7.4***	
GME	gmelinite	$[001]$ 12 7.0*	$\leftrightarrow$ $\perp [001]$ 8 $3.6 \times 3.9^{**}$
OFF	offretite	$[001]$ 12 6.7*	$\leftrightarrow$ $\perp [001]$ 8 $3.6 \times 4.9^{**}$
CHA	chabazite	$\perp [001]$ 8 $3.8 \times 3.8^{***}$	
ERI	erionite	$\perp [001]$ 8 $3.6 \times 5.1^{***}$	
LEV	levyne	$\perp [001]$ 8 $3.6 \times 4.8^{**}$	

[a] The numbers **12** and **8** refer to the number of O, Si, or Al atoms forming the rings that control the access to the zeolite channel system. The dimensionality of the channel system is denoted by the number of stars; interconnected channel systems are denoted by $\leftrightarrow$.

used in the experiments under isothermal conditions between 170 °C and 270 °C. Earlier experiments have shown that no zeolite products are obtained by using synthesis pressures lower than 500 bar—presumably for kinetic reasons. Up to 3/4 of the homogeneous glass pieces with a maximum diameter of 4 mm were hydrothermally converted to crystalline products. All zeolite phases formed show, within the accuracy of the EDX measurements of 10%, the chemical composition of their natural counterparts^[3a, 6, 7] (Table 2). Figure 1 presents a scanning electron microscope image of each of the formed crystals of the respective phase and the crystal face orienta-

Table 2. The JCPDS files applied for phase identification.

Zeolite phase	JCPDS Nr.
faujasite	39-1380
gmelinite	38-435
offretite	25-1186
chabazite	34-137
erionite	39-1379
levyne	26-1381

tion obtained from dihedral angle measurements between neighboring crystal planes.^[8] The measured values lay within the experimental error of 3% according to the accuracy of the method. Other zeolite phases, namely chabazite and gmelinite, were detected by morphological examinations as by-products of nearly all syntheses, however, the amounts of these other zeolites were too low to be characterized by X-ray diffraction (XRD) investigations. Levynite was the only synthesis product obtainable in a phase-pure form even in the scanning electron micrographs.

The use of precursor glasses of the “idealized” composition of the natural zeolite, as given by single-crystal data, was in several cases not sufficient to obtain the desired zeolite

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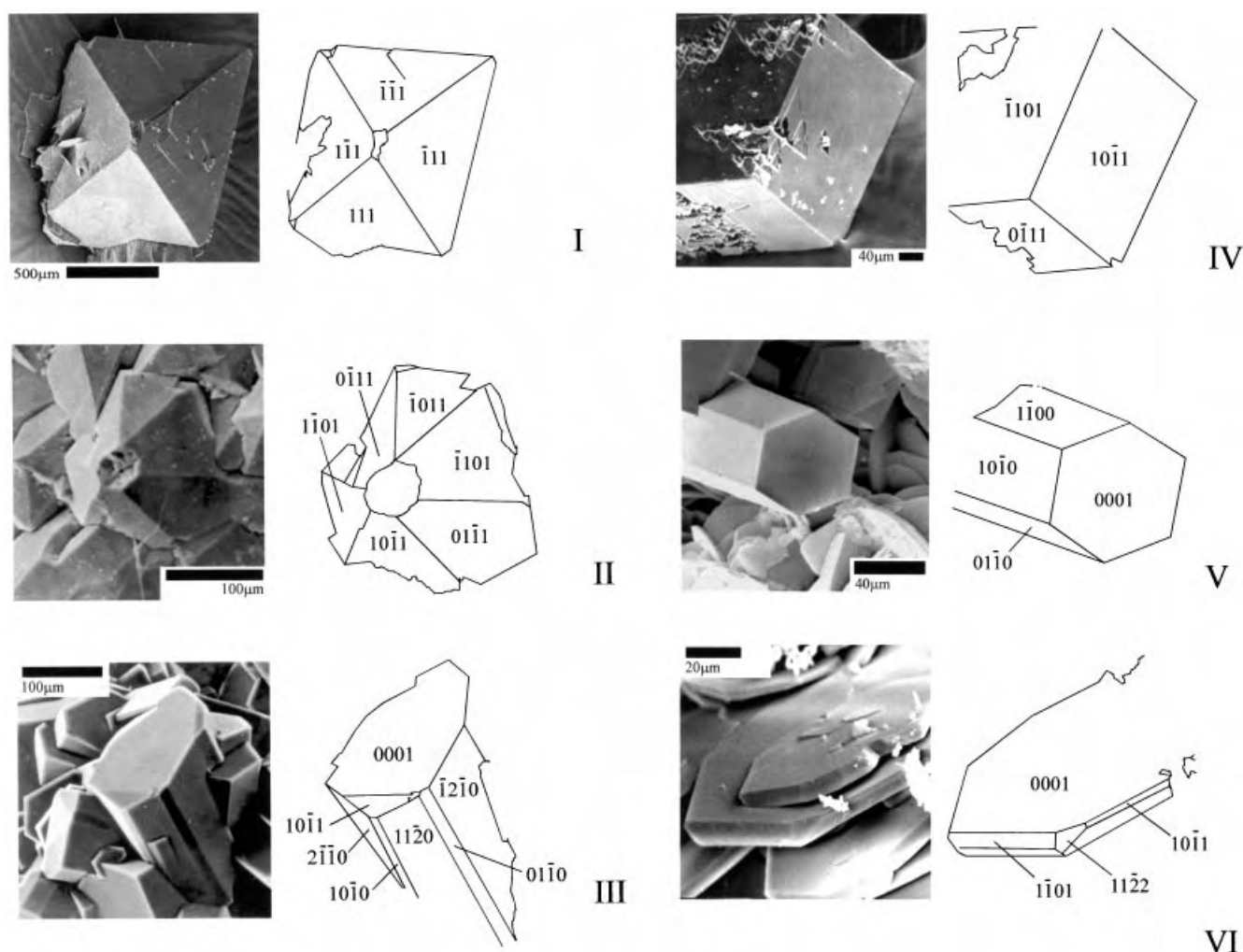


Figure 1. Scanning electron micrographs of single crystals of faujasite (I), gmelinite (II), offretite (III), chabazite (IV), erionite (V), and levyne (VI) synthesized from the precursor glass with the composition of the respective natural zeolite (see Table 3, reaction time 60 days, synthesis pressure 1 kbar, synthesis temperature 220 °C).

structure type:^[7] under the chosen high-pressure/high-temperature hydrothermal conditions the 6-ring zeolites faujasite, offretite, and erionite could only be prepared in the presence of iron as “catalyst” (5 mol % Fe_2O_3 added to the precursor glass). The chemical analysis of the surrounding rock matrices of these natural 6-ring zeolites show that they almost always contain iron. Furthermore, faujasite, gmelinite, and chabazite were only obtained if further cations (introduced as the oxide component in the precursor glass in an amount equal to 10 mol % of the total oxide content) were present according to the “actual” average natural zeolite composition as given by Gottardi and Galli.^[3a] The necessity of the addition of further channel cations as well as iron to the zeolite precursor glass is evidently due to their special hydration properties, since they act as a sort of ionic template for the formation of the respective channel system. Further investigations are necessary to clarify the mechanism of this behavior.

Based on the experimental results, the isothermal solution–crystallization process can be explained in principle as shown in Figure 2: the synthetic glasses of natural zeolite composition used as starting materials for the synthesis process are dissolved isothermally under the high-pressure

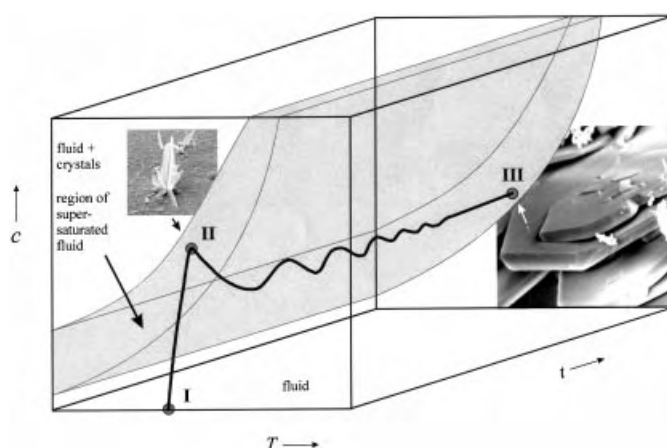


Figure 2. Temperature–concentration–time (T – c – t) diagram for the high-pressure hydrothermal synthesis process (see text for details): I) glass and fluid phase; II) nucleation at the frontier of supersaturated fluid; III) final state of grown microcrystals.

hydrothermal conditions. Therefore, the hydrothermal fluid consisting only of hydrothermal water at the starting point of the experiment (I) becomes more and more concentrated with

time. The glass can still be dissolved even when the solubility limit of the fluid with respect to the crystalline phase is attained (supersaturation). However, at a certain level of concentration (marked as point II in the region of supersaturated fluid) spontaneous crystallization of the zeolite phase occurs, leading to a decrease of the concentration in the hydrothermal fluid. The zeolites are, therefore, synthesized by a process in which the precursor glass is dissolved in the fluid phase and then crystallizes as zeolite.

Crystal growth only occurs in the region of supersaturated fluid. If the isothermal–isobar conditions are carefully maintained during the long duration of the experiment, neither etching of the zeolite crystals nor the formation of a second zeolite phase (by repeated spontaneous crystallization and growth) is observed. From this it can be concluded that the dissolution–crystallization process continues in the range of supersaturated fluid in such a way that the system is self-stabilizing. These are the time-dependent conditions of crystal growth between point II and III (Figure 2). The process will continue as long as there is enough glassy material for the continuous dissolution–crystallization process—if the synthesis process is not interrupted before.

Experimental Section

Glasses of the appropriate zeolite composition (see Table 3) were repeatedly molten for five minutes and quenched and crushed each time in a high-frequency furnace in open carbon crucibles in air (Schunk Kohlenstofftechnik, Germany) at temperatures up to 1800 °C using a blend of the appropriate water-free alkali metal and/or alkaline earth metal

investigated by scanning electron microscopy (SEM). The resulting micrographs were evaluated with the stereo-comparator for crystal indexing and crystallographic analysis.^[8]

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Table 3. The chemical composition of the glass precursors of the aluminosilicate 6-ring zeolites.

Zeolite phase	Precursor glass composition ^[a]
faujasite ^[b]	5 Na ₂ O × 6 CaO × 4 MgO × 15 Al ₂ O ₃ × 66 SiO ₂ × 9.6 (Sr, Ba, K ₂)O × 4.8 Fe ₂ O ₃
gmelinite	1 Na ₂ O × 1 Al ₂ O ₃ × 4 SiO ₂ × 0.6 (Ca, K ₂)O
offretite ^[b]	1 K ₂ O × 2 CaO × 2 MgO × 5 Al ₂ O ₃ × 26 SiO ₂ × 1.8 Fe ₂ O ₃
chabazite	1 CaO × 1 Al ₂ O ₃ × 4 SiO ₂ × 0.6 (Li ₂ , K ₂)O
erionite ^[b]	1 Na ₂ O × 2 K ₂ O × 2 MgO × 3 CaO × 8 Al ₂ O ₃ × 54 SiO ₂ × 3.5 Fe ₂ O ₃
levyne	1 Na ₂ O × 5 CaO × 6 Al ₂ O ₃ × 24 SiO ₂

[a] The cations of the additional mixed oxide components are present in equal proportions. [b] Synthesis only possible in the presence of Fe ions.

carbonate, iron oxide, α -alumina, and silicon dioxide (quartz). Visually homogeneous glasses were amorphous according to powder X-ray-diffraction investigations (XRD, Cu_{K α} radiation, Bragg–Brentano geometry). Then, pieces of the glasses (maximum length 4 mm) were placed in copper capsules (about 1 cm³ volume), filled up with distilled H₂O as pressure and reaction medium (water:glass ratio approximately 10:1) and tightly closed. Three of these capsules were placed in a high-pressure autoclave (MRA/112R type, TEM-PRESS research division, USA). The whole system was set under pressure by using distilled water as the pressure medium. The hydrothermal experiments were conducted in a temperature range between 170 and 270 °C for 60 days at a synthesis pressure of 1 kbar. Every experiment was repeated twice. These conditions were chosen based on experience with previous zeolite syntheses using this method.^[3b,c, 5, 9]

The crystalline phases formed at the surface of the glasses were subsequently investigated by XRD and energy-disperse X-ray analysis for chemical composition (EDX), and the crystal morphology was finally

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Which Structural Elements Are Relevant for the Efficacy of Neocarzinostatin?*

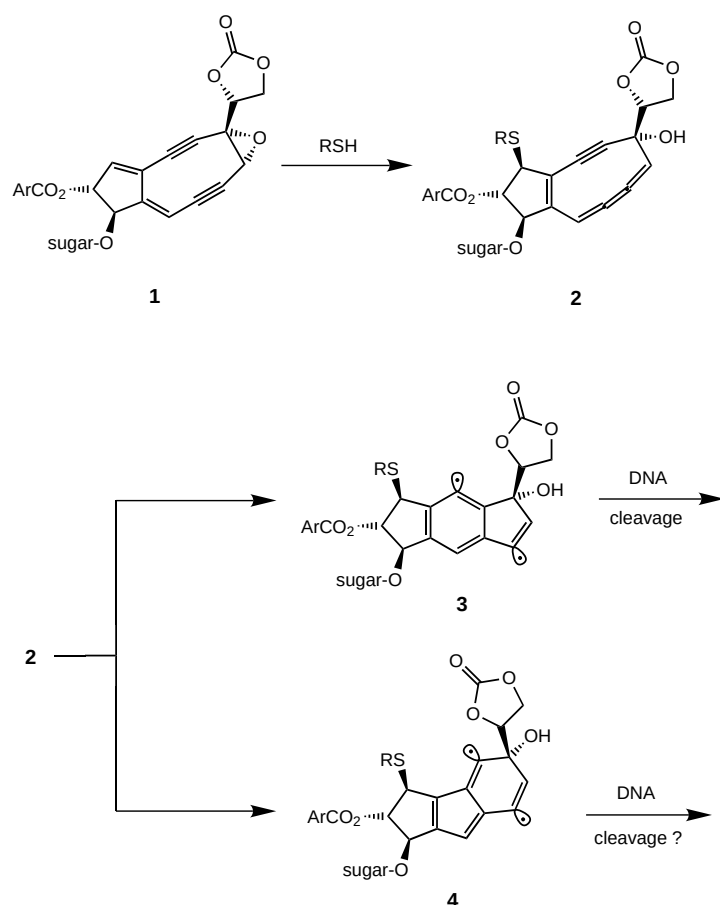
Patrick W. Musch and Bernd Engels*

Neocarzinostatin (NCS) is one representative of the family of natural enediynes that exhibit a high efficacy as antitumor antibiotics.^[1] It consists of a 1:1 complex of an apoprotein and a bioactive non-protein chromophore (**1** in Scheme 1).^[1, 2] In the first step of the mode of action of NCS^[2b, 3] the chromophore **1** is carried to the minor groove of the DNA by the apoprotein which at the same time serves as its stabilizer. After **1** is bound to the DNA the apoprotein is separated off, a stereospecific nucleophilic addition of thiol rearranges **1** to the highly strained enyne-[3]-cumulene **2**.

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



Scheme 1. Mode of action of the neocarzinostatin chromophore **1**.

In the next step the six-membered ring cyclization between the centers C³ and C⁷ leads to the biradical **3**, which through a double hydrogen abstraction from adenine and thymine induces a DNA strand cleavage and as a consequence the cytotoxicity.

While the general course of the mode of action of NCS is clarified, it is still unclear which structural elements are relevant for the high efficacy of NCS. Based on high-level *ab initio* investigations, we present new insight into this topic which is of great interest for the development of new antitumor antibiotics. We first compare the six-membered ring cyclization found in the mode of action of NCS with an alternative five-membered ring cyclization between the C² and C⁷ centers. The latter yields the intermediate **4** instead of **3**; formally both species represent biradicals. For a nine-membered monocyclic enyne-allene, a model compound for the chromophore of NCS (**2**), this alternative route was predicted to be kinetically preferred to the six-membered ring cyclization.^[4] From a comparison of both cyclization modes a new model concerning the tasks of the substituents present in **2** arises. To test this model we discuss the influence of the substituents and the solvent on the kinetics of both cyclization modes. Finally, we study the capability of the arising biradicals for the subsequent hydrogen abstraction leading to the final DNA cleavage. Our investigations provide new insights into the subtle effects which nature uses to obtain powerful antitumor antibiotics. Valuable information for further im-

provements of these substances can be deduced, since some of factors that the limit the efficacy become clear.

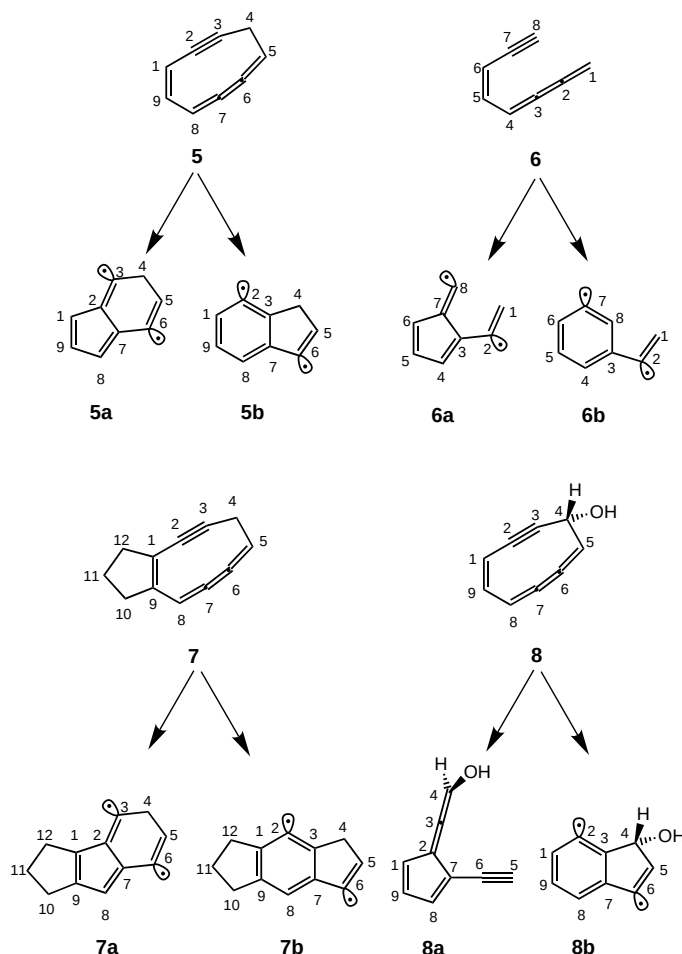
Initial insight into the topics mentioned above can be taken from Table 1, which summarizes the computed activation barriers of the six-membered (C³–C⁷) and of the five-membered (C²–C⁷) ring cyclization for various model compounds.^[5] Our CCSD(T) computations^[6] represent the most reliable approach for the transition states, which possess a

Table 1. Transition states of both possible cyclization modes. All values are in kcal mol^{−1}.

Method	C ² –C ⁷ cyclization ^[a]		C ³ –C ⁷ cyclization ^[b]	
	$\Delta E^\ddagger$	$\Delta G^\ddagger_{298K}$	$\Delta E^\ddagger$	$\Delta G^\ddagger_{298K}$
5	UB3LYP/6-31G(d)	+18.6	+17.6	+21.1
	CCSD(T)/cc-pVDZ	+13.8		+16.5
6	UB3LYP/6-31G(d)	+31.9	+31.9	+22.2
	CCSD(T)/cc-pVDZ	+29.7		+20.1
7 ^[c]	UB3LYP/6-31G(d)	+22.8	+21.4	+22.2
	UB3LYP/6-31G(d)	+19.5	+18.3	+21.6
8	UB3LYP/6-31G(d)	+19.5	+18.3	+21.6
	CCSD(T)/cc-pVDZ	+16.1		+18.3

[a] For **6**: C³–C⁷ cyclization. [b] For **6**: C³–C⁸ cyclization. [c] CCSD(T) calculations could not be performed due to computational limitations.

closed-shell electronic structure. At this level of theory we predict for the parent ring system of the NCS chromophore (**5**; Scheme 2) the C²–C⁷ cyclization to be kineti-



Scheme 2. Model compounds used in this work to investigate ring strain and substituent effects on the cyclization of NCS.

cally preferred to the C³–C⁷ cyclization ($\Delta E^\ddagger(\text{C}^2\text{--C}^7) = +14 \text{ kcal mol}^{-1}$ vs. $\Delta E^\ddagger(\text{C}^3\text{--C}^7) = +17 \text{ kcal mol}^{-1}$), which was found to be the only mode of action in NCS.^[1] Our values obtained for the C³–C⁷ cyclization agree nicely with those calculated by Cramer and Squires employing the BD(T) method.^[7] Compared to **5**, the open-chain compound **6** possesses a considerably smaller activation barrier for the C³–C⁷ cyclization than the C²–C⁷ cyclization ($\Delta E^\ddagger(\text{C}^2\text{--C}^7) = +30 \text{ kcal mol}^{-1}$ vs. $\Delta E^\ddagger(\text{C}^3\text{--C}^7) = +20 \text{ kcal mol}^{-1}$). The comparison between **5** and **6** shows that the shift in the regioselectivity is induced by the ring strain present in **5**. It also indicates that the ring strain is important for the efficacy of **2** since it reduces the activation energy of both cyclization modes considerably. Additionally to **6b**, **5b** represents a biradical with a fixed distance of 3.55 Å between the two radical centers. One can imagine that such a fixed distance is also important for the efficacy of the double hydrogen abstraction in the last step of the mode of action of NCS. However, since in the mode of action of NCS only the C³–C⁷ cyclization is found, our calculations indicate that the substituents present in **2** shift the regioselectivity back to the C³–C⁷ cyclization.

Information on the importance of substituents for the control of the regioselectivity can also be taken from Table 1. The cyclopentene ring in **7** seems to be important for the control of the regioselectivity, since the induced strain increases the activation energy of the C²–C⁷ cyclization more than that of the C³–C⁷ cyclization. A similar trend was found experimentally for enyne-allenes.^[8] In contrast, the OH substituent at C⁴ (**8**) increases both activation barriers by about the same amount (2 kcal mol^{−1}) and therefore does not affect the regioselectivity of the cyclization. However, the substituent completely changes the reaction path of the C²–C⁷ cyclization. Along with the ring closure between C² and C⁷ the ring opens between C⁴ and C⁵ leading to the final product **8a**. In contrast, the C³–C⁷ cyclization still proceeds along a biradical route. Polar solvents also favor the C³–C⁷ cyclization to some extent, since the activation energy of the C³–C⁷ cyclization for **5** and **7** is lowered by approximately 0.5 kcal mol^{−1}, while the activation energy of the C²–C⁷ cyclization is increased by about the same amount. Besides the activation energies also the reaction energies have to be taken into account for the regioselectivity. The reaction energies given in Table 2 show that for the systems considered in this study the C³–C⁷ cyclization is thermodynamically favored.

Our findings suggest that one of the major tasks of the substituents present in the chromophore of NCS is to prevent the five-membered ring cyclization. A possible reason for the control of the regioselectivity can be seen from the computed

reaction energies of both cyclizations and the singlet–triplet gap ($E_{\text{S-T}}$) of both intermediates (Table 2).^[9] The intermediate of the C²–C⁷ cyclization **5a** lies energetically so high that its lifetime is considerably limited by the reverse reaction, which possesses nearly no activation barrier. Additionally, the computed $E_{\text{S-T}}$ value of about 12 kcal mol^{−1} indicates that **5a** does not have distinctive biradical character. In contrast, **5b** lies energetically well below the reactant and represents a true biradical ($E_{\text{S-T}} \approx 4 \text{ kcal mol}^{-1}$). The differences concerning lifetime and biradical character indicate that an efficient hydrogen abstraction, which is the important final step of the mode of action of NCS, will only be possible with **5b**. A similar observation is found for **7**, showing that this behavior seems to represent a general motif for bicyclic enyne-cumulene compounds. The small singlet–triplet gap of the acyclic enyne-cumulene **6a** indicates that the ring strain of the cyclic enyne-cumulene system is responsible for the large values obtained for **5a** and **7a**. Consequently, we expect enyne-cumulene systems in which the C²–C⁷ cyclization is not suppressed to be less efficient antitumor antibiotics.

Our investigations show that the chromophore of NCS represents a fascinating example for natural products in which a subtle balance of various influences leads to the desired result. While the monocyclic enyne-cumulene moiety seems to be important to provide a biradical with a fixed distance between both radical centers and a low activation barrier for the cyclization process, the substituents present in **2** are necessary to prevent the competing C²–C⁷ cyclization.

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Table 2. Heat of reactions for both cyclization reactions and singlet–triplet gaps ($E_{\text{S-T}}$) for the corresponding intermediates. All values are in kcal mol^{−1}.

Method	5a	5b	6a	6b	7a	7b
UB3LYP/6-31G(d)	+17.3	+0.8	+16.4	−8.5	+22.2	+2.0
MR-CI + Q/cc-pVDZ	+12.0	−3.7	−	−	−	−
$E_{\text{S-T}}$ (UB3LYP/6-31G(d))	+11.9	+4.5	−3.4	+1.3	+13.0	+4.41

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Synthetic Inhibitors of Cell Adhesion: A Glycopeptide from E-Selectin Ligand 1 (ESL-1) with the Arabino Sialyl Lewis^x Structure**

Markus Rösch, Holger Herzner, Wolfgang Dippold,
Martin Wild, Dietmar Vestweber, and Horst Kunz*

*Dedicated to Professor Leopold Horner
on the occasion of his 90th birthday*

In the course of the inflammatory cascade, carbohydrate-recognizing receptors are expressed on endothelial cells: P-selectin within some minutes; E-selectin, however, with a

delay of 4–6 hours after the chemotactic stimulus.^[1] The sialyl Lewis^x epitope has been identified as the ligand of both selectins.^[2, 3]

The carbohydrate-binding domain of E-selectin has been investigated by using transfer-NOE NMR spectroscopic experiments on a complex of sialyl Lewis^x with a recombinant E-selectin–IgG fusion protein, molecular modeling studies,^[4] and X-ray crystal structure analysis.^[5] These studies give evidence of the decisive role of the fucose moiety of sialyl Lewis^x in the binding to E-selectin which is mediated by the coordination to a calcium ion.^[5–7] In the case of the natural selectin ligands, other structural elements are evidently also involved in the specific binding. O-Linked *N*-acetylglucosamine saccharides with sialyl Lewis^x determinants are important for the binding of the P-selectin-selective ligand PSGL-1. However, a peptide sequence that is rich in acidic amino acids and contains O-sulfatyl tyrosines also contributes to the binding.^[8, 9] In the case of the endogenous E-selectin adhesion ligand ESL-1, the sialyl Lewis^x ligand is present on an N-glycan.^[10, 11] A contribution of peptide epitopes of ESL-1 has not been reported for the binding to E-selectin, which also plays a role in metastasis^[2b] and, for example, specifically binds to gastrointestinal tumor cells.^[12]

ESL-1 contains five potential N-glycosylation sites.^[11] The amino acid sequences in their neighborhood is conserved to a large extent compared to those of other E-selectin-binding sialoglycoproteins. In this sense, the amino acid sequence 672–681 of ESL-1 **1** around the sequon NLT is identical to the sequence 676–685 of the E-selectin ligand MG160.^[13]

–Gly-Asn-Leu-Thr-Glu-Leu-Glu-Ser-Glu-Asp- **1**

In earlier investigations, a modulating influence of the peptide portion on the carbohydrate recognition was found in the binding of synthetic sialyl Lewis^x glycopeptides to P-selectin^[14] as well as to E-selectin.^[15] As the segment **1** of ESL-1 with its accumulation of acidic amino acids is similar to the binding domain of PSGL-1, we selected this sequence for the construction of a synthetic E-selectin ligand. An additional aim was to find an E-selectin ligand which, like sialyl Lewis^x mimetics,^[16] is stabilized against enzymatic degradation. The fucoside bond is a site for the enzymatic attack on sialyl Lewis^x.^[17] The fucose portion, however, is considered essential for the binding of sialyl Lewis^x to E-selectin (see above).^[4, 5]

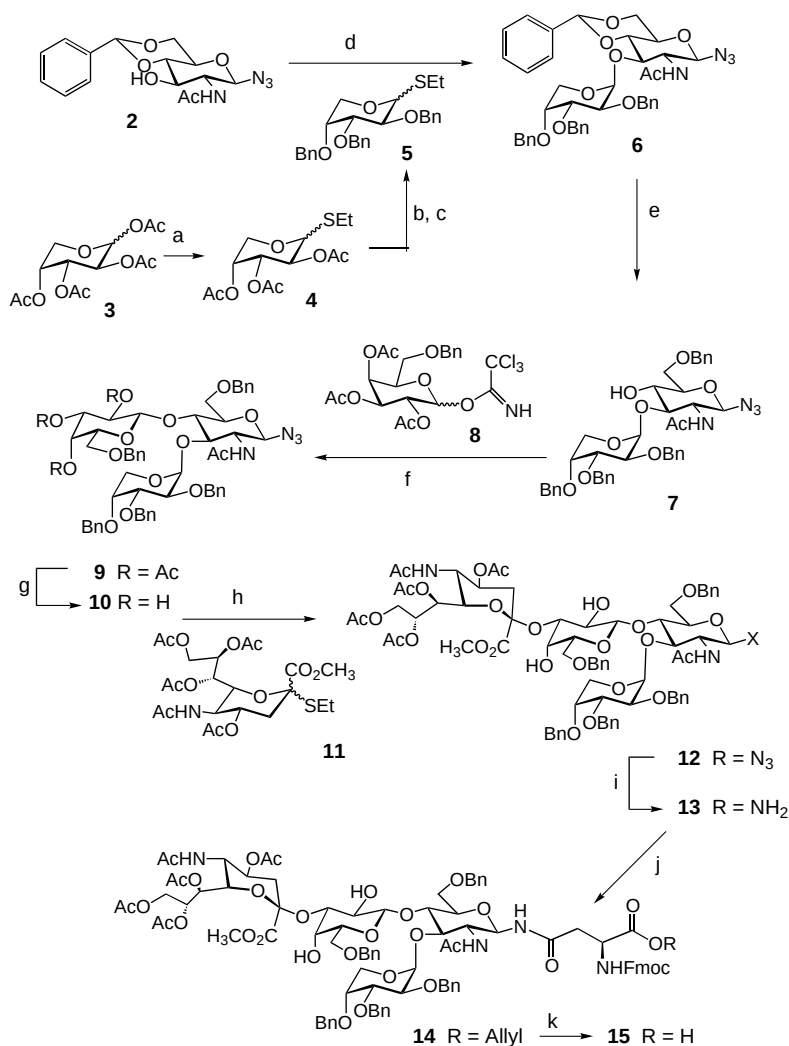
It should now be examined whether the α -L-fucoside can be substituted by a β -D-arabinopyranoside, which exposes its three secondary hydroxy groups in the same spatial arrangement as the fucoside. D-Arabinopyranose, however, is absent in mammals and its glycosides should therefore be biologically more stable.

As in the previous syntheses of glycopeptides,^[14, 15] the azido group was used as the protecting group at the anomeric center of the glucosamine unit in the synthesis of the arabino sialyl Lewis^x saccharide.^[18] The in situ anomerization method^[19] was used to glycosylate 4,6-*O*-benzylidene-*N*-acetylglucosaminyl azide **2**^[20] with ethylthio-2,3,4-tri-*O*-benzyl- α , β -D-arabinopyranoside **5** to give β -D-arabinosylglucosamine azide **6** (Scheme 1).

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Scheme 1. Reagents and conditions: a) EtSH, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -15°C , 49%; b) NaOMe, MeOH, 20°C , quantitative; c) $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$, NaH, DMF, 0°C , 88%; d) CuBr_2 , Bu_4NBr , $\text{CH}_2\text{Cl}_2/\text{DMF}$, 20°C , 57%; e) NaCNBH₃, THF, HCl in Et₂O, THF, 0°C , 68%; f) TMSOTf, CH_2Cl_2 , -15°C , 2 d, 49%; g) MeONa, MeOH, 93%; h) NIS, TFOH, $\text{CH}_3\text{CH}_2\text{CN}$, $-78 \rightarrow -32^\circ\text{C}$, 24 h, 56%; i) Raney Ni, H₂, *i*PrOH/H₂O (9:1), 20°C , 94%; j) Fmoc-Asp-OAll, HATU/HOAT, *N*-methylmorpholine, DMF, 69%; k) $(\text{Ph}_3\text{P})_4\text{Pd}$, *N*-methylaniline, THF, 86%; (TMSOTf = trimethylsilyl trifluoromethanesulfonate, DMF = *N,N*-dimethylformamide).

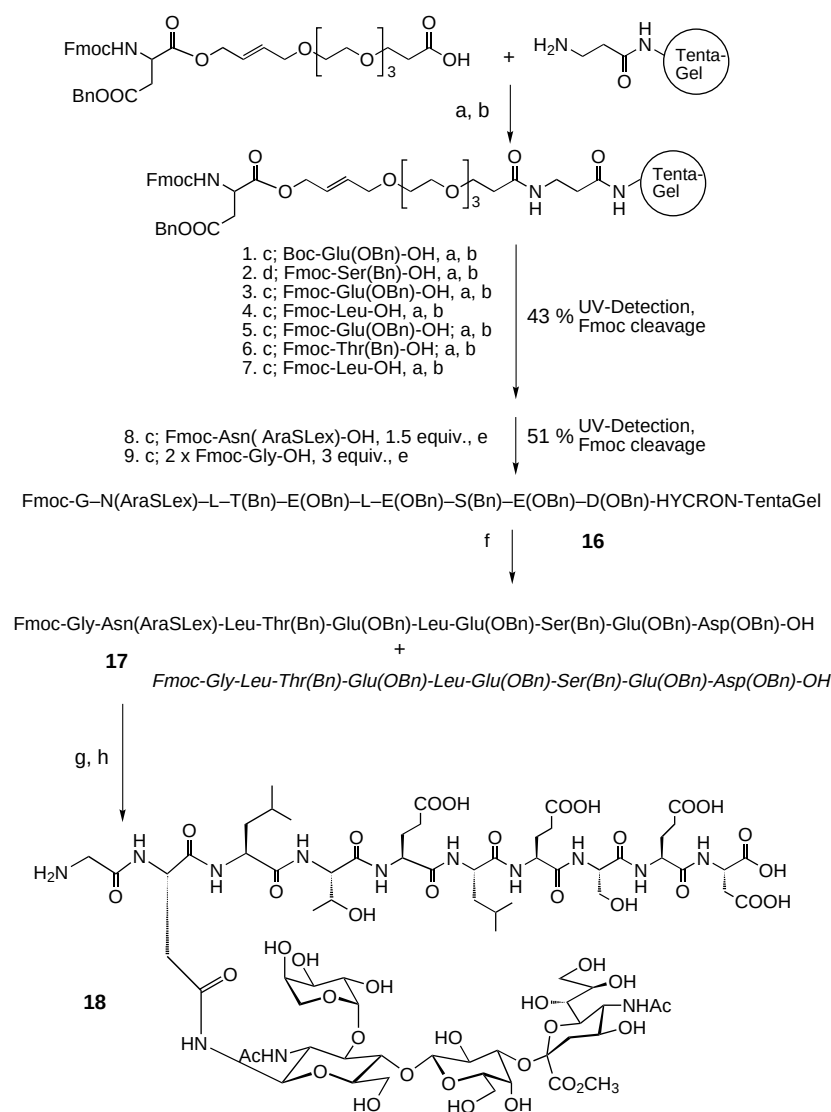
Owing to the high acid sensitivity of arabinopyranose derivatives, tetra-*O*-acetyl arabinopyranose **3**^[21] was treated with ethanethiol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -15°C , and the reaction mixture was neutralized prior to the isolation of ethylthio-tetra-*O*-acetyl- α , β -D-arabinopyranoside by the addition of triethylamine in amounts equimolar to BF_3 . Removal of the *O*-acetyl groups from **4** by using catalytic sodium methanolate in methanol and subsequent benzylation gave the arabinosyl donor **5**. During the regioselective opening of the benzylidene acetal of **6**^[22] with sodium cyanoborohydride, hydrogen chloride in dry diethyl ether was added dropwise and monitored by using thin-layer chromatography because of the acid sensitivity of the arabinopyranoside bond. Galactosylation at the rather unreactive 4-OH group of the arabinosyl glucosamine derivative **7** was carried out with the reactive trichloroacetimidate **8**.^[23] The *O*-acetyl groups were then removed from trisaccharide **9** by Zemplén-transesterification.

To achieve a regioselective sialylation at the 3'-OH group of the Lewis^x derivative **10**, the ethylthiosialoside **11** was a more favorable donor than the methylthio analogue. Furthermore, the activation had to be carried out with *N*-iodosuccinimide (NIS) and trifluoromethane sulfonic acid (TFOH)^[24] (not with methylsulfonyl triflate) in propionitrile at -32°C in the presence of molecular sieves (4 Å) without stirring. Only then was the arabino sialyl Lewis^x azide **12**^[25] obtained in satisfying yield after two chromatographic purifications. The arabino sialyl Lewis^x amine **13** was obtained by the Raney nickel (neutrally washed) catalyzed hydrogenolysis of the azide.^[26] Lewis^x amine **13** was isolated and immediately condensed with Fmoc aspartic acid α -allyl ester^[27, 28] by using [2-*O*-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU)^[29] and 1-hydroxy-7-azabenzotriazole (HOAT) to give the *N*⁴-[arabino sialyl Lewis^x] asparagine conjugate **14**. Palladium(0)-catalyzed cleavage of the allyl ester by using *N*-methylaniline as the allyl-trapping nucleophile^[30] gave the arabino sialyl Lewis^x asparagine building block **15**^[31] required for the glycopeptide synthesis.

The solid-phase synthesis of the glycopeptide partial sequence **1** of ESL-1 with the arabino sialyl Lewis^x side chain at Asn⁶⁷³ was carried out by using the allylic HYCRON anchor^[32] on TentaGel resin^[33] (Scheme 2). According to a previously described general procedure,^[32, 34] Fmoc aspartic β -benzyl ester was linked to the allylic anchor and coupled to TentaGel resin loaded with β -alanine as the standard amino acid. Except for the first chain-extending step, the solid-phase synthesis was carried out according to Fmoc strategy, with benzylic protection of amino acid side chain functionalities. In this way, final acidolytic removal of the protecting groups, which would affect the β -arabinosyl linkage, is prevented. To form the resin-linked dipeptide,

however, the β -benzyl ester of Boc-glutamic acid was used (Boc = *tert*-butoxycarbonyl). The cleavage of the Boc group with trifluoroacetic acid minimizes the undesired release of peptide in the form of diketopiperazine.^[35] The first seven coupling reactions were carried out by using four equivalents each of *N*-protected amino acid, (2-*O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate) (TBTU),^[36] 1-hydroxy-benzotriazole (HOBt), and *N*-methylmorpholine. Protection with Ac₂O/pyridine followed each coupling step. The Fmoc group was removed with morpholine/DMF and monitored by using UV spectroscopy. The UV analysis of the Fmoc removal showed that the coupling of the *O*-benzyl-threonine building block to the glutamic β -benzyl ester remained incomplete, possibly as a result of a back-folding effect.

For the coupling of the arabino sialyl Lewis^x building block **15**, only 1.5 equivalents of this complex component



Scheme 2. Reagents and conditions: a) TBTU, HOBT, *N*-methylmorpholine, DMF; b) Ac₂O, pyridine; c) morpholine/DMF (1:1); d) TFA/CH₂Cl₂ (1:1); e) HATU/HOAT, *N*-methylmorpholine, DMF, (Ph₃P)₄Pd, *N*-methylaniline, DMF, DMSO, 3 d, overall yield of mixture 22%; g) Pd(OH)₂/H₂, MeOH, dioxane, AcOH, 10 d, h) NaOH, H₂O, pH 10.5, 24 h; (Fmoc = 9-fluorenylmethoxycarbonyl).

(Scheme 2) was available. Therefore, the coupling time was extended from 15 h to 36 h and, as in the subsequent coupling of Fmoc glycine, the reactive coupling reagent HATU/HOAT was used. No capping by acetylation was applied after the last two coupling reactions to prevent incomplete acetylation, which usually occurs at the 2- and 4-OH of the galactose of sialyl Lewis^x saccharides and results in mixtures of products. Moreover, the complete removal of O-acetyl groups from these positions of the carbohydrate is often difficult.^[28]

Palladium(0)-catalyzed cleavage of the allylic HYCRON anchor of **16** by using *N*-methylaniline as the allyl scavenger^[30] gave the glycopeptide **17** together with the nonapeptide that lacks the glycosyl asparagine unit. The separation of these compounds proved difficult, because of the poor solubility of the mixture in solvents that are suitable for HPLC. Therefore, the solution of the crude products in dichloromethane was extracted with dilute hydrochloric acid and brine, and the

benzyl ester, benzyl ether, and the Fmoc protecting groups were hydrogenolyzed in MeOH, 1,4-dioxane, and acetic acid. Subsequently, the O-acetyl groups and the methyl ester of NeuNAc were hydrolyzed by using aqueous NaOH at pH 10.5. Nonpolar impurities were removed from the obtained product mixture (overall yield 22 %) by reversed-phase HPLC. The pure arabino sialyl Lewis^x glycopeptide **18** of ESL-1 was isolated by means of two exclusion-chromatography purification steps on Sephadex G15 and monitored by NMR spectroscopy.

The inhibition of adhesion of 32Dc3 cells (a murine neutrophil cell line) to an E-selectin IgG-construct^[38] was determined in the presence of sialyl Lewis^x as the standard ligand (IC₅₀ ~ 1 mM), a divalent sialyl Lewis^x glyco-cyclooctapeptide^[39] (IC₅₀ ~ 0.8 mM), the completely deprotected arabino sialyl Lewis^x asparagine conjugate **15** (IC₅₀ ~ 2.6 mM), a RGDA-arabino sialyl Lewis^x glycopeptide^[39] (IC₅₀ ~ 2.2 mM), and the arabino sialyl Lewis^x-ESL-1 glycododecapeptide **18** (IC₅₀ ~ 0.12 mM). It was revealed in these investigations that **18** is an efficient inhibitor which shows a more than twentyfold affinity to E-selectin than that of the completely deprotected asparagine conjugate (deprotected **15**), and a tenfold higher affinity than that of the sialyl Lewis^x ligand. The influence of the peptide chain becomes clear by the comparison of the RGDA- with the ESL-1-glycopeptide **18**, since the latter exhibits a 19-fold higher inhibition of the adhesion of the neutrophils to E-selectin. It is concluded from these results that the peptide sequence **1** of ESL-1 may be biologically important for the binding of the ligand to the E-selectin. In addition, these results demonstrate that arabino analogues of sialyl Lewis^x^[40] can form efficient, metabolically stabilized inhibitors of the inflammatory cascade and of the invasion of metastatic tumor cells.

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Monolithic Materials: New High-Performance Supports for Permanently Immobilized Metathesis Catalysts

Monika Mayr, Betina Mayr, and Michael R. Buchmeiser*

Olefin metathesis and variations thereof are among the most important tools for C–C bond formation.^[1] Polymer chemistry and materials sciences have seen the introduction of new trends by metathesis-based techniques, such as ring-opening metathesis polymerization (ROMP) or acyclic diene polymerization (ADMET). Complementary, cross-metathesis and ring-closing metathesis find ample application in organic chemistry.^[2] Molybdenum- and ruthenium alkylidenes (the latter based on N-heterocyclic carbenes, NCH ligands) are used for this purpose but, until recently, only in homogeneous catalysis.^[3] The first heterogeneous ruthenium systems have already been described by Grubbs et al. but these in particular turned out to be less suited to polymerization.^[4] Meanwhile, a few non-permanently immobilized Grubbs catalysts have been reported,^[5–7] although the system described by Blechert et al. basically represents the only recyclable heterogeneous Grubbs catalyst.^[8] Despite the good catalytic data that has been reported for RCM, we investigated a new method to reach heterogeneous metathesis catalysts. The final goal was to combine the advantages of homogeneous and heterogeneous catalysis and, simultaneously, eliminate the disadvantages typical for many heterogeneous systems, such as diffusion-controlled reactions and catalyst bleeding, among others. Again, NHC ligands appeared highly attractive for these purposes. On one hand they allow the generation of highly active ruthenium carbenes,^[9–12] on the other hand the corresponding NHC/phosphane-based systems are quite sta-

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ble. Since the dissociating ligand is always the phosphane, an enhanced stability and reduced catalyst bleeding may be expected. Finally, a major way to a one-way cartridge as well as reusable reactor systems could be generated by the manufacture of pressure-stable supports. While this goal is comparably hard to achieve with standard organic supports such as divinylbenzene-crosslinked polystyrene (PS-DVB), we were able to take advantage of the latest developments in organic monolithic supports. Monolithic materials prepared by radical polymerization have been known since the 1970s^[13, 14] and have been further developed since mainly by Fréchet and Svéc. They developed modern monolithic high-performance separation media,^[15, 16] as well as scavenger- and reagent-bearing supports.^[17, 18] The main advantage of monolithic media, a result of their unique structure and pore size distribution, is the comparatively fast mass transfer between the support and liquid phase that may be accomplished. In combination with a suitable interparticle porosity, high flow rates ($> 1 \text{ cm min}^{-1}$) may be achieved. We already reported on the tailor-made synthesis and functionalization of monolithic systems using ring-opening metathesis polymerization (ROMP) and on selected applications in separation science (HPLC).^[19, 20] Because of their highly attractive properties, the extension of the area of functionalized monolithic supports to the synthesis of supported catalytic systems appeared a logical consequence.

The synthetic protocol entails the generation of a continuous matrix through ring-opening metathesis copolymerization of norbornene (NBE) and 1,4,4a,5,8,8a-hexahydro-1,4,5,8-*exo-endo*-dimethanonaphthalene (DMN-H6) in the presence of dichloromethane and 2-propanol within a borosilicate column (Figure 1, step 1). In order to achieve the above-mentioned permeability and to avoid any intraparticle diffusion, a sufficient macroporosity had to be achieved yet microporosity had to be avoided. In terms of functionalization as well as in view of the final application, monolithic structures with a microglobule diameter of $1.5 \pm 0.5 \mu\text{m}$

(Figure 2) and an interparticle porosity of 40% turned out to be optimal. The determination of structurally relevant parameters was accomplished by inverse gel-permeation chromatography (IGPC).^[21] Swelling of the organic support is drastically reduced by the lack of basically any microporosity, which consequently is a basic requirement for functionalization. This consecutive in situ functionalization is accomplished by feeding the “living” ruthenium termini with a solution of **1** and norbornene in dichloromethane (Figure 1, step 2). The number of the active termini may be determined separately by termination and elution of the ruthenium moiety with ethyl vinyl ether and subsequent plasma emission spectroscopic analysis (ICP-OES). Interestingly, more than 98% (!) of the ruthenium centers are active and located on the microglobule surface. Despite the comparably low surface of approximately $25 \text{ m}^2 \text{ g}^{-1}$, high loadings of **1** may be achieved by taking advantage of the high number of “living” sites and the “grafting from” approach, that results in surface-bound tentacles. This graft polymerization of **1** is additionally facilitated by addition of approximately 10 equivalents of norbornene. The latter represents a very reactive

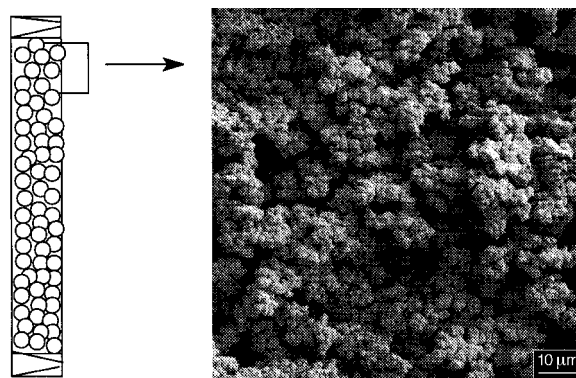
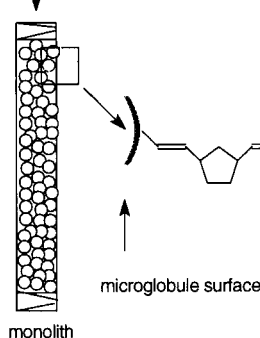


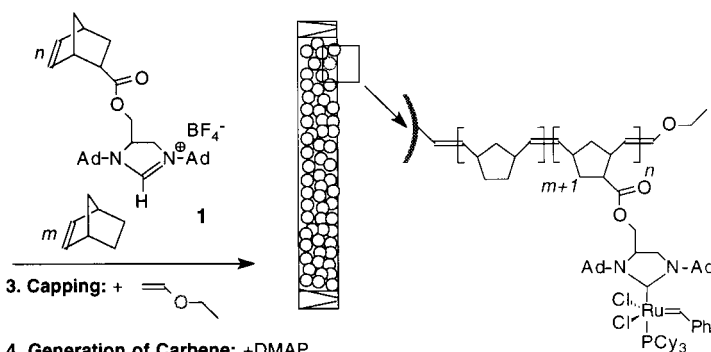
Figure 2. Electron microscopic image of the microstructure of the monolithic support.

1. Synthesis of monolithic structure:

Norbornene
DMN-H6
 CH_2Cl_2
2-Propanol



2. Derivatization:



3. Capping: + $\text{CH}_2=\text{CH}_2$

4. Generation of Carbene: + DMAP

5. Immobilization: + $[\text{Cl}_2\text{Ru}(\text{PCy}_3)_2(\text{CHPh})]$

Figure 1. Synthesis and functionalization of a monolithic support and subsequent immobilization of the metathesis catalyst. Ad = adamantyl.

monomer and is therefore grafted first onto the support. Consequently, the active termini are moved away from the structure-forming microglobuli, thus facilitating the consecutive polymerization of the sterically demanding monomer **1**. For grafting experiments based on such a block copolymer approach, the average degree of oligomerization for **1** within the tentacle is 2–5; in the absence of norbornene, lower grafting yields are obtained. These grafting yields may be estimated quite accurately from the amount of nitrogen (as obtained from elemental analysis) and the amount of ruthenium sites active after the structure-forming process. The additionally necessary quantitative initiation of **1** by the $[\text{Cl}_2\text{Ru}(\text{CHPh})(\text{PCy}_3)_n]$ -terminated polymer domains was confirmed by preliminary experiments. For this purpose, a $[\text{Cl}_2\text{Ru}(\text{PCy}_3)_2(\text{CHPh})]$ -initiated homogeneous polymerization of **1**, carried out at 40 °C in dichloromethane, was terminated with ethyl vinyl ether after 12 h. Due to the insolubility of oligomer in THF and because of the fact that oligo-**1** represents a polycation, the degree of oligomerization was determined by ^1H NMR endgroup analysis. Experimental (16.3 ± 1.5) and calculated values (14.6) were in excellent agreement. The last step in the graft polymerization of **1** onto the monolithic supports represents the termination of the ruthenium termini with ethyl vinyl ether (Figure 1, step 3), resulting in the elution of the ruthenium with methylene chloride. Control experiments consisting of an aqua regia digest of the final monolithic structure followed by ICP analysis revealed the basically quantitative removal ($\geq 99\%$) of the catalyst. Since the monolithic structures do not tolerate THF, the generation of the carbene necessary for catalyst immobilization is accomplished with (dichloromethane solu-

ble) 4-dimethylaminopyridine (DMAP), a strong base (Figure 1, step 4). Published procedures consist of the synthesis of *tert*-butoxide-protected carbenes, which are thermally converted to the free carbene in the presence of a Grubbs catalyst.^[8, 9] In the present system, heterogenization and the entailed reduced ligand mobility does not require this protective procedure. Consequently, the last synthetic step involves the careful removal of excess DMAP (ruthenium alkylidenes are base labile) and treatment of the monolith with a solution of $[\text{Cl}_2\text{Ru}(\text{CHPh})(\text{PCy}_3)_2]$ in CH_2Cl_2 (Figure 1, step 5). As determined by ICP, loadings up to 1.4 % of NHC-based Grubbs catalyst may be achieved according to this procedure. A comparison of this value with the nitrogen tenor as determined by elemental analysis reveal that $\geq 42\%$ of the NHC ligands present are involved in the formation of the desired catalytic species.

Ruthenium carbene immobilized onto monoliths possess high activity towards RCM as well as towards ROMP. The *cis/trans* ratio of the polymers is exactly the same as the one obtained in homogeneous polymerizations (90 % *trans*). Table 1 summarizes the results. For all experiments, chain-transfer agents (CTAs) such as *cis*-1,4-diacetoxybut-2-ene (**I**), diethyldiallylmalonate (**II**), and *cis*-2-hexene (**III**) were used. These compounds allow the regulation of the degree of polymerization in ROMP in particular with cyclooctene. In addition, CTAs rapidly convert intermediary ruthenium methylidenes in RCM to the more stable alkylidenes, thus significantly enhancing the lifetime of the catalyst (Figure 3). In particular, **I** permits loading one single monolithic system consecutively with different substrates and to run the corresponding metathesis reactions. The tentaclelike struc-

Table 1. Results from RCM (No. 1–3) and ROMP (No. 4–6) experiments obtained by flow-through (1, 4, and 5; these experiments were carried out consecutively with the same monolith) and cartridge experiments (2, 3, and 6). $[\text{M}]/[\text{I}] = \text{constant}$ (M = monomer). R = CTA-derived group.

No.	Compound	Product	CTA	M:CTA	T [°C]	$t^{[23]}$ [min]	Yield [%]	$\text{TON}_{\text{max}}^{[a]}$ [min ⁻¹]	TOF ^[a]	M_n	PDI ^[b]
1			–	–	43	3	71	62	25		
2			I		56	50	100	63	–		
					56	5	92	55	–		
3			I		56	30	41	56	1.9		
4			II	21:1	40	3				24 000	2.4
					40	3				34 000	2.2
					40	3				40 000	2.1
					40	3				45 000	2.0
5			III	18:1	40	3				2 500	1.2
					40	3				1 100	2.6
					40	3				1 500	1.9
					40	3				1 500	1.7
6			I	5:1	56	30				12 000	1.4

[a] Heterogeneous conditions. [b] Polydispersity index.

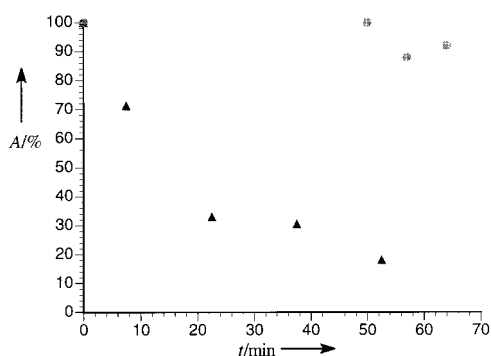


Figure 3. Influence of the chain transfer reagent **I** on the stability of the immobilized catalyst as determined from RCM experiments carried out with diethyldiallylmalonate with (●) and without (▲) CTA. *A* = Activity of the catalyst.

ture and the lack of basically any microporosity reduce diffusion to a minimum. This results in turnover frequencies (TOFs) up to 25 min⁻¹, thus even exceeding homogeneous analogues. In comparison, the TOF for diethyldiallylmalonate using [Cl₂Ru(Mes₂-NHC)(PCy₃)(CHPh)] is 4 min⁻¹ (45 °C).^[8]

In terms of a most simple handling, the monolithic systems presented here may be used either as pressure-stable reactors or (in miniaturized form) as cartridges for applications in combinatorial chemistry. The use of NHC ligands even in RCM successfully suppresses any bleeding of the column, thus allowing the synthesis of virtually ruthenium-free cyclization products with a ruthenium content ≤ 70 ppm.

Experimental Section

All experiments were carried out by means of Schlenk techniques using degassed and dried solvents throughout. Borosilicate columns (3 × 50 mm, 3 × 150 mm) were surface-derivatized using bicyclo[2.2.1]hept-2-en-5-yltrichlorosilane. Nitrogen and ruthenium contents were determined by elemental analysis and aqua regia decomposition followed by ICP, respectively. Molecular weights were determined by GPC (in THF) using a consecutive UV, refractive index (RI), and light scattering detectors.

Synthesis of monoliths: Solutions of A (NBE/DMN-H6/2-propanol, 25/25/40 wt %) and B (CH₂Cl₂/[Cl₂Ru(=CHPh)(PCy₃)₂], 9.6/0.4)^[22] were combined at 0 °C and the reaction mixture was transferred to a borosilicate column prechilled to 0 °C. Polymerization temperature was 0 °C for 15 min and room temperature for 1 h. For functionalization, the monolith was flushed with CH₂Cl₂ and subsequently fed with 2 mL of a solution of **1** (51.8 mg, 0.09 mmol) and norbornene (47.1 mg, 0.5 mmol) in CH₂Cl₂. Columns were closed and kept at 40 °C overnight. The monolith was flushed with CH₂Cl₂ (1 mL), a 10% solution of ethyl vinyl ether in CH₂Cl₂ (2 mL), and finally CH₂Cl₂ (2 mL) again. 4-Dimethylaminopyridine (10.9 mg, 0.09 mmol, dissolved in 1 mL CH₂Cl₂), CH₂Cl₂ (1 mL), and finally [Cl₂(PCy₃)₂Ru(=CHPh)] (10.9 mg, 0.09 mmol, dissolved in 1 mL CH₂Cl₂) were pumped over the column which was then kept for 1 h. at 40 °C. Finally, the monolith was flushed with CH₂Cl₂ for a few hours at a flow rate of 0.1 mL min⁻¹. IGPC data (polystyrene, *M*_p = 274 Da, THF): specific surface area *σ* = 25 m² g⁻¹, pore porosity *ε*_p = 17%, intergranular porosity *ε*_z = 40%, apparent density *ρ*_{app} = 0.37 g cm⁻³. Electron microscopy: microglobule diameter *d*_p = 1.5 ± 0.5 μm.

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An Intramolecular Case of Sharpless Kinetic Resolution: Total Synthesis of Laulimalide**

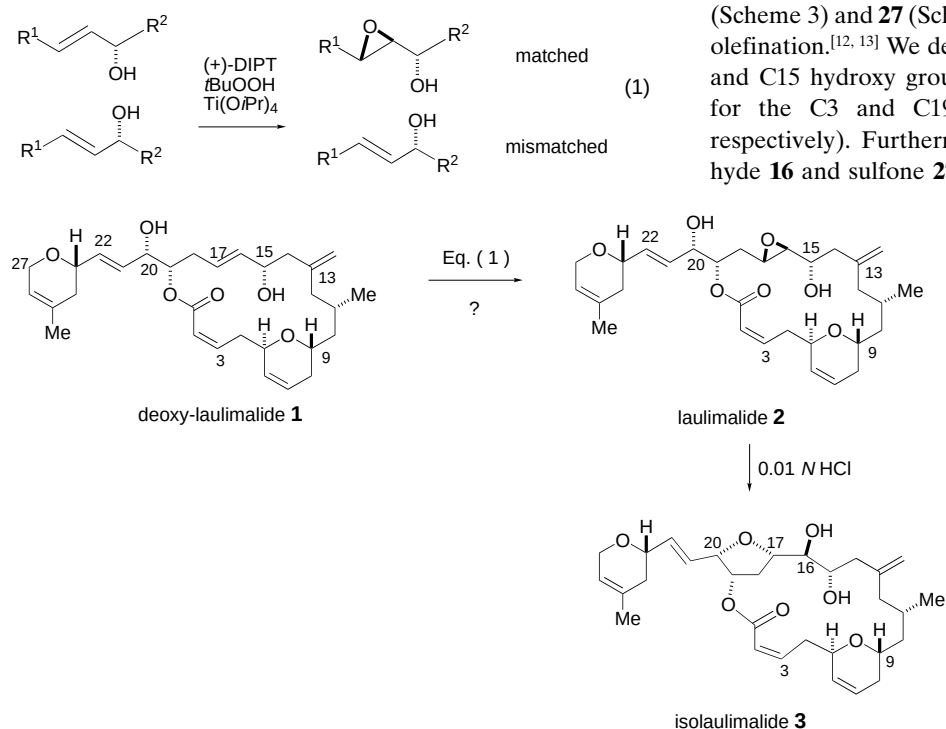
Johann Mulzer* and Elisabeth Öhler*

The Sharpless asymmetric epoxidation (SAE) is an efficient method for resolving racemic mixtures of secondary allylic alcohols: the matched pair of substrate and reagent generates an enantiomerically enriched epoxyalcohol, whereas the mismatched pair remains unreacted (Scheme 1, Eq. (1)).^[1] We decided to change this intermolecular selection to an intramolecular one when we embarked on a total synthesis of

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 Scheme 1. The SAE route to laulimalide **2**.

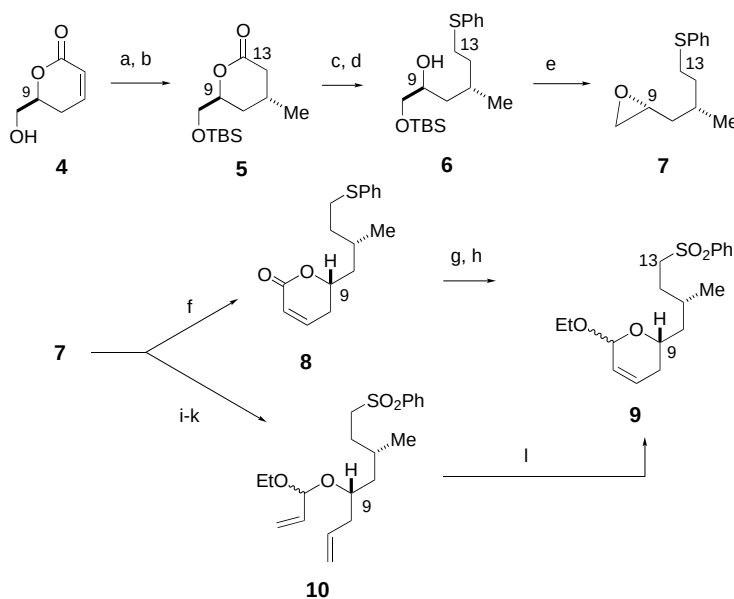
the antitumor macrolide laulimalide (**2**). The last step of this synthesis was envisaged as the epoxidation of 16,17-deoxy-laulimalide (**1**), in which the C15–C17 section represents a matched and the C20–C22 section a mismatched SAE situation with respect to Equation (1). This implies that **1** would be converted into **2** without the protection of the allylic alcohols. This strategy would be highly advantageous in view of the reported tendency of **2** to undergo cyclization to isolaulimalide (**3**), even under mildly acidic (and probably also basic) conditions,^[2] which would place high demands on the removal of a protecting group from the C20 hydroxy group in the presence of the 16,17-epoxide.

The interest in a total synthesis of **2** has been kindled by the striking success of paclitaxel^[3] as a novel drug against previously incurable tumors. However, in view of several problems associated with the clinical application of paclitaxel, a great deal of effort has been focused on the search for potential successors with the same mode of microtubule-stabilizing antitumor action, but with better bioavailability and higher activity against multidrug-resistant tumor cells. Among recent advances have been epothilone B and its derivatives,^[4] discodermolide^[5] and eleutherobin.^[6] It was discovered quite recently that **2**, a metabolite from various marine sponges,^[2, 7] also shows microtubule stabilization in eukaryotic cells and is distinguished by an unusually high antitumor activity against multidrug-resistant cell lines.^[8] To date, only one total synthesis of **2** has been published,^[9] along with several approaches to major fragments.^[10]

Retrosynthetically, we envisaged a Still–Gennari macrocyclization^[11] of phosphonate aldehyde **29** (Scheme 6), which was expected to give 2,3-olefin with high *Z* selectivity. The *E* 16,17 olefin bond could be generated from fragments **16**

(Scheme 3) and **27** (Scheme 5) by means of a Julia–Kocienski olefination.^[12, 13] We decided to use MOM to protect the C20 and C15 hydroxy groups, and orthogonal protecting groups for the C3 and C19 hydroxy groups (TBS and PMB, respectively). Furthermore, we planned to synthesize aldehyde **16** and sulfone **27** from inexpensive chiral carbon pool compounds such as D-mannitol, (*S*)-malic acid, and D-glucose.

The synthesis of the C3–C16 aldehyde **16** started from the known α,β -unsaturated lactone **4** (Scheme 2), which was readily available from tri-*O*-acetyl-D-glucal in four steps.^[14] After conversion into the TBS derivative, addition of dimethyl copper lithium smoothly provided the desired 9,11-*trans*-disubstituted lactone **5** as a single diastereomer.^[15] The formation of epoxide **7** required an inversion of the configuration at C9. Therefore, lactone **5** was reduced to the 1,5-diol, and the



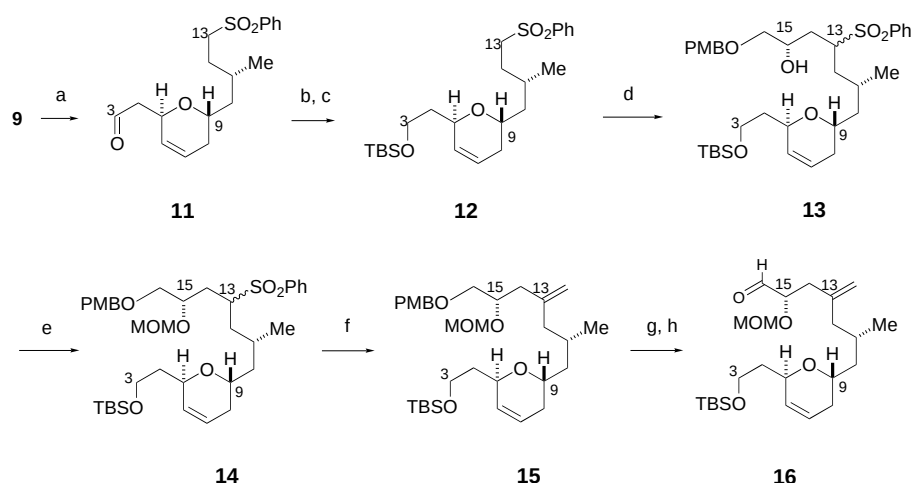
Scheme 2. Synthesis of **9**. Reagents and conditions: a) TBSCl, imidazole, DMAP, 5 °C to RT, 16 h, 89 %; b) Me_2CuLi (2 equiv), Et_2O , 0 °C, 1 h, 84 %; c) $LiBH_4$ (2.4 equiv), THF, 0 °C to RT, 17 h, 98 %; d) nBu_3P (2 equiv), $(PhS)_2$ (1.5 equiv), 0 °C to RT, 17 h, 83 %; e) 1. $MsCl$, Et_3N , CH_2Cl_2 , –10 °C to RT, 1 h; 2. TBAF, THF, 0 °C, 1 h, then aq. NaOH (15 %), 0 °C, 1 h, 89 %; f) 1. $PhSO_2(CH_2)_2C(OMe)_3$ (3 equiv), $nBuLi$, THF, –78 °C, 30 min, then $BF_3 \cdot Et_2O$ (3 equiv) and **7**, –78 °C, 1.5 h; 2. TFA/ CH_2Cl_2 (9:1), RT, 3 h; 3) DBU (3.4 equiv), CH_2Cl_2 , 0 °C, 30 min, 88 %; g) MMPP, $EtOH$, 10 °C, 1.5 h, 89 %; h) 1. DIBAL, (1.5 equiv), CH_2Cl_2 , –78 °C; 2) $EtOH$, PPTS, RT, 16 h, 93 %; i) MMPP, $EtOH$, RT, 2 h, 96 %; j) $CH_2=CHMgBr$ (4 equiv), CuI (0.1 equiv), THF, –40 °C, 30 min, 96 %; k) $CH_2=CH-CH(OEt)_2$ (20 equiv), PPTS, toluene, 35 to 40 °C, 80 mbar, 86 %; l) 1. $[(C_6H_{11})_3P]_2Cl_2Ru=CHPh$ (5 mol %), CH_2Cl_2 , 40 °C; 2. $EtOH$, PPTS, RT, 16 h, 90 %. TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylamino-pyridine, Ms = methanesulfonyl, TBAF = tetrabutylammonium fluoride, TFA = trifluoroacetic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MMPP = magnesium salt of monoperoxyphthalic acid, DIBAL = diisobutylaluminum hydride, PPTS = pyridinium *p*-toluenesulfonate.

primary alcohol at C13 was selectively transformed into the corresponding phenyl sulfide **6**.^[16] Mesylation of the C9 hydroxy group, desilylation, and ring closure with sodium hydroxide delivered epoxide **7**. Elaboration into the dihydropyran **9** was accomplished by means of ring-closing metathesis (RCM)^[17] of diolefin **10**^[18] as shown. A slightly higher overall yield was achieved by using Ghosez's one-pot lactonization^[19] of **7** to give **9** via lactone **8** in 82% overall yield. The C3–C4 unit was stereoselectively introduced (Scheme 3) with vinyl *tert*-butyldimethylsilyl ether^[20] to form aldehyde **11**, which was reduced with sodium borohydride and the resulting alcohol protected with a TBS group to give the C3–C13 fragment **12**. Compound **12** was converted into a 1:1 mixture of the C13-epimeric sulfones **13** by deprotonation and subsequent treatment with (*S*)-*p*-methoxybenzyl glycidyl ether.^[21] The methylene group was introduced at C13 of MOM ether **14** by means of a Julia methylenation^[22] to give **15**, which was transformed into aldehyde **16** by means of a two-step operation.

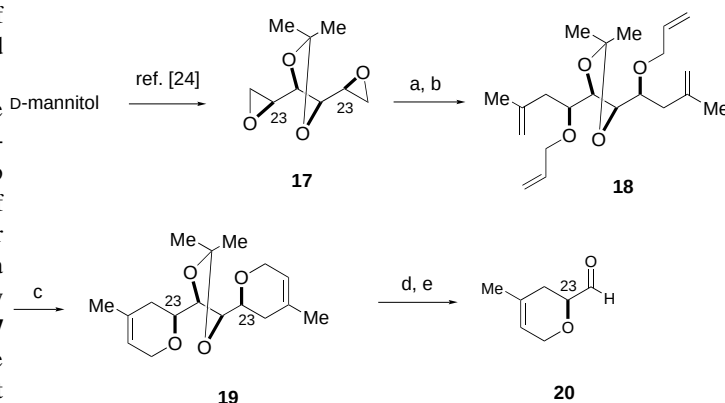
Fragment **27** was prepared by means of an *E*-selective olefination of aldehyde **20** with phosphonate **23** and subsequent *syn*-selective reduction of the C20 carbonyl group (Scheme 5). The synthesis of **20** from (*R*)-glycidol by means of RCM has been reported independently by Ghosh^[10c] and our group.^[10g] In a novel approach (Scheme 4) we applied a bidirectional^[23] RCM to tetraolefin **18**, which was readily prepared from the known D-mannitol-derived bis-epoxide **17** in two steps.^[24] No RCM products were formed across the central acetonide ring,^[25] which served as a barrier against cross-over metathesis.^[26]

The synthesis of β -oxophosphonate **23** (Scheme 5) started from the known butyrolactone **21**,^[27] which was easily obtained from natural (*S*)-malic acid. Treatment of **21** with the lithium salt of diethyl methanephosphonate and subsequent deprotonation with one equivalent of lithium diisopropylamide^[28] provided enolate **22**, which was silylated to give **23** after hydrolytic workup. Olefination^[29] with aldehyde **20** afforded enone **24** stereoselectively and in high yield. Luche reduction^[30] at -95°C produced a 7.8:1 C20-epimeric mixture in favor of the desired epimer *syn*-**25**. After separation by HPLC (high-pressure liquid chromatography), the *anti* epimer was recycled by Parikh–Doering oxidation to give **24**.^[31] Alcohol *syn*-**25** was converted into alcohol **26**, which was treated with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions.^[32] Oxidation of the resulting thioether^[33] furnished the crystalline sulfone **27**.^[34]

For the completion of the synthesis (Schemes 6 and 7), sulfone **27** and aldehyde **16** were connected by using a one-pot Julia–Kocienski olefination^[12] to give olefin **28** as an 11.4:1

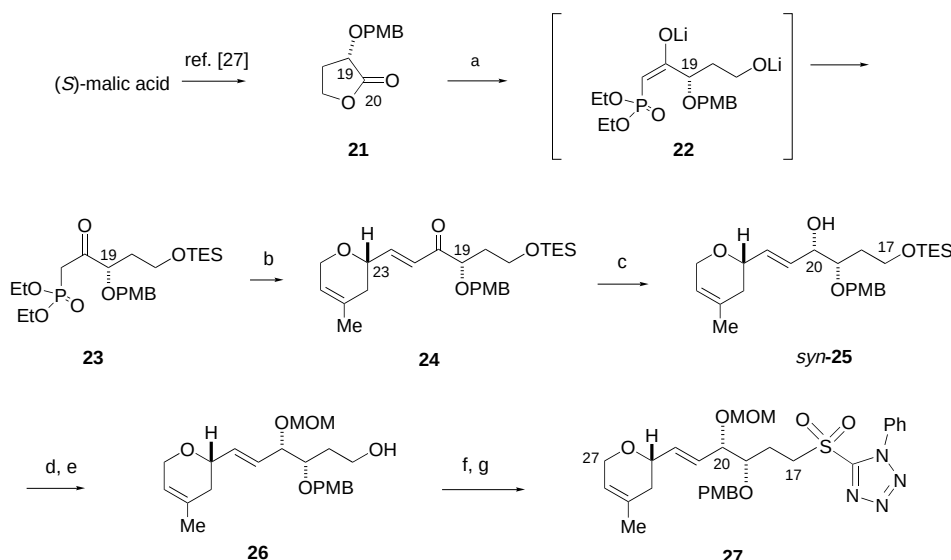


Scheme 3. Synthesis of **16**. Reagents and conditions: a) 1. $\text{CH}_2=\text{CHOTBS}$, (2 equiv), montmorillonite K10 clay, CH_2Cl_2 , $0-5^{\circ}\text{C}$, 45 min; 2. montmorillonite K10 clay, wet CH_2Cl_2 , RT, 1.5 h; b) NaBH_4 (1.2 equiv), MeOH , 0°C , 20 min, 86% over two steps; c) TBSCl , imidazole, DMAP, CH_2Cl_2 , 0°C to RT, 16 h, 98%; d) **12** (1.25 equiv), *n*BuLi, THF, -78°C , 25 min, then $\text{BF}_3 \cdot \text{Et}_2\text{O}$, then (*S*)-*O*-PMB-glycidol, -78°C , 2.5 h, 86%; e) MOMCl (10 equiv), Et NiPr_2 (20 equiv), CH_2Cl_2 , 0°C to RT, 24 h, 94%; f) *n*BuLi, THF/HPMA (10:1), -78°C , 30 min, then ICH_2MgCl (5 equiv), -78°C to -25°C , 4 h, 75%; g) DDQ (1.5 equiv), $\text{CH}_2\text{Cl}_2/\text{pH } 7 \text{ buffer}$ (20:1), RT, 2.5 h, 81%; h) $(\text{COCl})_2$ (1.5 equiv), DMSO (2.6 equiv), CH_2Cl_2 , -78°C , 3 min, then add alcohol, -78°C , 30 min, Et NiPr_2 (5.2 equiv), -78°C to RT, 45 min, 93%. MOM = methoxymethyl, HMPA = hexamethyl phosphoramide, PMB = *para*-methoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.



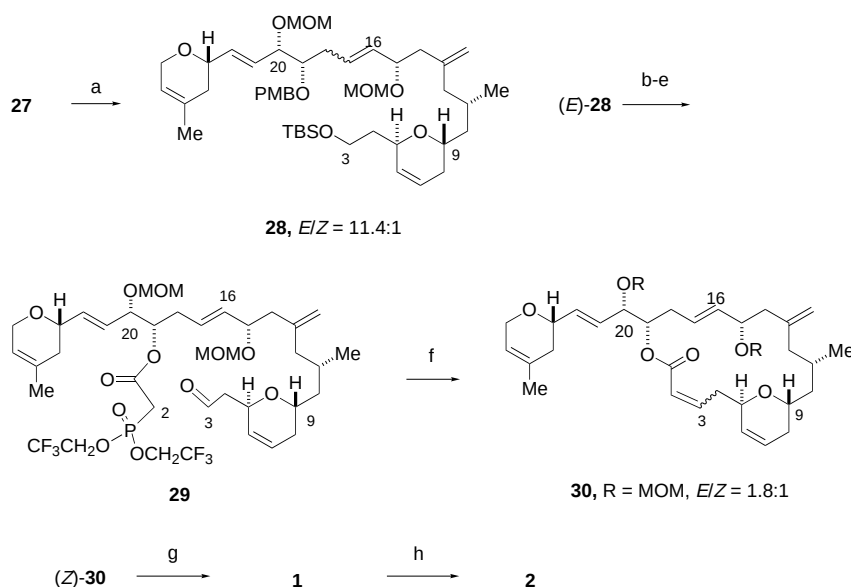
Scheme 4. Synthesis of **20**. Reagents and conditions: a) $\text{CH}_2=\text{CMeMgBr}$ (4 equiv), CuI (0.4 equiv), THF, -40°C , 2 h, 92%; b) 1. KORBu (3.5 equiv), THF, 45°C , 1.5 h, 2. $\text{CH}_2=\text{CHCH}_2\text{Br}$ (4 equiv), RT, 17 h, 89%; c) $[(\text{C}_6\text{H}_{11})_3\text{P}]_2\text{Cl}_2\text{Ru}=\text{CHPh}$ (3 mol%), CH_2Cl_2 , RT, 5 h, 83%; d) TFA/ CH_2Cl_2 (4:1), 0°C , 3.5 h, 93%; e) HIO_4 (1.5 equiv), Et_2O , 0°C to RT, 2 h, 95%.

E/Z mixture from which (*E*)-**28** was isolated by chromatography. Deprotection of the C19 hydroxy group and acylation with bis(2,2,2-trifluoroethyl)phosphonoacetyl chloride,^[35] followed by 3-*O*-desilylation and Dess–Martin oxidation^[36] gave aldehyde **29**, which underwent cyclization under Still conditions^[11] to furnish a 1.8:1 *E/Z* mixture^[9a] of the macro-lactones **30**. Separation of (*E*)- and (*Z*)-**30** by chromatography, followed by deprotection with dimethylboron bromide^[37] generated the hitherto unknown deoxylaualimalides **1** and **31**, respectively. Exposure of **1** to SAE^[38] with (+)-diisopropyl tartrate (DIPT) provided laulimalide (**2**).^[39] Careful HPLC analysis revealed no other products, so that our initial strategy was successful. Admittedly, the regiocontrol of the epoxida-

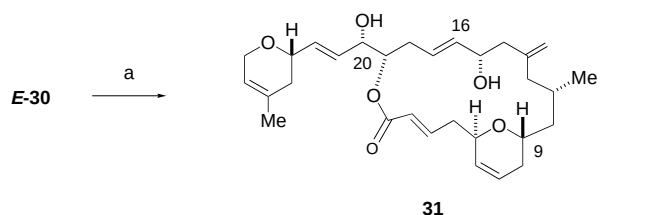


Scheme 5. Synthesis of **27**. Reagents and conditions: a) MeP(O)(OEt)₂ (1.0 equiv), *n*BuLi (1.0 equiv), THF, –78 °C, 15 min, then **21**, –78 °C, 30 min, then LDA (1.0 equiv), –78 °C, 30 min, then TESCl (2.0 equiv), –78 °C to RT, 16 h, 83 %; b) LiCl (2.5 equiv), Et₃N (2.5 equiv), THF, 0 °C, 10 min, then **20**, 0 °C, 2 h, 86 %; c) 1. CeCl₃ · 7H₂O (1.5 equiv), NaBH₄ (1.2 equiv), MeOH, –95 °C, 75 min; 2. HPLC separation (*syn*-**25**: 85 %, *anti*-**25**: 11 %); d) MOMCl (5 equiv), Et₃NiPr₂ (10 equiv), CH₂Cl₂, 0 °C to RT, 24 h; e) TBAF, THF, RT, 15 min, 93 % over two steps; f) PPh₃ (1.5 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (1.5 equiv), DEAD (1.8 equiv), THF, 0 °C, 30 min, 90 %; g) (NH₄)₆Mo₇O₂₄ · 4H₂O, H₂O₂ (30 %), 0 °C to RT, 74 %. LDA = lithium diisopropylamide, TES = triethylsilyl, DEAD = diethyl azodicarboxylate.

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Scheme 6. Completion of the synthesis of **1** and **2**. a) KHDMS, DME, –60 °C, 25 min, then **16** (1.15 equiv), –60 °C to RT, 4 h (57 % (*E*)-**28** + 5 % (*Z*)-**28**); b) DDQ, CH₂Cl₂/pH 7 buffer (10:1), RT, 50 min, 87 %; c) (CF₃CH₂O)₂P(O)CH₂COCl (3.5 equiv), DMAP (3.5 equiv), CH₂Cl₂, –78 °C, 10 min, then pyridine, –78 °C to RT, 45 min, 91 %; d) AcOH/H₂O/THF (3:1:1), 3.5 h, RT, 89 %; e) Dess–Martin periodinane (2.5 equiv), wet CH₂Cl₂, RT, 30 min, 96 %; f) **29** (10^{–3} M in THF), [18]crown-6 (6 equiv), –78 °C, then KHDMS (0.95 equiv), –78 °C, 50 min, 80 %; g) 1. Me₂BBr (6 equiv), CH₂Cl₂, –78 °C, 25 min; 2. aq. NaHCO₃/THF (1:2), 80 %; h) (+)-DIPT (1.2 equiv), Ti(OiPr)₄ (1.0 equiv), *t*BuOOH (1.34 equiv), 4-Å molecular sieves, –20 °C, 2 h: 70 % (**2**) and 30 % (**1**; recovered). KHDMS = potassium 1,1,1,3,3,3-hexamethyldisilazane, DME = 1,2-dimethoxyethane.



Scheme 7. Synthesis of **31**: a) 1. Me₂BBr (6 equiv), CH₂Cl₂, –78 °C, 25 min; 2. aq. NaHCO₃/THF (1:2), 84 %.

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Methylenetriimidosulfate H₂CS(NtBu)₃²⁻— The First Dianionic Sulfur(vi) Ylide**

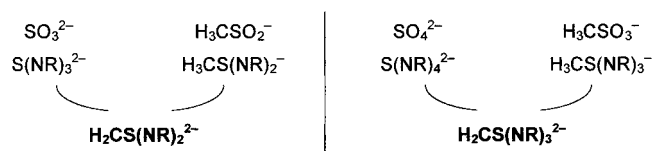
Bernhard Walfort and Dietmar Stalke*

Isoelectronic replacement of the oxygen atoms in simple p-block element oxoanions by an NR imido group is currently a flourishing area of main group chemistry.^[1] These new species are soluble in nonpolar organic solvents because they form contact-ion pairs, whose periphery consists of lipophilic substituents. In contrast, the simple oxoanions form infinite solid-state lattices as a result of the multiple oxygen–metal cation contacts. We were particularly interested in the polyimidosulfur anions because of the rich redox chemistry.^[2]

Triimidosulfite S(NR)₃²⁻,^[3] which is analogous to sulfite SO₃²⁻, can be radically oxidized to S(NR)₃ (Scheme 1).^[4] The cap-shaped S(NR)₃²⁻ ion is the first tripodal coordinating dianion.^[5] Tetraimidosulfate S(NR)₄²⁻, which is analogous to sulfate SO₄²⁻,^[6] gives soluble monomeric metal complexes.^[7]

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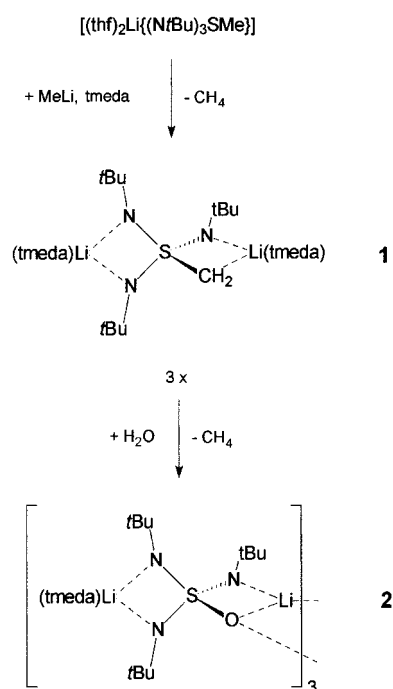
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 Scheme 1. Isoelectronic C and N analogues of SO_3^{2-} and SO_4^{2-} .

We now focus on isoelectronic replacement of the oxygen atoms in the sulfur oxoanions and the imido groups in polyimidosulfur anions by a R_2C^- group. Sulfur compounds containing a metalated α -carbon atom are well established.^[8] Sulfur ylides, which like Wittig ylides can be employed for C–C coupling reactions, are utilized most frequently in synthesis.^[9] Sulfoximines are also used in asymmetric C–C coupling reactions.^[10] The C_α -deprotonation of the S-bonded substituent in diimidosulfonates $\text{R}_2(\text{H})\text{CS}(\text{NR})_2^-$ ^[11] yields the dianionic methylenediimidosulfites $\text{R}_2\text{CS}(\text{NR})_2^{2-}$ (Scheme 1), the carba/imido analogues of SO_3^{2-} .^[12] Herein we present the alkylenetriimidosulfate $[(\text{tmeda})_2\text{Li}_2[\text{H}_2\text{CS}(\text{N}t\text{Bu})_3]]$ (**1**) ($\text{tmeda} = \text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$), the first carba/imido analogue of SO_4^{2-} .

Compound **1** can be synthesized readily starting from lithium *S*-methyltri(*tert*-butyl)triimidosulfonate $\text{H}_3\text{CS}(\text{N}t\text{Bu})_3^-$ by deprotonation of the *S*-methyl group with methyllithium in high yields (Scheme 2). The addition of two equivalents of MeLi to *S*-alkyltri(*tert*-butyl)triimidosulfonic acid $\text{RS}(\text{N}t\text{Bu})_2\text{NH}t\text{Bu}$ provides a second route to **1**.^[2b, 13] $[(\text{tmeda})_2\text{Li}_2[\text{H}_2\text{CS}(\text{N}t\text{Bu})_3]]$ (**1**) crystallizes in the presence of the donor base tmeda.

Compound **1** is, like $[(\text{thf})_2\text{Li}_2[(\text{N}t\text{Bu})_4\text{S}]]$ ^[6] and $[(\text{Li}_2-(\text{N}t\text{Bu})_3\text{S})_2]$,^[3] air- and moisture-sensitive. Reaction of **1** with one equivalent of water gives the trimeric triimidosulfate $[(\text{tmeda})\text{Li}_2[\text{OS}(\text{N}t\text{Bu})_3]]_3$ (**2**), indicating that the methylene substituent is hydrolyzed to form methane preferentially to the hydrolysis of an imido substituent to give an amine.


 Scheme 2. Synthesis of **1** and **2**.

The crystal structure of **1** (Figure 1) consists of separated contact-ion pairs.^[14] The sulfur atom is surrounded in a distorted tetrahedral fashion by three imido groups and one

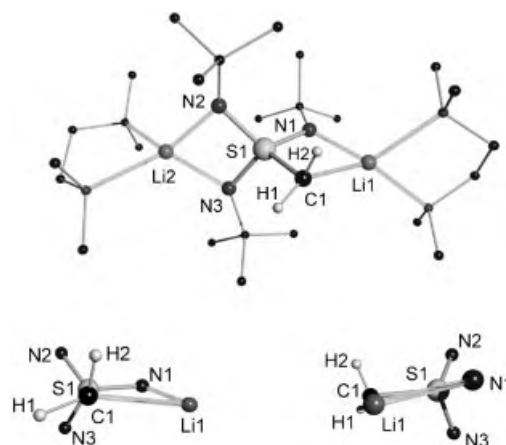


Figure 1. Top: Crystal structure of **1**. Bottom left: Projection along the S1–C1 bond. Bottom right: Projection along the Li1–C1 bond. Selected bond lengths [pm] and angles [°]: S1–C1 172.5(2), S1–N1 160.50(19), S1–N2 159.0(2), S1–N3 161.4(2), C1–H1 101(3), C1–H2 85(3), C1–Li1 213.2(5), N1–Li1 195.9(5), N2–Li2 195.4(4), N3–Li2 199.8(4); C1–S1–N1 97.66(12), N2–S1–N3 96.05(10), N1–S1–N2 117.32(11), C1–S1–N3 120.47(13), C1–S1–N2 111.64(14), N1–S1–N3 115.08(11).

methylene moiety (Figure 1, top). The two lithium atoms bridge two opposite edges of the SN_3C tetrahedron, narrowing the related S–N–N ($\text{N2–S1–N3 } 96.05(10)^\circ$) and S–N–C angles ($\text{C1–S1–N1 } 97.66(12)^\circ$ in contrast to the angle between the nonbridged coordinating atoms of $\text{av } 116.0(2)^\circ$). The average S–N and Li–N bond lengths of 160.3 and 197.0 pm, respectively, are similar to those found in $[(\text{thf})_4\text{Li}_2\{\text{S}(\text{N}t\text{Bu})_4\}]$.^[6] The most remarkable structural feature involves the bonding and orientation of the CH_2 group to the central sulfur atom. The S1–C1 bond length in **1** is only 172.5(3) pm and thus 6.7 pm shorter than the average value of 179.2 pm in *S*-methyltri(*tert*-butyl)triimidosulfonate $\text{H}_3\text{CS}(\text{N}t\text{Bu})_3^-$.^[13] However, this bond shortening upon deprotonation should not be attributed to S=C bonding in the sulfur ylenic mesomeric form. Although this distance is considerably shorter than in most α -sulfonyl carbanions,^[15] in the 2,2-diphenyl-1-(phenylsulfonyl)cyclopropyllithium complex $[(\text{dme})\text{Li}[\text{Ph}_2\text{C}_2\text{H}_2\text{SO}_2(\text{Ph})]]_2$ ($\text{dme} = 1,2\text{-dimethoxyethane}$) the corresponding distance is only 167.6(7) pm.^[15d] Despite this short distance the lithiated carbon atom resides in a tetrahedral environment. The S–C bond length in **1** is similar to the observed S–C(sp) bond length of 171.8(3) pm in $[(\text{thf})_2\text{Li}_2\{(\text{N}t\text{Bu})_3\text{SC}\equiv\text{CPh}\}]$.^[13] The metalated C1 center in **1** is only about 26 pm above the H1/H2/Li1 and H1/S1/Li1 plane suggesting that hybridization state of C1 lies between sp^3 and sp^2 . The shortening of the S–C bond is attributed to a radius reduction on the change in hybridization $\text{sp}^3 \rightarrow \text{sp}^2$, electrostatic $\text{S}^{\delta+} - \text{C}^{\delta-}$ attraction and hyperconjugation, rather than to a d-orbital contribution.^[16] It is remarkable that the freely refined hydrogen atoms of the methylene group are not located along the bisector of the S1–C1–Li1 angle. H2 is tilted towards Li1 causing a relatively close Li1...H2 contact of 223(3) pm (Figure 1, bottom).

Isoelectronic replacement of the methylene group in **1** by an oxygen atom gives the trimer **2**.^[14] The triimidosulfate dianion is (*N,N'*),(*N,O*)-chelated to two lithium cations on opposite edges of the OSN₃ tetrahedron (Figure 2, left). While the outer *N,N'*-chelated lithium cation is tetrahedrally coordinated by the additional chelating donor base tmeda, the *N,O*-chelated lithium atom is trigonal planar coordinated providing the second intramolecular Li–O link around the

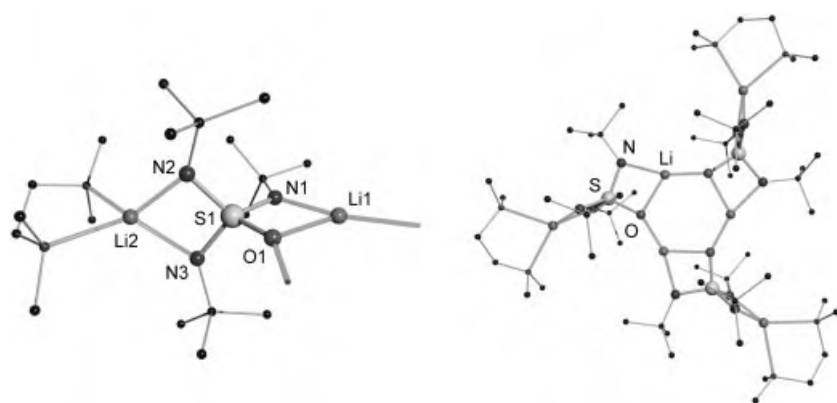
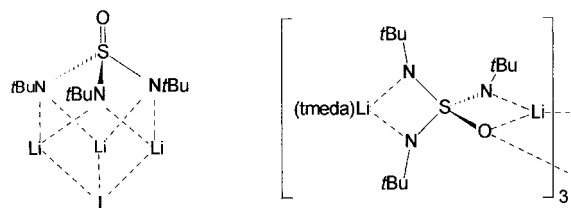


Figure 2. Left: Asymmetric unit of **2**. Right: Structure of the trimer with the threefold axis orthogonal to the paper plane in the centre of the Li₃O₃ six-membered ring. Selected bond lengths [pm] and angles [°]: S1–O1 151.73(19), S1–N1 157.5(3), S1–N2 156.8(6), S1–N3 153.8(6), O1–Li1 181.3(6), O1–Li1A 196.5(6), N1–Li1A 190.4(6), N2–Li2 187.8(14), N3–Li2 205.5(12); O1–S1–N1 97.09(12), N2–S1–N3 98.57(15), N1–S1–N2 118.9(4), O1–S1–N2 111.8(3), O1–S1–N3 115.1(3), N1–S1–N3 116.3(4), Li1A–O1–Li1 117.2(3), O1–Li1–O1A 122.8(3).

threefold axis (Figure 2, right). Hence the trimer consists of a planar central Li₃O₃ six-membered ring with three annelated planar LiOSN four-membered rings. The three peripheral LiN₂S rings are arranged orthogonal relative to these four fused rings.

The S1–O1 bond with the lithium-coordinated O atom in **2** of 151.73(19) pm is considerably longer than the terminal S–O bond in the only other known triimidosulfate dianion OS(*Nt*Bu)₃^{2–} (145.5(5) pm).^[4] This difference is caused by the different coordination mode in the two compounds. In **2** the electron density has to be shared between the two lithium cations and the electropositive sulfur atom (Scheme 3).



Scheme 3. Different coordination modes of the two known triimidosulfate dianions

In the 36-atom clusters of [(Li₂[OS(NR)(NR')])₆], which contain a pyramidal diimidosulfite dianion, the six oxygen atoms are each coordinated by three lithium atoms, which leads to an elongation of the average S–O bond to 154.6(13) (R = *t*Bu, R' = SiMe₃) and to 158.7(7) pm (R = R' = *t*Bu).^[17] The metal diimidosulfates O₂S(*Nt*Bu)₂^{2–} tend to form clusters as well because of two metal-bridging oxygen atoms. The

lithium diimidosulfate comprises an octamer,^[18] while the mixed-metal Li/Mg cluster contains twelve dianions, as well as eight lithium and two magnesium cations.^[19] The mixed-metal Li/Al compounds form polymeric strands in the solid state.^[20]

In conclusion, both the elongation of the S–O and shortening of the S–C bond can be attributed to electrostatics. We favor ylidic S⁺–C[–] rather than ylenic S=C bonding.^[21] This interpretation and the preferred hydrolysis of the methylene group over the imido group in the reaction of **1** to give **2** suggests that **1** could be employed as a methylene transfer reagent similar to the Wittig phosphonium ylides.

Experimental Section

All manipulations were performed under an inert gas atmosphere of dry N₂ with Schlenk techniques or in an argon glovebox. All solvents were dried over Na/K alloy and distilled prior to use. ¹H, ⁷Li and ¹³C NMR spectra were recorded in C₆D₆ (internal standards C₆HD₅: δ = 7.15 (¹H), C₆D₆: δ = 128.0 (¹³C)) using a Bruker AMX 400 spectrometer. Elemental analyses were performed by the Microanalytisches Labor der Universität Würzburg.

Synthesis of [(tmeda)₂Li₂[H₂CS(*Nt*Bu)₃]] (**1**): Methyl-lithium (10.14 mmol, 3.4 mL of a 3 M solution) was added slowly at –78 °C to a solution of [(thf)₂Li₂–{(N*t*Bu)₃SMe₂}] (5.07 mmol, 3.0 g), prepared as described in ref. [6], in THF (20 mL) and stirred for 1 h. Instantaneous formation of methane gas was observed. The solution was then stirred for two hours at room temperature. Subsequently, THF was removed in vacuum and the white precipitate was redissolved in warm hexane and tmeda. Storage of the solution at –36 °C for three days afforded colorless crystals which were suitable for single-crystal X-ray structure analysis (yield 2.6 g, 78%). ¹H NMR (400.13 MHz, C₆D₆): δ = 1.58 (2H; SCH₂), 1.73 (s, 9H; NC(CH₃)₃), 1.77 (s, 18H; NC(CH₃)₃), 1.89 (s, 8H; NCH₂CH₂N), 2.13 (s, 24H; N(CH₃)₂); ¹³C NMR (100 MHz, C₆D₆): δ = 34.61 (SCH₂), 34.85 (NC(CH₃)₃), 35.03 (NC(CH₃)₃), 46.55 (NCH₂CH₂N), 51.65 (NC(CH₃)₃), 52.17 (NC(CH₃)₃), 57.26 (s, 24H; N(CH₃)₂); ⁷Li NMR (155.5 MHz, ext. sat. LiCl solution): δ = 0.85, 1.24; elemental analysis (%): calcd: C 59.37, H 12.16, N 19.39, S 6.34; found: C 57.43, H 10.24, N 20.45, S 7.26.

Synthesis of [(tmeda)Li₂[OS(*Nt*Bu)₃]] (**2**): H₂O (1.48 mmol) in tmeda (10 mL) was slowly added at –10 °C to a solution of **1** (1.48 mmol, 0.75 g) in hexane (20 mL). The reaction mixture was stirred for 1 h at –10 °C and then 2 h at room temperature. The solvent was removed in vacuum and the white precipitate was redissolved in warm hexane and tmeda. Storage of the solution at –36 °C for several days afforded colorless crystals which were for single-crystal X-ray structure analysis (yield 0.3 g, 51%). ¹H NMR (400.13 MHz, C₆D₆): δ = 1.47 (s, 9H; NC(CH₃)₃), 1.49 (s, 18H; NC(CH₃)₃), 1.61 (s, 8H; NCH₂CH₂N), 2.05 (s, 24H; N(CH₃)₂); ¹³C NMR (100 MHz, C₆D₆): δ = 33.39 (NC(CH₃)₃), 33.63 (NC(CH₃)₃), 34.62 (NCH₂CH₂N), 46.25 (N(CH₃)₂), 51.70 (NC(CH₃)₃), 51.95 (NC(CH₃)₃); ⁷Li NMR (155.5 MHz, ext. sat. LiCl solution): δ = 0.5, 1.79; elemental analysis (%): calcd: C 55.22, H 11.07, N 17.89, S 8.19; found: C 52.11, H 12.32, N 19.28, S 7.78.

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Total Synthesis of Apoptolidin: Part 1. Retrosynthetic Analysis and Construction of Building Blocks**

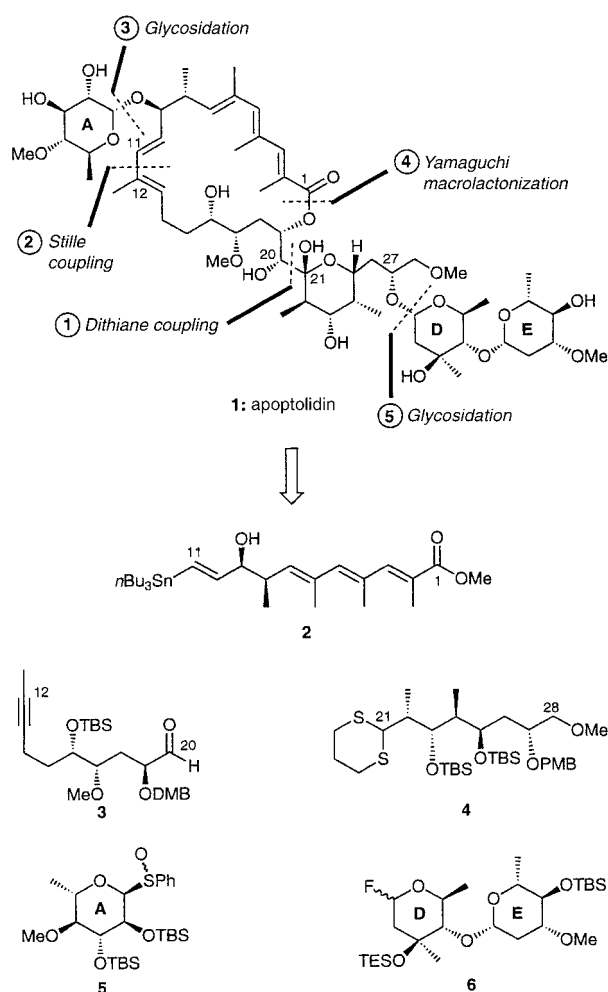
K. C. Nicolaou,* Yiwei Li, Konstantina C. Fylaktakidou, Helen J. Mitchell, Heng-Xu Wei, and Bernd Weyershausen

From the many macrolide type structures recently isolated from nature, that of apoptolidin (**1**, Scheme 1),^[1] isolated from *Nocardiopsis* sp., stands out. Its distinction as a synthetic

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Supporting information for this article (selected physical properties of compounds **2**, **3**, **4**, **51**, and **69**) is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 1. Molecular structure and retrosynthetic analysis of apoptolidin (1). TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; DMB = 3,4-dimethoxybenzyl; PMB = 4-methoxybenzyl.

target emanates from its molecular architecture which includes no less than 30 stereogenic elements (25 stereocenters and 5 geometrical sites), a highly unsaturated 20-membered macrocyclic system, and four carbohydrate units. The appeal of apoptolidin (1) as a synthetic target is enhanced by its unique biological activities, prominent among which are the selective induction of apoptosis in rat glia cells transformed with adenovirus E1A oncogene in the presence of normal cells^[2] and inhibition of the mitochondrial F_0F_1 -ATPase.^[3] In this and the following communication,^[4] we report the first total synthesis of this fascinating natural product.^[5]

The retrosynthetic scheme for apoptolidin (1) outlined in Scheme 1 was chosen on the basis of convergence and the molecule's chemical sensitivity. The latter issue was of major concern given the potentially labile nature of apoptolidin's conjugated systems, glycoside bonds, lactol moiety, and macrocyclic ring. Specifically, the susceptibility of 1 to both base and acid had to be addressed in any synthetic planning, particularly regarding manipulation and final removal of protecting groups.

Disconnection of the five strategic bonds ①–⑤ as indicated in Scheme 1 revealed intermediates 2–6 as suitable

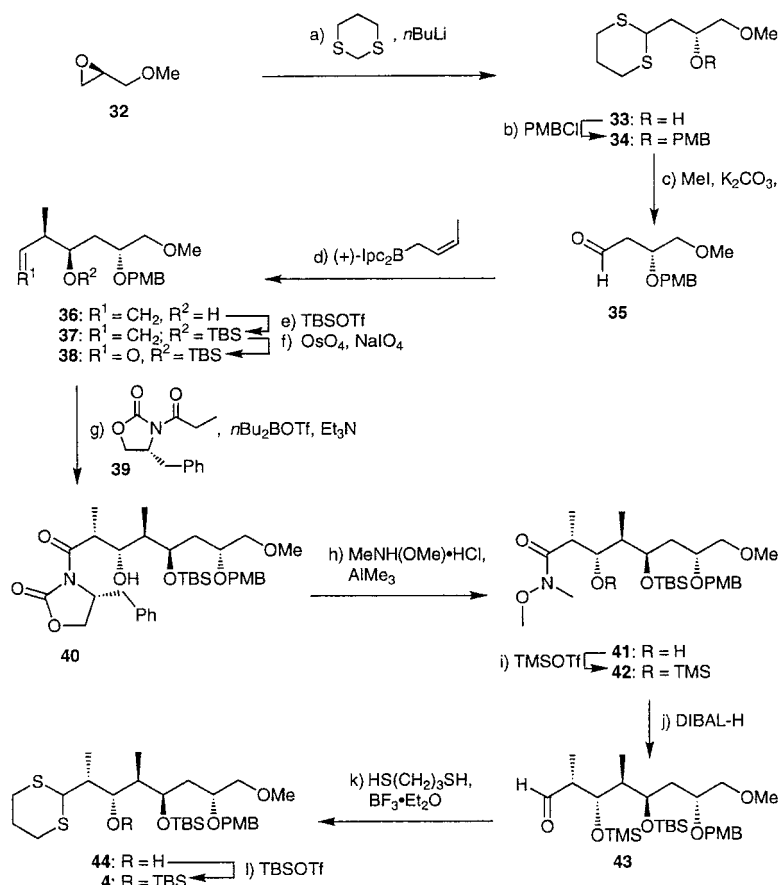
building blocks. The synthetic strategy for assembling these intermediates into the apoptolidin framework envisioned, in order of construction, the following key steps:

- ① A dithiane-based coupling reaction^[6] to join building blocks 3 (C12–C20 fragment) and 4 (C21–C28 fragment)
- ② A subsequent Stille coupling^[7] reaction to introduce the C1–C11 segment 2
- ③ A glycosidation step incorporating carbohydrate unit 5 (ring A)
- ④ A Yamaguchi macrolactonization^[8] to close the 20-membered ring
- ⑤ A final glycosidation step to attach the remaining disaccharide system 6 (rings D and E)

The flexibility of this plan which, in principle, allows changes in the order of steps in the construction sequence that might be dictated by unforeseen events, was considered an additional and decisive advantage.

The synthesis of the C1–C11 fragment 2 commenced with acetylenic aldehyde 7^[9] (Scheme 2). Thus, 7 was treated with (*Z*)-(+)-crotyldiisopinocampheyl borane^[10] to afford alcohol 8 selectively and in 82% yield. Protection of this alcohol as a TBS ether (9, 97% yield), followed by ozonolysis of the olefinic bond, gave, upon reduction with PPh_3 , aldehyde 10 (90% yield). The latter compound was treated with Bestmann's reagent ($MeC(O)C(N_2)P(O)(OMe)_2$)^[11] to afford the diacetylene 11 (85% yield), which, upon methylation with *n*BuLi and MeI, led to compound 12 (90% yield). Regio- and stereoselective hydroboration of 12 with catecholborane and catalytic amounts of 9-BBN, followed by hydrolysis, furnished the vinyl boronic acid 13 in 60% yield. Finally, a Suzuki type coupling^[12] (81% yield) of 13 with vinyl bromide 19 (obtained in 84% overall yield from the allylic alcohol 16^[13] by one-pot reaction^[14] with MnO_2 and $MeC(=PPh_3)CO_2Et$, and subsequent ester exchange, see Scheme 2), followed by desilylation (TBAF, 98% yield) of the resulting product (14) and regio- and stereoselective Pd-mediated hydrostannylation^[15] (69% yield), provided the desired vinyl stannane 2 via propargylic alcohol 15.

Fragment 3 (C12–C20) was synthesized from commercially available (+)-glycidol (20) as outlined in Scheme 3. Thus, 20 was protected as its PMB ether 21 (90% yield) and reacted with allenyl magnesium bromide^[16] to afford acetylenic alcohol 22 in 90% yield. The latter compound was then protected as a TBS ether (23, 97% yield) and methylated (*n*BuLi, MeI) to give acetylenic compound 24 in 95% yield. Removal of the PMB group from 24 (DDQ, 97% yield), followed by oxidation (TPAP, NMO) of the resulting alcohol (25) furnished aldehyde 26 (90% yield). The subsequent reaction of aldehyde 26 with (+)-allyldiisopinocampheyl borane^[17] in diethyl ether at $-100^\circ C$ was both efficient (85% yield) and stereoselective (ca. 10:1 ratio), and produced the desired alcohol 27. Treatment of 27 with MeOTf in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine led to methyl ether 28 in 85% yield. Asymmetric dihydroxylation of 28 under the Sharpless conditions^[18] (AD-Mix- α) provided the corresponding diol (29, 85% yield, ca. 6:1 ratio of diastereoisomers) from which the benzylidene derivative 30 was formed by exposure to 3,4-dimethoxy benzaldehyde and CSA (99% yield). Regioselective opening of this acetal (30) with



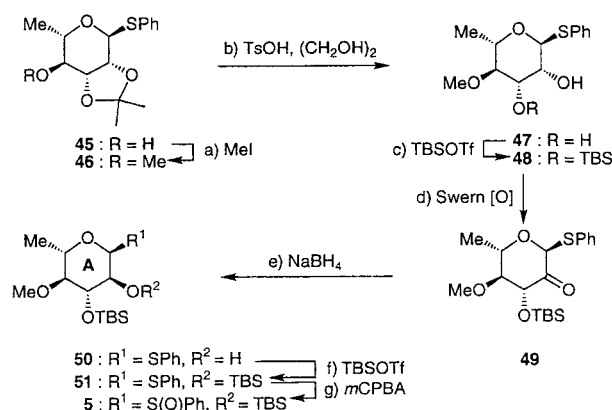
Scheme 4. Synthesis of dithiane **4**. a) 1,3-dithiane (1.5 equiv), *n*BuLi (1.5 equiv), THF, $-78 \rightarrow 25^\circ\text{C}$, 2 h, 91%; b) PMBCl (1.3 equiv), NaH (1.3 equiv), *n*Bu₄NI (0.1 equiv), DMF, 0°C , 1 h, 99%; c) MeI (10.0 equiv), K₂CO₃ (2.0 equiv), CH₃CN/H₂O (10:1), 45°C , 5 h, 92%; d) (Z)-(+)-crotyldiisopinocampheyl borane (4.0 equiv), BF₃·Et₂O (4.0 equiv), THF, -78°C , 2 h; then NaBO₃·4H₂O (15 equiv), THF/H₂O (1:1), 25°C , 12 h, 98%; e) TBSOTf (2.5 equiv), 2,6-lutidine (2.5 equiv), CH₂Cl₂, $0 \rightarrow 25^\circ\text{C}$, 2 h, 97%; f) OsO₄ (0.03 equiv), NMO (2.0 equiv), *t*BuOH/H₂O/THF (10:1:2), 25°C , 12 h; then NaIO₄ (5.0 equiv), pH 7.0 buffer, 25°C , 2 h, 94%; g) **39** (1.15 equiv), *n*Bu₂BOTf (1.4 equiv), Et₃N (1.6 equiv), CH₂Cl₂, $-78 \rightarrow 25^\circ\text{C}$, 2 h; then H₂O₂ (15 equiv), $0 \rightarrow 25^\circ\text{C}$, 2 h, 93%; h) MeNH(OMe)·HCl (2.5 equiv), AlMe₃ (2.5 equiv), CH₂Cl₂, $-10 \rightarrow 25^\circ\text{C}$, 12 h, 90%; i) TMSOTf (2.5 equiv), 2,6-lutidine (2.5 equiv), CH₂Cl₂, -35°C , 1 h; j) DIBAL-H (3.0 equiv), CH₂Cl₂, -78°C , 2 h, 89% over two steps; k) HS(CH₂)₃SH (2.0 equiv), BF₃·Et₂O (1.0 equiv), CH₂Cl₂, -30°C , 15 min, 78%; l) TBSOTf (2.5 equiv), 2,6-lutidine (5.0 equiv), CH₂Cl₂, $0 \rightarrow 25^\circ\text{C}$, 5 h, 97%. TMS = trimethylsilyl.

whose free hydroxy group was protected as a TBS ether (97% yield) to afford the targeted C21–C29 fragment **4**.

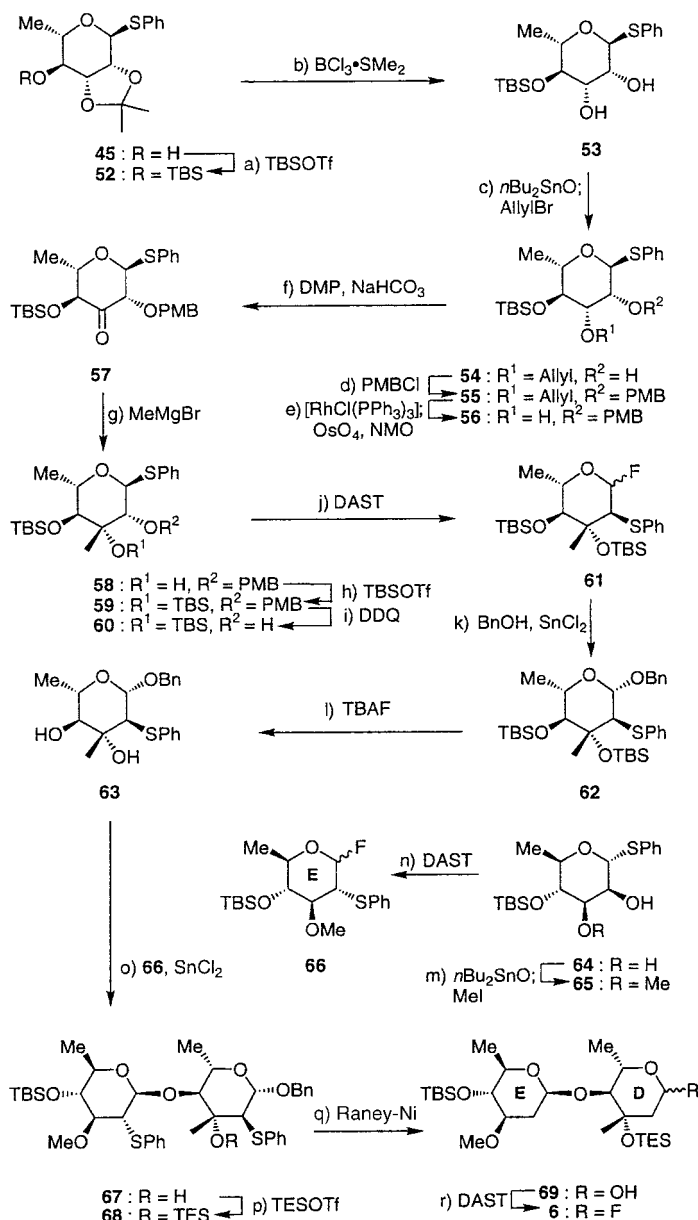
The two carbohydrate domains (**A** and **DE**) were obtained by stereoselective routes starting with readily available sugar derivatives as depicted in Schemes 5 and 6. For fragment **5**, the readily available (from L-rhamnose) hydroxy thioglycoside **45**^[23] (Scheme 5) was first selectively methylated (NaH, MeI, 92% yield) and the resulting methyl ether **46** was exposed to TsOH in ethylene glycol to afford diol **47** (91% yield). The C3 hydroxy group of compound **47** was selectively protected as its TBS ether to furnish compound **48** in 95% yield. The stereochemistry of the remaining C2 hydroxy group of **48** was then inverted following a two-step sequence, involving Swern oxidation and NaBH₄ reduction, to afford the L-glucose derivative **50** via ketone **49** in 70% overall yield. Finally, silylation (100% yield) of **50** followed by S-oxidation with *m*CPBA led to the desired sulfoxide **5** in 80% yield via compound **51**.

The hydroxy thioglycoside **45**^[23] was also utilized for the construction of the **DE** carbohydrate domain **6** (Scheme 6). Thus, a TBS group was installed on **45** by treatment with TBSOTf and 2,6-lutidine (95% yield) to furnish derivative **52**. The acetonide group was then removed (92% yield) to afford the corresponding 2,3-diol system (**53**). Regioselective mono-allylation of diol **53** was effected through the tin acetal technology^[24] (*n*Bu₂SnO; allylbromide, 90% yield, ca. 3:1 ratio favoring the desired 3-*O* derivative) which lead to hydroxy compound **54**. Protection of the C2 hydroxy group of intermediate **54** as a PMB ether **55** (83% yield) was then followed by cleavage of the allyl ether (92% yield) to furnish hydroxy compound **56**. Oxidation of the latter with DMP afforded the corresponding ketone (**57**) in 96% yield. Stereoselective conversion of **57** to the desired tertiary alcohol (**58**) was accomplished by treatment of MeMgBr in diethyl ether at -78°C (91% yield, ca. 7.5:1 favoring the desired diastereoisomer). Protective group manipulations furnished intermediates **59** and **60**, respectively. The 2-hydroxy phenylthioglycoside **60** was then subjected to a DAST-induced 1,2-migration reaction^[25, 26] to afford, quantitatively, the glycosyl fluoride **61**, which was subsequently reacted with benzyl alcohol in the presence of SnCl₂ in diethyl ether to afford, stereoselectively, the β-benzyl glycoside **62** (97% yield). Exposure of **62** to TBAF furnished the 3,4-dihydroxy compound **63** (98% yield).

Coupling of acceptor **66** (obtained from the known 2,3-dihydroxy thioglycoside **64**^[26] by regioselective methylation followed by a DAST-induced 1,2-migration^[25, 26] in 83% yield as shown in Scheme 6) with glycosyl donor **63** in the presence of SnCl₂ in diethyl ether gave disaccharide **67** in 45% yield.^[27] The tertiary hydroxy group of derivative **67** was then protected as a TES ether (84% yield) and the resulting disaccharide **68** was exposed to



Scheme 5. Synthesis of carbohydrate building block **A** (**5**). a) MeI (5.0 equiv), NaH (2.5 equiv), DMF, 25°C , 1.5 h, 92%; b) TsOH (0.1 equiv), (CH₂OH)₂ (1.2 equiv), MeOH, 25°C , 12 h, 91%; c) TBSOTf (1.05 equiv), 2,6-lutidine (1.5 equiv), CH₂Cl₂, $0 \rightarrow 25^\circ\text{C}$, 3 h, 95%; d) (COCl)₂ (2.0 equiv), DMSO (2.5 equiv), Et₃N (4.0 equiv), CH₂Cl₂, -78°C , 4.5 h, 100%; e) NaBH₄ (1.2 equiv), MeOH, 0°C , 5 min, 70%; f) TBSOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH₂Cl₂, $0 \rightarrow 25^\circ\text{C}$, 1 h, 100%; g) *m*CPBA (1.0 equiv), CH₂Cl₂, -78°C , 5 h, 80%. *m*CPBA = *m*-chloroperoxybenzoic acid; TsOH = *p*-toluenesulfonic acid.



Scheme 6. Synthesis of carbohydrate building block **D** (**6**). a) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2 , -78°C , 0.5 h, 95%; b) $\text{BCl}_3 \cdot \text{SMe}_2$ (0.5 equiv) (2.0 M solution in CH_2Cl_2), CH_2Cl_2 , 0°C , 10 min, 92%; c) $n\text{Bu}_2\text{SnO}$ (1.3 equiv), toluene, reflux, 6 h; AllylBr (1.5 equiv), CeF (1.2 equiv), DMF, 70°C , 12 h, 90% (ca. 3:1 ratio); d) PMBCl (1.5 equiv), $n\text{Bu}_4\text{NI}$ (0.5 equiv), NaH (1.6 equiv), DMF, 0°C , 1.5 h, 83%; e) 1. $[\text{RhCl}(\text{PPh}_3)_3]$ (0.05 equiv), DABCO (1.5 equiv), $\text{MeOH}/\text{H}_2\text{O}$ (10:1), reflux, 1 h; 2. NMO (1.2 equiv), OsO_4 (0.05 equiv), $\text{Me}_2\text{CO}/\text{H}_2\text{O}$ (10:1), 25°C , 12 h, 92%; f) DMP (1.5 equiv), NaHCO_3 (2.0 equiv), CH_2Cl_2 , 25°C , 10 min, 96%; g) MeMgBr (2.0 equiv) (3 M solution in Et_2O), Et_2O , -78°C , 10 min, 91% (ca. 7.5:1 ratio); h) TBSOTf (2.0 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2 , $0 \rightarrow 40^\circ\text{C}$, 24 h, 93%; i) DDQ (1.5 equiv), $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (5:1) 0°C , 1.5 h, 97%; j) DAST (1.5 equiv), CH_2Cl_2 , 0°C , 20 min, 100%, α/β ca. 1:10; k) BnOH (5.0 equiv), SnCl_2 (1.0 equiv), Et_2O , $0 \rightarrow 25^\circ\text{C}$, 5 h, 97%; l) $n\text{Bu}_4\text{NF}$ (2.5 equiv), THF, 25°C , 6 h, 98%; m) $n\text{Bu}_2\text{SnO}$ (1.2 equiv), toluene, reflux, 6 h; MeI (1.5 equiv), CsF (1.2 equiv), DMF, 55°C , 1 h, 83%; n) DAST (1.5 equiv), CH_2Cl_2 , 0°C , 0.5 h, 100%, α/β ca. 1:7; o) **63** (0.73 equiv), SnCl_2 (1.0 equiv), Et_2O , $0 \rightarrow 25^\circ\text{C}$, 12 h, 45% of the 4-O glycoside, 26% of the 3-O glycoside; p) TESOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 6 h, 84%; q) Raney-Ni (ca. 4 equiv) (w/w), EtOH , 55°C , 5 h, 92%; r) DAST (1.5 equiv), CH_2Cl_2 , 0°C , 15 min, 100%, α/β ca. 15:1. Bn = Benzyl; DAST = (diethylamino)sulfur trifluoride; DABCO = 1,4-diazabicyclo[2.2.2]octane; DMP = Dess–Martin Periodinane.

Raney-Ni hydrogenolysis conditions which concomitantly removed the phenylsulfanyl groups and caused cleavage of the benzyl ether to furnish disaccharide lactol **69** (92% yield). Lactol **69** was then converted to the desired glycosyl fluoride building block **6** in quantitative yield by reaction with DAST.

The described sequences provided all five requisite building blocks (**2–6**) for the projected total synthesis of apoptolidin (**1**) in large quantities and set the stage for the next phase of the program directed at their coupling and elaboration to the final target. The following communication^[4] details the successful accomplishment of this goal.

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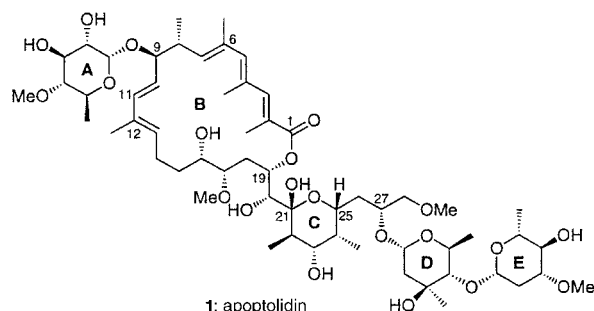
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Total Synthesis of Apoptolidin: Part 2. Coupling of Key Building Blocks and Completion of the Synthesis**

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In the preceding communication^[1] we described the construction of five building blocks destined to provide the molecular framework of apoptolidin (**1**).^[2] In this communication we report the successful coupling of these intermediates in the proper manner and the completion of the total synthesis of **1**.



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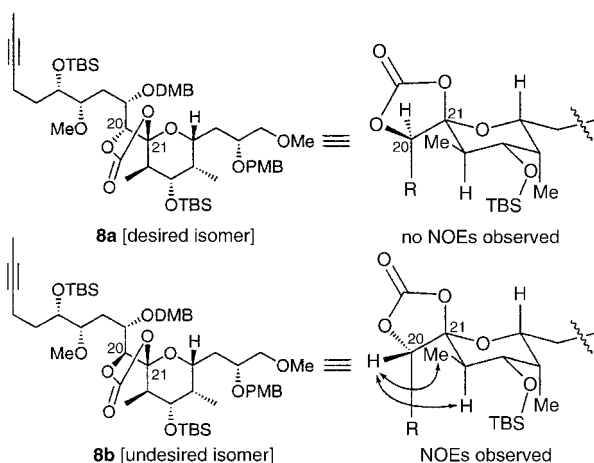
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According to the strategy delineated in the preceding paper,^[1] the first objective was the coupling of dithiane **2** (C21–C28 fragment) with aldehyde **3** (C12–C20 fragment), a task that was accomplished as shown in Scheme 1. Thus, generation of the anion from **2** followed by addition of aldehyde **3** resulted in the formation of coupling products **4a** and **4b** as a ca. 1.5:1 mixture of diastereoisomers at C20. Since we had no direct way of knowing the stereochemistry of the newly formed stereocenter, we decided to continue with each of the two isomers **4a** and **4b** (after chromatographic separation) expecting to be able to carry out the necessary stereochemical assignment, and possibly correct the stereochemistry of the wrong isomer, at a later stage. Thus, the bulky silyl groups were removed from **4a** and **4b** (90 % yield) to generate tetraols **5a** and **5b**, from which the dithiane protecting group was now easily removed by using $\text{PhI}(\text{CF}_3\text{CO}_2)_2$ ^[3] to afford lactols **6a** and **6b**. Their resilylation with TBSOTf in the presence of 2,6-lutidine proceeded smoothly and regioselectively, and lead to the bis-silyl ethers **7a** and **7b** (78 % overall yield for two steps).

At this stage we attempted to assign the C20 stereochemistry of the two stereoisomers by forming the corresponding carbonates, **8a** and **8b** (triphosgene, py, 80 % yield). Indeed, NOE studies on **8a** and **8b** revealed **8a** (major) as the desired stereoisomer (see Scheme 2). Knowing that ways and means had to be found soon to correct the stereochemistry of the wrong isomer (**7b**), we took both compounds, **7a** and **7b**, to the next stage. Originally, we envisioned that a methoxy group at the anomeric center (C21) could allow the implementation of an oxidation–reduction protocol for the inversion of the C20 hydroxy group, but we were disappointed to find out that this rather labile group was removed during the hydrozirconation step that was required to convert the acetylenic group to the vinyl iodide (see below). A solution to this problem was provided by the use of an orthoester as a protecting group for the C20–C21 diol system. Thus, treatment of **7a** and **7b** with trimethyl orthoacetate in the presence of PPTS led to orthoesters **9a** and **9b** (95 % yield). Exposure of **9a** (ca. 5:1 mixture of orthoester diastereoisomers) and **9b** (single orthoester stereoisomer) to the hydrozirconation and Zr–I exchange conditions^[4] ($[(\text{Cp})_2\text{ZrClH}]$; I_2) led to the corresponding vinyl iodides (**10a** and **10b**) as a ca. 6:1 mixture with their regioisomers (90 % combined yield).

The remarkable collapse of the methyl orthoester to the methyl glycoside moiety at C21 in this reaction requires a migration of the methoxy group from the orthoester moiety to the anomeric position, an event presumably facilitated by the pyranoside oxygen atom and initial complexation (presumably by zirconium) at the departing orthoester oxygen atom. The undesired methyl glycoside **10b** was then conveniently converted to the correct C20 stereoisomer (**10a**) by oxidation (DMP, 88 %) followed by reduction (NaBH_4 , 90 % yield). Removal of both the PMB and DMB groups from **10a** was achieved by a two-step procedure. Thus, upon exposure of **10a** to excess DDQ, the PMB group was cleaved off while the DMB moiety at C20 became initially engaged with the free hydroxy moiety at C21 as a benzylidene group, which finally broke up as a mixture of C20 and C21 DMB esters. Exposure of this mixture to LiOH then completed the deprotection

Scheme 1. Synthesis of vinyliodide **14**. a) dithiane **2** (3.0 equiv), *t*BuLi (2.95 equiv), THF, -78° $\rightarrow$ -50°C , 2 h; **3** (1.0 equiv), THF, -100°C , 2 h, 91 %, ca. 1.5:1 mixture of diastereoisomers **4a**:**4b**; b) *n*Bu₄NF (6.0 equiv), THF, 25°C , 12 h, 90 %; c) PhI(CF₃CO₂)₂ (1.1 equiv), MeCN/pH 7.0 buffer (3:1), 0°C , 5 min; d) TBSOTf (2.5 equiv), 2,6-lutidine (5.0 equiv), CH₂Cl₂, -78°C , 3 h, 78 % over two steps; e) (CCl₃O)₂CO (5.0 equiv), py (20 equiv), CH₂Cl₂, -78°C , 1 h, 88 %; f) (MeO)₃CMe (50 equiv), PPTS (0.5 equiv), CH₂Cl₂, 25°C , 1 h, 95 %; g) [(Cp)₂ZrCl₂(iH)] (3.0 equiv), THF, 65°C , 1.5 h; **I**₂ (3.0 equiv), THF, -25°C , 2 min, 90 %; h) DMP (2.0 equiv), NaHCO₃ (20 equiv), CH₂Cl₂, 0°C , 1 h, 88 %; i) NaBH₄ (5.0 equiv), MeOH, 0 $\rightarrow$ -25°C , 4 h, 86 %; j) DDO (4.0 equiv), CH₂Cl₂: buffer pH 7.0 (1:1), 0 $\rightarrow$ -25°C , 4 h; LiOH (2.0 equiv), MeOH, 25°C , 12 h, 85 % over two steps; k) (CCl₃O)₂CO (5.0 equiv), py (20 equiv), CH₂Cl₂, -78°C , 1 h, 88 %; l) TESOTf (1.5 equiv), 2,6-lutidine (3.0 equiv), CH₂Cl₂, -78°C , 95 %. DMP = Dess–Martin Periodinane; DMB = 3,4-dimethoxybenzyl; PPTS = pyridinium *p*-toluene sulfonate; PMB = *p*-methoxybenzyl; Tf = trifluoromethane sulfonyl; DDO = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; py = pyridine.

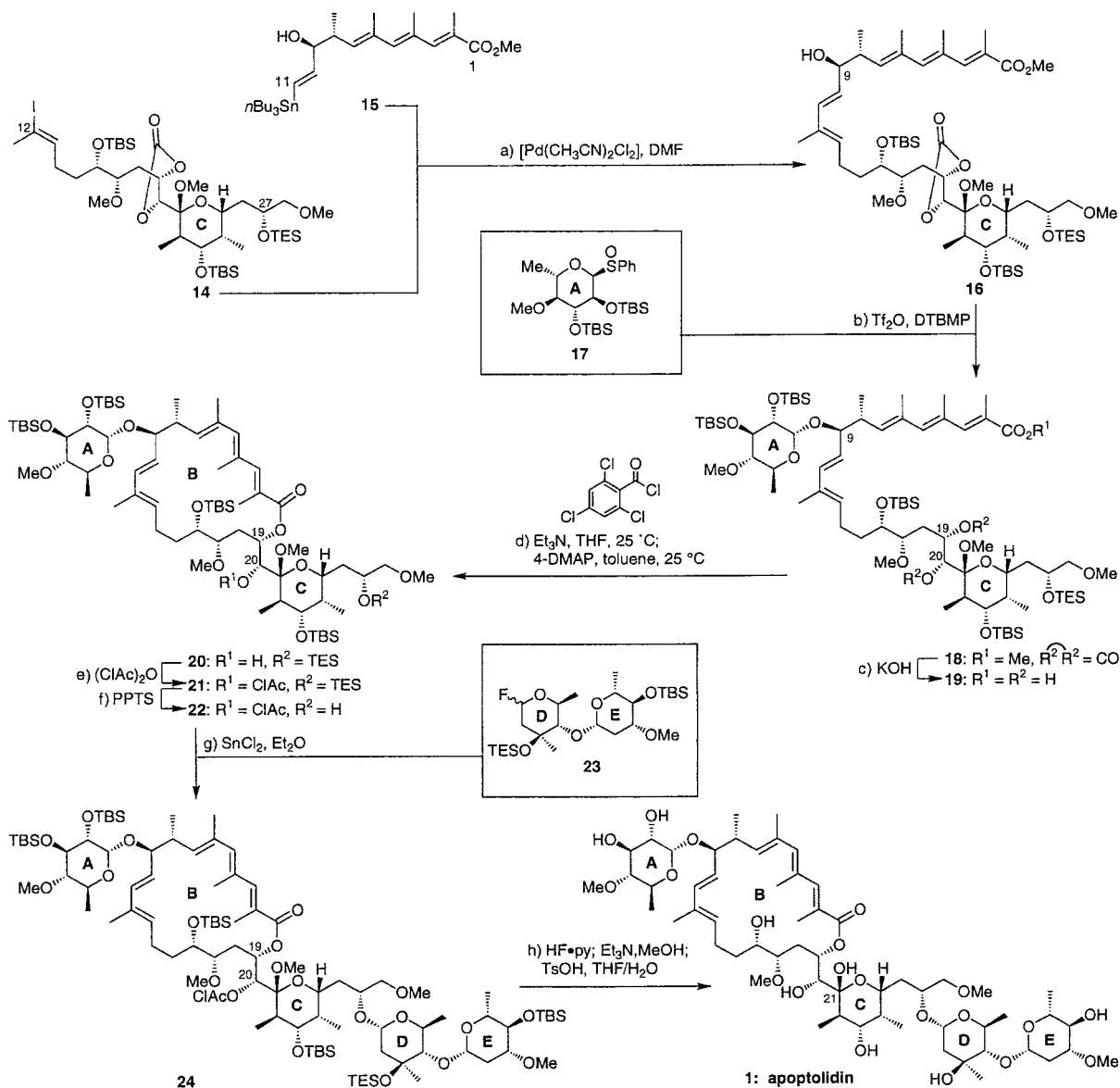


Scheme 2. NOE experiments with compounds **8a** and **8b** allowed stereochemical assignment of C20 stereoisomers.

With the C12–C28 advanced intermediate (**14**) appropriately functionalized and protected, we then proceeded to couple it to the vinyl stannane **15** (see Scheme 3). This was accomplished by a Stille coupling reaction^[5] in the presence of [Pd(CH₃CN)₂Cl₂] in DMF at ambient temperature which furnished the desired C1–C28 segment **16** (86% yield). Allylic alcohol **16** was then coupled with carbohydrate donor

17^[6] which lead to α -glycoside **18** (65 % yield). The α stereochemistry of this glycoside was confirmed by NMR spectroscopy ($J_{1,2} = 3.5$ Hz). Both the carbonate moiety and methyl ester group were then cleaved from compound **18** upon exposure to KOH in dioxane/H₂O at 60 °C to afford dihydroxy carboxylic acid **19** (80 % yield) which set the stage for the planned Yamaguchi macrolactonization reaction.^[7] Reasoning that the C19 hydroxy group would be more accessible than the sterically hindered C20 hydroxy group in this ring closure, we proceeded to the next step without protection. Indeed treatment of **19** with excess 2,4,6-trichlorobenzoyl chloride and triethylamine in THF (0 $\rightarrow$ 25 °C), followed by addition of the resulting mixed anhydride to excess 4-DMAP in dilute toluene solution at ambient temperature resulted in the formation of macrolactone **20** in 63 % yield (for selected physical properties, see Table 1). The remaining hydroxy group in **20** (C20) was then protected with a chloroacetyl group (90 % yield) to afford **21**, from which the TES group was selectively removed by exposure to PPTS in MeOH at ambient temperature to afford hydroxy compound **22** (80 % yield).

The last fragment, glycosyl fluoride **23** carrying the **DE** disaccharide domain, was attached to the main frame **22** via SnCl₂-induced coupling to furnish protected apoptolidin **24** in 70 % yield (for selected physical properties, see Table 1). The desired α -glycoside bond in **24** connecting the **DE** carbohydrate domain to the rest of the molecule was formed exclusively, as indicated by NMR spectroscopy ($J_{1,2} = 3.0$ Hz). While intermediate **24** was stable, its global deprotection to apoptolidin (**1**) proved quite challenging due to its chemical sensitivity. This was finally accomplished by employ-



Scheme 3. Completion of the total synthesis of apoptolidin (**1**). a) **15** (4.0 equiv), $[\text{Pd}(\text{MeCN})_2\text{Cl}_2]$ (0.05 equiv), DMF, 25 °C, 15 h, 86 %; b) **17** (3.0 equiv), TiF_2O (2.5 equiv), DTBMP (5.0 equiv), Et_2O , –78 °C, 1.5 h, 65 %; c) KOH (20 equiv), dioxane/ H_2O (20:1), 60 °C, 12 h, 80 %; d) 2,4,6-trichlorobenzoyl chloride (20 equiv), Et_3N (40 equiv), THF, 0 → 25 °C, 7 h; 4-DMAP (80 equiv), toluene (0.01 mm), 25 °C, 12 h, 63 %; e) $(\text{ClAc})_2\text{O}$ (10 equiv), pyridine, 0 °C, 3 h, 90 %; f) PPTS (0.5 equiv), MeOH, 0 → 25 °C, 15 min, 80 %; g) **23** (2.0 equiv), SnCl_2 (2.0 equiv), Et_2O , 0 °C, 4 h, 70 %; h) $\text{HF}\cdot\text{py}$ (50 equiv), THF, –25 °C, 48 h; Et_3N (100 equiv), MeOH, 25 °C, 36 h; TsOH (1 equiv), THF/ H_2O (5:1), 25 °C, 2.5 h, ca. 30 %. 4-DMAP = 4-dimethylaminopyridine; ClAc = chloroacetyl; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

ing carefully controlled conditions involving sequential exposure of **24** to $\text{HF}\cdot\text{py}$ in THF at –25 °C to remove the silyl groups), followed by Et_3N in methanol (to remove the chloroacetyl group) and TsOH in THF/ H_2O at room temperature (to cleave the methyl glycoside) (ca. 30 % overall yield from **24**). The chromatographic (TLC, HPLC), spectroscopic (^1H NMR, IR and UV), and high-resolution mass spectrometric properties of synthetic apoptolidin (**1**) matched those of an authentic sample.^[8, 9]

The described total synthesis of apoptolidin (**1**) in its naturally occurring form is characterized by a highly convergent strategy and considerable flexibility for the construction of simpler analogues. Of particular importance in this synthesis are the noted chemical idiosyncrasies of the target

molecule toward a variety of reagents and conditions, the specific protecting group combinations, and the collapse of the anomeric orthoester to the corresponding methyl glycoside during the hydrozirconation step. Details will be given in a full account of this work.

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Table 1. Selected physical properties of compounds **13**, **20**, and **24**.

Carbonate **13**: Colorless oil; $R_f = 0.20$ (silica, 20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{\max} = 3530, 2931, 2860, 1807, 1461, 1378, 1255, 1073, 832, 707 \text{ cm}^{-1}$; $^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta = 6.15$ (dd, $J = 3.9, 3.9 \text{ Hz}$, 1H, H-13), 4.98–4.92 (m, 1H, H-19), 4.33 (d, $J = 4.9 \text{ Hz}$, 1H, H-20), 4.06 (bd, $J = 10.9 \text{ Hz}$, 1H, H-25), 4.01–3.92 (m, 1H, H-27), 3.90–3.79 (m, 1H, H-16), 3.77 (dd, $J = 10.3, 4.6 \text{ Hz}$, 1H, H-23), 3.47–3.34 (m, 2H, H-28, H-17), 3.41 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.28 (s, 3H, OMe), 3.22 (dd, $J = 8.6, 8.6 \text{ Hz}$, 1H, H-28), 2.37 (s, 3H, Me-12), 2.26–2.17 (m, 1H, H-14), 2.10–1.91 (m, 4H, H-22, H-18, H-15, H-14), 1.75–1.67 (m, 1H, H-24), 1.66–1.56 (m, 2H, H-26, H-18), 1.39–1.20 (m, 2H, H-26, H-15), 0.99 (d, $J = 6.5 \text{ Hz}$, 3H, Me-22), 0.89 (bs, 18H, $t\text{BuSi}$), 0.85 (d, $J = 7.0 \text{ Hz}$, 3H, Me-24), 0.10, 0.08, 0.06, 0.03 ($4 \times s$, $4 \times 3 \text{ H}$, MeSi); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta = 153.9, 140.7, 100.0, 93.9, 81.0, 79.3, 77.3, 75.2, 73.2, 70.0, 67.6, 66.8, 59.2, 58.5, 48.7, 39.3, 36.1, 35.4, 34.5, 30.3, 29.9, 27.5, 25.9$ (6C), 18.1, 18.0, 11.6, 5.0, –4.2, –4.3, –4.7, –4.8; HRMS (MALDI-FT-MS): calcd for $\text{C}_{36}\text{H}_{69}\text{IO}_{10}\text{Si}_2\text{Na}$ [$M + \text{Na}^+$]: 867.3366, found 867.3344

Macrolactone **20**: Colorless oil; $R_f = 0.54$ (silica, 30% Et_2O in hexanes); $[\alpha]_D^{25} = -1.4$ ($c = 0.05$, CHCl_3); IR (thin film): $\tilde{\nu}_{\max} = 2934, 2856, 1722, 1700, 1459, 1380, 1246, 1095, 1072, 1027, 831, 775 \text{ cm}^{-1}$; $^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta = 7.12$ (s, 1H, H-3), 6.09 (d, $J = 15.8 \text{ Hz}$, 1H, H-11), 6.04 (s, 1H, H-5), 5.47–5.46 (m, 2H, H-13, H-19), 5.10 (dd, $J = 15.8, 9.2 \text{ Hz}$, 1H, H-10), 5.07 (d, $J = 8.8 \text{ Hz}$, 1H, H-7), 4.79 (d, $J = 3.5 \text{ Hz}$, 1H, H-1'), 3.96–3.92 (m, 1H, H-27), 3.86–3.82 (m, 1H, H-25), 3.83 (dd, $J = 8.8, 8.8 \text{ Hz}$, 1H, H-3'), 3.77–3.71 (m, 3H, H-9, H-16, H-23), 3.60 (bd, $J = 4.4 \text{ Hz}$, 1H, H-20), 3.51 (dd, $J = 9.2, 3.5 \text{ Hz}$, 1H, H-2'), 3.50 (s, 3H, OMe-4'), 3.41 (s, 3H, OMe-17), 3.37 (dd, $J = 9.7, 4.0 \text{ Hz}$, 1H, H-5'), 3.35 (s, 3H, OMe-28), 3.31 (dd, $J = 4.9, 1.3 \text{ Hz}$, 1H, H-28), 3.29 (d, $J = 5.7 \text{ Hz}$, 1H, H-28), 3.25 (s, 3H, OMe-21), 2.68–2.62 (m, 3H, H-4', H-8, H-17), 2.47–2.41 (m, 1H, H-14), 2.10 (s, 3H, Me-4), 2.09 (s, 3H, Me-2), 1.84 (s, 3H, Me-6), 1.82–1.78 (m, 4H, H-15, H-18, H-22, H-26), 1.75–1.64 (m, 2H, H-18, H-24), 1.58 (s, 3H, Me-12), 1.55–1.45 (m, 3H, H-26, H-14, H-15), 1.30 (s, 3H, Me-8), 1.13 (d, $J = 6.5 \text{ Hz}$, 3H, Me-6'), 1.04 (d, $J = 6.5 \text{ Hz}$, 3H, Me-22), 0.96 (dd, $J = 8.0, 8.0 \text{ Hz}$, 9H, $\text{CH}_3\text{CH}_2\text{Si}$), 0.93, 0.93, 0.92 ($3 \times s$, $3 \times 9 \text{ H}$, $t\text{BuSi}$), 0.90 (d, $J = 6.5 \text{ Hz}$, 3H, Me-24), 0.88 (s, 9H, $t\text{BuSi}$), 0.64–0.57 (m, 6H, CH_2Si), 0.14, 0.13, 0.09, 0.08, 0.05, 0.04, 0.02, 0.02 ($8 \times s$, $8 \times 3 \text{ H}$, MeSi); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta = 169.2, 145.1, 144.2, 140.5, 140.1, 132.8, 132.4, 130.9, 129.1, 125.0, 124.7, 101.6, 95.1, 87.6, 82.3,$

81.6, 77.7, 76.2, 75.2, 74.2, 73.7, 72.8, 70.9, 69.5, 69.4, 69.1, 68.2, 67.1, 63.9, 61.2, 61.1, 58.9, 47.8, 39.5, 38.7, 38.3, 37.9, 37.7, 36.2, 35.6, 30.4, 28.9, 26.4 (3C), 26.4 (3C), 26.2 (3C), 25.8 (3C), 25.1, 23.7, 23.0, 18.4, 18.3, 18.2, 18.1, 17.7, 16.4, 14.0, 11.7, 7.0, 5.3, 5.2, –3.0, –3.7, –4.1, –4.1, –4.2, –4.5, –4.9; MS (ESI), calcd for $\text{C}_{75}\text{H}_{144}\text{O}_{15}\text{Si}_5\text{Na}$ [$M + \text{Na}^+$]: 1448, found 1448

Fully protected apoptolidin **24**: Colorless oil; $R_f = 0.19$ (silica, 10% EtOAc in hexanes); $[\alpha]_D^{25} = -0.35$ ($c = 0.02$, CHCl_3); IR (thin film): $\tilde{\nu}_{\max} = 2931, 1737, 1707, 1455, 1378, 1249, 1096, 1020, 861, 832, 773, 732, 673 \text{ cm}^{-1}$; $^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta = 7.05$ (s, 1H, H-3), 6.08 (d, $J = 15.8 \text{ Hz}$, 1H, H-11), 6.01 (s, 1H, H-5), 5.47–5.40 (m, 2H, H-13, H-19), 5.10–5.03 (m, 2H, H-10, H-7), 4.98 (d, $J = 7.4 \text{ Hz}$, 1H, H-20), 4.86 (d, $J = 3.0 \text{ Hz}$, 1H, H-1'), 4.76 (d, $J = 3.5 \text{ Hz}$, 1H, H-1'), 4.75 (dd, $J = 8.8, 1.8 \text{ Hz}$, 1H, H-1'''), 4.31–4.27 (m, 1H, H-27), 4.11–4.08 (m, 1H, H-25), 3.97, 3.80 (AB, $J = 14.9 \text{ Hz}$, 2H, ClCH_2CO), 3.85–3.78 (m, 2H, H-3', H-28), 3.77–3.71 (m, 4H, H-9, H-16, H-23, H-5'), 3.51–3.42 (m, 3H, H-28, H-2', H-5'), 3.47 (s, 3H, OMe-4'), 3.35 (s, 3H, OMe-17), 3.32 (s, 3H, OMe-28), 3.28 (s, 3H, OMe-21), 3.27 (s, 3H, OMe-3'''), 3.35–3.28 (m, 1H, H-4'), 3.15–3.05 (m, 2H, H-4''', H-5'''), 3.00–2.85 (m, 1H, H-3'''), 2.71–2.60 (m, 3H, H-4', H-8, H-17), 2.40–2.32 (m, 2H, H-2''', H-18), 2.08 (s, 3H, Me-4), 2.04 (s, 3H, Me-2), 2.07–2.01 (m, 1H, H-22), 1.97–1.87 (m, 1H, H-2''), 1.82 (s, 3H, Me-6), 1.82–1.61 (m, 6H, H-15, H-14, H-18, H-24, H-26, H-2''), 1.54 (s, 3H, Me-12), 1.47–1.34 (m, 3H, H-26, H-14, H-15), 1.39 (s, 3H, Me-3''), 1.35–1.20 (m, 10H, H-2''', Me-6'', Me-6'), 1.10 (d, $J = 6.6 \text{ Hz}$, 3H, Me-8), 1.03 (d, $J = 6.5 \text{ Hz}$, 3H, Me-22), 0.98–0.85 (m, 57H, $\text{CH}_2\text{CH}_2\text{Si}$, $t\text{BuSi}$, Me-24), 0.64–0.54 (m, 6H, CH_2Si), 0.12, 0.10, 0.06, 0.06, 0.05, 0.05, 0.05, 0.03, 0.00, –0.01 ($10 \times s$, $10 \times 3 \text{ H}$, MeSi); $^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta = 168.2, 166.5, 145.9, 144.8, 141.1, 140.1, 132.8, 132.4, 131.8, 131.5, 124.9, 122.5, 101.0, 101.0, 96.7, 95.1, 87.6, 85.7, 82.9, 82.3, 81.4, 81.0, 78.3, 76.0, 75.33, 75.26, 74.8, 74.4, 74.1, 73.7, 73.0, 72.8, 72.5, 69.5, 68.8, 67.1, 66.3, 61.23, 61.16, 59.1, 56.0, 47.8, 45.1, 43.2, 40.8, 39.2, 37.9, 36.3, 35.7, 35.6, 35.4, 35.0, 30.6, 26.41$ (3C), 26.39 (3C), 26.1 (3C), 26.0 (3C), 25.8 (3C), 23.4, 23.1, 19.2, 18.5, 18.39, 18.37, 18.2, 18.09, 18.05, 17.7, 16.3, 15.3, 14.2, 13.9, 13.7, 7.1, 6.95, 6.85, 6.6, –3.0, –3.7, –3.9, –4.0, –4.1, –4.2, –4.2, –4.5, –4.8, –4.8; HRMS (MALDI-FTMS), calcd for $\text{C}_{97}\text{H}_{183}\text{ClO}_{22}\text{Si}_6\text{Na}$ [$M + \text{Na}^+$]: 1926.1397, found 1926.1465

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[8] We thank Dr. C. Khosla and Dr. Y. Hayakawa for generous gifts of natural apoptolidin.
 [9] Apoptolidin's rather labile nature proved challenging in the final deprotection, purification, and characterization procedures. Specifically, upon standing at ambient temperature in solution or during chromatographic manipulations, apoptolidin initially converted to an isomer (presumably its C21 anomer) and, subsequently, to a number of other unidentified products. The $^1\text{H NMR}$ spectra of **1** (synthetic or natural), therefore, included a number of additional signals due to these contaminants. Characterization of these products is currently in progress.

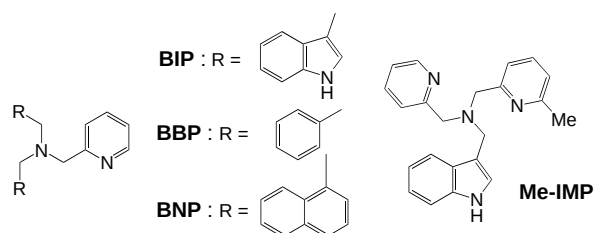
Effects of a Side Chain Aromatic Ring on the Reactivity of Copper(I) Complexes with Dioxygen**

Yuichi Shimazaki, Takeo Nogami, Fumito Tani, Akira Odani, and Osamu Yamauchi*

Close contact between a metal ion and an aromatic ring has been observed for planar metal complexes with an aromatic ring in the side chain, such as the tryptophan indole and the tyrosine phenol ring,^[1] and for complexes where intramolecular aromatic-ring stacking occurs.^[2] We reported previously that the Cu^I complex of a tripodal N3 ligand with a pendent indole ring has a unique Cu^I–indole η^2 -type bond through the C2–C3 moiety.^[3] A pendent naphthyl group of a Cu^I complex of a NS2 macrocyclic ligand has been reported to form a similar bond.^[4]

These observations suggest that the proximity of indole or other aromatic rings to the metal center may affect the reactivity of the complex, such as in the formation of a metal–dioxygen adduct in the course of dioxygen activation—which is of current interest for its importance in biological as well as chemical systems.^[5] Significant progress has been made in the chemistry of the intermediate complexes formed in the course of the reaction of Cu^I species with dioxygen.^[6] *trans*- μ -Peroxodicopper(II),^[7] (μ - η^2 : η^2 -peroxy)dicopper(II),^[8] and bis(μ -oxo)dicopper(III)^[9–14] complexes have drawn particular attention as a consequence of their known or potential relevance to intermediates in biological oxygenation. The bis(μ -oxo)dicopper(III) species was characterized by X-ray crystallography and shown to have a unique diamond-shaped structure formed by two Cu^{III} and two bridging oxo ions, Cu₂(μ -O)₂,^[9–12] and the reactivities of this and other species have been explored in connection with the oxidative activation of C–H bonds.^[9–15] These intermediates often reacted with aliphatic C–H bonds^[15] and in a few cases activated the aromatic ring.^[14]

Here we report that the Cu^I complexes of N-donor ligands with one or two pendent indole rings (Scheme 1) form a dioxygen adduct as an intermediate which decomposes to give a product formed by a unique radical-coupling reaction between the indole rings.



Scheme 1. Structures of N-donor ligands with pendent aromatic rings.

The bidentate ligand *N,N*-bis[(3-indolyl)methyl]-*N*-[(2'-pyridyl)methyl]amine (BIP) reacted with Cu^I ions to give a dimeric complex [Cu(bip)I]₂·2CH₃COCH₃ (**1**), the X-ray crystal structure analysis^[16] of which has shown that each Cu^I site has a distorted tetrahedral geometry formed by two bridging iodine atoms, a tertiary amine nitrogen atom, and a pyridine nitrogen atom (Figure 1). The two side-chain indole

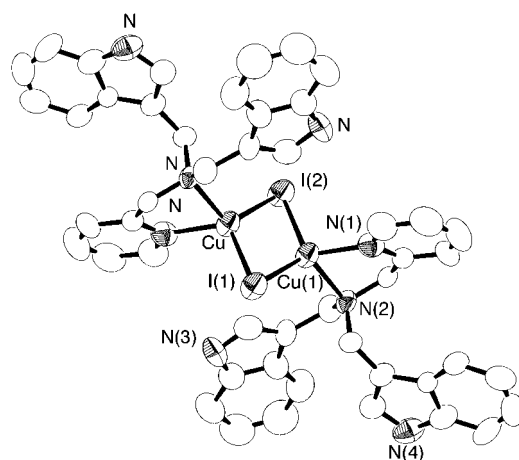


Figure 1. ORTEP view of [Cu(bip)I]₂·2CH₃COCH₃ (**1**) drawn with the thermal ellipsoids at the 50% probability level and atomic numbering scheme (CH₃COCH₃ molecules omitted for clarity). The hydrogen atoms and solvents are omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu(1)–N(1) 2.075(6), Cu(1)–N(2) 2.223(5), Cu(1)–I(1) 2.585(1), Cu(1)–I(2) 2.625(1); N(1)–Cu(1)–N(2) 79.5(3), N(1)–Cu(1)–I(1) 112.7(2), N(1)–Cu(1)–I(2) 105.9(2), I(1)–Cu(1)–I(2) 120.51(3).

rings are uncoordinated, and neither the stacking nor the Cu^I–indole η^2 -type bond^[3] were detected in the solid state or in solution. The reaction of a similar ligand, Me-IMP (*N*-(3-indolylmethyl)-*N*-(6-methyl-2-pyridylmethyl)-*N*-(2-pyridylmethyl)amine),^[3] and CO with [Cu(CH₃CN)₄]ClO₄ gave [Cu(Me-imp)(CO)]BPh₄ (**2**), which was revealed to have a tetrahedral geometry (Figure 2).

A colorless solution of **1** in THF reacted with O₂ at –90 °C to give a brown solution with an intense absorption band centered at 374 nm and a shoulder peak at 516 nm. The resulting solution was ESR inactive at 77 K. Complex **2** also reacted with O₂ in THF to give a brown solution exhibiting an absorption spectrum with similar peaks at 379 and 510 nm.^[17] The resonance Raman spectrum of this solution gave a Raman peak at 595 cm^{–1} with ¹⁶O₂ which shifted to 568 cm^{–1} upon substitution with ¹⁸O₂ (406.7-nm Kr⁺ laser excitation; Figure 3). No peaks were observed in the 700–800 cm^{–1} region, where the band resulting from the μ -peroxo dimer is

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

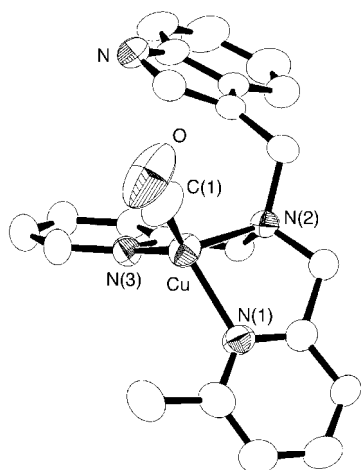


Figure 2. ORTEP view of the $[\text{Cu}(\text{Me-imp})(\text{CO})]^+$ ion in **2** drawn with the thermal ellipsoids at the 50% probability level and atomic numbering scheme. The hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu(1)–N(1) 2.048(4), Cu(1)–N(2) 2.134(4), Cu(1)–N(3) 2.021(4), Cu(1)–C(1) 1.790(9); N(1)–Cu(1)–N(2) 81.6, N(1)–Cu(1)–N(3) 108.1(2), N(2)–Cu(1)–N(3) 83.4(2), N(1)–Cu(1)–C(1) 122.0(3), N(2)–Cu(1)–C(1) 125.5(3), N(3)–Cu(1)–C(1) 123.6(2).

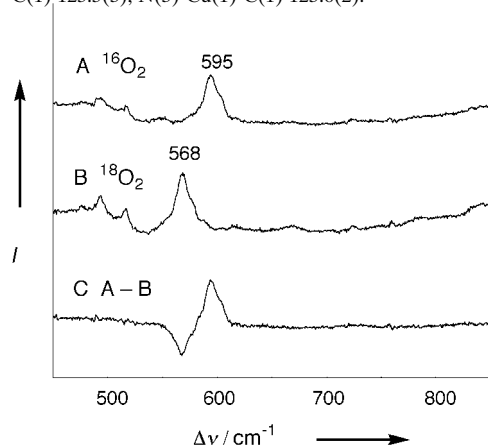
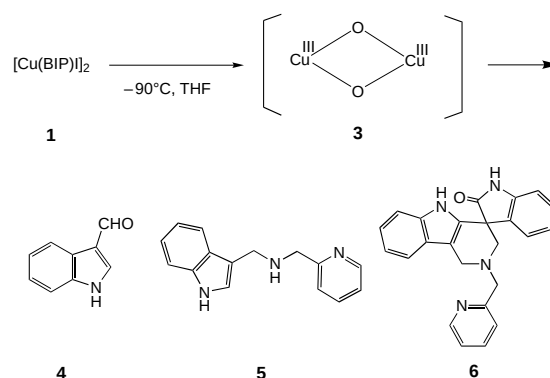


Figure 3. Resonance Raman spectra of **2** after oxygenation with $^{16}\text{O}_2$ and $^{18}\text{O}_2$ in THF at -90°C (406.7-nm Kr^+ laser excitation).

expected. We measured the resonance Raman spectrum with 514.5-nm laser excitation in order to detect the possible existence of the peroxo species. The spectrum showed a weak band at 590 cm^{-1} , but no peroxo band at about 750 cm^{-1} . The absorption and resonance Raman spectra of **3** agreed well with the values of 378 and 494 nm, and 590 cm^{-1} , respectively, reported for $[\text{Cu}_2(\text{O})_2(\text{Me}_2\text{-tpa})_2]^{2+}$ ($\text{Me}_2\text{-tpa}$ = bis(6-methyl-2-pyridylmethyl)-2-(pyridylmethyl)amine) which was isolated and structurally established by Suzuki and co-workers.^[12] In this latter complex each Cu^{II} ion has two weakly bound 6-methyl-2-pyridylmethyl side arms in the axial positions. Our spectra also corresponded with other previous observations^[9b, 10, 11, 13b, 18, 19] and are typical of the $\text{Cu}_2(\mu\text{-O})_2$ core, and gives support to the assumption that the brown solution contained an intermediate species (**3**) having the same bis(μ -oxo) dimer structure (Scheme 2). However, we should mention that while the above resonance Raman data suggest the presence of the bis(μ -O) core, they do not rule out the formation of the peroxo species during the course of the reaction.



Scheme 2. Reactions of Cu^{I} -BIP complexes with dioxygen.

The formation and decay of the oxygenated species **3** followed the first-order rate law, which indicates that the peroxo species was not formed or was too unstable to be detected during the reactions. On the other hand, BBP and BNP (BBP = *N,N*-bis(benzyl)-*N*-[(2'-pyridyl)methyl]amine; BNP = *N,N*-bis[(1-naphthyl)methyl]-*N*-[(2'-pyridyl)methyl]amine (Scheme 1)) reacted with CuI to give $[\text{Cu}(\text{bbp})\text{I}]$ and $[\text{Cu}(\text{bnp})\text{I}]$,^[20] respectively, and both reacted with O_2 in THF at -90°C to give a green color almost instantaneously. In order to examine the difference in reactivity in detail we measured the difference spectra for the reaction of $[\text{Cu}(\text{bnp})\text{I}]$ with O_2 under the same conditions by the rapid-scan technique. This study revealed a transient shoulder peak at approximately 380 nm during the first 5–20 s and finally peaks at around 360 and 600 nm.^[17] This observation indicates that an oxygenated intermediate similar to **3** is also formed with BNP, but it may be much less stable than that formed from **1** or **2**. This fact suggests there is a stabilizing effect of the $\text{Cu}_2(\mu\text{-O})_2$ core in the complexes by the pendent indole rings.

Intermediate **3** was short-lived compared with some of the reported $\text{Cu}_2(\mu\text{-O})_2$ species and changed to a green species below -80°C . The first-order decay constant k_{obs} of the brown species in THF was estimated to be $1.5 \times 10^{-2}\text{ s}^{-1}$ (half-life $t_{1/2} < 1\text{ min}$) at -90°C , as determined by UV/Vis spectroscopy. Indole-3-carboxaldehyde (**4**; 10%) and *N*-(3-indolyl)-methyl-*N*-[(2'-pyridyl)methyl]amine (**5**; 10%) were detected among the decomposition products formed by *N*-dealkylation (Scheme 2), which has been reported to occur with other $\text{Cu}_2(\mu\text{-O})_2$ species.^[9c, 12] In addition to these products, an interesting decay product **6** was isolated as crystals (15%). The X-ray structure analysis^[16] of the product disclosed that it has a bis(indolyl) moiety which is considered to have resulted from a radical-coupling reaction (Scheme 2).^[17] This structure supports the theory that the indole ring was located sufficiently close to the metal center to undergo an indole C–H bond scission, to form an indolyl radical in the course of the oxidative decomposition. $[\text{Cu}(\text{bbp})\text{I}]$ and $[\text{Cu}(\text{bnp})\text{I}]$ were observed to undergo *N*-dealkylation to give the corresponding aldehydes and secondary amines in low yields (<5%), but no radical-coupling product was detected.

In conclusion, the Cu^{I} complexes of ligands with pendent aromatic rings exhibited different reactivities with O_2 which depended on the nature of the aromatic rings. The present finding indicates that the vicinal noncoordinating indole ring

containing the NH moiety, as compared with the phenyl and naphthyl rings without it, may stabilize the bis(μ -oxo)dicopper(III) intermediate and affect subsequent reactions. Further studies along this line are under way.

Experimental Section

Synthesis of BIP: Indole (2.34 g, 20 mmol), formalin (37%, 1.62 g, 20 mmol), and a few drops of acetic acid were added to a solution of 2-pyridylmethylamine (1.08 g, 10 mmol) in methanol (100 mL). The reaction mixture was stirred overnight at room temperature and then concentrated almost to dryness in vacuo. The residue was dissolved in a saturated aqueous solution of NaHCO₃ (50 mL) and extracted with CHCl₃. The white powder obtained from the extract was recrystallized from ethyl acetate. Yield: 1.89 g (52%); ¹H NMR (300 MHz, CDCl₃): δ = 3.82 (s, 2H), 3.88 (s, 4H), 7.08 (dd, 1H), 7.09 (dt, 2H), 7.17–7.19 (m, 4H), 7.34 (d, 2H), 7.54–7.60 (m, 2H), 7.69 (d, 2H), 8.07 (brs, 2H), 8.48 (d, 1H).

Synthesis of BBP and BNP: BBP was prepared by the reaction of dibenzylamine (1.97 g, 10 mmol) with 2-pyridinecarboxaldehyde (0.63 g, 10 mmol) in methanol and subsequent reduction by sodium cyanotrihydroborate (0.63 g, 10 mmol). Yield: 1.28 g (35%); ¹H NMR (300 MHz, CDCl₃): δ = 3.62 (s, 4H), 3.74 (s, 2H), 7.12 (m, 1H), 7.23 (m, 2H), 7.31 (t, 2H), 7.32 (t, 2H), 7.41 (d, 4H), 7.64 (t, 2H), 7.66 (dt, 1H), 8.49 (d, 1H). BNP was prepared in a similar way from 2-pyridylmethylamine (1.07 g, 10 mmol), 1-naphthaldehyde (3.12 g, 20 mmol), and sodium cyanotrihydroborate (1.26 g, 20 mmol). Yield: 3.32 g (87%); ¹H NMR (300 MHz, CDCl₃): δ = 3.82 (s, 2H), 4.08 (s, 4H), 7.10 (m, 1H), 7.20 (m, 2H), 7.38 (t, 2H), 7.42 (t, 2H), 7.51 (t, 2H), 7.56 (d, 2H), 7.77 (d, 2H), 7.80 (d, 2H), 7.86 (d, 2H), 8.47 (d, 1H).

Synthesis of complexes: Complex **1** was prepared as pale yellow crystals from BIP (0.366 g, 1.0 mmol) and CuI (0.190 g, 1.0 mmol) in acetone/CH₃CN (4/1) under a nitrogen atmosphere. Yield: 0.372 g (74%); elemental analysis (%) calcd for **1**·2CH₃COCH₃ (C₃₄H₅₆N₈O₂Cu₂I₂): C 52.73, H 4.59, N 9.11; found: C 52.68, H 4.47, N 8.95. [Cu(bbp)I] and [Cu(bnp)I] were prepared in THF in a similar way. Elemental analysis (%) calcd for [Cu(bbp)I] (C₂₀H₂₀N₂CuI): C 50.17, H 4.21, N 5.85; found: C 50.11, H 4.24, N 5.85. Elemental analysis (%) calcd for [Cu(bnp)I] (C₂₈H₂₄N₂CuI): C 58.09, H 4.18, N 4.84; found: C 58.13, H 4.20, N 4.87. Complex **2** was prepared as colorless crystals from Me-IMP^[3] (0.205 g, 0.6 mmol), [Cu(CH₃CN)]ClO₄ (0.164 g, 0.6 mmol), and sodium tetraphenylborate (0.205 g, 0.6 mmol) in CH₃OH under a CO atmosphere. Elemental analysis (%) calcd for **2** (C₄₇H₄₂N₄OBCu): C 74.95, H 5.62, N 7.44; found: C 75.59, H 5.60, N 7.41.

Ligand recovery:^[14, 21] In a typical experiment, **1** (1.23 g, 1.0 mmol) was dissolved in THF (20 mL) under a nitrogen atmosphere, and O₂ was passed through the solution for 10 min at –80 °C. The solution was kept standing for one day at room temperature, and the resulting green solution was evaporated to dryness in vacuo. The residue was dissolved in concentrated NH₃ (10 mL) and extracted with CHCl₃ (3 × 10 mL). The combined organic fractions were dried over Na₂SO₄, filtered, and concentrated in vacuo to leave a brown oil. The decomposition products **4**–**6** were separated by column chromatography on silica gel, and their structures and relative amounts were determined by ¹H NMR spectroscopy. Crystals of **6** suitable for X-ray structure determination were prepared by recrystallization from CHCl₃. Elemental analysis (%) calcd for **6**·1.5CHCl₃ (C_{25.5}H_{21.5}N₄OCl_{4.5}): C 54.74, H 3.87, N 10.01; found: C 54.44, H 3.99, N 9.70; ¹H NMR (300 MHz, CD₃OD): δ = 3.02 (dd, 2H), 3.96 (dd, 2H), 3.98 (q, 2H), 4.12 (d, 1H), 6.97 (t, 3H), 7.03 (t, 1H), 7.19 (t, 2H), 7.27 (t, 1H), 7.35 (d, 1H), 7.39 (d, 1H), 7.67–7.78 (m, 2H), 8.43 (d, 1H).

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- [16] The X-ray experiments for complexes **1** and **3** were carried out on a Rigaku RAXIS imaging plate area detector with graphite monochromated MoK α radiation (λ = 0.71070 Å). The crystals were mounted on a glass capillary tube. In order to determine the cell constant and orientation matrix, three oscillation photographs were taken with an oscillation angle of 2° and the exposure time of 8 min for each frame. Intensity data were collected by taking oscillation photographs. Refraction data were corrected for both Lorentz and polarization effects. The unit-cell parameters used for the refinement were determined by least-squares calculations on the setting angles for 25 reflections that were collected on a Rigaku AFC-5R four-circle automated diffractometer. The measurement for **6** was carried out on

a Rigaku AFC-5R four-circle automated diffractometer using a rotating anode generator with graphite monochromated $\text{Cu}_{K\alpha}$ radiation ($\lambda = 1.54178 \text{ \AA}$). The crystals were mounted on a glass capillary tube. The reflection intensities for **6** were monitored by three standard reflections at every 2 h and 150 measurements, and the decay of intensities for the crystals was within 2%. Refraction data were corrected for both Lorentz and polarization effects. **1**: $\text{C}_{54}\text{H}_{56}\text{N}_8\text{O}_2\text{-Cu}_2\text{I}_2$, pale yellow crystals, monoclinic, space group $P2_1/n$, $a = 13.704(9)$, $b = 8.349(2)$, $c = 23.318(4) \text{ \AA}$, $\beta = 89.88(3)^\circ$, $V = 2667(1) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.531 \text{ g cm}^{-3}$, $R = 0.081$, $R_w = 0.141$ for all 6345 reflections ($I > 2.0\sigma(I)$) and 308 parameters. **2**: $\text{C}_{47}\text{H}_{42}\text{N}_4\text{OBCu}$, colorless crystals, monoclinic, space group $P2_1/n$, $a = 11.5365(3)$, $b = 22.5800(5)$, $c = 15.8994(5) \text{ \AA}$, $\beta = 107.8117(6)^\circ$, $V = 3934.2(2) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.269 \text{ g cm}^{-3}$, $R = 0.061$, $R_w = 0.100$ for all 7975 reflections ($I > 2.0\sigma(I)$) and 488 parameters. **6**: $\text{C}_{26}\text{H}_{22}\text{N}_4\text{OCl}_6$, colorless crystals, monoclinic, space group $P2_1/c$, $a = 10.743(3)$, $b = 17.820(4)$, $c = 15.673(3) \text{ \AA}$, $\beta = 105.72(2)^\circ$, $V = 2887(1) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.424 \text{ g cm}^{-3}$, $R = 0.085$, $R_w = 0.088$ for all 4287 reflections ($I > 2.0\sigma(I)$) and 335 parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-159430–159432, for **1**, **2**, and **6**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Immobilization of π -Assembled Metallo-Supramolecular Arrays in Thin Films: From Crystal-Engineered Structures to Processable Materials**

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Material and device performance is critically dependent on the spatial arrangement of the functional constituents. The ability to control the short- and long-range correlation of position and orientation of components is crucial for full exploitation of a material's potential and the encoding of new properties.^[1] Supramolecular synthetic methodologies enable the systematic design and construction of tailored architectures through a sequence of directed assembly processes.^[2] Metallo-units are particularly attractive functional components because of their inherent magneto-,^[3] electro-,^[4] and/or photochemical^[5] properties.

By means of crystal engineering, solid-state multimetal arrays can be constructed by using interactions of metal ions with multitopic ligands^[6] or other intermolecular forces to organize metallo-units.^[7–9] However, processing a crystalline solid into a device remains a challenge. Moreover, in a single crystal, it is difficult to achieve attractive features such as gradients, often necessary for vectorial functions. Thin films play an important role in applications^[10] such as storage, display, and sensing, yet to date there are no generic methodologies for incorporating and ordering discrete cationic metal complexes into thin films.^[11] To address this challenge and to attempt to bridge the gap between fundamental supramolecular crystal engineering and layered materials, we investigated whether π -aggregated metallo-arrays can be incorporated into ordered two-dimensional thin films.

A particularly attractive method to assemble thin films is the layer-by-layer (LbL) method, which rests primarily on

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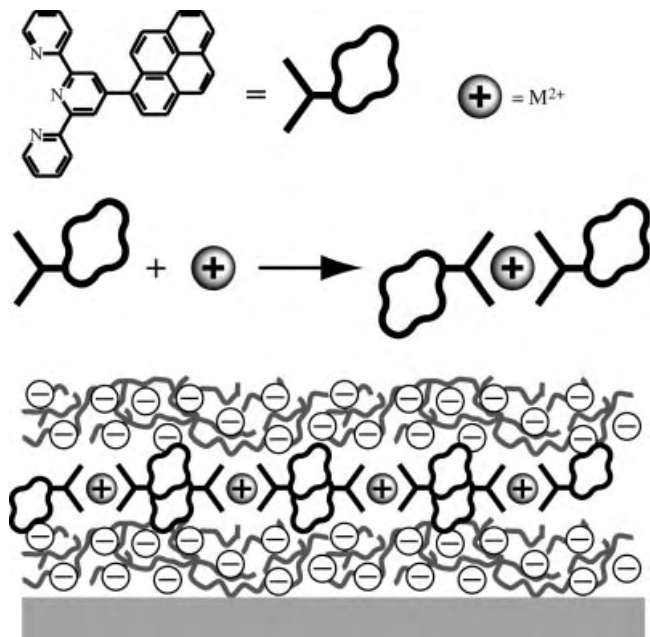
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electrostatic interactions between charged species in solution and an oppositely charged surface.^[12, 13] The experimental implementation of this technique is straightforward and relies simply on dipping the substrate into solutions containing the species to be deposited. The method permits thickness control on a nanometer scale, can be applied to arbitrary substrates (including nanoparticles), and is readily automated. In addition, layers of different functional components can be systematically placed within the thin film. While this method has been successfully applied to metallo-supramolecular coordination polyelectrolytes,^[14] it has never been convincingly demonstrated with discrete metallo-units.^[15]

Previously, it was demonstrated that aryl tails can be used to control the aggregation of metallo-units into ordered linear rodlike arrays assembled by π - π interactions.^[9] Such arrays have several advantages over conventional coordination polymers: Facile ligand synthesis; reversible assembly, even with inert metal ions; good solubility; and straightforward characterization. Reasoning that π - π interactions might be sufficient to order a structure at an interface, we examined whether these structures can be placed in films by LbL deposition (Scheme 1).



Scheme 1. Immobilization of discrete metallo-units in thin films by combining electrostatic attraction of oppositely charged species with aryl aggregation of metallo-units.

We selected pyrene as the aryl moiety to achieve control over the supramolecular organization. Pyrene has a strong propensity to form face-to-face pyrene-pyrene stacks, which can be detected spectroscopically by their characteristic excimer emission bands, and this suggests that pyrenyl tails might be ideal not only as π -aggregation motifs but also as spectroscopic tags for monitoring stacking and aggregation.^[16] Reaction of 4'-(1-pyrenyl)-2,2':6',2''-terpyridine (Pyr-tpy) with transition metal (M) dications afforded the $[M(\text{Pyr-tpy})_2]^{2+}$ complex cations, as anticipated from the coordination chemistry of unsubstituted tpy.^[17] Crystallographic analysis of the

Fe^{II} complex confirmed the anticipated pyrene-pyrene stacking motif (Figure 1).^[18] The structure contains six-coordinate Fe^{II} bis-terpyridyl units linked into a rodlike linear array by pyrene-pyrene π stacking (interplanar separation ca. 3.5 Å; closest C...C 3.43 Å).

Using polystyrenesulfonate (PSS) as counterpolyelectrolyte, we observed multilayer formation with $[M(\text{Pyr-tpy})_2]^{2+}$ complexes ($M = \text{Zn}, \text{Fe}$). In contrast, simple bis-terpyridine complex cations $[M(\text{tpy})_2]^{2+}$, which do not bear aryl tails, do not form multilayers under these conditions. While such complexes are adsorbed on PSS surfaces, the layer is generally removed in the following step when the next layer of PSS is deposited. From this it is clear that the aryl tails play a vital role in the deposition of Pyr-tpy complexes at the interface.

The UV/Vis absorption spectra of multilayers of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ are shown in Figure 2a. The presence of the characteristic absorption bands at 420, 334, 290, and 250 nm demonstrate the incorporation of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ in the multilayer film. Compared to the spectrum in methanol solution (inset 1), the bands are somewhat broadened and shifted. The loss of fine structure is associated with packing effects, while the shift is due to the different local polarity in the multilayer.^[19] A plot of the absorption maxima as a function of the number of layers confirms linear multilayer buildup, that is, equal amounts of material are deposited at the interface in each deposition step (Figure 2a, inset 2). Spectra recorded after deposition of PSS reveal that $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ is partly removed from the surface. Partial desorption during LbL deposition was observed in other cases and was attributed to weakly bound excess material.^[20] Layer deposition involves concomitant desorption of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ and deposition of PSS, and therefore quantification of the amount deposited is meaningful only for a {PSS/metallo-unit} layer pair. From the absorbance at 338 nm, the surface coverage is approximately 1.1 metallo-units per square nanometer or 0.9 nm² per metallo-unit.^[21] The dimensions of the metallo-unit can be estimated from the crystal structure.^[18] The unit is about 2.5 nm long (pyrene to pyrene), and the width of the terpyridine moieties is about 1.1 nm. For surface coverage, the two limiting cases would be for the units to lie flat with their long axis parallel to the substrate or, alternatively, to stand perpendicular. The occupied surface area is about 3.0 nm² per unit if independent (non- π -stacked) units lie flat on the

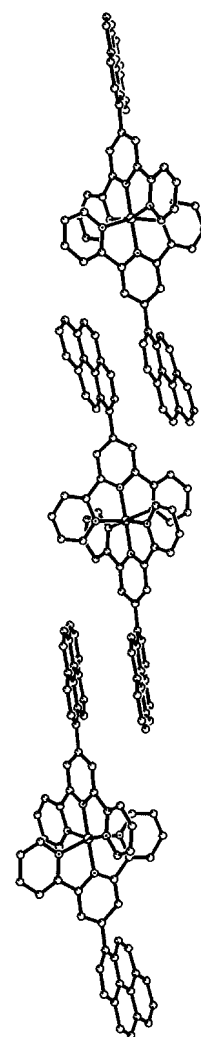


Figure 1. Packing of the cations to give a linear rodlike array in the crystal structure of $[\text{Fe}(\text{Pyr-tpy})_2](\text{ClO}_4)_2$.

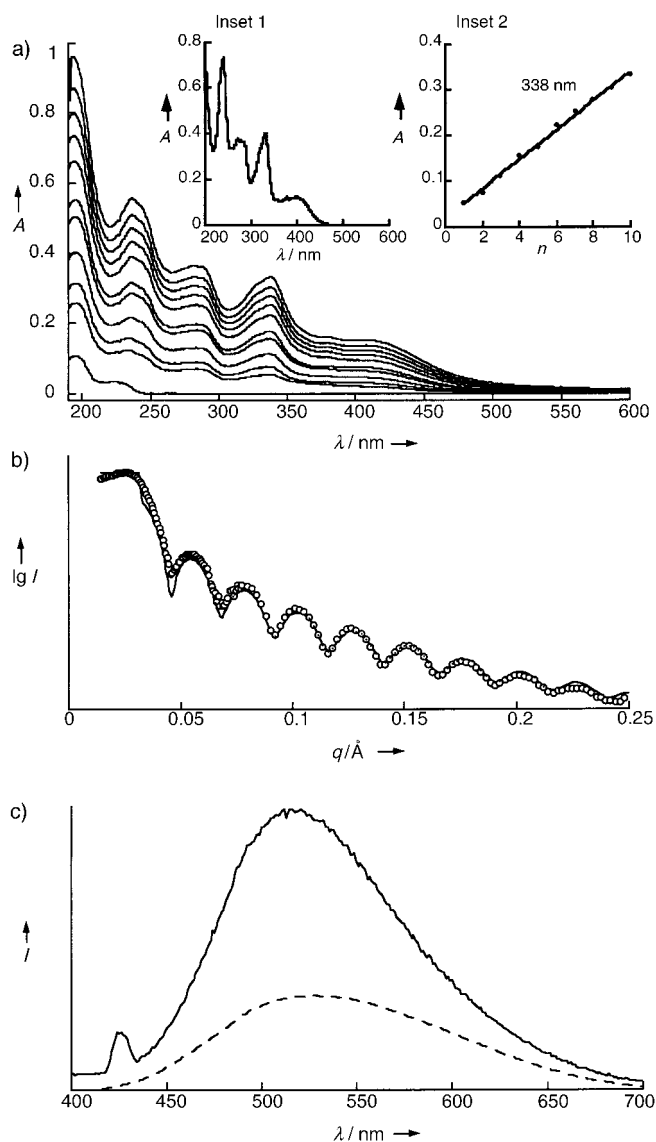


Figure 2. a) UV/Vis absorption spectra of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}/\text{PSS}$ multilayers. Inset 1) Spectrum of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ in methanol. Inset 2) Absorbance at 338 nm as a function of the number of layers. b) X-ray reflectance data (dots) and curve fit (solid line) for a $\text{PEI}/\text{PSS}/[\text{Zn}(\text{Pyr-tpy})_2]^{2+}/\text{PSS}_{10}$ multilayer on silicon. c) Emission-spectra of a $\text{PEI}/\text{PSS}/[\text{Zn}(\text{Pyr-tpy})_2]^{2+}/\text{PSS}_{13}$ multilayer on quartz (solid line) and solid $[\text{Zn}(\text{Pyr-tpy})_2](\text{PF}_6)_2$ deposited on the quartz plate (intermittent line) ($\lambda_{\text{exc}} = 330 \text{ nm}$).^[26] A = absorbance, I = intensity, q = scattering vector.

surface, and about 1.2 nm^2 if they stand upright. However, if the units lie flat with the long axis parallel to the substrate and are π -stacked (as in the crystal structure; metal–metal distance ca. 1.7 nm) the area occupied falls to about 2.0 nm^2 . From these dimensions, the experimentally determined surface coverage therefore corresponds approximately to one to two molecular layers.

The multilayers are very smooth, as demonstrated by the occurrence of Kiessig interference fringes in the X-ray reflectance spectrum shown in Figure 2b for a $[\text{PSS}/[\text{Zn}(\text{Pyr-tpy})_2]_{10}/\text{PSS}]$ multilayer. From the fit of the curve, shown as solid line, we determine the surface roughness to be less than 1 nm , and the thickness of a layer pair to be 2.5 nm .^[22] The thickness was independently confirmed by

optical ellipsometry (data not shown). The thickness suggests that films are composed approximately of molecular layers of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ and PSS, which is in agreement with the UV/Vis data. This value also precludes orientation of the units perpendicular to the substrate. We therefore propose that the metallo-units lie flat on the surface, which would permit full π aggregation. Experimental confirmation of this is presented below.

Similar results were obtained with Fe^{II} as central metal ion. The structural integrity of the metallo-unit in the multilayer is confirmed by the characteristic metal-to-ligand charge-transfer (MLCT) absorption at 579 nm . As with Zn^{II} as central metal ion, the absorption data (not shown) confirm linear growth of multilayers. Likewise, these multilayers are very smooth and homogeneous, as indicated by the X-ray reflectance measurements (data not shown).

A solution of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ in methanol shows a characteristic fluorescence band at 455 nm attributed to the luminescence of the molecular units, as was observed with previously reported zinc terpyridyl complexes.^[9] In contrast, upon irradiation of the $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ multilayer film at 330 nm we observe a very broad and structureless emission band centered around 520 nm (Figure 2c). Solid $[\text{Zn}(\text{Pyr-tpy})_2](\text{PF}_6)_2$ deposited on quartz shows a very similar emission band. The band is characteristic of excimer or excimerlike emission^[23] from the π -stacked pyrene units. This band is also observed in the solid free Pyr-tpy ligand, which also contains stacked pyrene units.^[24] The observation of excimer emission in the thin film of the zinc complex is conclusive evidence that the pyrene tails are stacked in the film in the same structural motif as in the solid state. The absence of any detectable 455 nm fluorescence in multilayers of $[\text{Zn}(\text{Pyr-tpy})_2]^{2+}$ implies that virtually all metallo-units engage in π stacking in each layer (as in the crystal). Multilayers or solid samples of the Fe^{II} complex do not exhibit excimer luminescence due to the MLCT, which lies close in energy to the excimer state and quenches the luminescence. We are currently investigating the application of these metallo-units in other film-forming technologies^[25] and extending this LbL approach to a range of other metallo-units and tails.

Experimental Section

The ligand Pyr-tpy and the metal complexes were prepared by procedures analogous to those previously reported for aryl terpyridines.^[9] Emission experiments used instrumentation as previously described.^[9] Multilayers were prepared and characterized according to a published procedure.^[14] Compound **1** was dissolved in water/methanol (1/3). The concentration used for layer-by-layer deposition was 10^{-3} M .

$[\text{Zn}(\text{Pyr-tpy})_2](\text{PF}_6)_2$: $^1\text{H NMR}$ (CD_2Cl_2 , 300 MHz , 298 K): $\delta = 8.99$ (2H, s, $\text{H}3'$), 8.58 (2H, d, $J = 7.6 \text{ Hz}$, $\text{H}3$), 8.54 – 8.33 (8H, Pyr), 8.21 (3H, m, $\text{H}4$, Pyr), 8.06 (2H, d, $J = 5.5 \text{ Hz}$, $\text{H}6$), 7.59 (2H, ddd, $J = 7.6, 0.9 \text{ Hz}$, $\text{H}5$); MS (FAB⁺): m/z : $930 [\text{Zn}(\text{Pyr-tpy})_2]^+$.

$[\text{Fe}(\text{Pyr-tpy})_2](\text{ClO}_4)_2$: $^1\text{H NMR}$ (CD_3CN , 300 MHz , 298 K): $\delta = 9.31$ (2H, s, $\text{H}3'$), 8.89 (1H, d, Pyr), 8.66 (2H, d, Pyr), 8.61 (2H, d, $J = 8.1 \text{ Hz}$, $\text{H}3$), 8.50 – 8.41 (5H, Pyr), 8.25 (1H, Pyr), 7.97 (2H, td, $J = 7.7, 2.1 \text{ Hz}$, $\text{H}4$), 7.47 (2H, d, $J = 5.1 \text{ Hz}$, $\text{H}6$), 7.24 (2H, ddd, $J = 7.0, 1.1 \text{ Hz}$, $\text{H}5$); MS (FAB⁺): m/z : $922 [\text{Fe}(\text{Pyr-tpy})_2]^+$, $1021 [\text{Fe}(\text{Pyr-tpy})_2\text{ClO}_4]^+$.

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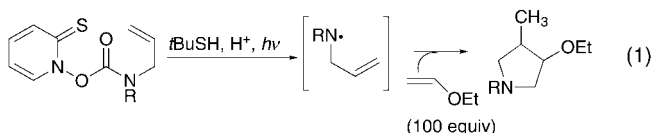
data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Iodoaziridine Derivatives as Novel Azahomoallyl Radical Precursors for [3+2] Cycloaddition Reactions with Alkenes

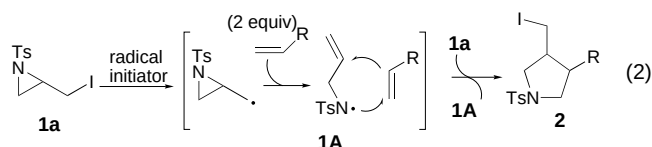
Osamu Kitagawa, Yoichiro Yamada, Hiroki Fujiwara, and Takeo Taguchi*

The [3+2] cycloaddition of a homoallyl radical with an alkene is a powerful method for the one-step synthesis of a cyclopentanoid skeleton.^[1] If such a cycloaddition could be achieved with an azahomoallyl (allylaminyl) radical, it would provide a new and useful methodology for the preparation of pyrrolidine derivatives from simple substrates. As far as we know, only one example of the generation of an azahomoallyl radical and its reaction with an alkene has been reported, by Newcomb et al. [Eq. (1)].^[2] This method using *N*-allyl *N*-hydroxypyridine-2-thione carbamates as an azahomoallyl



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radical precursor requires 100 equiv of alkene to give reasonable yields of products (52–59%). Moreover, a Brønsted acid for the formation of the reactive allylaminium radical^[3] and a thiol as a hydrogen donor for the resulting pyrrolidinylmethyl radical are required in these reactions. In addition, due to the limited number of examples, the scope and limitations of this reaction are unclear. Application to alkenes other than enol ethers and reactions with other azahomoallyl radicals such as cycloalkenyl- and prenylaminy radicals were not investigated. In the addition of a nitrogen-centered radical to an alkene, intramolecular cyclization with a 4-pentenylaminyl radicals has been extensively demonstrated,^[1f, 4] while the intermolecular version has so far been uncommon.^[5] This may be due to the lower reactivity of nitrogen-centered radicals relative to carbon-centered radicals^[1f, 4b, 6] and the lack of a suitable radical precursor. Here we report on radical, iodine-transfer [3+2] cycloaddition with various alkenes and *N*-tosyliodoaziridine derivatives **1** as novel azahomoallyl radical precursors [Eq. (2)].



We expected that: 1) In the presence of a suitable radical initiator, *N*-tosyliodomethylaziridine (**1a**) might efficiently produce *N*-tosylallylamidyl radical **1A** by regioselective cleavage of the C–N bond of an aziridinylmethyl radical;^[7] 2) the reaction of **1A** with an alkene would possibly give an iodoalkylated pyrrolidine derivative **2** by a radical iodine-transfer mechanism; 3) *N*-Tosylamidyl radical **1A** may be more reactive toward alkenes than an aminyl radical because of its more electronegative character;^[8] and 4) the mild reaction conditions for the generation of **1A** and its addition to alkenes would make a wide range of alkenes employable.^[3] Furthermore, **1a** and various other iodoaziridine derivatives **1b–d** can be easily prepared by iodoaziridination of *N*-allyltosylamide derivatives.^[9] Thus, the generation of various azahomoallyl radicals such as allyl-, prenyl-, and cycloalkenylamidyl radicals may be also possible.

The [3+2] cycloadditions of **1a–d** with alkenes (2 equiv) were investigated in the presence of several radical initiators. The reaction of **1** with electron-rich alkenes such as enol ethers proceeded smoothly (Table 1). For example, the reaction of iodomethylaziridine **1a** with butyl vinyl ether under conditions A (1 equiv Et₃B, O₂ in CH₂Cl₂) efficiently proceeded even with only 2 equiv of the alkene to give functionalized iodomethylpyrrolidine **2a** in good yield (64%; entry 1).^[10] The reaction under conditions B (0.1 equiv (*n*Bu₃Sn)₂, *hν*) gave a lower yield (48%; entry 2). Since the present reaction can be performed under nonaqueous and neutral conditions,^[3] application to acid-sensitive silyl enol ethers is also possible. Thus, hydroxypyrrolidine **2b** was obtained in good yield (conditions A, 66%; conditions B, 80%) after desilylation of the cycloaddition product with 2 %

Table 1. Radical [3+2] cycloaddition of various iodoaziridines **1** with enol ethers.

		or			+		$\xrightarrow{\text{A or B}}$	Products 2
1a ($R^1 = \text{H}$)		1c ($n = 1$)	A: Et_3B (1 equiv), O_2 / CH_2Cl_2					
1b ($R^1 = \text{Me}$)		1d ($n = 2$)	B: $(n\text{Bu}_3\text{Sn})_2$ (0.3 equiv), $h\nu$ / C_6H_6					
Entry	Aziridine	$\text{R}^{2[\text{a}]}$	Condi- tions	Products 2	Yield [%] ^[b]	<i>cis/trans</i>		
1	1a	<i>n</i> Bu	A		64	1 ^[c]		
2	1a	<i>n</i> Bu	B	2a	48	1 ^[c]		
3	1a	TMS	A		66	1.3 ^[d]		
4	1a	TMS	B	2b	80	1.5 ^[d]		
5 ^[e]	1b	TMS	A		63 ^[f]	–		
6 ^[e]	1b	TMS	B	2c	37 ^[g]	–		
7	1c	TMS	A		60	1/1.5 ^[d,h]		
8	1d	TMS	A		62	1.4 ^[d,h]		

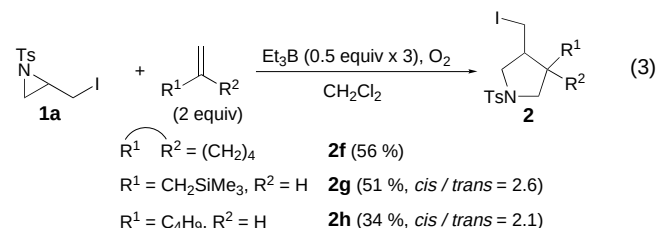
[a] TMS = trimethylsilyl. [b] Yield of isolated product. [c] The ratio was determined by ¹H NMR spectroscopy. [d] The ratio was determined on the basis of isolated products. [e] The product (tertiary iodide) was subsequently treated with DBU because of its instability. [f] A mixture of internal double bond product (internal-**2c**) and terminal double bond product (terminal-**2c**) was obtained in a ratio of 4:1. The diastereomer ratio of terminal-**2c** was 5:1, while the configurations were not determined. [g] Internal-**2c**/terminal-**2c** = 4.3. A diastereomer ratio of terminal-**2c** = 5:1 [h] The formation of two stereoisomers was observed. The ratio corresponds to α-OH/β-OH.

HCl (entries 3 and 4). In the reaction of **1a** with silyl enol ethers, conditions B gave better results than conditions A.

The radical [3+2] cycloaddition reaction with 2 equiv of silyl enol ether can also be applied to the iodoalkylated aziridine derivatives **1b–1d**, which produce prenyl- and cycloalkenylamidyl radicals (entries 5–8). Under conditions A, reaction of **1b** with silyl enol ether also proceeded efficiently to give **2c** in good yield (63%) after treatment of the cycloadduct with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; entry 5), while under conditions B, a lower yield was obtained (37%, entry 6). The reactions of bicyclic iodoaziridines **1c** and **1d** gave functionalized bicyclic nitrogen-containing compounds **2d** and **2e** in 60 and 62% yield, respectively (entries 7 and 8).

The present reaction using iodoaziridine **1a** can also be applied to alkyl-substituted alkenes (2 equiv) such as methylenecyclohexane and allylsilane because of the higher reactivity of the *N*-tosylamidyl radical compared to a simple aminyl radical. In these reactions, gradual generation of an *N*-

tosylallylamidyl radical by portionwise addition of Et₃B (3 × 0.5 equiv) increased the yield.^[11] Thus, the [3+2] cycloaddition products **2f** and **2g** were obtained in 56 and 51 % yield, respectively [Eq. (3)]. When 1 equiv of Et₃B was added in one



portion, considerably lower yields of **28** and **33** %, respectively, were obtained, and *N*-allyltosylamide was formed as a side product. The reaction with the simple 1-alkene 1-hexene gave **2h** in low yield (34 %), even with portionwise addition of Et₃B. These results may indicate that the reactivity of the *N*-tosylamidyl radical towards the alkene decreases with decreasing electron richness of the alkene.

In all reactions shown in Table 1 and Equation (3), formation of regioisomers was not observed. Thus, both cleavage of the C–N bond in the *N*-tosylaziridinylmethyl radical and the attack of the resulting *N*-tosylamidyl radical on the terminal carbon atom of alkene should proceed with complete regioselectivity, while the diastereoselectivities of the reactions are generally low (*cis/trans* = 1–2.6).

In conclusion, we have developed the radical iodine-transfer [3+2] cycloaddition of various alkenes with iodoaziridine derivatives as novel precursors of azahomoallyl radicals. The present reaction should provide a new and efficient methodology for the synthesis of functionalized pyrrolidine derivatives.

Experimental Section

cis/trans-2b: Et₃B (0.5 mL, 1 M in hexane) was added to a solution of iodoaziridine **1a** (169 mg, 0.5 mmol) and trimethylsilyl vinyl ether (0.15 mL, 1 mmol) in CH₂Cl₂ (4 mL) under Ar. Dry air (20 mL) was subsequently introduced with a syringe. After stirring for 10 h at room temperature, 5 % HCl (4 mL) and MeOH (15 mL) were added, and the mixture was then stirred for 2 h at room temperature. After removal of MeOH by evaporation, the residue was extracted with Et₂O. The Et₂O extracts were washed with brine, dried over MgSO₄, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt 1/1) gave a mixture of *cis*-**2b** and *trans*-**2b**. Further purification of the mixture by MPLC (hexane/AcOEt 2/1) gave *cis*-**2b** (71 mg, 37 %, less polar) and *trans*-**2b** (56 mg, 29 %, more polar). The configurations of *cis*-**2b** and *trans*-**2b** were determined by NOE experiments.

cis-2b: white solid, m.p. 130–131 °C; IR (KBr): $\tilde{\nu}$ = 3492, 1322, 1152 cm^{−1}; ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS) δ = 7.72 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.31 (q, *J* = 3.8 Hz, 1H), 3.60 (dd, *J* = 7.9, 9.6 Hz, 1H), 3.51 (dd, *J* = 3.8, 11.6 Hz, 1H), 3.43 (dd, *J* = 1.0, 11.6 Hz, 1H), 3.17 (dd, *J* = 9.0, 9.8 Hz, 1H), 3.10 (dd, *J* = 6.8, 9.8 Hz, 1H), 3.01 (dd, *J* = 9.6, 10.6 Hz, 1H), 2.44 (s, 3H), 2.42 (m, 1H), 1.59 (d, *J* = 4.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS) δ = 143.8, 133.6, 129.8, 127.4, 71.2, 56.4, 50.9, 47.3, 21.5, 0.4; MS: *m/z*: 381 [*M*⁺]; HRMS calcd for C₁₂H₁₆INO₃S [*M*⁺]: 380.9896; found 380.9869.

trans-2b: white solid, m.p. 136–137 °C; IR (KBr): $\tilde{\nu}$ = 3501, 1338, 1160 cm^{−1}; ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.05 (m, 1H), 3.56 (dd, *J* = 5.9, 10.5 Hz, 1H), 3.51 (dd, *J* = 7.5, 10.5 Hz, 1H), 3.05–3.15 (m, 3H), 2.97 (dd,

J = 7.8, 10.5 Hz, 1H), 2.44 (s, 3H), 2.28 (m, 1H), 2.17 (brs, 1H); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = 144.0, 132.8, 129.9, 127.5, 74.6, 54.3, 52.2, 48.7, 21.6, 4.9; MS: *m/z*: 381 [*M*⁺]; HRMS calcd for C₁₂H₁₆INO₃S [*M*⁺]: 380.9896; found: 380.9877.

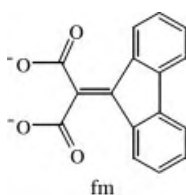
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- [11] **Caution:** When Et₃B was added to the reaction mixture at a high concentration of O₂, an explosion occurred once. Hence, further addition of Et₃B must be performed under Ar or N₂ atmosphere.

Unusual Fluorenylidene-philic Interactions for Effective Conformational Induction**

Young-A. Lee and Ok-Sang Jung*

The observation and modulation of unusual noncovalent interactions is of central importance in the field of functional molecules since the interactions play critical roles in the determination of structural motifs and reaction pathways.^[1–5] Conformational equilibria have often been studied to deduce general structure–stability relationships, and the results can be extended beyond the initial goal to such diverse areas as quantum-mechanical calculations, spectroscopic studies, molecular biology, chiral catalysts, and tunable receptors.^[6–10] Switchable conformation through such specific interactions may serve in the development of sensing or recognition materials. Herein we report a systematic study of conformational induction by intramolecular fluorenylidene-philic interactions during the oxidative addition of [Pt^{II}(fm)] to [Pt^{IV}(fm)] complexes (fm = 9-fluorenylidene-malonate). The coordination chemistry of platinum(II) compounds is subtly dependent upon the electronic and steric effects of ligands and coligands.^[11, 12]



Moreover, the oxidation of Pt^{II} to Pt^{IV} compounds has been utilized in various aspects of platinum chemistry, such as mixed-valence chain compounds, oral antitumor (pro)drugs, and reaction mechanisms.^[13–16]

Reaction of [Pt^{II}(NO₃)₂(dpda)] (dpda = 2,2-dimethyl-1,3-propanediamine) with fm afforded [Pt^{II}(fm)(dpda)] (**1**). The oxidative addition of **1** with a 30 % aqueous solution of H₂O₂ in methanol produced the mixed-axial hydroxo/methoxo-platinum(IV) complex *trans,cis,cis*-[Pt^{IV}(OH)(OCH₃)(fm)(dpda)] (**2**) in 81.3 % yield. When ethanol was used as solvent instead of methanol, the oxidative addition gave an ethoxo analogue. The structure of **2** was confirmed by an X-ray crystallography^[17] (Figure 1), and the relevant bond lengths and angles are not exceptional. The local geometry around the platinum atom approximates to a typical octahedral arrangement with the added hydroxo/methoxo ligands in *trans* coordination sites. The 9-fluorenylidene (flu) moiety is bent towards the methoxo group instead of the smaller hydroxo group, and snugly interacts with the methoxo group. The distances C22...C9 (C22–H...C9) and O5...C9 are 3.45 Å (2.75 Å) and 3.47 Å, respectively, which are comparable to usual values for a C–H...π interaction.^[4, 18] The substitution reaction of **2** with acetic anhydride gives *trans,cis,cis*-[Pt^{IV}(OOCCH₃)(OCH₃)(fm)(dpda)] (**3**) in 80.3 % yield. The

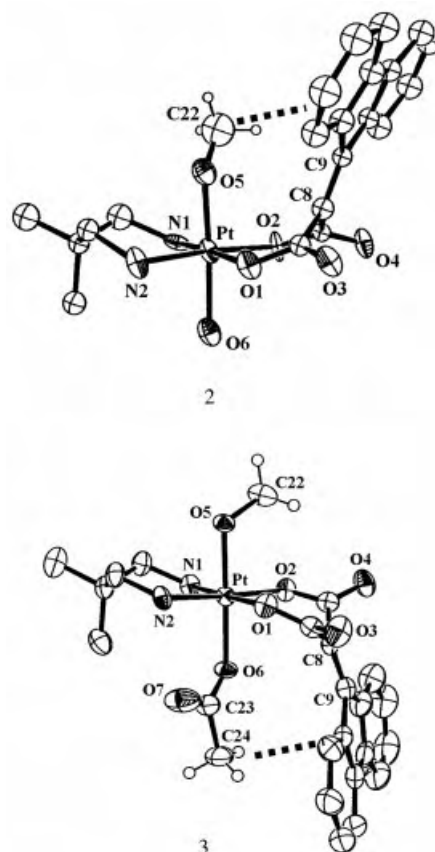


Figure 1. Crystal structures of **2** and **3**. The solvate molecules are omitted for clarity. The dashed line designates the flu-philic interaction.

crystal structure analysis of **3** (Figure 1)^[17] shows that the molecular configuration is retained during the reaction of **2** to **3**. Interestingly, in **3** the flu moiety is directed towards the OOCCH₃ group. Thus, the axial acetato group lies parallel to the flu moiety at distances usual for C(H)...π interactions (O6...C9, 3.33 Å), indicating that the flu moiety prefers an acetato to a methoxo group.

The aliphatic region of ¹H NMR spectra of **1** and **3** in *N,N*-dimethylformamide are depicted in Figure 2. Resonances were assigned by ¹H/¹³C COSY NMR spectroscopy (see Supporting information). The proton resonances of **1** exhibit a marked temperature dependence in the range –10–40 °C. The NH₂, NCH₂, and CH₃ groups each display a pair of resonances at –10 °C. Warming the sample results in broadening of the peaks; by 40 °C the pairs have coalesced to singlets at δ = 5.68 (NH₂), 2.27 (NCH₂), and 0.91 (CH₃). The fluxional process indicates interconversion between the “bent-up” and “bent-down” positions of the flu moiety at elevated temperature (*T*_c = 20 °C; Δ*G*[‡] = 58.8 kJ mol^{–1}). In contrast, ¹H NMR spectra of **3** did not change significantly over the same temperature range except for the sharpness of the signals. This fact indicates that the flu conformation in **3** is rigid (in contrast to that in **1**) on the ¹H NMR time scale even in solution. In addition, the chemical shift of OOCCH₃ (δ = 0.99) is apparently shielded relative to that (δ ≈ 2.0) usually observed for (acetato)platinum(IV) compounds.^[19] The high-field shift is explained in terms of a π-shielding effect: in the

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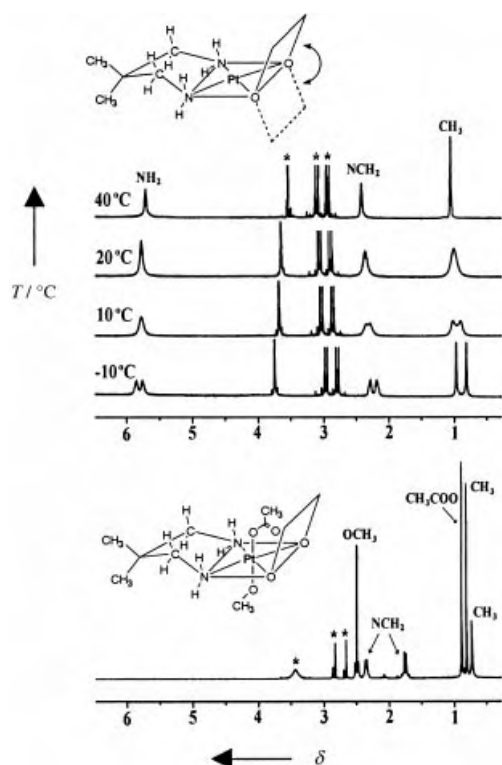


Figure 2. Variable-temperature ^1H NMR spectra of **1** (top) and ^1H NMR spectrum of **3** (bottom) (500 MHz, $[\text{D}_7]\text{DMF}$, TMS, aliphatic region). Asterisk indicates the solvent.

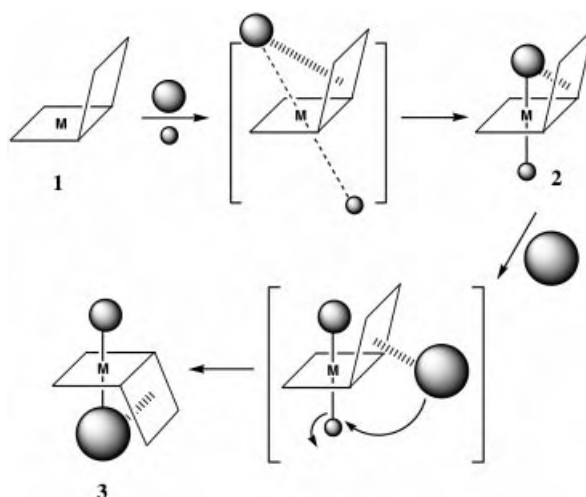
conformation depicted by the X-ray structure analysis, the acetato protons lie above the flu plane. The rigid structure of **3** may be attributed to both the flu interaction and the crowded coordination of the octahedral platinum(IV) compound. The behavior of **2** in solution is very similar to that of **3**, and the flu-axial interaction is not merely the result of crystal packing.

The electron-donor ability^[10, 20] of the anionic fm ligand may contribute to a critical driving force for the conformational induction through the interaction with the flu moiety. Even though the fm ligand is an α,β -unsaturated carboxylato ligand, the bending conformation prevents delocalization of π electrons. Thus, the fm ligand is an effective electron-rich plane for π interactions. Evidence in support of the localization is found in the C8–C9 bond lengths (1.32(4) Å for **2** and 1.34(1) Å for **3**) which correspond to that (1.34 Å) of a normal ethylene group.^[21] The angle between the platinum square and the flu plane is clearly dependent on the strength of the flu interaction, which in turn is dependent on the axial substituent X in the *trans,cis,cis*-[Pt^{IV}(X)(Y)(fm)(dpda)] compounds (Table 1). The plane angle suggests the pronounced order of flu-philicity decreases $\text{OOCCH}_3 > \text{OCH}_3 > \text{OH}$, that is, inversely proportional to the bulkiness of the axial ligand. For the oxidative addition of **1** to **2**, the OCH_3 group competes with the OH group for the flu interaction. The successive substitution of **2** to **3**, in which OOCCH_3 replaces OH, effectively induces the conversion of the flu conformation, resulting in the formation of $\text{OOCCH}_3 \cdots \text{flu}$ interactions (Scheme 1). We attribute the order of flu-philicity to the felicitous “shape-confluence” rather than the “acidic” character of the axial ligand.

Table 1. The plane angle between the platinum(IV) square and the flu plane in *trans,cis,cis*-[Pt^{IV}(X)(Y)(fm)(dpda)] compounds.

<i>trans,cis,cis</i> -[Pt ^{IV} (X)(Y)(fm)(dpda)] compounds	Plane angle ^[a]
X = OH, Y = OH ^[b]	113.0(4)
X = OCH_3 , Y = OH (2)	112.2(7)
X = OAc, Y = OCH_3 (3)	105.1(2)

[a] The plane angle between the platinum plane (Pt, O1, O2, N1, and N2) and the flu plane (C6, C7, C8, C9, C10, C11, C16, and C17). [b] The compound for comparison was prepared by the reaction of **1** with a 30% aqueous solution of H_2O_2 in acetone. Crystal data for *trans,cis,cis*-[Pt(IV)(OH)₂(fm)(dpda)] · 3 $\text{C}_2\text{H}_5\text{OH}$: $P2_1/a$, $a = 10.312(2)$, $b = 22.044(5)$, $c = 14.225(3)$ Å, $\beta = 110.25(2)^\circ$, $V = 3034(1)$ Å³, $R = 0.0572$.



Scheme 1. Procedures of oxidative addition and substitution in reactions to give **2** and **3**.

Although the example of flu-induced conformation described is probably unique to fm complexes, we believe it represents an important conceptual advance. It demonstrates that noncovalent interactions critically influence conformational structure. Our observation should allow us to employ the “noncovalent interaction assistance” concept as an effective strategy in the design and reaction of structural components. The flu-axial ligand interaction is the first noncovalent interaction existing in solution that has been demonstrated for noncage compounds.

Experimental Section

1: $\text{K}_2(\text{fm}) \cdot 2\text{H}_2\text{O}$ (0.76 g, 2.0 mmol) in water (50 mL) was added to a suspension of $[\text{Pt}^{\text{II}}(\text{NO}_3)_2(\text{dpda})] \cdot 2\text{H}_2\text{O}$ (0.91 g, 2.0 mmol) in water (50 mL). The reaction mixture was stirred for 3 h, and the resulting yellow precipitate was washed with water. Recrystallization from a mixture of DMF and diethyl ether gave yellow crystals of **1** in 85.2% yield. M.p. 212 °C (decomp); ^1H NMR (500 MHz, $[\text{D}_7]\text{DMF}$, TMS): $\delta = 0.91$ (br, 6H), 2.27 (br, 4H), 5.68 (br, 4H), 7.26 (t, 2H, $J = 7.5$ Hz), 7.43 (t, 2H, $J = 7.7$ Hz), 7.92 (d, 2H, $J = 7.3$ Hz), 8.14 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (125.76 MHz, $[\text{D}_7]\text{DMF}$, TMS): $\delta = 23.8, 36.0, 53.6, 120.0, 125.9, 126.5$ (C=C), 127.5, 128.8, 138.0, 140.1 (C=C), 140.5, 172.8 (C=O); IR (KBr): $\tilde{\nu} = 1648, 1620$ ($\nu(\text{COO})_{\text{asym}}$); 1338 ($\nu(\text{COO})_{\text{sym}}$) cm^{-1} ; elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3\text{Pt} \cdot 2\text{C}_2\text{H}_7\text{NO}$: C 45.82, H 5.13, N 7.92; found: C 45.70, H 5.10, N 7.87.

2: A 30% aqueous solution of H_2O_2 (1 mL) was added to a solution of $[\text{Pt}^{\text{II}}(\text{fm})(\text{dpda})] \cdot 2\text{DMF}$ (0.71 g, 1.0 mmol) in methanol (100 mL). The

reaction mixture was stirred for 6 h. After the solid material had been filtered off, the filtrate was condensed to 5 mL, to which excess diethyl ether was added to obtain the solid product. Slow evaporation of the methanol solution gave crystals of **2** in 81.3% yield. M.p. 147 °C (decomp). ¹H NMR (500 MHz, [D₇]DMF, TMS): δ = 0.95 (s, 3H), 1.02 (s, 3H), 2.19 (br, 4H), 2.96 (s, 3H), 6.84–7.18 (m, 4H), 7.30 (t, 2H, *J* = 7.3 Hz), 7.45 (t, 2H, *J* = 7.4 Hz), 7.91 (d, 2H, *J* = 7.5 Hz), 8.19 (d, 2H, *J* = 7.8 Hz); ¹³C NMR (125.76 MHz, [D₇]DMF, TMS): δ = 23.4, 23.6, 35.7, 50.3, 55.8 (OCH₃), 120.1, 126.2, 127.8, 129.9, 132.8 (C=C), 136.0 (C=C), 137.0, 141.1, 170.9 (C=O); IR (KBr): $\tilde{\nu}$ = 1666, 1652, 1634 (ν(COO)_{asym}); 1324 (ν(COO)_{sym}) cm⁻¹; elemental analysis (C, H, N) gave erratic results presumably due to the easy evaporation of solvate methanol molecules.

3: Compound **2** (1.0 mmol) was dissolved in acetic anhydride (20 mL), and the resulting solution was then stirred for 3 h. After the solid residue had been filtered off, the filtrate was evaporated to dryness. Slow evaporation of the DMF solution gave crystals of **3** in 80.3% yield. M.p. 168 °C (decomp). ¹H NMR (500 MHz, [D₇]DMF, TMS): δ = 0.84 (s, 3H), 0.92 (s, 3H), 0.99 (s, 3H), 1.77–1.93 (m, 2H), 2.39–2.52 (m, 2H), 2.58 (s, 3H), ³*J*_{pt,h} = 27.10 Hz, 7.16–7.38 (br, 2H), 7.25 (t, 2H, *J* = 7.6 Hz), 7.39 (t, 2H, *J* = 7.6 Hz), 7.84 (d, 2H, *J* = 7.5 Hz), 7.98–8.22 (br, 2H), 8.15 (d, 2H, *J* = 7.8 Hz); ¹³C NMR (125.76 MHz, [D₇]DMF, TMS): δ = 22.2, 23.0, 24.8 (OOCCH₃), 35.8, 50.2, 57.3 (OCH₃), 120.0, 126.5, 127.7, 129.9, 133.9 (C=C), 134.6 (C=C), 137.2, 141.2, 170.6 (C=O), 180.2 (C=O); IR (KBr): $\tilde{\nu}$ = 1666, 1601 (ν(COO)_{asym}); 1302 (ν(COO)_{sym}) cm⁻¹; elemental analysis calcd (%) for C₂₄H₂₈N₂O₇Pt · C₃H₇NO: C 44.75, H 4.87, N 5.80; found: C 44.60, H 4.85, N 5.88.

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drick, University of Göttingen, Germany, **1997**. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163484 (**2**) and CCDC-163485 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Design, Synthesis, and Biological Evaluation of α₄β₁ Integrin Antagonists Based on β-D-Mannose as Rigid Scaffold

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The tuning of protein–protein interactions by small non-peptidic molecules remains one of the great challenges in medicinal chemistry. Although already proposed in 1980 by Farmer,^[1] only a few successful examples on the synthesis of peptidomimetics based on rigid scaffolds such as cyclohexane and pyranose sugars have been reported so far.^[2] Starting from the β-D-mannose scaffold we developed peptidomimetics in a rational combinatorial approach focusing on the interaction of the α₄β₁ and α₄β₇ integrins with their ligands. The basis of this research were cyclic hexapeptides as potent and selective α₄β₇ integrin antagonists recently developed by our group using the “spatial screening” procedure.^[3]

α₄β₁ and α₄β₇ integrins play an important role in numerous inflammatory and autoimmune disorders.^[4] The most important biological ligands for these α₄ integrins are fibronectin

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(Fn), vascular cell adhesion molecule-1 (VCAM-1), and mucosal addressin cell adhesion molecule-1 (MAdCAM-1), the latter being an exclusive ligand for $\alpha_4\beta_7$ integrin under physiological conditions.^[4, 5]

The cyclic hexapeptide *cyclo*(-Leu-Asp-Thr-Ala-D-Pro-Ala-) **P1** and several related peptides with the general formula *cyclo*(-Leu-Asp-Thr-Xaa-D-Pro-Xbb-), which include the bioactive Leu-Asp-Thr (LDT) motif of the MAdCAM-1 ligand,^[6] were recently developed in our group as potent and selective inhibitors of the MAdCAM-1/ $\alpha_4\beta_7$ ligand/integrin interaction.^[3] The bioactive conformation of these constrained cyclic peptides consists of two β -turns with the D-proline in the $i+1$ position of a β II'-turn and aspartic acid in the $i+1$ position of a β I- and/or β II-turn.^[7]

The elucidation of the bioactive conformation of these peptides led us to the replacement of the whole peptidic backbone by a sugar scaffold which should present the pharmacophoric LDT side chain mimetics in similar spatial orientation. A successful implementation of Farmer's approach^[1] would then imply that the amide backbone is not necessarily involved in receptor binding while all essential functional groups are maintained in their active conformation by the scaffold.

The orientation of the LDT side chain mimetics attached to a β -D-mannose core at positions 6, 1, and 2 (all facing upwards) resembles the configuration of the pharmacophoric side chains in our lead peptides (Figure 1).^[3] The free hydroxyl groups at positions 3 and 4 of the carbohydrate scaffold were modified to methyl ethers in order to introduce further hydrophobicity.

Molecular modeling studies (InsightII, DISCOVER, CVFF) confirmed that β -D-mannopyranose is indeed a proper scaffold as the LDT-mimetic sequence is presented in the bioactive arrangement. The superposition of the 2-methyl-

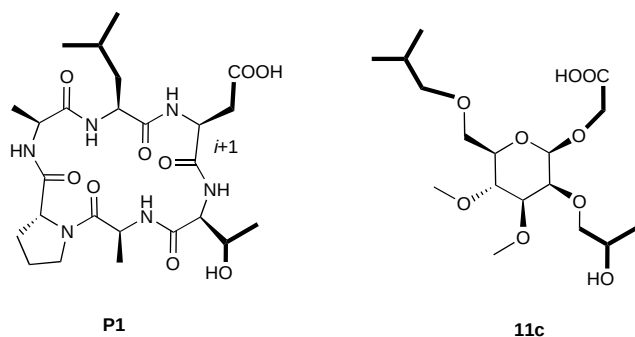


Figure 1. Cyclic peptide **P1** and carbohydrate-based peptidomimetic **11c** (see also Scheme 1). In the peptide, the pharmacophoric LDT motif is localized within a β -turn with the aspartic acid in the $i+1$ position. The carbohydrate scaffold presents the essential pharmacophoric groups in the same relative orientation as the lead peptide.

propylene, carboxymethylene, and (2*R*)-hydroxypropylene groups of the mannose derivative **11c** with the LDT side chains of the potent and selective *cyclo*(-Leu-Asp-Thr-Ala-D-Pro-Phe-) **P2** revealed a good match of these key pharmacophoric groups (Figure 2). An energy minimized conformation of compound **11c** was used for the superposition representing one of the accessible structures in solution.

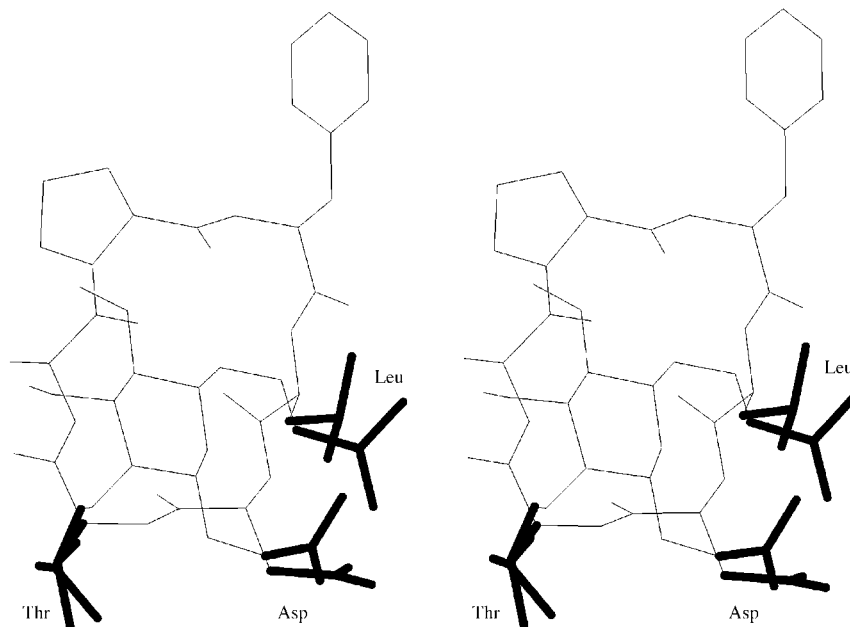
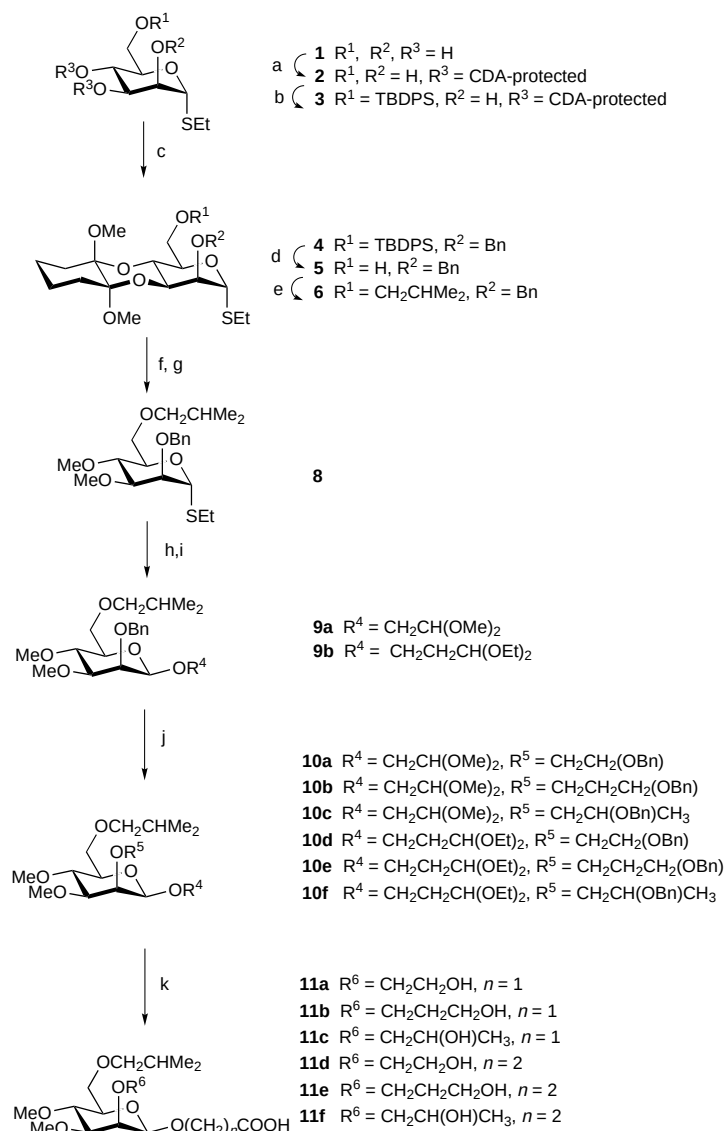


Figure 2. Stereoview of the superposition between an energy minimized structure of **11c** and the structure of **P2** as determined by NMR spectroscopy.

In Figure 2, the leucine, aspartic acid, and threonine side chains and the respective mimetics attached to the mannose core are highlighted using the stick model. The peptidic and sugar backbone are given as thin lines. The relative distance between the aspartic acid and threonine pharmacophores in **P2** ($C^\beta-C^\beta = 4.60 \text{ \AA}$), which is controlled by the positioning of these two amino acids in the $i+1$ and $i+2$ position of the β -turn, is being maintained in the mannose derivative ($4.56 \text{ \AA}$). The leucine side chain mimetic at the primary hydroxyl group of the mannose core exhibits high flexibility as in its peptidic precursor and it is therefore likely to mediate the binding to the receptor by an induced fit mechanism.

Based upon our model a small biased library of peptidomimetics with β -D-mannose as the rigid core was synthesized. The anchoring of aspartic as well as glutamic acid-type side chains at the hydroxyl group in position 1 and the attachment of the serine-type side chain and its homologue together with the use of a racemic threonine mimetic at position 2 led to eight different mannose derivatives.

The synthetic protocol is shown in Scheme 1. The desired products **11a–f** were synthesized in eleven steps starting from ethyl thio- α -D-mannopyranoside (**1**). The key compound in our synthetic strategy was the fully protected mannose derivative **4**.^[8] The orthogonal protecting groups of compound **4** were successively cleaved and replaced by the pharmacophoric side chains. Starting with desilylation of the primary



Scheme 1. a) 1,1,2,2-Tetramethoxycyclohexane^[8] (1.5 equiv), CSA, TMOF, MeOH (43 %); b) TBDPSCI (1.5 equiv), imidazole, DMF (85 %); c) KN(SiMe₃)₂, BnBr (96 %); d) TBAF, THF (96 %); e) KN(SiMe₃)₂, BrCH₂CHMe₂ (89 %); f) 90 % TFA (73 %); g) KN(SiMe₃)₂, MeI (87 %); h) NBS, cat. HCl, CH₃CN/H₂O (91 %); i) SOCl₂, CH₂Cl₂ then Ag₂CO₃, CH₂Cl₂, RT, **9a**: HOCH₂CH(OMe)₂ (72 %), **9b**: HOCH₂CH₂CH(OEt)₂ (62 %); j) 10 % Pd/C, H₂ then KN(SiMe₃)₂, THF, **10a**: BrCH₂CH₂OBn (60 %), **10b**: BrCH₂CH₂CH₂OBn (58 %), **10c**: BrCH₂CH₂(OBn)CH₃ (60 %), **10d**: BrCH₂CH₂OBn (60 %), **10e**: BrCH₂CH₂CH₂OBn (58 %), **10f**: BrCH₂CH₂(OBn)CH₃ (60 %); k) 1) 3N HCl, THF, RT; 2) *t*BuOH, 2-methyl-2-butene, NaClO₂ (1 equiv), NaH₂PO₄, H₂O, RT; 3) 10 % Pd/C, H₂, MeOH, products **11a** (62 %), **11b** (92 %), **11c** (60 %), **11d** (65 %), **11a** (71 %), **11f** (35 %), **11f** (21 %). Bn = Benzyl, CSA = camphorsulfonic acid, NBS = *N*-bromosuccinimide, TBAF = tetra-*n*-butylammonium fluoride, TBDPSCI = tert-butyldiisopropylsilyl chloride, TFA = trifluoroacetic acid, TMOF = trimethyl orthoformate.

alcohol function with tetra-*n*-butylammonium fluoride (TBAF), the leucine side chain mimetic was introduced by ether formation using 1-bromo-2-methylpropane and potassium bistrimethylsilylamide as base. The resulting compound **6** was isolated in 89 % yield. Subsequently, cleavage of the cyclohexane-1,2-diacetal (CDA) protecting group and conversion of the free *trans* vicinal diol into methyl ethers

afforded the mannose derivative **8** in 87 % yield. Compound **8** was hydrolyzed after activation with *N*-bromosuccinimide/H⁺ and subsequently dissolved in thionyl chloride leading to the corresponding mannosyl chloride. Coupling of the activated mannose derivative with glycolaldehyde dimethyl acetal and 3-hydroxypropionaldehyde diethyl acetal in CH₂Cl₂ using solid silver carbonate as the halogenophil led to compounds **9a** and **9b** as the required β-*D*-mannoglycosides in 72 % and 62 % yields, respectively.^[9] After cleavage of the remaining benzyl ether protecting group at position 2, 2-benzyl-3-bromopropyl ether, and 2-benzyl tosylpropyl ether were introduced by ether formation using potassium bistrimethylsilylamide as base. The products **10a–f** were isolated in yields between 58 % and 60 %. The reaction of the mannose derivative **9a** and **9b** with racemic 2-benzyl tosylpropyl ether resulted in two pairs of diastereomeric products **10c** and **10f** as a 1/1 mixtures. The acetal protected aldehyde functions at the anomeric position of compounds **10a–f** serve as precursors of carboxylic acid groups. This strategy was chosen to avoid by-products during the ether formation as a result of the C^α acidity of the carboxylic acid derivatives. After cleavage of the acetals the free aldehydes were immediately oxidized to the corresponding carboxylic acids using sodium chlorite and 2-methyl-2-butene as the scavenger.^[10] The remaining benzyl protecting groups of the side chains of position 2 were removed by hydrogenation with Pd/C under neutral conditions. The final products **11a–f** were purified by HPLC. Thereby, the two diastereomeric compounds **11f** could be separated yielding products **11f1** and **11f2**. However, compounds **11c1** and **11c2** were not resolved (see Table 1).

To evaluate the biological activity of the carbohydrate-based peptidomimetics **11a–f**, we tested whether these compounds interfered with the binding of integrin α₄β₁ to its VCAM-1 ligand or with the binding of integrin α₄β₇ to the VCAM-1 and MAdCAM-1 ligand. The integrin ligands VCAM-1 and MAdCAM-1 were immobilized on tissue culture plates and adhesion of the lymphoid cell lines 38-β7 (α₄β₇^{pos}, α₄β₁^{neg}) and Jurkat (α₄β₁^{pos}, α₄β₇^{neg}) was analyzed in the presence or absence of compounds **11a–f** at 5 mM concentration as described.^[11] The results are summarized in Table 1. The inhibitory activity of the α₄β₁ integrin antagonist cyclo[1,7](C-Q-I-D-S-P-C) was measured at 1 mM as a control.^[12]

Although our approach started with potent and selective α₄β₇ antagonists, no activity was found for this integrin. However, variation of the pharmacophoric groups led to an enhanced activity towards the cognate α₄β₁ integrin. Compound **11a** inhibited integrin α₄β₁-mediated binding of Jurkat cell to VCAM-1 by 70 % (Table 1) at 5 mM concentration. This compound was also tested at the concentration of 2.5 mM. In this case the cell adhesion was inhibited by 34 %. In contrast, α₄β₇ integrin-dependent adhesion of 38-β7 cells to MAdCAM-1 or VCAM-1 was not affected by compound **11a**; this indicates selective antagonist activity for the α₄β₁ integrin (Table 1). Compounds **11b–e**, **11f1**, and **11f2** did not exhibit significant biological activity in any of the assays investigated.

The side chains at positions 6, 1 and 2 of the active mannose derivative **11a** mimic the LDS peptide sequence. The inhibitory activity reported in Table 1 can therefore be

Table 1. Effect of mannose-based peptidomimetics at 5 mM concentration on Jurkat and 38- β 7 lymphoma cell binding to immobilized VCAM-1 and MAdCAM-Ig.

	Jurkat ($\alpha_4\beta_1$) VCAM-1		38- β 7 ($\alpha_4\beta_7$) VCAM-1		38- β 7 ($\alpha_4\beta_7$) MAdCAM-Ig
	[%] ^[a]	<i>n</i> ^[b]	[%]	<i>n</i>	[%]
11a	30 ± 15	7	78 ± 9	8	104 ± 26
11a ^[c]	66 ± 3	3	n.t. ^[d]		n.t.
11b	75 ± 9	9	89 ± 5	6	108 ± 18
11c1,2 ^[e]	79 ± 23	8	85 ± 3	6	122 ± 15
11d	93 ± 10	3	79 ± 1	2	130 ± 10
11e	81 ± 19	10	85 ± 8	6	132 ± 19
11f1	68 ± 8	5	88 ± 4	3	104 ± 11
11f2	n.t.		94 ± 10	3	126 ± 26
Ref. ^[f]	9 ± 6	5	n.t.		n.t.

[a] Cell adhesion is presented as % of medium control. The data represent the mean values ± the standard deviation; [b] number of experiments; [c] adhesion at 2.5 mM concentration of the inhibitor; [d] n.t.: not tested; [e] racemic mixture not resolved; [f] Ref.: reference peptide at 1 mM concentration.

explained by the similarity with the IDS(P) sequence which represents the key motif in VCAM-1 necessary for binding to $\alpha_4\beta_1$ integrin.^[13] These data demonstrate that inhibition of the VCAM-1/ $\alpha_4\beta_1$ integrin interaction does not necessarily require amide bonds. Based upon this result physiologically more stable and bioavailable drugs might be accessible, which overcome the well known restriction of conventional peptide or peptide-related compounds. Further investigations are currently in progress in our group.

In summary, we have reported on the design and synthesis of a biological active sugar derivative which can be considered as a new lead structure for rational combinatorial development of anti-inflammatory drugs. Starting from large proteins the cell adhesion molecules VCAM-1 and MAdCAM-1 highly potent cyclic peptides were designed^[3] which served as a basis for the sugar derivatives presented here. This class of peptidomimetics have all requirements necessary for orally available drugs. Furthermore, active compound **11a** fulfills Lipinski's rules^[14] for bioavailability ($MG = 366.4$; $\log P = -0.60$;^[15] number of hydrogen donors: 2; number of hydrogen acceptors: 9). Therefore, it represents a promising starting platform for lead optimization.

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Direct Comparison of Hydrogenation Catalysis by Intact versus Fragmented Triruthenium Clusters**

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Unraveling the mechanisms by which clusters catalyze reactions is complicated by the variety of reaction pathways available.^[1] It is likely that a greater understanding of these mechanisms will lead to the design and subsequent synthesis of improved cluster catalysts that may compete with mononuclear counterparts. One key issue that is of paramount importance when considering the role of clusters is to separate the impact of fragmentation from that of intact cluster transformation.^[2] Herein we report on the use of parahydrogen-induced polarization (PHIP)^[3] to delineate the pathways involved in the catalytic hydrogenation of alkenes and alkynes by $[\text{Ru}_3(\text{CO})_{12-x}(\text{PPh}_3)_x]$ ($x=1$ or 2) and show that the mechanism is highly dependent on the solvent.

When a sample of $[\text{Ru}_3(\text{CO})_{10}(\text{PPh}_3)_2]$ (**1**) was examined with parahydrogen ($p\text{-H}_2$) in C_6D_6 or CDCl_3 by NMR spectroscopy at 296 K three pairs of enhanced resonances and an emission signal were observed in the hydride region (Figure 1a, C_6D_6). The complexes that yield these resonances have been assigned to species **2**–**5** (Scheme 1), and their NMR spectroscopic data is presented in Table 1. The ratio of the intensities of the hydride resonances of **2**, **3**, and **4** in CDCl_3 at 296 K is 58:9:1. Consequently, if the enhancement factors are the same, K_{23} is 6.4, and **2** corresponds to the dominant form in solution. This suggestion is consistent with the data observed under Boltzmann conditions at 244 K where the species become visible after 10000 scans. The PHIP resonances observed in C_6D_6 at $\delta = -10.2$, -11.2 , and -10.4 (Figure 1a) arise from terminal hydrides (namely **2t**, **3t**, and **4t**, respectively, where *t* indicates a terminal position), while those at $\delta = -17.3$, -17.8 , and -17.5 are due to bridging hydrides (namely **2b**, **3b**, and **4b**, respectively, where *b* indicates bridging).^[4]

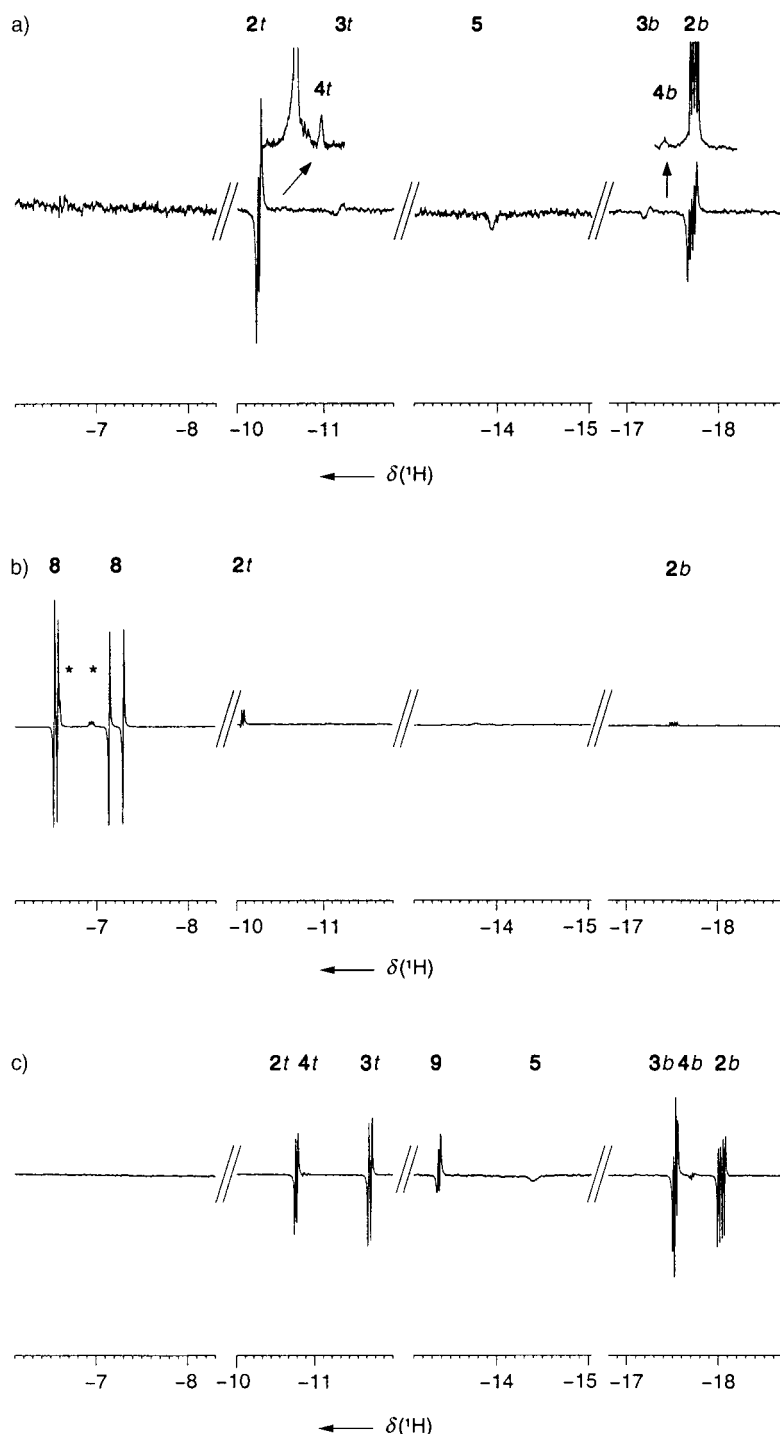


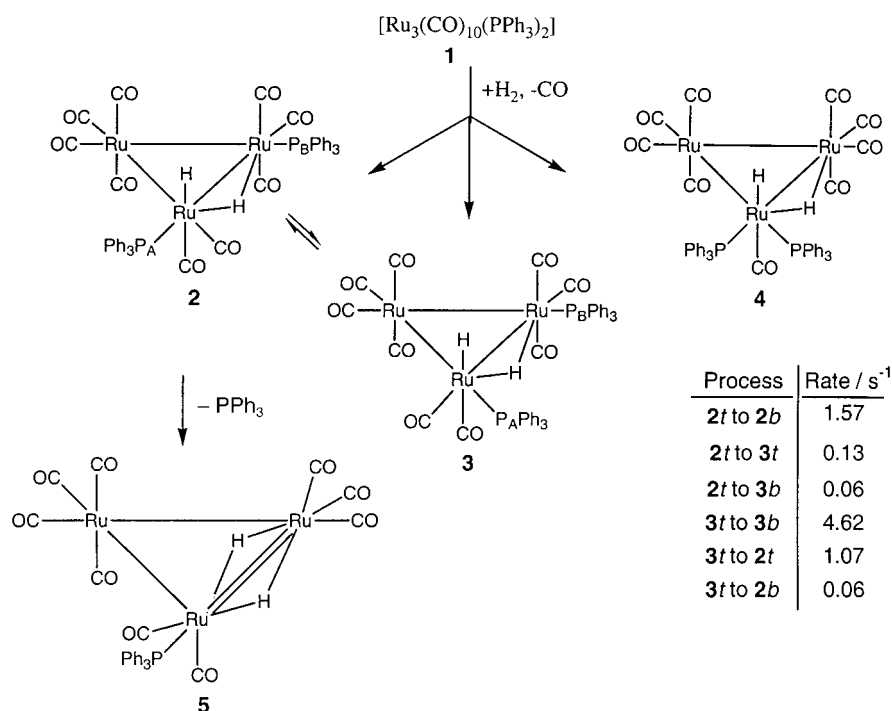
Figure 1. ^1H NMR spectra (256 scans) at constant vertical expansion showing selected parts of the hydride region of a series of samples of **1** obtained during reaction with $p\text{-H}_2$ at 296 K: a) In C_6D_6 , with insets showing very weak signals due to species **4**, detected after 10000 scans at 244 K in $[\text{D}_8]\text{toluene}$. b) In C_6D_6 in the presence of a 100-fold excess of styrene. Enhanced resonances due to the *cis,trans* isomer of **8** are clearly visible. The peaks marked (*) are due to the corresponding *cis,cis* isomer of **8**.^[4] c) In CDCl_3 in the presence of a 100-fold excess of diphenylacetylene.

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Notably, **2t** and **3t** couple to a single ^{31}P nucleus that is *cis* to each hydride ($J(\text{P}_\text{A},\text{H})$ values are 11 and 8 Hz, respectively). In contrast, **2b** and **3b** couple to two phosphorus nuclei. Since the resonance for **2b** appears as a doublet ($J(\text{P}_\text{A},\text{H}) = 20$ Hz) of doublets ($J(\text{P}_\text{B},\text{H}) = 10$ Hz) of antiphase doublets, and that for **3b** appears as a triplet ($J(\text{P},\text{H}) = 9$ Hz) of antiphase



Scheme 1. Structure and observed reaction pathways connecting products formed by p -H₂ addition to **1**. Rate constants for hydride interchange between **2** and **3** obtained in CDCl₃ at 301 K are tabulated.

Table 1. ¹H and ³¹P NMR data at 296 K for **2**–**9** with labeling according to Scheme 1 (400 MHz, CDCl₃, **7** at 233 K, **8** in C₆D₆).

	δ (hydride)	δ (PPh ₃)
2	–10.84, dd, $J(P_A, H) = 11$ Hz, $J(H, H) = -4.5$ Hz, (2t)	44.60, s (P _A)
	–17.57, ddd, $J(P_B, H) = 10$ Hz, $J(P_A, H) = 20$ Hz, $J(H, H) = -4.5$ Hz, (2b)	31.25, s (P _B)
3	–11.68, dd, $J(P_A, H) = 8$ Hz, $J(H, H) = -4.5$ Hz, (3t)	22.91, s (P _A)
	–17.76, ddd, $J(P_B, H) = 9$ Hz, $J(P_A, H) = 9$ Hz, $J(H, H) = -4.5$ Hz, (3b)	30.13, s (P _B)
4	–10.87, td, $J(P, H) = 15.0$ Hz, $J(H, H) = -4.5$ Hz, (4t)	41.1, s
	–17.47, dd, $J(P, H) = 10$ Hz, $J(H, H) = -4.5$ Hz, (4b)	
5	–14.35, br s	32.1, s
7	–11.43, s (7t)	30.7, s
	–18.34, d, $J(P, H) = 10$ Hz, (7b)	
8	–6.54, dd, $J(P, H) = 16$ Hz, $J(H, H) = -5.5$ Hz	44.91, s
	–7.22, dd, $J(P, H) = 62$ Hz, $J(H, H) = -5.5$ Hz	
9	–13.32, dd, $J(P, H) = 10$ Hz, $J(H, H) = -4.5$ Hz	36.6, s
	7.5, d, $J(H, H) = -4.5$ Hz	

doublets, **2b** is *trans* to one phosphane and *cis* to a second, while **3b** is *cis* to both phosphanes. The appearance of the hydride resonances for complex **4** differ significantly from those observed for **2** and **3** because both **4t** and **4b** couple to two ³¹P nuclei in accordance with both phosphanes being coordinated to the same Ru center. COSY and HMQC measurements are consistent with all these assignments.

The remaining signal at $\delta = -13.7$ failed to show resolvable fine structure even at 233 K. Since this hydride resonance was initially observed as an emission signal, it must be formed by a cluster with inequivalent hydrides in an analogous manner to that described by Aime et al.^[5] The identity of this species, namely **5** (Scheme 1), is supported by the kinetic behavior described later.

Examination of the related mono-phosphane cluster [Ru₃(CO)₁₁(PPh₃)] (**6**) with p -H₂ in CDCl₃ at 296 K revealed a new species (**7**) with two broad hydride resonances (see Table 1). Since the signal at $\delta = -11.43$ due to **7t** does not couple to ³¹P, while that at $\delta = -18.34$ due to **7b** couples to a single ³¹P nucleus, the structure of the product is analogous to that for **2** (Scheme 1) but with phosphane P_APh₃ replaced by CO.

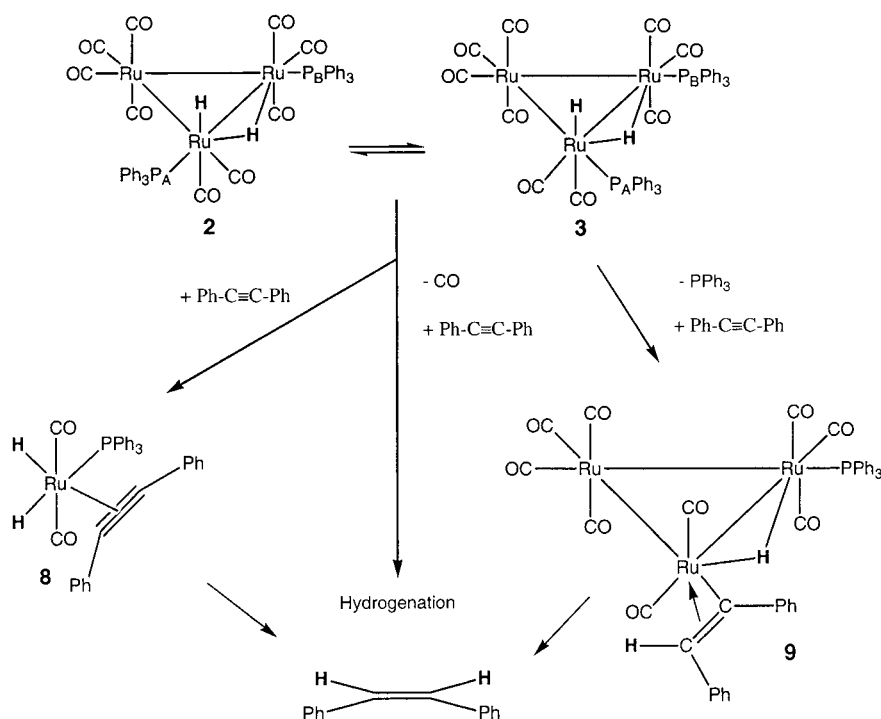
When a sample of **1** was monitored in C₆D₆ with p -H₂ in the presence of a 100-fold excess of styrene, in addition to signals described above, two new PHP-enhanced resonances were observed at $\delta = -6.54$ (doublet of anti-phase doublets (*dad*), $J(P, H) = 16$ Hz) and $\delta = -7.22$ (*dad*, $J(P, H) = 62$ Hz) as shown in Figure 1b. This species (**8**) has signals which have similar characteristics to those reported for [Ru(H)₂(CO)₃PPh₃].^[4] When the same experiments were repeated with 3-nitrostyrene as the substrate, the cor-

responding product resonances moved to $\delta = -6.65$ and -7.35 , whilst with phenylacetylene they moved to $\delta = -8.57$ and -9.46 . The associated species therefore contains the substrate, namely [Ru(H)₂(CO)₂(L)PPh₃] (L = styrene, 3-nitrostyrene and phenylacetylene). Surprisingly, when **1** was treated with p -H₂ and styrene in CDCl₃, the resonances for [Ru(H)₂(CO)₂(styrene)PPh₃] were five times less intense than those observed in C₆D₆, while the resonance for **2t** was 25 % larger and that for **3t** remained unchanged.

When a sample of **1** was examined in CDCl₃ with p -H₂ in the presence of a 100-fold excess of diphenylacetylene the spectrum shown in Figure 1c was obtained. Enhanced hydride resonances matching those described for **2**–**5** were present with similar initial intensities to those seen in the absence of substrate. However, the signal intensities associated with **2** and **3** rapidly increase in size (by a factor of 5 for **2** and a factor of 32 for **3**) until after 1 min they have the same relative intensity. Since hydrogenation is evident in these spectra as enhanced signals for PhH¹³C=CHPh,^[6] this effect can be explained by promotion of the rate of hydrogen cycling by sacrificial hydrogenation.^[7] Since the hydride signals associated with **4** show only minor enhancement this species is a poor hydrogenation catalyst.

Surprisingly, a new signal due to a bridging hydride that coupled to a single phosphorus center was now observed at $\delta = -13.32$ (*dad*, $J(P, H) = 10$ Hz; Figure 1c). Since the associated coupling partner surprisingly appears at $\delta = 7.5$, the new species (**9**) contains a pendant vinyl unit (μ - η^2) and bridging hydride (see Scheme 2).^[8] When **6** was used as the precursor, the signals for **9** were substantially larger requiring **9** to contain only one phosphane.

It has previously been demonstrated that the dynamic behavior of p -H₂ enhanced hydride ligands can be explored by



Scheme 2. Intermediates derived from **2** and **3** during the hydrogenation of Ph-C≡C-Ph.

exchange spectroscopy (EXSY).^[7,9] This technique allows chemical reactions to be monitored by examining magnetization exchange as a function of the reaction time as illustrated in Figure 2 for **3**.^[10] Notably, for mixing times in

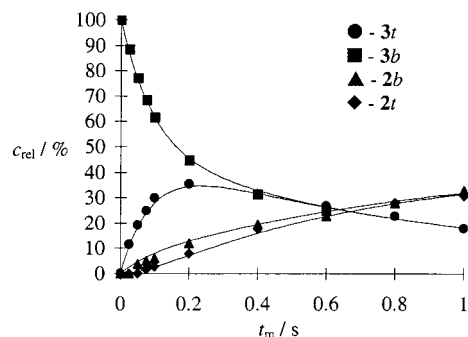


Figure 2. Simulation/experimental trace showing exchange processes starting from site **3b** of **3** in CDCl₃ at 301 K in the presence of a 100-fold excess of alkyne. The points corresponding to sites **3t**, **3b**, **2b**, and **2t**, defined according to the inset key, represent experimental data, while the solid line indicates the simulated values (t_m = mixing time).

excess of 500 ms, transfer of magnetization from **3b** into **4**, **5**, **9**, and the hydrogenation product *cis*-stilbene was observed in accordance with Figure 3a and b. The associated rate constants are tabulated in Scheme 1.

Experiments involving varying the concentrations of CO, PPh₃, and alkyne at constant [H₂] revealed that 1) the rate of interconversion of **2** and **3** into **5** and **9** is reduced as the concentration of PPh₃ increases, 2) the interconversion between **2** and **3** and the rate of hydrogenation decrease with increase in CO concentration, and 3) increasing the alkyne

concentration has no visible effect. However, since **2** and **3** correspond to minor reaction products the relative excess of alkyne is always substantial.

Collectively, these data suggest that *interchange* between **2** and **3** involves CO loss. The ratio $(k_{3t \rightarrow 2t} + k_{3t \rightarrow 2b}) / (k_{2t \rightarrow 3t} + k_{2t \rightarrow 3b})$ deduced from the exchange data collected in the presence of alkyne equates to a sixfold preference for **2** and matches that determined in the absence of substrate. This confirms that the hydride signal intensities of **2** and **3** become comparable because **3** is the more active hydrogenation catalyst. Compound **3** converts directly into **9**, and **2** into **5**, with rates that decrease with increase in [PPh₃]. It can therefore be concluded that both **5** and **9** are formed by PPh₃ loss with complex **5** corresponding to the coordinatively unsaturated 46-electron species [Ru₃(μ-H)₂(CO)₉-PPh₃] with equivalent hydrides. Interestingly, the vinyl hydride **9** was observed to eliminate PhCH=CHPh at longer mixing times.

The mechanism of hydrogenation can be deduced from these data (Scheme 2). First, in polar solvents products **2** and **3** undergo rapid CO loss to yield a vacant coordination site that reacts with PhC≡CPh. Rapid hydride transfer within the associated cluster-based intermediate subsequently generates *cis*-stilbene. Loss of PPh₃ from **2** and **3** competes with CO loss and leads to the formation of less active **5** and **9** (see also Scheme 1). Interestingly, it is the minor isomer **3** that proves to be the dominant hydrogenation catalyst in polar solvents. Second, in nonpolar solvents such as C₆D₆ catalyst fragmentation to [Ru(H)₂(CO)₂(PPh₃)(substrate)] (e.g., **8** in Scheme 2) is observed. Subsequent mononuclear-based hydrogenation then competes with that by the intact clusters **2** and **3**. The solvent therefore plays a central role in controlling the reaction selectivity shown by triruthenium clusters with the overall rate of hydrogenation increasing as the solvent polarity increases.

Experimental Section

The clusters [Ru₃(CO)₁₀(PPh₃)₂] and [Ru₃(CO)₁₁(PPh₃)] were prepared according to literature methods.^[11] For the PHIP experiments, *p*-H₂ was prepared as described previously.^[12] NMR spectra were recorded on a Bruker DRX-400 spectrometer with ¹H at 400.13 and ³¹P at 161.9 MHz and ¹H NMR chemical shifts are reported relative to [D₅]benzene (δ = 7.13) and CHCl₃ (δ = 7.27), while ³¹P NMR shifts are relative to external phosphoric acid. Hydride exchange pathways were examined by magnetization transfer experiments based on the EXSY approach.^[7,9] The sum of the integrals of the primary resonance and the corresponding exchange peaks were first normalized to 100%. A kinetic model was then constructed in Excel that allowed the peak intensities to be explicitly calculated as a function of the exchange rate constant and reaction time. The calculated peak intensities were then compared to the experimental values, noting the squares of the differences.^[13] Rate constants were varied to minimize the

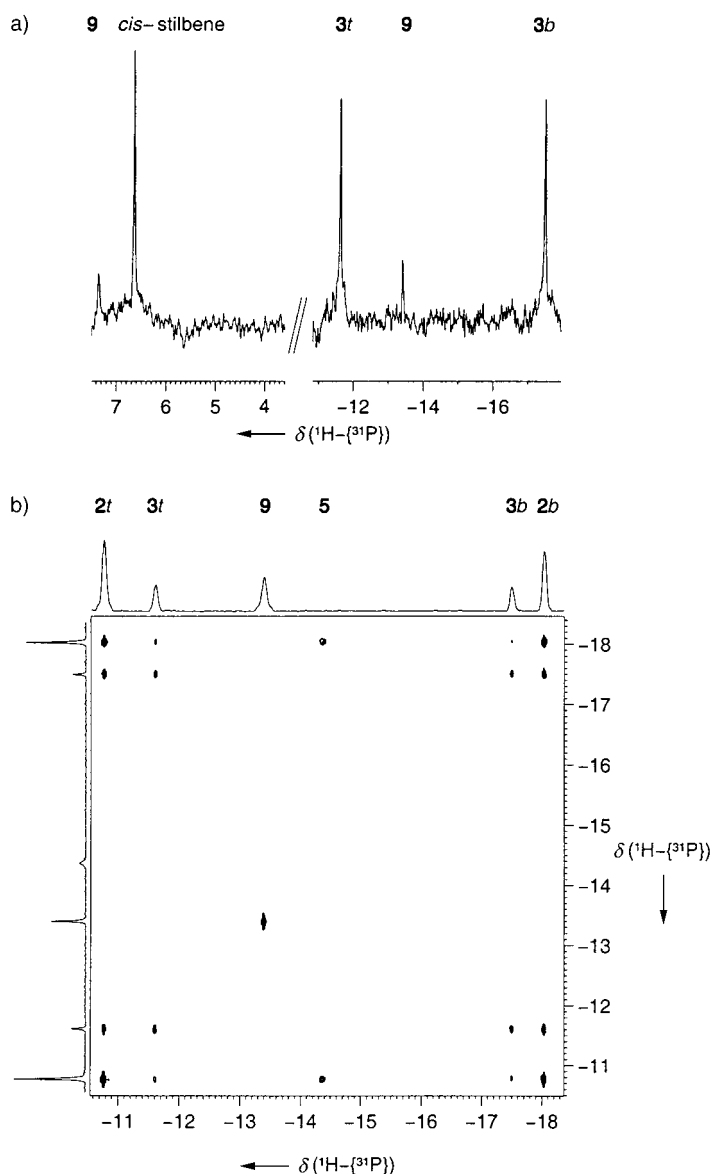


Figure 3. a) 1D $^1\text{H}\{-^{31}\text{P}\}$ EXSY NMR spectrum recorded in CDCl_3 at 301 K on a sample containing **1**, $p\text{-H}_2$, and a 100-fold excess of diphenylacetylene. The resonance for **3t** was selectively excited and the results for a reaction time of 700 ms are displayed. Exchange into **3b**, **9**, and *cis*-stilbene is indicated; b) 2D $^1\text{H}\{-^{31}\text{P}\}$ EXSY spectrum (positive contours) of an identical sample employing a mixing time of 400 ms. Off-diagonal peaks arise due to chemical exchange.

sum of the squares of the differences. The rate constants obtained in this way were multiplied by two.^[14]

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Samarium-Catalyzed Tandem Semipinacol Rearrangement/Tishchenko Reaction of α -Hydroxy Epoxides: A Novel Approach to Highly Stereoselective Construction of 2-Quaternary 1,3-Diol Units**

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Diastereoselective constructions of 1,3-diol units have always been in high demand in synthetic organic chemistry, and preparation of 2-quaternary 1,3-diol units is of major importance for the synthesis of many biologically significant molecules, such as the Furaquinocins,^[1] and chiral ligands.^[2] However, the quaternary carbon atom is generally difficult to construct with high diastereoselectivity, because a simple aldol reaction of carbonyl compounds is not efficient in this situation. Several procedures for construction of 2-quaternary 1,3-diol units have already been developed on the basis of the Lewis acid mediated semipinacol rearrangement of α -hydroxy epoxides. However, they generally need one equivalent or an excess of a promoter and produce only the β -

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Probing Transient Hydrate Structures with Hyperpolarized ^{129}Xe NMR Spectroscopy: A Metastable Structure II Hydrate of Xe

Igor L. Moudrakovski, Christopher I. Ratcliffe, and John A. Ripmeester*

The formation of gas hydrates involves the reaction of water or ice with small hydrophobic atoms or molecules in the size range of about 4.0 (Ar) to about 8.0 Å (methylcyclohexane).^[1] Several hydrate structural families are known, and these are designated as structure I, II, and H (Str. I, Str. II and Str. H), the structure usually being determined by the largest guest in the hydrate.^[1] Many questions remain about the nucleation of hydrates, their growth, and inhibition.^[2] Such issues are of importance in a number of areas, as hydrates exist both in nature and in industrial environments.^[2] To learn to control hydrate formation and decomposition is of continuing interest, especially to solve hydrate control problems in the hydrocarbon resource industry.^[2]

Methods capable of monitoring hydrate formation processes are relatively few, especially if molecular-scale information is desired. Vibrational and NMR spectroscopies do have

such capabilities.^[3, 4] For the latter, the chemical shift tensors or isotropic shifts of molecules in different guest sites can be observed, and in this way provide a signature that is characteristic of the structural type.^[4] ^{129}Xe was the first guest to be used this way;^[5] however, as the time required to record Xe NMR spectra is significant because of long spin-lattice relaxation times, it is not a suitable probe for studying processes. Advances in the development of optical pumping techniques for producing highly polarized Xe (HP Xe)^[6] have solved this problem, and it has already been demonstrated that kinetic studies of hydrate formation can be carried out on a subsecond time scale.^[7, 8] Herein we draw attention to the HP Xe approach as a powerful way of observing transient behavior and thereby yielding structural information in a time-resolved fashion. We show that unusual phenomena observed when HP Xe is placed in contact with a Str. II hydrate of tetrahydrofuran give new insights into hydrate formation reactions at the molecular level.

The experiment in which we were interested involved the exposure of a Str. II hydrate with empty small cages to a Str. I guest. In the case of THF hydrate, THF occupies the large cages in Str. II hydrate which has a crystal structure with a unit cell that can be formulated as $16\text{M}_s \cdot 8\text{M}_l \cdot 136\text{H}_2\text{O}$, where M_s and M_l are the small (5^{12}) and large cages ($5^{12}6^4$), respectively (where 5^{12} corresponds to a cage with twelve five-sided faces). In Str. II hydrate the small cages may be empty or they may be occupied by small molecules such as Ar, Kr, Xe, N_2 , O_2 , and CH_4 . On the other hand, Xe on its own forms a Str. I hydrate, with a structural designation of $2\text{M}_s \cdot 6\text{M}_l \cdot 46\text{H}_2\text{O}$, where M_s is a 5^{12} cage and M_l is the $5^{12}6^2$ cage.

Experiments were carried out on a Bruker AMX-300 NMR spectrometer (magnetic field 7.05 T, ^{129}Xe resonance frequency 83.03 MHz) by exposing powdered Str. II THF hydrate samples to HP Xe gas, which was prepared by optical pumping^[6] directly in the NMR probe.^[9, 10]

The time development of the Xe spectrum is shown in Figure 1. For closer scrutiny, selected spectra, along with those obtained for a control sample of powdered ice, are shown in

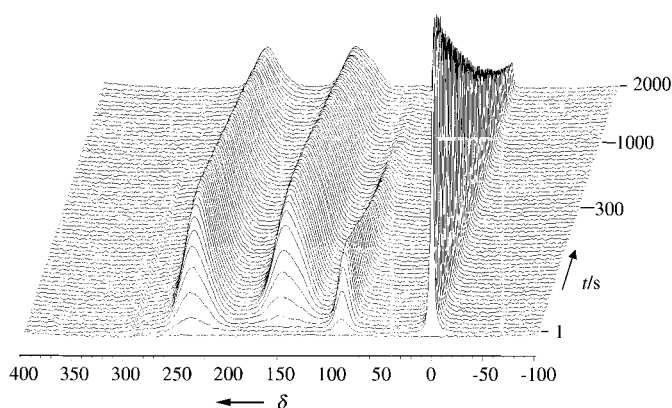


Figure 1. Time development of the ^{129}Xe NMR spectrum after exposure of a powdered THF sample to hyperpolarized Xe. The line at $\delta \approx 0$ can be assigned to the gas, the lines at $\delta \approx 90$, 150, and 240 to Xe in the large cage of Str. II, the large cage of Str. I, and the two small cages in the Str. I and Str. II, respectively. Experimental conditions: temperature 223 K; starting pressure of Xe 530 mbar. Before adsorption of HP xenon, the sample was evacuated for 30–40 min at 10^{-5} mbar to minimize the presence of adsorbed oxygen.

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Figure 2. For the control reaction, the spectral lines characteristic of Xe in the Str. I large ($\delta = 150$) and small cages ($\delta = 242$) appear after a characteristic induction time, and the reaction finishes after a layer of thickness of about 1000 Å has formed, as estimated from the pressure drop and the surface area of the samples. The decay of the signals is due to spin-lattice relaxation.

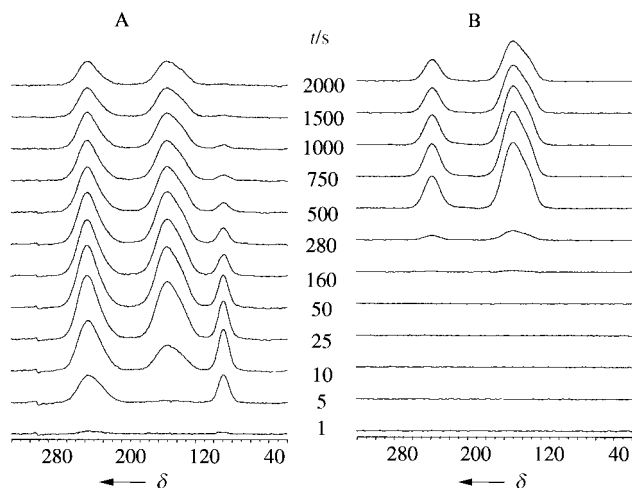


Figure 2. Selected spectra taken from Figure 1 (A), along with spectra obtained for a control sample of powdered ice (B), also at 223 K and with a starting Xe pressure of 580 mbar. In the latter case, formation of only Str. I hydrate is observed. Note the difference in the times when hydrates first appear.

When powdered THF hydrate is exposed to HP Xe, several surprising features become apparent. Almost immediately upon exposure of the Str. II hydrate sample to xenon, signals can be seen at $\delta \approx 230$ and 90. This indicates that Xe does not only occupy the small cage of Str. II, but the second signal indicates that Xe also occupies the large cage in Str. II, and to quite a high degree of occupancy. This is not a stable situation, and from the disappearance of the peak at $\delta \approx 90$ it is clear that on a somewhat longer time scale (~ 1000 s) this Str. II signature is transient. We also note that after a short delay, signals appear at $\delta \approx 242$ and 150, indicating that Str. I Xe hydrate has appeared and that the amount grows with time. The delay can be attributed to the need for Str. I hydrate to nucleate as a separate phase. Whether Str. I results from the decomposition of the Str. II Xe hydrate is not immediately apparent, although it is unlikely that it forms from ice. From the stoichiometry used for the THF hydrate there should not have been excess ice in the system. Also, direct nucleation from ice would require a much longer induction time, as seen in Figure 2B.

Although it is not immediately apparent from the spectra in Figure 1 and 2, one may guess that some Xe remains in the small cage of Str. II upon conversion of the metastable Xe hydrate to a double hydrate. One indication of this is the very low ratio of integral intensities of the lines from xenon occupying large and small cages. If only Str. I hydrate were present, the expected ratio would be between 3:1 and 4:1,^[5] however, the observed ratio is only 1.2:1 – 1.3:1. The residence of Xe in the small cage of Str. II is confirmed by examining the

spectra upon decomposition (Figure 3). In this case a vacuum was applied to pump away Xe after the Xe–THF hydrate reaction had progressed for some time. The Str. I large cage line disappears quickly, along with some of the signal at $\delta \approx 240$. However, a residual signal at $\delta = 230$ remains for quite a

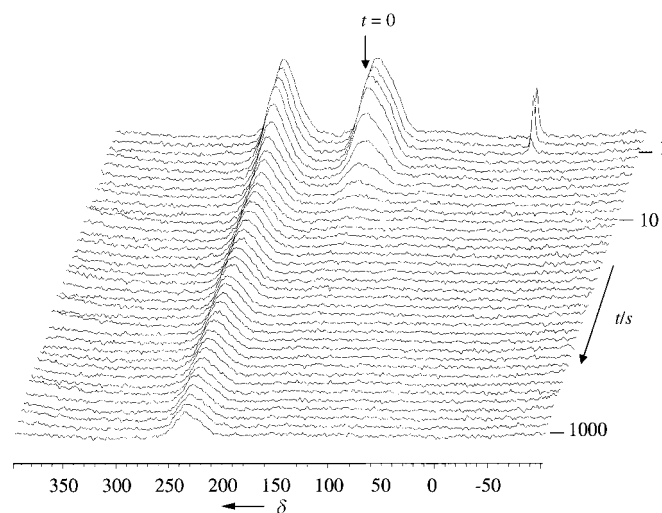
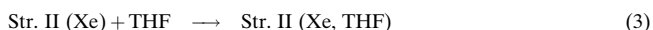
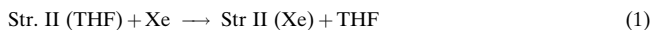


Figure 3. Time dependence of the Xe NMR spectrum of a sample of THF hydrate after its initial reaction with HP Xe and following the application of a vacuum (at time $t = 0$) to desorb Xe from the sample. Note the rapid decay of the gas line and the Str. I hydrate signals.

long time. This must be attributed to Xe in the small cage of the double hydrate of Xe and THF. Its lineshape also shows anisotropy of the chemical shift which is characteristic of Xe in the small cages of Str. II but not of those in Str. I.

Based on the discussion above, the reactions given in Equations (1)–(3) are suggested by the spectra.



The first step [Eq. (1)] is the formation of a metastable Str. II hydrate of Xe that most likely exists as an epitaxial layer on Str. II THF hydrate.^[11] The metastable Xe hydrate decomposes by either converting to Str. I Xe hydrate [Eq. (2)] or by reacting with THF that is liberated as shown in Equation (1) to form a double hydrate with Xe in the small cages [Eq. (3)]. On the time scale of the experiment, Str. I Xe hydrate and the double hydrate of Xe and THF continue to coexist. On a longer time scale, at true equilibrium, a single phase would be expected, that being a Str. II hydrate with partial occupancy of the small cages by Xe.^[12] Reactions similar to the one reported here might well occur in natural or industrial environments if the composition of gases in contact with a hydrate changes suddenly. The complex processes observed, which lead to unexpected hydrate structures, should also be taken into account if the design of structure-specific hydrate inhibitors is contemplated.

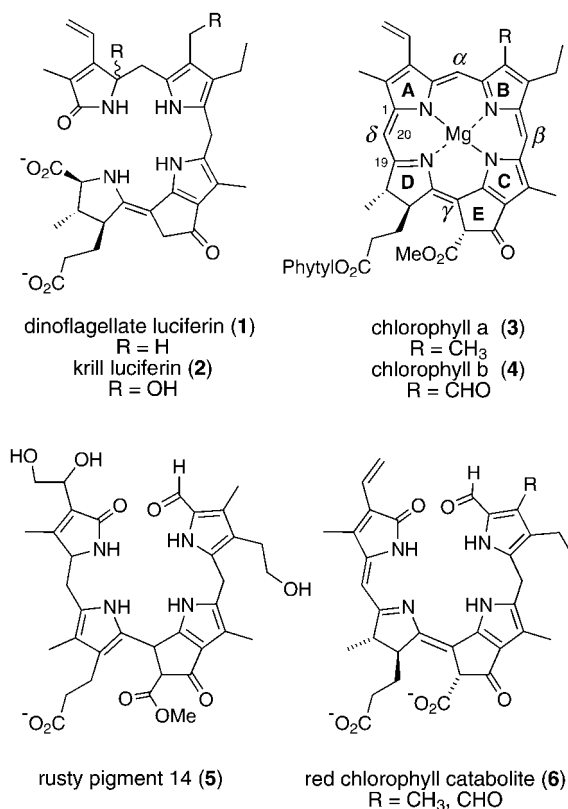
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Chlorophyll Catabolism Leading to the Skeleton of Dinoflagellate and Krill Luciferins: Hypothesis and Model Studies**

George Topalov and Yoshito Kishi*

In the late 1980s, we reported the structures of dinoflagellate luciferin (**1**) and krill luciferin (**2**) (Scheme 1).^[1] Recognizing their structural similarity with chlorophylls a and b (**3** and **4**, respectively), we speculate that dinoflagellate luciferin



Scheme 1. Structure of dinoflagellate and krill luciferins and representative chlorophyll catabolites.

(**1**) and krill luciferin (**2**) are derived through an oxidative ring cleavage at the C1–C20 bond of chlorophylls with retention of the C20 carbon atom as a carboxylate at ring D. Shortly after the structures of **1** and **2** were disclosed, chlorophyll catabolites from barley and *Chlorella protothecoides* were isolated and characterized (**5** and **6**, respectively; Scheme 1).^[2, 3] It is evident that, unlike dinoflagellate and krill luciferins, these catabolites are formed through cleavage of the C4–C5 bond of chlorophylls with retention of the C5 carbon atom as a

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Grafted Metal Oxide/Polymer/Carbon Nanostructures Exhibiting Fast Transport Properties**

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Rechargeable lithium batteries are a superior alternative energy source for a variety of applications that demand advanced energy-storage systems.^[1] However, accessing high charge/discharge rates without losing capacity is one of the biggest challenges, due to the often sluggish kinetics of Li^+ ion transport in solid electrodes.^[2] Many otherwise suitable intercalation materials do not meet the criterion of fast ion and/or electron transport. In contrast to attempting to tailor a single material, nanocomposites can provide an optimum way of crafting desired characteristics for a target application.^[3] Here, we describe a new class of materials which were prepared by the grafting of polymer electrolyte chains and metal oxide layers onto the surface of electronically conductive “graphite-like” carbon spheres. They exhibit an enhanced electrochemical response at remarkably high rates and improved electrochemical stability owing to their unique nanostructure.

A “nanostructure” containing two or more materials mixed on a nanometer scale, ideally is a composite in which the sum of the parts is greater than the whole. This concept, of fundamental interest for many years, is widely applicable.^[4] Electrochemical applications include those involving V_2O_5 , a widely studied cathode material that has kinetic limitations both for ionic and electronic transport.^[5] Layered polymer/metal oxide nanocomposites of xerogel– V_2O_5 ^[6] have shown tenfold enhancement of the Li^+ diffusion coefficient, owing to polymer “propping” of the host layers.^[7] Layered nanocomposites of clays and polyethylene oxide produce highly ionically conductive materials potentially suitable for solid electrolyte applications.^[8] Another approach has been to shorten the diffusion path. High surface area aerogel forms of V_2O_5 display a high capacity under pseudo-equilibrium conditions in thin films.^[9] V_2O_5 prepared by electrodeposition in the presence of surfactants displays a porous thin-wall structure, also resulting in good behavior with a capacity of 220 mA h g^{-1} at a fast rate.^[10, 11] Nonetheless, a potential drawback with high surface area materials is poor volumetric capacity, and the attendant increase in catalytically active surface sites if the sites are not blocked, ultimately resulting in electrolyte degradation. However, none of the above approaches gives rise to a readily prepared, nor stable electrochemical system, nor takes advantage of a chemically nanostructured design.

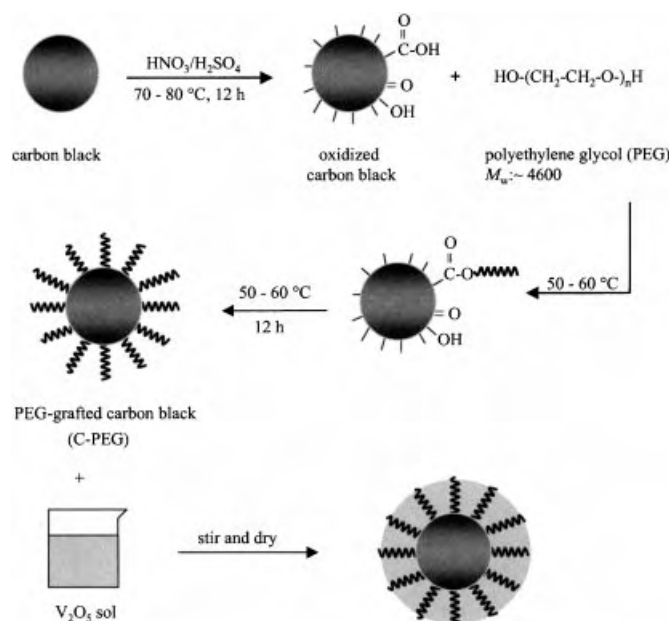
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 Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

Here, we have prepared nanocomposites by chemically wiring both polyelectrolytes and the active metal oxide (V_2O_5) onto the surface of semigraphitic carbon black nanoparticles that serve as an electronically conductive core. Although V_2O_5 serves to illustrate the concept, the method is also applicable to other materials. Importantly, as the polymer-functionalized carbon is readily dispersed ("soluble") in polar solvents, the conductive particles can also be used to impregnate the interstices of insulating or poorly conductive high surface area materials with accessible micropores.

Our procedure for coating active materials on polymer electrolyte-grafted carbon black is illustrated in Scheme 1. We chose acetylene black as the core carbon support, because of its well-known electronic conductivity and small particle size



Scheme 1. The process for coating V_2O_5 xerogel on PEG-grafted carbon black.

(average diameter ~ 44 nm). Polyethylene glycol (PEG) with a molecular weight of 4600 (corresponding to a stretched chain length of ~ 28 nm) was grafted onto carbon particles that were surface-treated to produce carboxylic functional groups to anchor the PEG chains.^[12, 13] The polyelectrolyte-functionalized carbon or C-PEG was coated with an aqueous dispersion of V_2O_5 lamellae ("sol"),^[14] and dried at 140°C to yield V_2O_5 /C-PEG.

The X-ray diffraction (XRD) pattern is representative of a lamellar material with an interlayer distance of $12.8\text{--}13.2\text{ \AA}$, which is greater than the value of anhydrous V_2O_5 ($8.7\text{ \AA}$). The interlayer expansion of $4.1\text{--}4.5\text{ \AA}$ indicates the PEG is intercalated between many of the V_2O_5 sheets, as a single layer in a stretched chain conformation, as seen in PEO/ V_2O_5 nanocomposites. The increased interlayer spacing favors the Li^+ ion insertion process. IR spectroscopy suggests that the intercalated PEG also shows some structural modifications relative to PEG grafted on carbon (Figure 1). These small but significant changes^[15] are due to steric interactions between

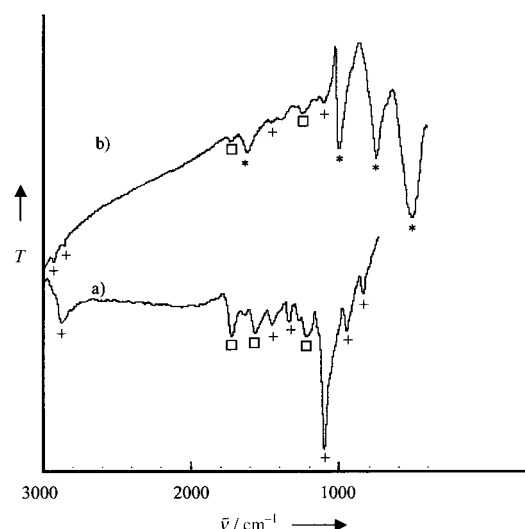


Figure 1. FT-IR spectra of a) C-PEG; b) V_2O_5 /C-PEG nanoparticles. Band assignments: (+) = PEG; (*) = V_2O_5 ; $\square$ = carbon.

the confined polymer and the framework and suggest subtle conformational differences between the incorporated and bulk forms of PEG. For electrochemical comparisons, V_2O_5 was also coated from the sol directly onto the carbon black, without functionalizing the surface with polyelectrolyte: these materials are referred to as V_2O_5 /C. All compositions were determined by standard analysis methods.^[16]

Atomic force microscopy (AFM) images of the C-PEG and V_2O_5 /C-PEG reveal that almost complete dispersion of the carbon particles can be achieved by grafting polyelectrolytes on their surface (Figure 2). The image of V_2O_5 /C-PEG (Figure 2a) shows an grouping of well-separated gum-drop-shaped particles on the mica surface with a mean diameter of about 85 nm , consisting of the carbon core ($\sim 44\text{ nm}$) with a polyelectrolyte/metal oxide coating of about 40 nm . The image of the C-PEG particles (Figure 2b) shows the particles have a size similar to V_2O_5 /C-PEG, but with a different appearance of sharp furrows that suggests polymer "feathering" on the carbon surface. No distinct features are visible for the oxidized, but unfunctionalized carbon particles cast on the mica surface using the same procedure (Figure 2c).

The electrochemical response of the hybrid nanostructured material over a wide range of current densities—measured by standard electrochemical methods and after thorough drying of the material—is greatly enhanced compared to that of a standard xerogel composite electrode (Figure 3). All experiments were performed under the same conditions with a current density of 10 mA g^{-1} and a voltage window of $3.8\text{--}1.8\text{ V}$ versus Li. Data on the V_2O_5 xerogel are comparable to results previously reported. Whereas less than theoretical capacity is observed for the xerogel ($1.3\text{ Li/V}_2\text{O}_5$) and some irreversibility (Figure 3a), for V_2O_5 /C-PEG compositions almost complete reversibility is achieved, along with significantly reduced hysteresis and an almost doubled capacity ($2.25\text{ Li/V}_2\text{O}_5$ or 320 mA h g^{-1} ; Figure 3c). These improvements are attributed to a short diffusion distance for Li^+ and an increase of electronic contact upon employing this hybrid nanostructure. Note that better response vis a vis the xerogel

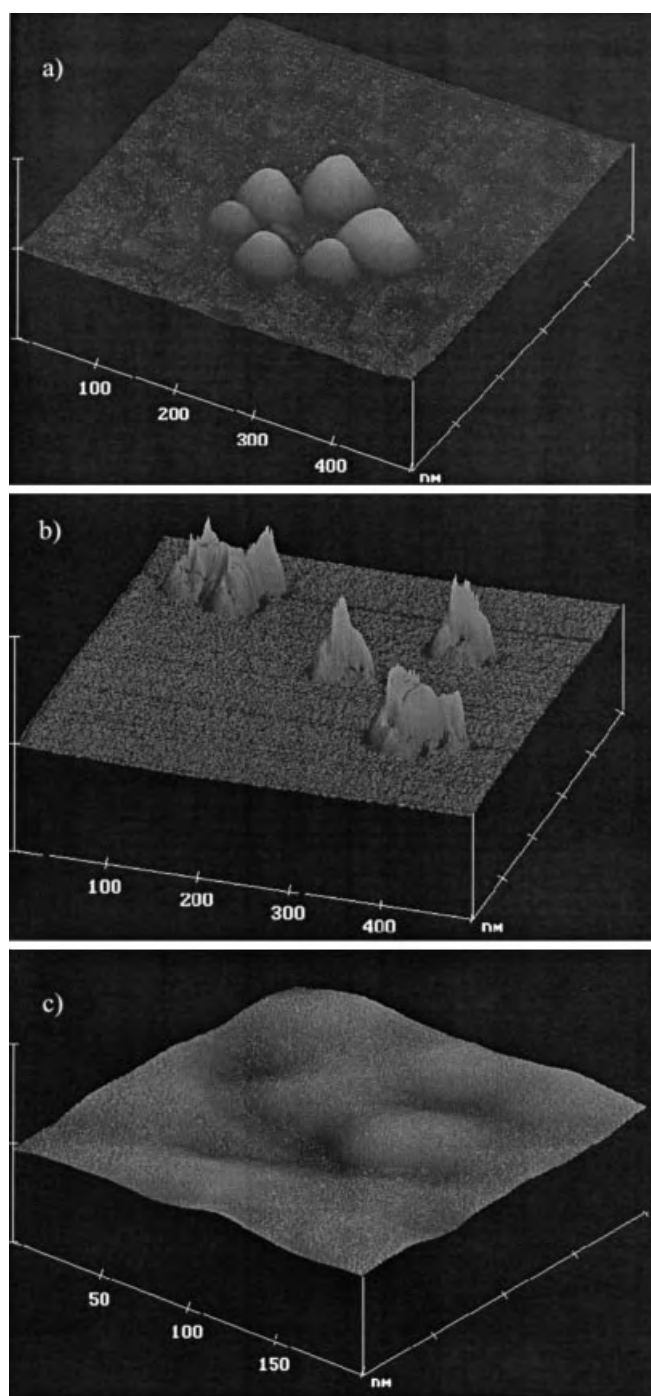


Figure 2. AFM images of a) $\text{V}_2\text{O}_5/\text{C-PEG}$ nanoparticles on a mica surface; b) C-PEG; c) acid-functionalized carbon particles.

is also seen for the V_2O_5 directly coated on the carbon black particle ($\text{V}_2\text{O}_5/\text{C}$; Figure 3b), but it is not as significant as with the polyelectrolyte present.

That there is rapid ion and electron transport in the hybrid nanostructured material is confirmed by varying the applied current (both for charging and discharging) to probe the comparative kinetic response. The effect of current density on working capacity on the three materials, up to current rates as high as 2000 mA g^{-1} (corresponding to a discharge rate of 14 C; that is, discharge or charge in 1/14 or 0.07 h) are summarized in Table 1. The capacity of the V_2O_5 xerogel

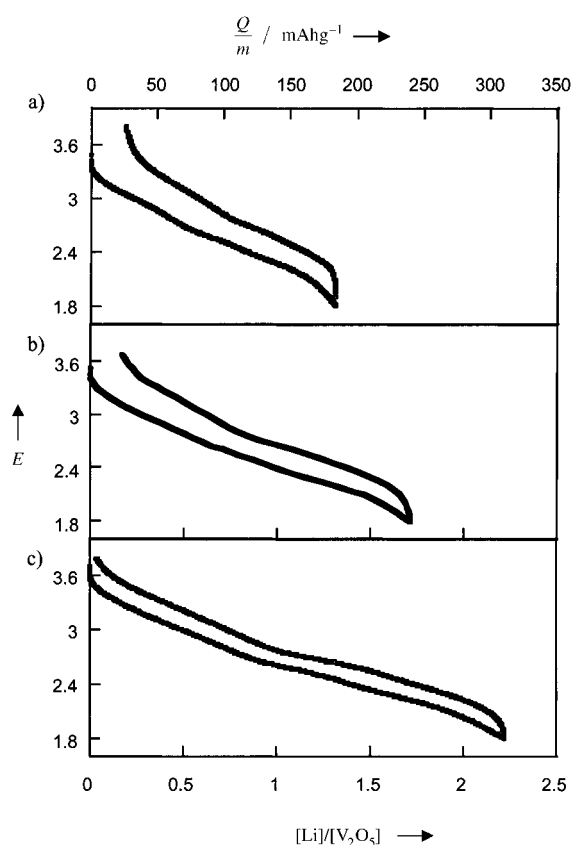


Figure 3. The first discharge–charge sweep for a) V_2O_5 xerogel, b) $\text{V}_2\text{O}_5/\text{C}$, and c) $\text{V}_2\text{O}_5/\text{C-PEG}$. Potential range: 3.8–1.8 V.

Table 1. Specific capacities of V_2O_5 , $\text{V}_2\text{O}_5/\text{C}$, and $\text{V}_2\text{O}_5/\text{C-PEG}$ at different current densities.

Current density [mA g ⁻¹]	V_2O_5 xerogel		$\text{V}_2\text{O}_5/\text{C}$		$\text{V}_2\text{O}_5/\text{C-PEG}$	
	specific capacity [mAh g ⁻¹]	[%]	specific capacity [mAh g ⁻¹]	[%]	specific capacity [mAh g ⁻¹]	[%]
10	159	100	242	100	318	100
20	143	90	237	98	314	99
50	118	76	219	91	299	94
100	95	60	205	85	289	91
200	62	39	191	79	278	88
500	30	19	159	66	248	78
1000			115	48	224	71
2000					191	60

decreased rapidly when a higher current was applied. At a current of 10 mA g^{-1} , the reversible capacity for the V_2O_5 xerogel was 160 mAh g^{-1} ; increasing the current to 500 mA g^{-1} ($\sim 3.5 \text{ C}$) curtailed the available capacity to only about 30 mAh g^{-1} , which is less than 20% of the initial value at the lower rate. This poor kinetic response is typical of a combination of electronic and ionic factors that limit redox accessibility under rapid rate conditions. Some improvement in the kinetic response is seen with $\text{V}_2\text{O}_5/\text{C}$ as a result of the intimate contact of the oxide with the carbon. For the novel nanostructured composite, however, the rate capability was greatly improved. $\text{V}_2\text{O}_5/\text{C-PEG}$ sustained current densities as high as 200 fold greater than the xerogel while maintaining an

even higher capacity than the initial capacity of V_2O_5 gel at a low rate. At extremely high current densities of 1000 and 2000 mA g^{-1} (14 C), capacities of 225 and 190 mAh g^{-1} , respectively, were obtained for $V_2O_5/\text{C-PEG}$ that correspond to about 71 % and 60 % of the capacity at a low current density. Based on its excellent kinetic response, this new nanostructured composite is very suitable for high current/power applications. This is summarized in the plot of specific power versus specific energy (Figure 4). The curve for the

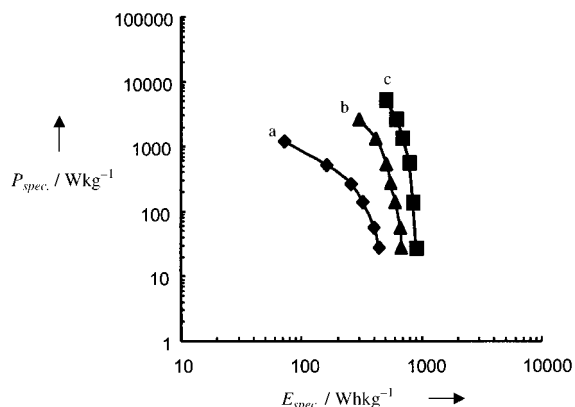


Figure 4. Power (P)–energy (E) plots of a) V_2O_5 xerogel, b) V_2O_5/C , and c) $V_2O_5/\text{C-PEG}$ that illustrate the rate response.

xerogel levels off at high power, indicating that the available energy becomes less. $V_2O_5/\text{C-PEG}$ exhibits much better high power output capability. Even at 5000 W kg^{-1} , 70 % of the specific energy is still available.

The comparison in Figure 5 with the other composite materials indicates that the hybrid nanostructured material has not only substantially higher sustainable capacities, but also better long-term stability. Note the almost complete

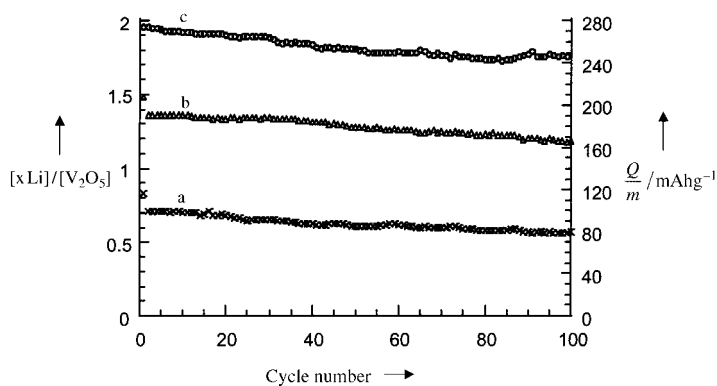


Figure 5. Capacity retention on cycling for a) V_2O_5 xerogel, b) V_2O_5/C , and c) $V_2O_5/\text{C-PEG}$. Current density: 100 mA g^{-1} ; potential range: 3.8–1.8 V.

reversibility does not lead to a drop in capacity in the initial few cycles, whereas the other two materials display a—relatively common—initial decrease in capacity. This behavior is usually ascribed to irreversible reaction of lithium with surface defects, or entrapment in the structure, which clearly does not occur in the nanostructure.

The grafted nanostructured materials we report here can be classified as fast transport materials on the basis of their kinetic response to high current densities. It is likely that the observed behavior is the result of the material being a multiphase composite; thus all factors (facile Li^+ transport owing to the polyelectrolyte component; electron transport due to the wiring of the V_2O_5 component to the conductive carbon surface, and the short diffusive path length) contribute. The advantages of such nanostructured materials arising from this combination are also synergistic: the mechanical strength of this composite is reinforced by the polymer chains, and the unique hybrid structure allows a contiguous V_2O_5 phase to bridge the gap between adjacent carbon particles, thus suppressing detrimental grain boundary effects. Experiments in progress will determine the relative contribution of these factors to the overall properties.

Experimental Section

Carbon black was treated with concentrated $\text{HNO}_3/\text{H}_2\text{SO}_4$ (1:1 v/v) at 70–80 °C for 12 h, and then washed with deionized water, and dried at 80 °C in an oven before use. Dispersal of 20 mg of this acid-treated carbon black in 100 mL H_2O gave a pH value of about 3.1, indicating that acidic groups were formed on the carbon surface. Confirmation was provided by the appearance of a new band in the IR spectrum at 1716 cm^{-1} , characteristic of the carboxylic group. The acid-oxidized carbon black was dispersed in deionized water and mixed with PEG solution with the desired weight ratio of carbon and polymer. The solution was heated and stirred at 50–60 °C for 12 h, and dried to give PEG-grafted carbon black (C-PEG). C-PEG is readily dispersed in water to form a completely stable non-settling suspension. IR spectra of C-PEG revealed that the grafting process led to broader bands of PEG compared to those of pure PEG, shifting the C=O and C–O bands of carbon black from 1716 and 1588 to 1736 and 1557 cm^{-1} , respectively, and producing a new band at 1643 cm^{-1} .

To form the V_2O_5 coating, V_2O_5 xerogel was dried to prepare free-standing films ($V_2O_5 \cdot x\text{H}_2\text{O}$, x : 1.6–1.8 depending on humidity), that displayed a typical lamellar structure with an interlayer distance d of 11.5 Å. The exact water content of the V_2O_5 xerogel film was determined by thermal analysis; the solid was then ground into powder and dissolved in water with the aid of ultrasound to obtain a clear dark red V_2O_5 sol, which was then mixed with well-dispersed C-PEG in different weight ratios.

Characterization: AFM was performed using a Digital Instruments Nano-Scope Scanning Probe Microscope. Samples of C-PEG and $V_2O_5/\text{C-PEG}$ for AFM were prepared by dispersing the material in methanol using ultrasound for 10 min, and then depositing the suspension onto mica and drying it at 60 °C for 2 h.

Working electrodes were prepared from the nanocomposite, acetylene black, and polyvinylidene fluoride (PVDF) with a weight ratio of 85 %, 10 %, and 5 %, respectively, as previously reported,^[7] with a loading of the active material of 3–4 mg. After evaporation of the solvent, all the electrodes were heated at 140 °C for at least 2 h prior to cell assembly to remove bound water. Swagelok-type cells were assembled in an argon-filled glove box and studied under galvanostatic condition between voltage limits using a MacPile system. All potentials were controlled and recorded relative to a Li metal electrode.

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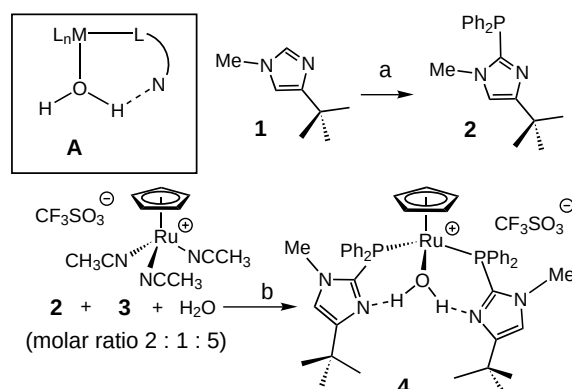
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- [16] Chemical composition for x(Li) for all materials were calculated from the formula weight of the materials determined by thermogravimetric and chemical analyses [%]; for V₂O₅/C-PEG: V₂O₅: 72.5, C: 12.1, PEG: 6.03; for V₂O₅/C: V₂O₅: 72.1, C: 16.6.

Combined Effects of Metal and Ligand Capable of Accepting a Proton or Hydrogen Bond Catalyze Anti-Markovnikov Hydration of Terminal Alkynes**

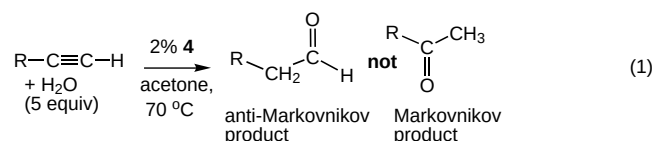
Douglas B. Grotjahn,* Christopher D. Incarvito, and Arnold L. Rheingold

Metalloenzyme catalysts such as carboxypeptidase use the cooperative effects of a metal ion and suitably placed organic functional groups capable of proton transfer or hydrogen bonding.^[1,2] Using this cue from Nature, we are making complexes of general structure **A** (Scheme 1) where L is a



Scheme 1. Design (**A**) and synthesis of catalyst **4**. a) *n*BuLi, THF, –78 to –50 °C, 3 h, then ClPPh₂, warming to RT, 51 %; b) CDCl₃ or CH₂Cl₂, RT, <2 h, 98 %.

ligating atom and N is part of a heterocycle, particularly imidazole. Our results clearly indicate that the combined effects of a metal and a proton or hydrogen bond acceptor as in **A** produce a binding pocket for a polar ligand. We report herein on the anti-Markovnikov hydration of terminal alkynes [Eq. (1)], which produces aldehydes, rather than the isomeric ketones, with selectivities of up to 1000 to 1.



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

Traditional methods of hydrating alkynes require catalysis by strong acids and environmentally objectionable Hg^{II} , or transition metal salts. All of these conditions give Markovnikov addition of water to the terminal alkyne, leading to the formation of the methyl ketone.^[3–9] Anti-Markovnikov hydration can be achieved indirectly by stoichiometric hydroboration or hydrosilation, followed by oxidation.^[10] Bruneau and Dixneuf recently reviewed anti-Markovnikov addition of weak nucleophiles with N–H or O–H bonds to terminal alkynes.^[11] Thus far, however, there have been only two reports of catalytic anti-Markovnikov hydration of terminal alkynes. In 1998, Tokunaga and Wakatsuki^[12] found after trying about 20 phosphanes that the combined use of $[(\text{C}_6\text{H}_5)_3\text{RuCl}_2(\text{C}_6\text{F}_5\text{PPh}_2)]$ (10 mol %) and $\text{C}_6\text{F}_5\text{PPh}_2$ (30 mol %) gave aldehydes in 50–75 % yield, with typical aldehyde-to-ketone selectivities of about 10 to 1. Hindered alkynes such as phenyl- or *tert*-butylacetylene gave less than 2 % yields of product. This year the same group reported improved results with chelating or electron-rich, small phosphanes on the CpRuCl fragment.^[13] For example, in favorable cases 1–2 mol % of $[\text{CpRuCl}(\text{Me}_2\text{PCH}_2\text{PMe}_2)]$ or $[\text{CpRuCl}(\text{PMe}_3)_2]$ could be used in 2-propanol/water at 100 °C. In some cases 10 mol % of catalyst was needed, moreover nitriles inhibit the reaction.

In contrast, here we report that electron-rich phosphanes are not needed. Significantly, hydrogen bonding in catalyst **4** (Scheme 1) leads to hydration of even *tert*-butylacetylene at the 2 mol % level, giving yields in excess of 90 %. Advantages of **4** over the other Ru^{II} catalysts reported include a lack of inhibition by nitriles, and the tolerance of acid-sensitive propargylic ether substituents.

Pursuing the design outlined above, we made the phosphinoimidazole ligand **2** (Scheme 1) by deprotonation of **1**^[14, 15] at C-2, followed by quenching with ClPPh_2 .^[16] We found that two moles of **2** rapidly react with **3**^[17] in the presence of five equivalents of water to give (after crystallization) a 98 % yield of catalyst **4**. The presence of a ^1H NMR signal near $\delta = 9.1$ (slightly broad singlet, 2H, $\text{H}_2\text{O}-\text{Ru}$) and satisfactory elemental analysis suggested that a water molecule was indeed coordinated to the metal center. However, unequivocal verification of the water molecule in the catalyst binding pocket was provided by an X-ray crystal structure determination (Figure 1).^[18] A piano-stool structure supports the *cis* coordination of the two phosphane ligands (P–Ru–P angle 97.77(3)°, the third leg of the stool consisting of the Ru–O bond (P–Ru–O angles 91.89(3) and 93.30(9)°). Of special interest for catalyst design, both (located) hydrogen atoms of the bound water molecule engage in hydrogen bonding to the two imidazoles, with N⋯H distances of 1.638(6) and 1.802(8) Å.

Gratifyingly, only 2 mol % of complex **4** catalyzed the clean conversion of 1-hexyne (Table 1, entry 1) to hexanal at temperatures near 70 °C. Reaction progress was monitored by ^1H NMR spectroscopy by using an internal standard. Within 1.5 days, consumption of alkyne was complete, and hexanal had been formed in 96 % yield. NMR spectroscopy showed that about half the catalyst remained intact. No peaks for the Markovnikov product 2-hexanone were evident in the 500 MHz ^1H NMR spectra, but to verify this result, 1 % of

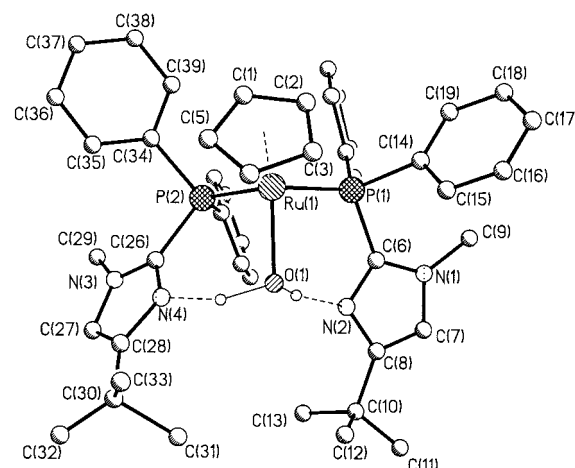


Figure 1. X-ray crystal structure of the cation of **4** (thermal ellipsoids are at 30 % probability). The CF_3SO_3^- counterion is not shown for clarity. Key bond lengths [Å] and angles [°]: Ru(1)–O(1) 2.164(3), Ru(1)–P(1) 2.3043(10), Ru(1)–P(2) 2.3251(10), Ru(1)–Cp(centroid) 1.836(4), N(2)–H 1.802(8), N(4)–H 1.638(6); P(1)–Ru(1)–P(2) 97.77(3), P(1)–Ru(1)–O(1) 93.30(9), P(2)–Ru(1)–O(1) 91.89(8).

Table 1. Catalysis of alkyne hydration [see Eq. (1)].^[a]

Entry	Catalyst	Alkyne substituent R	Aldehyde yield [%] after reaction time			Selectivity ^[b]
			3 h	21 h	later [h]	
1	4	Bu	39	92	96 [36]	1000
2	4	PhCH_2CH_2	40	88	92 [46]	150
3	4	$(\text{CH}_3)_3\text{C}$	3.5	21	91 ^[c]	≥ 130
4	4	Ph	9.6	20	54 ^[d]	135
5	4	$\text{Ph}^{\text{[e]}}$	24	64	75 [42]	32
6	4	$\text{TBSO}-\text{CH}_2^{\text{[f]}}$	28	91	96 [36]	≥ 200
7	4	$\text{THPO}-\text{CH}_2^{\text{[g]}}$	35	83	86 [50]	≥ 400
8	4	$\text{NC}(\text{CH}_2)_3$	34	96	98 [40]	n.d. ^[h]
9	5	Bu	0.1	0.3	n.d.	n.d.
10	6	Bu	0.3	0.5	n.d.	n.d.
11	6 + 1	Bu	< 0.1	< 0.1	n.d.	n.d.
12	6 + Et_3N	Bu	0	0	n.d.	n.d.
13	7	Bu	0.3	1.0	1.2 ^[i]	n.d.

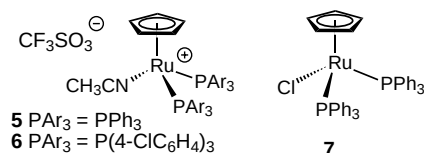
[a] Conditions: 0.5 mmol alkyne, 5 equiv water, 2 mol % catalyst, and $(\text{Me}_3\text{Si})_4\text{C}$ internal standard in $[\text{D}_6]\text{acetone}$ (1 mL) heated in a sealed NMR tube in an oil bath (67–72 °C). Yields and products identified by ^1H and in some cases ^{13}C NMR data. See Supporting Information for full details. [b] Ratio of aldehyde (value shown) to ketone (assigned value of 1). Authentic sample of ketone added at end of reaction period. See Supporting Information for full details. [c] Yield 49 % after 68 h; 91 % after an additional 108 h at 88–91 °C. [d] Yield 54 % after three additions of 2 mol % **4** and 36–45 h heating each time. [e] Using 10 mol % catalyst with substrate concentration of 0.2 M. [f] TBS = $(\text{CH}_3)_2\text{C}(\text{rBu})\text{Si}$. [g] THP = 3,4,5,6-tetrahydropyran-2-yl. [h] n.d. = not determined. [i] After 7 d at 90 °C.

an authentic sample was added. A very small peak increased in size, such that we estimate that only 0.1 % of 2-hexanone had been present before addition of authentic material, meaning that the aldehyde-to-ketone ratio was 1000 to 1. Our results compare favorably with those of Tokunaga and Wakatsuki with the same alkyne.^[12, 13] Moreover, Table 1 shows that **4** works with a wide variety of substrates, giving high selectivities. Alkyl-substituted alkynes work the best (Table 1, entries 1–3, 6–8). A *tert*-butyl group (Table 1, entry 3) slows hydration but on heating at 88–91 °C,

trimethylacetaldehyde is formed in 91 % yield. Phenylacetylene reacts about as sluggishly as *tert*-butylacetylene, but in this case NMR spectroscopy confirms that 2 mol % **4** (Table 1, entry 4) disappears after 21 h and hydration stops at about 30 % conversion unless additional catalyst is added, eventually producing 54 % aldehyde. Alternatively (Table 1, entry 5), starting with 10 mol % **4**, improved yield and rate are obtained.

A nitrile does not affect the catalyst (compare entries 8 and 1 in Table 1). Even alkynes with acid-sensitive alcohol protecting groups (Table 1, entries 6 and 7) are hydrated to give aldehydes made previously in multistep syntheses.^[19] Remarkably, neither an allenylidene complex nor propargyl alcohol (a potential hydrolysis product) are formed.^[20]

Several control experiments show that the imidazole groups play a key role in the catalysis. First, in hydration of 1-hexyne, simple triarylphosphane ligands of slightly different electronic properties on the [CpRu]⁺ ion (**5** and **6**; Table 1, entries 9 and



10, respectively) give less than 0.5 % yields of hexanal, with no 2-hexanone being detected.^[21] Further, if the imidazole groups function merely as a base, their placement in **4** is crucial: addition of 2 mol (per Ru center) of either the hindered imidazole base **1** or Et₃N to mixtures containing **6** led to virtually no production of aldehyde (Table 1, entries 11 and 12). Finally, complex **7** is also ineffective (Table 1, entry 13).

As to the probable mechanism of the alkyne hydration, ketones may come from attack of water on C-2 of alkyne π complexes (**B**, Scheme 2).^[22] In contrast, for aldehyde formation, likely intermediates include complexes with ligands

such as alkyne, vinylidene (**C**), hydroxycarbene (**D**), or related, tautomeric acyl and hydride (**E**).^[23] Any of the conversions between these species conceivably could be aided by the presence of the imidazole groups or their protonated forms (e.g., **F**).^[24] Alternatively, the hydrogen bonding in **4** may stabilize the catalyst. Judging from the lack of catalytic reactivity of other {CpRu(PAr₃)₂} fragments under the conditions used (e.g., Table 1 entries 9–13 and ref. [23b]), the effects of R = imidazol-2-yl are especially intriguing and are the subject of ongoing studies. We note that the most recent CpRuCl-based catalyst was inhibited by a nitrile-containing alkyne;^[13] the lack of inhibition of **4** may be related to the ability of **4** to exclude a coordinated nitrile in its resting state (**A**, Scheme 2).

In conclusion, regardless of mechanism, we provide clear evidence that the combined effects of a Ru^{II} center and imidazolylphosphanes create an excellent single-component catalyst for the anti-Markovnikov hydration of terminal alkynes under near-neutral reaction conditions. We are currently extending our design principle to other structures and reactions.

Experimental Section

Preparation of catalyst **4:** Deoxygenated solvents were used in an M. Braun glovebox. To solid phosphane **2** (120.0 mg, 0.372 mmol) and [CpRu(CH₃CN)₃OSO₂CF₃] (**3**; 78.3 mg, 0.179 mmol) was added CH₂Cl₂ (3 mL). Water (16 μ L, 0.89 mmol) was added and the resulting solution was stirred for 2 h before being concentrated in vacuo. The residual orange gum was dissolved in acetone (2 mL) containing water (16 μ L) and the resulting solution transferred to a tared vial. The vial was placed in a small jar containing hexanes. After one day, crystals of **4** had formed and the supernatant was removed from them by pipet. The crystals were rinsed with hexanes and placed under vacuum, leaving orange crystals and powder (172.2 mg, 98 % yield). ¹H NMR ([D₆]acetone, 500 MHz): δ = 9.12 (sl br s, 2H), 7.54–7.58 (m, 4H), 7.49–7.54 (m, 2H), 7.32–7.41 (m, 6H), 7.17 (s, 2H), 7.13 (sl br t, *J* = 7.5 Hz, 4H), 7.01 (sl br dd, *J* = 8.5, 10 Hz, 4H), 4.19 (s, 5H), 2.85 (s, 6H), 1.36 (s, 18H); ³¹P{¹H} NMR (CDCl₃, 80.95 MHz): δ = 26.72 (br s); elemental analysis (%) calcd for C₄₆H₅₃F₃N₄O₄P₂RuS (978.03): C 56.49, H 5.46, N 5.73; found: C 56.39, H 5.21, N 5.79.

Example of procedure used to monitor alkyne hydration: Conversion of 4-phenyl-1-butyne to 4-phenylbutanal (Table 1, entry 2): In the glovebox, catalyst **4** (9.8 mg, 0.010 mmol) and internal standard (Me₃Si)₄C (0.5 mg) were added to a vial. Using portions of [D₆]acetone (total volume 0.7 mL), the solid complex and standard were transferred by pipet to a resealable NMR tube. Not all **4** had dissolved at this point, so the transfer using solvent was partially mechanical. Water (45 μ L, 2.5 mmol) was added, followed by PhCH₂CH₂CCH (64.6 mg, 0.496 mmol) and enough [D₆]acetone to bring the total volume to 1.0 mL. The tube was sealed, removed from the glovebox, and briefly placed in a sonicating bath to dissolve all the catalyst to form a pale orange-yellow solution. The ¹H NMR spectrum of the resulting solution was recorded at this point and at intervals during heating of the NMR tube, using the same conditions (Varian 500 MHz spectrometer, four 30° pulses, 120 s delays between pulses). Monitoring reactions by NMR spectroscopy rather than by GC allowed us to determine if catalyst was still present. After 46 h, a sample of 4-phenyl-2-butanone (2 μ L, 0.013 mmol, 0.027 times the amount of alkyne added) was added to the NMR tube. A small singlet (ascribed to the methyl protons of the ketone) at δ = 2.086 grew in size. The increase in the singlet's integral indicated an aldehyde-to-ketone ratio of 150 to 1 before ketone addition. For the less volatile aldehydes made in entries 6 and 7 in Table 1, the mixture was worked up to provide pure aldehyde. Full details of these experiments are available in the Supporting Information.

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Scheme 2. Probable intermediates and mechanism of alkyne hydration.

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Metal-Catalyzed Selective Deoxygenation of Diols to Alcohols**

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Design and discovery of new catalysts that operate by nontraditional mechanisms offer the possibility of efficient and selective transformations that are difficult to achieve by conventional methods. Reactions proceeding through ionic mechanisms are attractive targets for development in this context. The traditional homogeneous catalytic hydrogenation of carbonyl groups^[1] involves the coordination of a ketone or aldehyde substrate to a metal center and insertion of the C=O bond into a metal hydride bond. In ionic hydrogenations, hydrogen gas is heterolytically cleaved by a metal complex and then added to an unsaturated organic compound through proton (H⁺) and hydride (H⁻) transfer steps. We recently reported Mo and W catalysts for ketone hydrogenation that operate by an ionic hydrogenation pathway under mild conditions.^[2] Magee and Norton discovered a Ru system that catalyzes the enantioface-selective hydrogenation of C=N bonds by an ionic mechanism.^[3] Shvo and co-workers reported a remarkable series of reactions catalyzed by ruthenium complexes with phenyl-substituted cyclopentadienone ligands,^[4] and recent studies by Casey et al. demonstrated that the proton and hydride transfer are concerted in such systems.^[5] The remarkably reactive Ru hydrogenation catalysts of Noyori and co-workers are now thought to proceed by a related mechanism in which H₂ is cleaved to form M–H and N–H bonds.^[6]

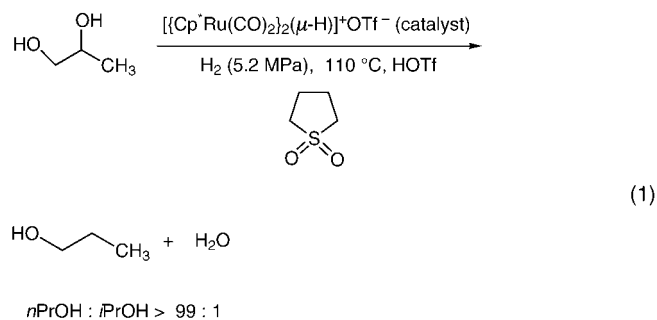
Synthetic procedures for deoxygenation of alcohols^[7] generally involve multiple steps and low atom efficiencies.^[8] Selective deoxygenation of one of the two OH groups of diols presents an even more formidable challenge than the deoxygenation of alcohols. Vicinal OH functionalities represent a ubiquitous feature of compounds derived from carbohydrates, but diols and polyols are unsuitable precursors for many industrial applications because they are overfunctionalized with an abundance of OH groups of very similar reactivity. Conversion of biomass to useful industrial chemicals^[9] offers an attractive solution to consumption of petroleum-based resources, an aspect of growing concern. We

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present here a homogeneous catalyst system that achieves the reductive deoxygenation of the model system 1,2-propanediol to *n*-propanol with high regioselectivity.

The ruthenium complex^[10] $[(\text{Cp}^*\text{Ru}(\text{CO})_2)_2(\mu\text{-H})]^+\text{OTf}^-$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$; $\text{OTf} = \text{OSO}_2\text{CF}_3$) catalyzes the reductive deoxygenation of diols to alcohols. The reaction is carried out under hydrogen at 110 °C with added HOTf in sulfolane. Equation (1) shows the catalytic deoxygenation of our model



compound 1,2-propanediol to *n*-propanol, and Figure 1 depicts the time profile of this reaction. After 6.4 h, the concentration of *n*-propanol was 0.38 M (38 %), and increased

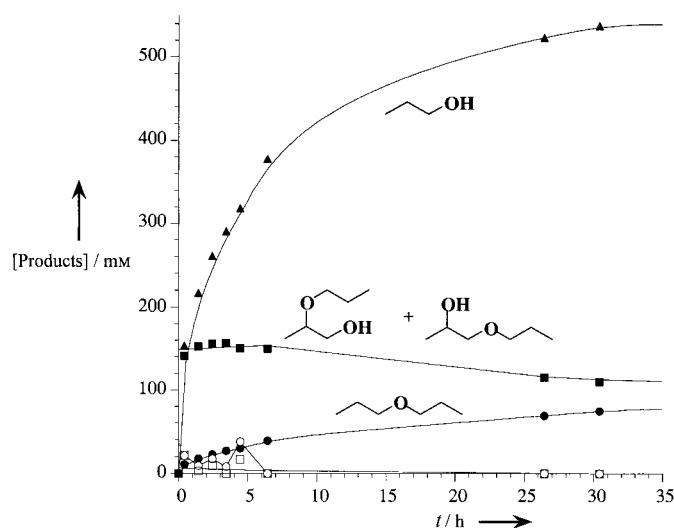
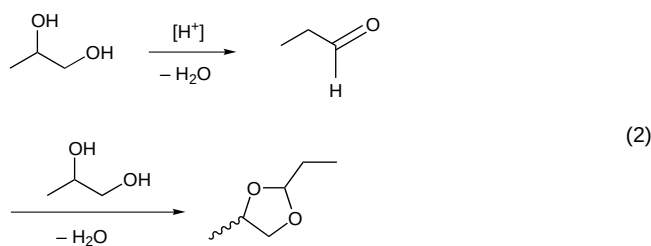


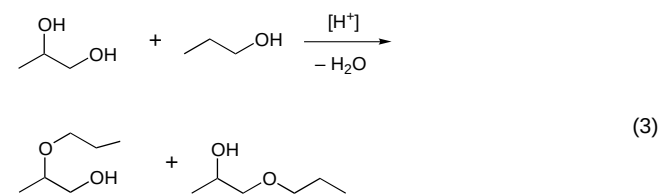
Figure 1. Time profile of products resulting from reaction of 1,2-propanediol. Initial concentrations and reaction conditions were 1.0 M 1,2-propanediol, 5 mM $[(\text{Cp}^*\text{Ru}(\text{CO})_2)_2(\mu\text{-H})]^+\text{OTf}^-$, and 60 mM HOTf under H_2 (5.2 MPa initial pressure before heating) at 110 °C in sulfolane. Final products are shown as solid symbols and are labeled. Intermediates propionaldehyde and 2-ethyl-4-methyl-1,3-dioxolane are shown as open circles and open squares, respectively.

to 0.52 M (52 %) after 26 h. This reaction exhibits a selectivity of >99 % for deoxygenation of the secondary over the primary OH group. Propionaldehyde, which results from acid-catalyzed dehydration of 1,2-propanediol [Eq. (2)], was observed as an intermediate (typically <5 %); its C=O bond is hydrogenated under the reaction conditions to give *n*-propanol. Separate experiments verify that aldehydes and ketones are catalytically hydrogenated to alcohols using $[(\text{Cp}^*\text{Ru}(\text{CO})_2)_2(\mu\text{-H})]^+$. We suggest that the observed selec-

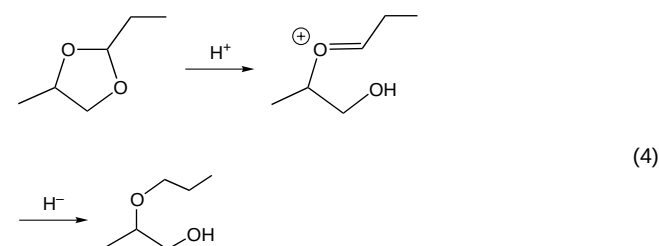


tivity is largely determined by the regiochemistry of the elimination of water from the protonated diol. Dehydration from the terminal OH group of the diol would be strongly disfavored, particularly if the loss of water more resembled an E1 mechanism than an E2 pathway, with the former being much more sensitive to the stability of the incipient carbenium ion. Another intermediate detected (also typically <5 %) in the deoxygenation reaction was the acetal 2-ethyl-4-methyl-1,3-dioxolane [*cis/trans* isomers; Eq. (2)] which results from reaction of propionaldehyde with 1,2-propanediol.

Additional ether products are observed under the deoxygenation reaction conditions. Cross-condensation of *n*-propanol with 1,2-propanediol would produce two isomers of propylene glycol propyl ether [Eq. (3)], and condensation of



n-propanol with itself would give di-*n*-propyl ether. Taking into account these ether products along with the *n*-propanol, a total of 160 turnovers (moles of hydrogenation products per mole of $[(\text{Cp}^*\text{Ru}(\text{CO})_2)_2(\mu\text{-H})]^+$) was observed after 30 h (80 % yield of hydrogenation products). An alternative mechanism for production of the propylene glycol propyl ether is ionic hydrogenation of the 2-ethyl-4-methyl-1,3-dioxolane, shown for one isomer in Equation (4). This acetal

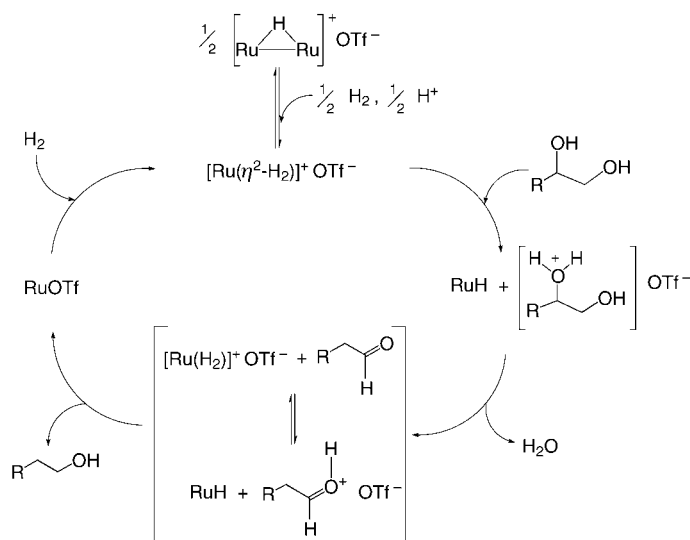


was independently synthesized and converted to *n*-propanol and propylene glycol propyl ether under the same catalytic reaction conditions. Similarly, a plausible route for production of the di-*n*-propyl ether would involve formation of a hemiacetal from the reaction of *n*-propanol with propionaldehyde, followed by deoxygenation of the hemiacetal to generate di-*n*-propyl ether.

Because of the formation of the condensation products and the associated equilibria, the kinetic profile of the reaction is complicated, and a detailed kinetic analysis has not been attempted. A key problem is the determination of the actual water concentration in the reaction mixture at any given time, and its influence on the position of the condensation equilibria and catalyst performance.

Most experiments were conveniently carried out with a starting pressure of 5.2 MPa (750 psi), but only small changes in the rate of catalysis were observed over the pressure range of 0.7–28 MPa. Indeed, catalytic deoxygenation was even achieved by bubbling H₂ at atmospheric pressure through the solution.

The proposed primary mechanism for the deoxygenation reaction is shown in Scheme 1. Cleavage of the two hydride-bridged ruthenium atoms by H₂, in the presence of HOTf,



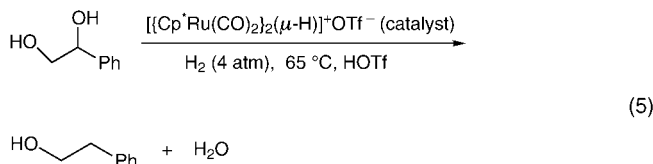
Scheme 1. Proposed mechanism for catalytic deoxygenation.

would produce the dihydrogen complex $[\text{Cp}^*\text{Ru}(\text{CO})_2(\eta^2\text{-H}_2)]^+\text{OTf}^-$. Heinekey and co-workers have previously shown^[11] that $[\text{Cp}^*\text{Ru}(\text{CO})_2(\eta^2\text{-H}_2)]^+$ can be prepared by protonation of $[\text{Cp}^*\text{Ru}(\text{CO})_2\text{H}]$, but that it decomposes below room temperature to give $[\{\text{Cp}^*\text{Ru}(\text{CO})_2\}_2(\mu\text{-H})]^+$, H₂, and H⁺.

The mechanism proposed in Scheme 1 shows the reverse of their reaction, which regenerates $[\text{Cp}^*\text{Ru}(\text{CO})_2(\eta^2\text{-H}_2)]^+$. Further evidence for this equilibrium comes from our observation by ²H NMR spectroscopy of $[\{\text{Cp}^*\text{Ru}(\text{CO})_2\}_2(\mu\text{-D})]^+$ from the reaction of $[\{\text{Cp}^*\text{Ru}(\text{CO})_2\}_2(\mu\text{-H})]^+$ with D₂ at 100 °C. Acid-catalyzed dehydration of propanediol generates propionaldehyde, which is observed under our reaction conditions. This dehydration may be catalyzed by free HOTf rather than by the ruthenium complex only, but the route shown appears feasible, in view of the remarkable acidity found^[11] for $[\text{Cp}^*\text{Ru}(\text{CO})_2(\eta^2\text{-H}_2)]^+$. The C=O bond of the propionaldehyde would then be hydrogenated in an ionic hydrogenation mechanism^[2] involving protonation of the aldehyde by $[\text{Cp}^*\text{Ru}(\text{CO})_2(\eta^2\text{-H}_2)]^+$, followed by hydride transfer to the protonated aldehyde by $[\text{Cp}^*\text{Ru}(\text{CO})_2\text{H}]$.

Release of the alcohol product generates $[\text{Cp}^*\text{Ru}(\text{CO})_2\text{OTf}]$, which then reacts with H₂ to regenerate $[\text{Cp}^*\text{Ru}(\text{CO})_2(\eta^2\text{-H}_2)]^+$ and complete the catalytic cycle. Employing $[\text{Cp}^*\text{Ru}(\text{CO})_2\text{OTf}]$ as the catalyst precursor gave essentially the same reactivity as that found with $[\{\text{Cp}^*\text{Ru}(\text{CO})_2\}_2(\mu\text{-H})]^+$, consistent with the proposed mechanism. Further mechanistic studies are underway.

Our studies to date have focused on the deoxygenation of 1,2-propanediol, but a similar catalytic deoxygenation of 1-phenyl-1,2-ethanediol to 2-phenylethanol [Eq. (5)] was also



found. This reaction proceeds under milder conditions (65 °C) but has only been studied thus far in NMR tubes in CD₂Cl₂, precluding a quantitative comparison to the deoxygenation of 1,2-propanediol. Preliminary results show that glycerol can also be deoxygenated, but the reaction has not yet been optimized, and further studies are needed. Reaction of glycerol (1.0 M) with $[\{\text{Cp}^*\text{Ru}(\text{CO})_2\}_2(\mu\text{-H})]^+\text{OTf}^-$ (10 mM) and 60 mM HOTf under H₂ (5.2 MPa) at 110 °C in sulfolane for 19 h gave 1,3-propanediol (2.9 turnovers based on $[\{\text{Cp}^*\text{Ru}(\text{CO})_2\}_2(\mu\text{-H})]^+$), 1,2-propanediol (0.9 turnovers), and *n*-propanol (3.1 turnovers). A similar experiment with higher HOTf (120 mM) produced no detectable (<0.3 turnovers) 1,2-propanediol, with larger amounts of 1,3-propanediol (4.6 turnovers) and *n*-propanol (5.7 turnovers). Product mixtures were also reported from prior attempts to develop homogeneous catalysts for deoxygenation of glycerol.^[12] These latter reactions were carried out under CO/H₂ mixtures, and higher temperatures and often higher pressures were employed than those in our work.

These results provide a highly selective catalytic method for deoxygenation of diols, a reaction that normally requires more than one step to accomplish in a stoichiometric transformation. This new approach may ultimately lead to a process that has utility for biomass conversions.

Experimental Section

In a drybox, a sulfolane solution (40 mL) containing 1,2-propanediol (1.0 M), $[\{\text{Cp}^*\text{Ru}(\text{CO})_2\}_2(\mu\text{-H})]^+\text{OTf}^-$ (0.147 g, 0.200 mmol, 5 mM), and toluene (0.1 M, internal standard for integration) was placed in a Parr autoclave, and CF₃SO₃H (213 μL, 2.40 mmol, 60 mM) was added dropwise. The autoclave was sealed, and the solution was heated to 110 °C under H₂ (5.2 MPa initial pressure before heating). The progress of the reaction was quantitatively monitored by gas chromatography. After 30 h, 0.08 M (8%) of the 1,2-propanediol remained, and the concentrations and yields of hydrogenated products were *n*-propanol (0.54 M, 54%), propylene glycol propyl ether (0.11 M, 11%), and di-*n*-propyl ether (0.074 M, 15%), for a total yield of hydrogenation equivalents of 80% yield. The di-*n*-propyl ether is considered as two hydrogenation equivalents, since two equivalents of *n*-propanol are required to produce one equivalent of di-*n*-propyl ether. The mass balance of identified products was generally 90–100% in this and related reactions.

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Probing Transient Hydrate Structures with Hyperpolarized ^{129}Xe NMR Spectroscopy: A Metastable Structure II Hydrate of Xe

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The formation of gas hydrates involves the reaction of water or ice with small hydrophobic atoms or molecules in the size range of about 4.0 (Ar) to about 8.0 Å (methylcyclohexane).^[1] Several hydrate structural families are known, and these are designated as structure I, II, and H (Str. I, Str. II and Str. H), the structure usually being determined by the largest guest in the hydrate.^[1] Many questions remain about the nucleation of hydrates, their growth, and inhibition.^[2] Such issues are of importance in a number of areas, as hydrates exist both in nature and in industrial environments.^[2] To learn to control hydrate formation and decomposition is of continuing interest, especially to solve hydrate control problems in the hydrocarbon resource industry.^[2]

Methods capable of monitoring hydrate formation processes are relatively few, especially if molecular-scale information is desired. Vibrational and NMR spectroscopies do have

such capabilities.^[3, 4] For the latter, the chemical shift tensors or isotropic shifts of molecules in different guest sites can be observed, and in this way provide a signature that is characteristic of the structural type.^[4] ^{129}Xe was the first guest to be used this way;^[5] however, as the time required to record Xe NMR spectra is significant because of long spin-lattice relaxation times, it is not a suitable probe for studying processes. Advances in the development of optical pumping techniques for producing highly polarized Xe (HP Xe)^[6] have solved this problem, and it has already been demonstrated that kinetic studies of hydrate formation can be carried out on a subsecond time scale.^[7, 8] Herein we draw attention to the HP Xe approach as a powerful way of observing transient behavior and thereby yielding structural information in a time-resolved fashion. We show that unusual phenomena observed when HP Xe is placed in contact with a Str. II hydrate of tetrahydrofuran give new insights into hydrate formation reactions at the molecular level.

The experiment in which we were interested involved the exposure of a Str. II hydrate with empty small cages to a Str. I guest. In the case of THF hydrate, THF occupies the large cages in Str. II hydrate which has a crystal structure with a unit cell that can be formulated as $16\text{M}_s \cdot 8\text{M}_l \cdot 136\text{H}_2\text{O}$, where M_s and M_l are the small (5^{12}) and large cages ($5^{12}6^4$), respectively (where 5^{12} corresponds to a cage with twelve five-sided faces). In Str. II hydrate the small cages may be empty or they may be occupied by small molecules such as Ar, Kr, Xe, N_2 , O_2 , and CH_4 . On the other hand, Xe on its own forms a Str. I hydrate, with a structural designation of $2\text{M}_s \cdot 6\text{M}_l \cdot 46\text{H}_2\text{O}$, where M_s is a 5^{12} cage and M_l is the $5^{12}6^2$ cage.

Experiments were carried out on a Bruker AMX-300 NMR spectrometer (magnetic field 7.05 T, ^{129}Xe resonance frequency 83.03 MHz) by exposing powdered Str. II THF hydrate samples to HP Xe gas, which was prepared by optical pumping^[6] directly in the NMR probe.^[9, 10]

The time development of the Xe spectrum is shown in Figure 1. For closer scrutiny, selected spectra, along with those obtained for a control sample of powdered ice, are shown in

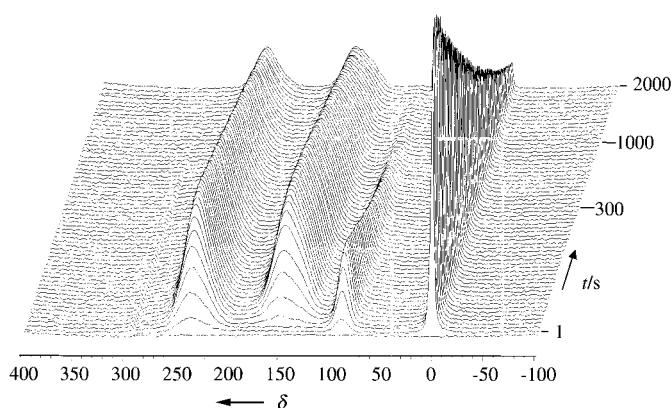


Figure 1. Time development of the ^{129}Xe NMR spectrum after exposure of a powdered THF sample to hyperpolarized Xe. The line at $\delta \approx 0$ can be assigned to the gas, the lines at $\delta \approx 90$, 150, and 240 to Xe in the large cage of Str. II, the large cage of Str. I, and the two small cages in the Str. I and Str. II, respectively. Experimental conditions: temperature 223 K; starting pressure of Xe 530 mbar. Before adsorption of HP xenon, the sample was evacuated for 30–40 min at 10^{-5} mbar to minimize the presence of adsorbed oxygen.

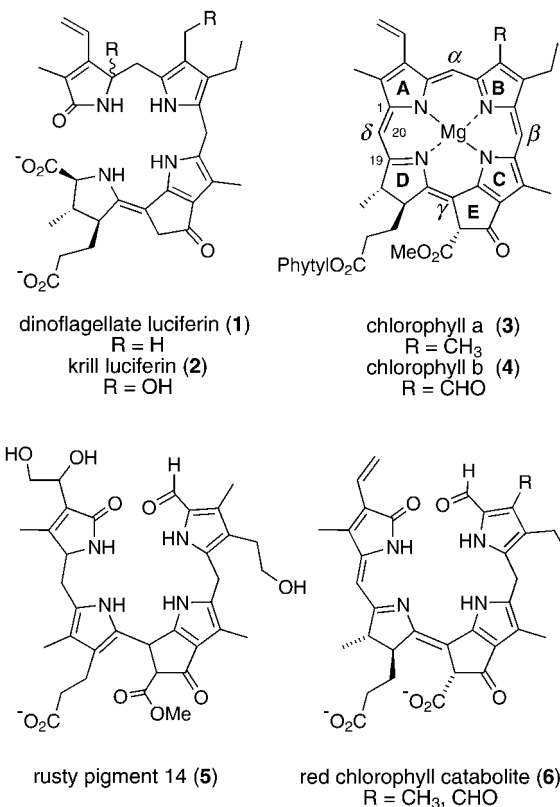
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- [10] In previous work,^[7] HP Xe was delivered to the ice sample in frozen form, and since it was necessary to wait for xenon to sublime, this contributed significantly to the uncertainty in the starting point for kinetic measurements. In this work, HP Xe was always delivered as a gas, allowing accurate sampling of the early stages of the interaction.
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- [12] This will also explain the persistence of the signal of Xe in the small cages of str. II hydrate on application of a vacuum. If Str. I is formed strictly from the decomposition of the metastable str. II hydrate it will always be on the surface and decompose readily. However, Xe atoms can migrate deep into the str. II hydrate to fill the small cages as it is the stable phase and the dynamic properties of the THF hydrate water lattice are favorable for easy transport.

Chlorophyll Catabolism Leading to the Skeleton of Dinoflagellate and Krill Luciferins: Hypothesis and Model Studies**

George Topalov and Yoshito Kishi*

In the late 1980s, we reported the structures of dinoflagellate luciferin (**1**) and krill luciferin (**2**) (Scheme 1).^[1] Recognizing their structural similarity with chlorophylls a and b (**3** and **4**, respectively), we speculate that dinoflagellate luciferin



Scheme 1. Structure of dinoflagellate and krill luciferins and representative chlorophyll catabolites.

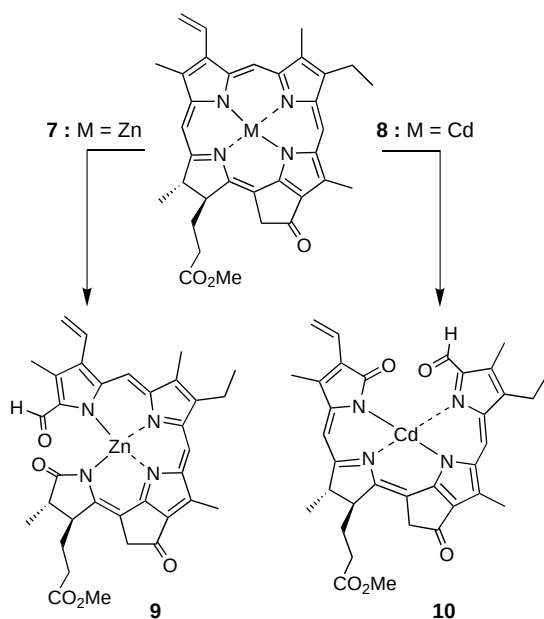
(**1**) and krill luciferin (**2**) are derived through an oxidative ring cleavage at the C1–C20 bond of chlorophylls with retention of the C20 carbon atom as a carboxylate at ring D. Shortly after the structures of **1** and **2** were disclosed, chlorophyll catabolites from barley and *Chlorella protothecoides* were isolated and characterized (**5** and **6**, respectively; Scheme 1).^[2, 3] It is evident that, unlike dinoflagellate and krill luciferins, these catabolites are formed through cleavage of the C4–C5 bond of chlorophylls with retention of the C5 carbon atom as a

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formyl group at ring B. Chemical bond cleavages are also known on Cd- and Zn-chelates of pyropheophorbide a (Scheme 2).^[4] Interestingly, C4–C5 bond cleavage occurred for the Cd-chelate **8** to give **10**, whereas C19–C20 bond cleavage occurred for Zn-chelate **7** to give **9**.

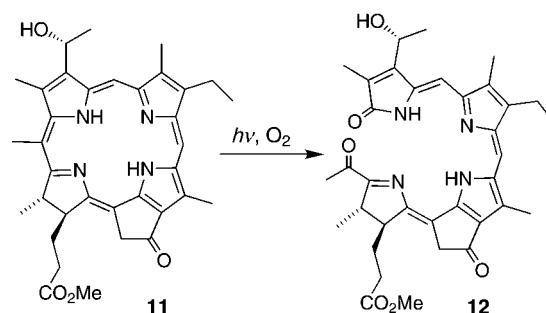


Scheme 2. Photooxidation of Cd- and Zn-chelates of pyropheophorbide a.

To the best of our knowledge, no example is known for the enzymatic or chemical cleavage of the C1–C20 bond, which would transform chlorophylls to the skeleton of dinoflagellate and krill luciferins (see Scheme 1). There are two intriguing aspects of this presumed mode of chlorophyll catabolism: 1) the selectivity in the bond cleavage at the α - versus δ -bridge, and 2) the selectivity in the bond cleavage at the C1–C20 versus C19–C20 bond.

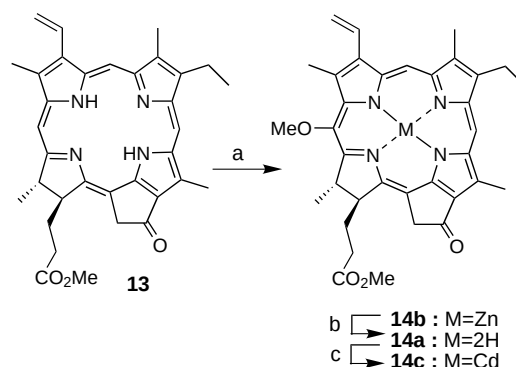
For several reasons, we have hypothesized that this presumed mode of chlorophyll catabolism may proceed through two distinct steps, that is, a hydroxylation or equivalent event at C20,^[5] followed by cleavage of the C1–C20 bond. First, the δ -bridge of pheophorbides is known to be most prone to electrophilic attack.^[6] Indeed, a C20-chlorinated chlorophyll was isolated from blue-green alga.^[7] Second, the C20 carbon atom of a chlorophyll is retained as a carboxylate, instead of a formyl, in the luciferins **1** and **2**, which could be explained by the oxidation of C20 prior to bond cleavage. Third, the photooxidation of bacteriochlorophyll e or its derivatives (cf., **11**) is known to involve a selective cleavage of the C1–C20 bond (Scheme 3).^[8] Although steric interactions between the methyl groups at C20 and C2 could be the source for the observed selectivity, electronic effects, exercised by the electron-donating methyl group, may also play an important role for an overall transformation of chlorophylls into the skeleton of dinoflagellate and krill luciferins.

To test this hypothesis, we planned to photooxidize a substrate bearing a methoxy group at C20 and its metal



Scheme 3. Photooxidation of bacteriochlorophyll e.

chelates. In practice, methyl 20-methoxychlorin (**14a**), along with its Zn- (**14b**) and Cd-chelates (**14c**), was synthesized from pyropheophorbide a methyl ester (**13**) (Scheme 4).^[9]



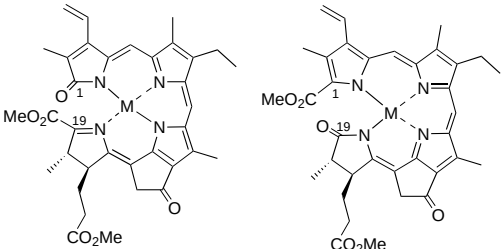
Scheme 4. Synthesis of methyl 20-methoxychlorin and its Zn- and Cd-chelates. Reagents and conditions: a) 1. $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, 1:1 $\text{MeOH}:\text{CH}_2\text{Cl}_2$, 4 h (90%); 2. $\text{Ti}(\text{O}_2\text{CCF}_3)_3$ (1.1 equiv), THF, 15 min (80%);^[16a] 3. 0.25 M NaOAc/MeOH , 1 h;^[16b] 4. $\text{MeI}/\text{K}_2\text{CO}_3$, 1:1 $\text{THF}:\text{CH}_3\text{CN}$ (30% over 2 steps). b) HCl aq./ MeOH , 5 min (70%). c) $\text{Cd}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, 1:1 $\text{MeOH}:\text{CH}_2\text{Cl}_2$, 2 h (80%).

Photooxidation was carried out by irradiation of a dilute solution (ca 7.10^{-5} M) of the substrate by using three 300 W tungsten lamps at 30 cm from a reaction flask provided with cooling and oxygen bubbling. The solvent and the reaction time varied with the substrate; Cd-chelate **14c** was irradiated for 20–25 min in benzene, Zn-chelate **14b** for 20 min in benzene or dichloromethane, and the metal-free substrate **14a** for 3 h in benzene.

Table 1 summarizes the product distribution observed under these conditions. Most significantly, the photooxidation of chlorin **14a** smoothly proceeded to yield exclusively the C1–C20 bond cleaved product **15a** (Figure 1) in 45% yield, along with a substantial amount of the unconsumed starting material.^[10]

The molecular weights of photooxidation products **15** and **16** were established by fast atom bombardment mass spectrometry (FAB-MS), and the presence of a carbomethoxy group but the absence of a formyl group in **15** and **16** were demonstrated by ^1H NMR spectroscopy. These experiments established that all the photooxidation products isolated were derived by cleavage of a δ -bridge by singlet oxygen, thereby leaving only two possible structures, that is, **15** and **16**. Differentiation of **15** from **16** could be made through

Table 1. Product distributions of the photooxidation of methyl 20-methoxychlorin and its Zn- and Cd-chelates.

		
	15a-c	16a-c
14a (M = 2H) →	15a (M = 2H) 45 %	16a (M = 2H) none
14b (M = Zn) →	15b (M = Zn) none	16b (M = Zn) 45 %
14c (M = Cd) →	15c (M = Cd) ~ 5 %	16c (M = Cd) ~ 20 %

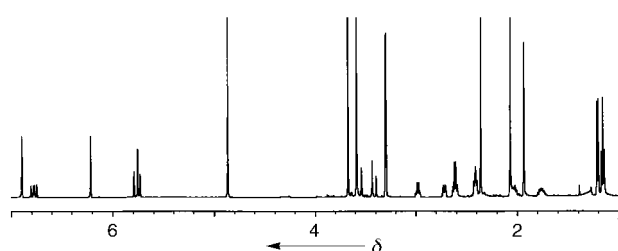


Figure 1. ^1H NMR spectrum of the photooxidation product **15a** (500 MHz, CD_3OD).

establishing the bond connectivity of the carbomethoxy group at C20 to the rest of the molecule. In spite of extensive efforts, however, we were unable to detect a cross-peak establishing the bond connectivity between the carbomethoxy group at C20 and the rest of the molecule through heteronuclear multiple bond correlation (HMBC) NMR experiments.^[11] Thus, we relied on UV/Vis spectroscopy. Two possible photooxidation products were obtained only in the Cd-chelate series. The UV/Vis spectrum of **15c** ($\lambda_{\text{max}} = 667, 437, 360 \text{ nm}$ (MeOH)) was dramatically different from that of **16c** ($\lambda_{\text{max}} = 886, 670, 571, 439, 380 \text{ nm}$ (MeOH)). Next, **15c** was chemically correlated with **15a**; upon treatment with sodium diethyldithiocarbamate hydrate in methanol at room temperature, **15c** was cleanly converted to the metal-free product **15a**.^[12] The UV spectrum of **15a** ($\lambda_{\text{max}} = 570, 357, 317 \text{ nm}$ (MeOH)) was almost superimposable on that of the methylketone **12** ($\lambda_{\text{max}} = 576, 344 \text{ nm}$ (MeOH)).^[13] On the other hand, the UV spectra of **16b** ($\lambda_{\text{max}} = 868, 612, 564 \text{ nm}$ (CH_2Cl_2); 883, 666, 552, 432, 388 nm (MeOH)) and **16c** ($\lambda_{\text{max}} = 886, 670, 571, 439, 380 \text{ nm}$ (MeOH)) were very similar to that of **9** ($\lambda_{\text{max}} = 858, 610, 568 \text{ nm}$ (CH_2Cl_2); 857, 581, 455, 433, 376 nm (MeOH)). These results show that **15a** and **15c** belong to the C1–C20 bond-cleaved series, whereas **16b** and **16c** belong to the C19–C20 bond-cleaved series. The ^{13}C spectra of **15** and **16** provided further support to the assigned structures. The ^{13}C chemical shifts for C1 and C19 of **16b** were $\delta = 145.5$ and 190.4 (CDCl_3), respectively, which compared well with the chemical shifts ($\delta = 150.4$ and 192.5 (CDCl_3)) reported for **9**.^[14] However, **15c** ($\delta_{\text{C1}} = 181.7$ and $\delta_{\text{C19}} = 172.1$

($[\text{D}_6]\text{acetone}$)) and **15a** ($\delta_{\text{C1}} = 172.9$ and $\delta_{\text{C19}} = 173.3$ (CD_3OD)) gave ^{13}C chemical shifts significantly different from those reported for **9**.

The remarkable selectivity observed in the photooxidation of **14a** to **15a** lends strong support to the hypothesis that a hydroxy or equivalent group at C20 directs the C1–C20 bond cleavage that transforms chlorophylls into krill and dinoflagellate luciferins. The methoxy substituent at C20 is a powerful δ -bridge directing group even in the case of Cd-chelate **14c**.^[15] This is in sharp contrast with the case where the Cd-chelate without the C20 methoxy substituent was photooxidized at the C4–C5 bond. The fact that δ -methoxy Zn-chelate **14b** is cleaved in the same way as the unsubstituted Zn-chelate **7** may imply that the methoxy group simply lowers the oxidation potential of the pyropheophorbide without influencing electron distribution within the aromatic system.

In conclusion, the photooxidation experiments suggest the existence of a new pathway for chlorophyll catabolism in dinoflagellates and krill. The selective and efficient bond cleavage at the C19–C20 bond reported immediately suggests a possible route for a synthesis of dinoflagellate and krill luciferins from chlorophylls a and b.

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- We would like to thank Dr. Lynn Hawkins at the Eisai Research Institute of Boston for a generous gift of pyropheophorbide a methyl ester.
- Up to 35 % of the starting material was recovered with reverse-phase (C-18) flash column chromatography.
- We are grateful to Dr. Kenichi Tezuka of this laboratory for performing the 2D NMR experiments.
- All attempts to demetalate **16b**, **c** to **16a** led to decomposition.
- The structure of a close analogue to **12** was established by X-ray analysis: W. S. Sheldrick, A. Borkenstein, U. Jürgens, H. Brockmann, Jr., *J. Chem. Res. (S)* **1981**, 266.
- The connectivity of the C20 formyl group to ring A was established through an NOE observed between the aldehyde proton and the methyl group at C2.^[4]
- We have recently shown that the photooxidation of methyl 20-benzoyloxchlorin (i.e., BnO instead of MeO in **14a**) yields the benzyl ester corresponding to **15a** in 45 % yield.
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Serial [5+2]/[4+2] Cycloadditions: Facile, Preparative, Multi-Component Syntheses of Polycyclic Compounds from Simple, Readily Available Starting Materials**

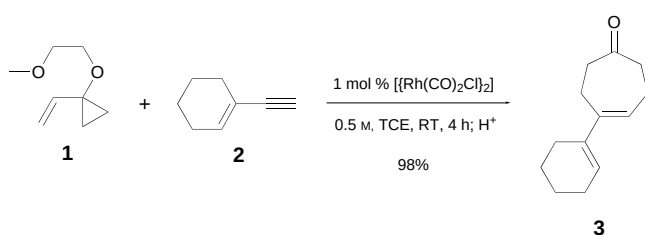
Paul A. Wender,* Gabriel G. Gamber, and Marc J. C. Scanio

The frontiers of organic synthesis are most clearly defined by the level of molecular complexity that can be achieved with efficiency. Ideally, the synthesis of complex targets would be based on readily available starting materials and proceed quickly and quantitatively in one simple, safe, environmentally acceptable, and resource-effective operation.^[1] However, most reactions do not provide sufficient increases in complexity to achieve such synthetic brevity. As a result, efforts to achieve complexity *and* brevity must rely on coupling multiple individual transformations into one synthetic operation.^[2–5]

Cycloaddition reactions are among the synthetically most useful individual processes for increasing molecular complexity.^[6, 7] The synergistic effects of linking multiple cycloaddition reactions in series can lead to highly desirable increases in molecular complexity.^[3, 4] We recently introduced a fundamentally new and remarkably general cycloaddition for seven-membered ring synthesis based on transition metal catalyzed [5+2] cycloadditions.^[8, 9] We now report our studies on a novel, serial [5+2]/[4+2] cycloaddition process, and the finding that the serial process proceeds more efficiently than the uncoupled individual steps.

We have reported that $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ catalyzes intermolecular [5+2] cycloadditions with complete chemoselectivity for alkynes.^[8b,c] Based on this selectivity, we envisioned that an intermolecular [5+2] cycloaddition with a conjugated enyne would yield a diene that could react in a [4+2] cycloaddition, affording a polycyclic compound from three simple starting materials in a single operation.

1,1,2,2-Tetrachloroethane (TCE) was selected as our initial solvent because it was found to work superbly in the [5+2] cycloaddition (Scheme 1). Furthermore, because of its rela-



Scheme 1. [5+2] cycloaddition of **1** and **2** is chemoselective and efficient at room temperature.

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tively high boiling point (147 °C), TCE enables thermally demanding [4+2] cycloadditions without the need for sealed tubes.

Our initial study of the [5+2]/[4+2] cycloadditions used a sequential addition protocol (Method A). The [5+2] cycloaddition was run to completion, the dienophile added and the reaction heated. Hydrolysis of the resultant enol gave good to excellent yields of a single diastereomeric product (Table 1, Method A). X-ray analysis indicates that the stereoselectivity is derived from the *endo* transition state of the Diels–Alder reaction.^[10] Tricycle **8**, a dihydroarene, is obtained smoothly under the reaction conditions but is easily aromatized with DDQ to the arene in 87%.

Sequential addition, while operationally easy, would be further simplified by addition of all three reactants at the outset of the reaction (Method B). Gratifyingly, this procedure afforded the target polycycles in better yields than the initial procedure (Table 1, Method B). Since diene **3** decomposes at elevated temperatures,^[11] the higher yields obtained by Method B are a consequence of the diene being trapped as

Table 1. Serial [5+2]/[4+2] cycloadditions with 1-ethynylcyclohexene (**2**).

Entry	Dienophile	Method	T [°C]	t [h]	Product	Yield [%]
1		A	100	1	4	87
2		B	60	5	4	91
3		A	100	1	5	86
4		B	60	3	5	92
5		A	100	2	6	79
6		B	80	5	6	89
7		A	140	9	7	77
8		B	140	21.5	7	84
9		A	130	24	8	77
10		B	60	2	9	87

Experimental Section

Full procedures and characterization data are given in Supporting Information.

Method A: To an oven-dried, septum-capped test tube was added $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (3.8 mg, 0.01 mmol) and anhydrous TCE (2 mL) under a positive argon pressure vented to a bubbler. To this was added **1** (142.2 mg, 1 mmol) and **2** (127.4 mg, 1.2 mmol). The reaction was stirred at room temperature for 6 h, the dienophile (1.2–1.5 mmol) was then added and the reaction heated to the temperature indicated in Table 1.

Method B: To an oven-dried, septum-capped test tube was added $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (7.6 mg, 0.02 mmol) and anhydrous TCE (2 mL) under a positive argon pressure vented to a bubbler. To this was added **1** (142.2 mg, 1 mmol), **2** (127.4 mg, 1.2 mmol), and the dienophile (1.5 mmol). The reaction was heated to the temperature indicated in Table 1.

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- [11] **3** was found to decompose with a half life of 30 h at 100 °C, 0.5 M in TCE. $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ accelerated the decomposition. See Supporting Information for additional detail.
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Synthesis of Isotopically Labeled (*E*)- β,γ -Unsaturated Esters with Total or High Diastereoselectivity by Using Samarium Diodide**

José M. Concellón,* Pablo L. Bernad, and Humberto Rodríguez-Solla

β,γ -Unsaturated esters are generally synthesized by isomerization of α,β -unsaturated esters,^[1] either by selective, conjugate reduction of alkyl alka-2,4-dienoates,^[2] or by carbonylation of allylic compounds,^[3] or from α -bromo- α,β -unsaturated esters.^[4] However, no simple, general, highly diastereoselective preparation of β,γ -unsaturated esters has been described.

Recently, we reported a highly diastereoselective synthesis of (*E*)- α,β -unsaturated esters^[5] and amides^[6] from 2-halo-3-hydroxyesters and amides, respectively, by using SmI_2 . Subsequently, we described a sequential elimination–reduction reaction promoted by SmI_2 , which gave 2,3-dideuterioesters and amides from 2-halo-3-hydroxyesters and amides, respectively, by using D_2O as the deuteration reagent.^[7] Here we report a new method to obtain β,γ -unsaturated esters **2**, with total or high diastereoselectivity by a sequenced elimination–reduction process of the readily available α -halo- β -hydroxy- γ,δ -unsaturated esters **1** by using SmI_2 and H_2O (see Table 1). Taking into account the usefulness of isotopically labeled compounds for establishing the mechanism of organic reactions and the biosynthetic pathways of many natural compounds,^[8] we have also applied this method to obtain α,δ -

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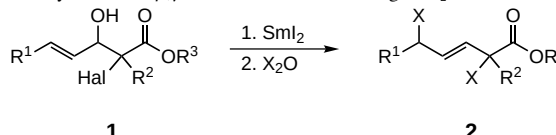
[**] We thank II Plan Regional de Investigación del Principado de Asturias (PB-PGI98-04) and Ministerio de Educación y Cultura (PB97-1278) for financial support and Dr. Francisco J. González for valuable discussions. J.M.C. thanks Carmen Fernández for her collaboration. H.R.S. thanks the Principado de Asturias for a predoctoral fellowship.

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

dideuterio- β,γ -unsaturated esters by using D_2O instead of H_2O .

Treatment of several α -halo- β -hydroxy- γ,δ -unsaturated esters **1** with a solution of SmI_2 (5 equiv) in THF for 30 min at room temperature, followed by reaction with D_2O or H_2O (2 mL) over a period of 30 min afforded the corresponding (*E*)- α,δ -dideuterio- β,γ -unsaturated or (*E*)- β,γ -unsaturated esters **2**, respectively, in high yield (Table 1). No differences

Table 1. Synthesis of β,γ -unsaturated esters using SmI_2 .



Entry	2	R ¹	R ²	R ³	X ^[a]	de ^[b]	Yield [%] ^[c]
1	a	Me	H	Bn	D	60	62
2	b	Me	Me	Et	D	> 98	66
3	c	Me	C ₆ H ₁₃	Et	H ^[d]	> 98	79
4	d	Me	C ₆ H ₁₃	Et	D ^[d]	> 98	82
5	e	Pr	H	Me	D	65	90
6	e	Pr	H	Me	D ^[e]	76	60 ^[f]
7	e	Pr	H	Me	D ^[g]	86	30 ^[f]
8	f	Pr	C ₅ H ₁₁	Et	D ^[d]	> 98	74
9	g	Pr	Ph	iPr	D	> 98	90
10	h	Ph	Me	Et	D	> 98	62
11	i	Ph	C ₆ H ₁₃	Et	D ^[d]	> 98	62

[a] Unless otherwise noted, reactions were carried out using Hal = Cl. See also Experimental Section and Supporting Information. [b] Diastereoisomeric excess (*de*) determined by GC-MS, and 300 MHz ¹H and ¹³C NMR analysis of the crude products **2**. [c] Yield of product isolated after column chromatography based on compound **1**. [d] Reaction was carried out using Hal = Br. [e] Reaction carried out at -15°C ; reaction time = 150 min. [f] Dimerization products at the δ -position were obtained. [g] Reaction carried out at -40°C ; reaction time = 18 h.

were observed in the reaction when D_2O or H_2O was used. In both cases, a C–C double bond was generated with total diastereoselectivity (except for **2a** and **2e**), while the incorporation of deuterium generated a new stereogenic center and consequently the deuterated compounds **2** were isolated as a mixture of diastereoisomers (roughly 1:1).

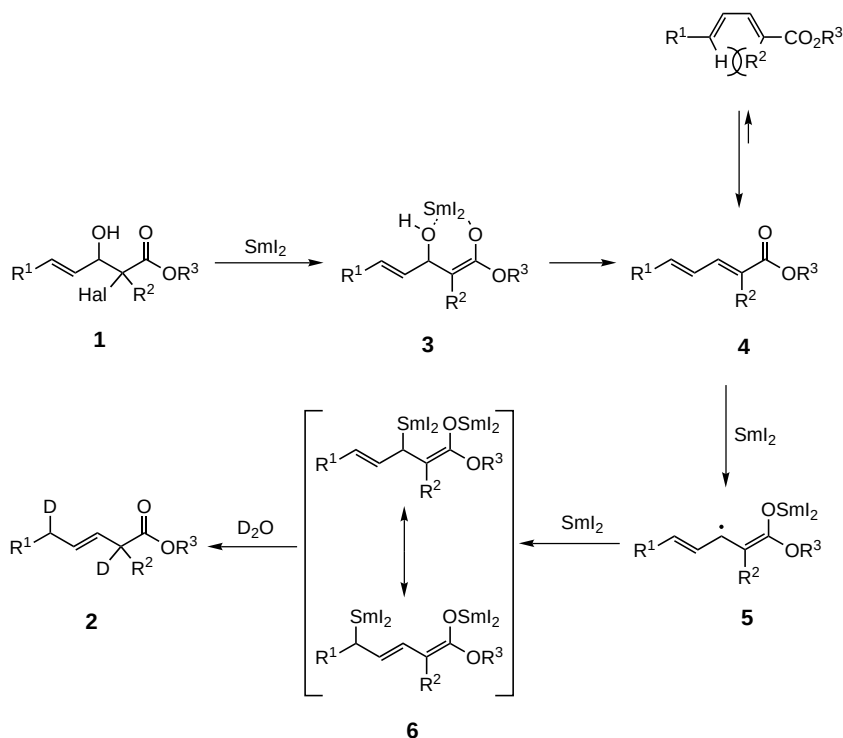
All starting compounds **1** were easily obtained by reaction of the corresponding lithium enolates of α -haloesters (generated by treatment of α -haloesters with lithium diisopropylamide (LDA) at -78°C) with α,β -unsaturated aldehydes at -78°C . The diastereoisomeric excess (*de*) in each case was determined on the crude reaction products by ¹H NMR spectroscopy (300 MHz) and GC-MS. The position of the C–C double bond and the deuterium atom was established by ¹H and ¹³C NMR spectroscopy of compounds **2**. The multiplicity of the signals of the olefinic protons was in accordance with the structure shown

in Table 1 (i.e. 1,4-reduction of the conjugated C–C double bond) and in disagreement with a possible reaction to give α,β -dideuterated- γ,δ -unsaturated esters (i.e. by 1,2-reduction). The *E* stereochemistry in the C–C double bond was assigned on the basis of the value of the ¹H NMR coupling constant between the olefinic protons of compound **2**. The complete deuterium incorporation (> 99 %) was confirmed by mass spectrometry.^[9] It is noteworthy that D_2O is the cheapest deuteration reagent available for obtaining organic compounds isotopically labeled with deuterium.

The proposed methodology to prepare (*E*)- α -alkylated- α,δ -dideuterio- β,γ -unsaturated esters **2** is general: R¹, R², and R³ can be varied widely (see Table 1); chloro and bromo hydroxyesters can be used as starting material, and even though mixtures of diastereoisomers of the starting halohydrins **1** were used, the C–C double bond of esters **2b–d** and **2f–i** was obtained with total diastereoselectivity.

When compounds **1** with R² = H were used, the C–C double bond of compounds **2** was obtained with high selectivity, the usual diastereoselectivity/temperature trend was observed by which diastereoselectivity increased as the temperature decreased. However, at low temperature, the previously reported formation of unsaturated diesters by a dimerization of alka-2,4-dienoates (see below) was also observed.^[10]

Synthesis of **2** may be explained by assuming that the metalation of the halogen of **1** with SmI_2 produces an enolate intermediate **3**, in which the chelation of the Sm^{III} center with the oxygen atom of the OH group produces a six-membered ring, which undergoes a β -elimination affording the alkyl (2*E*,4*E*)-alka-2,4-dienoate **4** with total diastereoselection (Scheme 1).^[11] Support for this is provided by isolation of ethyl (2*E*,4*E*)-2-hexylhexa-2,4-dienoate (**4c**) in 90 % yield (starting from ethyl-2-bromo-2-hexyl-3-hydroxyhex-4-enoate



Scheme 1. Proposed mechanism for the conversion of **1** into **2**.

and 2.5 equiv of SmI_2) when, after 30 min, excess SmI_2 was eliminated from the reaction mixture by bubbling a stream of air prior to the hydrolysis.

After formation of the alkyl (2*E*,4*E*)-2-alkylalka-2,4-dienoate **4**, the SmI_2 -promoted 1,4-reduction of the two conjugated C–C double bonds, which is initiated by oxidative addition of SmI_2 , produces an enolate radical **5**,^[12] which could explain the observed dimerization at the δ -position of compounds **4a**, and **4e**. A second electron transfer from SmI_2 affords an allylic dianion **6** and its hydrolysis with H_2O or D_2O produces the corresponding compound **2** (Scheme 1).

The observed lower diastereoselectivity in the formation of the C–C double bond in the synthesis of **2a** and **2e**, neither of which contain α -alkyl substituents, may be explained by assuming that in case of the α -alkylated esters **2b–d** and **2f–i** the *s-cis* conformation of the starting diene is disfavored by steric hindrance produced by the substitution at the α -carbon atom, while the 1,4-reduction of the conjugated C–C double bonds of **2a** and **2e** takes place through both the *s-cis* and *s-trans* conformations. The complete deuteration at C5 instead of at C3 of the dianion **6** could be explained by assuming that in this resonance-stabilized dianion, the 1,4-dianion structure is more stable than the 1,2-dianion structure due to the charge repulsions.

The proposed mechanism is supported by the fact that the synthesis of compounds **2** can be also carried out starting from the corresponding alkyl (2*E*,4*E*)-2-alkylalka-2,4-dienoate **4**. Thus, treatment of ethyl (2*E*,4*E*)-2-hexylhexa-2,4-dienoate (**4d**) with SmI_2 (2.5 equiv) and D_2O (2 mL) for 30 min at room temperature affords **2d** in 84% yield.

The described methodology can be applied to obtain δ -deuterio- β,γ -unsaturated esters. The reaction of **2h** with LDA, followed by treatment with H_2O afforded ethyl (*E*)-5-deuterio-2-methyl-5-phenylpent-3-enoate (**8h**) with total diastereoselectivity (89% yield). Taking into account that the C–C double bond of δ -deuterio- and α,δ -dideuterio- β,γ -unsaturated esters can be easily hydrogenated,^[13] the proposed methodology can be used to prepare saturated δ -deuterio- and α,δ -dideuterioesters, respectively.

In conclusion, in the presence of D_2O , the simple SmI_2 -promoted elimination/reduction sequence provides an efficient method for synthesizing α,δ -dideuterio- β,γ -unsaturated esters **2**, in which the C–C double bond is generated with total or high diastereoselectivity, starting from the readily available α -halo- β -hydroxy- γ,δ -unsaturated esters **1**.

Experimental Section

General procedure: A solution of SmI_2 (2.3 mmol) in THF (24 mL) was slowly added dropwise, under a nitrogen atmosphere, to a stirred solution of **1** (0.4 mmol) in THF (4 mL) at room temperature. After the solution had been stirred for 30 min at the same temperature, H_2O or D_2O (2 mL) were added. The mixture was stirred for 30 min at this temperature and then quenched with aqueous HCl (0.1M, 5 mL). Usual workup afforded crude β,γ -unsaturated esters **2**, which were purified by column flash chromatography over silica gel (10:1 hexane/ethyl acetate). Yields are given in Table 1.

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Allosteric Regulation of an HIV-1 Protease Inhibitor by Zn^{II} Ions**

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Alessandro Scarso, and Paolo Scrimin*

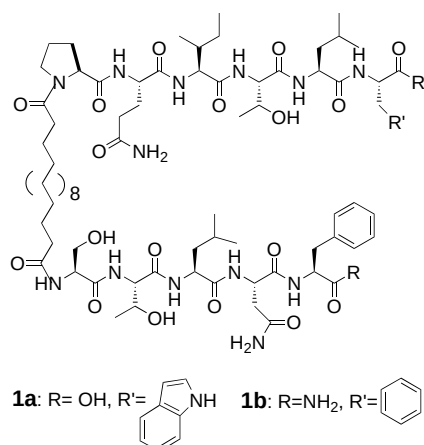
Allosteric regulation of protein activity by noncovalent modifiers (ions or neutral molecules) is a feature found in many natural systems including enzymes.^[1] The role of these modifiers is to induce conformational changes in the protein that trigger its activity while they are usually not directly involved in the specific function performed by the macromolecule.

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Examples of allosteric control of the properties of artificial systems have also been reported^[2] including a very recent example of a phosphodiesterase model^[3] whose activity is triggered by remote coordination to metal ions. The latter represents one of the few systems that show allosteric regulation of the activity of a designed synthetic molecular receptor. Herein we describe an example of the control of enzymatic activity by allosteric regulation of the efficiency of a putative inhibitor by Zn^{II} ions.

The enzyme we have studied is HIV-1 protease,^[4] a protein whose activity requires the dimerization of two identical subunits. Most of the driving force for the dimerization derives from an interdigitating N- and C-terminal four-stranded, antiparallel β -sheet. HIV-1 protease plays a critical role in viral replication and, consequently, is a key target for the design of inhibitors as potential anti-HIV drugs. Inhibition can result from binding at the active site or, because of the dimeric nature of the protein, from binding at the dimerization interface, which in this case leads to the disruption of the active species, the dimer.^[5] The group of Chmielewski,^[6] among others, has carried out research in this direction. They have shown that peptides that feature similar sequences as those present at the N and C termini of each monomer of HIV-1 protease and that are cross-linked by a C₁₄-hydrocarbon spacer display significant activity. For instance, **1a** has a remarkable *K_i* value of 220 nM. Peptide **1b**, in which TrpOH has been replaced with PheNH₂, is an even better inhibitor,

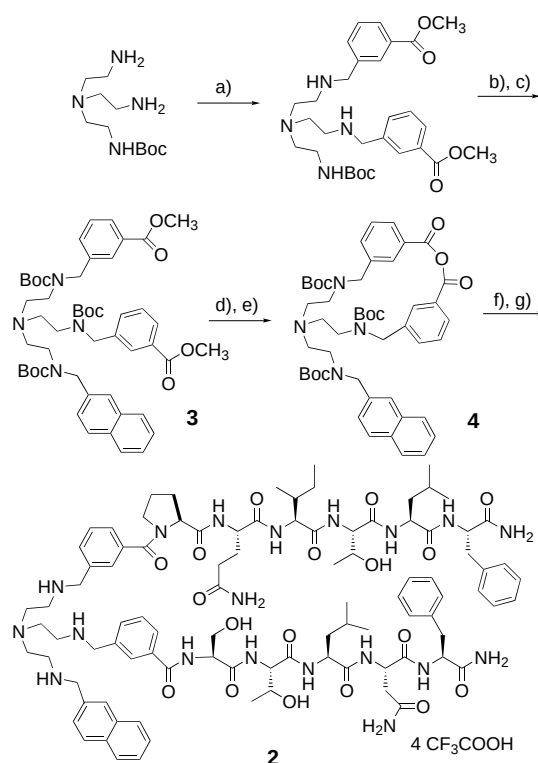


with a threefold increase in activity.^[7] A key aspect of the system is the length of the tether: 14 CH₂ units appears to be the most appropriate length for placing the amino termini of the two peptides approximately 10 Å apart, which is the distance found between the N and C termini of each monomer in the enzyme.^[8]

We reasoned that the reversible control of the distance between the two tethered peptides in an inhibitor like **1** would lead to the modulation of its activity. For this purpose, we selected tris(2-aminoethyl)amine (TREN) as a metal-binding template to which to cross-link two peptides (analogous to those in **1**) through a rigid aromatic spacer. Molecular modeling predicted that the two N termini of the peptides would be placed close to the 10 Å distance (presumably required for optimum activity) only in the presence of this spacer and when the TREN platform was bound to a metal

ion such as Zn^{II}, in accordance with the crystallographic data reported for a similar tetraamine.^[2c] On the contrary, the arms of the free ligand, whose nitrogens are protonated at neutral and lower pH values, are forced to stay at a larger distance because of the electrostatic repulsion. For this reason TREN appeared to be a good candidate as a platform for the control of the conformation of the inhibitor by Zn^{II} complexation, particularly as far as the distance between the two interfacial peptides is concerned. In the design of the system, the third arm, which is necessary to impart rigidity to the complex but is not used for the enzyme recognition process, was considered for the functionalization with a naphthalene unit, to be used as a fluorescent reporter of the protonation and/or Zn^{II} complexation of the TREN subunit. Indeed, molecular sensors for metal as well as for other ions have been reported which are based on this approach.^[9]

The synthesis of our target molecule **2** was rather challenging because it required the selective functionalization of the three arms of the tetraamine. Nevertheless **2** was synthesized in a fairly good yield (Scheme 1). Boc-monoprotected TREN



Scheme 1. Synthesis of inhibitor **2**: a) 3-carboxymethylbenzaldehyde, CH₃CN, 3 Å molecular sieves, RT, 12 h, then NaBH₄, dry CH₃OH, N₂, RT, overnight, 77%; b) TFA, dry CH₂Cl₂, then aqueous Na₂CO₃, 90%; c) 2-naphthaldehyde, CHCl₃, 75 °C, 4 h; NaBH₄, dry CH₃OH, N₂, RT overnight, then Boc₂O, N₂, CH₂Cl₂, RT overnight, 50%; d) NaOH, CH₃CH₂OH, 24 h, RT; dilute HCl, 90%; e) DCC, dry CH₂Cl₂, 20 min, RT, 76%; f) H-Ser(*t*Bu)-Thr(*t*Bu)-Leu-Asn(Trt)-Phe-, DMF/CH₂Cl₂, N₂, RT, 2.5 h; H-Pro-Gln-Ile-Thr-Leu-PheNH₂, HBTU, HOBt, dry DMF, *N*-ethyl-diisopropylamine, N₂, RT, 24 h; g) TFA (95%), TES (2.5%), H₂O (2.5%), 60% from **4**. Boc = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid, DCC = dicyclohexylcarbodiimide, DMF = *N,N*-dimethylformamide, HBTU = *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, HOBt = 1-hydroxy-1*H*-benzotriazole. represents the Rink resin.

was first converted into the bis(methyl benzoate) derivative. Deprotection, treatment with 2-naphthaldehyde followed by reduction led to the introduction of the fluorescent probe in **3**. Subsequent Boc-protection of the amino groups and hydrolysis of the ester functional groups led to the formation of the key anhydride intermediate **4** upon treatment with DCC. The two peptides, which were prepared by means of conventional solid-phase synthesis on Rink resin, were connected to the platform in two subsequent steps in an excellent overall yield of 60%. After the removal of the resin and of the protecting groups, the putative inhibitor **2** was isolated as the tetra- CF_3COO^- salt.

Although the reported binding constant of TREN to Zn^{II} is rather high ($K_b \sim 10^{15} \text{ M}^{-1}$ for the 1:1 complex),^[10] its apparent value is evidently pH dependent because of the competition with the protons. The dependence of the fluorescence intensity of a 50 μM solution of Boc-deprotected ligand **3** on the presence of one equivalent of $\text{Zn}(\text{NO}_3)_2$ ($\lambda_{\text{ex}} = 291 \text{ nm}$; $\lambda_{\text{em}} = 336 \text{ nm}$) indicates that there is no complex formation below pH 4.0, whereas the complex is fully formed above pH 6.5. The same behavior is expected with **2**. HIV-1 protease is an aspartyl protease and thus shows better activity at slightly acidic pH values (5.0–5.5) than at neutral pH. For this reason we decided to test the inhibitory ability of **2** and its Zn^{II} complex against this enzyme at pH 5.5, at which point approximately 80% of the complex is formed. The inhibition was evaluated by using a fluorogenic substrate assay developed by Toth and Marshall^[11] (see Experimental Section for details). The results for **2** and **2**– Zn^{II} , reported in Figure 1

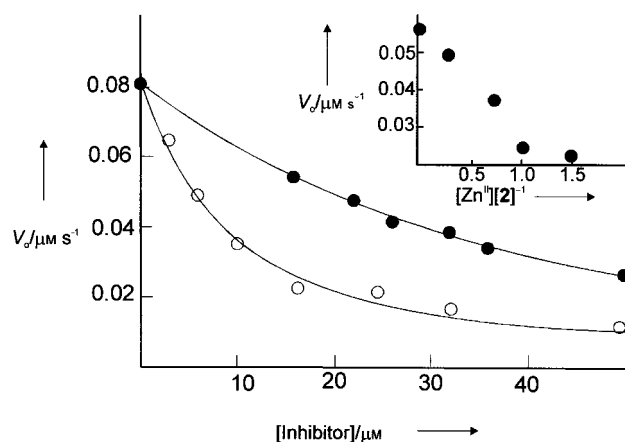


Figure 1. HIV-1 protease activity expressed as initial rate (V_0) of cleavage of the fluorescent substrate Abz-Ile-Nle-Phe(*p*- NO_2)-Gln-ArgNH₂^[11] as a function of the concentration of **2** (●) and its Zn^{II} complex (○). Conditions: [protease] = 25 nM; pH 5.5, 25 °C. Inset: dependence of V_0 on the $[\text{Zn}^{\text{II}}]:[\mathbf{2}]$ ratio at $[\mathbf{2}] = 16 \mu\text{M}$, same conditions as above.

clearly indicate a higher activity of the Zn^{II} complex than that of the free ligand, with apparent IC_{50} values of 6 μM and 28 μM , respectively. The role of Zn^{II} in triggering the enhanced inhibitory activity of the complex is further highlighted in the inset of Figure 1 in which the activity of HIV-1 protease is reported against the $[\text{Zn}^{\text{II}}]:[\mathbf{2}]$ ratio. The curve profile indicates that maximum inhibition is attained with the formation of a 1:1 complex, although in agreement with the

above-mentioned fluorescence experiments with deprotected **3**, there is not complete inhibition when one equivalent of metal ion is added. Control experiments showed that the efficiency of the Zn^{II} inhibitor is lost by the addition of a slight excess of ethylenediaminetetraacetate (EDTA), which depletes the TREN subunit of the metal ion.^[12]

The above results, although interesting, do not provide any evidence of the source of the enhanced potency of inhibitor **2** when it is transformed into its Zn^{II} complex. It has been shown that when the hydrophobic character of the tether is altered by the introduction of an ammonium ion, the activity of an inhibitor such as **1a** is adversely affected.^[13] Accordingly, it could well be that a change in the balance between the hydrophobic and hydrophilic character of the TREN platform upon Zn^{II} complexation is at the basis of the observed effect. Thus a Zhang–Poorman plot^[14] was used to evaluate if **2** and **2**– Zn^{II} are real competitive inhibitors. Such a plot (Figure 2)

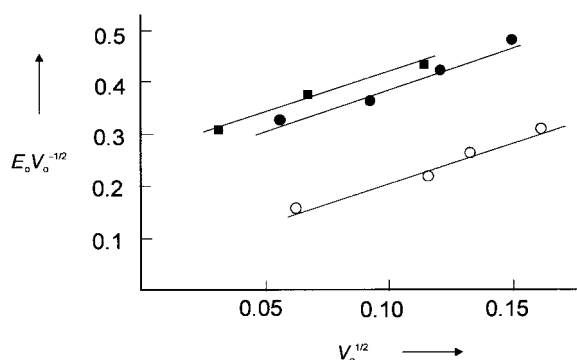


Figure 2. Zhang–Poorman plots^[14] for compounds **2**– Zn^{II} (■, 8 μM), **2** (●, 28 μM), and uninhibited protease (○). E_0 is the total enzyme concentration; all other conditions as in Figure 1. K_m and k_{cat} for the uninhibited enzyme under the experimental conditions used are 39 μM and 0.77 s^{-1} , respectively.

reports $E_0/V_0^{1/2}$ against $V_0^{1/2}$ and gives parallel lines in the case of dimerization inhibitors, whereas purely competitive inhibitors are characterized by lines with different slopes that point to a single intercept on the $E_0/V_0^{1/2}$ axis.^[15] Our results indicate that **2** and **2**– Zn^{II} are real dimerization inhibitors. The values of K_i for **2**– Zn^{II} and **2** are 1.2 μM and 8 μM , respectively, which shows that Zn^{II} plays a key role in a almost sevenfold enhancement of the activity of **2** upon metal ion complexation. This gain in activity derives from a better binding of the two peptides of the Zn^{II} complex to the dimerization interface of HIV-1 protease. This is in full agreement with molecular modeling studies that indicate a distance between the two peptides in the Zn^{II} complex close to that found between the N and C termini of the native protein.^[8] These studies also rule out a possible contribution to the binding^[15] by the coordination of the terminal carboxylate of the monomeric protein to Zn^{II} , because of the presence of the rigid aromatic spacer between the peptides and the TREN platform.

We note that in spite of the lack of the hydrophobic tether^[16] that is present in inhibitors **1**, which contributes to their binding efficiency, **2**– Zn^{II} has a remarkably high activity. The loss of the hydrophobic contribution in **2**– Zn^{II} is likely compensated by a tether between the two peptides which is constrained in a conformation more appropriate for the

formation of the interdigitating β -sheet between the metal-oinhibitor and the monomeric protein.

In conclusion we have demonstrated that the activity of a dimerization inhibitor of HIV-1 protease derived from cross-linked interfacial peptides can be enhanced by controlling the conformation of their connecting unit through Zn^{II} complexation.^[17] This provides a straightforward example of allosteric regulation of the activity of a synthetic inhibitor by a metal ion and shows that although the Zn^{II} -binding process occurs at a remote position, it in fact amplifies the chemical information present in the system (i.e. its ability to recognize a monomer of HIV-1 protease).

Experimental Section

Compound **2** was synthesized according to the route reported in Scheme 1. **4**: ESI-MS (m/z): 837 [M^+]. **2**: amino acid analysis: Phe(2) 2.01, Asn(1) 1.1, Leu(2) 2.06, Thr(2) 2.09, Ser(1) 1.03, Gln(1) 0.9, Pro(1) 0.98, Ile(1) 0.87; MALDI-MS (m/z): 1815 [$M+1$], 1321, 1115; HR-ESI-MS (m/z): 908.056 [MH_2^{2+}]. **2**– Zn^{II} : HR-ESI-MS (m/z) 939.013 [MZn^{2+}]. (HR = high-resolution, ESI = electrospray-ionization, MALDI = matrix-assisted laser-desorption ionization).

Enzyme assay: Inhibition experiments were performed by using 250 μ L of a standard HIV-1 protease solution [50 nM in a buffer prepared with phosphate (20 mM), glycerol (20%), dithiothreitol (DTT; 1 mM) and 3-[(3-cholamidopropyl)dimethylammonio]-1-propane sulfonate (CHAPS) (0.1%)], which was incubated for 1 h with a solution of the inhibitor with the required concentration (50 μ L). The solution was then added to the substrate (Abz-Thr-Ile-Nle-*p*-NO₂Phe-Glu-ArgNH₂; 200 μ L) in the same buffer diluted with dimethyl sulfoxide (DMSO; 10%) to give a substrate concentration of 60 μ M. The amount of DMSO was kept constant at 14%. The concentration of HIV-1 protease in the kinetic runs of Figure 1 was 25 nM while in the experiments of Figure 2 it was varied within the 10–80 nM interval. For the determination of K_m and k_{cat} , the substrate was varied within the 10–100 μ M interval. Kinetic runs were performed by following the increase of fluorescence emission at 430 nm (λ_{ex} = 360 nm) for 400 s.

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Regioselective Tetrametalation of Ferrocene in a Single Reaction: Extension of s-Block Inverse Crown Chemistry to the d-Block**

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Charles T. O'Hara, René B. Rowlings, and
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s-Block metal inverse crowns constitute an emerging family of special compounds in which polymetallic amide cationic rings complex anionic guests.^[1] They are “inverse” crowns in the sense that their Lewis acidic/Lewis basic sites have been interchanged relative to those in conventional crown ether complexes,^[2] that is, here the metal atoms belong to the ring and not to the core. However, the chemistry controlling their formation goes far beyond that of simple macrocyclic host–

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guest combinations. It appears that a powerful ring template effect brings about the regioselective deprotonation of certain substrates to create and to encapsulate unusual anions, which are inaccessible through the use of mainstream bases. The best example of this phenomenon to date is in the transformation of toluene to the arenediide ($\text{C}_6\text{H}_3\text{CH}_3$)²⁻ with twofold deprotonation occurring at thermodynamically unfavorable ring sites (2,5-positions), while the more acidic methyl substituent is left untouched.^[3] Scheme 1 shows the membership of the inverse crown family as it stood prior to the work reported here. These compounds of eight, twelve, or twenty-four ring atoms were the subject of a recent feature article.^[4] A product of a synthetic and structural synergism which is triggered by pairing together two distinct metal types (Li, Na, or K with Mg or Zn^[5]) within the same amide environment, these mixed-valent compounds exhibit a unique chemistry that cannot be replicated by complexes containing one or the other metal type on its own. Herein we describe the entry of inverse crown complexes into the domain of transition metal organometallic chemistry.^[6] The entrance is eye catching with ferrocene transformed regioselectively to a 1,1',3,3'-tetrayl derivative by the encapsulating action of a new sixteen-membered tetrasodium – tetramagnesium amide cationic ring. Previously the amide component of inverse crowns had been limited to either hexamethyldisilazide (HMDS) or 2,2,6,6-tetramethylpiperidine (TMP). Here a third sterically

demanding amide is added to the list of inverse crowns in diisopropylamide ($i\text{Pr}_2\text{N}^-$). This anion was generated by subjecting three equivalents of the parent amine $i\text{Pr}_2\text{NH}$ to an equimolar mixture of $n\text{BuNa}$ and Bu_2Mg . The resulting synergic solution^[7] of “[$\text{NaMg}[\text{NiPr}_2]_3$]” smoothly converts ferrocene to the spectacular new addition to the inverse crown family **1**. Remarkably this amounts to a “simultaneous” fourfold regioselective deprotonation. This contrasts greatly with the behavior of conventional alkali metal bases such as $n\text{BuLi}/N,N,N',N'$ -tetramethyl-1,2-ethylenediamine (TME-DA),^[8] which generally strip only one or two hydrogen atoms from ferrocene.

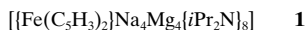
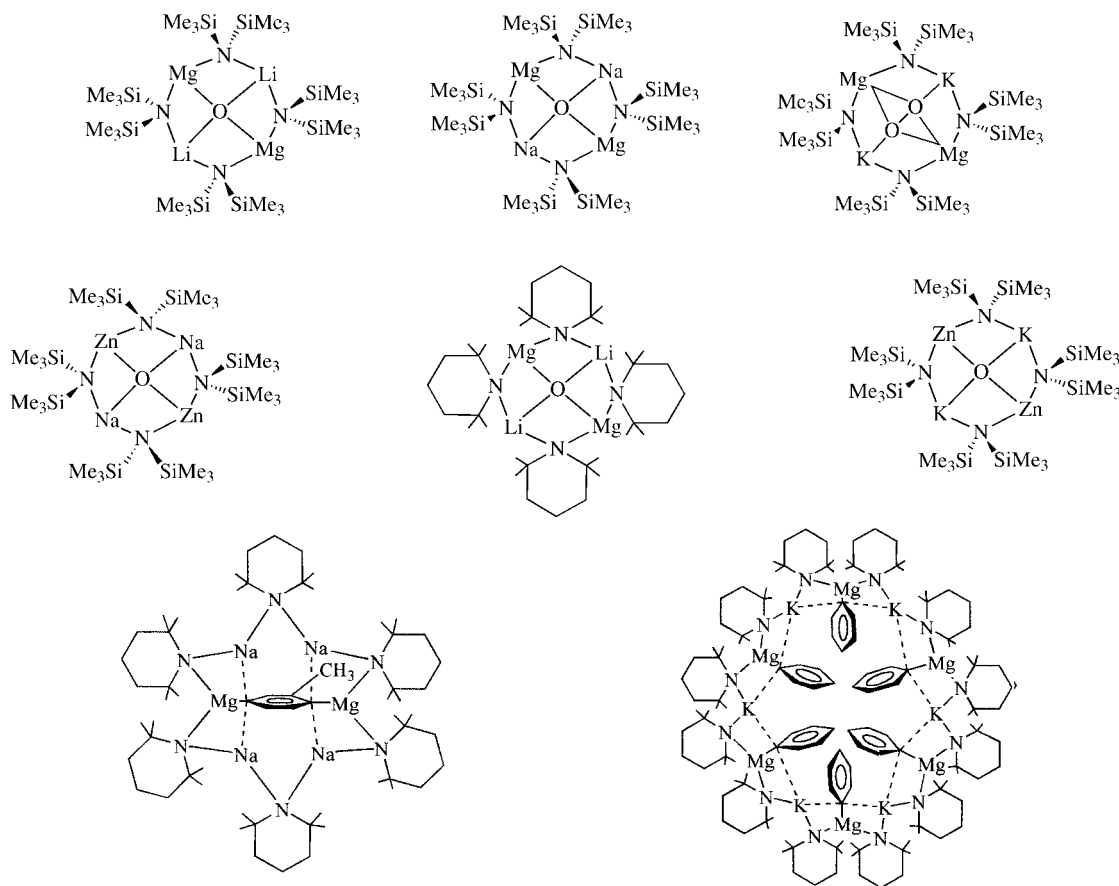


Figure 1 shows a view of the molecular structure of **1** through the face of its sixteen-membered ring.^[9] This centrosymmetric ring is made up of alternating nitrogen and metal atoms, with the latter atoms themselves alternately sodium and magnesium. A severe flexing of this ring is necessary to anchor the dideprotonated edge of each Cp ring (Figure 2). The missing hydrogen atoms of the Cp rings are lost from the 1,1',3,3' positions (corresponding to C27, C27', C29, C29'). Formally therefore the ferrocenyl captive carries a 4 – charge, which is balanced by the 4 + charge of its cyclic $\text{Na}_4\text{Mg}_4\text{N}_8$ captor. This captivity is enforced by a combination



Scheme 1. The inverse crown family.

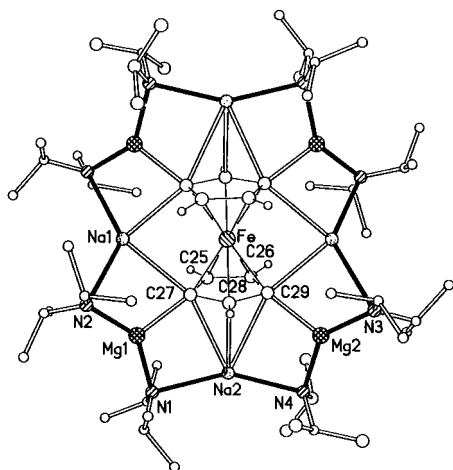


Figure 1. Molecular structure of **1**. Hydrogen atoms, except those belonging to the C_5H_3 rings, are omitted for clarity. Selected bond lengths [Å]: Mg1–N1 2.0397(13), Mg1–N2 2.0163(14), Mg2–N3 1.9965(13), Mg2–N4 2.0411(13), Mg1–C27 2.1469(15), Mg2–C29 2.1580(15), Na1–N2 2.5347(15), Na1–N3' 2.7113(15), Na2–N1 2.5068(14), Na2–N4 2.4661(14), Na1–C27 2.7546(16), Na1–C29' 2.6287(15), Na2–C27 2.8329(15), Na2–C28 2.6080(15), Na2–C29 2.9232(15).

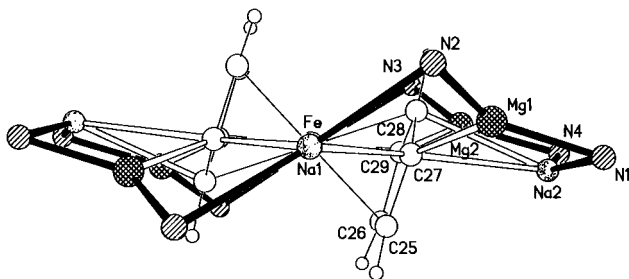


Figure 2. Side view of **1** looking along the Na1...Fe1...Na1' line. Isopropyl groups are omitted for clarity.

of Na–C and Mg–C bonds. Part of a linear Na...Fe...Na arrangement, Na1 occupies a μ_2 -bonding site between the Cp rings (mean Na–C bond length, 2.670 Å) and completes a distorted tetrahedral environment by binding to two N atoms (mean Na–N bond length, 2.623 Å). In contrast Na2 binds to the π face of one Cp ring. Involving the three C atoms of the long doubly deprotonated edge, this interaction is asymmetric (η^3) with the central C atom (C28) providing the shortest contact distance (2.608 Å). Two N atoms also complete the coordination sphere of Na2, but at significantly shorter distances (mean, 2.486 Å) than those to Na1. Following the pattern set in the other arene-based inverse crowns, the privileged positions within the Cp ring undergoing deprotonation are dictated by the positions of the Mg atoms within the host ring. This reflects the stronger, more covalent nature of the Mg–C bonding (mean, 2.153 Å), and the possibility (suggested in a previous paper^[4]) that the amide anion performing the deprotonation step (and subsequently leaving as an amine molecule) originates from a terminal position on Mg within a reactive mixed-metal tris(amide) cyclic intermediate. Unlike in the benzene- and toluene-based inverse crowns, the Mg–C bonds in **1** do not lie coplanar with the plane of the aromatic ring, but tilt away from it by 63.1 and 58.4° for the two independent Mg–C bonds. Clearly it is inherently more difficult for a host ring to accommodate a

molecule as large as ferrocene, and it appears that a “best fit” arrangement can only be reached at the expense of compromising the σ contribution to the Mg–C bonding. However, this has a negligible effect on the lengths of the Mg–C bonds as those in the toluene-based inverse crown are actually slightly longer at 2.200 Å. The structure of **1** also exhibits two distinct types of amide ligand in N2/N3 and N1/N4, which is a consequence of their attachment to the two distinct Na atoms (Na1 and Na2, respectively).

Crystalline **1** dissolves in toluene thus enabling a ^1H NMR spectrum to be recorded, whose appearance indicates a molecular structure exactly matching that found in the solid state. To elaborate, there are three Cp H resonances, two of which have nearly identical, but well-resolved chemical shifts (0.02 ppm apart), while the third one lies 0.66 ppm to lower frequency. Using the crystal structure labels, these can be assigned to the hydrogen atoms attached to C25/C26 and C28, respectively. Two sets of iPr_2N resonances are also discernible. Each set contains four diastereotopic Me groups, which leads to a complicated pattern of overlapping doublets caused by coupling to the CH units. The prochiral nature of their attached N atoms is a consequence of the geminal heterobimetallic bonding. It can therefore be concluded that the structure of **1** is retained in arene solution.

Looking to the future, the propensity of s-block metals to undergo exchange in reactions with electrophiles makes **1**, in effect, an invaluable synthon^[10] for a 1,1',3,3'-tetraanion of unsubstituted ferrocene. Thus in theory it offers chemists scope for designing new regioselectively tetrasubstituted ferrocenes. The potential utility of **1** could also have important implications for the synthesis of new ferrocene polymers. This field is currently being studied in the search for polymers with unusual properties (e.g., conductive, magnetic, electronic, optical). Also, following this first venture into organometallic chemistry the development prospects for inverse crown chemistry as a whole look decidedly bright with a vast pool of metallocenes now available as potential candidates for exploitation in this exciting new area.

Experimental Section

1: Freshly prepared $nBuNa$ (5 mmol) was suspended in hexane (10 mL) in an argon-filled Schlenk tube. The tube was then placed in an ultrasonic bath for 10 min to obtain a more reactive fine suspension. Commercial (from Aldrich) Bu_2Mg (5 mmol in heptane solution) was then added to give a brown mass. This was subsequently dissolved upon the addition of iPr_2NH (15 mmol) with gentle warming. Next, ferrocene (2.5 mmol) was introduced to give an orange solution, and the mixture was heated to reflux for 15 min by which time it had turned from orange to red. Much of the hydrocarbon solvent was removed in vacuo and replaced by toluene (2–3 mL), and the mixture was heated until complete dissolution was achieved. The resulting deep red solution was placed in a Dewar flask of hot water and allowed to cool slowly to ambient temperature. This yielded red cubelike crystals of **1** (yield, 42%). M.p. 161–164 °C. Satisfactory (C,H,N) analysis. ^1H NMR (400 MHz, $[D_8]$ toluene, 25 °C): δ = 4.20 (s; C_5H_3), 4.18 (s; C_5H_3), 3.52 (s; C_5H_3), 3.48 (m, CH $\times$ 8; iPr), 3.12 (m, CH' $\times$ 8; iPr), 1.42 (m, $CH_3 \times$ 16; iPr), 1.06 (m, $CH_3 \times$ 8; iPr), 0.97 (m, $CH_3 \times$ 8; iPr). Small traces of free ferrocene and diisopropylamine were also present due to slight hydrolysis. Repeating the preparation using a stoichiometry of ferrocene commensurate with that in the formula of **1** (1.25 mmol) also produced **1** in similar yields. Note that **1** is air- and moisture-sensitive, and pyrophoric.

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Chemical Reaction between Colliding Vesicles**

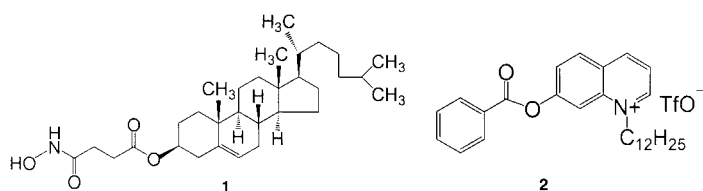
Fredric M. Menger,* Kevin L. Caran, and Victor A. Seredyuk

It is difficult to say exactly when the reaction kinetics of water-soluble agents with colloidal assemblies, now a venerable sector of chemistry, first came into prominence. Perhaps it occurred in the 1960s when scientists worldwide began studying the reactions of hydroxide and hydronium ions with micelle-adsorbed substrates.^[1] Modest rate increases or rate

inhibitions (depending upon the electrostatics of the situation) were the general rule. For example, hydroxide-catalyzed ester hydrolysis is accelerated by cationic micelles and inhibited by anionic micelles.^[2] A quantitative understanding of such rate effects is now in hand.^[3] Later on, attention turned to bimolecular reactions between species in solution and vesicular reactants. For example, rates of reduction between external dithionite and vesicle-bound dye were established.^[4] Owing in part to the hundreds of publications on the kinetics of reagent/colloid reactions, we now have an appreciation of colloids' interfacial polarity,^[5] concentration of bound counterions,^[6] molecular dynamics of assembly components,^[7] and various size, shape, and phase properties.^[8]

The next higher level of complexity, namely the reaction kinetics between two discrete molecular assemblies, has never received much attention. This is surprising considering the biological relevance of inter-assembly reactivity. One merely has to consider a sperm penetrating an ovum, or a virus penetrating a cell, to recognize the importance of membrane/membrane reactivity.^[9] It is for this reason that we began examining vesicle/vesicle reactions. The idea was to place a nucleophilic lipid in one phospholipid vesicle, and an electrophilic lipid in another, and to monitor the ensuing reaction efficiency as the two vesicles collided. In preliminary experiments, we found that vesicle/vesicle reactivity is indeed an observable phenomenon, and that its rates depend upon the exposure of the membrane-bound functionalities to the external water.^[10] Encouraged by these results, we continued our investigation and now report a reaction whose molecular features—including vesicle-to-vesicle transfer processes during collision—were revealed by the kinetics.

The reaction in question involves two amphiphilic compounds: a steroidal nucleophile **1** and a long-chain quinolinium ester **2**. Nucleophile **1** is a known hydroxamic acid^[10] (*pK_a* = ca. 9.4)^[11] which, under the basic conditions of our experi-



ments (pH 9.0), partially transforms into a powerful estero-lytic species: hydroxamate.^[12] The cholesterol moiety of **1**, with its known affinity for bilayer membranes,^[13] serves to “anchor” the molecule in the vesicles. Substrate **2** is a labile ester whose cleavage leads to a marked increase in absorbance and fluorescence. Membrane affinity, in this case, derives from a hydrophobic dodecyl chain.

Reactant **2** possesses a useful trait that, to our knowledge, is rare or nonexistent among reactive fluorescent probes. Hydrolysis of **2** produces a fluorescent hydroxyquinolinium ion that retains its hydrophobic chain. Consequently, this ion tends to remain within the membrane where it is initially formed. This facilitates direct visualization of membrane reactions (as by fluorescence microscopy) compared to systems in which the reactive probes eject their incipient

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fluorescent moiety into the outlying solution. Compound **2** can be obtained by preparing 7-benzoxiquinoline according to the method of Cavallito and Haskel.^[14] The quinoline (0.10 g, 0.40 mmol) and dodecyl triflate^[15] (0.40 mmol) in dichloromethane under N₂ is then refluxed overnight. Solvent is removed to give a solid which, upon trituration with diethyl ether, yields a pure white solid (m.p. 80.5–82 °C) with the correct ¹H, ¹³C, and ¹⁹F NMR spectroscopy, FAB-HRMS, and C, H, N, and S elemental analyses.

Two sets of vesicles were prepared (one with **1** and the other with **2**) in the following manner: Solvent from a solution of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (2.2 mg) in chloroform plus either 10 mol % **1** or 2 mol % **2** was removed under reduced pressure in a 5 mL round-bottom flask to form a thin film. The phospholipid film was hydrated for 5 min with 0.05 M carbonate buffer (1.0 mL; pH 9.0) under stirring, whereupon the resulting suspension was passed back and forth (19 times) through a polycarbonate membrane (100 nm pore diameter) using a LiposoFast vesicle extruder. The vesicles had mean hydrodynamic diameters of 110–130 nm (measured routinely with a Coulter N4 particle-sizer and found to remain constant before and after the kinetic runs).

As seen in Table 1, seven different reaction modes, including our controls, were carried out. All runs were initiated by bringing ester **2** to a concentration of 2×10^{-5} M in a cuvette containing buffer or buffered nucleophile. This was accom-

plished by either a) adding a 30 μ L aliquot of 2.0 mM **2** in acetonitrile to a 3.0 mL solution in a cuvette or b) adding a 1.0 mL suspension of vesicular **2** to a 2.0 mL solution in a cuvette. Nucleophile, already in the cuvette when the above additions occurred, consisted of 0.1 or 1.0 mM aqueous acetohydroxamic acid (in our control runs) or 0.1 mM vesicular **1** (in the vesicle/vesicle run). For convenience, experimental conditions are also specified in the table for each of the reaction modes. Note that all runs were carried out at 25.0 °C (a full 28 °C above the transition temperature of the carrier lipid).^[16] Thus, our results reflect exclusively the behavior of a fluid, liquid-crystalline membrane phase.

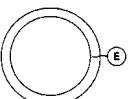
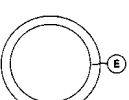
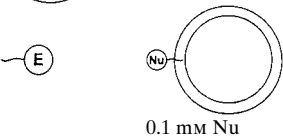
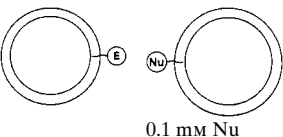
Reactions were monitored spectrophotometrically (427 nm; Varian DMS 300) and spectrofluorometrically ($\lambda_{\text{ex}} = 418$ nm, $\lambda_{\text{em}} = 521$ nm; Shimadzu RF-5000). The two methods gave rate constants that agreed, for example, to within 2% for the vesicle/vesicle reactions. All pseudo-first-order plots (processed with the aid of Microsoft Excel) were linear to greater than two half-lives. Half-lives listed in the Table 1 are averages from two to six runs in good agreement with each other. Since the infinity absorbances of the spectrophotometric runs were always within 10% of the absorbance expected from *total* hydrolysis of vesicular **2**, “flip-flop” of **2** from the inner leaflet to the outer leaflet of the bilayer (where exposure to the nucleophile occurred) must be fast on the time scale of our experiments.

Entry 1 of Table 1 shows that ester **2** in a pH 9.0 buffer at 25.0 °C hydrolyzes with a half-life $t_{1/2}$ of 38 min. Addition of 1.0 mM nucleophilic acetohydroxamate diminishes $t_{1/2}$ to 0.21 min (Table 1, entry 2). (Ester **2** is undoubtedly monomeric in the reactions given in entry 1 and entry 2 because its concentration of 2×10^{-5} M lies far below the critical micelle concentration for a 12-carbon surfactant).^[17] When the ester is incorporated into a phospholipid vesicle (Table 1, entry 3), the spontaneous hydrolysis rate becomes very slow ($t_{1/2} = 1700$ min). Presumably, the ester **2** head group resides at the membrane/water interface (owing to its cationic charge) where it is protected from attack by hydroxide. Several factors could contribute to this protection: electrostatic repulsion of hydroxide by the lipid's phosphate groups; a reduced dielectric constant at the bilayer surface; and steric inhibition at the adsorption site. The comparison between $t_{1/2} = 1700$ min (Table 1, entry 3) and $t_{1/2} = 38$ min (Table 1, entry 1) proves that a *minimum* of 98% **2** partitions into the vesicles. If, as is likely, vesicular **2** has an inherent reactivity, then the partitioning must be even greater than the minimum value.

A vesicular rate retardation was also found in the acetohydroxamate-induced hydrolyses. Thus, binding the ester to the vesicles inhibits the acetohydroxamate reaction by 162-fold (compare entry 4 and entry 2 in Table 1). Lowering the acetohydroxamate concentration from 1.0 mM to 0.10 mM (Table 1, entries 4 and 5) slows the reaction from a $t_{1/2}$ of 34 min to a $t_{1/2}$ of 180 min, respectively.

The fastest hydrolysis in our vesicle series occurred when monomeric **2** was added externally to 0.1 mM vesicular **1** (Table 1, entry 6). A half-life of only 0.75 min was observed. The most plausible explanation involves the incorporation of ester **2** into the nucleophile-bearing vesicles where a fast *intra*-vesicular hydrolysis then takes place. Electrostatic effects (i.e.

Table 1. Rates of a bimolecular reaction in vesicular systems.

Entry	Type of reaction	Schematic ^[a]	$t_{1/2}$ [min]
1	solution background	 in buffer	38
2	solution–solution	 1 mM AH	0.21
3	vesicle background	 in buffer	1700
4	vesicle–solution	 1 mM AH	34
5	vesicle–solution	 0.1 mM AH	180
6	vesicle–solution	 0.1 mM Nu	0.75
7	vesicle–vesicle	 0.1 mM Nu	4.2

[a] Carbonate buffer (0.05 M, pH 9.0) and 25 °C in all runs. Concentration of electrophile (*N*-dodecyl-7-benzoxiquinolinium triflate) = 2×10^{-5} M. AH = acetohydroxamic acid. Concentration of structural lipid (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) = 2.2 mg mL⁻¹. The Nu-bearing compound represents **1**, and the E-bearing compound represents **2**.

attraction between cationic ester **2** and vesicles rendered anionic by the presence of **1**) likely augment hydrophobic association. Adjusted for the concentration differences, the intra-vesicular reaction rate is equivalent to that of the intermolecular reaction between monomeric species (Table 1, entry 2). An entropically favorable confinement of the reactants within the bilayer assembly must evidently compensate for any inhibitory rate effects inherent to the membrane environment.

With all the control runs suitably investigated, we were able to examine the vesicle/vesicle reaction (Table 1, entry 7). Its $t_{1/2}$ of 4.2 min indicates a much faster reaction than vesicular **2** plus monomeric acetohydroxamate (Table 1, entry 4, $t_{1/2}$ = 180 min). This fact, plus the highly efficient intra-vesicular reaction evident in entry 6, suggests a reasonable mechanism for the vesicle/vesicle reaction: Collisions between vesicles containing **1** and vesicles containing **2** lead to a transfer of **2** from one vesicle population to the other.^[18] (Potent steroidal anchoring of **1** has been shown previously to prevent a corresponding migration of the nucleophile within our time-scale).^[10] A fast intra-vesicular catalyzed hydrolysis, depicted schematically in Figure 1, ensues.

A possible variation of the above vesicle-transfer mechanism was considered. Perhaps ester **2** departs from its vesicles, enters the water, and re-adsorbs into the vesicles containing nucleophile **1**. To test this idea, we studied the vesicle/vesicle reaction with an ester in which the dodecyl chain had been

replaced by an octadecyl group. Adding six more carbon atoms should seriously impede any partitioning of the ester from the membrane into the free solution. Yet the vesicle/vesicle rates with the octadecyl analogue are only fourfold smaller than with the dodecyl ester **2**. This result is fully consistent with a collision-induced vesicle-to-vesicle transfer that is mildly retarded by the longer chain length.

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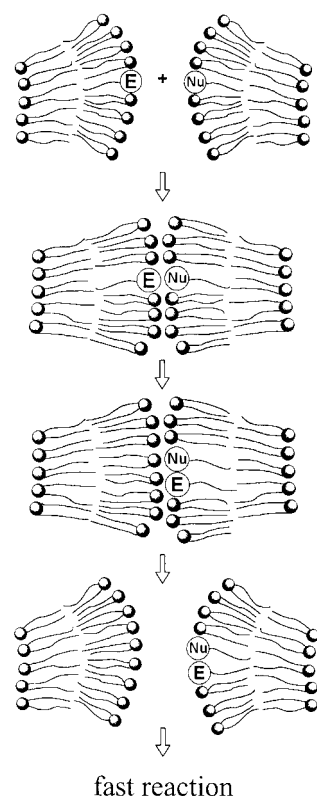


Figure 1. Proposed mechanism for a vesicle/vesicle reaction in which the vesicles collide, the electrophile gets transferred, and a fast intra-vesicular process ensues.

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Photochemical Activation of the N≡N Bond in a Dimolybdenum–Dinitrogen Complex: Formation of a Molybdenum Nitride**

Euro Solari, Carlos Da Silva, Barbara Iacono, Joëlle Hesschenbrouck, Corrado Rizzoli, Rosario Scopelliti, and Carlo Floriani*

Herein we describe a novel contribution to the developing field of N≡N bond cleavage reactions,^[1–3] in which we have for the first time cleaved the N≡N bond by using light and transition metal complexes. Only two groups^[1,2] have so far given detailed information on the pathways leading to the six-electron reduction of dinitrogen. Such a reduction is a stepwise metal-assisted transformation consisting, usually, of a four-electron reduction of N₂, leading to a dimetallahydrazine, L_nM=N–N=ML_n, followed by a final, thermally induced reductive cleavage of the residual N–N bond. The present report focuses on the generation of the d³–[Mo(Mes)₃] frag-

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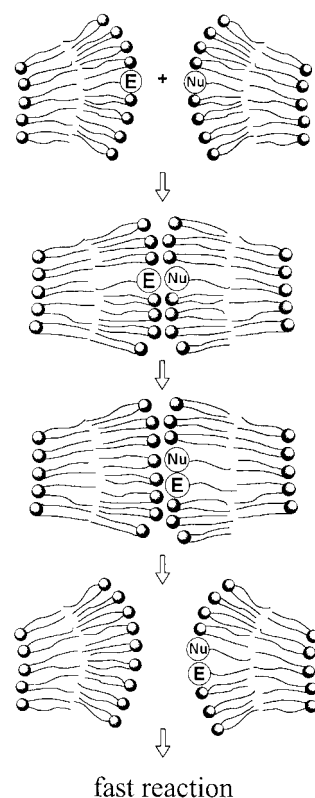


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Photochemical Activation of the N≡N Bond in a Dimolybdenum–Dinitrogen Complex: Formation of a Molybdenum Nitride**

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Herein we describe a novel contribution to the developing field of N≡N bond cleavage reactions,^[1–3] in which we have for the first time cleaved the N≡N bond by using light and transition metal complexes. Only two groups^[1,2] have so far given detailed information on the pathways leading to the six-electron reduction of dinitrogen. Such a reduction is a stepwise metal-assisted transformation consisting, usually, of a four-electron reduction of N₂, leading to a dimetallahydrazine, L_nM=N=N=ML_n, followed by a final, thermally induced reductive cleavage of the residual N–N bond. The present report focuses on the generation of the d³–[Mo(Mes)₃] frag-

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ment^[4] (Mes $\equiv$ 2,4,6-Me₃C₆H₂) as an active molecular species for achieving the four-electron reduction of dinitrogen in [(Mes)₃Mo=N=N=Mo(Mes)₃], which undergoes the photo-induced cleavage of the residual N–N bond. The wide occurrence of L_nM=N=N=ML_n functionalities^[5] that usually do not undergo further reduction to the corresponding metal nitrides makes the discovery of their potential photolability particularly interesting with regard to dinitrogen reduction.

Arylation of [MoCl₄·DME] in DME by using precisely four equivalents of MesMgBr led to a blue-green solution which slowly absorbs dinitrogen until a N₂:Mo molar ratio of 1:2 is reached. The solution turns red at the end of the N₂ absorption. The reaction solvent was evaporated to dryness, then the solid was extracted with benzene. The extraction, which can be equally well run either under N₂ or Ar, gave **1** in 60% yield as a red crystalline solid. The overall reaction producing **1** can be viewed as a reductive arylation of [MoCl₄·DME], leading formally to [Mo(Mes)₃], which performs the dinitrogen fixation. The proposed structure of **1** is supported by the results of an X-ray structure analysis (Figure 1).^[6, 9b] The three mesityl groups and the nitrogen atoms around each

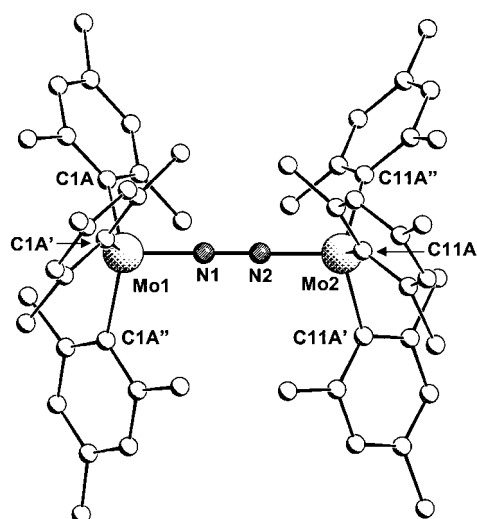
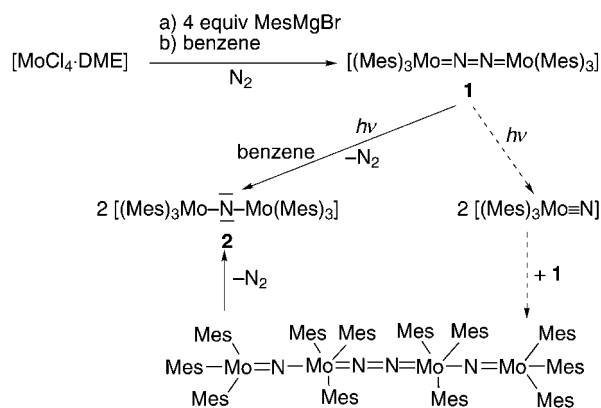


Figure 1. Structure of complex **1** (SCHAKAL drawing). Selected bond lengths [Å] and angle [°]: Mo1–N1 1.794(9), Mo2–N2 1.818(9), Mo1–C1A 2.131(7), Mo2–C11A 2.136(5), N1–N2 1.243(13); Mo1–N1–N2 = Mo2–N2–N1 180.0(–). Symmetry transformations: ' : –y, x – y, z; '' : –x + y, –x, z.

Mo center display a trigonal-pyramidal arrangement; Mo1 and Mo2 are displaced by 0.384(1) and 0.480(1) Å, respectively, from the basal plane towards the nitrogen atoms. The Mo–N_{av} (1.806(9) Å) and N–N distances (1.243(13) Å) support the cumulene structure and a significant degree of reduction of dinitrogen. Complex **1** is paramagnetic, with a μ_{eff} value of 1.54 μ_{B} at 298 K. This value is quite unusual,^[1] and might be explained by population of both the singlet and the triplet state of the [Mo^V–N₂–Mo^V] skeleton.^[7]

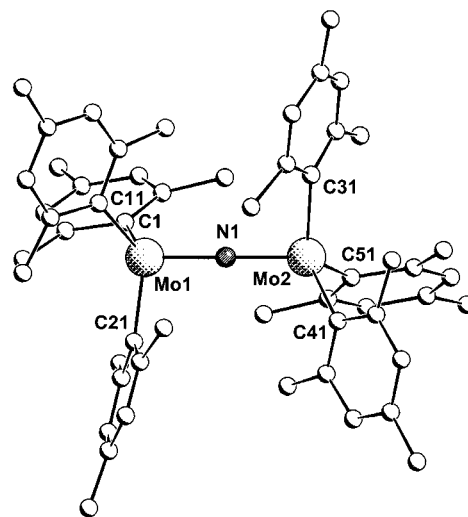
It should be mentioned that there is a major difference between the [Mo(Mes)₃] fragment and the [Mo(NR_{Ar})₃] (R = *t*Bu; Ar = 3,5-Me₂C₆H₃) fragment from the work by Cummins and co-workers.^[1] In the latter case, the σ - and π -donor properties of the ligand induce the spontaneous thermal cleavage of the N–N bond. Complex **1** is thermally

resistant (refluxing benzene), so that the cleavage of the residual N–N bonds was not achieved by such a pathway. In contrast, when a solution of **1** in benzene was exposed to UV light (λ = 365.0 nm), **2** was formed in good yield (79%). This finding supports the proposed pathway shown in Scheme 1. The photochemically induced cleavage of the



Scheme 1. The combined metal- and light-assisted cleavage of the N=N bond. Mes = 2,4,6-Me₃C₆H₂.

N–N bond presumably produces the monomeric nitride [(Mes)₃Mo≡N],^[8] which acts as a Lewis base on the as yet unreacted **1**, thus forming **2** and leading to the observed 50% loss in the dinitrogen content. The reaction of [(Mes)₃Mo≡N], synthesized according to the literature,^[8] with **1** is consistent with the proposed mechanism given in Scheme 1. The reaction led quantitatively to **2**, with the complete loss of N₂. Complex **2** is paramagnetic (μ_{eff} = 1.68 μ_{B} at 298 K), as expected for a doublet configuration, and its structure is displayed in Figure 2.^[9] Both metal atoms have a slightly distorted tetrahedral



though the Mo–N–Mo angle ($179.1(3)^\circ$) is in agreement with a bridging sp nitrogen atom.^[10] We believe that in the present case the structural parameters are the consequence of a particularly congested structure.

The photochemically induced cleavage of the N–N bond in a dimetalladinitrogen complex is a quite unique finding in this field and should provide new stimulus on how to achieve dinitrogen activation by the use of metals and light.^[11]

Experimental Section

1: A solution of MesMgBr (177.6 mL, 1.01 M, 179.4 mmol) in THF was added dropwise to a suspension of $[\text{MoCl}_4 \cdot \text{DME}]$ (14.70 g, 44.83 mmol) in DME (300 mL) cooled at -20°C . The brown suspension, which was allowed to warm to 20°C under stirring, turned blue-green in about 3 h. At this stage the N_2 absorption started and continued for 3 days. The gas-volumetric measurements showed the absorption of N_2 had taken place in a N_2 :Mo molar ratio of 1:2. The final red suspension was evaporated to dryness; all traces of THF were removed completely. The red residue, which was extracted with benzene, gave a purple solution. This solution was evaporated to dryness to give **1** (60%) as a powder containing very small amounts of magnesium salts. Further purification was achieved by extracting the solid with *n*-hexane. Dark red crystals of **1** suitable for X-ray analysis were obtained from a $\text{C}_6\text{H}_6/n$ -hexane mixture, as **1** · 1.5 THF. ^1H NMR ($[\text{D}_6]\text{benzene}$, 400 MHz, 25°C): δ = 66.98 (s, 18H; CH_3), 46.26 (s, 36H; CH_3), 25.63 (s, 12H; ArH); μ_{eff} (298 K) = $1.54 \mu_{\text{B}}$; elemental analysis calcd (%) for $\text{C}_{54}\text{H}_{66}\text{Mo}_2\text{N}_2$ (935.0): C 69.37, H 7.11, N 3.00; found: C 69.58, H 7.23, N 2.81. Complex **1** is thermally stable, but not photochemically stable in benzene.

2: A purple solution of **1** (2.12 g, 2.27 mmol) in benzene (125 mL) was irradiated with a high-pressure mercury lamp (λ = 365.0 nm) for 18 h. The purple solution turned green. The solvent was evaporated to dryness, and *n*-hexane (30 mL) was added to give a green powder which was collected and dried in vacuo (1.65 g, 79%). Recrystallization of the powder from $\text{C}_6\text{H}_6/n$ -hexane gave crystals of **2** · THF suitable for X-ray analysis. Elemental analysis calcd (%) for $\text{C}_{54}\text{H}_{66}\text{Mo}_2\text{N}$ (920.0): C 70.42, H 7.22, N 1.52; found: C 70.23, H 7.09, N 1.57; μ_{eff} (298 K) = $1.68 \mu_{\text{B}}$. A by-product of the photochemical reaction is a small amount of mesitylene, as confirmed by NMR spectroscopy and GC-MS. When the reaction was carried out in a gas-volumetric apparatus, 50% of the N_2 content was evolved.

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Synthesis of Exceptionally Stable Iron and Ruthenium η^1 -tetrahedro-Tetraphosphorus Complexes: Evidence for a Strong Temperature Dependence of M–P₄ π Back Donation**

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In recent years the coordination chemistry of white phosphorus has been carefully investigated and a plethora of transition metal complexes containing P_x fragments derived from either the degradation (P, P₂, and P₃ ligands) of the P₄ tetrahedron or the reaggregation (up to P₁₂) of fragments thereof have been synthesized and characterized.^[1] Considerable effort has been invested in the synthesis of stable coordination compounds containing the intact P₄ molecule, but in spite of the many attempts and of the existence of an old example, [[N(CH₂CH₂PPh₂)₃]Ni(η^1 -P₄)] (**1**),^[2] it is generally considered more easy to reductively open one,^[3] two,^[4] or three^[5] bonds of the P₄ tetrahedron than to coordinate the P₄ molecule as an intact η^1 -end-on ligand. Only recently, however, η^1 -P₄ compounds have been described either as thermally unstable species, [[P(CH₂CH₂PPh₂)₃]M(η^1 -P₄)]OTf (M = Co (**2**), Rh (**3**); OTf = OSO₂CF₃)^[6] and [M(CO)₃-(PR₃)₂(η^1 -P₄)] (M = W, R = Cy (**4**), iPr (**5**); M = Mo, R = Cy (**6**)),^[7] or as a slightly air-sensitive solid, [[MeC(CH₂PPh₂)₂]Re(CO)₂(η^1 -P₄)]Y (Y = OTf, BPh₄ (**7**)).^[8] In all of these compounds, which were characterized by either X-ray diffraction (**1**, **4**) or ³¹P NMR spectroscopy (**2**–**7**), the P₄ molecule is bonded to the organometallic fragment through a lone pair of electrons on one of the phosphorus atoms. Beautiful examples of thermally unstable side-on P₄ complexes have recently been reported.^[9]

We report here on the synthesis and the chemical-physical characterization of a family of novel η^1 -tetrahedro-tetraphosphorus complexes of iron and ruthenium of formula [Cp*M(L)₂(η^1 -P₄)]Y (L = phosphane or diphosphane ligand; M = Fe, Ru) which exhibit an exceptional stability in comparison to the few known η^1 -P₄ derivatives as well as to the free phosphorus molecule. Some preliminary data illustrating the electronic structure and reactivity of the new tetraphosphorus complexes are also provided.

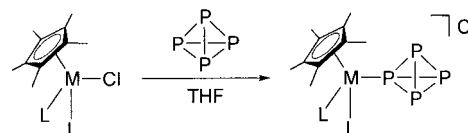
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Reaction of [Cp*M(L)₂]Cl (Cp* = η^5 -C₅Me₅; M = Fe,^[10] L₂ = Ph₂PCH₂CH₂PPh₂; M = Ru,^[11] L = PET₃, L₂ = Ph₂PCH₂CH₂PPh₂) with one equivalent of P₄ in THF at room temperature under a nitrogen atmosphere leads to removal of chloride and coordination of the P₄ molecule through one lone pair of electrons on phosphorus (Scheme 1). Addition of



Scheme 1. Synthesis of the P₄-transition metal complexes **8**–**10**. **8**: M = Fe, L = 1/2 dppe; **9**: M = Ru, L = PET₃; **10**: M = Ru, L = 1/2 dppe; dppe = Ph₂PCH₂CH₂PPh₂.

ethanol/*n*-hexane (1:2 v/v) and slow concentration of the resulting solution under a brisk current of nitrogen affords reddish purple (M = Fe) or orange (M = Ru) microcrystalline solids of formula [Cp*M(L)₂(η^1 -P₄)]Cl (M = Fe, L₂ = Ph₂PCH₂CH₂PPh₂ (**8**-Cl); M = Ru, L = PET₃ (**9**-Cl), L₂ = Ph₂PCH₂CH₂PPh₂ (**10**-Cl)) in excellent yields (> 80 %). Metathesis with NH₄PF₆, NaBPh₄, or NaBAR₄ (Ar = B(CF₃)₃C₆H₂) yields the corresponding hexafluorophosphate or tetraarylborate salts, respectively. Complexes **8**–**10** are thermally and air stable in the solid state, and dissolve in most common organic solvents. The iron derivative slowly decomposes in halogenated hydrocarbons to give back the chloride adduct, while the ruthenium salts are readily crystallized from dichloromethane/ethanol mixtures without decomposition even under aerobic conditions.

The coordination of the intact P₄ molecule as a *tetrahedro*- η^1 -P₄ ligand has been ascertained by X-ray diffraction analysis on crystals of **8**-BPh₄ grown by slow diffusion of *n*-pentane into a saturated solution of the complex in THF.^[12] The X-ray analysis reveals the expected η^1 -coordination of the tetraphosphorus ligand (Figure 1) with the iron atom Fe1 coordinated in a roughly octahedral arrangement by the two dppe P-donor atoms and the Cp* ring occupying three contiguous sites of the coordination polyhedron.

The Fe–P_{apical} distance is 2.1621(7) Å and is considerably shorter than the Fe–P distances in the related complexes prepared by Scherer et al., namely *exo,exo*-butterfly complex [(C₅H₂tBu₃)(CO)Fe]₂(μ , $\eta^{1:1}$ -P₄)] (*d*_{Fe–P_{av}} = 2.3516 Å)^[13] and the diiron species [(C₅H₃tBu₂)Fe](μ , $\eta^{4:1}$ -P₄)[Fe(CO)(C₅H₃-tBu₂)]^[14] in which the *exo*-cyclic Fe– η^1 -P₄ separation (2.211(1) Å) is still slightly longer than in **8**-BPh₄. The bond lengths within the P₄ molecule are slightly dissimilar; the basal P–P separation ranges between 2.2033(11) and 2.2363(11) Å and hence is longer than the *d*_{P_{apical}–P_{basal}} distances which vary from 2.1589(10) to 2.1664(10) Å. This type of deformation of the coordinated tetraphosphorus ligand is opposite to that found in **1** (*d*_{P_{basal}–P_{basal}} = 2.20(3) Å; *d*_{P_{apical}–P_{basal}} = 2.09(3) Å),^[2] but parallels the values reported by Scheer for the tungsten derivative **4** (av *d*_{P_{basal}–P_{basal}} = 2.190 Å; av *d*_{P_{apical}–P_{basal}} = 2.172 Å).^[7] The P₄ tetrahedron in the latter compound is less compressed than that in **8**, probably reflecting the differences in the distribution of the overall electron density in the two

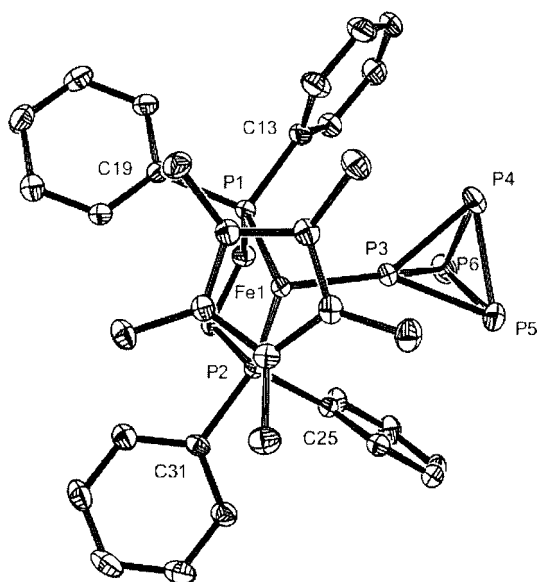


Figure 1. Structure of the complex cation in **8**-BPh₄ (ORTEP drawing). Selected bond lengths [Å] and angles [°]: Fe–P1 2.2343(7), Fe–P2 2.2502(7), Fe–P3 2.1621(7), P3–P4 2.1664(10), P3–P5 2.1615(10), P3–P6 2.1589(10), P4–P6 2.2112(12), P4–P5 2.2363(11), P5–P6 2.2033(11), Fe–Cp*_{centroid} 1.758(2); P3–Fe–P1 88.62(3), P3–Fe–P2 93.02(3), P1–Fe–P2 85.41(3).

isoelectronic d⁶ complexes (W⁰ vs. Fe^{II}) and the cationic charge of **8**.^[15]

The ⁵⁷Fe Mössbauer spectra recorded in the temperature window between 77 and 350 K exhibit *QS* parameters typical for [Cp*Fe(dppe)(L)]Y complexes containing an η^1 -coordinated L ligand, but quite large isomeric shifts ranging from 0.31 to 0.40 mm s^{−1}. In the rich family of [Cp*Fe(dppe)] complexes, δ values from ⁵⁷Fe Mössbauer spectra generally fall in the range between 0.15 and 0.30 mm s^{−1} and increase when the electron-releasing properties of L decrease. It is also noteworthy that for **8**-BPh₄ the δ parameter depends on the temperature; this is rather unusual for iron piano-stool complexes. The decrease of δ with temperature suggests that the electron density at the metal center increases with temperature. Accordingly, the π back donation could be weaker at high temperature.

The P₄ molecule remains firmly coordinated to the metal center in solution; the complexes **8**–**10** exhibit a temperature-invariant first-order A₂MX₃ pattern in the ³¹P NMR spectra. The four naked phosphorus atoms form the MX₃ part of the spectrum with the three nonmetalated atoms exhibiting a doublet at $\delta \sim -484$ roughly independent of the metal and the ancillary phosphane ligand(s). In contrast, the unique P atom of the P₄ unit coordinated to the metal (P_M) features a quartet of triplets shifted downfield with respect to the signal for free P₄ ($\delta = -526.9$). Remarkably, the iron complex displays the largest coordination chemical shift ($\delta_M = -299.54$) suggesting a considerable perturbation of the electronic density in the P₄ tetrahedron and pointing to a strong π back donation from the metal to the P₄ ligand.

Consistent with this intriguing view of the electronic structure of **8**, variable-temperature ³¹P{¹H} NMR measurements show that the high-field P_M multiplet experiences a quite surprising temperature dependence moving steadily

from $\delta = -289.22$ at -80°C to -303.01 at 40°C ($\Delta = \delta_{313\text{K}} - \delta_{193\text{K}} = 13.79$). Neither the P_X ($\Delta = 2.74$) nor the dppe ($\Delta = 1.24$) doublets exhibit such unusual temperature dependence of the chemical shift.^[16]

The reactivity of the robust *tetrahedro*-tetraphosphorus complexes described here is under scrutiny. Preliminary data indicate that once coordinated to the metal center the P₄ molecule is extremely resistant to oxidants, such as *meta*-chloroperbenzoic acid, H₂O₂, or O₂, and nucleophiles, such as water and alcohols, but still endowed with reactivity towards electrophilic transition metal moieties. Thus, bimetallic clusters incorporating a bridging P₄ ligand may be readily synthesized. As an example the heterobimetallic complexes [Cp*Fe(dppe)($\mu, \eta^{1:1}$ -P₄)]{Re(CO)₂[MeC(CH₂PPh₂)₃]}(BPh₄)₂, [Cp*Ru(PEt₃)₂($\mu, \eta^{1:1}$ -P₄)]{Re(CO)₂[MeC(CH₂PPh₂)₃]}(BPh₄)₂ and [Cp*Ru(dppe)($\mu, \eta^{1:1}$ -P₄)]{W(CO)₅}(BPh₄) were prepared by treating **8**, **9**, and **10** in THF with [[MeC(CH₂PPh₂)₃]-Re(CO)₂(OTf)] and [W(CO)₅(thf)], respectively.^[17] Remarkably, the reaction of **10** with iodine is straightforward and produces four equivalents of PI₃ at room temperature. One molecule of PI₃ is efficiently scavenged by the metal fragment affording the very rare PI₃ metal complex [Cp*Ru(dppe)-(PI₃)]BPh₄.^[18]

Experimental Section

General procedure for the synthesis of complexes **8**–**10**: A solution of [Cp*M(L₂)Cl] (M = Fe, L₂ = Ph₂PCH₂CH₂PPh₂; M = Ru, L = PEt₃, L₂ = Ph₂PCH₂CH₂PPh₂) (0.50 mmol) in THF (20 mL) was treated at 25 °C with a small excess of white phosphorus (0.08 g, 0.64 mmol) under nitrogen. Addition of ethanol/*n*-hexane (10 mL, 1:2 v/v) and slow concentration of the resulting solution under a current of nitrogen gave purple (**8**) or orange (**9**, **10**) microcrystals of the η^1 -P₄ complexes [Cp*M(L₂)(η^1 -P₄)]Cl (M = Fe, L₂ = Ph₂PCH₂CH₂PPh₂) (**8**-Cl); M = Ru, L = PEt₃ (**9**-Cl), L₂ = Ph₂PCH₂CH₂PPh₂) (**10**-Cl)) in yields higher than 80%. The solid complexes were filtered under nitrogen and washed twice with ethanol (2 × 3 mL) and light petroleum ether (2 × 5 mL). Metathesis with NaBPh₄ in THF/EtOH afforded the corresponding tetraphenylborate salts.

8-BPh₄: Purple crystals, yield 80%; ³¹P{¹H} NMR (81.01 MHz, [D₆]acetone, 20 °C, H₃PO₄, A₂MX₃ pattern): $\delta_A = 87.49$, $\delta_M = -299.54$, $\delta_X = -482.12$, $J(P_A, P_M) = 39.1$, $J(P_A, P_X) \sim 0$, $J(P_M, P_X) = 228.9$ Hz; ¹H NMR (200.13 MHz, CD₂Cl₂, TMS): $\delta = 1.49$ (br d, $J(H, P_M) = 1.8$ Hz, 15 H; C₅(CH₃)₅); MS (FAB +, *o*-nitrophenyl *n*-octylether): m/z (%): [M^+], 713 (4), [$M^+ - P_4$], 589 (100); elemental analysis calcd (%) for C₆₀H₅₉BFeP₆: C 69.79, H 5.76; found: C 69.45, H 5.79.

9-BPh₄: Orange crystals, yield 86%; ³¹P{¹H} NMR (81.01 MHz, CD₂Cl₂, 20 °C, H₃PO₄, A₂MX₃ pattern): $\delta_A = 20.97$, $\delta_M = -332.05$, $\delta_X = -480.96$, $J(P_A, P_M) = 55.3$, $J(P_A, P_X) \sim 0$, $J(P_M, P_X) = 228.9$ Hz; ¹H NMR (200.13 MHz, CD₂Cl₂, TMS): $\delta = 1.61$ (dt, $J(H, P_M) = 5.1$, $J(H, P_A) = 1.5$ Hz, 15 H; C₅(CH₃)₅); ¹³C{¹H} NMR (50.32 MHz, CD₂Cl₂, 20 °C, TMS): $\delta = 9.95$ (s; P(CH₂CH₃)₃), 11.23 (s; C₅(CH₃)₅), 22.20 (td, $J(C, P_A) = 13.3$, $J(C, P_M) = 5$ Hz, P(CH₂CH₃)₃), 96.90 (s; C₅(CH₃)₅); elemental analysis calcd (%) for C₄₆H₆₅BP₆Ru: C 60.33, H 7.15; found: C 60.03, H 7.33.

10-BPh₄: Orange crystals, yield 90%; ³¹P{¹H} NMR (81.01 MHz, CD₂Cl₂, 20 °C, H₃PO₄, A₂MX₃ pattern): $\delta_A = 70.44$, $\delta_M = -308.46$, $\delta_X = -490.29$, $J(P_A, P_M) = 44.1$, $J(P_A, P_X) \sim 0$, $J(P_M, P_X) = 233.5$ Hz; ¹H NMR (200.13 MHz, CD₂Cl₂, TMS): $\delta = 1.53$ (dt, $J(H, P_M) = 5.0$, $J(H, P_A) = 1.9$ Hz, 15 H; C₅(CH₃)₅); ¹³C{¹H} NMR (50.32 MHz, CD₂Cl₂, 20 °C, TMS): $\delta = 10.54$ (s; C₅(CH₃)₅), 22.50 (vt, $J(C, P_A) = 22.3$ Hz, CH₂), 97.13 (s; C₅(CH₃)₅); MS (FAB +, *o*-NPOE): m/z (%): [M^+] 759 (13), [$M^+ - P_4$] 635 (100); elemental analysis calcd (%) for C₆₀H₅₉BP₆Ru: C 66.86, H 5.52; found: C 66.67, H 5.38.

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- [18] The deep orange complex [Cp*Ru(dppe)(PI₃)]BPh₄ may be prepared from **10-BPh₄** and excess I₂ in CHCl₃. The compound was characterized by elemental analysis and NMR spectroscopy. I. de los Rios, M. Peruzzini, A. Romerosa, unpublished observations.

A Dual Channel Fluorescence Chemosensor for Anions Involving Intermolecular Excited State Proton Transfer**

Kihang Choi and Andrew D. Hamilton*

Effective fluorescence chemosensors must convert molecular recognition into changes in fluorescence that are both highly sensitive and easy to detect. A key issue in sensor design is the connection of substrate binding in a recognition domain to photophysical changes in a fluorophore with optimal sensitivity.^[1] In recent years there has been great interest in anion recognition and sensing, because of their importance in biological and environmental settings.^[2] Many fluorescence anion sensors utilizing competitive binding,^[3] photo-induced electron transfer,^[4] metal-to-ligand charge transfer,^[5] and excimer/exiplex formation^[6] mechanisms have been developed. Surprisingly, the strategy of linking a fluorophore with emission from an internal charge transfer (CT) excited state to an ion-binding domain, while widely used for cation sensing, has been rarely exploited for anion sensing.^[1a, 7] Anion binding close to the fluorophore could lead to the stabilization of positive charge developed in the fluorophore excited state and to the opening of another fluorescence emission channel through intermolecular excited state proton transfer (ESPT)^[8] (Figure 1). Herein we report the preparation of anion sensors using this strategy and show that one of them can function as a dual-channel sensor system.

As the anion-binding domain we used macrocycle **1** which can bind certain anions strongly and selectively through hydrogen bonding to the three amide NH groups.^[9] In a first design, we attached covalently a fluorophore onto the periphery of **1**. 4-Trifluoromethyl-7-aminocoumarin, which possesses an excited state where negative charge is transferred from the nitrogen atom to the coumarin ring,^[10] was connected to the monocarboxy derivative of **1** to give **2** (Boc = *tert*-butoxycarbonyl).^[11, 12] This fluorophore-appended macrocycle showed modest changes in the intensity of its fluorescence emission upon addition of different anions. The binding constants were determined by fluorescence titration and showed high selectivity for tetrahedral anions such as H₂PO₄⁻ (Table 1), which mirrors the properties of **1**. Although this high selectivity (especially for phosphate over chloride) is desirable for sensing applications,^[2a, c] the changes in emission intensity and wavelength (+2 nm for H₂PO₄⁻) induced by anion binding were small. It appears that the negative charge on the bound anion is not effectively positioned to interact with the increasing positive charge on the nitrogen atom of the fluorophore, and has little effect on the excited-state energy.^[13]

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[**] We thank the National Institutes of Health for financial support of this work.

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

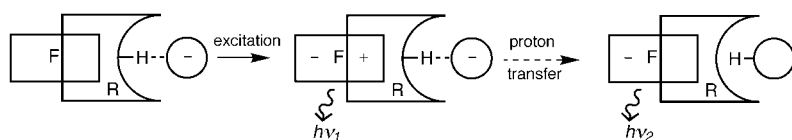
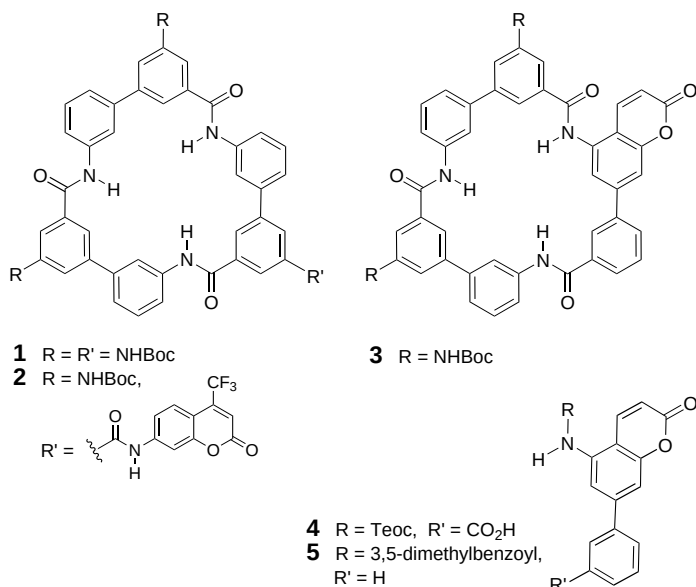


Figure 1. Two possible fluorescence emission channels from a CT excited state. An anion receptor (R) is connected to the electron-donating terminal of a fluorophore (F). Anion binding stabilizes the CT excited state by electrostatic interaction. The proton that becomes acidic by the localized positive charge on F is transferred to the anion and the second emission channel is opened.



The sensitivity problem was addressed by integrating the fluorophore into the macrocyclic ring in order to involve the coumarin NH group directly in hydrogen bonding to the anion. Preparation of this second-generation sensor centered on the synthesis of a fluorescent biphenyl monomer that could be incorporated into the modular macrocycle synthesis. Compound **4** (Teoc = 2-trimethylsilyloxyethylcarbonyl) was selected as the fluorescent monomer and synthesized in five steps from methyl 3,5-dihydroxy-2-formylbenzoate.^[14] This monomer was successfully incorporated into macrocycle **3** with a final cyclization yield of 30%.^[11, 15]

The anion-binding properties of **3** were similar to those of **2** (Table 1), with no significant difference in the association constants or the high selectivity for H₂PO₄[−] ions. However, the changes in the intensity of the fluorescence emission and wavelength were much stronger and anion dependent (Figure 2). The binding of all tetrahedral anions studied caused an increase in the fluorescence intensity and a red-shift of the peak maximum (10–20 nm). This red-shift is presumably the result of stabilization of the fluorophore excited state relative to the ground state on anion binding. There was

no change in the UV absorption spectrum of **3** on anion binding, which suggests that the intensity enhancement may be a consequence of a restriction in the conformational flexibility that would otherwise lead to nonradiative decay through rotatory motion of the amide group.^[10] The most remarkable change was the appearance of a second emission band at longer λ_{em} values. Titration of **3** with H₂PO₄[−] ions gave a simultaneous increase in the intensity of two bands, which, excitation spectra showed, came from the same ground state (Figure 3a).^[16] The maximum intensity change of this second band was largest for the most basic H₂PO₄[−] ion, modest for PhPO₃H[−] ions, and absent with the least basic tetrahedral anion studied, pTsO[−].

This correlation of the second emission band with bound anion basicity suggested that proton transfer from the fluorophore excited state was occurring. Although detailed photophysical studies are required to fully understand this phenomenon, the fluorescence properties of control molecule

Table 1. Association constants K_a (M^{−1}) and maximum intensity changes F/F_0 of macrocycle **2** and **3** with tetrabutylammonium salts.^[a]

Anion	2 K_a (F/F ₀)	3 K_a (F/F ₀)
Cl [−]	< 1000	< 1000
pTsO [−]	N/A ^[b]	3.8 × 10 ³ (2.55)
PhPO ₃ H [−]	5.9 × 10 ⁵ (0.63)	6.3 × 10 ⁵ (5.61) ^[c]
H ₂ PO ₄ [−]	2.7 × 10 ⁶ (0.56)	2.0 × 10 ⁶ (13.7) ^[c]

[a] [**2**] = 2 μ M, [**3**] = 3 μ M in 1/1 DMSO/1,4-dioxane. The emission change with the biggest $F - F_0$ value was curve-fitted to a 1/1 binding mode, and the F/F_0 value at this wavelength is included in parenthesis. The 1/1 binding stoichiometry was determined by the linearity of Benesi–Hildebrand plots.^[17] Estimated errors of association constants are within $\pm 15\%$. [b] Not available because of the small intensity change. [c] Calculated from ESPT emission bands.

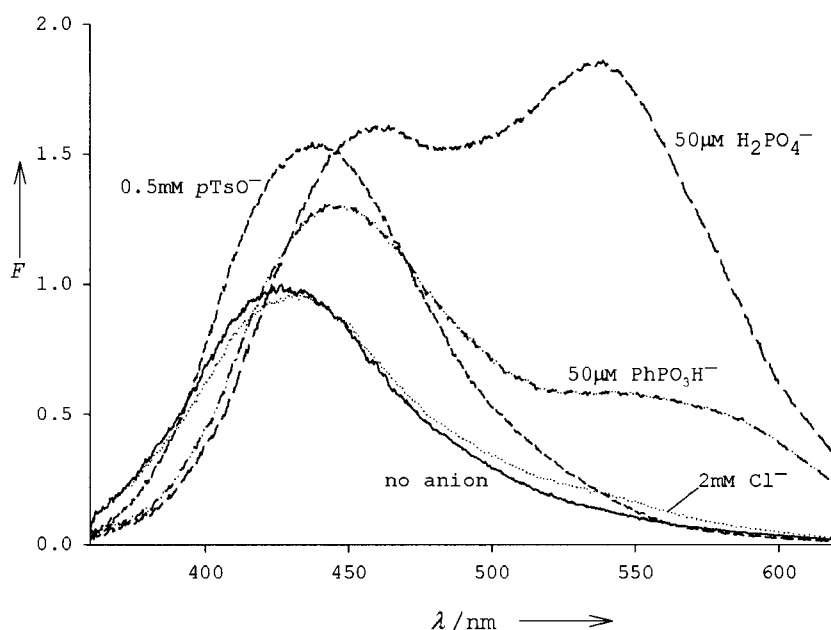


Figure 2. Emission spectra (λ_{ex} = 320 nm) of **3** (3 μ M in 1/1 DMSO/1,4-dioxane) with different anions.

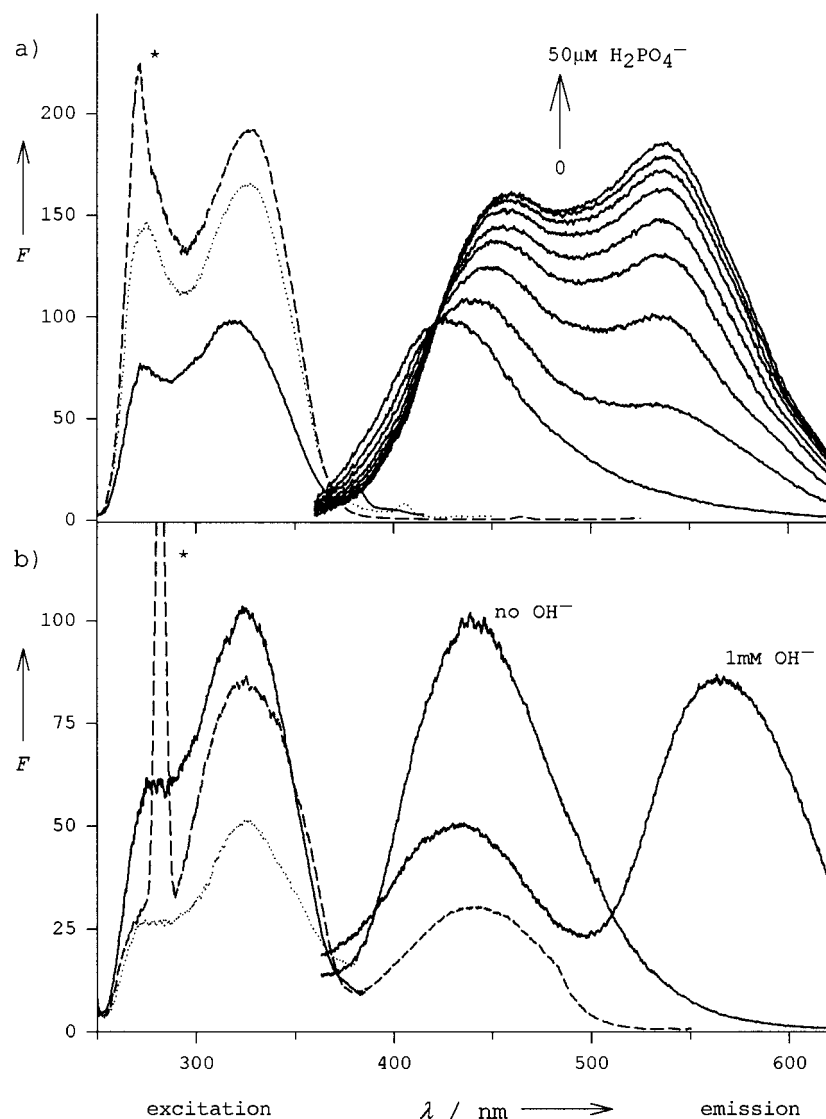


Figure 3. Excitation and emission spectra ($\lambda_{\text{ex}} = 320$ nm) of **3** and **5**. a) Excitation spectrum of **3** ($3 \mu\text{M}$) without (—, $\lambda_{\text{em}} = 429$ nm) and with $50 \mu\text{M H}_2\text{PO}_4^-$ (••••, $\lambda_{\text{em}} = 459$ nm; ---, $\lambda_{\text{em}} = 537$ nm). b) Excitation spectrum of **5** ($1 \mu\text{M}$) without (—, $\lambda_{\text{em}} = 440$ nm) and with 1 mM OH^- (••••, $\lambda_{\text{em}} = 434$ nm; ---, $\lambda_{\text{em}} = 565$ nm). (* : artifact caused by the second-order transmission.)

5 containing only one labile proton and no anion binding domain are informative. The addition of 1 mM tetrabutylammonium hydroxide increased the intensity of the UV absorption of **5** overall and a new lowest absorption band appeared around 440 nm and these changes were reversible and indicated partial deprotonation of the amide proton in the ground state. Compound **5** showed similar λ_{ex} and λ_{em} values as **3** and the second emission band was also observed under basic conditions (Figure 3b). The excitation spectrum ($\lambda_{\text{em}} = 565 \text{ nm}$) clearly shows that two pathways for this second band exist: direct excitation from the deprotonated ground state ($\lambda_{\text{ex}} = 443 \text{ nm}$) and excitation from the nondeprotonated ground state ($\lambda_{\text{ex}} = 320 \text{ nm}$) followed by deprotonation (proton transfer) from the excited state. The difference in the pK_a values between the ground and excited states was calculated as 14 by application of the Förster equation.^[8a, 12b] Addition of H_2PO_4^- ions (up to 1 mM) to the solution induced little change in the

UV and fluorescence spectra of **5**, which indicates that both the decrease in the pK_a value of the excited state and the increased local concentration of bound anion are necessary for proton transfer to weakly basic anions to occur at low anion concentration. An excitation spectrum of **3** complexed with H_2PO_4^- ions shows (Figure 3a) that proton transfer occurs only from the excited state.

In conclusion, we have presented a new mechanism for anion sensing by fluorescence spectroscopy that is based on proton transfer from a fluorophore excited state. The increased acidity of the fluorophore in the CT excited state was combined with selective recognition of the anion to open an ESPT channel in addition to a CT channel. Emissions from the two channels showed different anion dependencies and, as a result, more selective and sensitive sensing was achieved.

Experimental Section

Fluorescence spectra were obtained on a Hitachi F-4500 spectrophotometer with 5 nm excitation and emission slit widths. All stock solutions of anions and compounds were prepared in DMSO and the concentration was adjusted by adding DMSO and 1,4-dioxane (anhydrous grades from Aldrich) before recording the spectra. Association constants were determined by titrating a sensor solution with a tetrabutylammonium salt solution containing the sensor at its initial concentration. The intensity changes were analyzed by nonlinear regression methods using SigmaPlot (Version 5.0, SPSS Inc.). See the Supporting Information for the synthesis and characterization of compounds **2–5**.

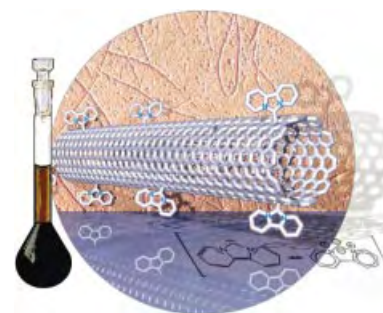
Received: July 6, 2001 [Z17447]

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COVER PICTURE

The cover picture shows a single-walled carbon nanotube (SWNT) functionalized with nucleophilic carbenes at the sidewall. Normally, single-walled nanotubes exist in the form of insoluble bundles. The sidewall addition of reactive organic groups such as radicals, nitrenes, or carbenes such as the ones shown in the cover picture disrupts the bundles. The background of the picture shows a typical AFM image of such derivatized SWNTs. The isolated SWNTs are soluble in organic solvents giving black solutions. This enables a spectroscopic characterization of nanotubes in solution. With this versatile sidewall functionalization the decisive requirements for the development of technological applications such as the production of ultrathin films or the processing to polymer composites with new electronic and mechanic properties have been compiled. Details about this new chemical functionalization of SWNTs is described by Hirsch et al. on pp. 4002 ff.

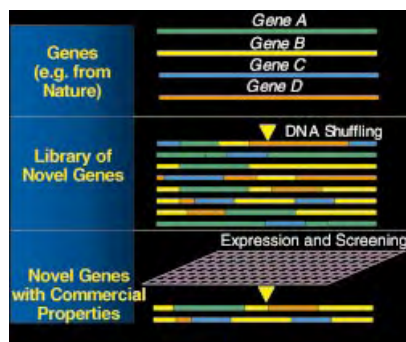


REVIEWS

Contents

Advances in directed molecular evolution are now having an impact on the field of biocatalysis. One can envision biocatalytic processes in which the enzyme has been designed to operate under optimal process conditions (see picture), instead of processes in which the conditions have been constrained to accommodate the enzyme.

Angew. Chem. **2001**, *113*, 4068–4080

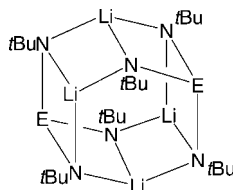


K. A. Powell,* S. W. Ramer,
S. B. delCardayré, W. P. C. Stemmer,
M. B. Tobin, P. F. Longchamp,
G. W. Huisman 3948–3959

Directed Evolution and Biocatalysis

Keywords: directed evolution •
DNA shuffling • enzyme catalysis •
enzyme libraries • proteins

The full or partial replacement of oxygen in salts of common oxo anions by imido (NR) groups generates a new class of polycyclic compounds. These ternary or quaternary clusters adopt structures derived from the aggregation of the simple building blocks formed by binary imido systems. The appropriate choice of NR groups may allow the production of functional materials with specific applications. These anions are also attracting attention as multidentate ligands with unusual electronic and stereochemical characteristics that may lead to new metal-centered chemistry. In the ternary cluster shown, E = S, Se, Te.



J. K. Brask, T. Chivers* 3960–3976

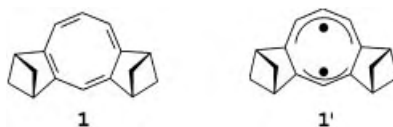
Imido Analogues of Common Oxo Anions: A New Episode in the Chemistry of Cluster Compounds

Keywords: cluster compounds • coordination modes • isoelectronic analogues • main group elements • transition metals

Angew. Chem. **2001**, *113*, 4082–4098

MINIREVIEW

A negligible antiaromatic destabilization is found in planar D_{4h} 1,3,5,7-cyclooctatetraene with alternating bond lengths. The same is also true for the delocalized D_{8h} structure, which has a stabilization energy of only 3–4 kcal mol⁻¹. According to quantum-chemical calculations, the ground state of **1** is expected to be the planar C_{2v} -symmetric (1,1) singlet diradical **1'**.



F.-G. Klärner* 3977–3981

About the Antiaromaticity of Planar Cyclooctatetraene

Keywords: antiaromaticity • cyclooctatetraene • diradicals • resonance energy

Angew. Chem. **2001**, *113*, 4099–4103

VIPs

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

Fluorescence Quenching via Sequential Hydrogen, Electron, and Proton Transfer in the Proximity of a Conical Intersection

Origin of Ferromagnetism in Cyano-Bridged Compounds Containing d^1 Octacyanomethylates

Lewis Acid/Base Stabilized Phosphanylalane and -gallane

Towards the Understanding of Solid-State Structures: From Cubic to Chain-like Arrangements in Group 11 Halides

Homogeneous Reactions in Supercritical Carbon Dioxide by Using a Catalyst Immobilized in a Microporous Silica Membrane

Design and Synthesis of a Peptide that Binds Specific DNA Sequences through Simultaneous Interaction in the Major and in the Minor Groove

Cesiumauride Ammonia (1/1: CsAu · NH₃)—A Crystalline Analogue of Alkali Metals Dissolved in Ammonia?

Enantiopure Double-Helical Acetylenic Cyclophanes

Supramolecular Cluster Catalysis: A Case Study of Benzene Hydrogenation Catalyzed by a Cationic Triruthenium Cluster under Biphasic Conditions

A. Sinicropi, R. Pogni,*
R. Basosi, M. A. Robb,
G. Gramlich, W. M. Nau,*
M. Olivucci*

L. F. Chibotaru,* V. S. Mironov,
A. Ceulemans

U. Vogel, A. Y. Timoshkin,
M. Scheer*

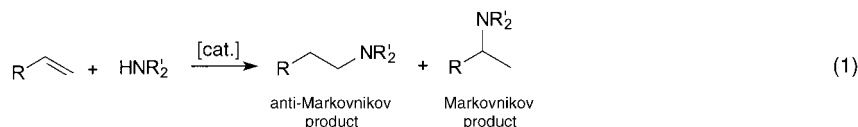
T. Söhnle, H. Hermann,
P. Schwerdtfeger*

L. J. P. van den Broeke,*
E. L. V. Goetheer, A. W. Verkerk,
E. de Wolf, B.-J. Deelman,
G. van Koten, J. T. F. Keurentjes
M. E. Vázquez, A. M. Caamaño,
J. Martínez-Costas, L. Castedo,
J. L. Mascareñas*

A.-V. Mudring, M. Jansen,*
J. Daniels, S. Krämer,
M. Mehring, J. P. Ramalho,
A. H. Romero, M. Parrinello
D.-L. An, T. Nakano, A. Orita,
J. Otera*

G. Stüss-Fink,* M. Faure,
T. R. Ward

In terms of an optimum material balance, intermolecular catalytic hydroamination reactions [Eq. (1)] are one of the much discussed atom-economical processes. The problems of hydroamination have not yet been properly solved; however, recent publications describe some very promising work on the homogeneous catalysis of intermolecular hydroamination reactions with transition metal catalysts. This work is described and discussed herein.



Angew. Chem. **2001**, *113*, 4105–4108

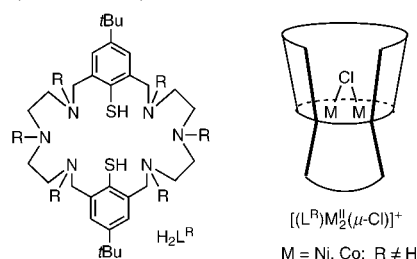
M. Nobis,
B. Driessen-Hölscher* 3983–3985

Recent Developments in Transition
Metal Catalyzed Intermolecular
Hydroamination Reactions—
A Breakthrough?

Keywords: density functional
calculations • homogeneous catalysis •
hydroamination • transition metal
catalysis

COMMUNICATIONS

 **The unusual reactivity** of binuclear complexes of the macrocyclic ligand ($\text{L}^{\text{R}}\text{R}'$)²⁻ can be attributed to the hydrophobic microenvironment about the free coordination site. The new compounds can be used for the stabilization of reactive intermediates or for the activation of small molecules such as carbon dioxide (see scheme).



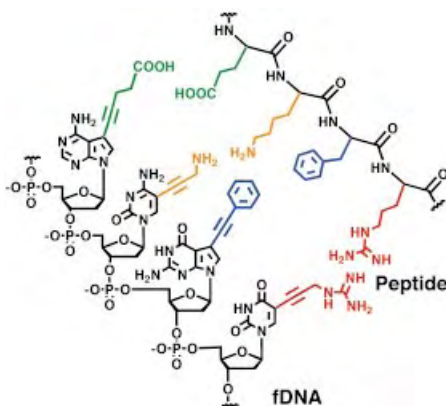
Angew. Chem. **2001**, *113*, 4109–4112

B. Kersting* 3987–3990

Carbon Dioxide Fixation by Binuclear
Complexes with Hydrophobic Binding
Pockets

Keywords: binuclear complexes • carbon
dioxide fixation • hydrophobic effect •
ligand effects • macrocyclic ligands

New DNA: By enzymatic polymerization of base-modified nucleoside triphosphates, a functionalized DNA (fDNA; see picture) was generated in which every base bears an additional amino acid like residue, thus mimicking the functional group repertoire of peptides on a nucleic acid backbone. These modified oligonucleotides can in turn serve as templates for polymerase chain reaction amplification, thus utilizing fDNA as a novel class of biopolymers for in vitro selection techniques.



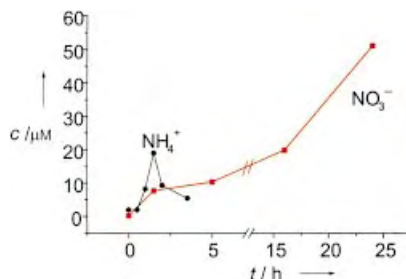
Angew. Chem. **2001**, *113*, 4112–4115

O. Thum, S. Jäger,
M. Famulok* 3990–3993

Functionalized DNA: A New Replicable
Biopolymer

Keywords: combinatorial chemistry •
in vitro selection • nucleotides •
oligonucleotides

Mild reducing agents such as ethanol, sodium formate, and humic acids effect the photofixation of nitrogen to ammonia and nitrate at thin films of nanostructured iron titanates (see diagram). The reaction occurs in the presence of air and light, but is inhibited by the presence of carbon monoxide.



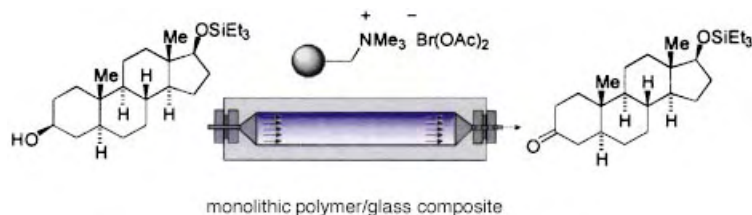
Angew. Chem. **2001**, *113*, 4115–4117

O. Rusina, A. Eremenko, G. Frank,
H. P. Strunk, H. Kisch* 3993–3995

Nitrogen Photofixation at Nanostructured
Iron Titanate Films

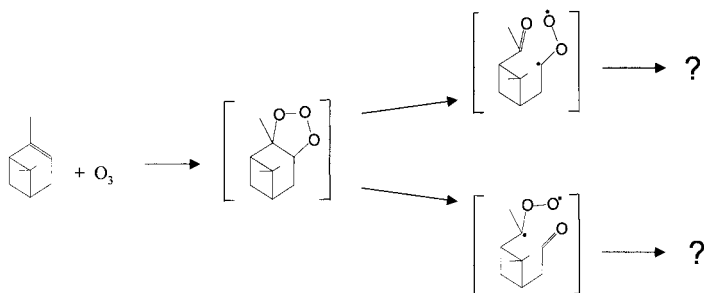
Keywords: iron • nanocrystals • nitrogen
fixation • photochemistry • thin films •
titanium

A chemist's wish finally becomes reality: microreactors for every synthetic laboratory! By precipitation polymerization various polymers are introduced into the irregular pore system of a porous glass rod. By embedding these rods into a housing, followed by functionalization and immobilization of reagents onto the polymer phase, versatile microreactors are obtained. With this apparatus, chemical transformations in solution can be performed, for example, a steroid derivatization (see picture).



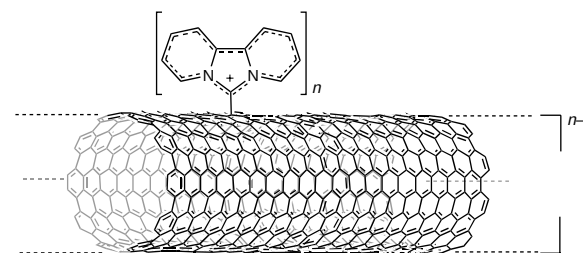
Angew. Chem. **2001**, *113*, 4118–4120

Unknown products identified precisely: The coupling of liquid chromatography to NMR spectroscopy, mass spectrometry, and infrared spectroscopy and the use of high-resolution mass spectrometry is utilized to investigate the formation of atmospheric-relevant organic aerosols. The investigation focussed on the gas-phase reaction of α -pinene with ozone (see scheme) and the subsequent identification of the reaction products by the coupled analytical techniques.



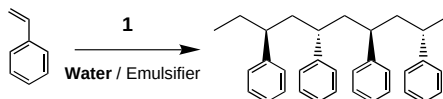
Angew. Chem. **2001**, *113*, 4129–4132

The addition of nitrenes, nucleophilic carbenes, and radicals affords soluble, individual single-walled nanotubes (shown here is a carbene-functionalized adduct) by covalent sidewall functionalization. The characterization, a fundamental problem in nanotube chemistry, is simple to carry out.



Angew. Chem. **2001**, *113*, 4132–4136

Water-sensitive catalysts work in water! Metallocene catalysts that normally have to be handled under the strict exclusion of air and moisture, for example [TiCp*(OMe)₃] (**1**, Cp* = pentamethylcyclopentadienyl), are successfully employed in the aqueous emulsion polymerization of styrene to syndiotactic polystyrene. The catalyst is encapsulated inside the monomer droplets and thus protected against attack by water.



Angew. Chem. **2001**, *113*, 4139–4141

A. Kirschning,* C. Altwicker, G. Dräger, J. Harders, N. Hoffmann, U. Hoffmann, H. Schönfeld, W. Solodenko, U. Kunz* 3995–3998

PASSflow Syntheses Using Functionalized Monolithic Polymer/Glass Composites in Flow-Through Microreactors

Keywords: immobilization • microreactor • polymerization • solid-phase syntheses • synthetic methods

W. Schrader,* J. Geiger, M. Godejohann, B. Warscheid, T. Hoffmann 3998–4001

An Analytical Approach for a Comprehensive Study of Organic Aerosols

Keywords: analytical methods • atmospheric chemistry • liquid chromatography • terpenoids

M. Holzinger, O. Vostrowsky, A. Hirsch,* F. Hennrich, M. Kappes, R. Weiss, F. Jellen 4002–4005

Sidewall Functionalization of Carbon Nanotubes

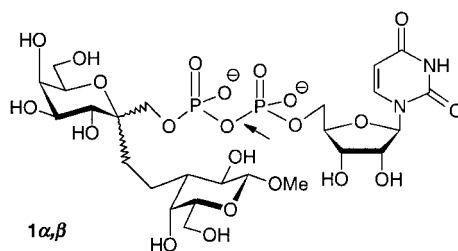
Keywords: carbenes • carbon allotropes • cycloaddition • nanotubes • nitrenes

B. Manders,* L. Sciandrone, G. Hauck, M. O. Kristen* 4006–4007

No Polymerization with Metallocenes in Water?—A Prejudice is Refuted

Keywords: homogeneous catalysis • metallocenes • polymerization • polystyrene • titanium

How do retaining glycosyltransferases function? To answer this question, UDP-Gal and galactose were covalently linked to form disubstrate analogues **1**, of which surprisingly **1 β** and not **1 α** inhibited α (1-3)-galactosyltransferases very well. An understanding of this inhibition is a key to the pharmacological prevention of hyperacute rejection in pig to primate xenotransplantation.



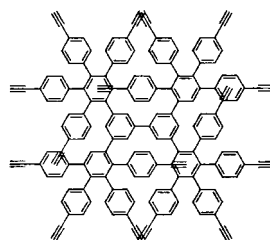
Angew. Chem. **2001**, *113*, 4120–4124

B. Waldscheck, M. Streiff, W. Notz, W. Kinzy, R. R. Schmidt* ... 4007–4011

α (1-3)-Galactosyltransferase Inhibition Based on a New Type of Disubstrate Analogue

Keywords: C-glycosides • C-ketosides • disubstrate analogues • inhibitors • transferases

Rigid, dendritic poly(paraphenylene)s (see picture) are excellently suited as sensitive and selective coatings for gravimetric sensors (quartz microbalances), since they incorporate guest molecules reversibly into their interior voids. The variety of their potential designs allows an optimal match of these multitiered hosts to the guests (analytes) to be monitored.



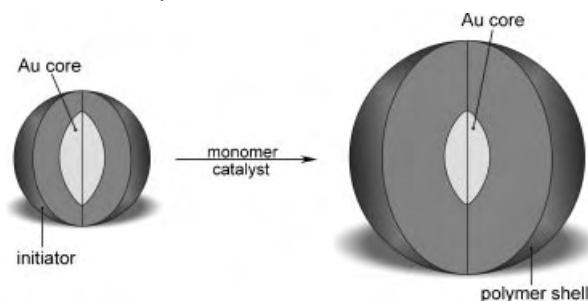
Angew. Chem. **2001**, *113*, 4124–4129

M. Schlupp,* T. Weil, A. J. Berresheim, U. M. Wiesler, J. Bargon,* K. Müllen* 4011–4015

Polyphenylene Dendrimers as Sensitive and Selective Sensor Layers

Keywords: dendrimers • host–guest chemistry • polyphenylene • quartz microbalance • sensors

“Living”/controlled radical polymerization according to the atom transfer radical polymerization mechanism is a suitable method for the graft-polymerization of nanoparticles (see scheme). With this method, in which the core nanoparticles remain unchanged, the chain length and therefore the thickness of the polymer shell can be adjusted.



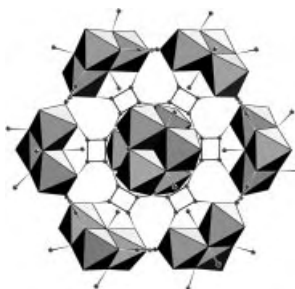
Angew. Chem. **2001**, *113*, 4137–4139

S. Nuß, H. Böttcher, H. Wurm, M. L. Hallensleben* 4016–4018

Gold Nanoparticles with Covalently Attached Polymer Chains

Keywords: colloids • gold • nanostructures • organic–inorganic hybrid composites • polymers

Polydentate bridging ligands can be used to link small polyoxo-alkoxo-metalate units to form supramolecular clusters. In the title compound, twelve μ_4 -bridging squarato groups connect eight trinuclear methoxo-oxo-vanadate units to form a tetradodecanuclear cubic framework (see picture), in whose cavity six *n*-butyl groups of the tetra-*n*-butylammonium cations are anchored.



Angew. Chem. **2001**, *113*, 4141–4143

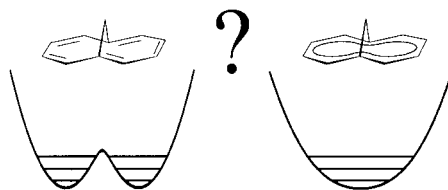
J. Spandl, I. Brüdgam, H. Hartl* 4018–4020

Solvothermal Synthesis of a 24-Nuclear, Cube-Shaped Squarato-oxovanadium(IV) Framework:

$[N(nBu)_4]_8[V_{24}O_{24}(C_4O_4)_{12}(OCH_3)_{32}]$

Keywords: cage compounds • polyoxometalates • solvothermal synthesis • squarates • structure elucidation • vanadium

For the ground state of the Hückel aromatic ring 1,6-methano[10]annulene (MA) both a localized and a delocalized structure (see scheme) have been proposed in the past, depending on the theoretical methods used. A high-resolution electronic spectrum in a supersonic jet unambiguously shows that isolated, ultracold MA has a delocalized structure in its S_0 ground state as well as in its S_1 excited state.



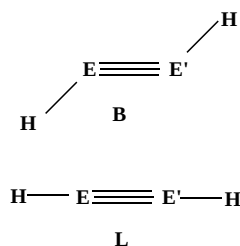
R. Seiler, B. Dick* 4020–4023

1,6-Methano[10]annulene has a Delocalized Structure in S_0 and S_1 : High-Resolution Spectroscopy in a Supersonic Jet

Keywords: aromaticity • delocalization • laser spectroscopy • VB methods

Angew. Chem. **2001**, *113*, 4144–4146

Bond stabilization through bending! Valence bond analysis shows that the σ frames of **1–3** (**1**: E = Si, E' = C; **2**: E = E' = Si; **3**: E = E' = C) are stabilized by *trans* bending (**B**), while π bonding is weakened. In acetylene (**3**) π bonding overrides the σ frame and establishes a linear molecule (**3L**). In contrast, the σ frames dominate in silyne (**1**) and disilyne (**2**) and lead to *trans*-bent structures (**1B** and **2B**).



D. Danovich, F. Ogliaro, M. Karni, Y. Apeloig,* D. L. Cooper,* S. Shaik* 4023–4026

Silynes ($RC\equiv SiR'$) and Disilynes ($RSi\equiv SiR'$): Why Are Less Bonds Worth Energetically More?

Keywords: bond theory • multiple bonds • silicon • valence bond calculations

Angew. Chem. **2001**, *113*, 4146–4150

Really a triple bond? According to quantum-chemical calculations of inverted Hessian matrices (compliance matrices), the strength of the $C\equiv Si$ bond in **I** is only marginally stronger than the $C=Si$ bond in silaethylene (**II**). Real-space force constants overestimate the $C\equiv Si$ bond in **I** and should therefore be abandoned as bond strength descriptors.



J. Grunenberg* 4027–4029

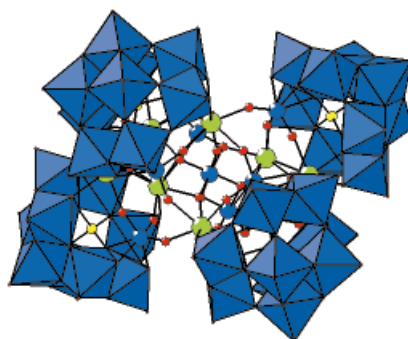
Intrinsic Bond Strengths of Multiple C–C, Si–Si, and C–Si Bonds

Keywords: ab initio calculations • bond theory • density functional calculations • multiple bonds • silicon

Angew. Chem. **2001**, *113*, 4150–4153



Four lacunary $PW_9O_{34}^{9-}$ ions (blue polyhedra) are held together by eight M^{III} ($M = Y, Eu$) ions and seven W atoms that form a $[M_8W_7O_{30}]^{6+}$ network (center) in the novel heteropolyoxometalates $[(PM_2W_{10}O_{38})_4(W_3O_{14})]^{30-}$. In the solid state, the anions interact strongly with K^+ counteranions, which thus play a role in the formation of this particular structure.



R. C. Howell, F. G. Perez, S. Jain, W. DeW. Horrocks, Jr., A. L. Rheingold, L. C. Francesconi* 4031–4034

A New Type of Heteropolyoxometalates formed from Lacunary Polyoxotungstate Ions and Europium or Yttrium Cations

Keywords: europium • lanthanides • polyoxometalates • tungsten • yttrium

Angew. Chem. **2001**, *113*, 4155–4158

Are adaptations in the nanocosmos observable? Or in other words, can

formation or self-assembly of nanoparticles be achieved with a variety of characteristic modifications of a parent structure based solely on the variation of boundary conditions? This possibility exists for the ring-shaped nanostructured giant molybdenum clusters—known as “big wheels” (see picture)—in which well-defined transformations and reactions can be observed at various well-defined positions on the surface and even internally. The integration of magnetic copper centers into cavities (violet tetrahedra) of exactly the right size is described.



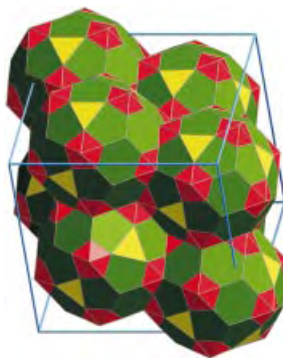
A. Müller,* E. Krickemeyer, H. Bögge, M. Schmidtman, P. Kögerler, C. Rosu, E. Beckmann 4034–4037

“Nanoobjects” by Self-Assembly Concomitant with Modifications under Alterable Boundary Conditions: Incorporation of Paramagnetic Metal Centers (Cu^{2+}) in Ring-Shaped Molybdenum-Oxide Based Clusters

Keywords: cluster compounds • magnetic properties • nanostructures • polyoxometalates • self-assembly

Angew. Chem. **2001**, *113*, 4158–4161

The closest cubic approximant to the $\text{MCd}_{5.7}$ ($M = \text{Ca}, \text{Yb}$) quasicrystals known so far, namely $\text{Ca}_{13}\text{Cd}_{76}$, was obtained by high-temperature reaction of the elements. It exhibits a new type of structure for intermetallic compounds with an unprecedented arrangement of triacontahedral clusters (see structure), which could prove useful in modeling the structures of the $\text{MCd}_{5.7}$ quasicrystals.



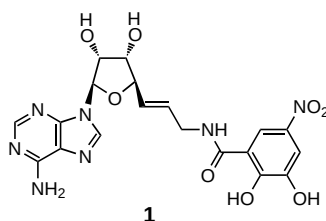
Angew. Chem. **2001**, *113*, 4161–4163

C. P. Gómez,* S. Lidin 4037–4039

Structure of $\text{Ca}_{13}\text{Cd}_{76}$: A Novel Approximant to the $\text{MCd}_{5.7}$ Quasicrystals ($M = \text{Ca}, \text{Yb}$)

Keywords: cadmium • calcium • high-temperature chemistry • quasicrystals • solid-state structures

With an IC_{50} value of 9 nM, **1 is the most potent** known disubstrate inhibitor for catechol-*O*-methyltransferase (COMT). Inhibition of COMT is of significant interest in the therapy of Parkinson's disease since it ensures that a larger percentage of orally administered L-dopa reaches—in the form of dopamine—its target in the brain. The X-ray crystal structure of a complex formed by COMT and **1** has been solved at 2.6-Å resolution.



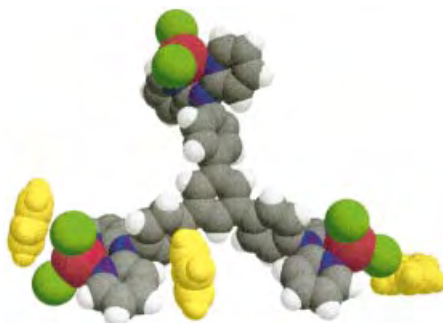
Angew. Chem. **2001**, *113*, 4164–4166

C. Lerner, A. Ruf, V. Gramlich, B. Masjost, G. Zürcher, R. Jakob-Roetne, E. Borroni, F. Diederich* ... 4040–4042

X-ray Crystal Structure of a Bisubstrate Inhibitor Bound to the Enzyme Catechol-*O*-methyltransferase: A Dramatic Effect of Inhibitor Preorganization on Binding Affinity

Keywords: drug research • enzyme inhibitors • medicinal chemistry • structure–activity relationships • transferases

Binding benzene: A novel blue luminescent star-shaped Zn^{II} complex has been found to be able to detect benzene selectively by fluorescent quenching. This is attributed to the compound's high affinity to benzene, as demonstrated in the crystal structure (see picture; yellow: benzene, red: zinc).



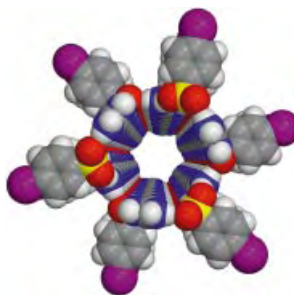
Angew. Chem. **2001**, *113*, 4166–4169

J. Pang, E. J.-P. Marcotte, C. Seward, R. S. Brown,* S. Wang* 4042–4045

A Blue Luminescent Star-Shaped Zn^{II} Complex that Can Detect Benzene

Keywords: benzene • luminescence • N ligands • sensors • stacking interactions • zinc

Inclusion compounds based on a flexible hydrogen-bonded sheet of guanidinium ions and sulfonate moieties display lamellar and tubular architectures, depending on the guest and the organic substituent attached to the sulfonate. The observed single-crystal architectures resemble lamellar and hexagonal microstructures (see picture) in block copolymers and surfactant assemblies.



Angew. Chem. **2001**, *113*, 4169–4172

M. J. Horner, K. T. Holman, M. D. Ward* 4045–4048

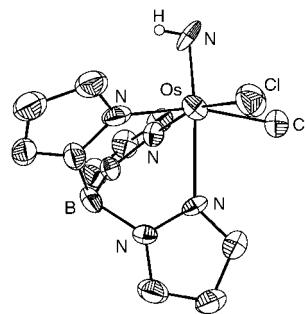
Lamellae-Nanotube Isomerism in Hydrogen-Bonded Host Frameworks

Keywords: clathrates • crystal engineering • inclusion compounds • nanotubes • self-assembly • template synthesis



Trapped by a proton: In the formation of $\text{Os}^{\text{II}}\text{--N}_2\text{--Os}^{\text{II}}$ dimers, an $\text{Os}^{\text{V}}\equiv\text{N}$ complex has been invoked as a transient intermediate but not isolated. Herein conditions are reported that allow $\text{Os}^{\text{V}}\equiv\text{N}$ species to be trapped either in acidic, aqueous solutions as a neutral osmium(v) imido complex ($\text{Os}^{\text{V}}\text{NH}$, see structure) or in non-aqueous solvents, with high concentrations of added reductant, by N^- ion transfer before coupling can occur.

Angew. Chem. **2001**, *113*, 4173–4175

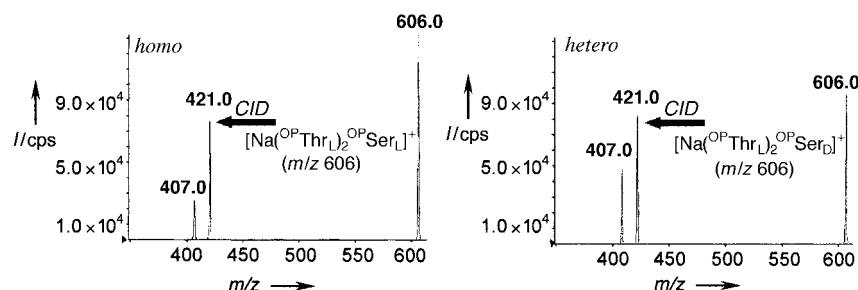


M. H. V. Huynh,* P. S. White, K. D. John, T. J. Meyer* 4049–4051

Isolation and Characterization of the Osmium(v)–Imido Complex $[\text{Os}^{\text{V}}(\text{Tp})(\text{Cl})_2(\text{NH})]$

Keywords: electrochemistry • N ligands • osmium • protonation • tripodal ligands

Identification and quantification of the enantiomeric excess of *O*-phosphoserine ($^{\text{OP}}\text{Ser}$) residues from post-translational modified proteins is now possible by the application of a very reproducible and sensitive mass spectrometric method. This technique is based on the different mass-spectral fragmentation patterns of the diastereomeric cluster ions generated in water/methanol solutions of the analyte ($^{\text{OP}}\text{Ser}_{\text{D/L}}$) with a suitable chiral compound ($^{\text{OP}}\text{Thr}_{\text{L}}$) by collision-induced dissociation (CID; see mass spectra).



Angew. Chem. **2001**, *113*, 4175–4178

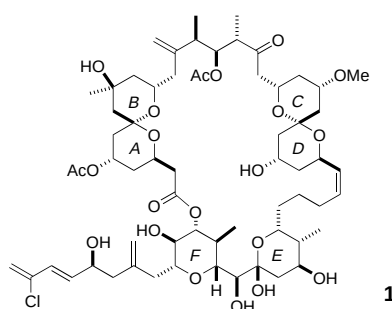
G. Fago, A. Filippi, A. Giardini, A. Laganà, A. Paladini, M. Speranza* 4051–4054

Chiral Recognition of *O*-Phosphoserine by Mass Spectrometry

Keywords: chirality • enantioselectivity • mass spectrometry • proteomics



As an exceptionally potent antimicrobial macrolide, althoyrtin A/spongistatin **1** shows great promise in cancer chemotherapy but its extreme scarcity in the natural sponges has halted its further preclinical development. A highly stereocontrolled total synthesis, which exploits boron-mediated aldol bond constructions, has been realized to provide, for the first time, a useful amount of synthetic material.



I. Paterson,* D. Y.-K. Chen, M. J. Coster, J. L. Aceña, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, R. D. Norcross 4055–4060

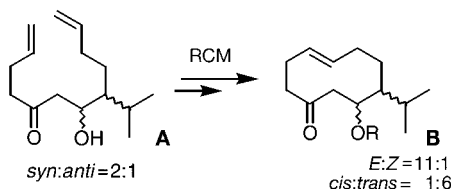
Stereocontrolled Total Synthesis of (+)-Althoyrtin A/Spongistatin **1**

Keywords: aldol reactions • macrolides • natural products • total synthesis

Angew. Chem. **2001**, *113*, 4179–4184



Even 10-membered rings can be obtained by ring-closing metathesis (RCM). The synthesis of carbocycle **B** by RCM, which is the key step in the synthesis of the pine-resin sesquiterpene 1,6-germacradien-5-ol, was improved by protecting the hydroxy group of the precursor bisolefin **A** as a bulky *tert*-butyldimethylsilyl ether and by complexing its carbonyl group with $\text{Ti}(\text{O}i\text{Pr})_4$.



M. Nevalainen, A. M. P. Koskinen* 4060–4062

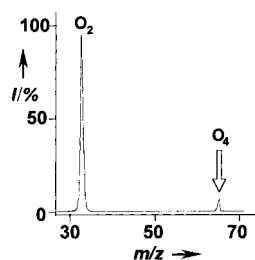
Synthesis of a 10-Membered Carbocycle By Olefin Metathesis

Keywords: carbocycles • cyclization • metathesis • ruthenium • terpenoids

Angew. Chem. **2001**, *113*, 4184–4186

Although suggested by Lewis in 1924 and theoretically predicted, O_4 has so far proved extremely elusive, defying all attempts at the positive experimental detection of a bound, intact O_4 species. The search has now been brought to an end by the conclusive proof, achieved by neutralization–reionization mass spectrometry (see picture), of the existence of intact O_4 as a gas-phase species with a lifetime in excess of $1\ \mu\text{s}$, whose dissociation requires overcoming a barrier of the order of $10\ \text{kcal mol}^{-1}$.

Angew. Chem. **2001**, *113*, 4186–4189



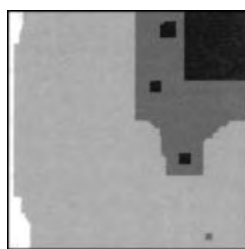
F. Cacace,* G. de Petris,
A. Troiani 4062–4065

Experimental Detection of Tetraoxygen

Keywords: ion–molecule reactions • mass spectrometry • metastable compounds • oxygen

An accurate model of the surface growth of one of the most important industrial zeolites, zeolite A, has been created. Comparison of the simulation (see picture) with experimental data in the form of atomic force micrographs highlights the non-diffusion-limited nature of zeolite growth and provides the first ever quantification of fundamental crystal growth processes in zeolites.

Angew. Chem. **2001**, *113*, 4189–4191



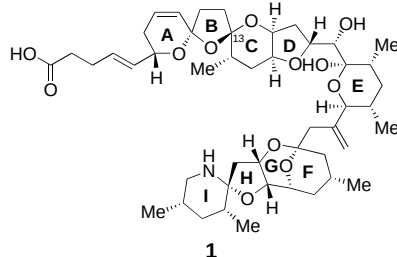
J. R. Agger,* N. Hanif,
M. W. Anderson* 4065–4067

Fundamental Zeolite Crystal Growth Rates from Simulation of Atomic Force Micrographs

Keywords: computer chemistry • crystal growth • scanning probe microscopy • surface chemistry • zeolites

Previously attempted spirocyclizations to form the ABCD ring system of azaspiracid (**1**) have proven unsuccessful owing to the anomeric effects that favor the formation of the undesired $13S$ diastereomer. By the use of a hydrogen bond donor as an auxiliary group, such anomeric effects were successfully overcome. Thus, the first synthesis of the ABCD ring system of azaspiracid with the proper $13R$ configuration of the C13 stereocenter was achieved.

Angew. Chem. **2001**, *113*, 4192–4195



K. C. Nicolaou,* W. Qian, F. Bernal,
N. Uesaka, P. M. Pihko,
J. Hinrichs 4068–4071

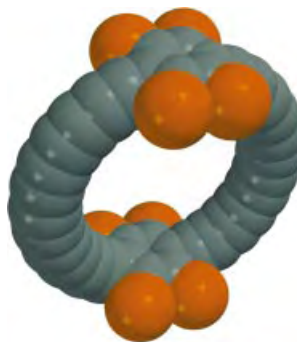
Synthesis of the ABCD Ring System of Azaspiracid

Keywords: azaspiracid • natural products • spiro compounds • stereoelectronic effects



The smallest $[n,n]$ cyclophynes known, $[12.12]$ paracyclophanedodecaynes $C_{36}H_8$ and $C_{36}Cl_8$ (see picture), were generated by $[2+2]$ cycloreversion of its precursor under photolytic and mass spectrometric conditions. The stepwise loss of chlorine atoms from the anion of the octachloro derivative $C_{36}Cl_8^-$ produced a carbon cluster anion C_{36}^- in the gas phase.

Angew. Chem. **2001**, *113*, 4196–4198

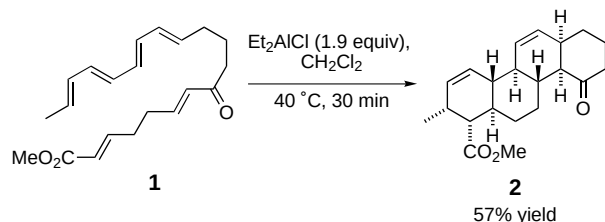


Y. Tobe,* R. Furukawa, M. Sonoda,
T. Wakabayashi 4072–4074

$[12.12]$ Paracyclophanedodecaynes $C_{36}H_8$ and $C_{36}Cl_8$: The Smallest Paracyclophynes and Their Transformation into the Carbon Cluster Ion C_{36}^-

Keywords: carbon clusters • cyclophanes • fullerenes • macrocycles • polyynes

Four C–C bonds, four rings, and eight contiguous stereocenters in one go! Tetracyclic product **2**, which results on warming simple acyclic precursor **1** with a mild Lewis acid, is formed through an efficient and highly stereoselective domino sequence of two intramolecular Diels–Alder reactions. Pharmacologically important norsteroids are just one potential application of this extremely effective approach to fused polycyclic systems.



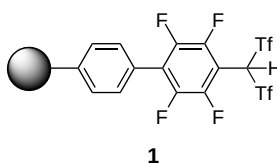
Angew. Chem. **2001**, *113*, 4198–4200

M. Nörret, M. S. Sherburn* 4074–4076

The Zipper-Mode Domino Intramolecular Diels–Alder Reaction: A New 0 → ABCD Strategy for Steroids and Related Compounds

Keywords: cycloaddition • diastereoselectivity • domino reactions • polycycles • steroids

Several advantages over inorganic solid acids such as zeolites and perfluororesinsulfonic acids such as Nafion are offered by the new reusable polystyrene-bound catalyst **1**: a broader range of applications, improved yields, improved selectivity, and milder reaction conditions. Tf = F₃CSO₂.



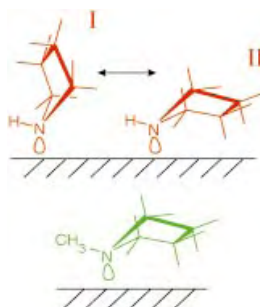
K. Ishihara, A. Hasegawa, H. Yamamoto* 4077–4079

Polystyrene-Bound Tetrafluorophenylbis(triflyl)methane as an Organic-Solvent-Swellable and Strong Brønsted Acid Catalyst

Keywords: Brønsted acids • fluorine • heterogeneous catalysis • superacidic systems • supported catalysts

Angew. Chem. **2001**, *113*, 4201–4203

Negative differential resistance (NDR), mediated by vibrational excitation, is strongly dependent on molecular structure and dynamics, according to scanning tunneling microscopy on Cu(001)-bound pyrrolidine and *N*-methylpyrrolidine at 9 K. Tunneling electrons cause the former to switch between conformations I and II (see picture), so that NDR is observed. The methyl group of the latter compound restricts it to a single conformation (see picture), and a linear current–voltage characteristic results.

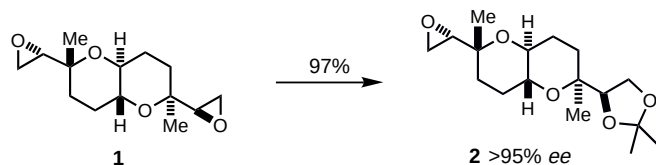


J. Gaudioso, W. Ho* 4080–4082

Steric Turnoff of Vibrationally Mediated Negative Differential Resistance in a Single Molecule

Keywords: molecular devices • molecular dynamics • nitrogen heterocycles • scanning probe microscopy • vibrational spectroscopy

Exploitation of molecular symmetry can greatly improve the efficiency of syntheses. The symmetry embedded in the centrosymmetric AB dioxepane fragment of hemibrevetoxin B was exploited for the first time in the preparation of an established intermediate in its total synthesis. Desymmetrization of the centrosymmetric diepoxide **1** by enantioselective epoxide hydrolysis followed by acetonization gave the known synthetic intermediate **2**.



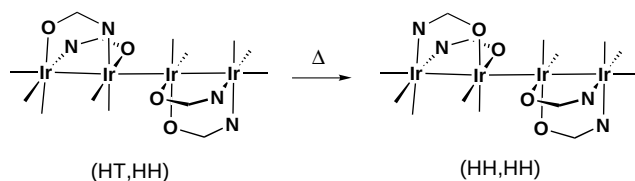
Angew. Chem. **2001**, *113*, 4206–4208

J. M. Holland, M. Lewis, A. Nelson* 4082–4084

First Desymmetrization of a Centrosymmetric Molecule in Natural Product Synthesis: Preparation of a Key Fragment in the Synthesis of Hemibrevetoxin B

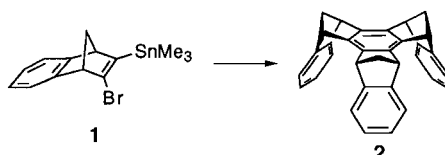
Keywords: asymmetric synthesis • desymmetrization • heterocycles • natural products

Binuclear complexes with head-to-tail (HT) configurations are appropriate for building tetrametallic chains, contrary to previous speculations. Moreover, the isolated HT,HH tetrametallic species are converted into the thermodynamically more stable HH,HH compounds (see scheme).



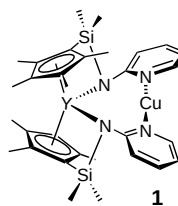
Angew. Chem. **2001**, *113*, 4208–4210

The challenge to generate all-syn architecture has prompted the synthesis of *syn* cyclotrimers **2** from racemic bromotrimethylstannyl polycyclic alkenes **1**. The *syn*-selective Cu^I-catalyzed cyclotrimerization process is both regio- and chemo-selective.



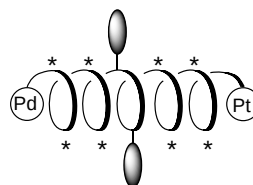
Angew. Chem. **2001**, *113*, 4210–4213

The use of a Me₂Si-bridged amido-cyclopentadienyl ligand containing pendant pyridine functionality allows clean “yttrate metathesis” to occur and the synthesis of the unusual C₂-symmetric Y/Cu bimetallic compound **1**.



Angew. Chem. **2001**, *113*, 4213–4216

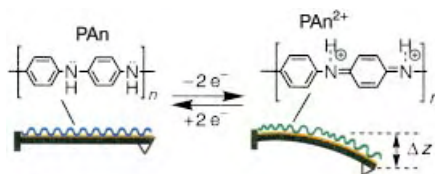
Exciton-coupled circular dichroism of the porphyrin Soret band of triblock copolymers prepared from chiral isocyanide monomers and an achiral tetraphenylporphyrin derivative (TPP) provides a novel method for determining the helical sense of poly(aryl isocyanide)s (see the schematic representation of the structure).



Angew. Chem. **2001**, *113*, 4216–4218



Bent by oxidation! A polyaniline (PAn, blue) coated cantilever acts as an electro-driven microdevice. Reversible oxidation/reduction of the PAn results in reversible deflection of the cantilever (see picture) originating from the electrostatic repulsion of the charged polymer chains of PAn²⁺ (green).



Angew. Chem. **2001**, *113*, 4219–4221



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

C. Tejel, M. A. Ciriano,* B. E. Villarroja, R. Gelpi, J. A. López, F. J. Lahoz, L. A. Oro* 4084–4086

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Iridium Pyridonate Blues

Keywords: iridium • metal–metal interactions • N,O ligands

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Keywords: C–C coupling • chemoselectivity • molecular recognition • polycycles • regioselectivity

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Keywords: copper • cyclopentadienyl ligands • metathesis • N ligands • yttrium

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Keywords: circular dichroism • helical structures • polyisocyanides • polymers • porphyrinoids

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Redox Activation of a Polyaniline-Coated Cantilever: An Electro-Driven Microdevice

Keywords: electrochemistry • interfaces • molecular devices • polymers • thin films

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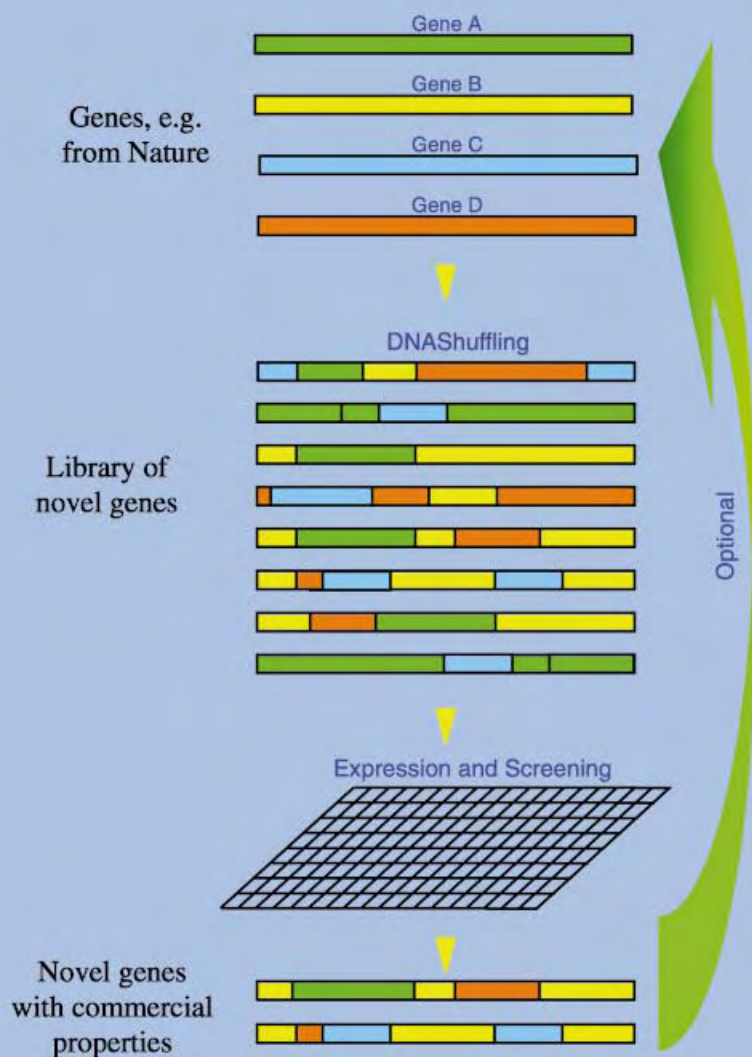
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Directed Evolution and Biocatalysis

Keith A. Powell,* Sandra W. Ramer, Stephen B. del Cardayré, Willem P. C. Stemmer, Matthew B. Tobin, Pascal F. Longchamp, and Gjalb W. Huisman

This review describes the current state of biocatalysis in the chemical industry. Although we recognize the advantages of chemical approaches, we suggest that the use of biological catalysis is about to expand dramatically because of the recent developments in the artificial evolution of genes that code for enzymes. For the first time it is possible to consider the rapid development of an enzyme that is designed for

a specific chemical reaction. This technology offers the opportunity to adapt the enzyme to the needs of the process. We describe herein the development of enzyme evolution technology and particularly DNA shuffling. We also consider several classes of enzymes, their current applications, and the limitations that should be addressed. In a review of this length it is impossible to describe all the enzymes with potential

for industrial exploitation; there are other classes, which given appropriate activity, selectivity, and robustness, could become useful tools for the industrial chemist. This is an exciting era for biocatalysis and we expect great progress in the future.

Keywords: DNA shuffling • directed evolution • enzyme catalysis • enzyme libraries • proteins

1. Introduction

Most reviews on biocatalysis start with the assumption that chemistry is waiting for inherently better biocatalytic processes. On the other hand, chemistry has effectively delivered compounds from drugs to domestic cleaning products without the help of biocatalysts for 200 years. Thus there is no reason to believe that chemistry should not be as successful for centuries to come. Since the great advantages of chemistry are simplicity, speed (increased by the use of heat and pressure), and low cost, why should biocatalysts be of interest? These advantages are irrelevant when the product required needs regio- or stereospecific reactions in which the starting material or product is labile, or in which side products are problematic contaminants. Biocatalysts are attractive because of their exquisite chemo-, regio-, and stereoselectivity, their impressive catalytic efficiency, and their reactivity in aqueous media. Although these characteristics can be useful, they can also limit the exploitation of biocatalysts. The last twenty years have seen significant commercial advances in biocatalysis (Figure 1). Some of these processes are spectacularly successful on a large scale. What is it that makes these processes successful?

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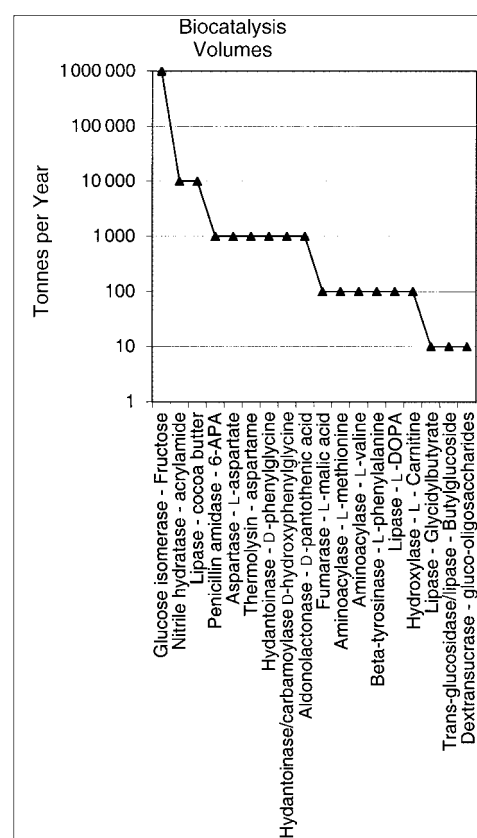


Figure 1. Commercial compounds currently produced in biocatalytic processes.

- The enzyme existed in a natural isolate with an activity that is close to that required for a commercial process.
- The enzyme could be immobilized with retention of activity, or the activity was such that a single use was still economically viable.
- No cofactors were required for enzyme activity, or whole cells could be used to provide the activity without any significant side reactions.

If some reactions can be run commercially with enzymes, then what limits the broader use of biocatalysis (Table 1)?

Table 1. Current limitations of biocatalysis that need to be addressed.

Limited substrate range
Limited stability to temperature, pH, solvent
Limited enantioselectivity
Limited lifetime
Limited turnover number

- The enzyme may not exist in nature or it may be difficult to procure or produce.
- The properties of the enzyme may be unsuitable for chemical synthesis.
- The activity may be insufficient.
- The enzyme may be inhibited by the substrate or the product, it may not work well under suitable operating temperatures or pH values, or it may simply be too labile for effective industrial use.
- The reaction may require an expensive cofactor that cannot be effectively recycled.

What, then, is the future of enzyme-based chemistry?

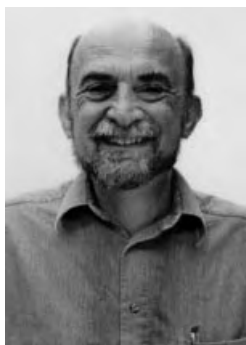
There are now examples of enzymes that have been isolated and then modified into effective biocatalysts.^[1–3] Recent advances have shown that directed evolution techniques can be used to develop enzymes that are modified to fit the demands of the chemical process. Whereas in the past commercial enzymes were often tested and, when appropriate, rejected for specific reactions, they can now be selected from a library of related enzymes with a range of properties: stability over a temperature range, increased activity, enantioselectivity, novel substrate activity, or compatibility under different physical and chemical conditions. The combination of flexibility in enzyme characteristics and a rapid approach to the generation of this flexibility has given rise to a new paradigm in the development of biocatalytic processes.

In this review we will describe some of the advances in enzyme improvement technology, as well as some classes of biocatalysts, the current state of the art, and the future potential for improved biocatalysis. We focus primarily on hydrolytic and oxidative enzymes. The very successful application of other enzyme classes will not be discussed. However these biocatalysts are also prime targets for improvement through directed evolution.

2. Genetic Approaches to Improved Biocatalysis

All the beautifully complex biological structures and sequences that Nature has provided us with have been designed by a single process, that of natural evolution. However, natural evolution has selected the most suitable enzymes that ensure the survival of the organism in its natural environment. No matter how extreme that natural environment, the enzyme is unlikely to be ideal for a chemical process. Enzymes have been successfully improved for many years by mutation and selection, but because of the long and slow nature of this process, it has not been possible to rapidly develop catalysts with novel properties in the timescale acceptable to process chemists. Many improvements have been made to this technology, and a recent review describes the resulting biocatalytic processes.^[4] Existing approaches to improve single proteins or parts thereof include modeling-based point mutagenesis, cassette library mutagenesis (including random, biased, saturation, and codon-based cassette mutagenesis), and random point mutagenesis (including error-prone polymerase chain reaction (PCR), mutator strains, and UV or chemical mutagenesis), which introduce (partially) random mutations either into a selected small region of a gene or throughout a gene.

Molecular biologists have been using a fundamentally different approach to manipulate these same molecules—rational design by molecular modeling. Although molecular modeling can be powerful, it has limitations and cannot be used for proteins that have not yet been crystallized, for determining protein–environment interactions, or for predicting the effect of mutations beyond protein structure. Although rational design is a beautiful approach and will be extremely valuable in the future, a process is currently required to develop poorly understood proteins into useful



Keith Powell started his career with a degree in Microbiology and Chemistry at the University of Reading. After a PhD in the genetics of heme synthesis, he joined Glaxo to improve the yield in the synthesis of vitamin B12. Finding a need to do some more dangerous research, he moved to the University of Newcastle where he became involved in research into the mechanism of DNA repair. Later, he joined ICI to develop the genetic system for Methylophilus methylotrophus, the organism used in single-cell protein synthesis. After studying the synthesis of biopolymers and various enzymes, he joined ICI Plant Protection to develop biological methods for crop protection. Unable to keep away from chemicals, he joined Zeneca Agrochemicals to discover new chemical entities and later managed groups in biotechnology, environmental science, and even patents. The lure of biocatalysis drew him to Maxygen in 1999, where he is currently vice-president of Chemicals and Applied Technology.

catalysts without the need for a fundamental understanding of their structure and function.

A logical approach to adapt natural sequences further is to apply the same proven evolutionary tools that created these sequences in the first place. The green revolution clearly demonstrated that complex, multigenic traits of whole organisms can be optimized without any sequence or structural information of the underlying genes. Breeding is a conceptually simple, recursive process that involves homologous DNA recombination between related genomes, followed by screening of the progeny for clones with improved properties. If whole genomes could readily be improved by classical breeding, then a variation of this approach should be useful for the improvement of the much shorter sequences used by molecular biologists. We have adopted the term “MolecularBreeding” (directed molecular evolution) for the concept of rapid breeding of subgenomic sequences by using recursive recombination and functional selection. In contrast to classical breeding, which is a proven but slow method for optimizing whole, typically eukaryotic genomes, MolecularBreeding comprises a variety of recombination and screening techniques that together allow the rapid evolution of single genes, pathways, episomes, viruses, and bacterial and eukaryotic genomes. An aim of MolecularBreeding is to reduce the generation time to only a few days, typically by performing the screening process in bacteria or in single cells. The selection is focused on commercially relevant properties.

MolecularBreeding has the greatest advantage over rational design, cassette mutagenesis, and random point mutagenesis when the target is complex, for example, a multi-component protein with complex interactions, when structural information is not yet available, or when the principal target does not involve a protein structure.^[5] MolecularBreeding involves the recombination of multiple DNA sequences to create a library of chimeras. A preferred format for MolecularBreeding, also called DNA shuffling, involves the random fragmentation of a pool of homologous DNA sequences with DNase I.^[6] After denaturation of the fragments, homologous sequences from different templates hybridize and prime each other, and the resulting crossovers are locked in by polymerase extension. Multiple cycles of this fragment reassembly result in a library of full-length, homologously recombined chimeric sequences caused by a variable number of crossovers. After insertion of this library of DNA sequences into an expression vector and transfer into a host cell for expression, the clones are screened for new or improved properties. The screening identifies the best combinations of the permuted sequence diversity. As in classical breeding, a pool of the best clones is then used as the input for the next round of breeding (Figure 2). Important variables for MolecularBreeding are the length of the shuffled DNA, the DNA homology, the quality and conservative nature of the sequence diversity (natural proven diversity versus random point mutations), the crossover number (determined by fragment size), as well as the number and molar ratio of the parents. Several other formats for in vitro and in vivo recombination have been developed.

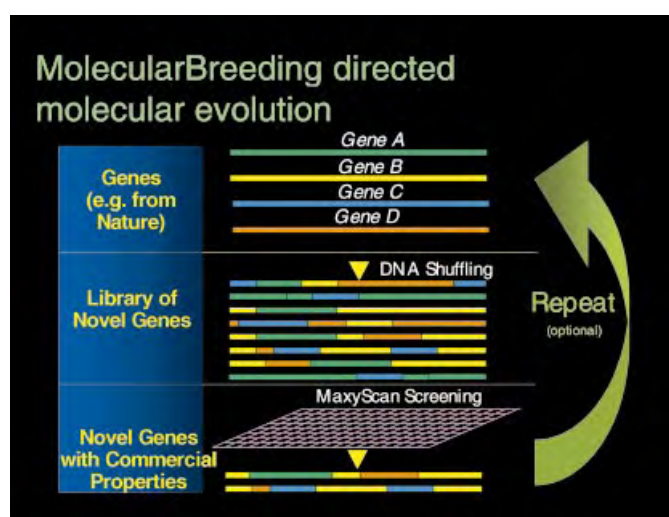


Figure 2. The MolecularBreeding directed molecular evolution process.

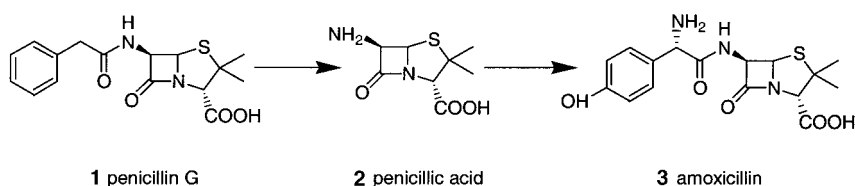
MolecularBreeding has been applied to a variety of enzymes to improve the substrate selectivity, catalytic efficiency, stability, pH optima, and function under diverse physical and chemical conditions. We believe that directed evolution is the key to realizing the potential of biocatalysis in the near future. In the next chapter we describe a variety of important chemical reactions that currently take advantage of biocatalysis, as well as some that may soon benefit as a result of directed evolution technology.

3. Enzymes as Biocatalysts

3.1. Acylation Reactions

Acylation chemistry is integral to the synthesis of numerous antibacterial, antifungal, and small-molecule pharmaceuticals. Despite the robust nature of acylation chemistry, biocatalysts play important roles in the synthesis and hydrolysis of a variety of commercial acyl compounds. Historically, the penicillin acylases (penicillin amidohydrolase E.C. 3.5.1.11) have received considerable attention for their role in the manufacture of semisynthetic penicillins and cephalosporins. The natural acyl side chains of penicillin G (**1**), penicillin V, and cephalosporin C are hydrolytically removed, and the resulting nucleus is reacylated to produce a variety of commercial derivatives, such as amoxicillin (**3**), carbenicillin, piperacillin, cephalexin, cefaclor, and cefotaxime (Scheme 1). This industry now has annual sales of more than \$1 billion.

The natural side chains of penicillin G, penicillin V, and cephalosporin C are phenylacetyl-, phenoxyacetyl-, and aminoadipyl-, respectively. Once hydrolyzed, the resulting 6-ami-



Scheme 1. Reactions that are catalyzed by penicillin acylase.

nopenicillic acid (6-APA) and 7-aminocephalosporic acid (7-ACA) form the nucleus for modification. The commercial hydrolysis of the natural aromatic penicillins was originally an inefficient three-step process in CH_2Cl_2 at -40°C , but is now carried out by means of a single enzymatic reaction with penicillin G acylase in water at 37°C . An efficient cephalosporin C acylase has not yet been described; however, other approaches to the biocatalytic production of the cephem nuclei, 7-ACA and 7-aminodeacetoxycephalosporic acid (7-ADCA), have been developed.

The penicillin acylases catalyze both the addition and the hydrolysis of the acyl side chain. Unfortunately, penicillin G acylase is specific for the phenylacetyl side chain of penicillin G. This prevents the use of this enzyme for the enzymatic acylation of 6-APA and 7-ADCA with different acyl donors. An evolved enzyme with a broad substrate specificity for such donors could potentially provide a biocatalytic route to the semisynthetic β -lactams. Broadened specificity, as well as increased specific activity, altered pH and temperature optima, and overall stability are desired traits for these enzymes. Activity at low pH values is particularly desired since synthesis is favored over hydrolysis under these conditions.

In semisynthetic β -lactam-manufacturing processes, the competing acylation and hydrolysis reactions are either thermodynamically or kinetically controlled. In a thermodynamically controlled process, the reaction equilibrium is established by controlling pH, temperature, ionic strength, and solvent composition. Enzyme variants that exhibit optimal activity under thermodynamically favorable conditions^[7] are expected to support the most efficient process. In kinetically controlled reactions, the substrate is converted into the product before equilibrium is reached. To obtain superior product yields, enzyme variants that have optimal kinetic constants for the substrate are desired.

Rational protein engineering of penicillin acylases from *Kluyvera citrophila*, *Escherichia coli*, and *Pseudomonas* has been used to obtain insight into the function^[8–11] and the maturation pathway of this enzyme.^[11, 12] A hypermutagenic *E. coli* strain was used to expand the substrate specificity of the *K. citrophila* acylase.^[13] Ishii et al. employed site-directed mutagenesis based on data from chemical modification experiments to improve the activity of a cephalosporin C acylase from *Pseudomonas*.^[14] Typically, small improvements in enzyme activity were observed.

Most industrial enzymes are produced heterologously. The heterologous production of the acylase enzyme is not trivial, as most acylases are modified post-translationally. Early site-directed mutagenesis revealed some of the critical residues for this processing.^[11, 12] Subsequently, host–vector systems were developed for improved acylase production, but these resulted in the formation of inclusion bodies.^[15] While problems that are encountered in transcription and translation may be approached rationally,^[16] it is expected that the expression of foreign proteins can have deleterious effects on the viability of the host and on the quality of the expressed protein. Directed evolution and screening for cells that produce high levels of the desired catalyst is a simple means to address the complex interaction of the target protein and the host environment. For example, DNA shuffling has been employed to improve recombinant protein production by increasing protein solubility.^[17]

Acylases have also been used for the deacylation of natural products. The isolation of microbial strains that produce acylases for the hydrolysis of the acyl side chain of a cyclic lipopeptide with antifungal activity is described in patent US6146872.^[18] Other examples are listed in Table 2.

In analogy to the β -lactams, it can be expected that with the identification of more and more bioactive natural products, the need will increase for acylases that hydrolyze the existing amide bonds and catalyze the acylation in the manufacture of semisynthetic derivatives. Because of significant economic investments, the development of industrial processes for these new compounds will only be successful if the modifying enzymes are promptly available. We foresee that DNA shuffling will play an important role in the commercialization of these novel bioactive molecules.

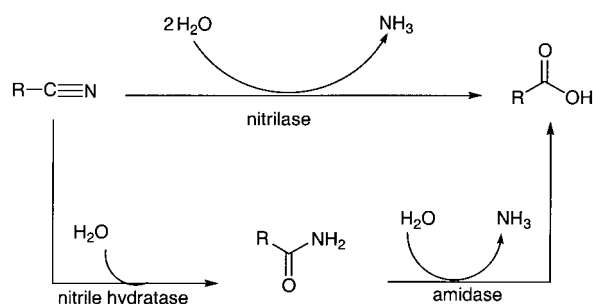
3.2. Nitrile Conversion

Nitriles are convenient and synthetically important chemical building blocks because they are readily generated and can be converted into useful amides and carboxylic acids. Chemically, this conversion requires hydrolysis at high temperatures in the presence of strong acids or bases. Enzymatically, the conversion of a nitrile into a carboxylic acid can be accomplished in a single step by the action of a nitrilase with the incorporation of two mole equivalents of water and the liberation of a mole equivalent of ammonia, or

Table 2. Examples of industrial applications of acylase enzymes from the patent literature.

Patent	Title	Ref.
US5316944	Enzymatic resolution of a racemic mixture of gamma-amino acids using penicillin acylase	[85]
US5068189	4'-O-Isovaleryl acylase for the production of novel antibiotic compounds	[86]
US4877734	α -Acetyl amino cinnamic acid acylase for enzymatic conversions which run via the intermediary stage α -imino- β -phenylpropionic acid or phenylpyruvic acid	[87]
US4699879	Streptomyces or Streptovorticillium acylase for 3-(3,4-dihydroxyphenyl)serine manufacture	[88]
US5916774	D-aminoacylase from <i>Amycolatopsis</i> for producing D-amino acids	[89]
US5733754	Acylase from <i>Alcaligenes denitrificans</i> for preparing (S)-pipecolic acid	[90]
US5637768	Penicillin acylase for making (2S,5S)-5-fluoromethylornithine	[91]
US5212069	N-Acetyl-2,3-didehydroleucine acylase for the preparation of D- or L-tryptophyl glycine, D- or L-tryptophyl-D-methionine or L-tryptophyl-D-cysteine	[92]
US5219741	N-Acyl-L-proline acylase for making L-proline, L-pipecolic acid and L-thiazolidine-4-carboxylic acid	[93]
US5057607	Penicillin G amidase(acylase) for enantiomerically selective acylation of racemic 3-amino azetidinone intermediates	[94]

in a two-step process by the sequential actions of a nitrile hydratase to generate an amide and its subsequent hydrolysis by an amidase to yield the carboxylic acid (Scheme 2). There is considerable industrial interest in the enzymatic conversion of nitriles owing to the desirability of conducting such conversions under mild reaction conditions that would not alter other labile reactive groups. Additionally, the existence of nitrile-hydrolyzing enzymes that show enantioselectivity and/or regioselectivity offers synthetic possibilities that are difficult or impossible to achieve by conventional catalytic approaches.



Scheme 2. Two pathways for the enzymatic conversion of nitriles into carboxylic acids.

The first and most successful industrial application of nitrile-hydrolyzing enzymes on a commercial scale is the Nitto process for the production of acrylamide from acrylonitrile.^[19] The process, which originally used whole cells of *Pseudomonas chlororaphis* B23 or *Rhodococcus* sp. N-774, currently uses *Rhodococcus rhodochrous* J1, which is 10-fold more productive. This strain produces two different nitrile hydratase enzymes as well as a nitrilase and an amidase. The reaction is run at 2–4 °C, at which temperature the formation of contaminating acrylic acid is barely detectable, and the productivity of the reaction is >7 kg of acrylamide per gram of cells with a conversion of 99.7%. The strain is tolerant of concentrations of acrylamide up to 50%, but is used only for a single batch conversion. This process is currently run on an annual scale of 40 000 tons. *Rhodococcus rhodochrous* J1 is also used by Lonza in its commercial process for the conversion of 3-cyanopyridine into nicotinamide, a vitamin used in animal feed supplements.^[20] Annually, 3000 tons are produced by using immobilized whole cells, and no nicotinic

acid, a common by-product in the chemical synthesis of nicotinamide, is found.

The isolation and use of nitrile-hydrolyzing enzymes, especially for the production of specific chiral synthetic intermediates, has been described (Table 3). To our knowledge, there is no industrial process that currently uses these enzymes for such production. Enantioselective enzymes have been described that preferentially hydrolyze either the D- or L- form of a variety of nitrile-containing substrates.^[21–29] In general, the nitrilases show more enantioselectivity than the nitrile hydratases, and the enantioselectivity is highly substrate dependent. In the case of the nitrile hydratases, these nonspecific enzymes are often co-expressed with highly enantioselective amidases.

Although nitrile-hydrolyzing enzymes offer attractive mild reaction conditions, their routine industrial use has been hampered by other factors. The half-lives of the enzymes that have been purified and studied to date range from 7.5 minutes at 45 °C for a *Corynebacterium* sp. to 58 minutes at 60 °C for the *Rhodococcus rhodochrous* J1 nitrile hydratase.^[30–32] Both the acrylamide and nicotinamide processes require *Rhodococcus* whole cells, partly because the purified nitrile hydratase is too unstable. Although systems that involve whole cells avoid expensive enzyme purifications, they are in general undesirable, as contaminating side products can result from the reactions of other enzymes within the cell. There is currently no commercial source for purified nitrilase or nitrile hydratase. Although Novo previously sold a combination of nitrile hydratase and amidase from *Rhodococcus* sp. CH5, this product is no longer available. For reactions in which regio- or stereoselectivity is desired, it has been found that the degree, extent, and even absolute configuration of the final product are highly dependent on the substrate. Thus it is difficult to predict which, if any, of the known nitrilases or nitrile hydratases will efficiently convert a given substrate into the desired product.

There have been no published reports of successful attempts to utilize directed evolution to improve the characteristics of the nitrile-hydrolyzing enzymes or to adapt them to industrial use. Classical mutagenesis and screening were used to improve the characteristics of the original acrylamide-producing strains, making them less mucoid, easier to separate by centrifugation, and less inhibited by substrate concentration,^[33] but these improvements were largely superseded by the isolation of *Rhodococcus rhodochrous* strain J1. Directed evolution continues to deliver enzymes with improved

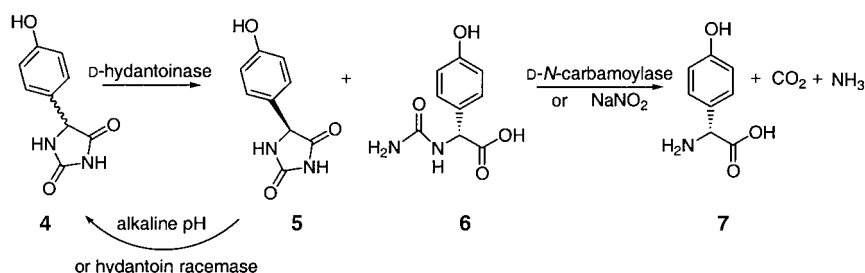
Table 3. Patents on the isolation and use of nitrile-hydrolyzing enzymes.

Patent	Title	Ref.
US05811286	Nucleic acid fragments encoding stereospecific nitrile hydratase and amidase enzymes and recombinant organisms expressing those enzymes useful for the production of chiral amides and acids	[95]
US06133421	Polypeptides and polypeptide subunits of a stereospecific nitrile hydratase enzyme	[96]
US05888785	Method for using hydratase or a hydratase–amidase fusion for stereospecifically bioconverting certain racemic nitriles to the corresponding enantiomeric <i>R</i> - or <i>S</i> -amide or <i>S</i> -carboxylic acid	[97]
US05814497	Enzymatic hydrolysis of racemic α -substituted 4-methylthiobutyronitriles using a nitrilase from <i>Alcaligenes faecalis</i> , <i>Gordona terrae</i> , or <i>Rhodococcus</i> sp.	[98]
US05443973	Method of producing α -hydroxyisobutyramide from acetone cyanohydrin by nitrile hydratase	[99]
JP08131188	Production of optically active α -hydroxyacid or α -hydroxyamide	[100]
US05206158	Process for the preparation of difluorobenzamide	[101]

substrate specificity, stability, and activity under a variety of physical and chemical conditions;^[34] thus, the evolution of stable nitrile-hydrolyzing enzymes that are active under optimal process conditions and that regio- or stereoselectively hydrolyze commercial nitrile-containing substrates may be achievable. Such enzymes would be a valuable addition to the biocatalytic toolbox currently available to the synthetic chemist.

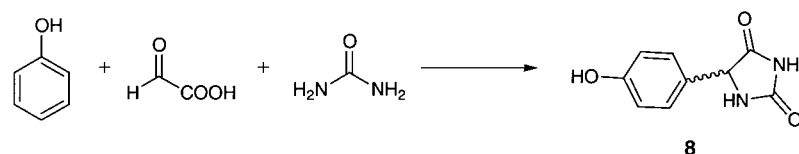
3.3. Hydantoinases

Hydantoinases are used commercially in the production of non-natural amino acids on a scale of several thousand tons per year. The most significant processes are the production of D-phenylglycine and D-*p*-hydroxyphenylglycine, which are important building blocks for semisynthetic β -lactams such as ampicillin, amoxicillin, and cephalexin.^[35] They are used also to make D-tryptophan, D-phenylalanine, D-valine, D-alanine, D-methionine, and a variety of substituted amino acids.^[36] Hydantoinases catalyze the stereospecific hydrolysis of 5-monosubstituted hydantoins **4** to give *N*-carbamoyl α -amino acids **6**. The *N*-carbamoyl α -amino acids are then hydrolyzed either in the presence of a carbamoylase (in the Recordati process) or in a solution of sodium nitrite (in a process commercialized by Kanegafuchi) to yield the amino acid **7**, carbon dioxide, and ammonia (Scheme 3).^[37] Most hydantoinases identified to date are specific for the D form of the hydantoin.



Scheme 3. Enantioselective preparation of **7** from **4** by using D-selective hydantoinase and D-selective *N*-carbamoylase.

Racemic hydantoins **8** are generally synthesized in the Mannich condensation of phenol derivatives, glyoxylic acid, and urea (Scheme 4). Many 5-substituted hydantoins racemize readily as a result of their acidic hydrogen atom through keto-enol tautomerism, thus allowing a dynamic kinetic resolution and a 100% theoretical yield of the desired product. In practice, however, the actual rate of racemization is highly dependent on the nature of the substitution at C5. For example, the $\tau_{1/2}$ for phenylhydantoin racemization is



Scheme 4. Preparation of racemic **8** by means of a Mannich condensation.

0.3 h, whereas that for isopropylhydantoin is 56 h.^[38] Furthermore, many hydantoins are sparingly soluble to insoluble, so in practice the substrate is often added to the reaction mixture as a suspension, and the dissolution of the substrate can be the rate-limiting step. Currently, the commercially available hydantoinases require Mn^{2+} as a cofactor and are irreversibly inactivated if the Mn^{2+} center is oxidized. Therefore, the reaction must be run anaerobically, which typically requires that the oxygen be replaced with nitrogen each time a new cycle is started. Thus, although native hydantoinases are currently being used commercially, the properties of both the enzyme and the substrate suggest that the process could be improved through directed evolution. A catalyst that functions at elevated temperatures would allow a process in which the substrate is more soluble and racemization is enhanced. If the evolution of the enzyme removed or altered the Mn^{2+} requirement, the process could then be carried out aerobically.

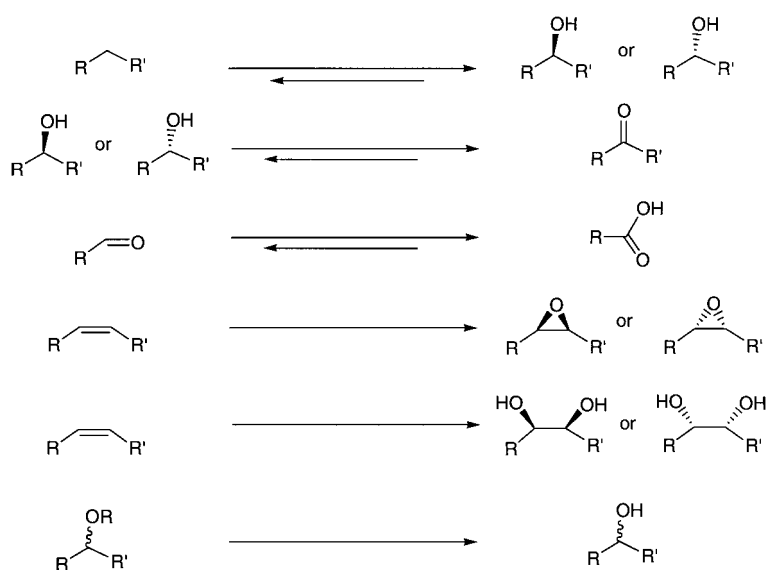
In contrast to many industrially promising enzymes, the hydantoinases have been subjected to intensive directed evolution studies. Early mutagenesis efforts have been followed by increasingly sophisticated strategies. Hybrid enzymes that pair the amino-terminal half of a hydantoinase from *Bacillus stearothermophilus* with the carboxy-terminal half of a hydantoinase from *Bacillus thermocatenulatus* showed altered substrate specificities relative to both parent enzymes.^[39] Kim et al. fused a hydantoinase and a carbamoylase in an attempt to circumvent unequal expression, inclusion body formation, and substrate transport problems, which are

inherent in traditional co-expression systems.^[40] The resulting *N*-carbamoylase-D-hydantoinase fusion enzyme proved to be as active and catalytically as efficient as the co-expressed wildtype enzymes. However, the fusion enzyme was unstable as a result of extensive proteolysis, and DNA shuffling was used subsequently to enhance the stability of the fusion enzyme. An evolved enzyme was identified that was six times as active as the parent fusion enzyme in converting the hydantoin into the D-amino acid.^[41] A direct comparison of the performance of

the evolved fusion enzyme with the best available co-expression system has yet to be reported. Finally, in a striking example of the utility of directed molecular evolution, May et al. have overcome a key drawback to hydantoinase-mediated amino acid production: the rigid stereoselectivity of known hydantoinases. By using gene shuffling, this group inverted the stereospecificity of an *Arthrobacter* hydantoinase from the D to the L enantiomer of methionine hydantoin.^[3] Roche now employs this evolved enzyme in a commercial process for the production of L-methionine. There are no reports to date of efforts to alter the thermal activity profile or to reduce/replace the cofactor requirement of hydantoinases, two properties that might translate directly to process improvements.

3.4. Oxidoreductases

Oxidoreductases (EC1) catalyze a myriad of chemo-, stereo-, and regioselective reactions (Scheme 5), and currently are used for the production of a variety of pharmaceutical



Scheme 5. Reactions that are catalyzed by oxidases and oxidoreductases.

and chemical products (Table 4). Oxidoreductases are generally employed in fermentation-based processes, or for whole cell biotransformations, which, as mentioned earlier, can be undesirable. To better exploit the industrial potential of oxidoreductases, processes that utilize isolated enzymes

important technical milestones, the need for NAD(P)H in more than catalytic concentrations is still a serious issue for cell-free formats.

Directed evolution offers hope that the NAD(P)H requirement may be addressable. In particular, Arnold and co-workers have successfully produced mutants of bacterial cytochrome P450 enzymes that catalyze the hydroxylation of naphthalene approximately 20 times better than the wildtype, and use a hydrogen peroxide shunt pathway that does not require NAD(P)H.^[45] The same group also developed a high-throughput digital imaging screen for arene-specific oxygenases by coupling them to horseradish peroxidase.^[46] The peroxidase catalyzes the oxidative coupling of hydroxylated aromatics that are produced by the oxygenases, resulting in the creation of fluorescent compounds. Different substrate hydroxylation patterns result in compounds that have different fluorescent spectra. Arnold and co-workers used this system to identify evolved oxidases that have new hydroxylation specificities. Such screens should assist the development of mono- and dioxygenases as useful biocatalysts for the production of hydroxylated aromatic compounds.

Of the oxidoreductases, the ubiquitous cytochrome P450 enzymes, of which several hundred have been characterized, are particularly intriguing. Structural and mutational studies have shown that minor alterations in the P450 protein structure can lead to changes in chemo-, regio-, and stereoselectivity^[47]. The directed evolution of these enzymes has also begun to produce biocatalysts that are useful for the selective oxidation of a variety of interesting substrates. For example, directed evolution was used to create an indole hydroxylase from cytochrome P450 BM-3, a fatty acid hydroxylase that is not active on this substrate.^[48] Arnold and co-workers also used directed evolution to improve the solubility of a mammalian cytochrome P450 that is normally membrane associated.^[49] Hybrid cytochrome P450 genes were created from a membrane-associated human cytochrome P450 and the heme domain of a bacterial cytochrome P450 by using SHIPREC (sequence homology-independent protein recombination). Screening for the activity of the mammalian gene identified two functional hybrids that were more soluble in the bacterial system.

Other oxidoreductases have also been manipulated by evolutionary approaches. For example, directed evolution was used to increase the peroxidase activity of horse heart myoglobin, an effort that enabled the direct enzymatic high-throughput screening of peroxidase-producing *E. coli* strains.^[50] A more thermostable catechol 2,3-dioxygenase was created by DNA shuffling of *nahH* and *xylE* 2,3-dioxygenases.^[51, 52] By using a combination of rational and evolutionary methods, Cherry et al. improved the oxidative and thermal stability of a heme peroxidase for use as a laundry additive.^[53] Horseradish peroxidase has also been evolved to express better in a soluble form in *E. coli*.^[54] Ultimately, it is possible that the stability of cytochrome P450 and other heme-dependent enzymes may be limited by the instability of

Table 4. Examples of biocatalytic processes with oxidoreductases.

Reaction Product	Enzyme	Ref.
L-tert-leucine	Leucine dehydrogenase	[102]
6-hydroxynicotinic acid	<i>Achromobacter xylosoxidans</i>	[103]
5-methylpyrazine-2-carboxylic acid	<i>Pseudomonas putida</i>	[103]
(R)-2-(hydroxyphenoxy)propionic acid	<i>Beauveria bassiana</i>	[103]
Steroids	Several	[104]

(preferably immobilized) would be desirable. However, oxidoreductases are not practical for use in vitro since they require expensive cofactors (e.g. NAD(H) or NADP(H)), and are often membrane associated. As with most enzymes, improvements in stability, turnover, and specificity would benefit many applications.

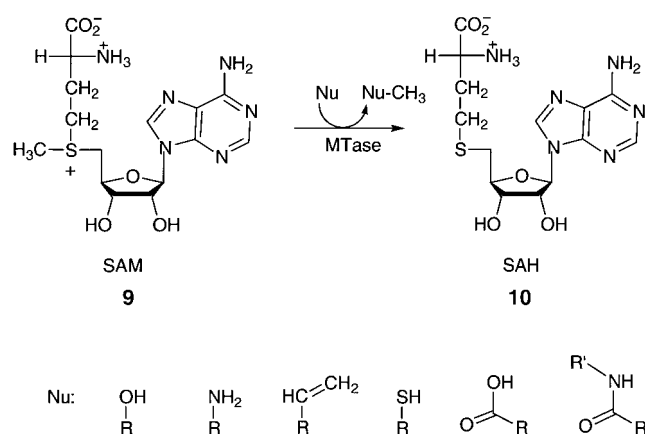
There have been several attempts to overcome these challenges. For example, several NAD(P)H-regeneration systems have been developed to make NAD(P)H a cofactor (catalytic) rather than a substrate in the reaction. Process-based solutions include chemical and electrochemical regeneration techniques, whereas host-cell-based solutions involve the overproduction of NAD(P)H-regeneration enzymes.^[42] More appropriate to the use of purified or immobilized enzyme catalysis are gene fusions between an enzyme of interest and a gene that codes for a redox partner.^[43, 44] Although these NAD(P)H-regeneration systems are all

the porphyrin structure under oxidative conditions.^[55] It has been suggested that monooxygenases that are not dependent on heme and that catalyze similar reactions as the cytochrome P450 enzymes might also be excellent targets of directed evolution.^[56]

3.5. Methyl Transfer

We have discussed a variety of important chemical reactions that have been addressed by using biocatalysis. There are other chemical reactions that might be suitable for biocatalysis and that have not yet been fully explored, for example, methylation. Methylation is particularly useful because it is so subtle. Methylation is generally effected by using a methyl halide such as MeI. The reaction is promiscuous, although regioselective methylation can be accomplished if the reactivity of competing nucleophiles within a molecule can be differentiated by the manipulation of solvent, solute, and physical parameters or by selective protection. Selectivity is generally not complete and purification of the desired isomer is required. A biocatalytic route to regio- and stereospecific methylation could greatly improve yields and avoid costly downstream processing.

S-Adenosylmethionine (SAM; **9**) is a methyl donor in enzymatic methylation reactions, that is, SAM is the biological equivalent of methyl halides. The active group of SAM is a methyl sulfonium cation. Enzyme-catalyzed nucleophilic attack at the methyl group displaces S-adenosylhomocysteine (SAH; **10**) (Scheme 6). The loss of the positive charge on the sulfur atom is thermodynamically favorable and drives the reaction to completion. Biological methylation of most biological nucleophiles is documented. Unlike chemical methylation, enzymatic methylation is regio- and enantioselective, as expected from biological catalysts.



Scheme 6. S-adenosylmethionine (SAM) acts as a methyl donor in enzyme-catalyzed methyl-transfer reactions. Methyltransferases (MTase) catalyze the methylation of a diverse set of biological nucleophiles.

The use of methyltransferases for biocatalysis is limited. SAM is expensive and methyltransferases react notoriously slowly ($k_{\text{cat}} \approx 1 \text{ s}^{-1}$) and are often membrane associated. Working in vitro requires stoichiometric amounts of SAM, since no alternative methyl donors or SAM regeneration

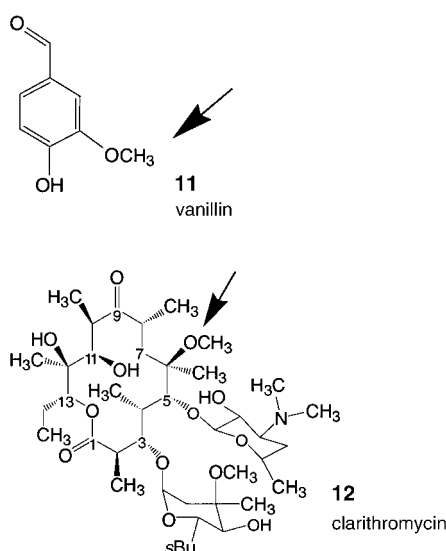
systems have been described. Increased solubility, stability, selectivity, and catalytic efficiency would be desirable for useful industrial processes. These all represent opportunities for enabling biocatalytic methyl transfer through directed evolution, and there is precedence for the tailoring of methyltransferase specificity by rational design. Trautner et al. produced chimeric DNA methyltransferases that are specific for different DNA sequence combinations.^[57] Methyltransferases have also been discussed for combinatorial biosynthesis.^[58] However, cited examples of biocatalytic exploitation of methyltransferases are difficult to find.

In vivo there are presently a variety of useful targets for the application of methyltransferases. In the natural products arena, methyltransferases are commonly involved in the terminal step of the synthesis of small molecule antibiotics such as erythromycin, tylosin, rapamycin, and daunomycin.^[59, 60] For example, macrocin methyltransferase, which is encoded by the *tylF* gene in *Streptomyces fradiae*, is rate limiting in the production of the commercial antibiotic tylosin. Additional copies of the *tylF* gene result in measurable increased levels of tylosin in fermentations of *S. fradiae*.^[61] DNA shuffling of *tylF* for improved catalytic efficiency could further increase the yield and productivity of tylosin fermentations. Li and Frost described a method for the biocatalytic methylation of the 3-hydroxy group of protocatechuate by catechol OMTase (COMTase).^[62] Unfortunately, COMTase methylates both the 3- and the 4-hydroxy groups of protocatechuate. Directed evolution of COMTase to be specific for the 3 position would provide an improved biocatalytic route to vanillic acid; subsequent reduction by aryl aldehyde reductase would provide a complete route to natural vanillin (**11**; Scheme 7).

The specific methylation of the 6-hydroxy group of erythromycin A has become something of a holy grail. Such an enzyme would provide a single step synthesis of clarithromycin (**12**; Scheme 7), a billion dollar drug that presently requires a seven-step chemical methylation.^[63] Methyltransferases that are specific for tertiary alcohols are rare, perhaps because they are more sterically hindered than primary or secondary alcohols. One such enzyme is EryG, which methylates the tertiary alcohol group of the mycarose moiety of erythromycin C.^[59] Thus tertiary O-methylation is not unprecedented, and the evolution of an erythromycin 6-O-methyltransferase may be quite feasible.

3.6. Hydrolytic Enzymes: Lipases, Esterases and Proteases

Hydrolytic enzymes (EC 1) have been used as catalysts in organic synthesis more than any other class of enzyme. Hydrolases catalyze the selective hydrolysis of esters, amides, halides, peptides, and glycosides. Many of these enzymes have been adapted to function in environments with low water content in which they catalyze the thermodynamically more favorable synthetic reaction. Lipases, which naturally function on hydrophobic compounds, in particular have shown the ability to catalyze ester and lactone synthesis in organic solvents.^[64, 65] Commercial hydrolase-mediated processes in-



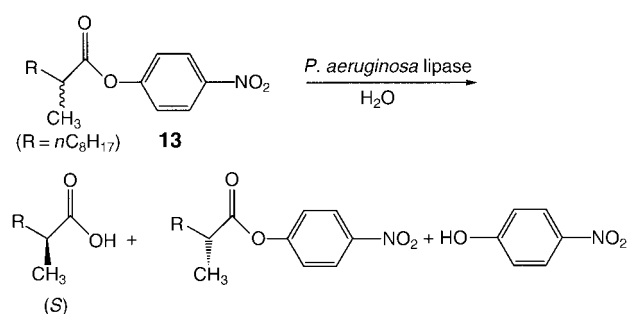
Scheme 7. Molecular targets for evolved methyltransferases. An erythromycin 6-O-methyltransferase would provide a biocatalytic route to clarithromycin (**12**). A catechol 3-O-methyltransferase would provide a biocatalytic route to natural vanillin (**11**). The arrows indicate the position of the desired addition of the methyl group.

clude the production of intermediates for pharmaceuticals, pesticides, and drugs, the production of chiral synthons for asymmetric synthesis, as well as applications in the food industry, such as the production of high-fructose syrup, low-lactose milk, and aspartame. Current examples have been compiled and discussed previously.^[37, 66, 67]

As is the case with most enzymes, natural hydrolases are generally not optimal biocatalysts. Multiple parameters could be improved by directed evolution to enhance their performance. Hydrolase enzymes are by nature active on a broad range of substrates but paradoxically maintain a high degree of chemo-, regio-, and stereoselectivity. Directed evolution provides a means to tune this specificity for desired processes. To this end, improvements in substrate specificity,^[68] enantioselectivity,^[1, 69] specific activity, thermostability,^[70–74] solvent tolerance,^[70, 75] activity over a broad pH range, and combinations thereof^[34] have been described.

3.6.1. Lipases and Esterases

Lipases and esterases both catalyze the hydrolysis of esters. Lipases prefer less soluble esters, and have a broader substrate specificity and a higher enantioselectivity than esterases. Lipases have been used extensively to produce optically active alcohols, acids, esters, and lactones by kinetic resolution. Such applications are of great importance since industry generally demands compounds with an optical purity $\geq 95\%$. For this reason, Reetz et al. improved the enantioselectivity of a *Pseudomonas aeruginosa* lipase by directed evolution.^[69] The native lipase catalyzes the hydrolysis of racemic **13** with an *ee* of 2% (*S*) (Scheme 8). Four cycles of mutagenesis and screening produced an evolved lipase with an improved *ee* of 81%. Additional rounds of error-prone PCR combined with saturated mutagenesis resulted in an *ee* of more than 90%.^[1] Modeling of the evolved lipase structure



Scheme 8. Kinetic resolution of **13** by lipase-catalyzed hydrolysis.

revealed that the amino acid substitutions might increase the conformational flexibility of the enzyme. In a similar fashion, Bornscheuer and co-workers increased the *ee* of 3-hydroxyethyl ester resolution by means of the directed evolution of an esterase.^[68, 76, 77] Increased catalytic activity and stability in the presence of an organic solvent is of particular interest,^[78] as these conditions are often necessary to dissolve the substrate or to favor reaction thermodynamics. For this reason, Moore and Arnold improved the activity of a *Bacillus subtilis* esterase 150-fold in 15% DMF by using directed evolution.^[79, 80]

3.6.2. Proteases

Proteases catalyze the selective hydrolysis of peptides, amides, and esters in a manner mechanistically similar to lipases and esterases. They are primarily used in organic synthesis for the enantioselective hydrolysis of α -amino acid esters and carboxylic acid esters. As is the case with esterases, they also catalyze transamination, transesterification, and synthetic reactions under the appropriate conditions. Commercial proteases such as subtilisin are primarily used in laundry detergents and have been engineered extensively for improved stability and activity at high temperatures and pH values. Despite 30 years of rational improvements, only recently did gene shuffling of subtilisin with 25 homologues result in impressive improvements in activity under a variety of chemical and physical extremes.^[34] In a different study, the specific activity of subtilisin E was improved 470-fold.^[81] The temperature optimum of this enzyme was also broadened and its half-life at 65 °C was extended 200-fold.^[82, 83] Taguchi et al. evolved subtilisin BPN' and thus doubled the activity at 10 °C,^[84] which showed that the activity could be improved at relatively low temperatures.

Clearly, directed evolution is expanding biocatalytic options for the organic chemist. Hopefully, the development of additional hydrolytic enzyme families such as dehalogenases and epoxide hydrolases will result in further applications of commercial biocatalysis.

4. Summary and Outlook

We stand on the edge of a new era for industrial biocatalysis. The capacity to improve enzymes provides the opportunity to effect regio- and stereospecific chemical

reactions with selected enzymes as biocatalysts. The potential for cooperation between chemists and biologists to design and implement these catalysts will become clear in the near future. The potential for libraries of enzymes that are rapidly available and the further development of targeted and specific catalysts for a desired reaction are intriguing and exciting developments for the future of chemical synthesis.

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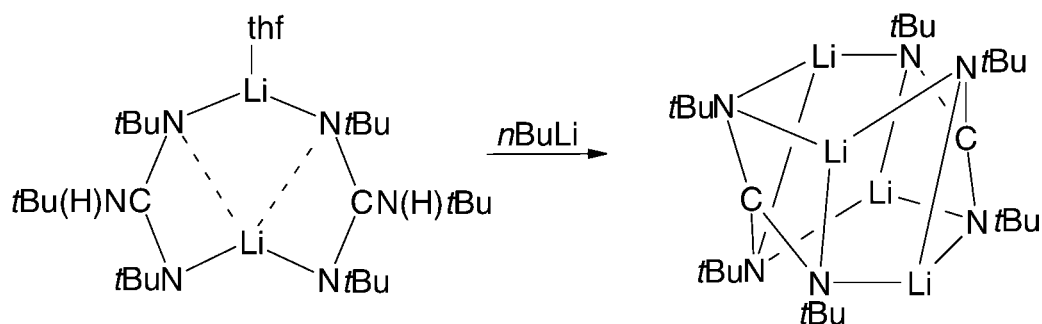
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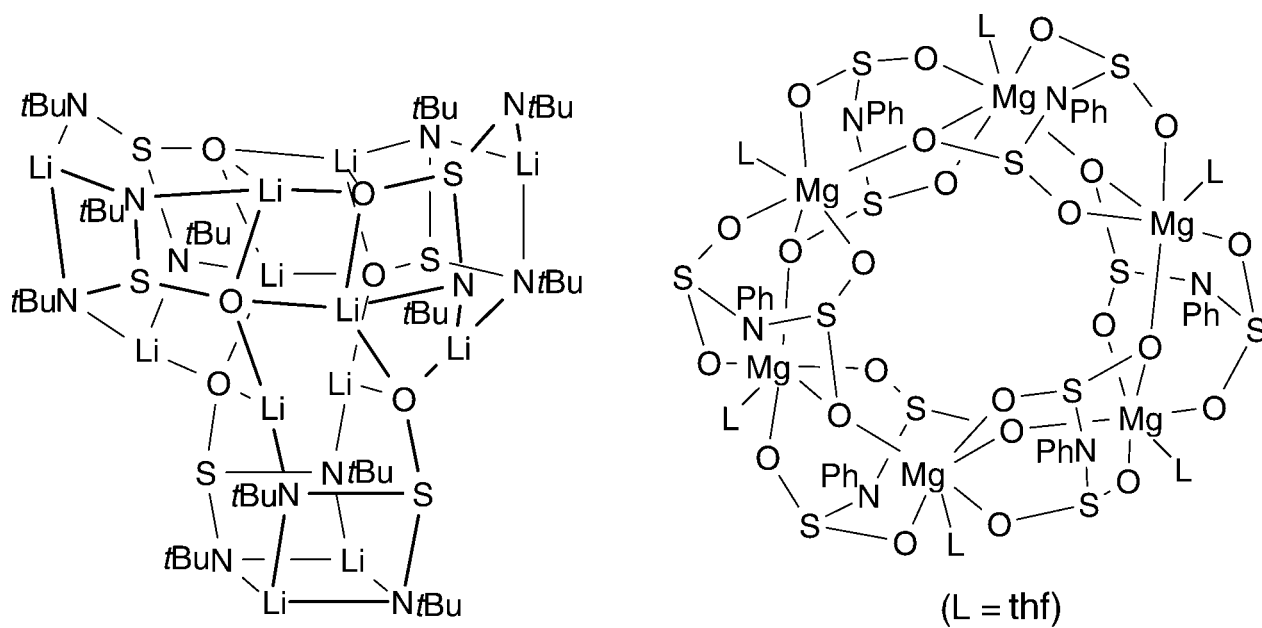
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Imido Anions

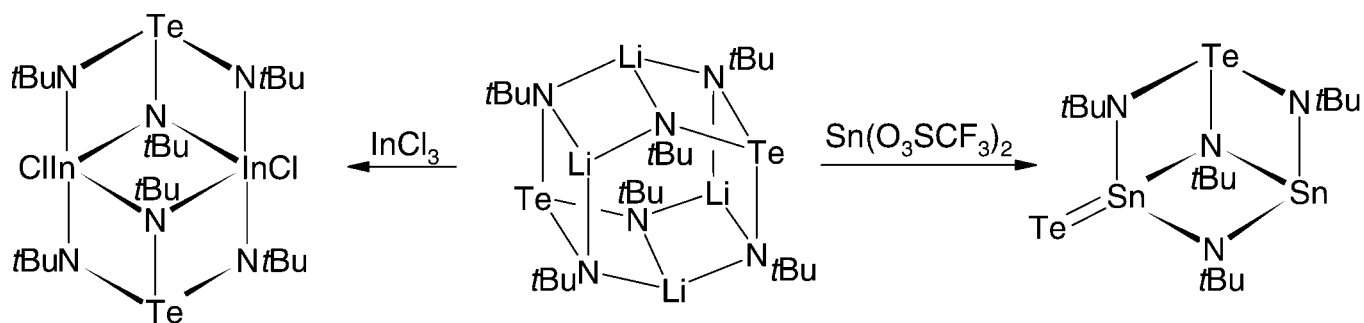
Synthesis



Structures



Ligand Behavior



Imido Analogues of Common Oxo Anions: A New Episode in the Chemistry of Cluster Compounds

Justin K. Brask and Tristram Chivers*

Oxo anions of p- and d-block elements, for example, SiO_4^{4-} , PO_4^{3-} , SO_4^{2-} , and CrO_4^{2-} , are commonly encountered species. The full or partial replacement of the oxo ligands by isoelectronic imido (NR) groups generates homoleptic polyimido anions of the type $[\text{E}(\text{NR})_x]^{z-}$ or heteroleptic imido-oxo anions with the general formula $[\text{O}_y\text{E}(\text{NR})_{x-y}]^{z-}$ (where E = main group element or transition metal).

The alkali metal derivatives of this new class of anions form ternary or quaternary cluster systems, respectively. The structures of these clusters can be rationalized in terms of the self-assembly of fundamental building blocks. An understanding of the factors that control this process may allow the design of functional materials with specific properties. In addition, these anions are attracting attention as mul-

tidentate ligands with unique electronic and stereochemical properties that may engender novel metal-centered chemistry.

Keywords: cluster compounds • coordination chemistry • isoelectronic analogues • main group elements • transition metals

1. Introduction

The “isoelectronic principle”, first espoused by Langmuir,^[1] is a simple and useful concept, especially in inorganic chemistry. It is frequently invoked in the application of Valence Shell Electron Pair Repulsion Theory for the prediction of the shapes of molecules with a central p-block element. The polyhedral skeletal electron-pair counting (Wade’s) rules,^[2] which are so successful in predicting the structures of electron-deficient main group element and transition metal clusters,^[3] also rely on this idea. For the synthetic chemist the first preparation of an unknown compound has often been prompted by the existence of an isoelectronic analogue. Furthermore, many isoelectronic species undergo analogous reactions.

The NR (R = H, alkyl, aryl) group is isoelectronic with an oxo (O) ligand, but the organic substituent in the former gives rise to significant differences in the properties of isoelectronic

analogues. For example, CO_2 and $\text{C}(\text{NR})_2$ are both multiply bonded monomers, but carbon dioxide is a gas whereas N,N' -dialkyl carbodiimides are liquids. More dramatically, tellurium dioxide $(\text{TeO}_2)_\infty$ is a three-dimensional polymer^[4] while the tellurium diimide $t\text{BuN}(\mu\text{-N}t\text{Bu})_2\text{TeN}t\text{Bu}$ is dimeric.^[5] The imido ligand is a versatile cornerstone for the construction of cluster molecules as exemplified by the iminoalanes $(\text{RAINR}')_n$ which may adopt cubane ($n=4$), hexagonal prismatic ($n=6$), or larger structures ($n=7, 8$) depending on the steric requirements of the R and R' groups.^[6] Interestingly, the industrially important alkylalumoxanes $(\text{RAIO})_n$, isoelectronic with iminoalanes, form larger clusters such as a nonamer (R = $t\text{Bu}$).^[7a,b] Moreover, recent density functional theory (DFT) calculations indicate that a dodecamer (R = Me, $n=12$), formed by the dimerization of two hexagonal prisms, is the most stable oligomer.^[7c]

Oxo anions of the general formula $[\text{EO}_x]^{z-}$ (E = p- or d-block element) are frequently encountered species in all areas of chemistry and, indeed, in everyday life. The full or partial replacement of the oxo ligands by imido groups leads to a new class of anions, that is, polyimido anions of the type $[\text{E}(\text{NR})_x]^{z-}$ or imido-oxo anions with the general formula $[\text{O}_y\text{E}(\text{NR})_{x-y}]^{z-}$. As a further extension, the oxo ligands in the heteroleptic systems can be replaced by S or Se substituents.

The first homoleptic polyimido anions of p- or d-block elements, $[\text{S}(\text{NH})_4]^{2-}$ and $[\text{Te}(\text{NH})_3]^{2-}$, were obtained as their dipotassium salts more than thirty years ago, but characterization was limited to elemental analyses.^[8] More recently the lithium derivatives of $[\text{P}(\text{NMes}^*)_2]^{-[9]}$ ($\text{Mes}^* = 1,3,5$ -

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$t\text{Bu}_3\text{C}_6\text{H}_2$) and $[\text{Si}(\text{N}t\text{Bu})_3]^{2-}$ ^[10] were reported by the groups of Lappert and Veith, respectively, but structural information was lacking. In 1989 Wilkinson et al. described the first structural determination for this novel class of cluster compounds.^[11] The core of the dimeric d-block element complex $[\text{Li}_2\{\text{W}(\text{N}t\text{Bu})_4\}]_2$ was shown to consist of an $\text{Li}_4\text{W}_2\text{N}_6$ hexagonal prism.^[11] In the last decade these ternary cluster systems, and the related quaternary systems formed by alkali metal derivatives of imido-oxo anions of p-block elements, have been extensively investigated. Their structures can be understood in terms of the self-assembly of fundamental building blocks. In addition to this structural interest, the anions themselves are attracting attention as multidentate ligands with novel electronic and geometric properties. Curiously, although neutral imido transition metal complexes have been widely studied,^[12] the polyimido anions of p-block elements have attracted more attention than their d-block counterparts, as illustrated by the examples given in Tables 1 and 2. This review begins with a discussion of synthetic approaches to these anionic species. Subsequently, the focus is on the structural principles involved in cluster formation and the behavior of the anions as coordinating ligands. Selected aspects of the chemistry of polyimido anions of Group 15 and 16 elements have been reviewed previously.^[13, 14]

2. Synthetic Strategies

A variety of methodologies have been employed for the synthesis of polyimido and imido-oxo systems. However, three general strategies have emerged as the most versatile: a) deprotonation of amido complexes, b) transamination re-

actions, and c) nucleophilic addition. Examples of the advantages and limitations of each of these approaches will be discussed in this section.

2.1. Metallation of Primary Amido Complexes

The metallation of compounds with primary amido groups, NHR (R = alkyl or aryl), is perhaps the most obvious route to polyimido anions of p- or d-block elements. Indeed the monolithiation of $\text{Mes}^*\text{N}=\text{P}(\text{NHMe}^*)$ with $n\text{BuLi}$ represents the first preparation of a well-defined complex containing a polyimido anion [Eq. (a), $\text{Mes}^* = 1,3,5\text{-}t\text{Bu}_3\text{C}_6\text{H}_2$].^[9] The related complexes $[(\text{L})\text{Li}\{\text{P}(\text{NR})(\text{NR}')\}]_n$ ($\text{R} = \text{Mes}^*$, $\text{R}' = \text{CPh}_3$, $\text{L} = \text{Et}_2\text{O}$, $n = 1$;^[19] $\text{R} = \text{Mes}^*$, $\text{R}' = t\text{Bu}$ or 1-adamantyl



(1-Ad), $n = 2$;^[19] $\text{R} = \text{R}' = t\text{Bu}$, $\text{L} = \text{thf}$, $n = 2$ ^[20]) and $[(\text{thf})_2\text{Mg}\{\text{P}(\text{N}t\text{Bu})_2\}]_2$ (generated by magnesiation with MgBu_2),^[20] which also contain examples of bisimidophosphorus(III) monoanions, were subsequently prepared in a similar manner. Interestingly the order of addition of the reagents sometimes affects the outcome of these lithiation reactions. Thus the addition of the amidoimido compound $t\text{BuNHP}(\mu\text{-N}t\text{Bu})_2\text{PNH}t\text{Bu}$ to the alkyllithium reagent produces the unsolvated tetramer $[\text{Li}\{\text{P}(\text{N}t\text{Bu})_2\}]_4$ whereas the reverse addition yields the adduct $[\text{Li}\{\text{P}(\text{N}t\text{Bu})_2\}]_4 \cdot 0.25\text{P}_4(\text{N}t\text{Bu})_6$.^[21]

Polyimido analogues of the metaphosphate ion, PO_3^- , have also been prepared from the corresponding amido compounds. Thus lithiation of $(\text{Mes}^*\text{N})_2\text{P}(\text{NHMe}^*)$ with $n\text{BuLi}$ in THF produces the ion pair $[(\text{thf})_4\text{Li}][\text{P}(\text{NMe}^*)_3]$, which

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T. Chivers



J. K. Brask

Justin Kirkegaard Brask was born in Aarhus, Denmark in 1973 and moved to Banff, Canada in 1977. He graduated with first class honours in Chemistry (with a minor in Pure Mathematics) from the University of Calgary, Canada, in 1996. He obtained his Ph.D. from the same university in 2000 under the supervision of Professor T. Chivers in the area of main group element chemistry. Dr. Brask is currently an NSERC (Canada) post-doctoral fellow at the Massachusetts Institute of Technology, Cambridge, USA, in the group of Professor C. C. Cummins working with highly reactive early transition metal complexes.

Table 1. Polyimido and imido/oxo(chalcogenido) anions of p-block elements.

Periodic group	Polyimido or imido/oxo(chalcogenido) ion	Related oxo anion	E or X
14		carbonate, CO ₃ ²⁻ metasilicate, SiO ₃ ²⁻	C ^[15, 16] Si ^[10]
14		orthosilicate, SiO ₄ ⁴⁻	[17]
15		nitrite series, EO ₂ ⁻	N ^[18] P ^[9, 19–21] As ^[22, 23] Sb ^[24, 25] Bi ^[25]
15		arsenite, AsO ₃ ³⁻ stibinite, SbO ₃ ³⁻	As ^[26] Sb ^[27]
15		metaphosphate, PO ₃ ⁻	NR ^[28] S ^[29] Se ^[29]
15		phosphate, PO ₄ ³⁻	[30]
16		sulfite, SO ₃ ²⁻ selenite, SeO ₃ ²⁻ tellurite, TeO ₃ ²⁻	S ^[31] Se ^[32] Te ^[33]
16		sulfite, SO ₃ ²⁻	NR ^[34, 35] O ^[36]
16		disulfite, S ₂ O ₃ ²⁻	[35]
16		sulfate, SO ₄ ²⁻	[37]
16		sulfate, SO ₄ ²⁻	NR ^[38] O ^[39]

contains the homoleptic ion [P(NMes*)₃]⁻.^[28] Similarly, the isoelectronic imidothio and imidoselena ions [SP(NtBu)₂]⁻ and [SeP(NtBu)₂]⁻, respectively, are generated as the dimers [(thf)₂Na{EP(NtBu)₂}]₂ and polymers [(thf)_xK{EP(NtBu)₂}]_∞ (E = S, x = 1; E = Se, x = 1.5) by metallation of (tBuNH)(E)P(μ-NtBu)₂P(E)(NHtBu) (E = S, Se) with two equivalents of MN(SiMe₃)₂ (M = Na or K).^[29]

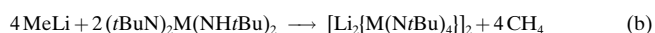
Lithiation is also effective for the preparation of polyimido anions of Group 14 elements. The trisimidocarbonate and trisimidometasilicate complexes [(thf)₃Li₂{C(NPh)₃}]₂^[15] and [Li₂{Si(NtBu)₃}]_n^[10] are formed by treatment of PhN=C(NHPh)₂ or (tBuNH)₂Si(μ-NtBu)₂Si(NHtBu)₂, respectively, with *n*-butyl- or methyllithium in the appropriate molar ratios. The resulting dianions [E(NR)₃]²⁻ (E = C, Si) are

Table 2. Polyimido and imido-oxo anions of d-block elements.

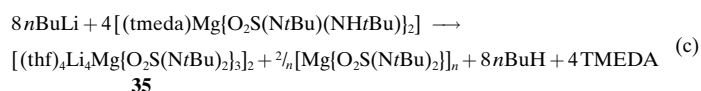
Periodic group	Transition metal polyimido anion	Related oxo anion	M or X
5		niobate, NbO ₄ ³⁻	[40]
6		chromate, CrO ₄ ²⁻ molybdate, MoO ₄ ²⁻ tungstate, WO ₄ ²⁻	Cr ^[41] Mo ^[42] W ^[11, 42]
7		unknown	Tc ^[43] Re ^[44]
7		manganate, MnO ₄ ²⁻	[45]
7		perrhenate, ReO ₄ ⁻	NR ^[11, 46] O ^[44]

isoelectronic with the common oxo anions CO₃²⁻ and SiO₃²⁻, respectively.

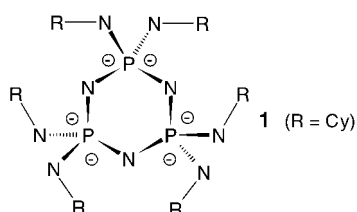
Most of the known polyimido anions of d-block elements (Table 2) have been obtained by the lithiation method. The dilithium derivatives of the homologous series of tetrahedral Group 6 ions [M(NtBu)₄]²⁻ (M = Cr, Mo, W) are produced by lithiation of (tBuN)₂M(NHtBu)₂ [Eq. (b)].^[11, 41, 42] The isoelectronic tetrakisimidoperrhenate ion is similarly prepared as the complex [(tmeda)Li{Re(NtBu)₄}] (tmeda = *N,N,N',N'*-tetramethyl 1,2-ethanediamine) from (tBuN)₃Re(NHtBu).^[11, 46] Treatment of the monoamido species [(thf)₂Li]₂[Nb(NMes)₃(NHMes)] with one equivalent of *t*BuLi generates the trilithium complex [(thf)₄Li₃{Nb(NMes)₄}]^[40]



The strategy of deprotonating amido complexes has also proven fruitful for studies of imido-oxo systems. In particular, the sulfamides O₂S(NHR)₂ (R = *i*Pr, *t*Bu) have been utilized as precursors to bisimidodisulfate ions, for example, the complexes [Li₂{O₂S(NtBu)₂}]_n and [(thf)₂Li₂{O₂S(NtBu)₂}]_n are prepared by dilithiation reactions with *n*-butyllithium.^[39b] On the other hand, magnesiation of O₂S(NHtBu)₂ with one equivalent of dibutylmagnesium is incomplete, yielding the amidoimidodisulfate complex [(tmeda)Mg{O₂S(NtBu)(NHtBu)₂}]₂. The mixed-metal species [(thf)₄Li₄Mg{O₂S(NtBu)₂}]₂ is obtained upon further deprotonation of this complex with *n*BuLi in THF [Eq. (c)].^[39a]

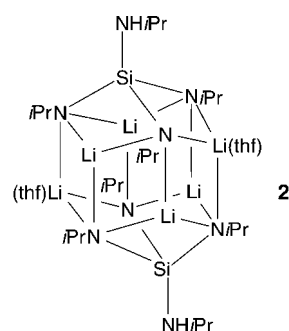


Polyolithiation is successful for generating the hexakisimido-*c*-triphosphazene hexaanion [NP(NCy)₂]₃⁶⁻ (**1**), by treatment of the corresponding amido derivative [NP(NHCy)₂]₃ with six

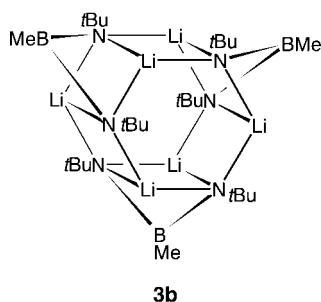
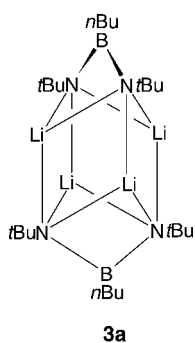


equivalents of $n\text{BuLi}$ in TMEDA/toluene.^[47] The dimeric complex $[(\text{thf})_2\text{Li}_6\{\text{NP}(\text{NCy})_2\}_2]$ is obtained upon recrystallization from THF/hexane.^[47] However, the putative intermediate trianion $[\text{NP}(\text{NCy})(\text{NHCy})]_3^{3-}$ can only be isolated by treatment of $[\text{Li}_6\{\text{NP}(\text{NCy})_2\}_2]$ with three equivalents of $n\text{BuOH}$ and not by trilithiation of $[\text{NP}(\text{NHCy})_2]_3$ with $n\text{BuLi}$.^[48]

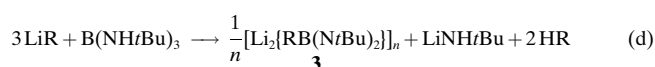
In many cases, however, polyolithiation of amido compounds is incomplete. For example, the reaction of $\text{Si}(\text{NH}i\text{Pr})_4$ with an excess of $n\text{BuLi}$ yields the dimeric trilithiated complex $[(\text{thf})\text{Li}_3\{\text{Si}(\text{N}i\text{Pr})_3(\text{NH}i\text{Pr})\}]_2$ (**2**).^[17] For amido derivatives of



Group 13 elements incomplete lithiation is accompanied by fascinating, unanticipated consequences. For example, the attempted trilithiation of the trisaminoborane $\text{B}(\text{NH}t\text{Bu})_3$ with alkylolithium reagents yields dilithium boraamidates **3**

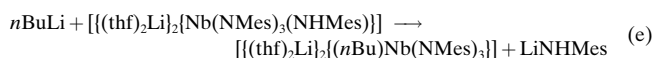


[Eq. (d)] rather than the trisimidoorthoborate ion $[\text{B}(\text{N}t\text{Bu})_3]^{3-}$.^[49] In effect the organolithium reagent behaves

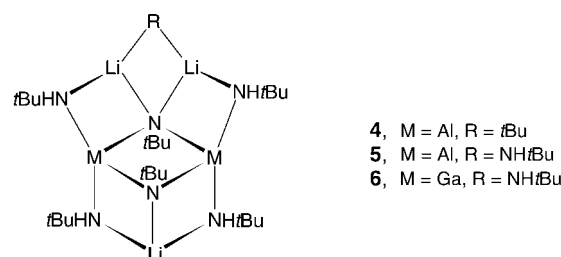


as a nucleophile, displacing a *tert*-butylamino group from boron, as well as a deprotonating agent. Similar behavior has

been reported for an amido–niobium system [Eq. (e) Mes = 2,4,6-trimethylphenyl].^[50] Alkyl or aryl boraamidates have previously been prepared by the dilithiation of diaminoboranes $\text{RB}(\text{NHR}')_2$,^[51] but the new route to these boron analogues of amidates avoids the need to prepare alkylboron dihalides.



The trisalkylamido complexes of heavier Group 13 elements $[\text{M}(\text{NH}t\text{Bu})_3]_2$ ($\text{M} = \text{Al}, \text{Ga}$) are dimeric. For these cases, partially lithiated complexes act as a template for the entrapment of monomeric or dimeric alkylolithium or lithium alkylamide fragments.^[52] Thus treatment of $[\text{Al}(\text{NH}t\text{Bu})_3]_2$ with an excess of *n*-butyl-, *tert*-butyl-, or methylolithium results in formation of the adducts $[\text{Li}_3\{\text{Al}_2(\text{N}t\text{Bu})_3(\text{NH}t\text{Bu})_3\}] \cdot (n\text{BuLi})_2$,^[52a] $[\text{Li}\{\text{Al}(\text{N}t\text{Bu})(\text{NH}t\text{Bu})_2\}]_2 \cdot t\text{BuLi}$ (**4**), or

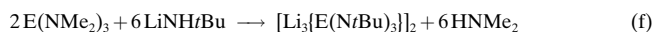


$[\text{Li}\{\text{Al}(\text{N}t\text{Bu})(\text{NH}t\text{Bu})_2\}]_2 \cdot \text{LiNH}t\text{Bu}$ (**5**),^[52b] respectively. The related gallium complex $[\text{Li}\{\text{Ga}(\text{N}t\text{Bu})(\text{NH}t\text{Bu})_2\}]_2 \cdot \text{LiNH}t\text{Bu}$ (**6**), generated by reaction of $[\text{Ga}(\text{NH}t\text{Bu})_3]_2$ with three equivalents of *t*BuLi, has also been prepared.^[52b] The unsolvated forms of $n\text{BuLi}$ and lithium *tert*-butylamide are hexameric and octameric, respectively, in the solid state.^[53, 54]

2.2. Transamination Reactions

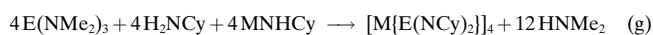
Wright and co-workers have demonstrated the versatility of transamination reactions for preparing homoleptic polyimido anions of Group 15 elements.^[22–25, 26a, 27] This approach employs the reagents $\text{E}(\text{NMe}_2)_3$ ($\text{E} = \text{As}, \text{Sb}, \text{Bi}$) in reactions with primary amines and/or s-block metal amides.

Unsolvated complexes containing trisimido analogues of arsenite and stibinite, that is, $[\text{E}(\text{N}t\text{Bu})_3]^{3-}$ ($\text{E} = \text{As}$ or Sb , respectively), are produced in good yields in hexane as shown in Equation (f).^[26a, 27b] The solvated dimers



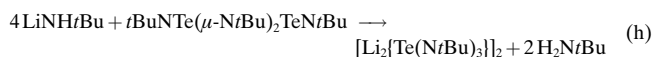
$[(\text{thf})\text{Li}_3\{\text{Sb}(\text{NR})_3\}]_2$ ($\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$ or 2,4-(MeO) $_2\text{C}_6\text{H}_3$) are obtained if THF is used as the reaction solvent.^[27] Interestingly, in the complex $[(\text{Me}_2\text{NH})\text{Li}_3\{\text{Sb}(\text{NCy})_3\}]_2$ ($\text{Cy} = \text{cyclohexyl}$) two of the ligands are HNMe_2 molecules generated by transamination.^[27b] By contrast, treatment of $\text{E}(\text{NMe}_2)_3$ with a 1:1 mixture of cyclohexylamine and MNHcy ($\text{M} = \text{Li}, \text{Na}$) gives s-block metal derivatives of the ions $[\text{E}(\text{NCy})_2]^-$ ($\text{E} = \text{As}, \text{Sb}$) [Eq. (g)],^[22–24] isoelectronic with oxo anions from the

nitrite series (Table 1). The heavier congener $[\text{Bi}(\text{N}t\text{Bu})_2]^-$, prepared in a similar manner, is obtained as the THF-solvated dimer $[(\text{thf})\text{Li}\{\text{Bi}(\text{N}t\text{Bu})_2\}]_2$.^[25]

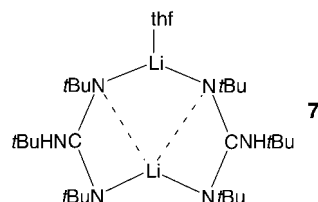


2.3. Nucleophilic Addition

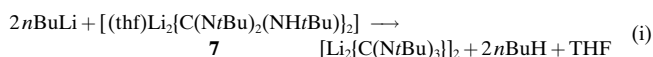
Nucleophilic addition of primary amidolithium reagents to heteroallenes (or their Group 16 analogues), followed by deprotonation, represents a versatile route to homoleptic polyimido and heteroleptic imido-oxo anions of Group 14 and Group 16 elements. For example, the trisimidotellurite complex $[\text{Li}_2\{\text{Te}(\text{N}t\text{Bu})_3\}]_2$ is prepared by reaction of the dimeric tellurium(IV) diimide $t\text{BuNTe}(\mu\text{-N}t\text{Bu})_2\text{TeN}t\text{Bu}$ and four equivalents of $\text{LiNH}t\text{Bu}$, a reaction in which the lithium reagent behaves both as a nucleophile and as a base [Eq. (h)].^[33a] The lighter congeners, $[\text{E}(\text{N}t\text{Bu})_3]^{2-}$ ($\text{E} = \text{S}$,



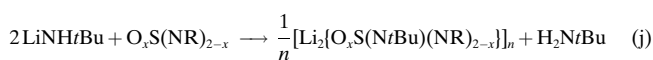
Se), can be obtained analogously from the corresponding monomeric diimides $\text{E}(\text{N}t\text{Bu})_2$.^[31, 32] This method may also be used for the preparation of the tetrakisimidodisulfate ion $[\text{S}(\text{N}t\text{Bu})_4]^{2-}$ by reaction of the sulfur(VI) triimide $\text{S}(\text{N}t\text{Bu})_3$ with two equivalents of $\text{LiNH}t\text{Bu}$.^[37] The analogous reaction of N,N' -di-*tert*-butylcarbodiimide with $\text{LiNH}t\text{Bu}$ yields the amidoimido complex $[(\text{thf})\text{Li}_2\{\text{C}(\text{N}t\text{Bu})_2(\text{NH}t\text{Bu})\}]_2$ (**7**). In



this case, the stronger base $n\text{BuLi}$ is necessary for the deprotonation step to give the trisimidocarbonate ion [Eq. (i)].^[16]

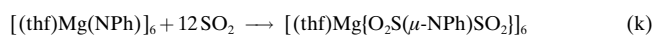
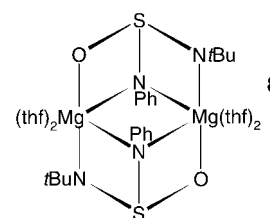


This method is readily applicable to the preparation of heteroleptic imido-oxo anions. For example, treatment of the sulfinylimines RNSO ($\text{R} = t\text{Bu}$, Me_3Si) or sulfur dioxide with two equivalents of $\text{LiNH}t\text{Bu}$ leads to lithium complexes of the imido-oxo sulfite ions $[\text{OS}(\text{N}t\text{Bu})(\text{NR})]^{2-}$ ^[34] or $[\text{O}_2\text{S}(\text{N}t\text{Bu})]^{2-}$,^[36] respectively [Eq. (j), $x = 1$: $\text{R} = t\text{Bu}$, SiMe_3 , $n = 6$; $x = 2$: n is not known].



The reagent $[(\text{thf})\text{Mg}(\text{NPh})]_6$ ^[55] has also been employed as an imide-transfer agent in nucleophilic addition reactions. The

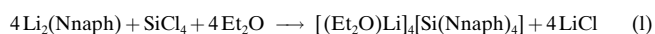
deck-chair cluster $[(\text{thf})_2\text{Mg}\{\text{OS}(\text{N}t\text{Bu})(\text{NPh})\}]_2$ (**8**) is prepared by treating $[(\text{thf})\text{Mg}(\text{NPh})]_6$ with $t\text{BuNSO}$ in THF.^[35] In a notable application of this approach the Mg^{2+} derivative of the novel imido-disulfite ion $[\text{PhN}(\text{SO}_2)_2]^{2-}$ is generated by reaction of $[(\text{thf})\text{Mg}(\text{NPh})]_6$ with SO_2 [Eq. (k)], which provides the first example of the double insertion of sulfur dioxide into a single functional group.^[35]



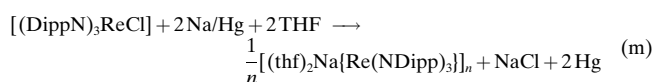
2.4. Miscellaneous Methods

The synthetic approaches outlined in Sections 2.1–2.3 account for the preparation of the majority of known polyimido or imido-oxo anions of p-block elements and transition metals. However, several important species have been generated in other ways.

The dilithium imide $\text{Li}_2(\text{Nnaph})$ ($\text{naph} = \alpha\text{-naphthyl}$)^[56] can be utilized as a source of the $[(\text{Et}_2\text{O})\text{Li}(\text{Nnaph})]^-$ ion to provide the tetralithium derivative of a tetrakisimidooorthosilicate ion $[\text{Si}(\text{Nnaph})_4]^{4-}$ [Eq. (l)].^[17] The isoelectronic $[\text{P}(\text{Nnaph})_4]^{3-}$ ion is obtained as the ion-pair complex $[(\text{thf})_4\text{Li}][(\text{thf})_4\text{Li}_2\{\text{P}(\text{Nnaph})_4\}]$ by the curious reaction of P_2I_4 with $\alpha\text{-naphthylamine}$ in THF/ NEt_3 , followed by the addition of $n\text{-BuLi}$.^[30] The complex $[\text{Li}_2\text{PH}(\text{NR})_3]_2$ ($\text{R} = 2\text{-C}_6\text{H}_4\text{OMe}$), which contains an imido analogue of the phosphite ion $[\text{HPO}_3]^{2-}$, is formed from the reaction of PCl_3 with three equivalents of $2\text{-MeOC}_6\text{H}_4\text{NH}_2$ and subsequent treatment with $n\text{-BuLi}$.^[57]



Polyimido anions of Group 7 metals have been prepared by reduction of trisimido metal(VII) halides. The tetrahedral Mn^{VI} ion $[\text{Mn}(\text{N}t\text{Bu})_4]^{2-}$ is obtained by treatment of $(t\text{BuN})_3\text{MnCl}$ with five equivalents of $\text{LiNH}t\text{Bu}$ in DME.^[45] The trisimido M^{V} monoanions $[\text{M}(\text{NDipp})_3]^-$ ($\text{M} = \text{Tc}$, Re , $\text{Dipp} = 2,6\text{-diisopropylphenyl}$) are generated by reduction of such halide complexes with sodium metal or sodium amalgam, [Eq. (m)].^[43, 44] Treatment of $[(\text{thf})_2\text{Na}\{\text{Re}(\text{NDipp})_3\}]_n$, obtained in this way, with an equimolar amount of Me_3NO in the presence of Et_4NCl yields the ion-pair complex $(\text{Et}_4\text{N})[\text{ORE}(\text{NDipp})_3]$.^[44] The trisimidoperrhenate ion $[\text{ORE}(\text{NDipp})_3]^-$ is a rare example of a transition metal centered imido oxo anion.



A potentially more versatile route to heteroleptic systems involves the direct replacement of an oxo ligand in an oxo anion by an imido (NR) group. An elegant example of this methodology, the reaction of the polyoxometallate $[\text{NBu}_4]_2\text{[Mo}_6\text{O}_{19}]$ with organic isocyanates RNCO to generate anions

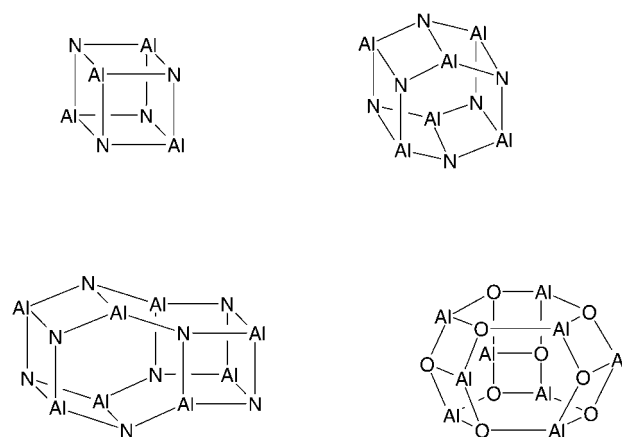
of the type $[\text{Mo}_6\text{O}_{19-x}(\text{NR})_x]^{2-}$ ($x = 1-5$), was reported recently.^[58a] An interesting development of this approach involves the incorporation of the styrylimido ligand into a polyoxometallate by the reaction of $(\text{NBu}_4)_2[\text{Mo}_6\text{O}_{19}]$ with $\text{Ph}_3\text{P}=\text{NC}_6\text{H}_4\text{CH}=\text{CH}_2$.^[58b] The complex $(\text{NBu}_4)_2[\text{Mo}_6\text{O}_{18}(\text{NC}_6\text{H}_4\text{CH}=\text{CH}_2)]$ was copolymerized with 4-methylstyrene.^[58b] The formation of imido derivatives of polyoxometallates from the reaction of $[\text{Mo}_6\text{O}_{19}]^{2-}$ with aromatic amines is generally facilitated by dicyclohexylcarbodiimide.^[58c]

3. Solid-State Structures

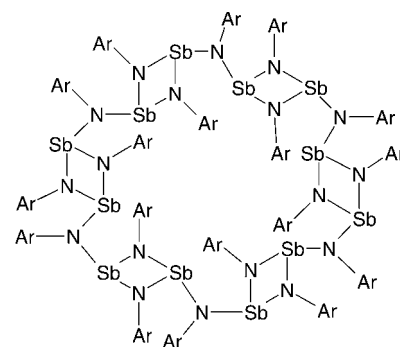
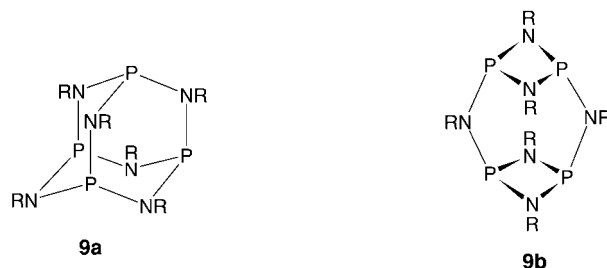
The determination of the solid-state structures of many organolithium and lithium amide reagents by X-ray crystallography has given rise to a rationalization of cluster formation in terms of a so-called laddering principle.^[59, 60] A conspicuous feature of such compounds is their tendency to form oligomeric units in the solid state. Ring laddering and, hence, cluster formation is facilitated by incorporation of the Li^+ ions, which leads to the aggregation of *contact* ion pairs (ladder rungs). Although the $\text{Li}-\text{C}$ bond is essentially ionic in character, multicenter (electron-deficient) bonding occurs in organolithium compounds as a result of the strongly polarizing nature of the Li^+ ion.^[61] The formation and subsequent aggregation of $\text{Li}-\text{N}$ (for example, lithium amides) and $\text{Li}-\text{O}$ units can be attributed to this phenomenon as well. Although coordination of Li^+ ions by donor solvents usually inhibits aggregation, a recent investigation of lithium thioamidates shows that solvation of lithium may actually promote polymer formation.^[62] The steric requirements of the alkyl or aryl substituents on the nitrogen atoms also play a significant role in dictating the cluster structure.^[59] These concepts are also applicable to the cluster structures adopted by alkali metal derivatives of polyimido and imidooxo anions of p- and d-block elements.

3.1 Cluster Structures of Imido Derivatives of p-Block Elements

The versatility of the imido ligand as a component of cluster compounds is exemplified by the variety of iminoalanes, $(\text{R}'\text{AlNR})_n$, which may adopt cubic, hexagonal prismatic, or larger arrangements depending on the steric requirements of the R and R' substituents (Scheme 1).^[6] The isoelectronic oxoalanes $(\text{RAlO})_n$ may also adopt larger cluster structures, for example, the 18-atom cluster $(t\text{BuAlO})_9$ (Scheme 1).^[7] The RN^{2-} ligand is also a well-established feature of Group 14 and 15 element clusters. Complexes of the type $(\text{MN}t\text{Bu})_4$ ($\text{M} = \text{Ge}, \text{Sn}, \text{Pb}$) form cubanes,^[63] while two isomers of the polycyclic P^{III} imides $\text{P}_4(\text{NR})_6$ are known: an adamantane-type cluster (**9a**, $\text{R} = \text{Me}, \text{Et}, i\text{Pr}$)^[64] and a tetracycle (**9b**, $\text{R} = i\text{Pr}, t\text{Bu}$),^[21, 65] which contains two four-membered P_2N_2 rings doubly bridged by NR groups. The 24-membered arylimido metallacycles $\text{Sb}_{12}(\text{NAr})_{18}$ (**10**, $\text{Ar} = 2\text{-OMe C}_6\text{H}_4$,^[66a] Ph ^[66b]) represent a particularly fascinating example of the adaptability of the imido ligand.



Scheme 1. Fundamental building blocks of imino- and oxoalanes, $(\text{RAINR}')_n$ and $(\text{RAIO})_n$. The R groups attached to Al and N are omitted for clarity.



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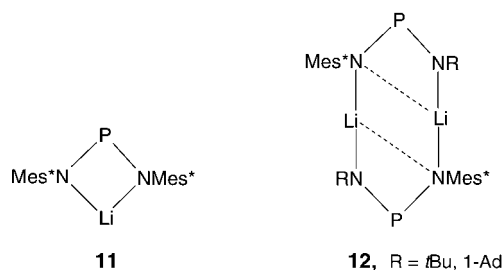
3.2 s-Block Metal Complexes of Polyimido Anions

Like the imido complexes of alkali and alkaline earth metals, for example, $[(\text{thf})\text{Mg}(\text{NR})]_6$ ($\text{R} = \text{Ph}, \text{naph}$)^[55] and $[(\text{Et}_2\text{O})_3\text{Li}_{10}(\text{Nnaph})_5]_2$,^[56] the s-block metal derivatives of homoleptic polyimido anions tend to form oligomers in the solid state. Such arrangements maximize electrostatic interactions between the polar RN^--M^+ units. The influence of solvation and the nature of the nitrogen R group on the formation of cluster structures by ternary and quaternary systems involving alkali metal derivatives of polyimido or imidooxo anions of p- or d-block elements is considered in the following sections.

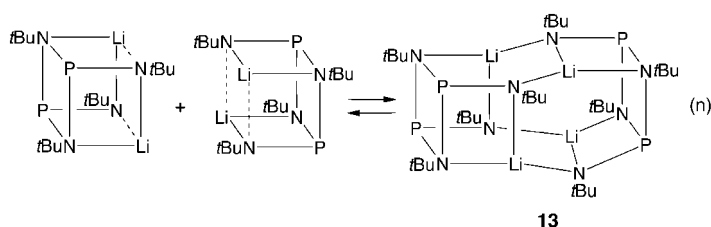
3.2.1. Fundamental Building Blocks

The effect of the steric bulk of the NR group is illustrated dramatically by the structures of P^{III} systems of the type

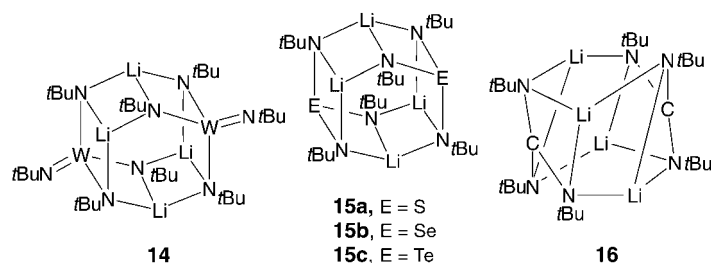
$[\text{Li}\{\text{P}(\text{NR})(\text{NR}')\}]_n$. The monomeric structure **11** is found for $\text{R} = \text{R}' = \text{Mes}^*$.^[21] Replacement of one of the Mes^* groups by a $t\text{Bu}$ or 1-Ad group results in dimerization to give the eight-membered rings **12**.^[19] When $\text{R} = \text{R}' = t\text{Bu}$ the unsolvated



tetramer $[\text{Li}\{\text{P}(\text{N}t\text{Bu})_2\}]_4$ (**13**) [Eq. (n)], which is similar to the iminoalane $(\text{RAINR}')_8$ (Scheme 1), is formed as a result of the face-to-face dimerization of two cubes.^[21] The related complexes $[\text{M}\{\text{E}(\text{NCy})_2\}]_4$ ($\text{M} = \text{Li}, \text{Na}$; $\text{E} = \text{As}, \text{Sb}$)^[22–25] are isostructural with **13**.



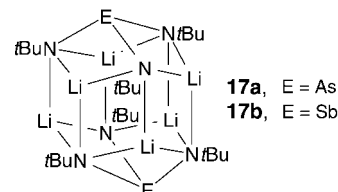
The binary 12-atom (A_6X_6) hexagonal prism, which may also be viewed as a six-runged cyclic ladder, is a common structural motif for main group element cluster compounds, for example, the iminoalanes and *tert*-butylaluminumoxanes (see Scheme 1). Lithium derivatives of homoleptic polyimido anions of p- or d-block elements represent the only ternary analogues of this fundamental building block. For example, the tetrakisimidotungstate complex $[\text{Li}_2\{\text{W}(\text{N}t\text{Bu})_4\}]_2$ (**14**) contains a C_{2h} -symmetric $\text{Li}_4\text{W}_2\text{N}_6$ hexagonal-prismatic core.^[11, 42b] The dilithium trisimidochalcogenite dimers $[\text{Li}_2\{\text{E}(\text{N}t\text{Bu})_3\}]_2$ (**15a–c**) also share this motif in forming $\text{Li}_4\text{E}_2\text{N}_6$ -based clusters.^[31–33]



The near tetrahedral or trigonal-pyramidal geometries at the Group 6 or 16 centers in **14** and **15**, respectively, allow for the formation of relatively undistorted hexagonal prismatic structures, especially in the case of **15c** for which the $\text{Li}-\text{N}$ and $\text{Te}-\text{N}$ rungs of the cyclic ladder are almost equal in length (ca.

2.0 Å).^[33] On the other hand, the structure of the trisimido-carbonate complex $[\text{Li}_2\{\text{C}(\text{N}t\text{Bu})_3\}]_2$ (**16**), which contains a $\text{Li}_4\text{C}_2\text{N}_6$ core, is based on a severely distorted hexagonal prism.^[16] This distortion arises from the requirement of planarity at the carbon centers and the disparity between $\text{C}-\text{N}$ and $\text{Li}-\text{N}$ bond lengths.

A more complex fundamental building block for unsolvated homoleptic polyimido anions is the 14-atom ($\text{Li}_6\text{E}_2\text{N}_6$) bicapped hexagonal prism, which provides a framework for the dimeric trisimidopnicogenite clusters $[\text{Li}_3\{\text{E}(\text{N}t\text{Bu})_3\}]_2$ (**17**).^[26a, 27b] These structures are best described as containing

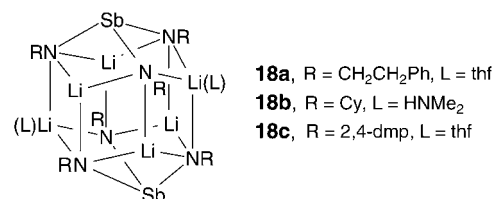


a cyclic Li_6N_6 ladder, the six-membered Li_3N_3 rings of which are capped by As or Sb atoms. The Li_6N_6 ladder adopts a puckered conformation to accommodate the rigid nature of the trianions (Group 15 elements).^[13a]

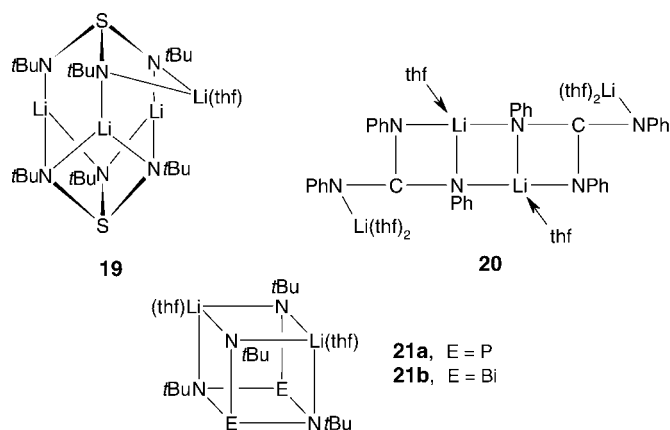
3.2.2. Effects of Solvation

The addition of Lewis-basic solvents has proven successful for aiding the characterization of several anionic polyimido systems; however, the specific effect of the added donor solvent on the resulting structures can vary significantly. Structural changes may include a) minor distortion of cluster structure, b) major disruption of cluster structure, or c) stabilization of smaller aggregates.

Occasionally solvation has no significant structural effect. The structures of $[(\text{L})\text{Li}_3\{\text{Sb}(\text{NR})_3\}]_2$ (**18**; 2,4-dmp = 2,4-(MeO) $_2\text{C}_6\text{H}_3$) are similar to those of the unsolvated cluster



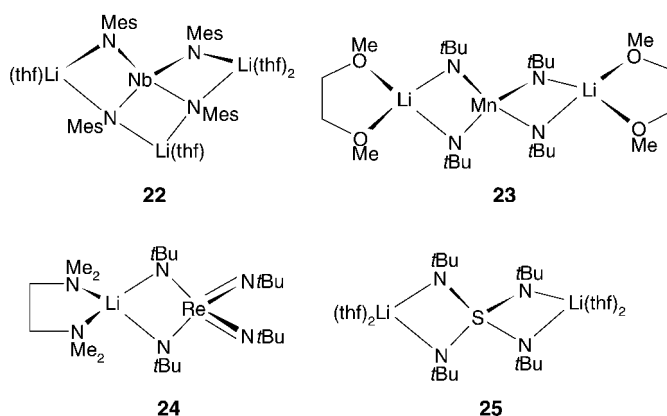
17b^[27] with the exception of subtle consequences arising from the presence of two 4-coordinate Li^+ ions. This observation is consistent with the concept of “structural direction by the dominant metal”, in the form of $[\text{Sb}(\text{NR})_3]^{3-}$, as advocated by Wright and co-workers.^[13a] An example of a minor disruption of cluster structure is provided by the monosolvated derivative $[(\text{thf})\text{Li}_4\{\text{S}(\text{N}t\text{Bu})_3\}]_2$ (**19**).^[31] One of the Li^+ ions in **15a** is pulled away from the $\text{Li}_4\text{S}_2\text{N}_6$ core, which results in the partially opened framework of **19**. A more dramatic structural change caused by solvation is observed for the hexakis THF-solvated dimer $[(\text{thf})_3\text{Li}_2\{\text{C}(\text{NPh})_3\}]_2$ (**20**).^[15] when compared to the unsolvated analogue **16**. The primary cause of the different structures of **16** and **20** is clearly the solvation of the Li^+ centers in **20** (rather than the change in the NR group).^[16]



An unraveling process conceptually relates the dimeric dilithium trisimidocarbonate complexes **16** and **20**.^[16] In effect, the initial coordination of THF molecules to the lithium ions of one Li_2N_2 face in the hexagonal-prismatic core of **16** leads, by Li–N bond-breaking, to the step-shaped ladder structure **20**.

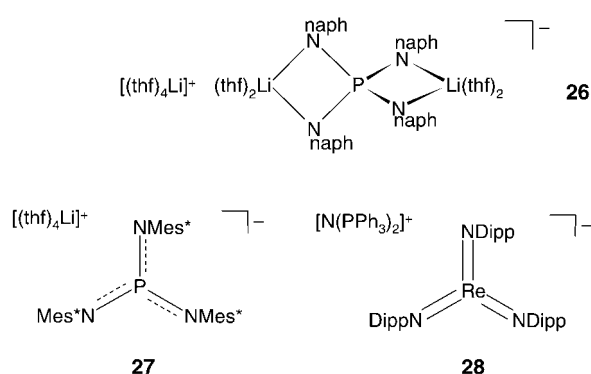
The stabilization of smaller oligomers by solvation of the s-block metal cations is exemplified by the $\text{Li}_2\text{E}_2\text{N}_4$ cubane clusters of the THF-solvated Group 15 dimers $[(\text{thf})\text{Li}\{\text{E}(\text{N}t\text{Bu})_2\}]_2$ (**21**).^[20, 25] Significantly, the isolation of **21a** gives credence to the suggestion that the tetramer **13** is formed from two $\text{Li}_2\text{P}_2\text{N}_4$ cubes [see Eq. (n)].^[21] Solvation of the Li^+ ions hinders, in the case of **21**, dimerization of these cubes at their Li_2N_2 faces, effectively trapping the cubane building blocks.

There are also several examples of complexes in which chelation or extensive solvation of Li^+ ions by Lewis bases prevents the aggregation of monomeric units, for example, $[(\text{thf})_4\text{Li}_3\{\text{Nb}(\text{NMes})_4\}]$ (**22**),^[40] $[(\text{dme})\text{Li}]_2[\text{Mn}(\text{N}t\text{Bu})_4]$ (**23**),^[45] $[(\text{tmeda})\text{Li}\{\text{Re}(\text{N}t\text{Bu})_4\}]$ (**24**),^[11] and $[(\text{thf})_4\text{Li}_2\{\text{S}(\text{N}t\text{Bu})_4\}]$ (**25**).^[37]



3.2.3. Solvent-Separated Ion Pairs

The structures of complexes **11**–**25** involve contact ion pairs. By contrast, the two known examples of homoleptic polyimido anions containing Group 15 element centers in the oxidation state v, that is, $[(\text{thf})_4\text{Li}][(\text{thf})_4\text{Li}_2\{\text{P}(\text{Nnaph})_4\}]$ (**26**)^[30] and $[(\text{thf})_4\text{Li}][\text{P}(\text{NMes}^*)_3]$ (**27**),^[28] consist of solvent-



separated ion pairs. The cation in these P^{V} complexes is a sequestered Li^+ ion coordinated by four THF molecules. The anion in **26**, $[(\text{thf})_4\text{Li}_2\{\text{P}(\text{Nnaph})_4\}]^-$, is both isoelectronic and isostructural with the neutral sulfur(vi) complex **25**. By contrast, the trigonal planar ion $[\text{P}(\text{NMes}^*)_3]^-$ in **27** does not incorporate Li^+ ions. Significantly, complex **27** and the ionic Re^{V} complex $[\text{N}(\text{PPh}_3)_2][\text{Re}(\text{NDipp})_3]$ (**28**)^[44b] are the only structurally characterized examples of free polyimido anions of p-block elements or transition metals.

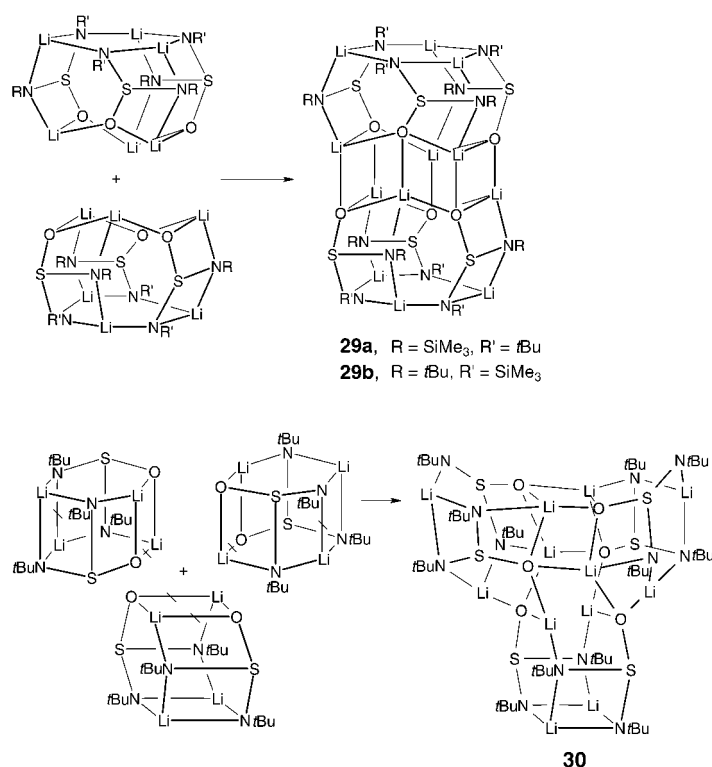
3.3. s-Block Metal Complexes of Imido-oxo Anions of p-Block Elements

The replacement of one or more of the imido (RN^{2-}) groups attached to the central p-block element in homoleptic polyimido anions by an isoelectronic oxo (O^{2-}) ligand allows for further aggregation of fundamental building blocks by interactions involving highly polar, sterically unencumbered $(\text{Li}-\text{O})_x$ ($x = 1-3$) units. Some examples of the novel structural architectures produced by this self-assembly process are presented below.

3.3.1. Bisimidosulfite and Imidosulfite Ions

The hexameric dilithium bisimidosulfite complexes $[\text{Li}_2\{\text{OS}(\text{N}t\text{Bu})(\text{NSiMe}_3)\}]_6$ (**29**) and $[\text{Li}_2\{\text{OS}(\text{N}t\text{Bu})_2\}]_6$ (**30**) both contain 36-atom ($\text{Li}_{12}\text{S}_6\text{N}_{12}\text{O}_6$) cluster structures.^[34] It is clear, however, that these cluster cores result from the assembly of different fundamental building blocks. As depicted in Scheme 2, the centrosymmetric clusters **29** can be viewed as dimers in which two quaternary 18-atom ($\text{Li}_6\text{S}_3\text{N}_6\text{O}_3$) clusters are joined by their Li_3O_3 faces. A structurally similar Al_9O_9 unit is observed for the nonamer $(\text{N}t\text{BuAlO})_9$ (see Scheme 1).^[7a,b]

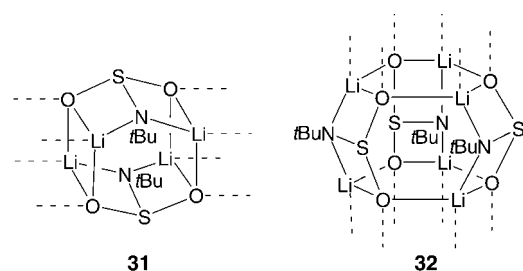
In a related, but more complex, process the 36-atom cluster in **30** can be envisaged to result from the trimerization of quaternary $(\text{Li}_4\text{S}_2\text{N}_4\text{O}_2)$ hexagonal prisms by their Li_2O_2 faces (Scheme 2). Importantly, the isomer that involves the juxtaposition of Li–O linkages is favored among the possible isomers for these fundamental building blocks. To date, **30** is the only representative of a discrete cluster derived from the self-assembly of hexagonal prisms, although the formation of



Scheme 2. Proposed formation of the cluster structures **29** and **30**. In the formation of **30** the designation $-/-$ indicates a bond broken in this process.

dimeric or tetrameric Li₄S₂N₄O₂ aggregates can readily be envisaged. The subtle effects that may result from changing the R group attached to nitrogen are illustrated strikingly by the different structures of the quaternary clusters **29** and **30**.

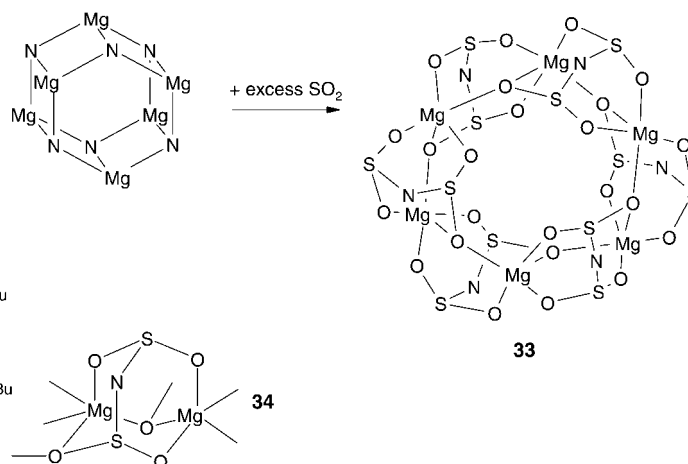
Quaternary complexes involving lithium and [O₂S(NR)]²⁻ ions are likely to form extended structures, since the fundamental building blocks now contain two Li_xO_x (*x* = 2, 3) faces (**31** or **32**). Consistently, the complex [Li₂{O₂S(*Nt*-Bu)}]_n exhibits low solubility in organic solvents and a tendency towards gel formation.^[36]



3.3.2. The Imidodisulfite Ion

Complexes **29** and **30** (Scheme 2) are constructed from discernible fundamental building blocks that can conceivably exist independently. The following example involves building blocks that are not independent, but rather form as a result of edge-sharing, that is, the fusion of the basic units. The formation of the hexameric imidodisulfite complex [(thf)Mg{O₂S(μ -NPh)SO₂}]₆ (**33**) involves the insertion of 12 SO₂ molecules into the Mg–NPh bonds of

[(thf)Mg(NPh)]₆ (Scheme 3).^[35] Complex **33** consists of a quaternary 48-atom (Mg₆S₁₂N₆O₂₄) cluster structure with *S*₆ molecular symmetry. Each of the [O₂S(μ -NPh)SO₂]²⁻ ions bischelates two Mg²⁺ ions, and one oxygen atom further

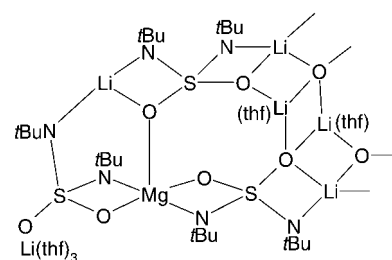


Scheme 3. Synthesis of **33** and the basic structural building block **34**. For clarity, the Ph substituents on the nitrogen atoms and the THF molecules coordinated to the Mg²⁺ ions are omitted.

exhibits monodentate coordination to a third Mg²⁺ ion. Thus the fundamental building block for **33** is a Mg₂S₂NO₅ adamantyl unit (**34**; Scheme 3). Each of these units is fused to two neighboring units by shared Mg–O edges.

3.3.3. Bisimidosulfate Ions

In contrast to the highly solvated tetrakisimidosulfate monomer **25**, the bisimidosulfate complexes [Li₂{O₂S(*Ni*Pr)₂}]_n and [(thf)Li₂{O₂S(*Nt*Bu)₂}]_n are amorphous in the solid state.^[39b] Consequently, a heterobimetallic strategy involving the combination of magnesiation followed by lithiation was used to prepare [(thf)₄Li₄Mg{O₂S(*Nt*Bu)₂}]₃ (**35**) [Eq. (c)].^[39a] The central framework for **35** consists of a



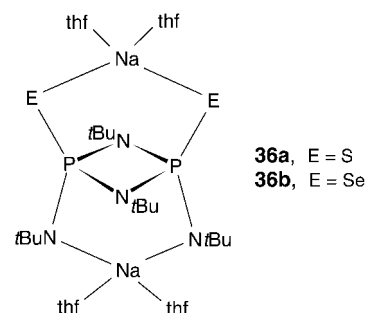
35 (half of dimer + Li₄O₄ ladder)

quinary 36-atom (Li₆Mg₂S₆N₁₂O₁₀) cluster core and two terminal O–Li(thf)₃ units. Each half of this centrosymmetric dimer contains one [Li₂{O₂S(*Nt*Bu)₂}]₂ molecule and one [(thf)₄Li₂Mg{O₂S(*Nt*Bu)₂}]₂ molecule. A central step-shaped Li₄O₄ ladder connects the two halves of **35**. The outer rungs of this ladder are formed by one Li–O bond from each [Li₂{O₂S(*Nt*Bu)₂}]₂ molecule, while the inner rungs involve

the O–Li(thf) bonds from the $[(\text{thf})_4\text{Li}_2\text{Mg}]\{\text{O}_2\text{S}(\text{N}t\text{Bu})_2\}_2$ molecules. Undoubtedly, solvation of the terminal Li^+ ions by THF molecules obviates formation of a more extended structure, which could otherwise occur by assembly through Li–O edges.

3.4. s-Block Metal Complexes of Imidochalcogenido Anions of p-Block Elements

By analogy with the structurally informative investigations of alkali metal derivatives of imidooxo anions of p-block elements, the corresponding imidochalcogenido anions are a potentially intriguing class of species. To date, the imidothio- and imidoselenametaphosphate ions $[\text{EP}(\text{N}t\text{Bu})_2]^-$ [$\text{E} = \text{S}$ or Se] are the only reported examples.^[29] The sodium derivatives of these monoanions form *cis* isomers of the dimers $[(\text{thf})_2\text{Na}\{\text{EP}(\text{N}t\text{Bu})_2\}]_2$ (**36**), which involve E, E'- and N, N'-chelation of the Na^+ ions, whereas the corresponding Li^+ salts

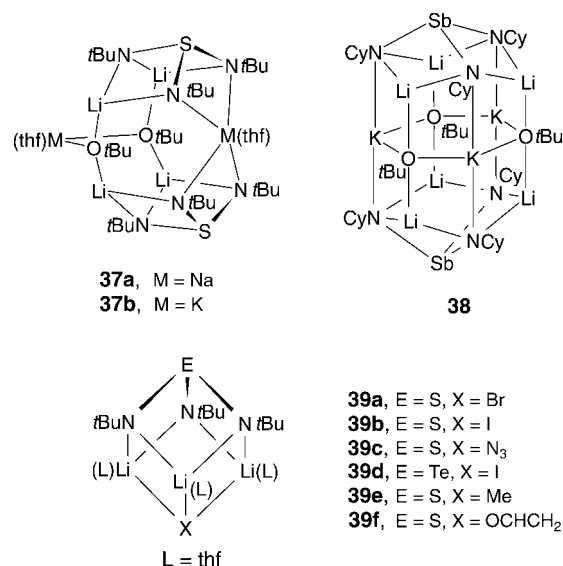


adopt 'side-on' bis-N, E-chelation.^[29b] Replacement of the Na^+ ions in **36** with K^+ results in formation of the extended structures $[(\text{thf})_x\text{K}\{\text{EP}(\text{N}t\text{Bu})_2\}]_\infty$ ($\text{E} = \text{S}$, $x = 1$; $\text{E} = \text{Se}$, $x = 1.5$), which involve weak $\text{K} \cdots \text{E}$ interactions.^[29]

4. Cluster Expansion and Contraction

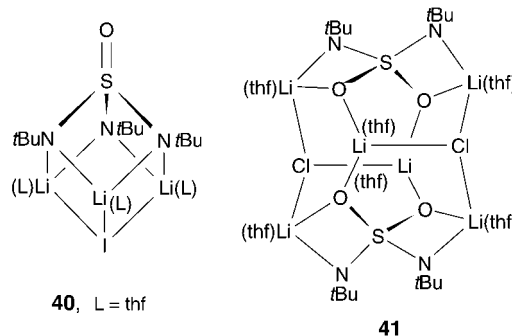
The incorporation of alkali metal alkoxides into ternary polyimido clusters leads to cage expansion. Addition of alkali metal *tert*-butoxides to the dimeric clusters $[\text{Li}_2\{\text{S}(\text{N}t\text{Bu})_3\}]_2$ (**15a**) and $[\text{Li}_3\{\text{Sb}(\text{NCy})_3\}]_2$ (unsolvated **18b**) produces the mixed-metal complexes $[\text{Li}_2\{(\text{thf})\text{M}\}\{\text{S}(\text{N}t\text{Bu})_3\}(\text{OtBu})_2]$ (**37**)^[67] and $[\text{Li}_3\{\text{Sb}(\text{NCy})_3\}]_2 \cdot (\text{KO}t\text{Bu})_3$ (**38**), respectively.^[68] The formation of **38** involves expansion of the 14-atom cluster core of **18b** to accommodate a six-membered $\text{K}_3(\text{OtBu})_3$ ring between two intact $[\text{Li}_3\{\text{Sb}(\text{NCy})_3\}]$ units.^[68]

By contrast to the behavior of alkali metal alkoxides the interaction of ternary or quaternary polyimido cluster systems with lithium halides results in disaggregation.^[14] The distorted cubane complexes $[\{(\text{thf})\text{Li}\}_2\{\text{S}(\text{N}t\text{Bu})_3\}\{(\text{thf})\text{LiX}\}]$ (**39a–c**) are obtained by the reaction of the dimer $[\text{Li}_2\{\text{S}(\text{N}t\text{Bu})_3\}]_2$ (**15a**) with *in situ* generated lithium halides^[38] or lithium azide.^[69a] The tellurium analogue **39d** is formed by direct addition of LiI to a THF solution of **15c**.^[70] Recently a monomeric LiMe fragment has been trapped by $\text{Li}_2\{\text{S}(\text{N}t\text{Bu})_3\}$ to give the complex **39e**.^[69b] A similar complex **39f** containing



$\text{LiOCH}=\text{CH}_2$ derived from cleavage of THF by $\text{Li}t\text{Bu}$ has been reported.^[69c]

The trisimidosulfate complex **40** was obtained by the oxidation of **15a** with I_2 in the presence of O_2 . Dilithium bisimidosulfates $[\text{Li}_2\{\text{O}_2\text{S}(\text{NR})_2\}]_n$ ($\text{R} = i\text{Pr}$, $t\text{Bu}$) are insoluble,



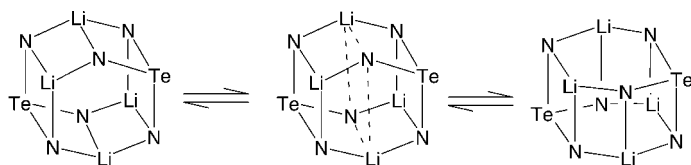
amorphous solids presumably with extended structures.^[39b] However, crystalline derivatives are formed by the incorporation of lithium halides. Thus the dimer $[\{(\text{thf})\text{Li}\}_2\{\text{O}_2\text{S}(\text{N}t\text{Bu})_2\}\{(\text{thf})\text{LiCl}\}]_2$ (**41**) was obtained and structurally characterized.^[39b] The assembly of extended structures through the Li–O edges in $[\{(\text{thf})\text{Li}\}_2\{\text{O}_2\text{S}(\text{N}t\text{Bu})_2\}]$ is inhibited by interactions of these edges with the polar LiCl molecules.

5. Solution Behavior: NMR Studies/Fluxional Processes

An important consideration for the characterization of aggregated complexes is that the solid-state structure may not reflect solution behavior and vice versa. In general, one of two phenomena can account for this dichotomy: a) intramolecular fluxional processes or b) dissociation of the complex into smaller oligomers.

As an example of the former behavior the hexagonal prism $[\text{Li}_2\{\text{Te}(\text{N}t\text{Bu})_3\}]_2$ (**15c**) exhibits a single resonance for $\text{N}t\text{Bu}$

groups in the ^1H NMR spectrum ($[\text{D}_8]\text{toluene}$) throughout the temperature range 185–298 K rather than the two resonances (2:1 ratio) expected on the basis of C_{2h} symmetry.^[33] A fluxional process (fast on the NMR time scale) involving the concerted stretching and contraction of transannular Li–N interactions across the six-membered rings of the hexagonal prism has been proposed to account for this observation (Scheme 4).^[33b]

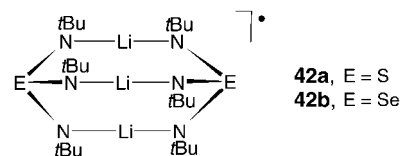


Scheme 4. Fluxional behavior of **15c**. For clarity, the *t*Bu groups are omitted.

A different type of solution behavior is indicated by NMR spectroscopic studies of tetramers of the type $[\text{Li}\{\text{E}(\text{NR})_2\}]_4$ ($\text{E} = \text{Group 15 element}$). Variable-concentration cryoscopic molecular-mass measurements in benzene together with variable-temperature/concentration ^7Li NMR spectra of $[\text{Li}\{\text{Sb}(\text{NCy})_2\}]_4$ in $[\text{D}_8]\text{toluene}$ revealed a dissociative equilibrium in which dimeric units are produced (cf. Eq. (n)).^[25]

6. EPR Investigations of Radical Anions

An intriguing and well-established characteristic of many chalcogen–nitrogen compounds is their ability to form deeply colored, long-lived radicals.^[71, 72] This phenomenon is vividly apparent when solutions of **15a** are exposed to traces of air. The air-oxidation of hexane or toluene solutions of **15a** produces a dark blue radical.^[31, 36, 38] The EPR spectrum of this radical comprises a septet (1:3:6:7:6:3:1) of decets, attributed to coupling of the unpaired electron with three equivalent ^{14}N nuclei and further interaction with three equivalent ^7Li nuclei.^[36, 38] The oxidation of **15a** appears to involve the removal of one electron and one Li^+ ion from the 12-atom ($\text{Li}_4\text{S}_2\text{N}_6$) cluster to give a neutral 11-atom radical **42a** in



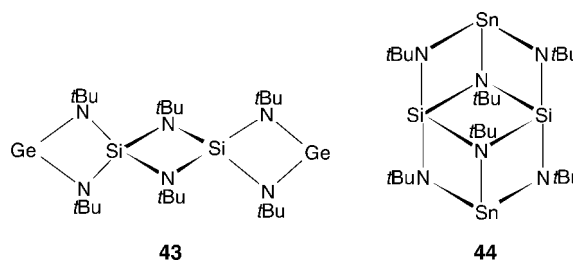
which the radical anion $[\text{S}(\text{N}t\text{Bu})_3]^{2-}$ is linked to the dianion $[\text{S}(\text{N}t\text{Bu})_3]^{2-}$ by three Li^+ ions.^[36, 38] On the basis of the EPR spectrum, which also consists of a septet of decets, a similar neutral radical cluster has been proposed for the Se congener **42b**.^[36] The oxidation of **15a** by bromine provides an improved route to the sulfur(vi) triimide $\text{S}(\text{N}t\text{Bu})_3$.^[38] The chemistry of sulfur triimides $\text{S}(\text{NR})_3$ ($\text{R} = t\text{Bu}, \text{SiMe}_3$) and related cations has been reviewed by Mews et al.^[73]

7. Ligand Chemistry

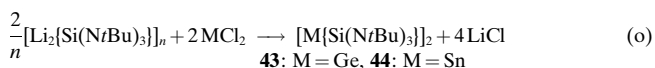
An important incentive for the study of polyimido and imidochalcogenido anions of p- and d-block elements involves their potential as multidentate ligands. The most common approach to coordination complexes utilizes the s-block metal derivatives of these ions as ligand-transfer agents in metathesis reactions, although transamination routes are also feasible. The majority of known coordination complexes exhibit ligation through the imido groups, but a few exceptions involving the central element have been reported. The reaction chemistry of the polyimido ions $[\text{Sb}(\text{NR})_3]^{3-}$, $[\text{S}(\text{N}t\text{Bu})_3]^{2-}$, and $[\text{S}(\text{N}t\text{Bu})_4]^{2-}$ has been reviewed,^[13, 14] and will therefore not be discussed here.

7.1. p-Block Element Centered Anions

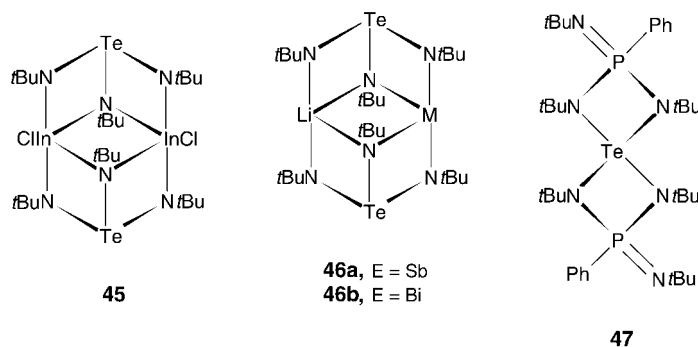
The first report to hint at the utility of polyimido anions as a source of novel ligands involved the reaction of $[\text{Li}_2\{\text{Si}(\text{N}t\text{Bu})_3\}]_n$, generated in situ, with the divalent Group 14 halides MCl_2 ($\text{M} = \text{Ge}, \text{Sn}$) [Eq. (o)].^[10] Two distinct arrangements are observed for the resulting complexes $[\text{M}\{\text{Si}(\text{N}t\text{Bu})_3\}]_2$ (**43**,



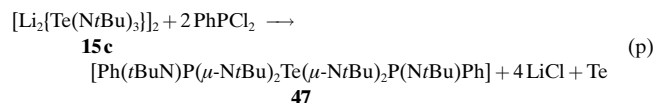
$\text{M} = \text{Ge}$; **44**, $\text{M} = \text{Sn}$). A spirocyclic structure forms the backbone for **43**, while **44** has a 10-atom ($\text{Sn}_2\text{Si}_2\text{N}_6$) deck-chair core.



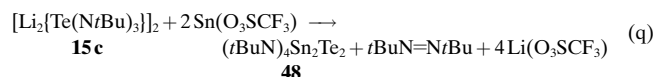
The complex $[\text{Li}_2\{\text{Te}(\text{N}t\text{Bu})_3\}]_2$ (**15c**) is less susceptible to redox reactions than the sulfur analogue **15a**.^[74] The $[\text{Te}(\text{N}t\text{Bu})_3]^{2-}$ ion acts as an N, N' -chelating ligand in the boron complex $[\text{PhB}(\mu\text{-N}t\text{Bu})_2\text{TeN}t\text{Bu}]$ ^[33a] or as a tridentate ligand in combination with In (**45**) or heavy Group 15 element



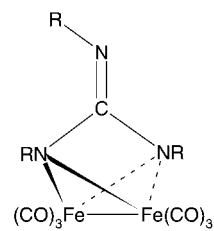
centers (**46**).^[75a, 76] Redox behavior is observed, however, in the reaction of **15c** with PhPCl_2 to give the spirocyclic tellurium(IV) complex **47**. This process involves the oxidation of two P^{III} centers to P^{V} with the concomitant formation of elemental tellurium [Eq. (p)].^[33a]



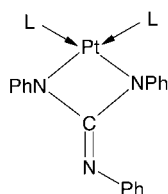
The redox process has an especially interesting outcome in the reaction of **15c** with $\text{Sn}(\text{SO}_3\text{CF}_3)_2$ which produces **48**, the first stannatellurone with four-coordinate tin [Eq. (q)].^[75b] In complex **48** which contains Sn^{II} , Sn^{IV} , Te^{IV} , and $\text{Te}^{\text{-II}}$ centers, one equivalent of $[\text{Te}(\text{N}t\text{Bu})_3]^{2-}$ effectively acts as a bridging, tridentate ligand (as in **45**) while the second equivalent serves as the source of tellurium for the SnTe unit and provides a $\mu\text{-N}t\text{Bu}$ group.



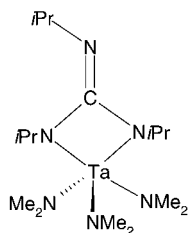
It is instructive to compare the ligand behavior of planar trialkyl(aryl)guanidinate ions $[\text{C}(\text{NR})_3]^{2-}$ with that of the pyramidal $[\text{Te}(\text{N}t\text{Bu})_3]^{2-}$ ion. A variety of synthetic methods have been used to prepare dianionic guanidinate complexes of p- and d-block elements. The reaction of $[\text{Fe}(\text{CO})_5]$ with carbodiimides $\text{RN}=\text{C}=\text{NR}$ ($\text{R} = i\text{Pr}, \text{Cy}$) yields the complexes $[\mu^2\text{-(RN)}_3\text{C}][\text{Fe}(\text{CO})_3]_2$ (**49**) in which two of the imido groups bridge the two iron centers.^[77] N,N'-chelation is observed for the complexes $[(\text{cod})\text{Pt}\{(\mu\text{-PhN})_2\text{CNPh}\}]$ (**50**),^[78] $[\text{Ta}(\text{NMe}_2)_3\text{-(}\mu\text{-}i\text{PrN)}_2\text{CN}i\text{Pr}]$ (**51**),^[79] and $[\text{Sb}\{(\mu\text{-}i\text{PrN)}_2\text{CNH}i\text{Pr}\}\{(\mu\text{-}i\text{PrN)}_2\text{-CNH}i\text{Pr}\}]$ (**52**).^[80] Complexes of the type **51** (and the



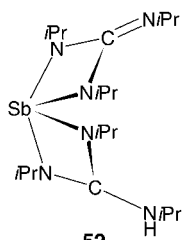
49a, $\text{R} = i\text{Pr}$
49b, $\text{R} = \text{Cy}$



50, $\text{L}_2 = \text{cod}$

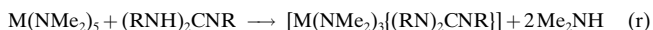


51

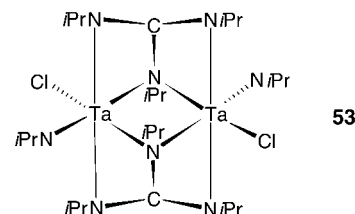


52

antimony complex **52**) are prepared by transamination routes [Eq. (r)] $\text{M} = \text{Nb}, \text{Ta}$; $\text{R} = i\text{Pr}, \text{Cy}$.^[79, 80]

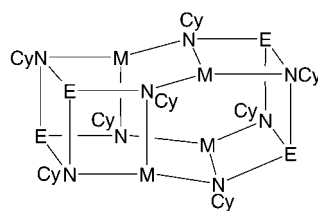


The dinuclear complex $[(\mu\text{-}\eta^2\text{-}\eta^2(i\text{PrN})_3\text{C})\text{Ta}(\text{N}i\text{Pr})\text{Cl}]_2$ (**53**)^[81] is the only example of the chelating bridging mode for the $[\text{C}(\text{N}i\text{Pr})_3]^{2-}$ ion (cf. **45**). In **53** the geometry at the

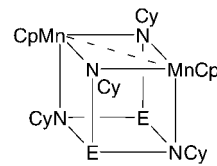


central C atom is planar whereas that at Te in **45** is pyramidal. Another bridging dianionic ligand $[(i\text{PrN})_2\text{C}]_2\text{NiPr}^{2-}$ for which no oxo analogue exists, has been generated from guanidinato-iron complexes.^[82] Finally, the $[\text{C}(\text{NPh})_3]^{2-}$ ligand behaves as an N-monodentate ligand towards Cd in the adduct $[(\text{Me}_3\text{Si})_2\text{N}]_2\text{Cd}\{(\text{PhN})_3\text{C}\}\text{Li}(\text{thf})_3$.^[83]

The robust nature of the ions $[\text{E}(\text{NCy})_2]^-$ ($\text{E} = \text{As}, \text{Sb}$) was demonstrated by the generation of the d^{10} complexes $[\text{M}'\{\text{E}(\text{NCy})_2\}]_4$ (**54**) by reaction of the alkali metal salts



54a, $\text{E} = \text{As}, \text{M} = \text{Cu}$
54b, $\text{E} = \text{Sb}, \text{M} = \text{Cu}$
54c, $\text{E} = \text{Sb}, \text{M} = \text{Ag}$

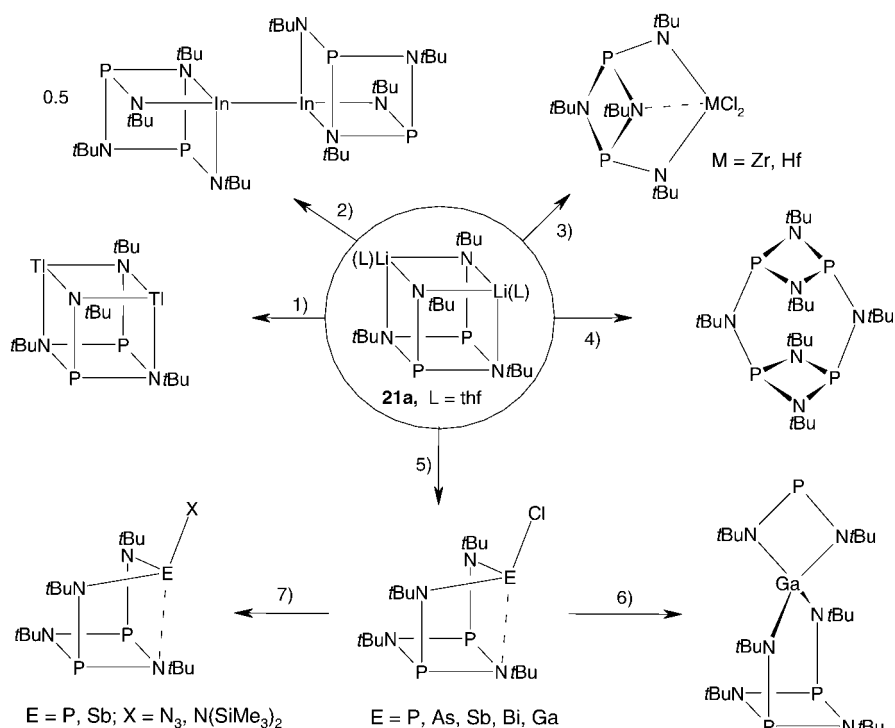


55a, $\text{E} = \text{As}$
55b, $\text{E} = \text{Sb}$

$[\text{M}'\{\text{E}(\text{NCy})_2\}]_4$ ($\text{M}' = \text{Li}, \text{Na}$) with the appropriate copper or silver reagent.^[23, 84, 85] This application was recently extended to include $[\text{CpMn}\{\text{E}(\text{NCy})_2\}]_2$ (**55**) [Eq. (s)], the first complexes to incorporate a paramagnetic metal ion into a p-block ligand framework.^[86]



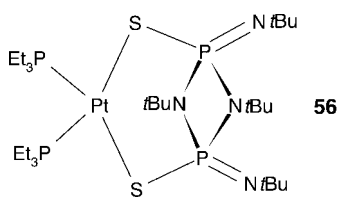
The ligating ability of the polyimido complex $[(\text{thf})\text{Li}\{\text{P}(\text{N}t\text{Bu})_2\}]_2$ (**21a**), the phosphorus analogue of $[\text{M}'\{\text{E}(\text{NCy})_2\}]_4$, has also been investigated extensively, as illustrated in Scheme 5. A noteworthy feature of the ligand behavior of this dimeric chelating ligand is the propensity to engage in intramolecular interactions involving one of the bridging $\text{N}t\text{Bu}$ groups. This type of base stabilization is observed for complexes of the metals Zr , Hf ,^[88] and Ga , In ,^[87, 90] and the heavier Group 15 elements (Sb, Bi).^[89] Another interesting observation is the formation of a monomeric 1,3-diaza-2-phosphaallyl ligand (cf. **11**) from the cyclo-



Scheme 5. Reactions of **21a**. 1) 2 TiCl₄, – 2 LiCl;^[87] 2) 2 InCl₃, – 2 LiCl; – In;^[87] 3) MCl₄, – 2 LiCl;^[88] 4) ClP(*m*-NtBu)₂PCL, – 2 LiCl;^[21] 5) ECl₃, – 2 LiCl;^[89–91] 6) ½[(thf)Li{P(NtBu)₂}]₂, – LiCl;^[90] 7) NaN₃ or LiN(SiMe₃)₂, – (Na, Li)Cl.^[89, 91] (The intramolecular E...N interaction is not observed for the small Group 15 elements E = P and As).^[91]

reversion (ring opening) of **21a** in the formation of a spirocyclic Ga complex (see (6) in Scheme 5).^[90] A comprehensive review by Stahl of the coordination chemistry of **21a** has appeared recently.^[92]

The bis(imido)chalcogenido anions [EP(NtBu)₂][–] (E = S, Se) form dimeric units (see **36**) with a *cis*-arrangement of the chalcogens. This framework conceivably allows for three different modes of ligation: N,N'-chelation (end-on), E,E'-chelation (end-on), or N,E-chelation (side-on). Although these dianions have yet to be exploited extensively, a preliminary investigation revealed that the square-planar platinum(II) complex [(Et₃P)₂Pt{SP(NtBu)₂}]₂ (**56**) displays

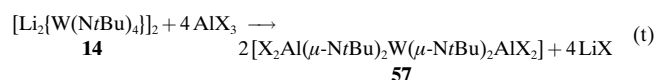
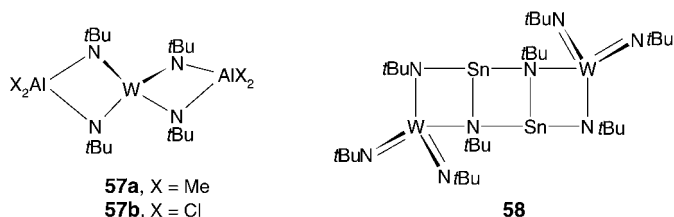


S,S'-coordination of the metal center by the [SP(NtBu)₂]₂^{2–} ion^[93] in contrast to the N,N'-chelation observed for [Me₂Sn{SP(NtBu)₂}]₂^[94] and the N,E-ligation found for the bis(dimethylaluminum) complexes [(Me₂Al)₂{EP(NtBu)₂}]₂ (E = O, S, Se).^[95]

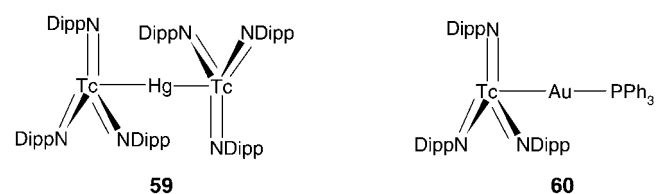
7.2. d-Block Element Centered Anions

The Group 6 complex **14** is a useful source of the ligand [W(NtBu)₄]^{2–} by metathesis. For example, reaction of **14** with AlX₃ (X = Me, Cl) leads to tetrakisimidotungstate complexes

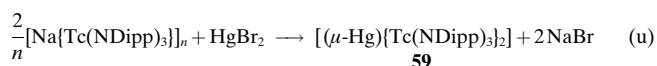
57 [Eq. (t)],^[42b] while a dimeric complex **58** was recently prepared by the treatment of **14** with two equivalents of SnCl₂.^[96]



The anion of the Group 7 complex [Na{Tc(NDipp)₃}]_n coordinates to various functional groups through the Tc^V center rather than the imido groups. Treatment of this d² complex with HgBr₂ generates the linear trimetallic species **59** [Eq. (u)].^[43] The rhenium analogue of **59** has also been



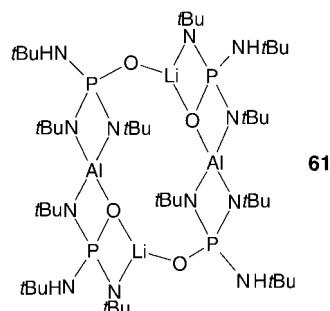
reported.^[44] Similarly, the 1:1 reaction of [Na{Tc(NDipp)₃}]_n with ClAuPPh₃ gives the complex [(DippN)₃TcAu(PPh₃)] (**60**).^[43]



8. Summary and Outlook

Alkali metal derivatives of homoleptic polyimido anions of the type $[E(NR)_x]^{z-}$ ($E = d\text{- or } p\text{-block element}$, $R = \text{alkyl or aryl}$) and their heteroleptic imido-oxo analogues, $[O_yE(NR)_{x-y}]^{z-}$, form cluster structures comprised of fundamental building blocks or an assembly of these units. An underlying objective for structural studies of these cluster systems is to develop an understanding of, and possibly the ability to control, the aggregation process. The preliminary findings suggest several principles for the rationalization and prediction of cluster structures: a) the cluster geometry of the homoleptic polyimido system is indicative of the fundamental building block for the corresponding imido-oxo analogue, b) the isomer of the fundamental building block that involves the juxtaposition of $Li-O$ linkages is favored for the heteroleptic systems, c) the aggregation of these fundamental building blocks takes place through the highly polar, sterically unencumbered Li_xO_x units ($x = 1$: edges, $x = 2$ or 3 : faces), and d) the replacement of one imido ligand in a homoleptic polyimido anion by an oxo ligand leads to discrete oligomeric clusters, while replacement of two imido ligands gives extended (polymeric) structures. Further work on imido-oxo analogues of other common oxo anions such as PO_4^{3-} and SiO_4^{4-} and an investigation of the influence of the size of the alkali metal counter ion are necessary to test the general applicability of these principles. Preliminary experiments indicate that novel chemistry will result from studies of imido analogues of thio or selenido anions owing to the lability of certain element–chalcogen bonds.^[29b, 97] The recent reports of the characterization of $[Li_2\{H_2C=S(NtBu)_2\}]_2$ draw attention to another isoelectronic analogy, that between RN and R_2C groups, that is worthy of further investigation.^[98]

An intriguing extension of the investigations of imido analogues of simple oxo anions involves the synthesis of imido analogues of complex oxo anions such as aluminosulfates,^[99] aluminosilicates $[Al(SiO_4)]^-$, and aluminophosphates $[Al(PO_4)_2]^{3-}$. In a preliminary investigation the reaction of $LiAlH_4$ with $OP(NHtBu)_3$ yielded **61**, the first imido analogue



of an aluminophosphate.^[100] The variables in this new class of cluster system include a) the size of the R group, b) the nature of the counter cation, and c) the O/NR ratio. Investigation of the structural effects of these variables is likely to lead to the preparation of larger cluster units. In addition, the presence of reactive exocyclic $NHtBu$ groups in **61** provides the possibility

of linking this and related clusters to generate extended structures with defined pore sizes.

The homoleptic polyimido anions of $p\text{- or } d\text{-block elements}$ also behave as adaptable ligands towards main group element and transition metal centers. The ability of these anions to stabilize low-coordinate, highly Lewis-acidic metal centers warrants further investigation in the context of possible catalytic applications.

We wish to thank all the co-workers who have contributed to our work on polyimido anions of $p\text{-block elements}$. In particular, the skillful synthetic work of Dr. Xiaoliang Gao, Dr. Gabriele Schatte, Andrew Downard, Mark Krahn, Pierre Blais, and Chantall Fedorchuk has played a key role in these investigations. The invaluable assistance of Drs. Gabriele Schatte and Masood Parvez (University of Calgary), Dr. Bob MacDonald (University of Alberta) and Dr. Glenn Yap (University of Ottawa) with X-ray structure determinations and collaborations with Dr. Bruce McGarvey (University of Windsor) and Dr. René Boéré (University of Lethbridge) in the area of EPR spectroscopy were also pivotal contributions. The continuous financial support of NSERC (Canada) is gratefully acknowledged.

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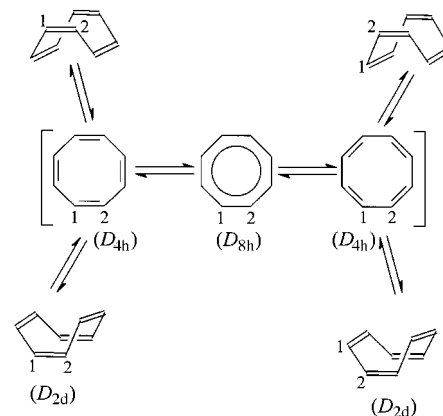
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About the Antiaromaticity of Planar Cyclooctatetraene**

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Aromaticity is one of the most important concepts in chemistry. Recently, special issues of *Chemical Reviews*^[1] and *Tetrahedron Symposium in Print*^[2] (May 2001) highlighted the current interest in this field, even though it is now 176 years since Faraday^[3] discovered benzene and 136 years since Kekulé^[4] made his famous proposal for the structure of benzene. It was 70 years ago that E. Hückel first explained why cyclic delocalized π systems that have $[4n+2]$ π electrons are unusually stable, for example, benzene ($n=1$, 6 π electrons). Based on his molecular orbital theory (HMO), these systems were classified as aromatic. Today, structural, magnetic, and energy properties, which result from the cyclic π -bond delocalization,^[11] such as the equal lengths of formal C–C and C=C bonds,^[7] the resonance energy,^[8] the nucleus-independent chemical shift (NICS),^[9] and the increased magnetic susceptibility^[10] are used as criteria for aromaticity.^[11] HMO theory predicts that the cyclic delocalization of the $[4n]$ π electrons should lead to open-shell systems with triplet ground states. Based on the extremely low acidity of substituted cyclopropenes, Breslow concluded that the cyclic conjugation of $[4n]$ π electrons leads to the destabilization of the system which he described as antiaromatic^[12]. This review was prompted by the current interest in 1,3,5,7-cyclooctatetraene (COT),^[13] the higher vinylogue of benzene. COT is an 8π -electron system ($[4n]$, $n=2$) and is predicted by HMO theory to have a triplet ground state, provided that the π electrons are delocalized. It is essential that the system is planar for an optimum conjugation interaction of the π electrons.

COT, however, adopts a nonplanar boat conformation (D_{2d}) with alternating single and double bonds, and behaves as a polyolefin (Scheme 1). The dihedral angle between vicinal double bonds is 56° (single-crystal X-ray structure analysis)^[14] so that the conjugation interaction between the π bonds is small. This is confirmed inter alia by the good agreement between the experimental and the calculated standard enthalpy of formation of COT (ΔH_f° [kcal mol⁻¹] = 71.13



Scheme 1. Ring inversion and π -bond shift.

(exp.), 71.56 (calcd)). This value was calculated by using an extended MM2 force field (MM2ERW),^[15] which was parametrized with 1,3-butadiene as a model for conjugated polyenes, and led directly to the resonance energy, which is now standardized for 1,3-butadiene ($E_{\text{res}} = \Delta H_f^\circ(\text{calcd}) - \Delta H_f^\circ(\text{exp.})$) and is negligible in the case of COT (D_{2d} ; $E_{\text{res}} = < 0.5$ kcal mol⁻¹).^[16]

The dynamic processes (ring inversion and π -bond shift) observed in the variable-temperature NMR spectra of substituted COT derivatives are particularly significant in the antiaromaticity of the cyclic 8π systems.^[17] Accordingly, the activation energy for the ring inversion (10–11 kcal mol⁻¹) is about 3–4 kcal mol⁻¹ lower than that for the π -bond shift. Planar COT conformations were proposed to be the transition states of these two processes: the D_{4h} conformation with alternating single and double bonds for the ring inversion, and the D_{8h} conformation with delocalized π bonds for the π -bond shift. The activation barrier for the π -bond shift, which is 3–4 kcal mol⁻¹ higher than that for the ring inversion, was taken as evidence for the antiaromatic destabilization of the delocalized 8π -electron system. A similar value was calculated for the resonance energy of the delocalized D_{8h} conformation ($E_{\text{res}} = 4.6$ kcal mol⁻¹) by using the MM2ERW force field. In contrast, the corresponding force-field calculations for the localized D_{4h} conformation result in a small, almost insignificant destabilization as a result of the cyclic interactions of the π electrons ($E_{\text{res}} \approx -1$ kcal mol⁻¹).^[16] The planar D_{4h} conformation is generally accepted to be the transition state of the ring inversion, whereas the D_{8h}

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conformation suggested to be the transition state of the π -bond shift has been questioned. Nonplanar crown-[18] and saddle-like COT conformations[19] have been discussed as alternative transition states. Especially the finding that substituents in COT derivatives bring about a decrease in the difference between the measured Gibbs enthalpy of activation of the π -bond shift and of the ring inversion (e.g. 1,2,3,4-tetramethyl-COT: $\Delta\Delta G^\ddagger = 32.0 - 31.8 = 0.2 \text{ kcal mol}^{-1}$) suggests a nonplanar geometry of the transition state of the π -bond shift.[20]

According to quantum mechanical *ab initio* calculations, both transition states should be planar in the parent COT system.[21] Although the triplet state of the delocalized D_{8h} structure can be regarded as aromatic,[22] the calculations show that in this case the open-shell singlet state is more stable than the triplet state, contrary to the predictions of simple HMO theory. The violation of Hund's rule is explained here by the phenomenon of the "disjoint diradicals".[23] The localized D_{4h} structure, however, exists in a closed-shell singlet state, which results from a second-order Jahn–Teller distortion, comparable to a polyolefin. The photoelectron spectrum of the planar cyclooctatetraene radical anion (COT $^{\cdot-}$) (used as transition-state spectroscopy) shows two transitions to two electronic states of COT: the first corresponds to the singlet D_{4h} ($^1A_{1g}$) state and the second to the triplet D_{8h} ($^3A_{2u}$) state.[24] The difference in energy between these two states, which is determined from the electron-binding energies, amounts to about 12 kcal mol^{-1} and is in good agreement with the *ab initio* calculations. The results of the spectroscopic measurements and quantum mechanical calculations are summarized in Figure 1.

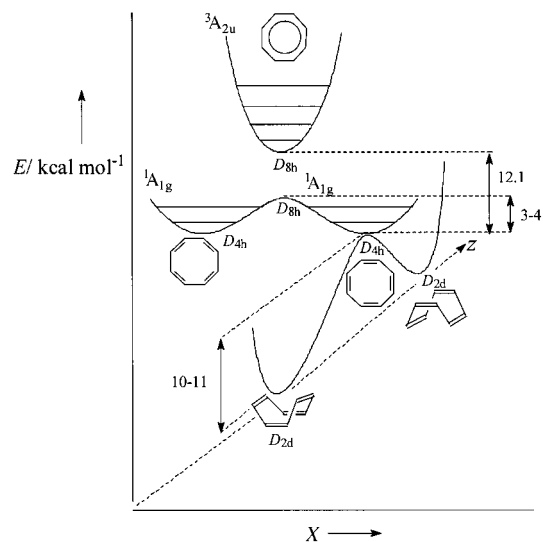
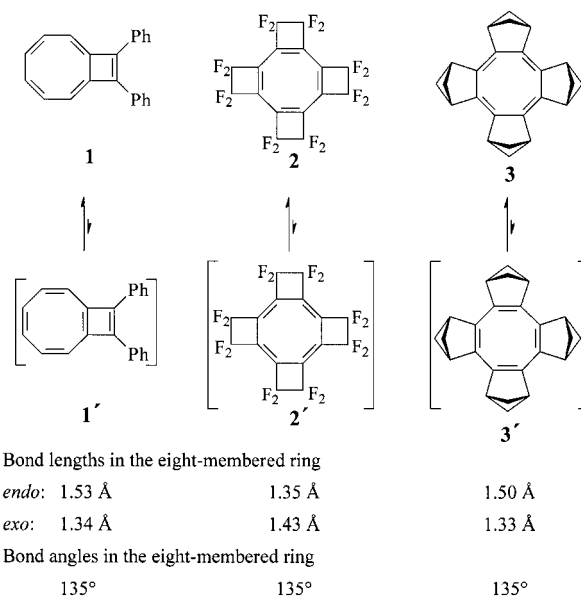


Figure 1. Schematic representation of the potential energy for singlet and triplet COT. The x axis represents the change in bond length, and the y axis reflects the change in the dihedral angle between vicinal double bonds.

COT derivatives that have planar ground states are of great interest to gain further insight into the electronic properties of cyclic conjugated 8π -electron systems. Such derivatives can be produced by the annelation of strained three- or four-membered rings to the COT skeleton or by the replacement of

endocyclic double bonds with triple bonds.[25–28] These structural modifications cause an expansion of the endocyclic bond angles and hence the planarization of the COT skeleton. Compounds **1–3** are discussed as examples (Scheme 2).



Scheme 2. Bond lengths and angles in the eight-membered rings of substituted COT derivatives **1–3**.

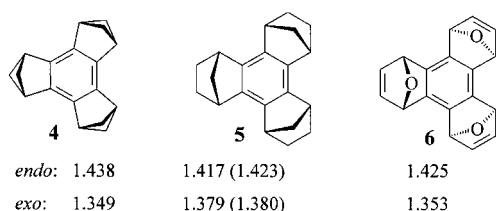
According to the single-crystal X-ray structure analysis, 9,10-diphenylbicyclo[6.2.0]decapentaene (**1**) possesses a nearly planar COT substructure with localized single and double bonds.[25] The diphenylcyclobutene unit not only results in the increase in the bond angle mentioned above, but also fixes one of the dihedral angles in the COT substructure at 0° and hence results in the planarization of the eight-membered ring. The π -bond fixation can be explained by the π -bond shift leading to valence-bond isomers, e.g. **1'**, which are less stable than the observed structure **1** as a result of the antiaromatic cyclobutadiene substructure. The valence-bond isomer **1** can be considered formally as a cyclic 10π -electron system, which should be aromatic according to the Hückel rule. However, the positive resonance energy of $0.3 \text{ kcal mol}^{-1}$, derived from the enthalpy of hydrogenation measured for the parent bicyclo[6.2.0]decapentaene,[29] is very small. Thus, the resonance energy gives no further insight into the electronic properties of the planar COT substructure of **1**.

Single-crystal X-ray structure analysis shows that perfluorotetracyclobutacyclooctatetraene (**2**) is also planar.[26] The surprising localization of the π bonds inside the annelated four-membered rings can be explained by the unique electronic effect of the fluoro substituents.[30] Compound **2** is $17.2 \text{ kcal mol}^{-1}$ more stable than its valence tautomer **2'**, as calculated by using the HDFT (Hybrid-Density Functional Theory) method[31]. Corresponding calculations for unsubstituted tetracyclobutacyclooctatetraene predict that the valence isomer with the double bonds outside the annelated four-membered ring is about $3.2 \text{ kcal mol}^{-1}$ more stable.

Single-crystal X-ray structure analysis shows that tetrakis(bicyclo[2.1.1]hexenyl)cyclooctatetraene (**3**) possesses an en-

tirely planar 8- π -electron system with alternating bond lengths.^[28] The alternation of the bond lengths can be explained by the distortions of the bond angles which result from the annelated bicyclohexene subunits. Furthermore, the unusually high enthalpy of formation for bicyclo[2.1.1]hexene, which can be attributed to steric and electronic effects, is evidently also important for the fixation of the π bonds in **3** outside the bicyclic subunits.^[32] According to quantum mechanical calculations, **3** is about 32.7 kcal mol⁻¹ more stable than the valence isomer **3'**, which contains four bicyclo[2.1.1]-hexene substructures.^[31]

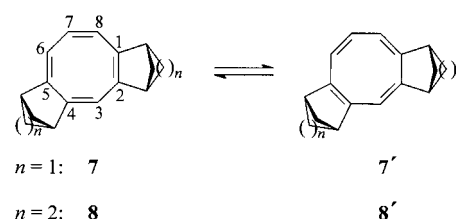
Bicyclo[2.1.1]hexene has the same effect on the benzene structure. The single-crystal X-ray structure analysis shows that tris(bicyclo[2.1.1]hexeno)benzene has the cyclohexatriene structure **4** with alternating bond lengths (Scheme 3).^[33] The annelation of strained norbornene and oxanorbornadiene



Scheme 3. Bond lengths in the benzene rings of substituted derivatives **4**–**6**.

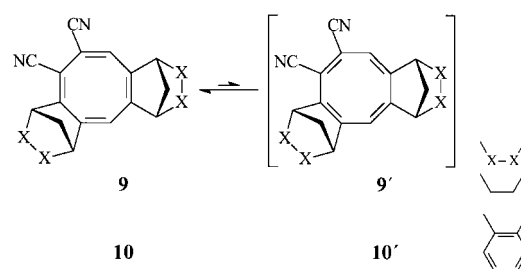
units also leads to the benzene structures **5** and **6** with alternating bond lengths.^[34, 35] The difference in the bond lengths is, however, smaller in the structures **5** and **6** than in **4**. To estimate the influence of the bicyclo[2.1.1]hexene subunits on the aromaticity and antiaromaticity of **3** and **4**, respectively, the nucleus-independent chemical shift (NICS), the increase in magnetic susceptibility (Δ), and the resonance energies of the pairs benzene/**4** and D_{4h} -COT/**3** were calculated by quantum mechanical methods and compared with each other. Whereas the NICS value calculated for **4** is similar to that for benzene (GIAO-HF/6-31+G*: benzene: $\delta = -9.7$, **4**: $\delta = -8.0$) thus indicating that a substantial degree of aromaticity is retained in **4**,^[36] the antiaromaticity of **3** is substantially lower than that of D_{4h} -COT (from NICS: $\delta = +10.6$ and $+27.2$, respectively). The values of the increase in magnetic susceptibility calculated for these systems show a similar trend. According to the calculated resonance energies, the bicyclo[2.1.1]hexene units should not have a considerable effect either on the antiaromaticity of **3** or on the aromaticity of **4**.^[28] Dia- and paramagnetic ring-current effects induce shifts of the signals in the ¹H NMR spectra, which are frequently employed to characterize aromatic or antiaromatic systems qualitatively.^[37] The ¹H NMR signals of bicyclohexene bridgehead protons of **3** and **4**, which are located in the plane of the eight- and six-membered rings, respectively, differ only by $\delta = 0.18$ ppm and therefore do not provide evidence for a ring-current effect in one or the other direction.

Another possibility to planarize cyclooctatetraene consists of the annelation of two bicyclo[2.1.1]hexene or bicyclo[2.2.1]heptene units at positions C1,C2 and C4,C5 of the eight-membered ring to give **7** and **8**, respectively (Scheme 4).^[19] In



Scheme 4. Substituted COT derivatives **7** and **8**.

these compounds, the planarization could essentially be achieved by fixing the dihedral angle C3-C4-C5-C6 at 0° as a result of the bicyclic subunit. The dinitriles **9** and **10** were the first derivatives with such a substitution pattern to be synthesized (Scheme 5).^[38] However, the single-crystal X-ray



Scheme 5. Nitrile-substituted COT derivatives **9** and **10**.

structure analysis of **9** shows a nonplanar eight-membered ring with alternating bond lengths (Figure 2). The experimentally determined structural parameters agree well with PM3 and DFT calculations (BP/DN**//pBP/DN).^[38] According to

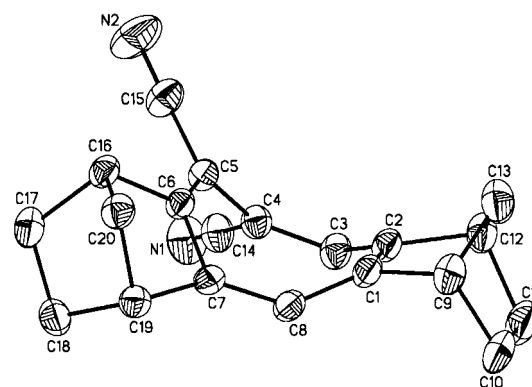
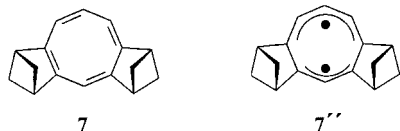


Figure 2. Crystal structure of **9** (single-crystal X-ray analysis).

the DFT calculations, the energies of the nonplanar valence isomers **9** and **9'** differ only by $\Delta E = 1$ kcal mol⁻¹. The difference in energy between the planar and the nonplanar structure is, accordingly, lowered from the value calculated for 1,8-dicyano-COT (15 kcal mol⁻¹) to that calculated for **9** (10 kcal mol⁻¹) and should be even lower in the case of **10** because the rigidity of the annelated bicyclic unit is increased by the additional benzene rings. For the comparison of the parent cyclooctatetraene with **7** and **8**, the difference in energy between the planar and the corresponding nonplanar COT structure was calculated by the same DFT method; a decrease from 12 kcal mol⁻¹ to 3 and 5 kcal mol⁻¹, respectively,

was found. The DFT calculations clearly show that the nitrile groups have a considerable effect on the COT structure, which disfavors the planarization of the eight-membered ring.

According to the most recent quantum mechanical calculations (MCQDPT/DZV-(2d,p)), the planar structure **7** (C_s symmetry; Scheme 6 left) with localized bonds and a relatively large HOMO/LUMO gap is only 0.6 kcal mol⁻¹ less



Scheme 6. The C_s -symmetric COT derivative **7** with localized bonds and the C_{2v} -symmetric (1,1) diradical **7''**.

stable than the nonplanar C_1 structure.^[31] In the C_{2v} structure of **7** with delocalized π bonds, the highest occupied molecular orbital (HOMO) and the lowest occupied molecular orbital (LUMO) converge, thus allowing three possible singlet states to exist with electron populations of (2,0), (0,2), and (1,1). The configurations (2,0) and (0,2) (both electrons occupy the same orbital) lie ~ 17 kcal mol⁻¹ higher than the localized C_s structure. According to the calculations, the delocalized singlet C_{2v} structure **7''** (Scheme 6, right) with the electron configuration (1,1) is the ground state, and was calculated to be 5.5 and 5.8 kcal mol⁻¹ lower than the localized C_s and the delocalized triplet C_{2v} structures, respectively. The structure **7''** is an example of a “disjoint diradical”^[23] in which the (1,1) singlet state is favored over the other possible singlet and triplet states because it benefits from the relief of electron repulsion in the half-occupied orbitals as well as from dynamic-spin polarization.

The question concerning the antiaromaticity of the planar COT system has certainly been answered for the parent cyclooctatetraene. Contrary to 1,3-cyclobutadiene in which the cyclic interaction of the π bonds leads to a substantial destabilization even in the localized structure ($E_{\text{res}} = 71.9$ (MM2ERW) – 114 = – 42.1 kcal mol⁻¹,^[39] this effect of the π bonds in the localized D_{4h} COT structure is negligible. The additional destabilization of the planar delocalized D_{8h} COT structure (3–4 kcal mol⁻¹) is also relatively small according to the experimental results as well as theoretical calculations. Substituents have a substantial effect on the COT structure. For future work it would certainly be interesting to verify experimentally the prediction resulting from quantum mechanical calculations^[31] that the ground state of compound **7** is the planar singlet diradical **7''** with C_{2v} geometry.

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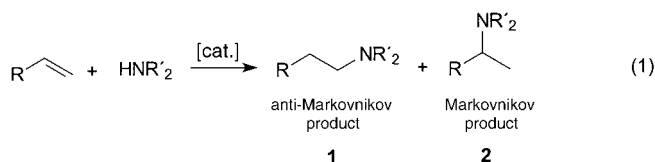
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Recent Developments in Transition Metal Catalyzed Intermolecular Hydroamination Reactions—A Breakthrough?

Markus Nobis and Birgit Drießen-Hölscher*

The addition of primary/secondary amines or ammonia to olefins is, in terms of an optimum material balance, one of the much discussed atom-economical processes.^[1] This reaction, known as hydroamination, allows the synthesis of higher-substituted amines of type **1** and **2** in a single step [Eq. (1)]. These amines are of great importance for synthetic chemists in basic research as well as for the chemical industry.



R' = Alkyl, Aryl, H
R = Alkyl, Aryl

The catalytic anti-Markovnikov addition of HNR_2 to olefins was listed as one of the so-called „Ten Challenges for Catalysis“ for a good reason.^[2] In recent years, great efforts have been made worldwide to develop effective hydroamination procedures; these met with little success until recently.^[3]

In recent months, several research groups have described homogeneous catalytic procedures for intermolecular hydroamination, which—it appears at the moment—have initiated a breakthrough in this area. The present developments can be divided into three categories and are discussed in the following sections:

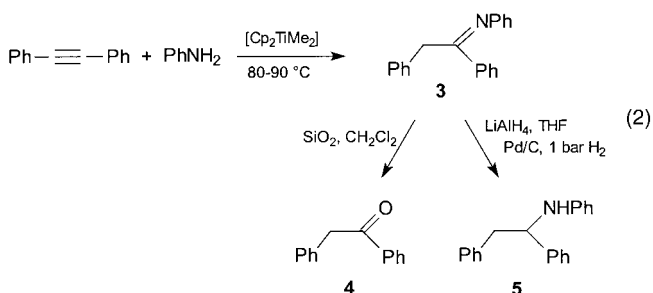
- 1) Hydroaminations of alkynes and allenes.
- 2) Hydroaminations of alkenes with catalysts based on transition metals of Groups 8–10
- 3) Ab initio/DFT investigations of catalytic hydroaminations

Hydroaminations of Alkynes and Allenes

Wakatsuki et al. reported in 1999 in *Angewandte Chemie* a ruthenium-catalyzed intermolecular hydroamination of terminal alkynes with anilines which used an efficient catalyst

consisting of 0.1 mol % $[\text{Ru}_3(\text{CO})_{12}]$ and 0.3 mol % NH_4PF_6 for the hydroamination of phenylacetylene with aniline.^[4] At 100 °C and reaction times of 3–12 h, ketimines were obtained in yields of up to 95 %. The reaction-accelerating influence of the protons and the corresponding base has not yet been explained.

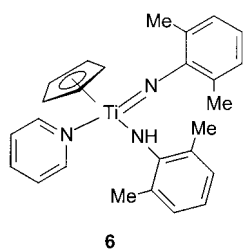
Based on work by Bergman et al.^[5] and Livinghouse et al.,^[6] the research group of Doye was able to develop a procedure for the catalytic intermolecular hydroamination of alkynes that used dimethyltitanocene $[\text{Cp}_2\text{TiMe}_2]$ ($\text{Cp} = \text{C}_5\text{H}_5$) as the catalyst.^[7] For example, the reaction of diphenylacetylene with aniline in the presence of 1 mol % $[\text{Cp}_2\text{TiMe}_2]$ in C_6D_6 at 80 to 90 °C gave *N*-(1,2-diphenylethylidene)aniline **3** [Eq. (2)], which was detected by ^1H NMR spectroscopy.



To avoid the need to isolate imines of type **3**, which are sensitive to hydrolysis, they were hydrolyzed to ketones, such as **4** ($\text{SiO}_2/\text{CH}_2\text{Cl}_2$) or reduced to amines, such as **5** ($\text{LiAlH}_4/\text{THF}$ or 1 bar H_2 , Pd/C). It is noteworthy that the amine addition to asymmetrically substituted alkynes is extremely regioselective: reaction of 1-phenylpropyne and aniline yields the anti-Markovnikov product 1-phenylpropan-2-one with high regioselectivity and in 99 % yield. However, the long reaction time of 72 h is a disadvantage, particularly for potential applications.

Recently, Bergman et al. reported an imidotitanium complex as a hydroamination catalyst for allenes and alkynes.^[8] During the search for titanium intermediates in the catalytic cycle, the stoichiometric reaction of $[\text{Cp}_2\text{TiMe}_2]$ with 2,6-dimethylaniline was studied at 75 °C in $[\text{D}_6]\text{benzene}$. The educt complex decomposed to give four compounds containing Cp as well as free CpH. If pyridine (py; 1.5 equiv) is added to this thermolysis mixture, then the unex-

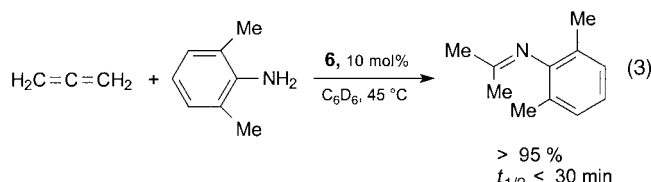
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pected monocyclopentadienyl(amido)-imidotitanium complex **6** is isolated in 62 % yield.

Pyridine appears to favor the formation of the monomeric imido complex rather than the dimer. The subsequent substitution of the pyridine by trimethylphosphane oxide

led to a crystalline compound the structure of which (Ti=N unit and an amido ligand) was confirmed by X-ray crystallography. Complex **6** was a very efficient catalyst for the hydroamination of allenes [Eq. (3)] at



an unusually low temperature of 45 °C. To obtain information on the reaction mechanism, kinetic studies were carried out which gave the rate law expressed by Equation (4).

$$r = \frac{k [\mathbf{6}] [\text{H}_2\text{C}=\text{C}=\text{CH}_2]}{[\text{py}]} \quad (4)$$

The data obtained from the kinetic experiments suggest the mechanism shown in Scheme 1 for the intermolecular hydroamination of allenes with **6** as the catalyst. Complex **6** is in equilibrium with the coordinatively unsaturated titanium compound **7**, which reacts with the allene in a [2+2] cycloaddition to give the azatitanacyclobutane **8**. The protonation of **8** by the amine leads to the tris(amido)titanium complex **9**. Finally, elimination of the enamine **10** regenerates the active catalyst **7**.

Compound **6** is also remarkably more active than $[\text{Cp}_2\text{TiMe}_2]$ for the hydroamination of alkynes. Overall, the work by Bergman's group provides the first concrete indica-

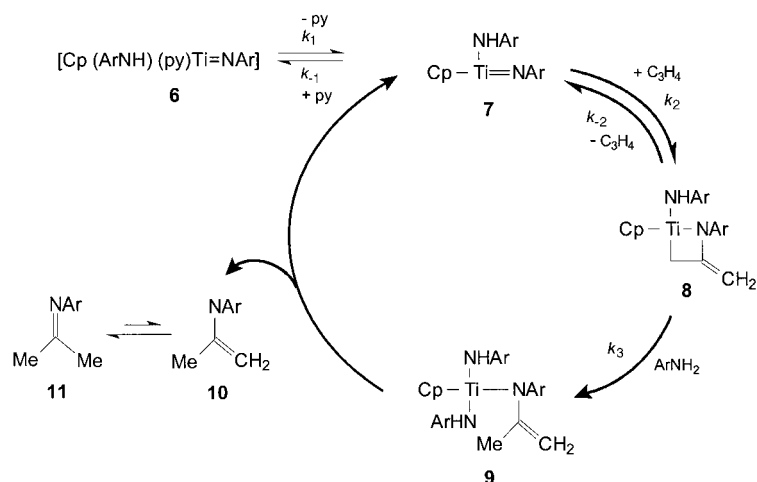
tions of the mechanism of intermolecular hydroamination of alkynes and allenes with $[\text{Cp}_2\text{TiMe}_2]$ as the precatalyst. An unexpected exchange of a Cp ligand from $[\text{Cp}_2\text{TiMe}_2]$ in the presence of 2,6-dimethylaniline led to the monocyclopentadienyltitanium complex **6**, which can be regarded as a very reactive intermediate on the way to the catalytic cycle.

Somewhat later, Doye et al., on the basis of kinetic experiments, also described the mechanism of intermolecular hydroamination of alkynes catalyzed by dimethyltitanocene.^[9] In this work they investigated the treatment of 1-phenylpropyne with 4-methylaniline with varying concentrations of the alkyne, the amine, and the catalyst. They found a complex relationship between the catalyst concentration and the reaction rate which is attributed to a reversible dimerization of the catalytically active species, a titanium-imido complex (see Scheme 1). In general, the hydroamination mechanisms postulated by Bergman et al. and Doye et al. are identical with regard to the principal intermediates.

Hydroaminations of Alkenes with Catalysts Based on Transition Metals of Groups 8–10

A remarkable study of the palladium-catalyzed hydroamination of various vinylarenes with anilines was published by Hartwig et al. at the end of 2000.^[10] The best yield (> 99 %) of the Markovnikov product **2** was found by high-throughput screening. An in situ catalyst system was used that consisted of 2 % palladium(II) trifluoroacetate, 3 % 1,1'-bis(diphenylphosphanyl)ferrocene, and 20 % trifluoromethane sulfonic acid (100 °C, 6 h). Trifluoroacetic acid was less suitable than trifluoromethane sulfonic acid as the cocatalyst; the authors attributed this to the counterion and not to the strength of the acid. Differently substituted styrenes, vinylnaphthalin, and anilines could be converted. An asymmetric hydroamination of *para*-trifluoromethylstyrene by aniline with 10 mol % $[\text{Pd}((R)\text{-binap})(\text{OTf})_2]$ (binap = [1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphane)) gave a yield of 80 % in 81 % *ee* after 72 h at 25 °C. This is a good yield with moderate stereoselectivity. In contrast, the first asymmetric intermolecular hydroamination of norbornene with aniline with only 2 mol % $[\text{IrCl}((S)\text{-binap})_2]/\text{F}^-$ gave a yield of 22 % and an enantiomeric excess of 95 %.^[11] Could a similarly good yield have been obtained with 10 mol % of the iridium catalyst?

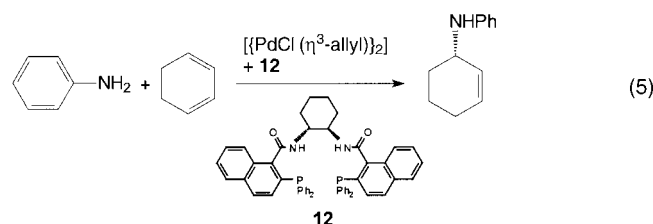
Recently, the hydroamination of acrylic acid derivatives was also described by Hartwig's group.^[12] Since these reactions were investigated by parallel synthesis in 96-well glass plates, a search was made for a colorimetric assay as well as for the formation of secondary alkylamines. Basic solutions of $\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}] \cdot 2\text{H}_2\text{O}$ and acetaldehyde turn blue in the presence of secondary alkylamines: this allowed the first visual estimation of the activities of various late transition metal catalysts. The addition of piperidine to methacrylonitrile was successful with palladium catalysts; however, the yields were lower than those obtained with rhodium(III) and iridium(III) catalysts. In contrast, for the addition of primary alkylamines or arylamines to crotonic acid deriva-



Scheme 1. Mechanism of the intermolecular hydroamination of allenes with **6** as the catalyst (ref. [8]).

tives a lower number of catalytically active transition metal compounds were found. Effective catalysts for this reaction are palladium(II) salts with PCP or PNP ligands; sterically less bulky, monodentate phosphanes with alkyl or aryl substituents are not suitable. Because of the relatively large number of active catalysts, it is certain that more than one mechanism can be considered for the hydroamination reaction.

Very recently, the same research group described the hydroamination of 1,3-dienes,^[13] for example, cyclohexa-1,3-diene with aniline. To detect the aniline consumption colorimetrically, furfural and acid were added after the reaction. Furfural reacts with aniline (2 equiv), but not with the allylamine, by condensation and ring opening to give a red product. The absence of red coloration therefore indicates the complete reaction of aniline. The most active catalysts found by this method were in situ systems from $[\{\text{PdCl}(\eta^3\text{-allyl})\}_2]$ and PPh_3 , which are known to react to give the palladium(0) complex $[\text{Pd}(\text{PPh}_3)_4]$. Therefore, this palladium compound (2 mol %), together with trifluoromethane sulfonic acid (10 mol %), were investigated as the catalyst system for various anilines and dienes. The hydroamination was successful with many substrates; exceptions were cyclooctadiene, which did not react under standard conditions, and 1,3-butadiene, which reacted to give a complex mixture of products. An enantioselective variant of this reaction occurred with an acid-free catalyst consisting of $[\{\text{PdCl}(\eta^3\text{-allyl})\}_2]$ and the Trost ligand **12** [Eq. (5)] in 87% yield for the product and 89% *ee*. Various other chiral diphosphanes only led to moderate enantioselectivities of 7–34% *ee*.



Just how difficult it is to carry out a catalytic hydroamination successfully, is also demonstrated in a publication by the research group of Keim on the hydroamination of ethene by piperidine.^[14] Various ruthenium(II) complexes were investigated as catalysts for this reaction. A stoichiometric hydroamination is possible with the mediators $[\text{RuCl}_2(\text{PPh}_3)_3]$ and $[\text{CpRu}(\text{C}_2\text{H}_4)(\text{PPh}_3)_2]^+\text{BF}_4^-$. However, free coordination sites on the ruthenium center are rapidly blocked by amines after one cycle to yield catalytically inactive ruthenium complexes.

Ab initio/DFT Investigations of Catalytic Hydroamination

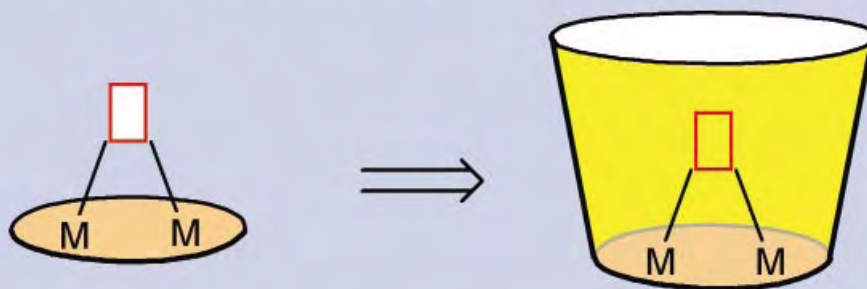
A very interesting publication by Senn et al.^[15] describes the use of density functional theory (DFT) calculations to investigate the pathway of the catalytic hydroamination of alkenes with model complexes of transition metals from Groups 9 and 10. These theoretical results essentially confirmed the experimental results of Hartwig's group, which were published at about the same time. Calculations were

carried out on intermediate complexes of the catalytic cycle for the activation of the alkene (nucleophilic attack on the coordinated alkene, cleavage of the metal–carbon bond, and ligand exchange) for d^8 transition metal complexes of the type $[\text{MCl}(\text{PH}_3)_2]^{z+}$ ($\text{M} = \text{Co}, \text{Rh}, \text{Ir}$ [$z = 0$] and $\text{Ni}, \text{Pd}, \text{Pt}$ [$z = 1$]) in which the two phosphane ligands were *cis*. The nucleophilic attack of an amine on an ethene coordinated to a transition metal is thermodynamically and kinetically favored for a transition metal of Group 10, but is very unfavorable for elements of Group 9. Thus complexes of Group 10 should be better catalysts for hydroamination reactions. According to the calculations, nickel complexes in particular are very promising. In this case, the activation barrier for the cleavage step is 108 kJ mol^{-1} . β -Hydride elimination, a possible side-reaction, can be suppressed by altering the steric and electronic properties of the ligand and by the selection of a suitable educt. In general, this theoretical work provides much impetus to form a suitable catalyst directly.

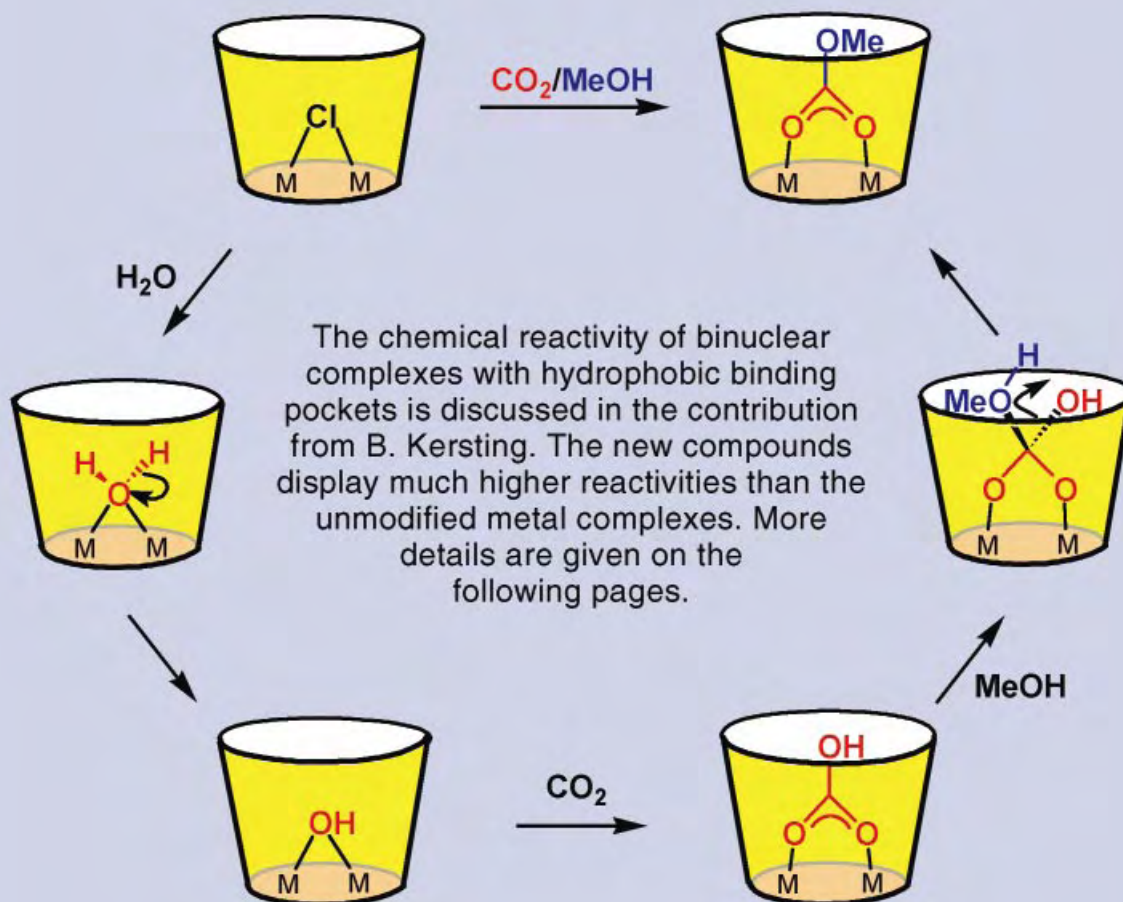
All the publications discussed here thus indicate an approach to further catalytic intermolecular hydroaminations. The use of other substrates, for example, ammonia, alkylamines, and nonfunctionalized olefins, is an interesting field for the future. For industrial applications, the catalyst concentrations are still too high and the use of palladium compounds is certainly not economically viable at the moment (current price of palladium (14.05.2001): $22.99 \text{ \$ g}^{-1}$). The future will show which possibilities are offered to organometallic chemistry and catalysis.

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Coordination chemistry...



...supramolecular catalysis...



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Carbon Dioxide Fixation by Binuclear Complexes with Hydrophobic Binding Pockets**

Berthold Kersting*

Metal complexes with hydrophobic binding pockets currently attract much interest, because of their unusual chemical reactivities. Most compounds are mononuclear species and have been used for the stabilization of reactive intermediates,^[1] for selective organic transformations,^[2] or as catalysts for reactions which depend on the reaction medium.^[3] Some complexes have also been designed to mimic the hydrophobic binding site of metalloproteins.^[4] These observations led us to study binuclear complexes of peralkylated amine–thiophenol macrocycles hoping to generate a hydrophobic cavity about a free coordination site. We report here the synthesis and

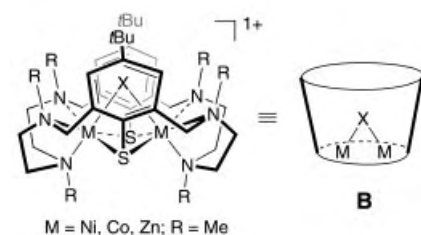
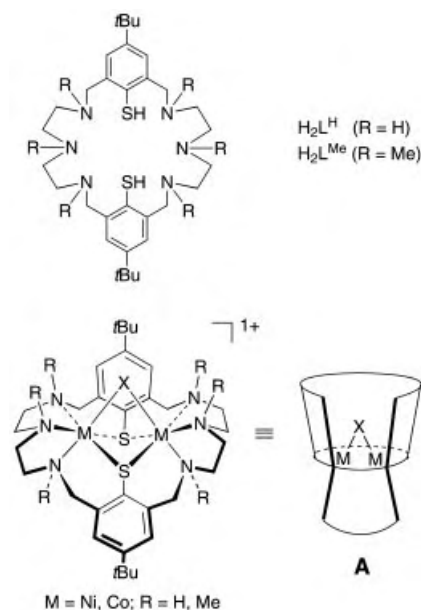
structures of binuclear Ni^{II}, Co^{II}, and Zn^{II} complexes of the permethylated macrocycle (L^{Me})^{2–} (see Scheme 1) and demonstrate their remarkable ability in the fixation and transformation of carbon dioxide.

It has already been demonstrated that utilization of the permethylated ligand (L^{Me})^{2–} in place of (L^H)^{2–} drastically alters the ease of substitution of the bridging ligands in binuclear nickel complexes of the type **A** (Scheme 1).^[5] Thus, the hydroxo-bridged complex **3** (Table 1), which represents the starting point of this investigation, can be prepared in high yields by reaction of the μ -Cl species **2** with sodium hydroxide in MeOH.

Table 1. Synthesized complexes, their structure type, and selected spectroscopic data.^[a]

Complex	Structure type (<i>d</i> (M...M) [Å])	$\nu(\text{RCO}_2^-)$ [cm ⁻¹]
[(L ^H)Ni ^{II} (μ -Cl)] ⁺ 1	A (3.098) ^[5]	
[(L ^{Me})Ni ^{II} (μ -Cl)] ⁺ 2	A (3.201) ^[5]	
[(L ^{Me})Ni ^{II} (μ -OH)] ⁺ 3	A (3.037) ^[5]	
[(L ^{Me})Ni ^{II} (μ -O ₂ COMe)] ⁺ 4	B (3.491) ^[6]	1633, 1332
[(L ^{Me})Ni ^{II} (μ -OH ₂)] ²⁺ 5	not known ^[8]	
[(L ^{Me})Ni ^{II} (μ -O ₂ COH)] ⁺ 6	B (3.471) ^[6]	1675, 1378
[(L ^{Me})Ni ^{II} (μ -O ₂ P(OH) ₂)] ⁺ 8	B (3.569) ^[6]	1200, 1130
[(L ^{Me})Ni ^{II} (μ -O ₂ COEt)] ⁺ 9	B (3.485) ^[6]	1641, 1316
[(L ^{Me})Ni ^{II} (μ -O ₂ COR)] ⁺ 10 ^[b]	B (3.490) ^[6]	1642, 1313
[(L ^{Me})Co ^{II} (μ -Cl)] ⁺ 11	A (3.180) ^[6]	
[(L ^{Me})Co ^{II} (μ -O ₂ COMe)] ⁺ 12	B (3.452) ^[6]	1630, 1336
[(L ^{Me})Co ^{II} (μ -O ₂ COEt)] ⁺ 13	B (3.467) ^[6]	1634, 1319
[(L ^{Me})Zn ^{II} (μ -O ₂ CH)] ⁺ 14a	B ^[c]	
[(L ^{Me})Zn ^{II} (μ -O ₂ CMe)] ⁺ 14b	B (3.427) ^[6]	1585, 1428
[(L ^{Me})Zn ^{II} (μ -O ₂ CPh)] ⁺ 14c	B ^[c]	
[(L ^{Me})Ni ^{II} (μ -O ₂ CMe)] ⁺ 15	B (3.483) ^[6]	1588, 1426

[a] The complexes were isolated as ClO₄⁻ or BPh₄⁻ salts. [b] R = CH₂CH₂OH. [c] The experimentally determined structures of **14b** and **15** suggest that complexes **14a** and **14c** adopt the form **B**.



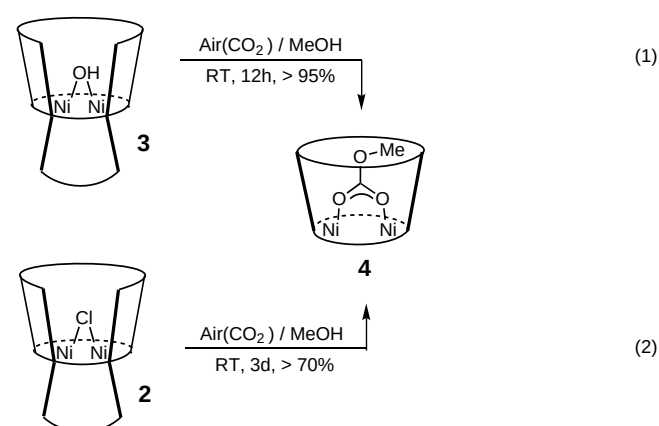
Scheme 1. Structures of the ligands and schematic representation of the structures of the corresponding metal complexes **A** and **B** (X = binding site of the complexes).

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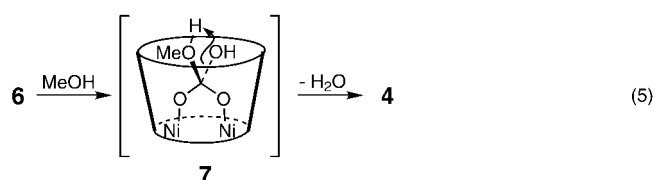
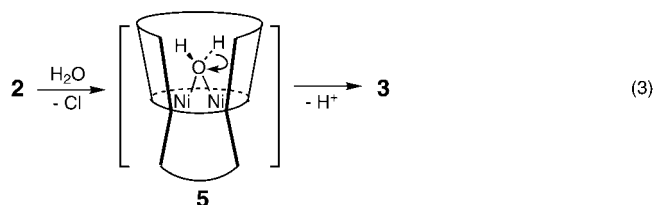
We have now found that complex **3** fixes carbon dioxide from air in the form of the methyl carbonate complex **4** in nearly quantitative yields [Eq. (1)]. The product was identi-



fied by IR spectroscopy (Table 1) and by X-ray crystal structure analysis.^[6] Surprisingly, exposure of a solution of the μ -Cl complex **2** in MeOH to air also gives **4** in high yields [Eq. (2)]. Complex **1**, on the other hand, was found to be unreactive, which is presumably due to the more hydrophilic

environment at the binding site. Note that the amine functions in **2** are methylated, precluding the possibility of hydrogen bonding.

In general, the fixation of carbon dioxide is only possible in a basic reaction medium, where a nucleophilic M–OH or M–OR unit attacks the electrophilic carbon atom of the CO₂ molecule.^[7] The reaction in Equation (2) proceeds under neutral to slightly acidic conditions and is thus rather unusual. A proposed mechanism for the formation of **4** is given in Equations (3)–(5).



The μ -aqua complex $[(L^{Me})Ni_2(\mu-OH_2)]^{2+}$ (**5**) can be formulated as the first intermediate [Eq. (3)].^[8] The aqua ligand is activated by two Lewis-acidic Ni^{II} centers, and this should favor its deprotonation to give the known μ -OH complex **3**. The production of HCl during the formation of **4** was ascertained readily by pH indicator paper. We reasoned that a bicarbonate complex was the next intermediate and sought to trap this species by carrying out the reaction in Equation (4) in MeCN as solvent. The tetraphenylborate salt of complex **6** crystallized in a form suitable for X-ray structure analysis. In the solid state the HCO₃[−] group bridges the two Ni^{II} centers in a symmetric fashion. Note that the structure of complex **6** is of the type **B**, which features a much more pronounced bowl-shaped binding pocket than in complexes of the type **A**. The methanolysis reaction in Equation (5) can then be considered as the final reaction step. This was confirmed by the experiment. The smooth conversion of **6** into **4** suggests that the two metal ions activate the carboxyl carbon atom of the HCO₃[−] ligand such that it is more susceptible for nucleophilic attack by the solvent.

Substitution reactions at carboxyl carbon atoms proceed via tetrahedral intermediates. In the case of **6**, the intermediate is the monomethyl orthocarbonate complex **7**, which is reversibly formed by attack of MeOH on the carbonyl group. Elimination of water then leads to the product. If this reaction proceeds in the coordination sphere of complex **6**, its binding pocket must be large enough to accommodate an orthocarbon-

ate group. This was supported by the coordination of a H₂PO₄[−] ion in complex $[(L^{Me})Ni_2\{\mu-O_2P(OH)_2\}]^+$ (**8**), which was prepared according to Equation (6). The H₂PO₄[−] group can be regarded as a substitute for the orthocarbonate group (Figure 1). Further support is provided by the different

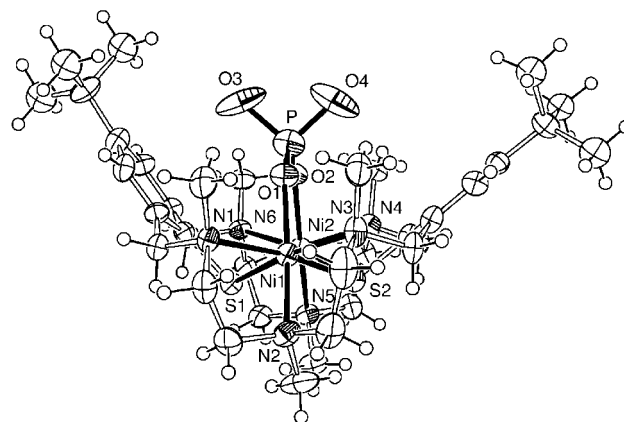
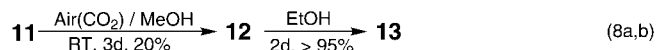
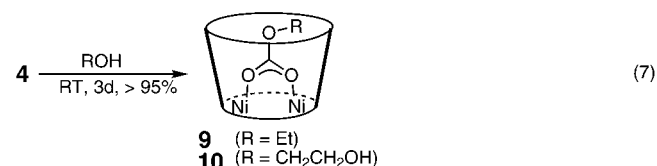
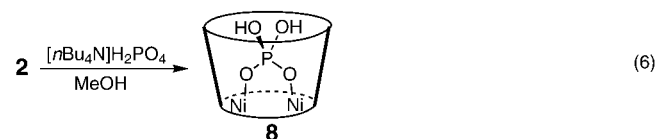


Figure 1. Molecular structure of the H₂PO₄[−] complex **8**.

reactivity of **4** towards primary, secondary, and tertiary alcohols. In the case of primary alcohols such as ethanol or ethylene glycol the formation of the corresponding products **9** and **10**, respectively, was observed [Eq. (7)]. In the case of



secondary (*i*PrOH) or tertiary alcohols (*t*BuOH) no reaction occurred. This is presumably due to the limited space in the binding pocket, which allows the formation of an alkyl orthocarbonate of a primary alcohol but not of a higher one.

Further experiments have shown that the chemical reactivity of the cobalt(II) complex **11** (Table 1) is very similar to that of **3**. Thus the preparation of the methyl and ethyl carbonate complexes **12** and **13** can be accomplished by treatment of the monocation **11** with the corresponding alcohol in the presence of air or by transesterification of the alkyl carbonate species [Eq. (8a,b)]. These results indicate that the chemical reactivity is based on the Lewis acidity of the complexes and not restricted to a specific metal dⁿ electronic configuration.

Hydrophobic effects may also be responsible for the enhanced chemical reactivity of complexes **2** and **3**. The hydrophobicity of a binding cavity can be probed by determining the binding constants of different guests.^[9] For this purpose the relative stability constants (K_{rel}) of the formiato, acetato, and benzoato-bridged zinc complexes **14a–c** were determined. The stability constants increase in the order **14a** < **14b** < **14c** and differ by two orders of magnitude ($K_{\text{rel}} = 0.1/1.0/5.0$). Thus the larger the organic residue R of the carboxylate anion (RCOO^-) the larger the binding constant. The observed trend is indicative of hydrophobic effects between the substituents of the carboxylate ion and the ligand matrix of the complex.

The synthesis of novel binuclear complexes with hydrophobic binding pockets has been described. The complexes show enhanced chemical reactivity towards the activation and transformation of small molecules such as CO_2 . We are currently probing the possibility whether the Lewis acidity can be increased by changing the metal oxidation state and whether variation of the alkyl residues allows fine tuning of the size of the binding pocket.

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Functionalized DNA: A New Replicable Biopolymer**

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During the past decade a number of methods have been developed that allow the isolation of biopolymers with tailored functionalities from highly diverse libraries of polypeptides or nucleic acids.^[1] Polypeptide-based libraries require coding strategies such as phage-,^[2] ribosome-,^[3] or mRNA-display^[4] that ensure an unmistakable combination of genotype and phenotype. Only then it is possible to identify a few molecules with the desired activities from mixtures of up to 10^{14} individual molecules.

In contrast, functional nucleic acids such as aptamers^[5] and ribozymes^[6] have the advantage that they carry along—at all times—the blueprint for their own replication, thereby making special encoding strategies for their detection and optimization obsolete. A potential disadvantage compared to polypeptides, however, is the low diversity of chemical functionalities provided by the four natural nucleotides. Expanding their functional-group repertoire will certainly further enhance their catalytic and binding properties.

Therefore, efforts currently concentrate on developing approaches that combine the advantages of the direct enzymatic amplification of nucleic acids with the chemical diversity of polypeptides by adding protein-like functionalities to the nucleobases of DNA. For example, DNA molecules containing functionalized residues were enzymatically synthesized from natural DNA templates^[7] and used for in vitro selection.^[8] Although the incorporation of four modified nucleotides bearing fluorescent dyes or alkynyl chains was recently reported,^[9] the ultimate goal of substituting all four nucleobases with different functionalized residues within a single oligonucleotide and the subsequent use of the resulting polymer as a template for enzymatic replication has not been achieved to date. Nucleic acids that are highly functionalized in this way would represent a novel class of enzymatically replicable biopolymers that, from a chemical point of view, bridge the gap between proteins and nucleic acids, and might exhibit interesting new properties.^[10]

Here we describe the first enzymatic synthesis of oligodeoxynucleotides, in which all four natural nucleobases are substituted by different synthetic residues which bring a broad range of additional chemical functionalities, and the conditions that are required for the enzymatic replication of the new oligodeoxynucleotides. Modifications were designed to include important amino acid side-chains such as carboxylic acid, alkylamino, guanidine, and hydrophobic residues. We

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found that the highly functionalized DNA template^[11] is fully compatible with procedures commonly applied in nucleic acid in vitro selection strategies.^[8a, 12]

The chemical modifications were positioned to ensure minimal interference with the face of the nucleobase involved in Watson–Crick pairing. Previous studies indicated that these requirements are best satisfied by introducing modifications at C5 in the pyrimidine bases,^[7, 13] and position C7 of 7-deaza purines.^[7d]

We synthesized the modified nucleoside triphosphates (dNTPs) **1–4**^[14] (Figure 1A) and enzymatically polymerized them to a highly functionalized oligonucleotide by template-directed primer extension, using commercially available DNA polymerase from *Thermus thermophilus* (*Tth*) (Figure 1B). Using a model template with approximately equal distribution of the four nucleotides and a length of 79 nucleotides, we first optimized the conditions for primer extension with respect to nucleotide, enzyme, and template concentration, temperature, and reaction time. We found that complete primer extension of 1.0 pmol primer on 3.0 pmol template^[15]

(final concentration: 50 nM and 150 nM, respectively) could be achieved with only 40 μ M of each modified nucleotide using 0.5 U of *Tth* polymerase per reaction at 72 °C for 2 min. Under these conditions, a single primer extension cycle led to efficient polymerization of the modified nucleotides directed by the unmodified DNA template (Figure 1B, lane 6). As negative controls, the same experiments were performed in the presence of only three modified bases omitting either **1** (lane 2), **2** (lane 3), **3** (lane 4), or **4** (lane 5), respectively. As shown in Figure 1B all four nucleotides are required to yield the full-length product. The smear that is observed in the product band that corresponds to fully extended primer (lane 6) may arise from secondary structures with different stability or higher aggregates that cannot be resolved under the conditions applied in standard denaturing polyacrylamide gel electrophoresis (PAGE).

For compatibility with in vitro selection methods in which sequence information must be reliably transferred from generation to generation it is essential to show that the enzymatically synthesized fDNA^[11] can serve as a template in

a polymerase chain reaction (PCR) using natural dNTPs. Thus, the fDNA was generated using a 5'-biotinylated template of unmodified DNA and the resulting fDNA/DNA hybrid was subsequently immobilized on streptavidin agarose. Unhybridized fDNA was recovered by elution with 0.1N NaOH and used as a template in a PCR in the presence of dNTPs. Under standard PCR conditions (denaturing at 95 °C, *Tth* DNA polymerase, *Tth* PCR buffer) however, no PCR product was obtained (data not shown). Since it was previously observed that the presence of modified 7-deaza purines in double stranded DNA (dsDNA) increases the dsDNA melting point^[16] we reasoned that our result might be because of incomplete melting of the fDNA/DNA hybrid under the conditions applied. Therefore, we increased the melting temperature to 100 °C, used the extremely thermostable DNA polymerase from *Pyrococcus Woeselii* (*Pwo*), and added "GC-Rich solution" (Roche), a commercial additive for improved amplification of GC-rich regions of dsDNA. Indeed, this combination resulted in successful amplification (Figure 2, lane 6). No amplification was obtained when the "GC-rich solution" was omitted (Figure 2, lane 5). The faint product band observed in the negative controls (biotinylated template in reaction buffer bound to streptavidin agarose, washed and eluted as described above, and

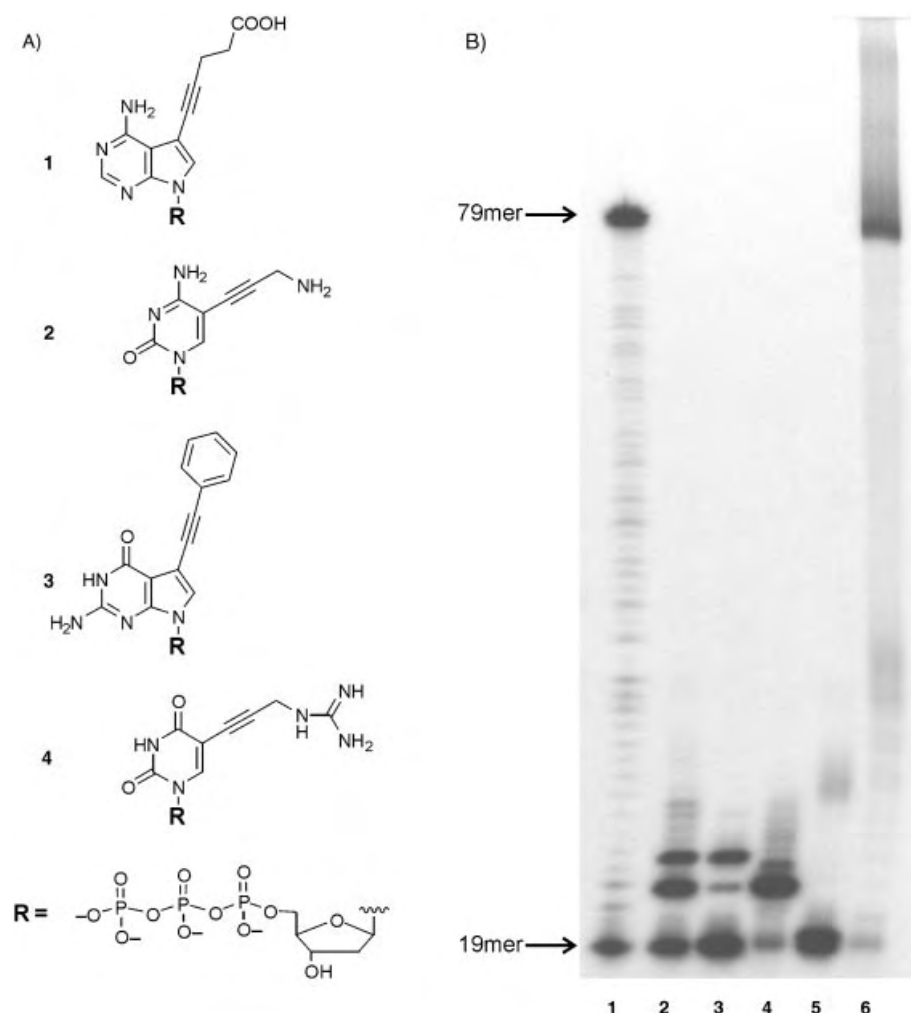


Figure 1. A) Structures of the modified deoxynucleotide triphosphates (dNTPs) **1–4** used in this study. Functional groups shown resemble the amino acids aspartate or glutamate (**1**), lysine (**2**), phenylalanine (**3**), and arginine (**4**). B) Autoradiogram of an 8% denaturing PAGE of primer extension products. Lane 1: 40 μ M of each natural dNTP; lane 2: 40 μ M each of **2–4**; lane 3: 40 μ M each of **1, 3**, and **4**; lane 4: 40 μ M each of **1, 2**, and **4**; lane 5: 40 μ M each of **1–3**; lane 6: 40 μ M each of **1–4**.

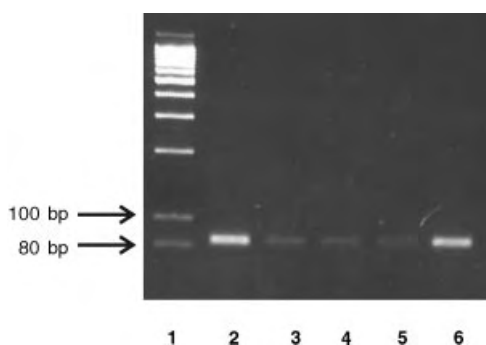


Figure 2. Ethidium bromide stained 2.5% agarose gel of PCR products. Lane 1: DNA marker; lane 2: amplification of unmodified DNA; lane 3: amplification of eluate from immobilized biotinylated template; lane 4: as lane 3 with addition of "GC-Rich solution"; lane 5: amplification of fDNA; lane 6: amplification of fDNA with addition of "GC-Rich solution"; bp = base pairs.

subjected to PCR; Figure 2, lanes 3 and 4) is a result of residual amounts of biotinylated template eluted from the agarose matrix during the treatment with 0.1N NaOH. Thus, we can define amplification conditions that are suitable for producing DNA from an fDNA template.

Finally, we purified and sequenced the DNA product that resulted from the fDNA template to check whether the sequence of the original template is retained during the enzymatic incorporation of modified dNTPs and the retransformation of fDNA into DNA. As a positive control, we used the PCR product of the unmodified DNA template. Figure 3 shows that both PCR products have identical sequences, thus verifying that incorporation of the modified nucleotides occurs sequence specifically and that fDNA can serve as a template for sequence-specific DNA amplification.

In conclusion, we present the first example of oligonucleotides with varying modifications at every single base position which can be enzymatically replicated. We demonstrated the suitability of our modified nucleotides for in vitro selection by carrying out a full cycle of primer extension and amplification by PCR. We show that nucleotides bearing amino acid like functionalities can replace natural dNTPs in primer extensions without detectable loss of sequence information. In general, functionalized DNA represents a novel class of biopolymers that bridge the gap between proteins and nucleic acids. Besides the potential application of fDNAs in combi-

natorial in vitro selection experiments they may exhibit interesting physico-chemical properties which will render fDNAs useful in diagnostics or functional genomics based on micro-arrays.

Experimental Section

Amplifications were performed with the 79-mer synthetic single-stranded DNA (ssDNA) template: 5'-CACTCACGTCAGTGACATGCATGCCGATGACTAGTCGTCAGTGCACGTAACGTGCTAGTCAGAAATTCGCACCAC-3'.

Primer extensions: An annealing mix containing 5'-[³²P]-labeled primer 5'-GTGGTGCAGAAATTCTGAC-3' (1 pmol) and template (3 pmol) in reaction buffer (9.4 μ L, 10 mM Tris-HCl, pH 8.9, 100 mM KCl, 1.5 mM MgCl₂, 50 μ g mL⁻¹ bovine serum albumin (BSA), 0.05 % Tween 20) was heated to 95 °C for 2 min and cooled to 25 °C. *Tth* DNA polymerase (Roche, 0.1 μ L, 5 U μ L⁻¹), thermostable inorganic pyrophosphatase (New England Biolabs, 0.5 μ L, 0.2 U μ L⁻¹), and 10 μ L of a reaction mix containing 80 μ M of the appropriate dNTPs or modified deoxynucleotides in the same reaction buffer were added, incubated at 72 °C for 2 min and then cooled to 4 °C. Reactions were quenched by adding formamide/water (4/1, 60 μ L), containing 20 mM ethylenediaminetetraacetic acid (EDTA), followed by heating to 95 °C for 10 min and immediate cooling to 0 °C. Aliquots (5 μ L) of each reaction were analyzed by 8 % denaturing PAGE containing 8 M urea. Gels were transferred to filter paper, dried, and exposed to an X-ray film.

To separate the fDNA from the fDNA/DNA hybrid, an annealing mix containing primer (8 pmol) and biotinylated template (24 pmol) was prepared. Reactions were carried out as described above in total reaction volumes of 40 μ L, using *Tth* DNA polymerase (0.2 μ L; 5 U μ L⁻¹) and thermostable inorganic pyrophosphatase (1 μ L; 0.2 U μ L⁻¹). As a negative control biotinylated template in reaction buffer without primer and nucleotides was used. All mixes were incubated at 72 °C for 10 min and then cooled to 4 °C. To each reaction buffer (10 μ L: 750 mM NaCl, 0.5 mM EDTA, 250 mM HEPES (2-[4-(2-hydroxyethyl)-1-piperazinyl] ethanesulfonic acid), pH 7.0) was added, the mixes were immobilized on streptavidin agarose (50 μ L), prewashed with wash buffer (5x100 μ L: 150 mM NaCl, 0.1 mM EDTA, 50 mM HEPES, pH 7.0), followed by washing with 15 column volumes of wash buffer at 25 °C. Desired oligonucleotides were eluted with elution buffer (2x40 μ L: 0.1M NaOH, 150 mM NaCl). Eluates were neutralized with 5 % acetic acid (6 μ L), and 10 μ L were used as template for PCR amplification.

PCR (100 °C, 1 min; 50 °C, 1 min; 72 °C, 2 min, 8 cycles) was performed in 50 μ L volumes, using dNTPs (200 μ M), 40 pmol of each primer 5'-GTG GTG CGA AAT TTC TGA C-3' and 5'-biotin-CAC TCA CGT CAG TGA CAT GC-3', and *Pwo* DNA polymerase (Roche, 0.5 μ L, 5 U μ L⁻¹). PCR products were analyzed on a 2.5 % agarose gel by staining with ethidium bromide. PCR products were purified on a preparative agarose gel, followed by desalting on a G-25 ion exchange column, and used for sequencing.

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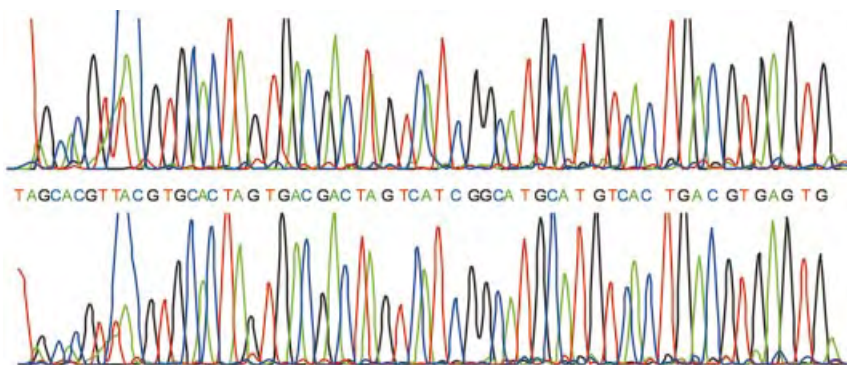


Figure 3. Cycle sequencing of PCR products using the control DNA (top) or the fDNA template (bottom). DNA sequences were obtained by cycle sequencing at PHAMISS, the DNA sequencing facility at the University of Bonn.

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Nitrogen Photofixation at Nanostructured Iron Titanate Films**

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*Dedicated to Professor Günter Hauska
on the occasion of his 60th birthday*

Next to photosynthesis nitrogen fixation is the second most important chemical process of the biosphere. The mild reaction conditions of the enzymatic reaction compared to the Haber–Bosch synthesis stimulated a large variety of

investigations on the formation and reactivity of N₂ transition metal complexes under thermal reaction conditions. Comparably little work is known on photofixation, especially in regard to a sunlight-induced nonenzymatic nitrogen fixation at a simple inorganic photocatalyst.

Schrauzer and Guth first reported that the electron–hole pairs generated by the absorption of light by a semiconductor powder can reduce molecular nitrogen to ammonia. Water vapor acted as the reducing agent, being oxidized to molecular oxygen during the process. Photoreduction occurred only when rutile-containing titanium dioxide powder was doped with 0.2 % of Fe₂O₃ and when it was exposed to humid dinitrogen. No ammonia was formed when dinitrogen was bubbled through an aqueous suspension of this powder. Higher iron contents resulted in inactive materials.^[1] Subsequent work confirmed these results, although the nature of the reducing agent was unknown in most cases, since the oxygen produced was only rarely characterized.^[2–14] Ammonia concentrations were in the range of 1–10 µM, and excitation by UV light was, in general, necessary. Very recently it was reported that an electrochemically formed titanium dioxide layer is also active without iron doping.^[15] These partly contradictory results induced adverse discussions, particularly by Edwards and co-workers, and culminated in the conclusion that all the previously published values resulted from traces of the ubiquitous ammonia.^[16] Since, however, it is well known that the photocatalytic properties of semiconductors are strongly influenced by the presence of impurities, the contradictory results may stem from difficulties in preparing the catalyst.

To clarify these adverse results we have prepared mixed iron titanium oxides by a simple and highly reproducible sol–gel method. In contrast to the previously employed titanium dioxide photocatalysts, the new materials were applied as nanostructured thin films containing up to 50 % iron. They also photocatalyze the formation of ammonia and nitrate under visible light.

The films were obtained by immersing a glass slide first into an alcoholic solution of iron(III) chloride and titanium tetraisopropylate (1:1), followed by hydrolysis in humid air and annealing at 600 °C; only an inactive film was produced at 500 °C. The iron-free titanium dioxide film was prepared in an analogous manner. Electron microscopy on the iron titanate film indicated the presence of a nanostructured matrix of about 300 nm thickness. It contains 15–20 vol % of cubic crystals with an average diameter of 150 nm (Figure 1). The ratio of Fe:Ti:O was found by energy-dispersive X-ray spectroscopy (EDAX) to be 1:1:3.5 for both the matrix and the crystals. This composition suggests that the compound Fe₂Ti₂O₇ is present, which was previously only obtained as an intermediary phase by heating ilmenite (FeTiO₃) minerals in an oxygen atmosphere to 700 °C.^[17] This assignment is corroborated by the good agreement between the published and measured X-ray diffraction (XRD) spectra. The doublet at $\delta = 0.462 \text{ mm s}^{-1}$ (relative to $\alpha\text{-Fe}$), $\Delta E_Q = 0.910 \text{ mm s}^{-1}$, line widths: 0.294 mm s^{-1} ^[18] in the Moessbauer spectrum points to the presence of a six-coordinated Fe^{III} ion. The UV/Vis spectrum reveals extended absorbance down to 800 nm (Figure 2).

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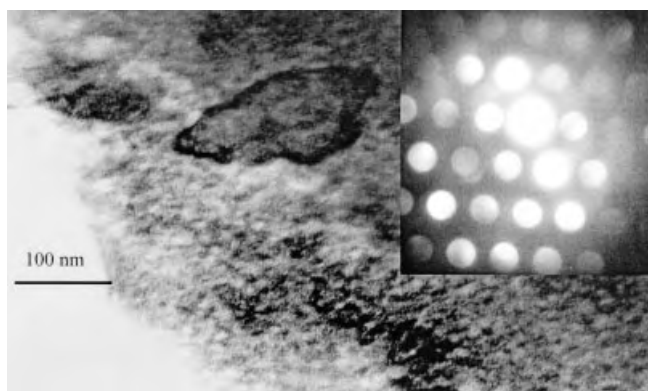


Figure 1. Electron micrograph of the iron titanate film.

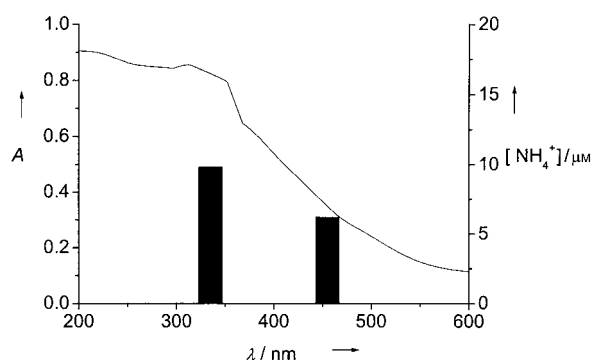


Figure 2. UV/Vis spectrum of the iron titanate film and the wavelength dependence of ammonia formation; the vertical bars indicate the cut-off wavelengths of the filters ($\lambda \geq 335$ and 455 nm); in 75 vol % EtOH; 90 min of irradiation.

Irradiation ($\lambda \geq 320$ nm) of the $\text{Fe}_2\text{Ti}_2\text{O}_7$ film in N_2 -bubbled 75 vol % aqueous EtOH induced the formation of ammonia in concentrations of 3–17 μM (Figure 3). The ammonia concentration decreased to the background value of 2 μM when carbon monoxide was present or when dinitrogen was

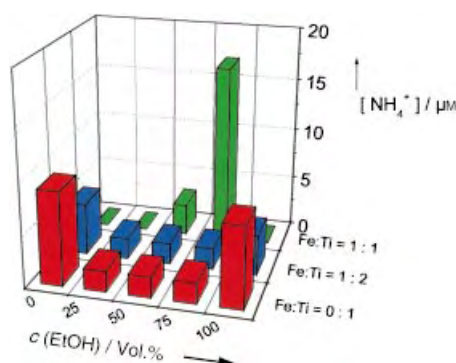


Figure 3. Dependence of the ammonia concentration on the alcohol content of water and on the Fe/Ti ratio employed in the preparation of the thin film; $\lambda \geq 320$ nm; 90 min of irradiation.

replaced by argon. A decrease of 60 % was observed when air was used instead of dinitrogen. Ethanol concentrations above or below 75 vol % led to partial inhibition, which became complete in pure water or pure alcohol. The film is an efficient photocatalyst even upon excitation with visible light ($\lambda \geq 455$ nm, Figure 2).

An iron titanate film with an Fe:Ti ratio of 1:2 exhibited a pronounced lower reactivity. The iron-free titanium dioxide film induced formation of ammonia at a concentration of 5 μM (Figure 3).^[19]

The ammonia concentration reaches a maximum after 90 min of irradiation and decreases to the background value after 180 min (Figure 4). This effect does not originate from catalyst deactivation since the ammonia concentration was lowered by only 15 % after washing the film with water and re-irradiation. Since it is known that ammonia is photooxidized

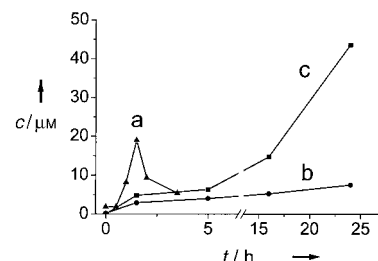


Figure 4. Concentrations of ammonia (a) and nitrate (b: in the solution, c: in the film) as a function of the irradiation time; 75 vol % EtOH; $\lambda \geq 320$ nm.

at titanium dioxide^[20] the solution and film were tested for nitrite/nitrate. Whereas only traces of nitrite were detectable, the nitrate concentration reached 45 μM in the film and 7 μM in the solution (Figure 4). When dinitrogen was substituted by air, the total concentration of nitrate was 30 μM . Nitrate was formed in appreciable amounts only when ammonia had reached its maximum concentration. This observation suggests that nitrate is formed through an ammonia intermediate rather than by direct oxidation of dinitrogen. In accordance with this postulate, no nitrite/nitrate was formed in the absence of ethanol. However, nitrate was produced in comparable concentrations (4 μM in the solution, after 90 min) when the reaction was conducted under oxygen or air in 75 % EtOH in the presence of ammonium chloride (50 μM).

Initial photoelectrochemical experiments with a $\text{Fe}_2\text{Ti}_2\text{O}_7$ thin film electrode of conducting glass revealed that the anodic photocurrent was amplified by methanol addition only when the electrode was annealed at 600 °C. When the electrode was annealed at 200 °C the film was inactive and the electrode did not exhibit the current-doubling effect.^[21] This effect is based upon the injection of an electron from the hydroxyethyl radical, which is formed by primary hole oxidation, into the semiconductor conduction band.

On the basis of these photoelectrochemical properties of the iron titanate film we postulate that the photofixation proceeds according to a semiconductor photocatalysis scheme. Photogenerated conduction band electrons reduce water to adsorbed hydrogen atoms^[1, 5a, 8, 10, 22] which then reduce dinitrogen. Holes formed simultaneously in the valence band oxidize the ethanol to the hydroxyethyl radical. The faster these reaction steps are, the less efficient is the undesired recombination of the charge carriers. The increasing catalytic activity upon increasing the alcohol concentration up to 75 vol % is in accordance with this assumption, and

arises as a result of an acceleration in the oxidative part of the process. The decreasing activity at larger alcohol concentrations may originate from the concomitant decrease in the water concentration. Consequently, the reductive reaction step may become too slow to efficiently compete with recombination of the charge carriers. The ammonia produced is further photooxidized to nitrate through traces of oxygen present in the system.

Aqueous solutions of sodium formate and humic acids of proper concentration also function as reducing agents. Since the latter compounds are ubiquitous in nature and $\text{Fe}_2\text{Ti}_2\text{O}_7$ phases could be formed through oxidative weathering of ilmenite in sunlight, this novel reaction may be an example of a light-driven nonenzymatic nitrogen fixation under natural conditions.^[23]

Experimental Section

After fast immersing a glass slide (26 × 76 mm) into an ethanolic solution of $\text{Ti}(\text{O}i\text{Pr})_4$ and FeCl_3 ($\text{Fe}:\text{Ti}=1:1$ or $2:1$) it was pulled out at a speed of 6 cm min^{-1} and left in air for 15 min. The film was subsequently tempered for 20 min at 600°C . Irradiations were performed on an optical train equipped with a high-pressure Hg lamp (HBO200) mounted at a distance of 35 cm from the solidex glass cuvette ($\lambda \geq 320\text{ nm}$, $80 \times 40 \times 10\text{ mm}$) which contained the glass slide. Unless otherwise noted, a film with a $\text{Fe}:\text{Ti}$ ratio of 1:1 was employed and unpurified dinitrogen was permanently bubbled through the suspension. The concentration of NH_4^+ ions was determined colorimetrically according to the method of Kruse and Mellon;^[24] the resulting absorbancies at 450 nm were in the range of 0.01 to 2.10. Blank experiments in the absence of the glass slide did not induce the formation of significant amounts of ammonia. The reproducibility of the film preparation was excellent as evident by the ammonia concentrations agreeing within $\pm 10\%$. Nitrite and nitrate were measured by ion chromatography (Dionex-120, Ion Pac AS 14 column, conductivity detector, $\text{NaHCO}_3:\text{Na}_2\text{CO}_3=0.001:0.0035\text{ mol L}^{-1}$ as eluting agent).

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PASSflow Syntheses Using Functionalized Monolithic Polymer/Glass Composites in Flow-Through Microreactors**

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After an “incubation time” of more than 25 years interest in polymer-supported reagents for the solid-supported synthesis in solution has increased dramatically of late.^[1] In this technique reagents or catalysts are immobilized on a solid

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support, in many cases, crosslinked polystyrenes have been used for this purpose. The intrinsic advantages of this hybrid solid-phase/solution-phase technique lie in the simple purification and the possibility to use these reagents in excess to drive reactions in solution to completion. The opportunity to employ this technique in conjunction with continuous-flow processes is particularly appealing as this application would create an ideal almost workup-free technique for automated solution-phase synthesis.^[2]

However, there are two key criteria to be considered when constructing a stoichiometrically working flow-through reactor. These are high loading and good accessibility of the soluble reactant to the active immobilized species. Both criteria can be controlled by the right choice of the solid support. For polymeric supports the degree of cross-linking is essential.^[3, 4] For kinetic reasons a low degree of cross-linking is desired. This feature leads to gels, which as a result of swelling in organic solvents such as THF or dichloromethane which makes the immobilized species more accessible. However, filled in tubes these polymers either block the flow (and cause a pressure drop) when swollen or, when shrunk, create a gap between the inner wall of the flow-through reactor and the polymer allowing the solution to bypass the polymer.

Herein we present the PASSflow (Polymer Assisted Solution-Phase Synthesis flow-through mode) technique, which allows solid-phase supported synthesis in solution to be performed in a flow-through mode. This concept is based on a monolithic flow-through microreactor, which is loaded with polymer-bound reagents or catalysts and allows organic transformations in solution to be performed with a low to moderate pressure drop. Essentially, the monolithic block contains a novel, chemically functionalized, highly porous polymer/glass composite. Polyvinylchlorobenzene (cross-linked with 2–20% of divinylbenzene) is prepared by precipitation polymerization in the pore volume of highly porous glass rods to yield a polymeric matrix inside the rod (Figure 1).^[5, 6] The polymeric structures obtained are small beads (1–5 μm diameter), and are all cross-linked with polymeric bridges. This property results in a monolithic polymeric phase, with a high surface area, which is wedged inside the microchannel pore system of the support. Even under forced convectional flow the polymer phase can not be washed out of the reactor. Furthermore, having a polymeric phase inside the fixed matrix of glass rods leads to reactor

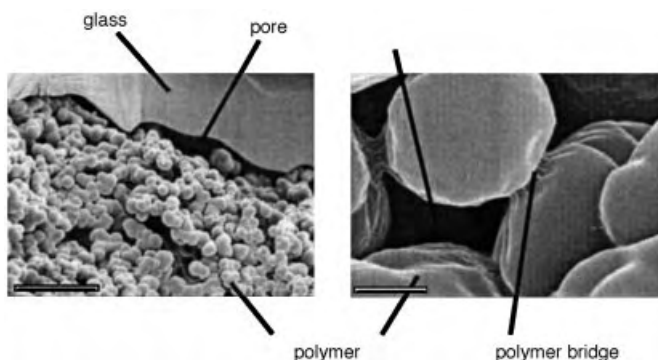


Figure 1. Scanning electron microscope image of the polystyrene/glass composite. The scale bars correspond to 10 μm (left) and 500 nm (right).

interiors with a stable shape. The polymer particles inside the pore volume can swell and shrink only in the pore volume, whereas the outer dimensions of the rod stay stable. Technical problems like bypassing or high pressure drop as observed in pure polymer packings can be avoided.

These chemically functionalized rods were first embedded inside a solvent-resistant tube. This was followed by encapsulation with a pressure-resistant fiber reinforced epoxy resin housing with two standard high-pressure liquid chromatography (HPLC) fittings (Figure 2). A particular difficulty

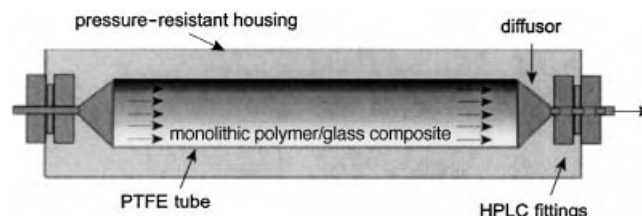


Figure 2. Schematic set up of the PASSflow reactor; PTFE = polytetrafluoroethylene.

associated with monolithic flow-through reactor systems is the suppression of the fluid bypass and forcing the fluid to flow through the microchannels of the rod. Dynamic NMR spectroscopy microscopic visualization with water as a fluid clearly showed that no solvent bypass is detected for this flow-through reactor for a pressure up to 20 bar.^[7] In the example reported here, the benzylic chlorine function was aminated with triethylamine in toluene to yield the corresponding polymer-anchored quaternary ammonium ion. The resulting strongly basic ion-exchange resin was loaded with various anions. The synthetic properties of these chemically functionalized flow-through reactors were tested with fundamental transformations such as substitution, oxidation, and reduction (Table 1).

The monolithic reactors (about 10 cm in length, about 5 mm diameter, about 10 to 20 mass % (ca. 1 mmol) polymer loading) enable the preparation of up to 1 mmol of product in shorter times than reactions promoted with conventional polymer-bound reagents. This is demonstrated for the reduction of acetophenone to 1-phenylethanol using polymer-bound borohydride (Figure 3). As expected, the reaction rate is much faster when the solvent is forced to flow through the microchannels of the monolithic reactor than when a bare polymer/glass composite rod is placed in a beaker of reactant solution or with a finely powdered borohydride-impregnated composite material.^[8] This result clearly demonstrates that the combination of a highly porous chemically inert glass rod and a functionalized polymer anchored inside the pores guarantees a short diffusion path for the soluble organic reactants and products and in addition enables a good convectional flow.^[9]

To test the utility of our microreactors for the derivatization of natural products or drugs, we employed three differently functionalized PASSflow reactors, modified with the oxidizing anion **2**,^[10] the fluoride anion **4**, and the reducing anion **6**. In a three-step sequence the partially *O*-silylated steroid **1** was transformed into the aminoderivative **7** (Scheme 1). Only

Table 1. Reactions performed with the PASSflow reactor.

Starting material	Chemical functionalization in the reactor	Conditions	Product
		MeOH, 60 °C, 6 h	
		CH ₂ Cl ₂ , RT, 6 h	
		Nu = N ₃ C ₆ H ₆ , 70 °C, 12 h	
		Nu = CN C ₆ H ₆ , 70 °C, 12 h	
		Nu = SCN C ₆ H ₆ , 70 °C, 12 h	
		Nu =	

[a] The products were isolated after removal of the solvent. In each case the yield was >95 %; according the NMR spectra the purity was >95 % for all cases.

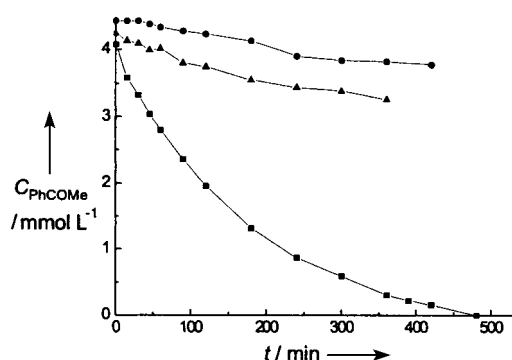
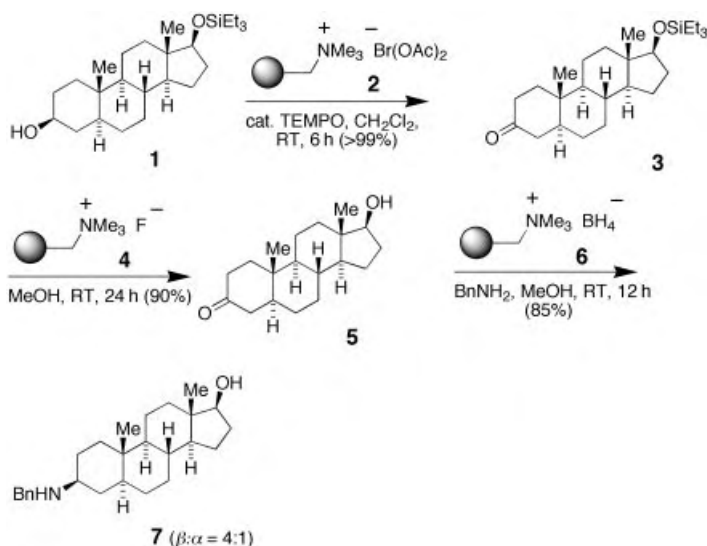


Figure 3. Borohydride-promoted reduction of acetophenone: reaction course using different composites (■ microreactor, ● bare chunks of monolithic glass rod, ▲ powdered composite).



Scheme 1. Polymer-assisted three-step derivatization of a steroid in PASS-flow reactors; TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxide OAc = acetate.

anions were immobilized which ensures the simple regeneration of the reactor column after each reaction.^[11] The TEMPO-catalyzed oxidation of alcohol **1** with the polymer-

bound bromate(i) anion **2** gave ketone **3**, which was desilylated to afford alcohol **5** after being pumped through a fluoride **4** loaded PASSflow reactor. The sequence was terminated by a reductive amination step in which the imine was generated in situ from ketone **5** with benzyl amine and the resulting solution was pumped through a microreactor loaded with borohydride to furnish amine **7** and small amounts of the corresponding diol.

In summary, we have developed a microreactor which can be incorporated into any conventional HPLC system. The key component is a novel monolithic composite material which is composed of a macroporous glass and a functionalized polymer. Changing the functionalization of the polymer allows various reactions to be efficiently performed in the flow-through mode. With this new reactor concept a cost-effective laboratory tool is available allowing easy flow-through applications in organic chemistry. This offers a high potential for automated polymer-assisted solution-phase synthesis.^[12, 13]

Experimental Section

Preparation of polymer/glass monoliths and application in organic synthesis: Polymerization: vinylbenzyl chloride (45 g) and divinylbenzene (3.9 g; 65 % ethylbenzene) was dissolved in C14–C17 *n*-paraffin (300 mL). After dissolution of azoisobutyronitrile (300 mg) porous glass rods with a diameter of 5.3 mm and a length of 110 mm were immersed in this solution. Air was removed from inside the pore volume by applying a vacuum for a short time. After heating at 70 °C overnight, the rods were cleaned of any adhering polymer and rinsed with trichloromethane.

Amination: The rods loaded with the polymer were covered with dry toluene and a continuous flow of trimethylamine was passed through this solution. After 4 days the rods were removed from the solution and dried in vacuo. Then, the rods, now functionalized with quaternary ammonium cations, were fitted with a casing and could be used as microreactors in organic synthesis.

Exchange with bromate(i) anions **2 and successive oxidation of **1**:** The microreactor (chloride ion loaded) was treated with: deionized water (10 mL), sodium hydroxide solution (1M, 10 mL), deionized water (10 mL), hydrobromic acid (2M, 10 mL), deionized water (10 mL), methanol (10 mL), and dry dichloromethane (25 mL). After this procedure, a solution of 1.5 mmol diacetoxydinebenzene in dry dichloromethane (10 mL) was pumped through the reactor under argon in a recycle mode for one night.

After washing with dry dichloromethane (10 mL), the compound **1** (0.125 mmol) and a catalytic amount of TEMPO (0.1 mol %) in dry dichloromethane (10 mL) were pumped in a recycle mode under argon for 6 h through the reactor. The reactor system was rinsed with dichloromethane (10 mL) and the combined organic solvents were removed in vacuo and the residue was used for the further reactions without additional purification.

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An Analytical Approach for a Comprehensive Study of Organic Aerosols**

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Since the first scientific explanation of the so-called “blue haze” phenomenon above forests by Went,^[1] the formation of natural organic aerosol particles in the atmosphere and their impact on the climate has drawn considerable attention. Airborne particles absorb, reflect, and scatter incoming solar radiation, play an important role in cloud droplet formation, and may even be involved in multiphase atmospheric chemistry.^[2]

In recent reports it was established that especially the reaction of mono- and sesquiterpenes with tropospheric ozone contributes to the formation of organic aerosols,^[3] however, our knowledge about reaction mechanisms leading to low-volatile products is still limited. Making things difficult is the fact that during the ozonolysis free OH radicals are formed that have to be considered.^[4]

However, the initial steps of the terpene ozonolysis in the gas phase corresponds to known mechanisms,^[5] exemplified in Scheme 1 for α -pinene **1**, the most abundant single monoterpene released by plants. The first step is the formation of the molozonide **2** that forms reactive Criegee intermediates **3a** and **3b**. Subsequent reactions lead to the formation of several low vapor-pressure products, such as pinonic acid (**4**), pinic acid (**5**), or hydroxy pinonic (**6**) acid which have been identified using mass spectrometric methods.^[6] Although possible mechanisms for the generation of these carboxylic products have been suggested,^[7] the overall understanding of the reaction mechanisms leading to condensable species is still inadequate.

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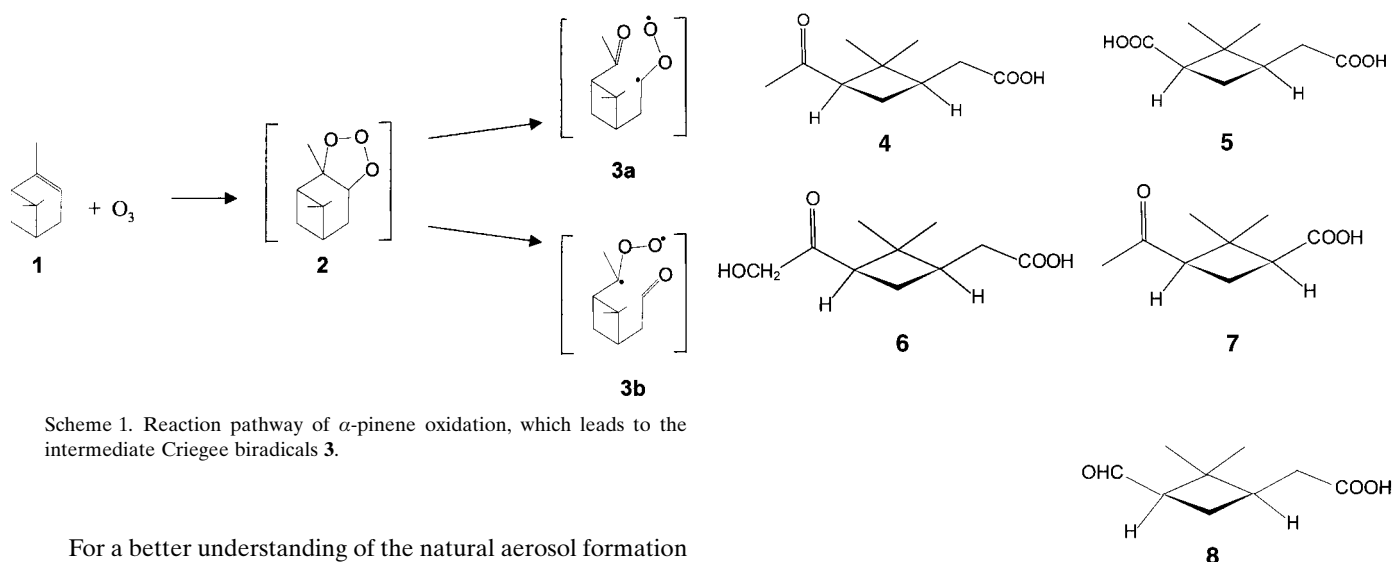
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 1. Reaction pathway of α -pinene oxidation, which leads to the intermediate Criegee biradicals **3**.

For a better understanding of the natural aerosol formation processes, ideally the complete set of products should be known. Since synthetic standards are not readily available, the most promising approach to reach this goal is the linking of sophisticated analytical techniques, such as the coupling of liquid chromatography (LC) to three different spectroscopic methods, namely nuclear magnetic resonance (NMR) spectroscopy,^[8] mass spectrometry (MS), and infrared (IR) spectroscopy.^[9]

The LC/NMR coupling, although not the most sensitive method, clearly allows direct structural information about compounds to be obtained. In Figures 1 and 2 the results of an

LC/NMR/MS experiment are presented. This online experiment is made possible through the combination of both a mass spectrometer and NMR spectrometer with a gradient high-pressure liquid chromatography (HPLC) system. The flow coming from the LC is divided into two flows in the ratio 1:20. The larger flow is introduced into a flow cell of the NMR spectrometer, the smaller part is used to obtain corresponding MS or MSⁿ data. NMR scans can be obtained either in the on-flow mode, which means a continuous flow through the NMR

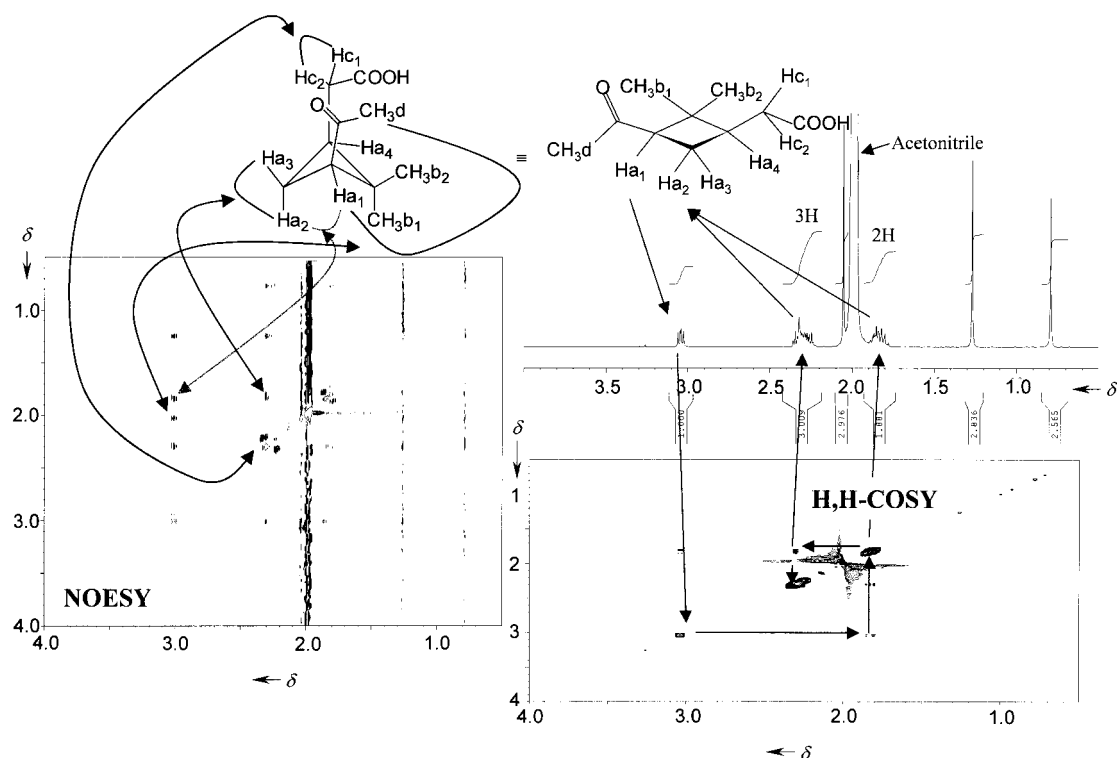


Figure 1. NMR spectra from *cis*-pinonic acid (**4**), obtained from an online experiment after LC separation; assignment of the signals using 1D, 2D NOESY (nuclear overhauser enhancement spectroscopy) and 2D COSY (correlated spectroscopy). Integration of the 1D ^1H NMR signal in combination with the corresponding 2D COSY shows that signals Ha_2 – Ha_4 and signals Hc_1 and Hc_2 (in total 5 protons) resonate at two positions around $\delta = 1.8$ and 2.3 (the correlation caused by J coupling between Ha_1 and Ha_2/Ha_3 is indicated in the figure by arrows). The 2D NOESY spectrum indicates correlations caused by dipole cross-relaxation between nuclei in a close spatial relationship. Some of the correlations not amenable to J -coupling spectroscopy are indicated.

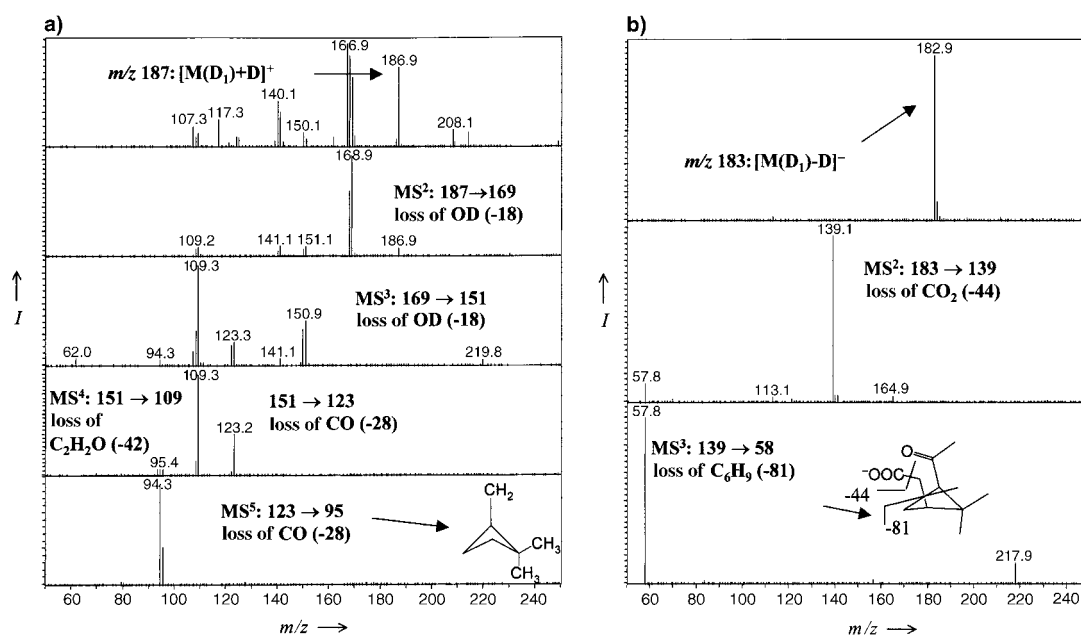


Figure 2. MS spectra from pinonic acid (4); [M] = 184; [M(D₁) - D]⁻ = 183; online LC/NMR/MS experiment. a) Positive ion MSⁿ spectra (n = 1–5) and b) Negative ion MSⁿ spectra (n = 1–3), the proposed fragmentation is shown.

probehead while the spectrometer constantly acquires one-dimensional (1D) proton spectra or in the loop-storage mode, in which fractions are stored in capillaries (loops) during the chromatography, the probes are then transferred to the NMR and mass spectrometers. This set up allows MS⁵ spectra of 4 to be obtained in the positive mode and even MS³ data in the negative mode (Figure 2).

In addition to the important structural information about reaction products, NMR spectroscopy allows the *cis* and *trans* isomers of ozonolysis products from the α -pinene/ozone reaction to be distinguished on the basis of the singlet resonance signal of the methyl protons (Figure 3). The Hb₁

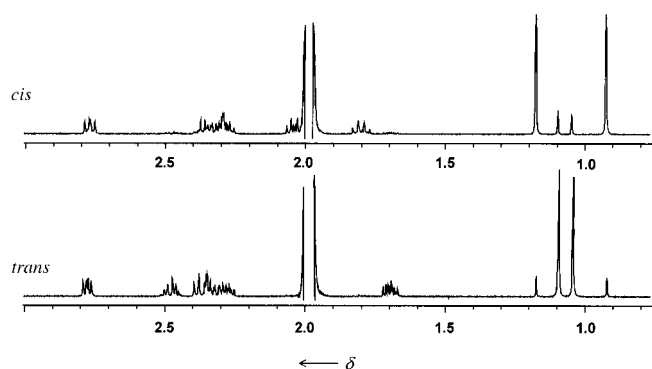


Figure 3. NMR spectra of *cis*-pinonic acid (top) below *trans*-pinonic acid (5) (bottom), with in each case traces of other isomers.

and Hb₂ signals of the methyl groups of *cis*-pinonic acid (5) are widely separated, while the difference between the corresponding signals of the *trans* isomer is rather small. However, in contrast to the results of recent field measurements,^[10] only *cis* isomers were found as reaction products when the reaction was performed in the absence of light in the laboratory.

The use of a FT-ICR-MS (Fourier-transform ion cyclotron resonance mass spectrometer) allows not only high-resolution mass data to be obtained, but also highly accurate mass determination, which permits the calculation of the respective molecular formula. Surprisingly, the high-resolution mass spectra revealed a higher complexity of the products than anticipated. While mass spectrometric observations with standard resolution suggested only one compound at a certain mass-to-charge ratio, the high-resolution mass spectra indicate that more than one product with the same nominal mass but different elemental composition can contribute to the signal. In the case of α -pinene oxidation products, which can only be composed of C, H, and O, the difference between CH₄ (16.0313) and an oxygen atom (15.994914) can easily be resolved by FT-ICR-MS. Figure 4 shows an example, where a C₁₀H₁₅O₄ ion (m/z 199.09769) is clearly separated from an additional product with a composition of C₉H₁₁O₅ (m/z 199.06133).

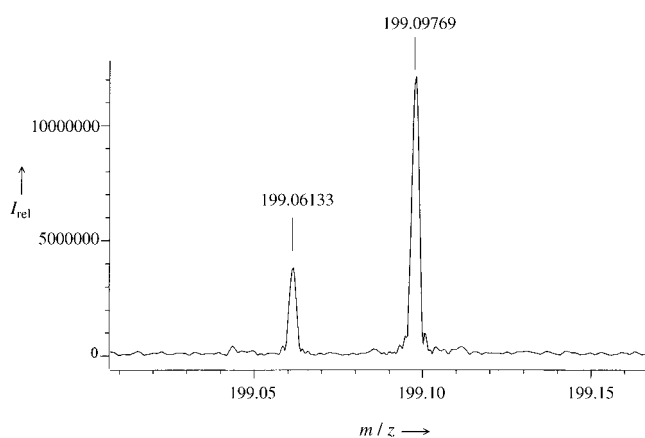
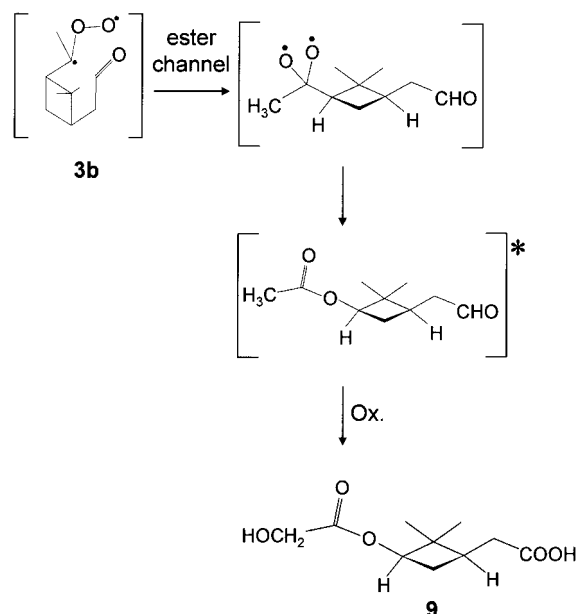


Figure 4. High-resolution mass spectrum of two reaction products at mass m/z 199.

Taking all of the spectrometric data into account a number of new compounds (**7**, **8**) can be identified with a high degree of confidence. For all of the identified compounds, which include the already described products (**4**–**6**), new analytical data could be obtained, that allows them to be included into a reaction scheme of the α -pinene ozonolysis that is based purely on identified compounds. In addition to these compounds, a structural suggestion can be made for an additional product **9** based on MS and IR data. This structure is supported by the ester channel mechanism suggested by Atkinson^[11] to be one of the leading mechanisms for the formation of terpene reaction products (Scheme 2).



Scheme 2. Proposed reaction scheme leading to the ozonolysis product **9** from **3b**; in accordance to Atkinson.^[11]

The results show that an analytical approach to the investigation of atmospheric relevant organic aerosols by coupling liquid chromatography with mass spectrometry, NMR spectroscopy, and infrared spectroscopy allows valuable information to be obtained about the structure of the reaction products. Even with high-resolution mass spectrometry it is not possible to differentiate between **7** and **8** which have the same composition (empirical formula). But with the structural information from both NMR and MS/MS a characterization is possible.

With this instrumentation we have for the first time tools at hand that are able to give enough information about such a complex and difficult problem as terpene gas-phase oxidation. While NMR spectroscopy allows *cis* and *trans* isomers to be distinguished, in addition the structural information from high-resolution and highly accurate mass determination make it possible to address with precision the formulas of the unknown products.

Experimental Section

Analytical data: NMR: (proton signals are referenced to the acetonitrile ($\delta = 1.93$); MS: accurate mass determination (m/z : accuracy in parentheses;

molecular formula in square parentheses corresponds to negatively charged ion).

cis-Pinonic acid (**4**): NMR: H_{a1} 2.990 (dd, 1 H); H_{a4} , H_{c1} , H_{c2} 2.187–2.348 (m, 3 H); H_d 2.032 (s, 3 H);^[12] H_{a2} , H_{a3} 1.782–1.905 (m, 2 H); H_{b1} 1.266 (s, 3 H); H_{b2} 0.797 (s, 3 H); MS: 183.1027330 [$C_{10}H_{15}O_3$] (0.33 ppm); IR: $\tilde{\nu} = 2957, 1707, 1369, 1226, 1184, 948\text{ cm}^{-1}$.

cis-Pinic acid (**5**): NMR: H_{a1} 2.769 (dd, 1 H); H_{a4} , H_{c1} , H_{c2} 2.246–2.401 (m, 3 H); H_{a3} 2.018–2.069 (m, 1 H);^[12] H_{a2} 1.794 (q, 1 H); H_{b1} 1.167 (s, 3 H); H_{b2} 0.913 (s, 3 H). MS: 185.0819860 [$C_9H_{13}O_4$] (0.29 ppm); IR: $\tilde{\nu} = 2961, 2657, 1713, 1419, 1246, 935, 740\text{ cm}^{-1}$.

Hydroxy pinonic acid (**6**): NMR: H_{a1} 2.994 (dd, 1 H); H_{a4} , H_{c1} , H_{c2} 2.182–2.370 (m, 3 H); H_{d1} , H_{d2} 4.093–4.230 (dd, 2 H); H_{a2} 1.891 (m, 1 H); H_{a3} possibly obscured; H_{b1} 1.204 (s, 3 H); H_{b2} 0.787 (s, 3 H); MS: 199.0976910 [$C_{10}H_{15}O_4$] (0.54 ppm).

cis-nor-Pinonic acid (**7**): H_{a1} 3.100 (dd, 1 H); H_{a4} 2.886 (dd, 1 H); H_{a2} 2.352 (q, 1 H); H_i 2.090 (s, 3 H) (partly obscured by signal of acetonitrile); H_{a3} 1.852 (qd, 1 H); H_{b1} 1.411 (s, 3 H); H_{b2} 0.868 (s, 3 H). MS: 169.0870480 [$C_9H_{13}O_3$] (0.56 ppm).

cis-Pinornalic acid (**8**): NMR: H_d 9.631 (s, 1 H); H_{a1} 2.817 (t, 1 H); H_{c1} 2.575 (dd, 1 H); H_{c2} 2.476 (dd, 1 H); H_{a4} 2.408 (m, 1 H); H_{a2} possibly obscured; H_{a3} 1.810 (dd, 1 H); H_{b1} 1.193 (s, 3 H); H_{b2} 0.917 (s, 3 H). MS: 169.0870480 [$C_9H_{13}O_3$] (0.56 ppm).

[Hydroxy acetic acid-((2,2-dimethyl)-cyclo-butyl)-ester] acetic acid (**9**): MS: 215.0925990 [$C_{10}H_{15}O_5$] (0.46 ppm); IR: $\tilde{\nu} = 2976, 1742, 1392, 1275, 1130, 961\text{ cm}^{-1}$.

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Sidewall Functionalization of Carbon Nanotubes*

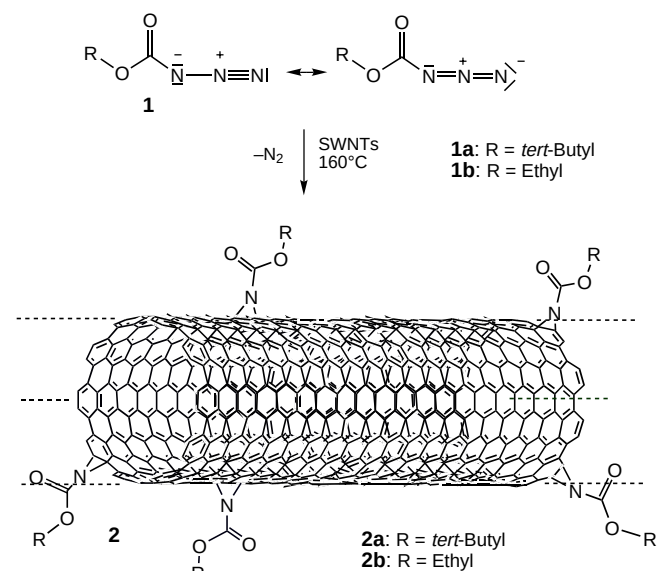
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Frank Hennrich, Manfred Kappes, Robert Weiss, and
Frank Jellen

Carbon nanotubes^[1] display a wide range of unique electronic, optical, and mechanical properties.^[2, 3] Single-walled nanotubes possess high strain resistance and can be metallic, semiconducting, or insulating, depending on diameter and helicity.^[3] To be able to apply these properties, chemical derivatization of the nanotubes is desirable to improve their solubility and processability. Such functionalization is interesting, since fundamental knowledge of the chemical properties of nanotubes is thus accessible. Chemical connection of other functional molecules will ultimately lead to new property profiles. Three methods for the exohedral functionalization of carbon nanotubes are open to study: 1) supramolecular complexation of the tube walls with detergents^[4] and polymers;^[5] 2) generation and functionalization of defect sites at the tube ends and side walls by oxidation^[6] and subsequent conversion into derivatives such as amides,^[7] and 3) direct chemical functionalization of the side walls using addition reactions, of which direct fluorination and subsequent nucleophilic substitution^[8a-d] and the addition of aryl radicals formed by the reduction of aryl diazonium salts^[8e] are the only procedures reported to date.

We report here a series of covalent sidewall functionalization reactions and the detailed characterization of the resulting organo-nanotubes. We have selected three types of reaction for direct addition to the unsaturated π -electron system of the nanotubes: 1) the [2+1] cycloaddition of nitrenes; 2) the addition of nucleophilic carbenes, and 3) the addition of radicals. Single-walled nanotubes (SWNTs) were used as starting materials, manufactured either by arc-discharge^[9] or laser vaporization.^[10] The SWNT raw material was purified by centrifugation and microfiltration of a dispersion in aqueous detergent solution (sodium lauryl sulfate (SDS) or Triton X 100), then precipitated with ethanol, washed, and dried.

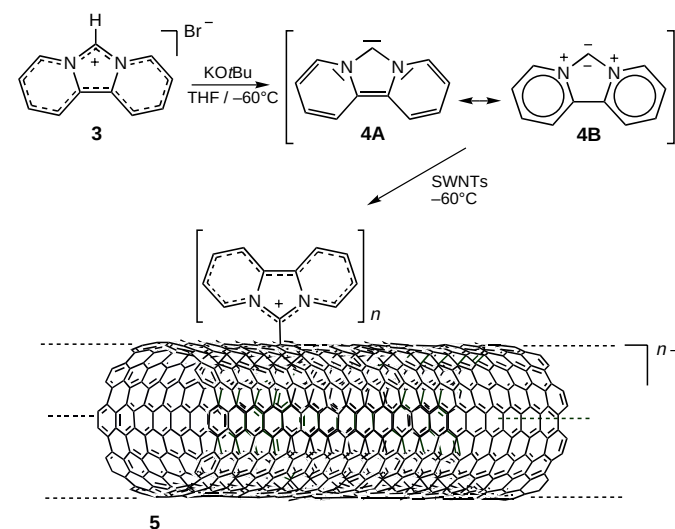
For the addition of nitrenes, the purified SWNTs were redispersed in 1,1,2,2-tetrachloroethane (TCE) in an ultrasound bath under a nitrogen atmosphere over several hours. The suspension was heated to 160 °C and a 200-fold excess of alkyl azidoformate **1a,b** as nitrene precursor was added

dropwise (Scheme 1). After thermally-induced N₂ extrusion from **1**, nitrene addition resulted in the formation of alkoxy-carbonyl-aziridino-SWNTs **2a,b**, which precipitated after a short time. Work-up proceeded by centrifugation and washing of the insoluble residue with diethyl ether. The derivatized SWNTs **2a,b** were soluble in DMSO, which allowed their separation from insoluble contaminants such as starting SWNTs.



Scheme 1. Sidewall functionalization by [2+1] cycloaddition of nitrenes.

The dipyridyl imidazolidene **4** was selected for the carbene addition. This compound is the prototype “selbstumpolung”-capable, nucleophilic carbene (cf. **4A/4B**).^[11a-d] Addend **4** is generated smoothly by deprotonation of the dipyridyl imidazolium system **3** (Scheme 2).^[12] Compound **4** reacts with electrophilic π systems to give zwitterionic 1:1 adducts rather



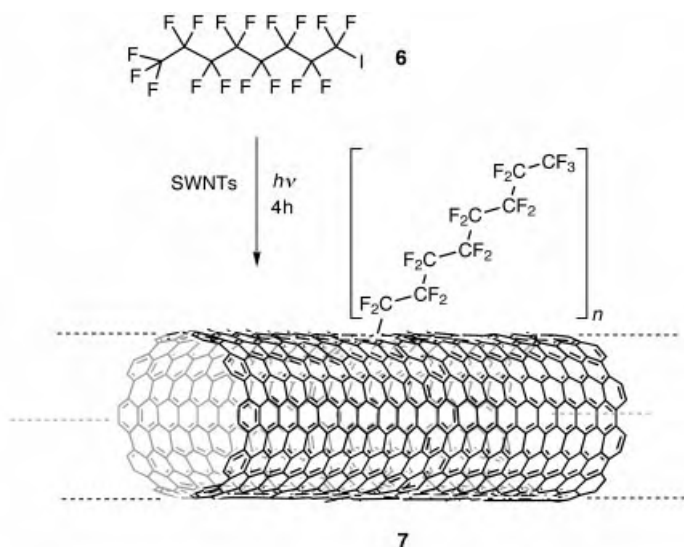
Scheme 2. Sidewall functionalization by the addition of nucleophilic carbenes.

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than cyclopropane systems because of the special stability of the resultant aromatic 14π perimeter.^[11d,e] The reaction with C_{60} also gives an adduct of this form.^[11d] Thus, because of its high nucleophilicity **4** should be well suited for the side-wall functionalization of SWNTs by nucleophilic polyaddition. In the addition reaction, one negative charge per addend is transferred to the tube surface, thus, alteration of the charge offers a further parameter for modifying tube properties (Scheme 2). After filtration through Celite under dry ice/acetone cooling, the freshly prepared, yellow, carbene solution (200-fold excess) was added to a SWNT dispersion in THF at -60°C . After stirring at -60°C for 3 h, the reaction mixture was slowly warmed to room temperature, then diluted with ethanol. The precipitated functionalized nanotubes **5** were isolated by centrifugation and washed with ethanol. Sufficiently derivatized nanotubes **5** were quite soluble in DMSO, giving a dark solution. This property permitted the separation of the DMSO-insoluble starting and insufficiently functionalized SWNTs by centrifugation. Because of the thermal lability of the adduct, the nanotubes **5** could be investigated by mass spectrometry. By heating a sample to 50°C , fragments corresponding to bipyridyl (m/z : 156) and the carbene **4** (m/z : 168) could be detected as degradation products under electron impact (EI) conditions.

As a reaction of SWNTs with radicals we selected the photoinduced addition of perfluorinated alkyl radicals. For this, SWNTs produced by the arc-discharge technique in the presence of a 200-fold excess of heptafluorooctyl iodide **6** dissolved in TCE were illuminated with a medium-pressure mercury lamp (150 W) for 4 h (Scheme 3). Workup was by



Scheme 3. Sidewall functionalization by the addition of a radical.

distillation to remove the solvent and the generated iodine. No difference in the solubility of the fluoroalkyl-substituted nanotubes **7** and the starting materials was observed.

The characterization of products represents a constant problem in nanotube chemistry. In the case of SWNTs, one always works with a polydisperse mixture of tubes or bundles of tubes of differing lengths, diameter, and helicity. The undefined distribution of addends and their addition pattern

over the whole cylinder wall aggravates the problem. In those situations where functionalization is successful, the conjugated double-bond system of the cylindrical surface is interrupted and defect sites will result. An extensive functionalization, this must lead to changes in structure and, therefore, changes in the electronic, optical, and physical properties. For satisfactory characterization of these new classes of substance, data from different measurement methods must be collected and compared. Alongside the standard methods such as NMR and UV/Vis/NIR spectroscopy, the use of atomic force microscopy (AFM) is essential.

The ^1H NMR spectrum of the Boc-aziridino nanotubes **2a** (Boc = *tert*-butoxycarbonyl Figure 1 a) in $[\text{D}_6]\text{DMSO}$ displays a clear upfield shift of 0.3 ppm and a considerable broadening of the signal of the *tert*-butyl protons compared to that of the corresponding protons in *tert*-butyl azidoformate **1a**. The shift indicates an interaction between the addend protons and the π system of the SWNTs. The signal broadening results from the statistical distribution of the addends on the tube surface. The ^1H spectrum of the carbene-modified SWNTs **5** (Figure 1 b) displays two strong, broadened signals in an intensity ratio of about 1:3. The upfield signal at $\delta = 7.7$ is assigned to the bipyridyl protons H_a of the carbene addend that lies close to the surface of the nanotube. The remaining protons of the bipyridyl subsystem lie further from the carbon tube and come into resonance as a poorly resolved signal at $\delta = 7.9$. The signal broadening relative to a methylated reference molecule (Figure 1 b) results from the absence of symmetry and of a preferred orientation of the addends relative to the SWNT axis. Furthermore, restricted mobility of these systems in solution is to be expected because of the large size of the nanotubes. These features all contribute to the observed line-broadening. As the radical adducts **7** incorporate fluorinated alkyl chains ^{19}F NMR spectroscopy can be used to aid characterization. The ^{19}F NMR spectrum of **7** (Figure 1 c), recorded in $[\text{D}_2]\text{TCE}$, displays a resonance signal at $\delta = -80.9$ for the CF_3 group of C8 and five distinct signals for the CF_2 groups of C3–7 at $\delta = -123$, -124 , -125 , and -127 . The signals of the CF_2 groups of C1 and C2 cannot be assigned. The shielding effect of the nanotube π system has little impact; the signals of the difluoromethylene groups are strongly broadened compared to the starting molecule **6** (Figure 1 c).

Nanotubes produced by laser vaporization display characteristic absorption maxima at 650 and 950 nm in their electronic spectra, (Figure 2).^[13] With the functionalized nanotubes, we find additional absorptions at 1427 nm (for **5**, Figure 2) and 1436 nm (for **2b**, Figure 2,) that are indicative of an alteration of the π system. Overall, however, the absorption behavior in this region was only slightly influenced by modification of the side walls. Even after reaction with carbene **4**, the charge donation to the functionalized SWNTs has no influence on their absorption behavior. Therefore, the addition density and the resulting number of defect sites appears to be very low.

Microscopy is one of the most important methods of characterization in nanotube research. AFM is the best suited method for obtaining authoritative evidence about the sample condition (aggregation, dimensions, and cleanliness), as one

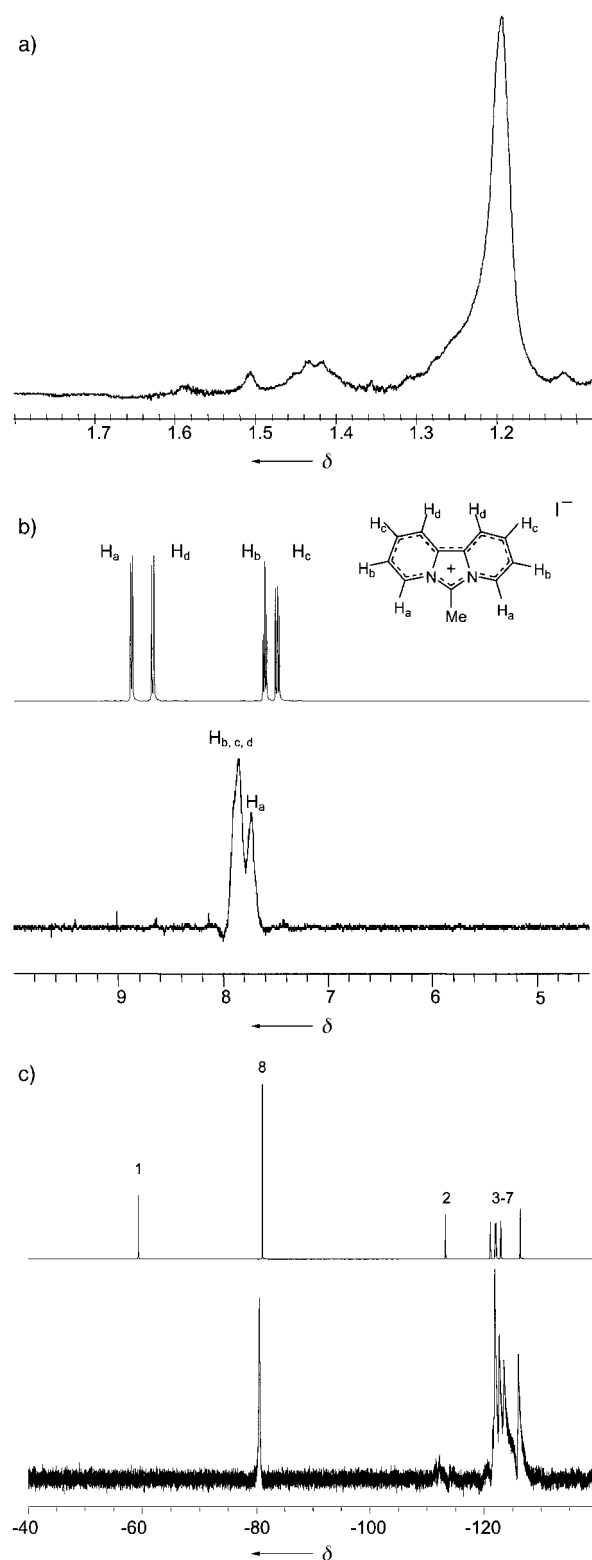


Figure 1. a) ^1H NMR spectrum of **2a** ($[\text{D}_6]\text{DMSO}$, RT); b) ^1H NMR spectrum of **5** (below) and of dipyrro[1,2-c;2',1'-e]-2-methylimidazolium iodide (above) ($[\text{D}_6]\text{DMSO}$, RT); c) ^{19}F NMR spectrum of **7** (below) and the starting materials perfluorooctyl iodide **6** (above; $[\text{D}_2]\text{TCE}$, RT).

can observe a relatively large area (Figure 3). Nanotubes obtained by laser vaporization (Figure 3a) order themselves in very large bundles with mean diameters up to 20 nm and are several micrometers long. The analysis of the AFM

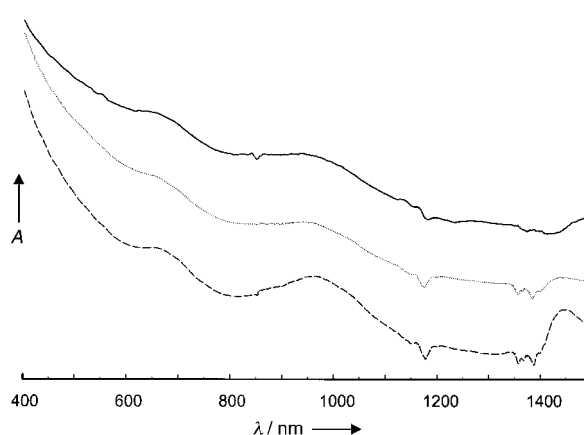


Figure 2. Electronic absorption spectra of purified laser vaporization nanotubes (THF, top curve), **5** from laser vaporization SWNTs (DMSO, middle curve) and **2b** from arc-discharge SWNTs (DMSO, bottom curve).

pictures from functionalized nanotubes showed that, after successful addition of side functionality the bundles were destroyed, so that essentially only individual SWNTs could be observed. This is shown for example in an AFM picture of functionalized nanotubes **2b** (Figure 3b). Their diameter of 2–4 nm, confirmed by the recording of their height profile, corresponds to that of a typical, individual nanotube produced by laser ablation.^[10] Furthermore, the lengths of the nanotubes remain unaltered after functionalization. The effect of the separation of tubes from the bundles is especially clear to see in the case of the carbene functionalized nanotubes **5** (Figure 3c). Their diameter corresponds to the generally thinner SWNTs obtained by arc-discharge, which have a diameter of 1.3 nm.^[9a] The height profile (1.0–1.4 nm) of the picture clearly shows the existence of individual, unaggregated SWNTs (Figure 3d).

Both nitrene addition and the carbene addition were carried out with SWNT material obtained by arc-discharge^[9] and by laser vaporization.^[10] It appeared that nanotubes made by the laser method were generally better suited for the different functionalizations. In contrast, a partial destruction of the tube structure could be observed when the tubes made by arc-discharge were subjected to nitrene addition. The smaller average diameter results in greater curvature and a larger number of defect sites on the side wall. The number of defects, holes, and amorphous areas in the tube wall causes higher reactivity of the arc-discharge produced tubes and impairs the stability of the tube framework. On the other hand, the defects promote the processibility of the arc-discharge material. Carbon nanotubes made by this method have a lower tendency to form bundles of more than 10 SWNTs and are soluble in significantly higher concentrations in organic solvents. This in turn results in a noticeable improvement in the solubility of the functionalized materials; in the case of the perfluoroalkyl-functionalized SWNTs **7** the solubilities of the starting materials and products were comparable.

With the three different methods of functionalization of the side walls of carbon nanotubes introduced here, the first steps towards general routes to a wide variety of new-nanotube derivatives are presented. With the choice of appropriate

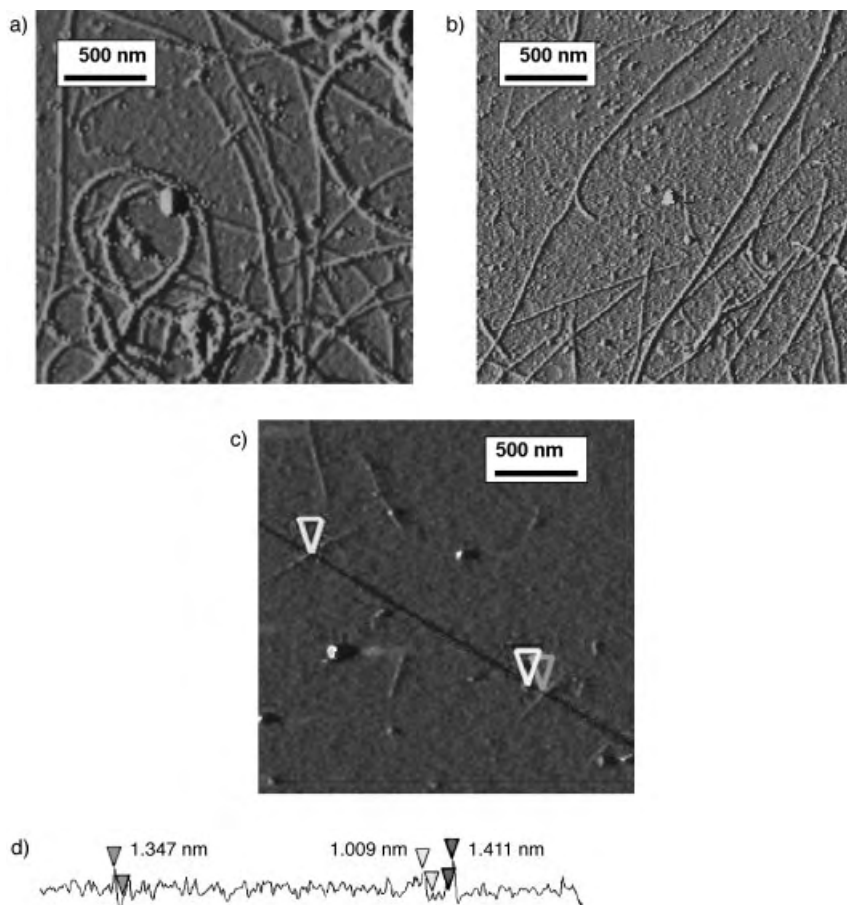


Figure 3. AFM pictures of a) untreated SWNT bundles (from laser vaporization, $\varnothing$ 20 nm), b) individual SWNTs **2b** (from laser vaporization, $\varnothing$ 2–4 nm), and c) **5** (from arc-discharge, $\varnothing$ 1.0–1.4 nm). d) Height profile of three functionalized SWNTs **5** (from Figure 3c) with diameters 1.0–1.4 nm.

addends, carbon nanotubes that possess better solubility, are easier to characterize, and feature more straightforward processibility for technological applications are accessible.

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No Polymerization with Metallocenes in Water?—A Prejudice is Refuted**

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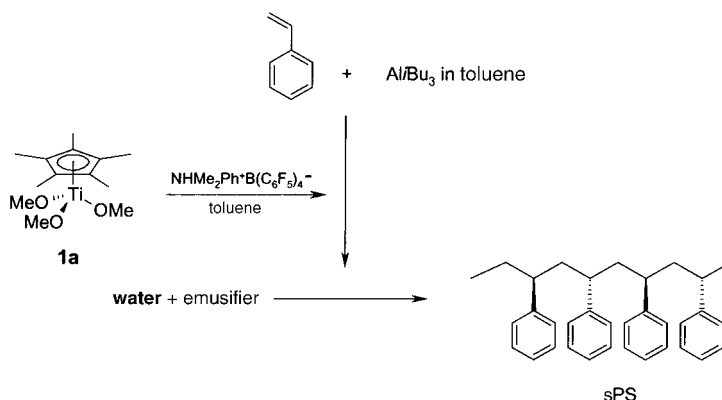
Emulsion polymerization is a process of significant industrial relevance.^[1] Especially the use of water as a reaction medium ensures its importance in terms of sustainable development. Important industrial products such as coatings and dye stuffs can be manufactured on a large scale using this polymerization process. Generally radical initiation is used in emulsion polymerization to obtain a polymer dispersion. To get a better control of the properties of the dispersion, controlled radical-polymerization methods have recently attracted attention.^[2] However, this method offers only limited control of the polymer structure. A much higher potential for controlling the polymer properties is possible by applying insertion-polymerization techniques, for example, with transition metal complexes.^[3]

In the aqueous emulsion polymerization of ethylene, the groups of Mecking,^[4] and Spitz and Claverie,^[5] introduced neutral nickel complexes as catalysts. These complexes as well as cationic palladium complexes, which are used for olefin polymerization in aqueous media,^[6] are much less water sensitive than complexes of the early transition metals. For the emulsion polymerization of butadiene in an aqueous environment cobalt catalysts have also been used.^[7]

Metallocene complexes^[8] of early transition metals are generally converted into the catalytically active form (the metallocenium cation) by methylalumoxane (MAO) or special boron reagents.^[3a,b] The metallocenium cations are very electrophilic and have to be handled under strictly inert conditions avoiding any contact with air or moisture. Therefore, the polymerization of olefinic unsaturated monomers with these catalysts has to be performed under these inert conditions as well.

We report here the first use of metallocene catalysts in aqueous emulsion polymerization. Styrene polymerization was chosen as a model system since it allows the easy differentiation of the two possible polymerization mechanisms (radical or catalytic insertion) by the type of polymer (atactic or syndiotactic,^[9] respectively) obtained.

Initially a prepolymerization was performed for 30 s (Scheme 1). A solution of the monocyclopentadienyl complex **1a** and a borate activator ($\text{NHMe}_2\text{Ph}^+\text{B}(\text{C}_6\text{F}_5)_4^-$)^[10] was prepared and then added to a solution of styrene in toluene to which an aluminum alkyl compound was added. This prepolymerization solution was then fed into water with added emulsifier. After the reaction was stopped polystyrene



Scheme 1. Preparation of syndiotactic polystyrene in water.

could be isolated (66% conversion). The analysis of the polymer by means of differential scanning calorimetry (DSC; Figure 1) and NMR spectroscopy demonstrated that exclusively syndiotactic polystyrene (sPS) was formed. This clearly

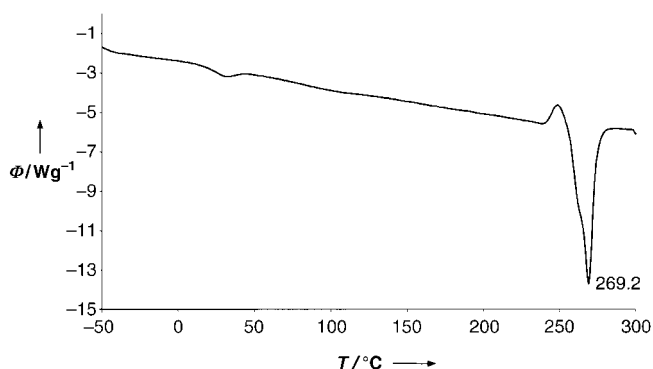


Figure 1. DSC curve of syndiotactic polystyrene.

shows that all the polymer was produced by insertion polymerization at the metal center since sPS is only obtainable by this route.^[9] We assume the catalyst was encapsulated by the prepolymerization process and its addition to the water/emulsifier mixture resulted in the formation of a type of mini emulsion. The styrene droplets shaped by the emulsifier are then completely polymerized by the catalyst inside the droplets. The crystalline sPS formed inside the droplets provides extra protection for the catalyst against water. Obviously the high degree of crystallinity of sPS is the reason why the dispersions have a poor long-term stability, and why by precipitation of sPS unusually large particles for emulsion polymerization are formed (500 μm).

Further experiments to increase the stability of the dispersions by variation of the emulsifier were performed. The use of cationic (cetyltrimethylammonium chloride) and nonionic (Lutensol AT18) emulsifiers (Figure 2) resulted in the formation of polymer, whereas reactions with anionic emulsifiers were not successful under the conditions examined. A possible explanation is the interaction of the anionic part of the emulsifier with the catalytically active, cationic metal center. On the other hand, the fact that no polymer was formed with the anionic emulsifier shows that the sPS formed

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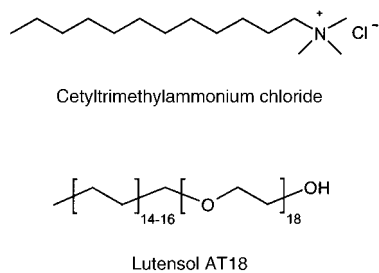


Figure 2. Successfully employed cationic and nonionic emulsifiers.

during the prepolymerization accounts for an insignificant amount of the sPS obtained with cationic and nonionic emulsifiers. Thus, the bulk of the polymer is produced in the aqueous environment in emulsion.

In attempts to further increase the shielding of the catalyst from water, the alkoxide substituent was varied. The original system contained methoxide ligands, which were subsequently replaced by more sterically demanding substituents (Figure 3). However, no improvement in terms of turnover or dispersion stability was observed.

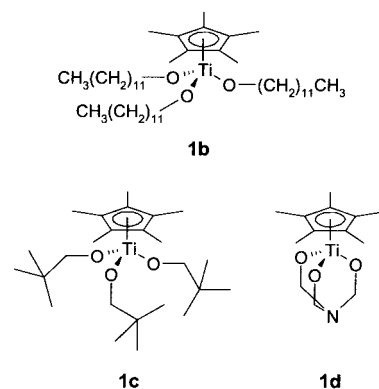


Figure 3. Monocyclopentadienyl complexes for the polymerization of styrene in aqueous emulsion.

The influence of other metal complexes and emulsifiers on the styrene polymerization is part of ongoing investigations as is the transfer to other monomers. In addition, particle size distribution as well as dispersion stability will be further optimized.

Experimental Section

The polymerizations were performed under the exclusion of air. All chemicals were obtained commercially.

Aqueous emulsion polymerization: In a 1 L flask styrene (75 g) was dissolved in toluene (300 g) and heated to 80 °C. Then a 25 % triisobutylaluminum solution in toluene (9.5 g) was added. A solution of *N,N*-dimethylanilinium tetrakis(pentafluorophenyl) borate (0.385 g) and of pentamethylcyclopentadienyl titanium trimethoxide (**1a**; 0.135 g) in toluene (10 mL) was prepared separately and added from a feed vessel. After 0.5 min the resulting mixture was added to a solution of 20 % Lutensol AT18 (18.75 g) in deionized water (300 g). The reaction was quenched with ethanol after 1 h. The suspension was dried at 80 °C in vacuo. Conversion: 66 %; tacticity: ¹³C NMR *rr* = 99 %, *mm* = 0 %, *rm* = 1 % (*r* = racemic diad (syndiotactic); *m* = meso diad (isotactic)); m. p. (DSC): 269 °C; average particle size (determined from scanning electron microscopy (SEM) pictures): ca. 500 μm.

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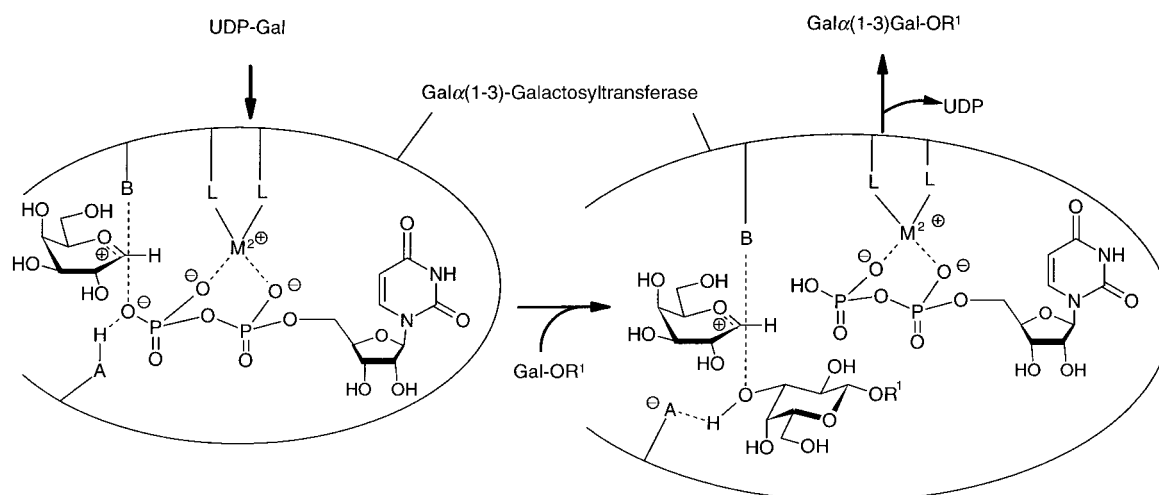
α(1-3)-Galactosyltransferase Inhibition Based on a New Type of Disubstrate Analogue**

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Oligosaccharides play an important role in various cellular recognition and signal transduction processes.^[1] Therefore, control of the biosynthesis of the structurally diverse oligosaccharides is of great interest for biological studies. An important control mechanism is the specific inhibition of the various glycosyltransferases.^[2] In enzymatic oligosaccharide synthesis, a glycosyl donor (commonly a nucleoside mono- or diphosphate) and an acceptor are generally coupled, with the

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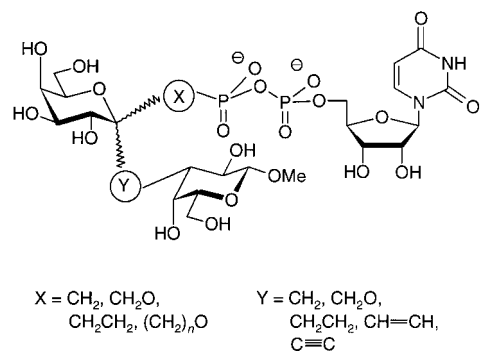


Scheme 1. Proposed course of the galactosyl transfer (B or UDP = catalytic nucleophile, A-H = acid).

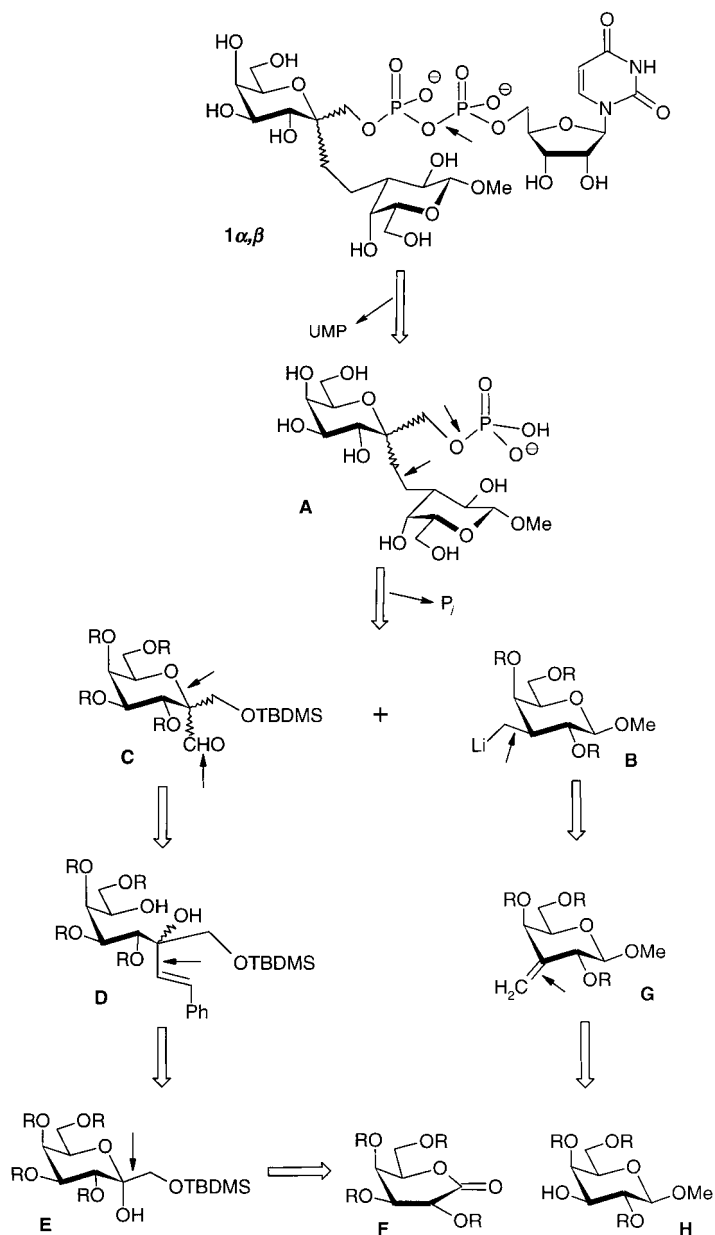
loss of the nucleoside mono- or diphosphate residue. Substrate analogues of the donor and of the acceptor have been investigated as inhibitors, but with limited success.^[3] Transition state analogues of the donor have also been constructed.^[4] They are often derived from the corresponding glycals, because it is assumed that an oxocarbenium ion is structurally closely related to the geometry of the transition state (Scheme 1).^[4-6] Disubstrate analogues^[7,8] that contain the glycosyl donor and acceptor in a steric arrangement that simulates the transition state may be of particular interest; for a retaining $\alpha(1-3)$ -galactosyltransferase reaction, see Scheme 1.^[9] Such compounds are expected to have a high affinity for the active site, thus leading to a higher specificity.

Potential disubstrate analogues are shown in Scheme 2. In the target molecules, both the leaving group and the acceptor are connected to the glycosyl moiety through hydrolytically stable linkages, and thus the synthesis of C-ketoside derivatives is of interest^[10]. The inhibition of $\alpha(1-3)$ -galactosyltransferase is a key to the prevention of hyperacute rejection in the xenotransplantation of organs from pigs to humans.^[11] Similarly, inhibitors of galactosyltransferases, which are required for the synthesis of glycosylphosphatidylinositol (GPI) membrane anchors in trypanosomes^[12-14] are interesting pharmacological targets. We focused on the synthesis of compounds **1a** and **1b** (in Scheme 2: X = CH₂O, Y = CH₂CH₂).^[15, 16]

The retrosynthesis of target molecules **1a** and **1b** is shown in Scheme 3. Retrosynthetic cleavage of uridine-5'-monophosphate (UMP) gives synthetic equivalent **A**. Removal of the



Scheme 2. Proposed disubstrate analogues.



Scheme 3. Retrosynthetic scheme for the synthesis of disubstrate analogues **1a** and **1b**.

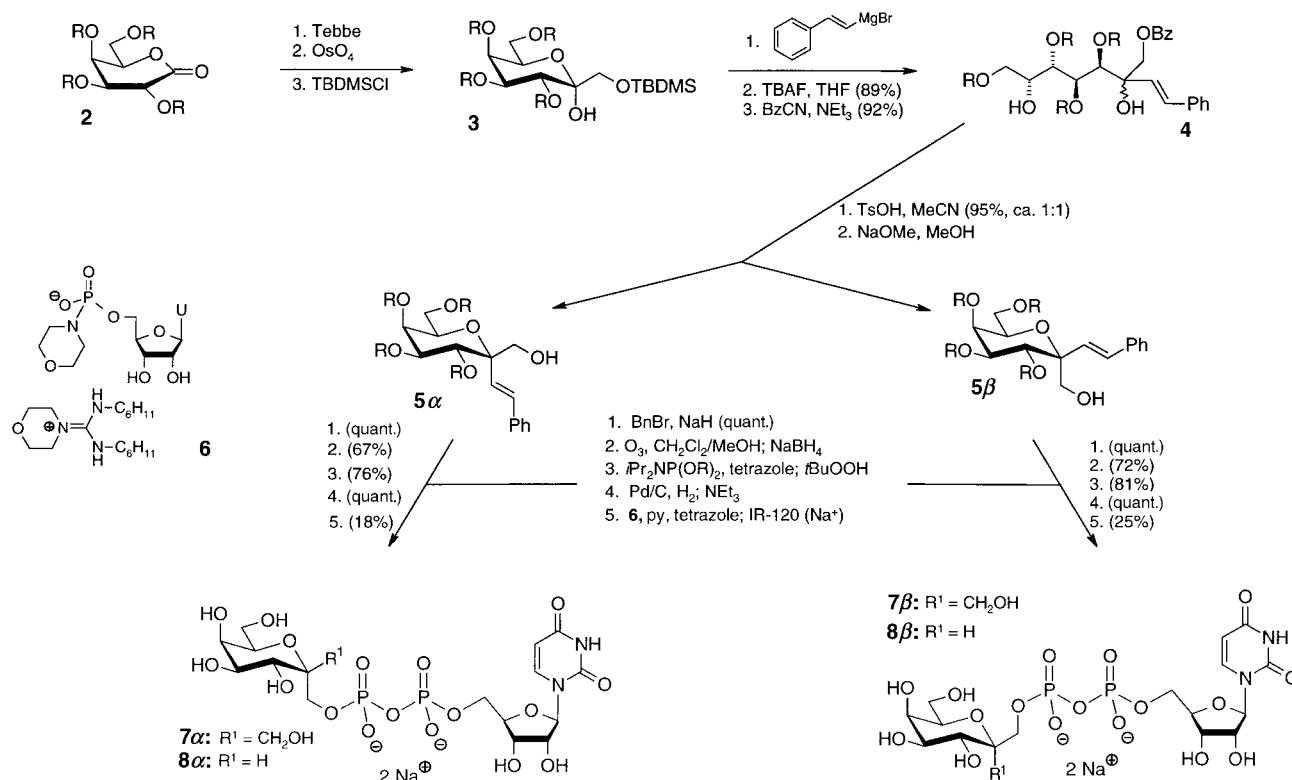
phosphate group (P_i) and further disconnection leads back to the two galactose residues **B** and **C**. Fragment **C** can be envisioned from the ring closure of precursor **D**, which is equipped with a latent functionality at C1. The two C₁ synthetic equivalents can be obtained from galactonolactone (**F**; R = H) via intermediate **E**. The 3-C-lithiomethylgalactoside fragment **B** is derived from 3-C-methylene derivative **G**, which can be obtained from 3-O-unprotected galactopyranoside **H**.

O-Benzyl-protected galactonolactone **2**^[17] was selected as the precursor for the synthesis of **1a** and **1b** and other UDP-Gal mimetics (Scheme 4). The two C₁ nucleophiles that are required were introduced by Tebbe methylenation of **2**, dihydroxylation of the resulting C–C double bond, and selective protection of the primary hydroxy group with *tert*-butyldimethylsilyl (TBDMS) chloride to furnish the protected 2-heptulose **3**. Addition of styrylmagnesium bromide to **3** as the latent C₁ functionality and replacement of the TBDMS group by a benzoyl group afforded alcohol **4** as a 1:1 mixture of diastereomers. The protecting groups and the styryl group allowed the facile cyclization of **4** under acid catalysis to afford a 1:1 mixture of diastereomeric tetrahydropyran derivatives. Removal of the *O*-benzoyl group gave the important intermediates **5a** and **5b** in high overall yield. These compounds were subjected to O-benzoylation, ozonolytic cleavage of the C–C double bond, and reduction of the resulting formyl group to form the hydroxymethyl derivatives. Subsequent phosphorylation of the primary hydroxy groups, complete hydrogenolytic O-debenzoylation, coupling of UMP with the help of activated intermediate **6**, and ion exchange gave UDP-Gal mimetics **7a** and **7b**, respectively, as disodium

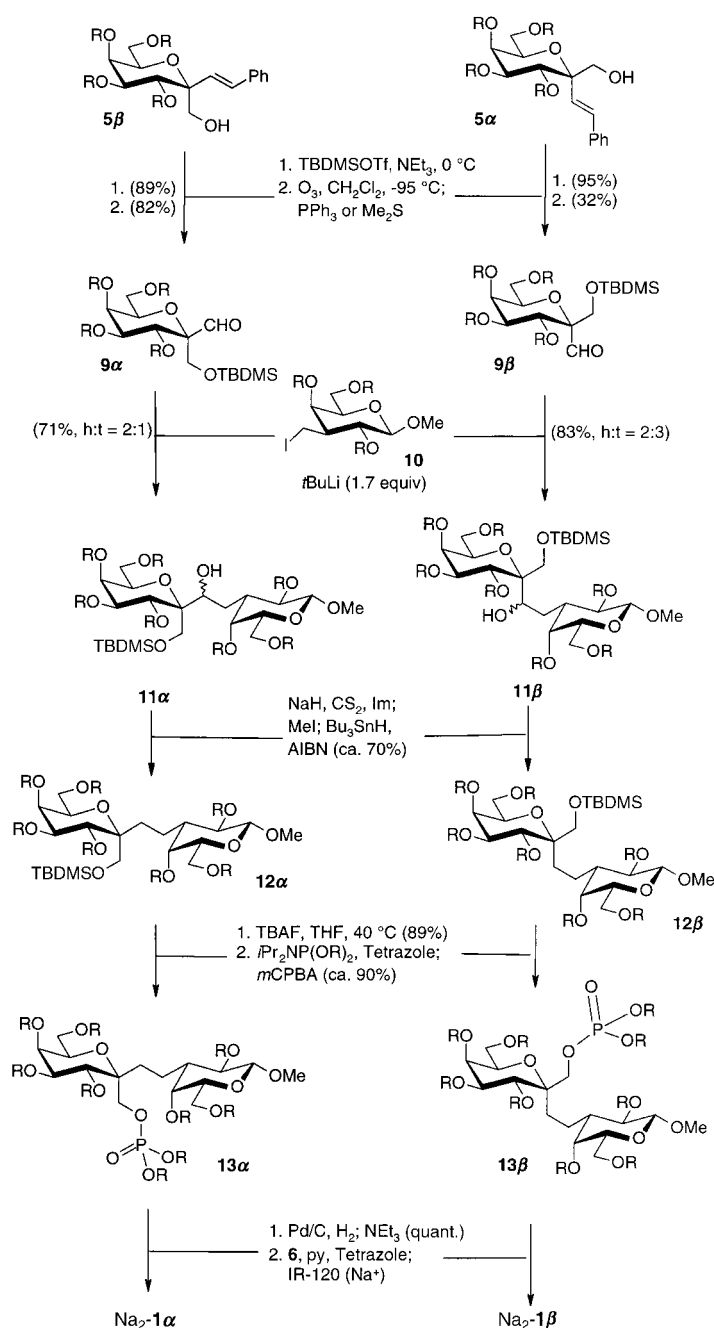
salts. As donor-substrate analogues, they are also potential galactosyltransferase inhibitors; as are the UDP homologues **8a** and **8b**, which were obtained by following reported procedures.^[4, 16, 18] All four compounds were investigated in the biological studies.

To construct the target molecules **1a** and **1b**, the primary hydroxy groups of **5a** and **5b** were protected with the TBDMS group (Scheme 5), and the styryl groups were then treated with ozone to generate the formyl groups in **9a** and **9b**, respectively. The aldehyde groups were used to attach the galactosyl moiety, which is the acceptor part of the disubstrate analogues **1a** and **1b**: 3-C-iodomethylgalactoside **10**, which was readily obtained from methyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside,^[19] was transformed with *tert*-butyllithium into the 3-C-lithiomethyl derivative, and then treated with **9a** and **9b** to furnish C-disaccharides **11a** and **11b**, respectively, both as mixtures of diastereomers. Removal of the hydroxy groups under Barton conditions led to **12a** and **12b** as single isomers. The TBDMS protecting group was replaced with the phosphate group under standard conditions in high yield, thus affording O-benzyl-protected phosphates **13a** and **13b**. Complete O-debenzylation by means of hydrogenolysis was followed by the reaction with activated UMP derivative **6** to furnish target molecules **1a** and **1b** as disodium salts after ion exchange. Compounds **1a** and **1b** and all intermediates were characterized by means of NMR spectroscopy (Table 1).

The compounds **1a**, **1b**, **7a**, **7b**, **8a**, and **8b** were tested in vitro for the inhibition of purified recombinant pig α(1-3)-galactosyltransferase (pα(1-3)GalT) by using radiolabeled UDP-Gal as donor and LacNAc-R as acceptor (for details see Experimental Section). At a concentration of 50 μM, only **1b**



Scheme 4. Synthesis of UDP-Gal homologues **7a**, **7b** and **8a**, **8b**. R = PhCH₂ (Bn), TBAF = Bu₄NF, Bz = PhCO, Ts = *para*-toluenesulfonyl, py = pyridine, IR-120(Na⁺) = ion exchange resin in the Na⁺ form.



Scheme 5. Assembly of the target molecules **1α**, **1β**. R = Bn, Tf = CF₃SO₂, Im = imidazole, AIBN = azobisisobutyronitrile, mCPBA = meta-chloroperoxybenzoic acid

inhibited the enzyme. An IC₅₀ of about 5 μM was found for **1β** (Figure 1).

In summary, disubstrate analogue **1β** was found to be a good inhibitor of the retaining pig α(1-3)-galactosyltransferase. The presence of UDP on the β-side of the galactose moiety leads to a higher affinity for the enzyme than when UDP is found on the α-side, as is the case in the natural galactosyl donor and in disubstrate analogue **1α**. This result is at first rather surprising and hints at the catalytic nucleophile within the active site which seems to be necessary for retaining glycosyltransferases, but yet could not be found for the retaining galactosyltransferase LgtC from *Neisseria*

Table 1. Physical data for **1α**, **1β**, **7α**, and **7β**.^[a]

1α: ¹H NMR: δ = 1.39–1.44 (m, 2H; 7a-H, 8a-H), 1.52 (m, 1H; 3-H), 1.59 (m, 1H; 8a'-H), 1.86 (m, 1H; 7a'-H), 3.24 (dd, ³J_{2,1} = 8.0, ³J_{2,3} = 10.8 Hz, 1H; 2-H), 3.49 (s, 3H; OCH₃), 3.60–3.67 (m, 6H; 1a-H, 1a'-H, 2a-H, 5-H, 6-H, 6'-H), 3.77 (dd, ³J_{4a,5a} = 10.3, ³J_{4a,3a} = 3.4 Hz, 1H; 4a-H), 3.79 (d, ³J_{4,3} ≈ 2.1, ³J_{4,5} ≤ 1 Hz, 1H; 4-H), 3.86 (d, ³J_{3a,4a} = 3.4, ³J_{3a,2a} ≤ 1 Hz, 1H; 3a-H), 3.97–4.00 (m, 3H; 1b-H, 1b'-H, 5a-H), 4.10–4.20 (m, 3H; 4c-H, 5c-H, 5c'-H) 4.24 (d, ³J_{1,2} = 8.0 Hz, 1H; 1-H), 4.25–4.30 (m, 2H; 2c-H, 3c-H), 5.82 (d, ³J_{5d,6d} = 7.7 Hz, 1H; 5d-H), 5.94 (d, ³J_{1c,2c} = 5.0 Hz, 1H; 1c-H), 7.76 (d, ³J_{6d,5d} = 7.7 Hz, 1H; 6d-H); ³¹P NMR: δ = –12.31 – –12.90 (2 × d, ³J_{PP} ≈ 21 Hz; 2P)

1β: ¹H NMR: δ = 1.46 (m, 3H; 3-H, 7a-H, 8a-H), 1.74 (pt, *J* ≈ 9.0 Hz, 1H; 8a'-H), 1.89 (pt, *J* ≈ 9.4 Hz, 1H; 7a'-H), 3.24 (pt, ³J_{2,1} ≈ ³J_{2,3} ≈ 9.0 Hz, 1H; 2-H), 3.49 (s, 3H; OCH₃), 3.59–3.62 (m, 4H; 1a-H, 1a'-H, 5-H, 6-H), 3.67–3.68 (m, 1H; 6'-H), 3.75 (d, ³J_{5a,4a} = 10.0 Hz, 1H; 5a-H), 3.84 (brs, 1H; 4-H), 3.89–3.93 (m, 4H; 1b-H, 2a-H, 3a-H, 4a-H), 4.10 (m, 1H; 5c-H), 4.16 (m, 1H; 5c'-H), 4.18 (m, 1H; 4c-H), 4.22 (d, ³J_{1,2} = 7.9 Hz, 1H; 1-H), 4.26–4.67 (m, 3H; 1b'-H, 2c-H, 3c-H), 5.85 (d, ³J_{5d,6d} = 7.8 Hz, 1H; 5d-H), 5.93 (d, ³J_{1c,2c} = 4.7 Hz, 1H; 1c-H), 7.81 (d, ³J_{6d,5d} = 7.8 Hz, 1H; 6d-H); ³¹P NMR: δ = –11.86 – –12.33 (2 × d, ³J_{PP} ≈ 21 Hz, 2P)

7α: ¹H NMR: δ = 3.40–3.70 (m, 6H; 1-H, 4-H, 5-H, 6-H, 7-H, 7'-H), 3.71–4.03 (m, 4H; 1a-H, 1a'-H, 1'-H, 3-H), 4.04–4.25 (m, 5H; 2b-H, 3b-H, 4b-H, 5b-H, 5b'-H), 5.89 (d, ³J_{5c,6c} = 8.1 Hz, 1H; 5c-H), 5.91 (d, ³J_{1b,2b} = 3.9 Hz, 1H; 1b-H), 7.87 (d, ³J_{6c,5c} = 8.1 Hz, 1H; 6c-H)

7β: ¹H NMR: δ = 3.60, (dd, ²J_{7,7'} = 11.6, ³J_{7,6} = 4.7 Hz, 1H; 7-H), 3.65–3.69 (m, 2H; 1-H, 7'-H), 3.71 (dd, ³J_{4,3} = 10.4, ³J_{4,5} = 3.3 Hz, 1H; 4-H), 3.79 (pt, ³J_{6,7} ≈ ³J_{6,7'} ≈ 6.0 Hz, 1H; 6-H), 3.85 (d, ³J_{5,4} = 3.3, ³J_{5,6} ≤ 1 Hz, 1H; 5-H), 3.93 (d, ²J_{1,1'} = 12.9 Hz, 1H; 1'-H), 3.95 (d, ³J_{3,4} = ³J_{4,3} = 10.4 Hz, 1H; 3-H), 3.98 (dd, ²J_{1a,1a'} = 10.8, ³J_{1a,P} = 4.2 Hz, 1H; 1a-H), 4.02 (dd, ²J_{1a',1a} = 10.8, ³J_{1a',P} = 5.9 Hz, 1H; 1a'-H), 4.05–4.19 (m, 3H; 4b-H, 5b-H, 5b'-H), 4.23–4.27 (m, 2H; 2b-H, 3b-H), 5.82 (d, ³J_{5c,6c} = 7.9 Hz, 1H; 5c-H), 5.90 (d, ³J_{1b,2b} = 4.8 Hz, 1H; 1b-H), 7.77 (d, ³J_{6c,5c} = 7.9 Hz, 1H; 6c-H); ³¹P NMR: δ = –12.13 – –12.60 (2 × d, ³J_{PP} ≈ 21 Hz, 2P)

[a] ¹H NMR (600 MHz) and ³¹P NMR (242 MHz) spectra were measured in D₂O (pt = pseudo triplet).

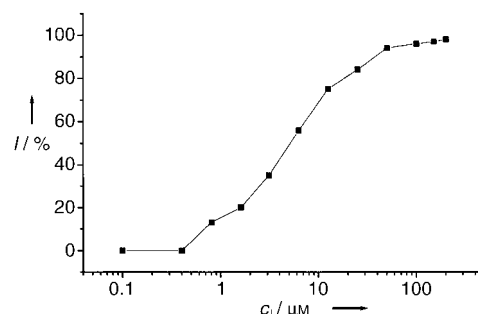


Figure 1. Inhibition of α(1-3)GalT by **1β**: The transferase assay was performed in the presence of **1β** (200–0 μM), UDP-Gal (50 μM), and LacNAcR (360 μM). *I* = inhibition, *c*₁ = concentration of inhibitor.

meningitidis^[9] therefore, UDP is not only the leaving group but also the catalytic nucleophile, that is, in retaining glycosyltransferases, UDP-Gal is first transformed into the corresponding β-anomer or perhaps its tight ion pair and then the acceptor is glycosylated at the α-side. Thus, it is proposed that arbitrarily chosen nucleophile B in Scheme 1 is UDP.

Experimental Section

Pig α(1-3)-galactosyltransferase (α(1-3)GalT) and activity assay: The α(1-3)GalT was cloned and expressed as soluble transferase in Baculovirus-infected Sf9 insect cells. The enzyme was purified by means of ion exchange and affinity chromatography. The assay used to assess the inhibitory potential of compounds is based on the transfer of radiolabeled

[³H]galactose from the donor UDP-Gal (50 μM) to the acceptor molecule LacNAc(CH₂)₆CO₂CH₃ (0.36 mM) by the *pa*(1-3)GalT (10 μM) in an assay buffer system consisting of sodium cacodylate (100 mM; pH 6.5), 15 mM MnCl₂, and BSA (bovine serum albumin; 50 μg mL⁻¹) at 37 °C for 30 min. The radiolabeled product, [³H]Gala(1-3)LacNAc(CH₂)₆CO₂CH₃, was separated from unincorporated label by adsorption onto a SepPac C₁₈ column^[20]. The ratio of incorporated to total radioactivity is proportional to the activity of *pa*(1-3)GalT. We took precautions to ensure that the enzyme was the limiting reagent and that all other cofactors were close to the saturation point. Strictly speaking, the reported inhibition is an IC₅₀ value because we have not carried out the assays with different concentrations of cofactors.

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Polyphenylene Dendrimers as Sensitive and Selective Sensor Layers**

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Polyphenylene dendrimers (PDs) are monodisperse macromolecules, which—because of their rigid framework—contain internal voids. This property differentiates them from other dendrimers, which consist of flexible, aliphatic groups, and makes them attractive as selective layers for gravimetric sensors. Such sensors based upon the quartz microbalance (QMB)^[1] are widely used to monitor the concentration of various volatile organic compounds (VOCs) in different environments. These types of sensors are of increasing significance in many aspects of daily life, be it monitoring the manufacture or storage of foodstuff,^[2] controlling chem-

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ical reactions such as polymerization,^[3] or safety standards in the chemical industry, such as monitoring the maximum allowed concentration of VOCs in the work environment.^[4] QMBs are mass-sensitive devices, which are easy to apply, yet of low cost, and they provide both high selectivity and excellent sensitivity down to concentrations of VOCs of only 5 ppm.^[5] Both properties of these gravimetric sensors crucially depend on the type of sensor-active layer coated on top of the QMBs. For this purpose, certain types of polymers^[6] or organic compounds—such as lactam macrocycles or rotaxanes^[7]—have been used successfully to date; even biomaterials have found application.^[8] However, polymers such as polyvinylchloride (PVC) lack selectivity, and organic hosts as sensor-active layers yield insufficiently reproducible results, probably because of rearrangements or aging. Biological sensor layers are frequently rather unstable both chemically as well as thermally. For many analytes and applications specific sensor layers have to be specially prepared. Therefore, because of the variety of applications and the multitude of simultaneous requirements, high-quality sensor-active materials have to satisfy there is a high demand for durable sensor-active layers with high selectivity for many types of target guest molecules.

Herein the suitability of polyphenylene dendrimers (PDs) as sensor layers for monitoring VOCs in the gas phase will be demonstrated. PDs are ideally suited as host molecules, since PET (Positron Emission Tomography) studies have shown that they contain stable cavities in their interior.^[9] Investigations of the crystal structure of different PDs of the first generation (G1) have revealed that solvent molecules are readily trapped within these cavities.^[10] Accordingly, the most important prerequisites are met for PDs to qualify as hosts, namely sufficient free internal space, and the tendency to fill these voids with small guest molecules.

The synthesis of PDs starts from core units of different structure and proceeds by a cascade of Diels–Alder–

type cycloadditions^[11] leading to structurally quite different three-dimensional (3D) dendrimer architectures (Figure 1).^[12]

The influx of functional groups in the periphery of the PDs on the sensor activity has also been investigated. For this purpose, dendrimers of the second generation (G2) have been synthesized carrying electron withdrawing (CN and COOH) or electron donating (N=CPh₂) substituents by using the correspondingly functionalized cyclopentadienone units **7–9** (Figure 2). This approach yields functionalized, monodisperse dendrimers in excellent yields.^[13]

The coating of the QMBs with the PDs is by using a procedure from mass spectrometry known as electrospray.^[7, 14] The PDs are dissolved in THF and accelerated by a high DC voltage through a thin capillary and sprayed onto the top electrode of the QMB. This leads to the formation of homogeneous, rigid layers, the thickness of which is controlled in situ by simultaneously monitoring the frequency of the QMBs to be coated. The resulting thickness is standardized corresponding to a frequency reduction of 10 kHz, at which point the coating is stopped. According to Sauerbrey this offset is equal to a mass of 44 $\mu\text{g cm}^{-2}$ of the coating on a 10 MHz QMB.^[15] A standardized thickness (or mass) of the host compound on the QMB is a prerequisite for comparing the sensitivity and selectivity of the coatings and to assure reproducible results. QMBs coated accordingly have been sequentially exposed to different VOCs in a gas mixing chamber at 50 °C and at a universal concentration of 1000 ppm. The associated lowering of the resonance frequencies of the QMBs because of the reversible incorporation of the VOCs into the host compound is termed “sensor response” $\Delta\nu$. That the inclusion of the VOCs into the coatings occurs into the volume and is not merely a surface adsorption phenomenon follows from the observation that doubling the thickness of a coating yields twice the sensor response.

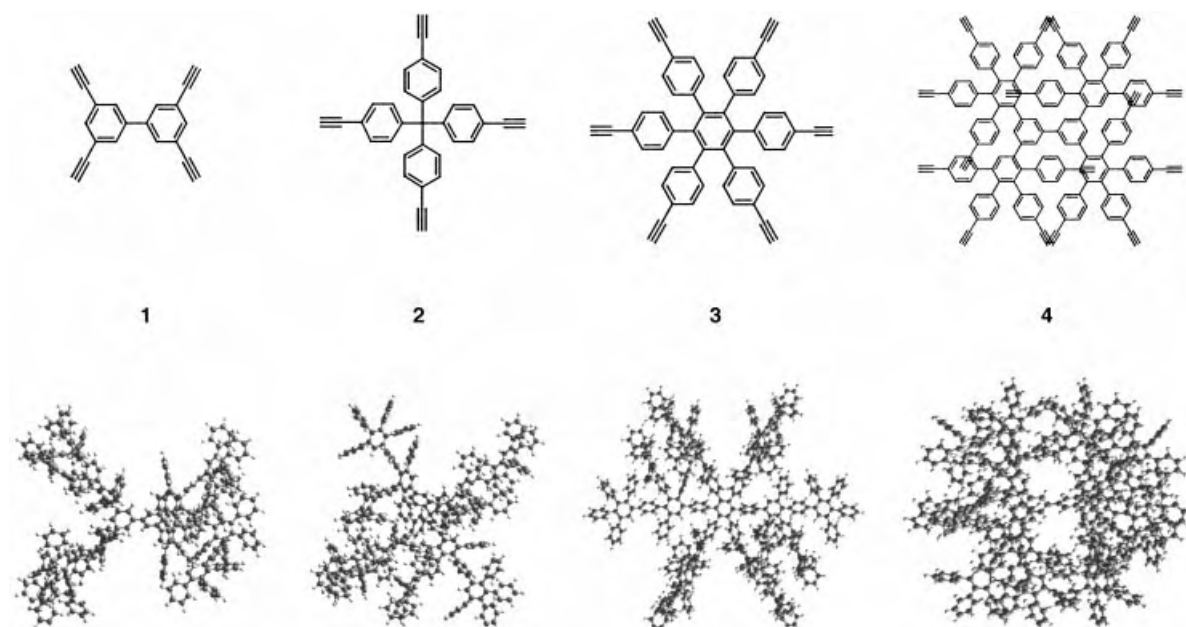


Figure 1. Various core units and resulting dendrimers. Tetraethynyl biphenyl (**1**; Biph), tetraethynyl tetraphenylmethane (**2**; Td), hexaethynyl hexaphenylbenzene (**3**; HPB) and the G1 dendrimer **4** with 16 ethynyl functions based upon the biphenyl core **1**.

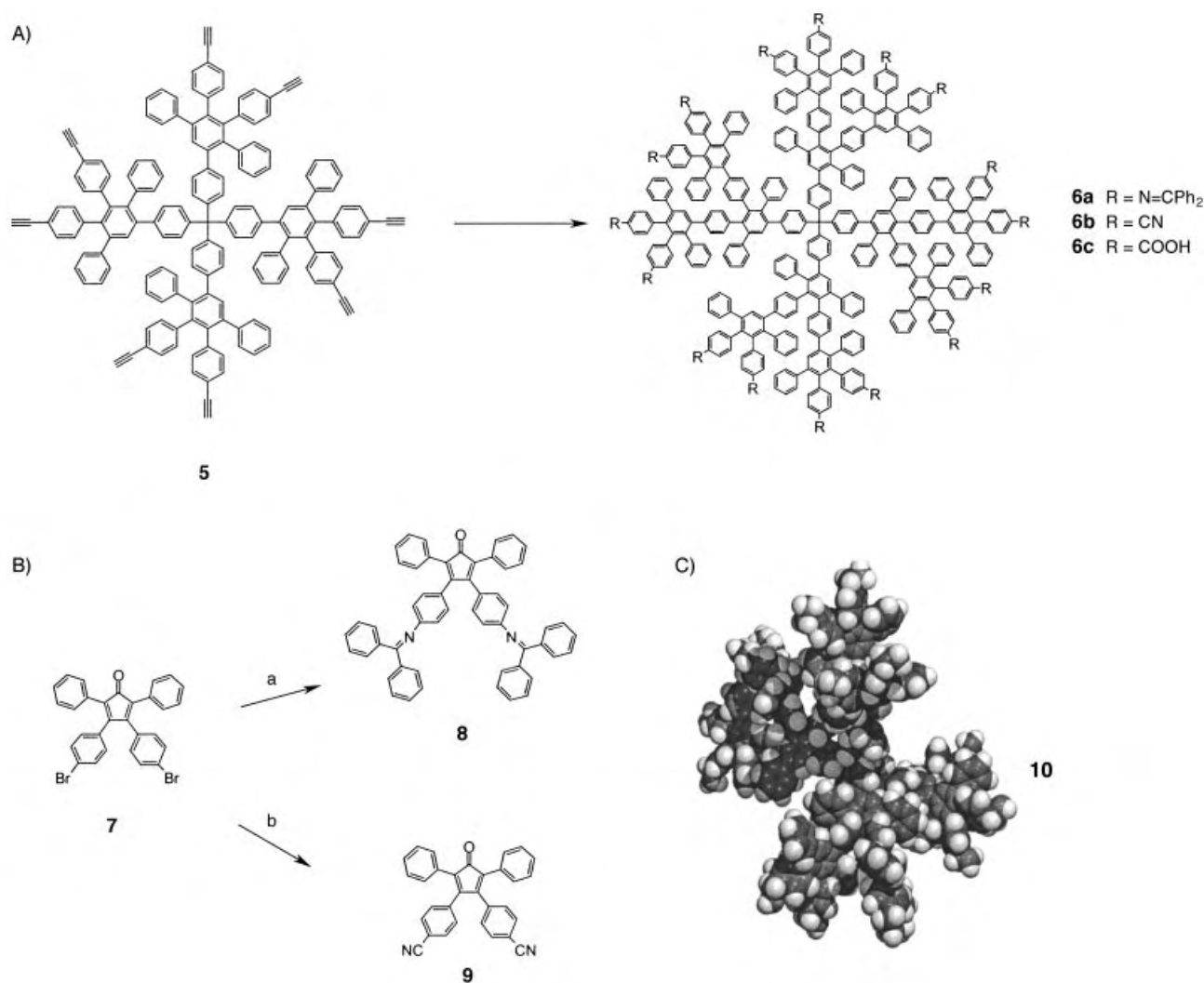


Figure 2. A) Functionalization of G2 PDs **6a–c** (Td-G2-(imine)₁₆, Td-G2-(CN)₁₆, and Td-G2-(COOH)₁₆), by Diels–Alder reaction of a G1 dendrimer **5**, which has eight ethynyl substituents, with functionalized cyclopentadienones. B) Syntheses of functionalized cyclopentadienones: **8** and **9** a) NH=CPh₂ (10 equiv), BINAP (12%), CsCO₃ (15 equiv), [Pd(dba)₂] (5 mol %), toluene, 3 days, 80 °C, 86 %; b) CuCN (2.5 equiv), DMF, 90 %; BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, dba = dibenzylideneacetone C) 3D structure of a G2 PD (Td-G2-(NH₂)₁₆) **10** based upon the tetrahedral core **2** and with surface amine functions.

The first series of measurements was conducted using unsubstituted PDs of G2 derived from the four core units as outlined in Figure 1. All the investigated dendrimers show a similar behavior: all compounds react very selectively to polar aromatic VOCs, such as acetophenone, anilin, benzaldehyde, benzonitrile, fluorobenzene, nitrobenzene, and 2-methyl-benzonitrile. It is remarkable that neither chlorinated nor unsubstituted aliphatic hydrocarbons, alcohols, amines, aldehydes, or carbonyl compounds become included into these hosts; therefore, members of this list of VOCs cannot be monitored with dendrimer coatings of the type studied here. However, this observation shows that PDs are very selective host molecules (Figure 3). The sensor responses are totally reversible and reproducible: after 4 min (adsorption plus desorption time) these sensors are ready for the next measurement. The response times are very short; *t*₉₀-times (=the time until 90% of the response is reached) below 2 min have been measured. A comparison of the data obtained using three different QMBs coated with the same

dendrimer yielded practically identical results (deviations below 5 %).

The observed selectivity of PDs is attributed to their exclusively aromatic skeleton, which may form $\pi\pi$ -electron-donor-acceptor complexes.^[16] Therefore, this type of dendrimer shows a relatively weak affinity for benzene and toluene (cf. Figure 3), since the π -electron densities of these guests are virtually identical to that of the host molecule.

The host–guest interaction between the dendrimers **1–4** and the guest molecule acetophenone was investigated. The concentration of the analyte acetophenone was altered between 5, 10, 25, 50, 75, 100, 200, 300, and 400 ppm, at each of five different temperatures (50, 55, 60, 65, 70 °C). The plot of the resulting frequency shifts of the correspondingly coated QMBs for any of these temperatures against the concentration of the acetophenone yields isotherms (Figure 4), termed “sensor characteristics”. At low concentrations they resemble the analogous Langmuir isotherms, whereas at higher concentrations they reach a linear domain. From the curvature

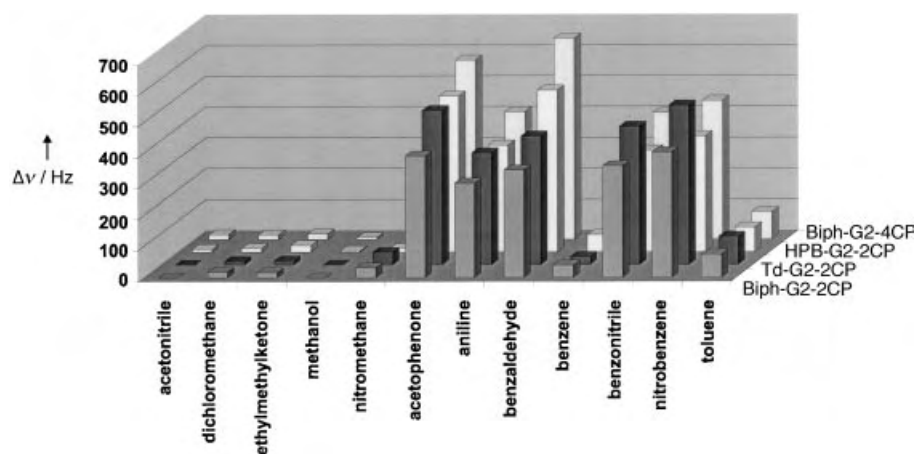


Figure 3. A selection of sensor responses of the unsubstituted G2 PDs to various volatile organic compounds (VOCs); measurement temperature = 50 °C, concentration = 1000 ppm (0.1 %). The nomenclature of the dendrimers follows from: 1) the core (Biph, Td, HPB, see Figure 1); 2) the generation; 3) the end group. 2Cp corresponds to the cyclopentadienone building-unit 3,4-bis-[4-(tri-*iso*-propylsilyl-ethyl)phenyl]-2,5-diphenylcyclopenta-2,4-dienone (AB₂-building unit) and 4Cp corresponds to 2,3,4,5-tetrakis-[4-(tri-*iso*-propylsilyl-ethyl)phenyl]-2,5-diphenylcyclopenta-2,4-dienone (AB₄-building unit) leading to a higher number of phenyl rings. Both building-units are already known.^[12]

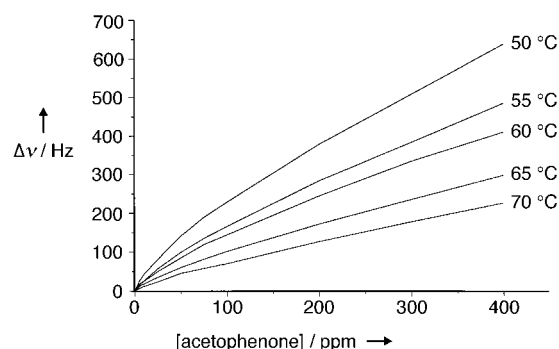


Figure 4. Plot of the sensor response $\Delta\nu$ of Td-G2-2CP to different concentrations of acetophenone at various temperatures (sensor characteristics).

parameter of the Langmuir component the host–guest interaction can be determined using Equation (1) where b = Parameter of curvature of the Langmuir isotherm, k_A = rate constant of adsorption, k_D = rate constant desorption, E_B = binding energy, k_B = Boltzmann constant ($1.381 \times 10^{-23} \text{ J K}^{-1}$), T = temperature.^[17]

$$b(T) = \frac{k_A}{k_D} \propto e^{\frac{E_B}{k_B T}} \quad (1)$$

The interaction energy for the four unsubstituted PDs of the G2 **1–4** (Figure 1) and acetophenone as the analyte gas lies between 13.4 and 21.3 kJ mol^{−1}. From Table 1 it can be concluded qualitatively that the identity of the specific

Table 1. Energy of interaction E between the PDs with acetophenone as the guest.

Host compound	E [kJ mol ^{−1}]	Number of phenyl rings
Biph-G2-2CP ^[a]	19.1	62
Biph-G2-4CP ^[a]	21.3	102
Td-G2-2CP ^[a]	13.4	64
HPB-G2-2CP ^[a]	14.4	97

[a] unsubstituted.

dendrimer used significantly influences the energy of the host–guest interaction with the analyte. Since the outer diameter of all four dendrimers is almost the same (about 4 nm), and since the different binding energies do not correlate with the number of the phenyl rings, the four dendrimers must contain voids of individual size or shape, into which the guests become incorporated by physisorption.

Next, the selectivity of the sensors has been analyzed as a function of the generation of the dendrimers. For this purpose members of the G3, G3, and G4 dendrimers have been used. Thereby it has to be considered that at constant thickness of sensor layer with the increasing size (or generation) of the dendrimers the number of the host molecules is cut in half

whenever the molecular weight of the dendrimer is doubled. However, whenever the size of the dendrimer is doubled, twice as many guest can be incorporated.^[18] Table 2 outlines the obtained results for acetophenone as the guest molecule (1000 ppm).

Table 2. Influence of the generation n (and thus diameter d) of the PDs on the inclusion of gaseous acetophenone (1000 ppm) and thus on $\Delta\nu$.

n	M [g mol ^{−1}]	d [nm]	$\Delta\nu$ [Hz]	Number of guest molecules ^[18]
2	4868	3.8	498	1.31×10^{15}
3	9544	5.1	835	2.21×10^{15}
4	20072	6.4	2175	5.75×10^{15}

Accordingly, PDs are capable of incorporating polar aromatic guest molecules very selectively into their voids, whereby the number of the included guest molecules depends upon their size and shape. To determine the significance of various factors for the sensor characteristic of the dendrimers in more detail, the influence of terminal substituents on the inclusion properties was investigated. It was found that the PDs of G2 **6a–c** (cf. Figure 2), namely those based upon the tetrahedral core, each carrying 16 cyano-, carboxyl-, or imino-substituents, respectively, yield the sensor responses outlined in Figure 5. Depending on the substituent, either an enhancement or an attenuation of the binding affinity has been found using acetophenone, benzaldehyde, or 1-methyl-2-pyrrolidine (NMP) as guests. Thereby, both the electron densities of the host as well as of the guests change, as do the possibilities for adsorption. In this fashion, even nonpolar, aromatic solvents such as benzene or toluene can be detected. Remarkable is the behavior of the acid-determined dendrimer **6c**, which—for the first time—shows a striking affinity for inclusion of guest molecules carrying amine substituents (NMP, diethylamine). Therefore, dendrimer **6c** can be used to detect even

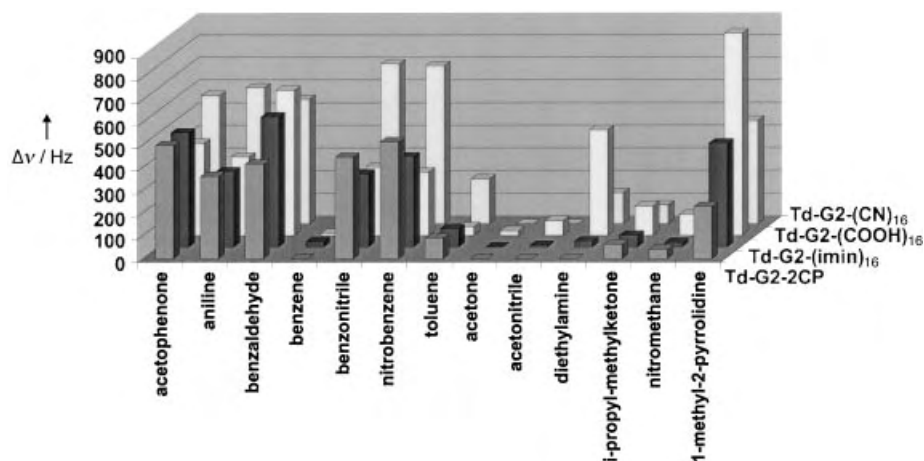


Figure 5. Change of the sensor characteristic upon terminal functionalization of the PDs; concentration of the gaseous guest compounds = 1000 ppm, measurement temperature = 50 °C.

the non-aromatic solvents acetone, acetonitrile, isopropyl methyl ketone, and nitromethane with very good sensitivity.

To demonstrate the uniqueness of these—admittedly difficult to synthesize—monodisperse macromolecules as highly selective sensor layers, series of measurements have also been performed using the hyperbranched polyphenylenes for comparison.^[19, 20] The results show that these compounds yield sensor characteristics similar to those of the PDs, that is, a high selectivity for substituted aromatic solvents. However, by contrast to the dendritic analogues, the sensor responses using the hyperbranched relatives of the PDs are not reproducible, as different measurements using one and the same host yield considerable deviations of up to 80%.^[20] Apparently, this is the consequence of the lack of a defined structure of the hyperbranched polyphenylenes; therefore, any individual coating of the QMBs results in different three-dimensional orientations of the macromolecules on the surface of the QMB electrodes, which gives rise to intrinsically different voids. Similar shortcomings have been observed when using commercially available, aliphatic Starburst-(PA-MAM)-dendrimers.^[20] The poor reproducibility of coatings consisting of the latter is probably because of their lack of structural stability. If namely the end groups of the dendrimers dive back into the interior, this causes a change in the density distribution, upon which the structures collapse.^[21] By contrast, the very rigid molecular framework of the PDs assures a rather narrow variation of the voids in their interior, which in turn guarantees a high degree of reproducibility and hence assures accurate recognition and quantification of the guest molecules.

Accordingly, PDs allow the selective detection with high sensitivity and accuracy of polar aromatic target molecules (=“analytes”). The number of included guest molecules depends both on the structure and the size of the dendrimer and may be predicted, that is, a structure-property relationship applies. Incorporating functional groups enables fine tuning of the sensor properties, which makes it possible to detect even aliphatic solvents. The sensitivity of dendrimer-coated QMB sensors is remarkably high: for aniline and acetophenone it is around 5 ppm. In addition, the PDs are very stable both chemically and temperature-wise, which

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Gold Nanoparticles with Covalently Attached Polymer Chains**

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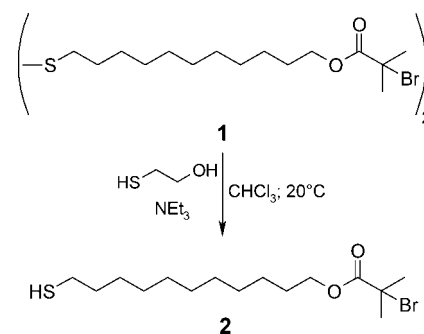
Over recent years thiol-stabilized gold nanoparticles (Au-NPs) have attracted increasing interest^[1] because of their potential in divergent fields such as nanoelectronics and -optics as well as DNA diagnostics.^[2]

Alkanethiolate-stabilized Au-NPs of narrow size distribution are easy to synthesize and of relatively high stability.^[3] The shell of these organic–inorganic hybrid materials can be functionalized by site-exchange reactions thus allowing the controlled change of the properties of the particles and the adjustment of the surface for further reactions.^[4]

Au-NPs modified with polymer chains covalently bound to the surface by a “grafting from” reaction have been described in only two examples.^[5] “Grafting from” by the use of the so-called “living”/controlled radical polymerization in accord with the mechanism of atom transfer radical polymerization (ATRP), which was first described in 1995,^[6] is promising but has not been applied to Au-NPs yet. It has, however, been shown that ATRP is a suitable method for preparing polymer layers covalently bound to the surface of different solid materials and even for the generation of block copolymer grafts.^[7]

A polymer shell is interesting for the control of surface properties, for an increase in chemical and/or thermal stability, and, if functional monomers are used, for the provision of functional groups in the bound polymer chains for further modification. Herein we show that ATRP grafting from polymerization is an efficient synthetic route to attach polymer chains covalently to nanoparticles.

The C₁₂S residues on dodecanethiol-stabilized Au-NPs are replaced by the thiol **2** by means of site-exchange reactions. Compound **2** is synthesized starting from the known compound **1**^[7d] (Scheme 1) by cleavage of the disulfide bond. Compound **2** contains a thiol group, which serves as an anchor to bind **2** to the surface of the Au-NPs, and a α -bromoester moiety, which is suitable as an initiator group for the ATRP Polymerization. Thus the site-exchange reaction leads to Au-NPs functionalized on the surface with initiator moieties for a “living”/controlled radical polymerization. The ratio of **2** to surface-bound dodecanethiol can be varied within narrow ranges and be confirmed by ¹H NMR spectroscopy. In



Scheme 1. Synthesis of thiol initiator **2**. This molecule can be attached to a gold surface by the thiol functionality and contains a α -bromoester moiety as an initiator unit for ATRP polymerization.

combination with thermogravimetric analysis (TGA) measurements the number of initiator groups per mg Au-NP can be calculated, which allows the preselection of a defined initiator/catalyst ratio for the polymerization.

ATRP polymerization starting from initiator-modified Au-NPs was carried out with Cu^IBr/Me₆tren (Me₆tren = tris(2-dimethylaminoethyl)amine) (Figure 1). This catalytic system



Figure 1. Generation of a polymer shell around the Au-NPs; *n*BuA = *n*-butylacrylate.

allows the polymerization of *n*-butylacrylate at room temperature.^[8] Dynamic processes at the surface such as desorption of initiator molecules or thermal initiation of the monomer are suppressed to a large extent under these reaction conditions. The organic part of this new organic–inorganic hybrid can be as much as 90 % w/w (TGA) after the polymerization. The ¹H NMR spectrum and glass transition temperature of the surface-bound polymer chains (determined by dynamic difference calorimetry) are almost identical with those obtained from investigations on free poly(*n*-butylacrylate).

Transmission electron microscopy (TEM) investigations reveal that the Au-NPs are still individual particles after the graft polymerization (Figure 2). The size distribution of the Au-NPs is unaffected by the grafting process; the average diameter is about 2 nm.

The high energy impact during TEM measurements almost completely destroys the attached polymer. However, scanning force microscopy (SFM) investigations convincingly demonstrate the successful grafting of the Au-NPs (Figure 3). The gold cores are depicted by the white protrusions in the SFM images; the polymer chains are shown in gray. Figures 3a

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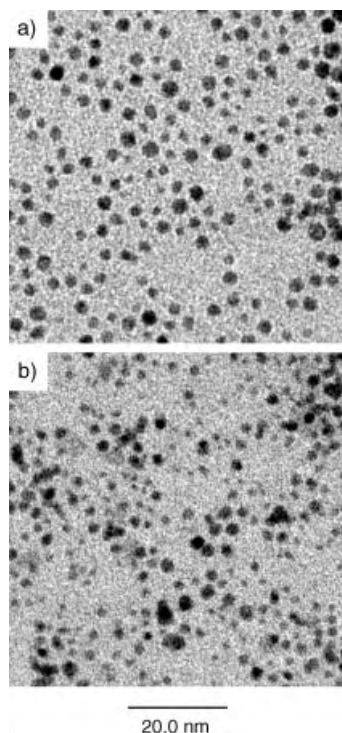


Figure 2. TEM images of a) dodecanethiol-stabilized, and b) polymer-coated Au-NPs.

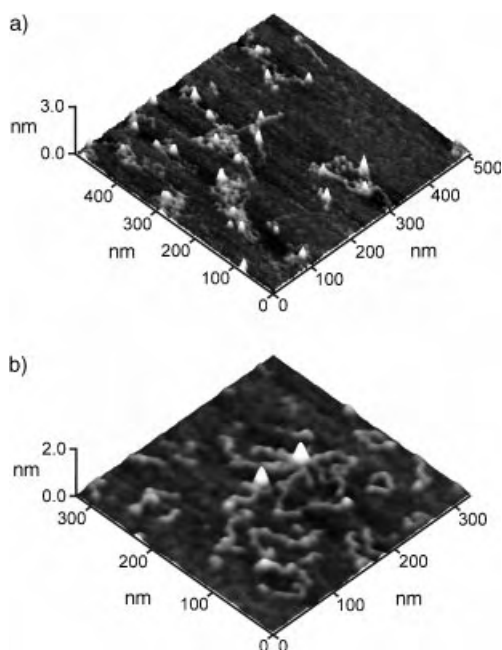


Figure 3. SFM images of Au-NPs with tethered polymer chains spin-casted onto mica from a) CHCl_3 , and b) THF solution.

and b clearly demonstrate that the polymer chains are bound to the gold cores, which confirms the success of the ATRP grafting-from polymerization. Figure 3b also shows that different numbers of chains of varying lengths are attached to the Au-NP and that even unbound chains are present.

The different number of chains on the surface may be the result of the statistical site-exchange reaction of dodecane-

thiol against compound **2**, but may also be caused by the size distribution of the Au-NP itself. This finding from the SFM investigation is in good agreement with GPC results (Figure 4). The polymer-grafted Au-NPs give a relatively broad distribution (chromatogram A, polydispersity index (PDI) = 1.63) compared to that for the cleaved polymer (chromatogram B, PDI = 1.25), showing that the single polymer chains

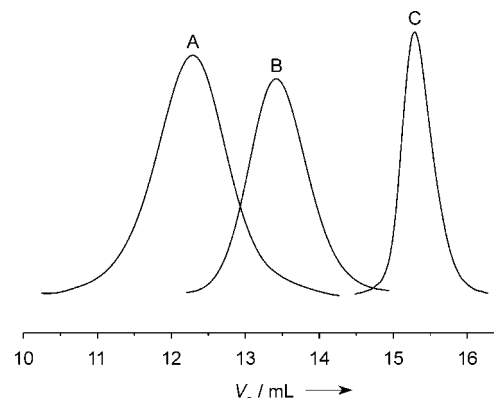


Figure 4. GPC chromatograms of A) polymer-grafted Au-NP ($\bar{M}_n = 206\,000 \text{ g mol}^{-1}$, PDI = 1.63), B) cleaved polymer ($\bar{M}_n = 75\,000 \text{ g mol}^{-1}$, PDI = 1.25), and C) dodecanethiol-stabilized Au-NPs ($\bar{M}_n = 4700 \text{ g mol}^{-1}$, PDI = 1.14); molecular mass relative to polystyrene standard; V_e = elution volume.

undergo controlled growth also on the surface. The monomodal distribution of trace A can be regarded as proof for the interpretation that the “free” polymer chains in Figure 3b are a result of the spin-casting process during the preparation of the SFM probes.

The GPC traces can be compared only qualitatively, since although calibrations were carried out with a polystyrene standard, the chemical structure of the materials is different. However, the polymer-grafted Au-NPs (chromatogram A) show a much shorter elution time than the dodecanethiol-stabilized Au-NPs (chromatogram C) and the detached polymer chains (chromatogram B). This is due to an increase of the hydrodynamic radii and of the molecular weight as a result of the grafting reaction. From the molecular weights one can estimate an average degree of grafting of three polymer chains per gold core, which is in full agreement with the results of SFM investigations (see Figure 3).

We have shown that Au-NPs can be grafted with polymer chains by the ATRP mechanism in a simple sequence of reactions. No free polymer chains are formed during the grafting reaction and the Au-NPs remain unchanged in size and size distribution.

Experimental Section

Dodecanethiol-protected gold colloids were prepared according to the method in reference [3]. The synthesis was carried out at room temperature with a threefold molar excess of dodecanethiol to tetrachloroauric acid. Compound **1** was synthesized according to the method in reference [7d].

2: Thioethanol (12 mL, 0.14 mol) and triethylamine (0.6 mL, 4.3 mmol) were added to a solution of **1** (1.69 g, 2.4 mmol) in degassed chloroform (40 mL). After stirring overnight at room temperature the solution was extracted repeatedly with water, dried over sodium sulfate, concentrated in

vacuo, and filtered over silica gel with petroleum ether/ethyl acetate (20:1 v/v) to give **2** as a colorless liquid; yield: 1.02 g (2.9 mmol, 60%). ¹H NMR (CDCl₃, 400 MHz): δ = 4.17 (t, *J* = 7 Hz, 2H; OCOCH₂), 2.52 (q, *J* = 7 Hz, 2H; HSCCH₂), 1.94 (s, 6H; CH₃), 1.70–1.57 (m, 4H; CH₂), 1.40–1.24 (m, 14H; CH₂); ¹³C NMR (CDCl₃, APT, 100 MHz): δ = 171.72, 66.12, 55.99, 34.01, 30.78, 29.43, 29.42, 29.41, 29.12, 29.03, 28.34, 28.32, 25.75, 24.62; MS: *m/z* (%): 354 (2) [*M*⁺], 87 (100).

Site-exchange process: C₁₂ colloid (385 mg) and thiol initiator **2** (69 mg, 0.2 mmol) were dissolved in toluene (190 mL) and stirred for 24 h at room temperature. The solution was evaporated to dryness in vacuo and the crude product intensively washed with ethanol to give initiator-functionalized Au-NPs (390 mg).

Tris(2-dimethylaminoethyl)amine (Me₆Tren) was synthesized according to the method given in reference [9].

ATR polymerization and cleavage of the grafted polymer chains: Initiator-functionalized Au-NPs (66 mg) were dissolved in toluene (1 mL) and *n*-butylacrylate (2 mL, 14.0 mmol), and CuBr (3.8 mg, 26 μmol) and Me₆Tren (7.0 mg, 30 μmol) were dissolved in *n*-butylacrylate (3 mL, 20.9 mmol). Both solutions were degassed with argon and combined. After the mixture had been stirred for 24 h at room temperature, the product precipitated in methanol, yielding a dark brown, viscous substance. The supernatant liquid was decanted, the residue was repeatedly washed with methanol and dried in vacuo to give the product (527 mg). The polymer-coated Au-NPs (38 mg) were dissolved in toluene (20 mL), and *n*-butanol (2 mL) and *p*-toluenesulfonic acid (20 mg) were added. Heating overnight under reflux, filtration over silica gel, and drying in vacuo gave the cleaved polymer.

TEM images were recorded on a Philips CM-300 microscope working at 300 kV. SFM measurements were performed on a Digital Instruments Multimode SPM with a Nanoscope IIIa controller in the tapping mode. The resonance frequency dependent on the Si-cantilever (*K* ≈ 42 N m⁻¹, Nanosensors) was set to about 330 kHz. Samples were prepared by spin casting of a dilute CHCl₃ or THF solution with a concentration of 0.01 mg mL⁻¹ at 2000 rpm on mica as a substrate. GP chromatograms were recorded on a Spectra-Physics SP 8100 (polystyrene calibration). Thermogravimetric measurements were carried out on a Netzsch TG 209.

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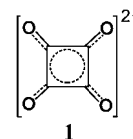
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Solvothermal Synthesis of a 24-Nuclear, Cube-Shaped Squarato-oxovanadium(IV) Framework: [N(*n*Bu)₄]₈[V₂₄O₂₄(C₄O₄)₁₂(OCH₃)₃₂]

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Polyoxometalates with organic oxygen donor groups show an impressive structural and electronic diversity. As a result, extensive synthetic research has been carried out in this field in the past few years, with the aim of synthesizing compounds with interesting magnetic or catalytic properties,^[1] as well as precursors for metal oxides of high purity.^[2] Notable successes were achieved in synthesizing polyoxo-alkoxo-metalates with chelating trisalkoxy ligands.^[3] Polyoxometalate fragments that are otherwise usually unstable can be stabilized by using suitable, highly symmetrical polydentate coligands such as oxalate and squarate. The high symmetry of the bis-bidentate squarato group **1**, as well as the suitable spacing of the four oxygen donor atoms favors the interconnection of small polyoxo-alkoxo-vanadate units to highly symmetric supermolecular polyoxometalate derivatives. Until now, surprisingly few squarato-oxovanadium compounds have been structurally characterized. In the anions [V₂O₂(C₄O₄)₂(OH)(H₂O)₃]⁴⁻,^[4,5] [V₂O₃(C₄O₄)₂(H₂O)₃]⁵⁻,^[5] [V₂O₂(C₄O₄)₂F₄]⁴⁻,^[4] [V₃O₃(C₄O₄)₃F₄]⁴⁻,^[6] and [V₄O₆(C₄O₄)₅(H₂O)₄]⁴⁻,^[5] the squarato group is a μ₂-bridging ligand; only in the polymeric compounds ∞[V(OH)(C₄O₄)] and ∞[V(OH)(C₄O₄)(H₂O)],^[7] is the squarato ligand found to be μ₃- and μ₄-bridging, respectively.^[7] Herein, we report the solvothermal synthesis and structure of the cube-shaped 24-nuclear oxo-alkoxo-squarato complex [N(*n*Bu)₄]₈[V₂₄O₂₄(C₄O₄)₁₂(OCH₃)₃₂] (**2**) (Figure 1), which is an astonishing example of a compound with μ₄-bridged oxo-alkoxo-vanadium fragments.



Vanadium(V) oxytrihaloxides prove to be auspicious starting materials for the synthesis of new polyoxometalates.^[8] In

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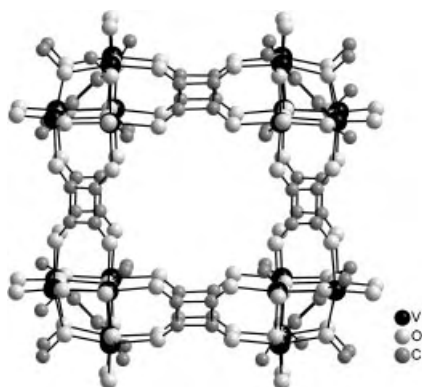


Figure 1. Structure of the cubic anion in **2** viewed on one of the cubic faces.

the course of dissolving vanadium(v)oxytri-(*tert*-butoxide), $\text{VO}(\text{OtBu})_3$, in methanol, an almost complete exchange of the OtBu groups for the methoxy groups in the solvent takes place. The resulting solution contains oligomeric fragments cut out of the infinite chains of solid vanadium(v) oxytrimethoxide $[\text{VO}(\text{OMe})_3]^{[8,9]}$. Solvothermal conditions and the presence of a stoichiometric amount of squaric acid and tetra-*n*-butylammonium hydroxide reduce V^{V} to V^{IV} in these solutions; excess methanol functions as the main reducing agent. This resulted in the formation of **2**, which was characterized by X-ray structure analysis.^[10]

The cube-shaped framework of **2** is made up of eight $\{(\text{VO})_3(\text{OMe})_4\text{O}_6\}$ subunits at its corners. Each of these trinuclear units is built up of three edge-sharing, distorted VO_6 octahedra with one corner oxygen atom in common (Figures 2 and 3). This structural unit can be considered an incomplete, distorted heterocubane unit, in which one of the vanadium positions remains unoccupied. A comparable arrangement of atoms occurs in the isolated anion $[\text{V}_3\text{O}_3(\text{C}_4\text{O}_4)_3\text{F}_4]^{4-}$;^[6] however, it contains fluoro ligands instead of methoxy groups.

The edge-sharing oxygen atoms in this trinuclear component come from three μ_2 - and one μ_3 -bridging methoxy groups. The $\{\text{VO}_6\}$ coordination sphere is completed by a terminal oxo group located *trans* to the triply bridging methoxy group and two oxygen atoms of one squarato ligand perpendicular to the

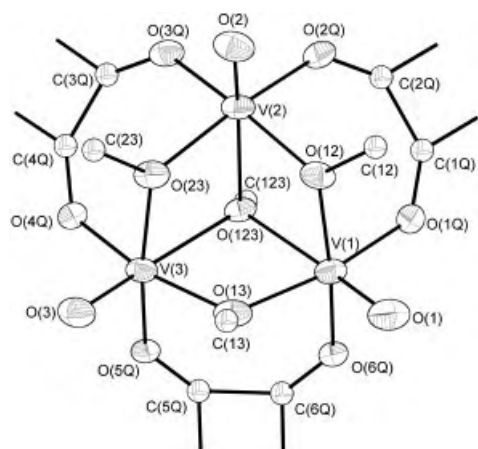


Figure 2. Section of the structure of **2** with selected bond lengths [Å]: V(1)-O(1) 1.604(5), V(1)-O(12) 1.974(4), V(1)-O(123) 2.220(4), V(1)-O(1Q) 2.019(4).

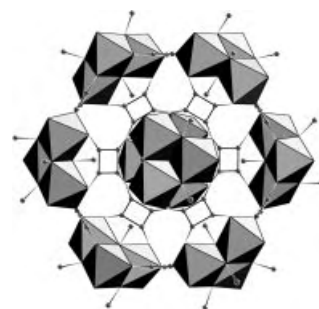


Figure 3. Polyhedral representation of the anion structure, $[\text{V}_{24}\text{O}_{24}(\text{C}_4\text{O}_4)_{12}(\text{OCH}_3)_{32}]^{8-}$, viewed along the space diagonal of the cube.

quadrangular arrangement of the $\text{V}_2(\text{OMe})_2$ groups. Eight $\{(\text{VO})_3(\text{OMe})_4\}$ subunits are connected by twelve μ_4 -bridging squarato ligands to form edges of the cube (Figures 1 and 3).

The eight μ_3 -bridging methoxy groups point towards the center of the cube, whereas the 24 μ_2 -methoxy groups face outwards. The tetra-*n*-butylammonium cations form unexpectedly close contacts with the anions. Six of the eight cations are located on top of the cube faces such that one of their butyl groups always protrudes into the hydrophobic cavity inside the anion (Figure 4). Thus, the anion and the six tetra-*n*-butylammonium cations accumulate to a twofold negatively

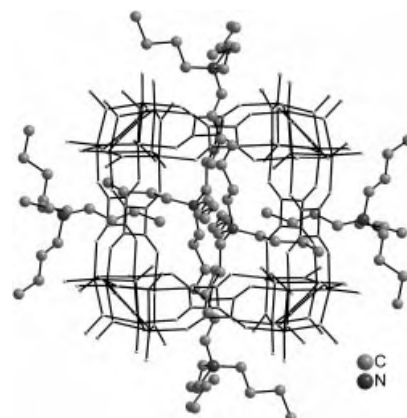


Figure 4. Cation-anion network in the structural unit $\{[\text{N}(\text{nBu})_4]_6[\text{V}_{24}\text{O}_{24}(\text{C}_4\text{O}_4)_{12}(\text{OCH}_3)_{32}]\}^{2-}$.

charged array, $\{[\text{N}(\text{nBu})_4]_6[\text{V}_{24}\text{O}_{24}(\text{C}_4\text{O}_4)_{12}(\text{OCH}_3)_{32}]\}^{2-}$, in which the vanadium-oxygen framework is completely surrounded by a hydrophobic shell that consists of 24 methyl and 18 *n*-butyl groups (outside) as well as eight methyl groups and six *n*-butyl groups (inside). The two remaining tetra-*n*-butylammonium cations and the huge anion are arranged to form a bulky ionic framework in which weakly bound solvent molecules are incorporated. Crystals lose the enclosed methanol even at low temperatures. For this reason, the number and positions of the remaining disordered methanol molecules could not be determined with a high degree of accuracy.^[10]

By replacing the tetra-*n*-butylammonium hydroxide in the synthesis with an equivalent amount of an alkali metal hydroxide or ammonia, it is possible to synthesize other salts with the anion, $[\text{V}_{24}\text{O}_{24}(\text{C}_4\text{O}_4)_{12}(\text{OCH}_3)_{32}]^{8-}$. The formation of this anion can be verified with aid of IR spectroscopy, because

the cation exchange implies almost no change in the range of the O–C(H₃) and V–O vibrations. For the potassium salt K₈[V₂₄O₂₄(C₄O₄)₁₂(OCH₃)₃₂] (**3**), the cubic structure of the anion, analogous to that of **2**, was determined by difference-Fourier analysis, whereas the potassium cations coordinated by methanol molecules as well as free solvent molecules in the crystal lattice were disordered and could not be clearly localized by crystal-structure analysis.^[11] Exchanging the cations led to a change in the environment of the anion, which led to significant differences in the cation–anion interactions. Because of the ion-pair formation with tetra-*n*-butylammonium, a low charge formed, which is more likely a hydrophobic anion to be protected by the *n*-butyl groups. In the case of the potassium cation, the anion is highly charged, and balanced by the solvated potassium cations. This inevitably leads to compounds with different solubility behavior. Furthermore, the composition of the vanadium–oxygen compounds obtained by thermal decomposition can be controlled by the choice of cation. It is also advantageous that the squarato and methoxy ligands can be removed easily with a simultaneous reduction of the vanadium.

Experimental Section

A 0.2 M solution of VO(O^tBu)₃ (23 mL, 4.6 mmol) in methanol (Merck p.a.), H₂C₄O₄ (0.27 g, 2.4 mmol) and a 0.8 M solution of tetra-*n*-butylammonium hydroxide (2 mL, 1.6 mmol) in methanol (Fluka) were heated for 24 h at 125 °C in a 50 mL Teflon-lined autoclave (Berghof). After the autoclave was cooled to room temperature, the content was left to stand for one day at –30 °C to complete crystallization. The extremely temperature-sensitive, green crystals of **2** · *x* MeOH were filtered in an argon atmosphere at room temperature, washed with methanol, and dried under vacuum for a complete removal of the weakly bound methanol. Yield (based on the solvent-free compound): 0.71 g (0.12 mmol), 63%. Elemental analysis calcd (% based on the solvent-free compound) for C₂₀₈H₃₈₄N₈O₁₀₄V₂₄ (*M* = 5883.90 g mol^{–1}): C 42.5, H 6.58, N 1.90; found: C 42.8, H 6.64, N 1.97; IR (KBr, 400–1600 cm^{–1}): $\tilde{\nu}$ = 424 (s), 464 (m) 573 (m), 967 (s), 976 (s) 1033 (s), 1069 (m), 1098 (w), 1446 (s), 1471 (s), 1523 cm^{–1} (vs, br).

3: The synthesis of the potassium salt was analogous to that of the compound **2**, with a stoichiometric amount of potassium hydroxide instead of tetra-*n*-butylammonium hydroxide. Green crystals were isolated by filtering immediately after cooling the autoclave to room temperature. Yield (based on the solvent free compound): 0.36 g (0.084 mmol), 41%. Elemental analysis calcd (% based on the solvent free compound) for K₈C₈₀H₉₆O₁₀₄V₂₄ (*M* = 4256.9 g mol^{–1}): C 22.6, H 2.27; found: C 21.5, H 2.32; IR (KBr, 400–1600 cm^{–1}): $\tilde{\nu}$ = 427 (s), 471 (m) 576 (m), 959 (s, br), 1013 (s, br), 1058 (m), 1099 (w), 1443 (s), 1483 (vs), 1521 cm^{–1} (vs, br).

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empirical absorption correction using symmetry-equivalent reflections (SADABS, Area-Detector-Absorption Correction, Siemens Industrial Automation Inc., Madison, WI, **1996**); the structures were solved by direct methods; the initial structures were refined against *F*² (Bruker-SHELXTL, version 5.1, **1998**). The hydrogen atoms were calculated in geometrically idealized positions. Crystal size 0.40 × 0.38 × 0.24 mm, *T* = 133 K, triclinic, space group *P*1̄, *a* = 20.277(2), *b* = 20.605(2), *c* = 20.631(2) Å, α = 115.07(1), β = 94.39(1), γ = 91.88(1)°, *V* = 7764.0(15) Å³, *Z* = 2, ρ_{calcd} = 1.258 g cm^{–3}, $2\theta_{\text{max}}$ = 47°, 54859 collected reflections, 22361 unique reflections, 1042 parameters, μ = 0.76 mm^{–1}, absorption correction, effective transmission max./min. = 0.7456/0.3775. *R*₁ (*I* > 2 σ (*I*)) = 0.0718, *wR*₂ (*I* > 2 σ (*I*)) = 0.1964, *R*₁ (all data) = 0.1149, *wR*₂ (all data) = 0.2166, largest difference peak and hole +/– = 1.767/0.743 e Å^{–3}. The crystals were picked directly out of the mother liquor under a cold nitrogen stream. Because of the loss of the enclosed solvent methanol even at low temperatures, it was not possible to determine the number and exact positions of the remaining methanol molecules. Therefore, a solvent-free data set was generated with the computer program SQUEEZE (T. Spek, PLATON, **1999**). This data set was used for the crystal structure refinement.^[12]

- [11] Crystal structure analysis of **3** (carried out analogously to details in reference [10]): tetragonal, *P*4/*ncc*, *a* = 26.356(3), *b* = 26.356(3), *c* = 31.290(5) Å, *V* = 21731.6 Å³, *T* = 143 K.^[12]
- [12] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-162386 (**2**) and CCDC-169184 (anion substructure of **3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

1,6-Methano[10]annulene has a Delocalized Structure in S₀ and S₁: High-Resolution Spectroscopy in a Supersonic Jet**

Reinhold Seiler and Bernhard Dick*

Aromatic molecules substantially differ from olefins in terms of their reactivity and spectroscopic properties. A common characteristic and necessary structural element of aromatic molecules is a planar, cyclically conjugated system of 4*n* + 2 π electrons, without bond-length alternation. The Hückel rule predicts that such systems are more stable than theoretical systems with alternating bond lengths.^[1] This rule emerges from a molecular orbital (MO) description of the wavefunction of the π electrons, and has been verified by ab initio calculations for benzene and a number of other polycyclic arenes. For some species, however, calculations on the electron-delocalized structure found it to be a transition state between two electron-localized structures. A noted example of this effect is 1,6-methano[10]annulene (MA): The semiempirical MNDO, AM1, and PM3 methods obtained a localized structure while ab initio calculations at the SCF level with a simple STO-3G basis set favored delocalized

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electrons, yet the use of more extensive basis sets predicts that a localized structure is more stable.^[2] Calculations accounting for correlation effects (CI or density functional theory (DFT)) again found that the delocalized structure is more stable, but the energy difference is only slight.^[2] Evidently, the question of which state is really the lowest depends on the subtle interplay of various factors.

This behavior can be clarified with valence bond theory (VB) if the wavefunction Ψ of an annulene is represented as the weighted superposition of two basis states ψ_1 and ψ_2 with localized electron pairs and alternating bonds [Eq. (1)].

$$\Psi = c_1\psi_1 + c_2\psi_2 \quad (1)$$

Here, both ψ_1 and ψ_2 are exchanged in all formal single and double bonds in the ring perimeter. In the case of benzene, this represents the two Kekule structures. However, a matching pair of mesomeric structures exists for other aromatic rings, as shown in Figure 1 for benzene and MA.

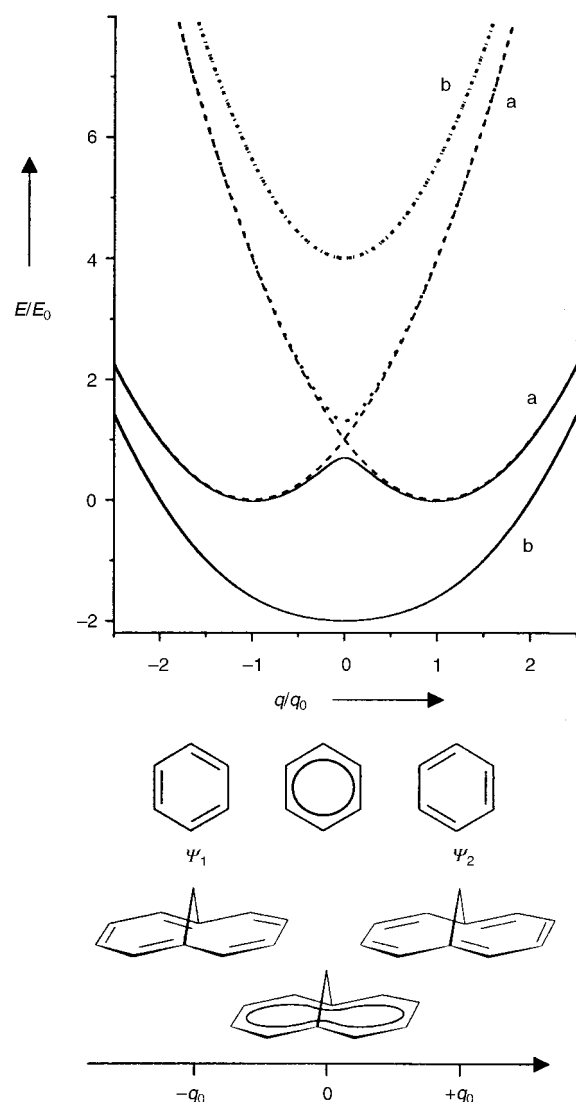


Figure 1. Potential function along the Kekule coordinate for an annulene with a) small and b) large resonance integral V . The curves of the uncoupled VB structures are dashed and those of the excited electronic states are dotted.

The coefficients of the wavefunction and their energy E are obtained from the Schrödinger equation [Eq. (2)], where H_1 and H_2 are the energy expectation values of the basis states and V is the resonance integral.

$$\begin{pmatrix} H_1 & V \\ V & H_2 \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} = E \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} \quad (2)$$

These energy expectation values naturally depend on the electronic structure of the molecule; H_1 minimizes at one Kekule structure, H_2 at the other. Along the coordinate q , in which the transition between the two Kekule structures is represented, the energies increase quadratically with the harmonic approximation [Eq. (3) and (4)], where q_0 and $-q_0$ represent the electron-localized Kekule structures.

$$H_1 = E_0(q/q_0 + 1)^2 \quad (3)$$

$$H_2 = E_0(q/q_0 - 1)^2 \quad (4)$$

The two parabolas intersect at the point of the delocalized structure, $q = 0$ (see the dashed curves in Figure 1). The nonvanishing resonance integral lifts the energetic degeneracy at $q = 0$. Two new potential functions thereby develop, which may be assigned to the electronic ground and excited state. The shape of the potential function for the ground state depends on the magnitude of the resonance integral. At $V < E_0$ this potential has two minima for the localized structures, but only one minimum at the delocalized structure for $V = E_0$. Both cases are illustrated in Figure 1 as curves (a) and (b) (for each case the solid line represents the ground state and the dashed curve the excited state). It is thus conceivable that molecules, which formally obey the Hückel rule, actually have a localized ground state. A double-minimum potential is in fact found for some homoaromatic systems, such as semi-bullvalene.^[3]

In arenes, $V > 0$ because both VB wavefunctions have an uneven number of electron pairs.^[4] The wavefunction Ψ_u of the excited state corresponds in this case to the antisymmetric linear combination, which, in the case of MA (space group C_{2v}), belongs to the irreducible representation B_1 . This state is in turn equivalent to the L_b state of MO theory. The electronic transition from the ground state is polarized along the long molecular axis. Of note, the VB model predicts that the excited electronic state should be always delocalized, and indeed with simple basis sets or semiempirical methods one finds that the first excited electronic state for MA is such a delocalized B_1 state. If the ground state is likewise delocalized, then the VB model predicts that the vibrational frequency, which belongs to the normal coordinate q (the Kekule mode), should be low in the ground state but very high in the excited state.

Recently, the symmetry of the electronic ground state of MA was investigated by IR and Raman spectroscopic measurements.^[5] Because of the good agreement of the measured frequencies and intensities with highly detailed ab initio calculations (DF/B3LYP, 6-31G**), the ground state

of the delocalized structure was assigned C_{2v} symmetry. In this space group, all vibrations are Raman active but those in the a_2 representation are IR inactive. However, no information on their polarization was gained to allow assignment of the vibrations to irreducible representations.

Herein we present measurements of the vibrational structure of the excited electronic state, which confirm the assumption of the delocalized structure of the ground state. If the ground state of MA had an energetic double minimum, then the electronic excitation would necessitate significant electronic structural changes. Following the Franck–Condon principle, the vertical transition should have the greatest intensity and the electronic origin of the absorption band should be only weak. In contrast, when both states have delocalized structures, one expects an intense electronic origin. Explicit evidence requires a spectrum of the excited state, in which the intensities and symmetries of the individual vibrational transitions can be determined. The first electronic transition of MA is, however, intrinsically very weak, a consequence of the pseudoparity selection rule, which is also responsible for the low intensity of the first band of naphthalene.^[6] Hence additional lines may appear in the spectrum which gain their intensity by Herzberg–Teller coupling with higher electronic states. That such vibrationally induced transitions contribute to the spectrum has been concluded already from the fact that the degree of polarization of the transition varies over the bands.^[7] The low resolution of the spectra in solution and organic glasses at low temperatures prevents separation of the vibrational transitions from each other. Measurement of samples in Shpol'skii matrices at 15 K still shows broad zero-phonon lines and even broader phonon sidebands.^[2]

Unambiguous, highly resolved spectra are available from isolated, ultracold MA in a supersonic jet. Such a fluorescence excitation spectrum of the $S_0 \rightarrow S_1$ transition is shown in Figure 2. For these conditions the single vibronic lines show widths of about 1 cm^{-1} , equivalent to a rotational temperature of 2 K. The most intense line is the longest wavelength transition assigned to the electronic origin. Double-resonance measurements show that some weak lines in Figure 2, marked

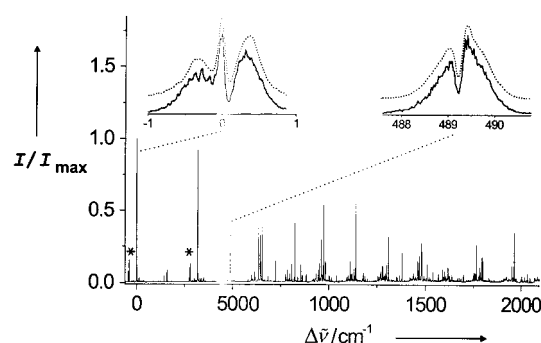


Figure 2. Fluorescence–excitation spectrum of the $S_0 \rightarrow S_1$ transition of MA in a supersonic jet. The rotational envelope of the electronic origin at 25154 cm^{-1} and the vibronic band at 489 cm^{-1} above the origin is enlarged. A comparison with simulated band contours, represented as dotted lines above the experimental bands, unambiguously proves the transition moment which, for the electronic origin, lies along the long axis and for the vibronic band lies along the short axis of the perimeter.

with an asterisk, stem from another species, most probably a van der Waals dimer of MA formed during the jet expansion. The spectrum of MA shows many lines attributable to progressions and combinations of a few fundamental vibrations, these are given in Table 1. The vibrational frequencies

Table 1. Wavenumbers of the vibrations [cm^{-1}] in the irreducible representations a_1 and a_2 for the excited electronic state.

Theory	a_1	Experiment	Theory ^[a]	a_2	Experiment ^[b]
186		159	161		143
354		318	387		350
506		477	539		489
700		643	782		725
720		655	940		856
869		824	967		947
929		884	1133		1142
998		975	1299		1301
1315		1310 ^[c]	1405		1379
1479		1479	1593		1590
1577		1568	1714		1698
1631		1617			
1680		1669			

[a] CAS ab initio calculation (6-31G basis).^[2] [b] This work. [c] This line coincides with the $\Delta n = 2$ transition of the mode at $\nu = 655\text{ cm}^{-1}$.

are in good agreement with the results of the best available ab initio calculations.^[2] The highly resolved measurement gave the rotational structure for each band, two examples of which are shown in Figure 2. From the characteristic structure exhibited by these bands, the electronic origin at 25154 cm^{-1} is shown to be polarized along the long axis of the perimeter. The electronic wavefunction of the excited state belongs therefore to the irreducible representation B_1 of the C_{2v} point group. The excited wavefunction of the VB model described above also belongs to this representation. Likewise the first transition of naphthalene is polarized along the long molecular axis. Vibronic bands with this polarization correspond to totally symmetric vibrations (the irreducible representation a_1). The vibronic band at 489 cm^{-1} is polarized along the short axis and must be assigned to a vibration with a_2 symmetry.

A quantitative analysis of the band shapes yields rotational constants for S_0 and S_1 . The very good agreement with the rotational constants for the ab initio (MP2/6-31G) calculated electronic structure of S_0 is a further indication of a delocalized structure. From these rotational constants the band shapes for the vibronic transitions polarized vertical to the perimeter may be calculated. Bands with this shape, which belong to vibrations of b_1 symmetry, were not observed. This result also supports the assumption of a delocalized structure. If MA had alternating bonds in the ground state, a progression in the Kekule mode with b_1 symmetry must appear. Progressions in only two modes, at wavenumbers 318 and 655 cm^{-1} , were observed. The rotational structure of these lines shows that both modes are totally symmetric. Hence the changes in geometry upon electronic excitation can largely be described with these two coordinates, whereby the molecular symmetry remains unchanged. In all progressions the intensity monotonously decreases with increasing energy. The

electronic origin is the most intense band of the complete spectrum. The structural changes are therefore smaller than the elongation of the classical harmonic oscillator at the zero-point energy, otherwise the intensity would initially increase with increasing quantum number. The electronic ground state also has the same symmetry and almost the identical geometry as the electronic excited state. For the latter, only the delocalized structure is applicable, and hence this structure must also be assigned to the ground state.

Experimental Section

MA was synthesized following the method of Vogel and Roth^[8] and purified by distillation. The ultracold supersonic jet was produced by the expansion of a mixture of MA (1.3 mbar) along with the helium carrier (2 bar) through a pulsed nozzle of 0.5 mm diameter. A dye laser pumped by an excimer laser was used for fluorescence excitation, and a second dye laser/excimer laser pair was used for the double-resonance measurements. The laser bandwidth (FWHM) limited resolution to 0.2 cm^{-1} in the survey spectra; for the measurement of the rotational structures a Fabry–Perot interferometer inside the laser cavity improved the resolution to 0.1 cm^{-1} .

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Silynes ($\text{RC}\equiv\text{SiR}'$) and Disilynes ($\text{RSi}\equiv\text{SiR}'$): Why Are Less Bonds Worth Energetically More?*

David Danovich, François Ogliaro, Miriam Karni, Yitzhak Apeloig,* David L. Cooper,* and Sason Shaik*

Dedicated to Professor Zvi Rappoport on the occasion of his 65th birthday

Since the first isolation in 1981 of stable silaethylene^[1] and disilene^[2] a variety of new compounds containing doubly bonded silicon have been synthesized and their chemistry explored.^[3] The next challenge has become the syntheses of compounds in which silicon has a triple bond.^[4] Until recently $\text{HSi}\equiv\text{N}$ was the only known silicon species with a triple bond, and was prepared by matrix isolation and identified by UV and infrared (IR) spectroscopy.^[5a] Other attempts to isolate $\text{RSi}\equiv\text{N}$ resulted in the isomeric RNSi species.^[5b–g] While the formation of transients of the form $\text{RSi}\equiv\text{SiR}$ ($\text{R} = \text{Me}$ ^[6a] and $\text{Tip}_2\text{C}_6\text{H}_3$,^[6b] ($\text{Tip} = 2,4,6\text{-triisopropylphenyl}$)) was suggested, no conclusive evidence has been presented to support these assignments. Only recently has the existence of stable $\text{FSi}\equiv\text{CH}$ and $\text{ClSi}\equiv\text{CH}$, under gas-phase conditions, been demonstrated.^[7] This successful assignment followed previous theoretical predictions.^[8] The computational studies^[7–9] have shown, however, that $\text{HSi}\equiv\text{CH}$ and $\text{HSi}\equiv\text{SiH}$ possess a *trans*-bent geometry (Figure 1, **1B** and **2B**) in contrast to the linear geometry of acetylene (**3**). Moreover, the linear isomers **1L** and **2L** are not even minima on the potential-energy surface (substituted silynes and disilynes behave likewise^[7, 8, 9d]). *Trans*-bending appears also in analogous $\text{E}\equiv\text{E}$ species ($\text{E} = \text{Ga}, \text{Ge}, \text{Sn}, \text{Pb}$) which are formally triply bonded,^[10] and it seems to be a characteristic feature of multiple bonding in higher-row compounds. The inherent preference for bending raises fundamental questions about the nature of CSi or SiSi bonding.^[11] Is it truly a triple bond such as $\text{C}\equiv\text{C}$? What is the

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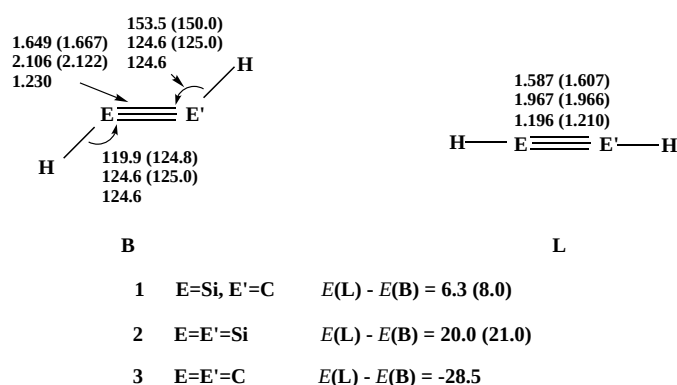


Figure 1. Optimized structures of bent (B) and linear (L) silyne (1), disilyne (2), and acetylene (3). Bond lengths [Å], angles [°] calculated at B3LYP/6-311G* are given in each case in the order 1–3 from top to bottom (CCSD(T)/cc-pVTZ values in parentheses) and the relative energies [kcal mol⁻¹] at the same computational levels.

effect of *trans*-bending on the bond energies? Why do these molecules prefer to be bent while acetylene remains linear?

Herein we address these questions by using valence bond (VB) computations. The VB analysis shows that approximately 2.5 bonds connect the heavy atoms in *trans*-bent HSiCH (1B) and HSiSiH (2B). But these 2.5 bonds are stronger than the triple bonds in linear HSi≡CH (1L) and HSi≡SiH (2L) as a result of a remarkable *strengthening* upon *bending* of the σ(C–Si) and σ(Si–Si) bonds, respectively.

Two complementary VB approaches^[12] were used. The first is the spin coupled (SC) method,^[12a, 13] which utilizes semi-localized atomic orbitals (AOs). As such, the ionic character of the electron-pair bond is embedded in a formally covalent SC wavefunction.^[14, 15] This method provides the indices to quantify the number of bonds in the CSi and SiSi moieties.^[13] The conclusions from the SC method can be compared with other bond indices.^[16] For each of the target molecules, we treated as active the 10 valence electrons, with simultaneous relaxation of the inactive orbitals that accommodate the core electrons.

The second VB approach enables the determination of the in situ π-bond energies.^[17] The essence of the method is illustrated in Figure 2. In the II state, called quasiclassical (QC), the two p_π electrons of the π bond are unpaired (and

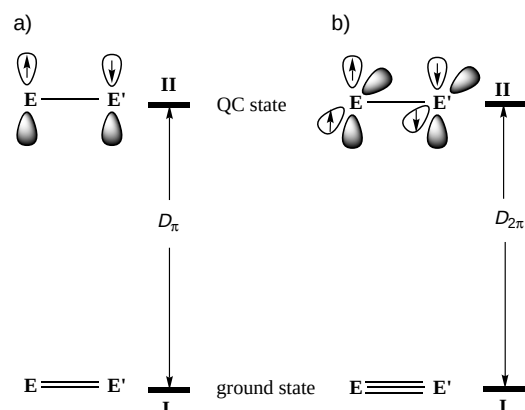


Figure 2. Definition of in situ π-bond energy based on the quasiclassical (QC) state reference a) for one π bond and b) for two π bonds.

maintain opposite spins) so that their net interaction is zero.^[17] The energy difference of state II, relative to the ground state I (determined by a normal VB calculation), gives the in situ π-bond energy (D_π) that does not involve geometric reorganization of the dissociated fragments. Similarly in a case of a triple bond, we can unpair two π bonds and obtain directly the total π-bond energy (D_{2π} in Figure 2b). These calculations were carried out with the VB package TURTLE.^[12b, 17, 18]

Table 1 shows the SC bond indices for the six target species alongside the NRT^[16a-c] and Wiberg^[16d] bond orders. The SC indices are itemized for the three bonds between the heavy atoms, that is, a σ bond (C–Si or Si–Si or C–C), a pseudo

Table 1. Bond-order indices for HCSiH (1), HSiSiH (2), and HCCH (3) in the linear (L) and *trans*-bent (B) isomers.

	SC calculations ^[a]			DFT calculations ^[b]	
	σ	π _{in}	π _{out}	NRT	Wiberg
1L	0.776 [–0.609]	0.607 [–0.599]	0.607 [–0.599]	2.9	2.8
1B	0.764 [–0.650]	0.207 [–0.635]	0.592 [–0.589]	2.6	2.5
2L	0.817 [–0.548]	0.620 [–0.572]	0.620 [–0.572]	2.9	3.0
2B	0.803 [–0.619]	0.277 [–0.577]	0.574 [–0.598]	2.6	2.6
3L	0.849 [–0.631]	0.688 [–0.617]	0.688 [–0.617]	2.9	3.0
3B	0.789 [–0.654]	0.264 [–0.641]	0.671 [–0.601]	2.9	3.0

[a] Using a cc-pVTZ basis set. [b] B3LYP/6-31G**.

π bond in the molecular plane of the bent isomer (π_{in}) and a π bond which is perpendicular to the molecular plane (π_{out}). The first SC index S_{ij}, gives the orbital overlap of the hybrids or AOs which constitute the respective bond. The second index P_s(i,j) is a measure of the extent of singlet coupling of the electrons in the bond.^[13] The P_s(i,j) index is –0.75 for a pure singlet-coupled pair, +0.25 for a pure triplet, and zero for an uncoupled situation (deviations from –0.75 are a result of the involvement of spin coupling other than perfect pairing).^[13] By comparison with the data for acetylene (3L), it is seen (Table 1) that the three E–E' bonds are essentially singlet coupled, in both linear and *trans*-bent isomers. However, the orbital overlap index S_{ij} shows that the *trans*-bending weakens the overlap of the π_{in} bond significantly, which reduces it to ≤ 35–45 % of its value in the linear isomer. Thus, the SC overlaps reveal that *trans*-bending reduces the C≡Si, Si≡Si, and C≡C multiple bonding from the formal three. According to calculated NRT and Wiberg bond orders, the bond order for the *trans*-bent isomers 1B–2B is 2.5–2.6 (Table 1). Unlike the SC results, the NRT and Wiberg indices for 3L and 3B seem oddly equal. However, for 1 and 2, all the bond-indices methods lead to the same conclusion of π-bond weakening because of bending.

Why should 1 and 2 undergo *trans*-bending if this causes reduction of the CSi and SiSi bonding? The density functional calculations (DFT) and CCSD(T)/cc-pVTZ,^[19] as well as the SC calculations show that despite the reduction in π bonding, *trans*-bending results in a significant energy lowering, for example, 8.0 kcal mol⁻¹ for 1B and 21.0 kcal mol⁻¹ for 2B (Figure 1). The solution to this puzzle is revealed by the in situ bond energies^[17] given in Table 2 as well as by the behavior of the QC state that represents the σ frame in Figure 3.

Table 2. In situ bond energies for the linear and *trans*-bent isomers of HCSiH (**1**), HSiSiH (**2**), and HCCH (**3**) in the linear (**L**) and *trans*-bent (**B**) isomers.^[a]

Entry	Type	Bond energies [kcal mol ⁻¹]					
		HCSiH		HSiSiH		HCCH	
		1L	1B	2L	2B	3L	3B ^[b]
1	$D(\pi_{\text{out}})$	57.7	556.5	545.5	534.0	88.2	574.1
2	$D(\pi_{\text{in}})$	557.7	~35 ^[c]	545.5	~27 ^[c]	88.2	~44 ^[c]
3	$D_{2\pi}$	~105 ^[c]	~71 ^[c]	~80 ^[c]	~56 ^[c]	169.8	~110 ^[c]
4	ΔE_{σ} ^[d]		-42.1		-53.0		-33.9

[a] Calculated using the VB procedure described in ref. [17] with the 6-311G* basis set. The $D(\pi_{\text{out}})$ values are calculated with the BOVB method.^[18] [b] The H-C-C angle was fixed at 124.6° (as in **2B**) and all other geometrical parameters were optimized. [c] These are estimated BOVB bond energies which were calculated by adding dynamic correlation increments obtained for the out-of-plane π bonds. For these cases BOVB calculations are too CPU-time demanding. [d] $\Delta E_{\sigma} = E_{\sigma}(\mathbf{B}) - E_{\sigma}(\mathbf{L})$. Obtained by comparing the total energy of the corresponding σ frames with all the π electrons uncoupled (Figure 3).

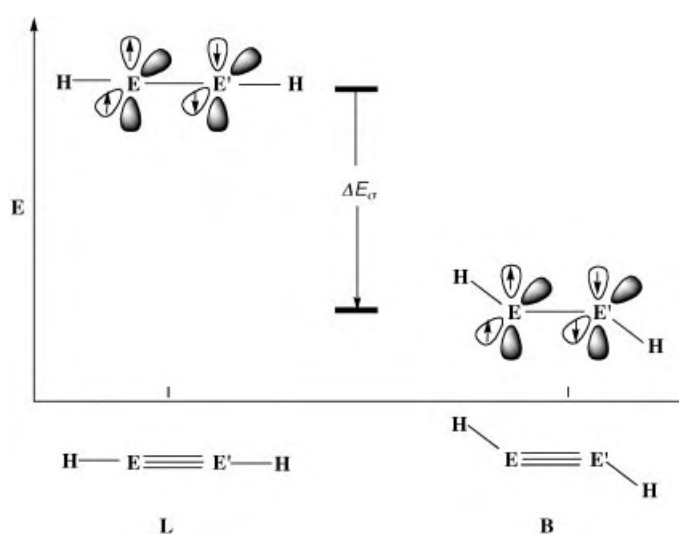


Figure 3. Representation of the stabilization of the σ frame of $\text{HE}\equiv\text{E}'\text{H}$ upon *trans* distortion. The σ frame is represented by the QC state (see Figure 2).

Entries 1 and 2 in Table 2 show the individual π -bond energies determined by unpairing one bond at a time. It is seen that the in-plane pseudo π bond in the *trans*-bent isomer (**1B** and **2B**) is considerably weaker than the out-of-plane π bond. The $D_{2\pi}$ values (entry 3) obtained by unpairing simultaneously the two π bonds, also show that the total π bonding is weakened by 24–34 kcal mol⁻¹ by *trans*-bending for both **1** and **2**. The same conclusion applies also to acetylene (**3**) the total π -bonding, $D_{2\pi}$, of which is weakened by 60 kcal mol⁻¹ upon bending.

The behavior of the σ frame upon bending can be appreciated by inspection of Figure 3 and entry 4 in Table 2. Thus, as seen in Figure 3, the σ frame obtained by unpairing the two π bonds (the QC state of Figure 2b) is stabilized by the distortion of the linear frame. Entry 4 in Table 2 shows that these stabilization energies; the ΔE_{σ} values for **1–3**, are significant, 33.9–53.0 kcal mol⁻¹.^[20] All the σ frames, including that of acetylene (**3**), prefer the bent structure, which strengthens σ bonding. This σ -bond strengthening^[20] overrides the π -bond weakening in **1** and **2** and, therefore, the two

molecules undergo *trans*-bending. In contrast, for acetylene (**3**) the π -bond weakening exceeds the σ -bond strengthening by a significant amount and the molecule remains linear.

What are the roots of the σ -bond strengthening? These appear to be a mix of a few effects:

- The SC calculations show that in addition to the classical bond-pairing interactions, there are a variety of other spin-coupling modes^[21] which involve interactions between the hybrids of π_{in} and those of all other σ bonds in the molecule. The net effect of these hyperconjugative interactions is some backbonding from E (E = Si, C) into the Si–H (or C–H) bond. To estimate this “backbonding” effect ($\Delta E_{\text{backbond}}$), the SC wavefunction was restricted to the perfectly paired (PP) structure. The SC energy of the PP structure was 7.4 and 7.0 kcal mol⁻¹ higher than the full SC energy for HCSiH and HSiSiH, respectively. These increments account for only part of the full σ -bond strengthening effect in entry 4 of Table 2.
- The second factor is caused by bond-length relaxation. Thus, the bond distance between the heavy atoms is too short in the linear structures for an optimal σ bond. The *trans*-bending lengthens the distance between the heavy atoms (Figure 1) and consequently the σ bond is strengthened. In **3** the bond lengthening confers 10.3 kcal mol⁻¹ of σ -bond strengthening,^[22] which is about one third of the entire effect (in entry 4 of Table 2). For **1** and **2**, the effects of bond-length relaxation are 8.2 and 9.3 kcal mol⁻¹. Clearly, the bond-length relaxation does not account for the entire effect. What remains from the total ΔE_{σ} in Table 2, appears to be associated with the increase of s-orbital participation in bonding through rehybridization caused by the *trans*-bending distortion.^[23]

Thus, by itself, the σ frame is *more* stable in the *trans*-bent geometry, but this comes at the expense of π -bond weakening. The final geometry of $\text{HE}\equiv\text{E}'\text{H}$ is then a result of delicate interplay between the opposing effects of σ and π bonding. When the π bonding becomes very strong as in acetylene **3**, it overrides the σ frame and leads to a linear molecule. When π bonding gets weaker as in **1** or **2**, the σ frame overrides and the molecule adopts a *trans*-bent geometry with an extra strength in the σ frame. This σ – π interplay is reminiscent of the benzene story.^[24]

In summary, the CSi and SiSi bonding in the bent structures is formally approximately 2.5 bonds. The propensity for *trans* bending arises from the remarkable *strengthening* upon *bending* of the $\sigma(\text{C}–\text{Si})$ and $\sigma(\text{Si}–\text{Si})$ bonds. Thus, HCSiH and HSiSiH demonstrate that “less bonds pay more” when the smaller number of bonds undergo significant strengthening. The generality of these findings will be explored in the future.

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- [21] For 10 electrons there are 42 SC structures.
- [22] Calculating **3L** at $r_{\text{C-C}} = 1.196 \text{ \AA}$ (equilibrium structure) and $1.23 \text{ \AA}$ (see Figure 1) with all the π electrons unpaired leads to a $10.3 \text{ kcal mol}^{-1}$ σ -bond strengthening for the longer bond.
- [23] The increase in s-orbital population is $0.044 e^-$ for **3**, $0.262 e^-$ for **1**, and $0.604 e^-$ for **2**. The same conclusion is obtained from a natural population analysis. The computed σ preference for *trans*-bending, **2** > **1** > **3**, follows the rehybridization effect. The increase of s-orbital participation is associated with partial reduction of the promotion energy ($\Delta E(\text{^2}\Pi \rightarrow \text{^4}\Sigma^-)$) of the EH (E = C, Si) fragments within the molecule. In the promoted $\text{^4}\Sigma^-$ state, the fragments are able to make a triple bond at the expense of raising their self-energies, because of the high population of their p-orbitals. *Trans*-bending triggers more s-orbital participation, which partially demotes the fragments back to their ground state situations. This demotion lowers the energy of the fragments and thereby stabilizes the σ frame.
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Intrinsic Bond Strengths of Multiple C–C, Si–Si, and C–Si Bonds**

Jörg Grunenberg

Like other chemical concepts, for example aromaticity^[1] or hybridization,^[2] the idea of bond orders recently led to a heated discussion in the literature.^[3–5] Though those concepts often lack a solid physical ground, without a classification of different bonding situations as single or multiple bonds, there would be no systematic representation of the boundless diversity of possible chemical structures. Nevertheless, though modern quantum chemistry is able to predict a variety of observable quantities, it is by no means trivial to decide whether there is a bond between two specific atoms at all.^[6] This dilemma led to a number of methods, which analyze the complexity of the wavefunction, with the aim to obtain information about local data.^[7,8] Unfortunately, there are many ways to localize the unique set of canonical molecular orbitals,^[8,9] which most of the electronic structure calculations are based on. Furthermore, any partition scheme of the basis functions or electrons between atomic centers is, strictly speaking, arbitrary. Given this, it is then not surprising that different methods of population analysis or charge-density analysis give different results when studying specific bond strengths or partial charges.^[10] For example, the computed bond orders of a multiple Ga–Ga bond in a recently synthesized organogallium compound, range between less than two^[5] and higher than three.^[4]

Therefore, it might be useful to consider the quantum-chemical calculation of the inverted matrices of all energy second derivatives (compliance force constants).^[3b] These calculations offer a complete, different, and simple way to compute directly intrinsic bond strengths, without using sophisticated analysis methods. A quantum-chemical calculation of the complete set of force constants overturns the classical way of evaluating a small number of force constants from experimental frequencies of vibrations by using a constrained force field.^[11a] Such selected force constants (or better potential constants) are of limited use as a description for intrinsic bond strength^[11b] since their transferability and hence their comparison is difficult. Furthermore, even if the complete matrix of force constants is available—which is now computational feasible for medium-sized systems by using correlated wave functions—their numerical value strongly depends on the internal coordinate system.^[12] However, real-space theoretical force constants are frequently used in chemical literature.^[13] Only after inversion of the complete set of theoretical force constants, is their numerical stability

guaranteed. Doing so, a higher compliance force constant is connected unambiguously and directly with a higher intrinsic bond strength.^[14]

Herein the method of compliance force constants is used to study the strength of a triple bond between carbon and silicon atoms by comparing the bond strengths of different single and multiple C–C, Si–Si, and C–Si bonds. Theoretical studies on the C–Si triple bond date back to the 1970s and 1980s,^[15] while experimental hints first appeared in 1994.^[16] Only recently was the first experimental evidence of a C–Si triple bond published.^[17] Earlier, in 1997, Apeloig and Karni used high-level quantum-mechanics calculations followed by population analysis to predict a bond order of three for a C–Si bond in a *trans*-bent RCSiR arrangement.^[18] Interestingly, this study found no strengthening of the C–Si bond going from a *trans*-bent arrangement to linear acetylene-like RCSiR geometry.

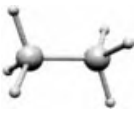
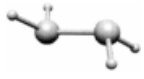
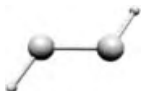
In the present study, the compliance matrix method was used to learn more about the C–Si triple bond. All the quantum-chemical calculations used are based on hybrid density functionals, B3LYP.^[19] Geometry optimizations and calculations of Cartesian force constants were performed with the Gaussian 98 program.^[20] The setup of non-redundant internal coordinates and the transformation of the Cartesian force constants were carried out with Fogarasi's and Pulay's INTC/FCTINT set of algorithms.^[21] The inversion of the internal Hessian matrix was accomplished by standard methods.^[22]

The results are compiled in Table 1 and Figure 1. The well-known special position of C–C bonds is evident. There is more than a doubling of the intrinsic bond strength going from typical C–C (4.035 aJ Å^{-2}) to a C=C bond (9.551 aJ Å^{-2}) and it nearly doubles in going from a C=C to a C≡C (17.301 aJ Å^{-2}) bond (Figure 1). In the case of Si–Si single (1.617 aJ Å^{-2}), double (2.127 aJ Å^{-2}), and triple (2.654 aJ Å^{-2}) bonds, we again see a linear trend, though the slope is not as steep (Figure 1, solid line with squares). Both, the double and the triple bond strengths are diminished relatively to their planar or linear arrangement, which are not minima on the energy surface (dotted line, squares in Figure 1). It is noteworthy, that these findings are in contrast to a study by West et al., which concludes that “deformations have only a small influence on the electronic characteristics of the Si=Si bond”.^[23] Now we turn to C–Si bonds. Only, if a linear HCSiH geometry (second order saddle point) is assumed, is this near linear relationship also present for C–Si single (2.744 aJ Å^{-2}), double (5.402 aJ Å^{-2}), and triple (8.818 aJ Å^{-2}) bonds (dotted line with triangles in Figure 1). However, when the C–Si bond strength of the *trans*-bent minimum geometry (5.464 aJ Å^{-2}) is compared with the strength of a C=Si bond (5.402 aJ Å^{-2}) there is hardly a difference (solid line, triangles in Figure 1). The bending of the H–Si–C angle in the *trans*-bent HSiCH minimum geometry leads to a pronounced weakening ($\sim 40\%$) of the C–Si bond in comparison with a linear HSi≡CH arrangement (second order saddle point). Because the C=Si bond (in contrast to the Si=Si bond) does not suffer from any pyramidalization, there is no significant strengthening of the C–Si bond going from $\text{H}_2\text{C=SiH}_2$ to *trans*-bent HSi≡CH.

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Table 1. Total energy (E_{tot}), bonding distance ($r(\text{X}-\text{X})$), and reciprocal compliance force constants ($F(\text{X}-\text{X})$; relaxed force constants) of several systems containing single and multiple C-C, C-Si, and Si-Si bonds by using the B3LYP/6-311++G(d,p) method.

X-X						
C-C	$E_{\text{tot}}^{[a]}$	-79.85657	-78.61553	nsp ^[i]	-77.35662	nsp
	$r(\text{X}-\text{X})^{[b]}$	1.531	1.329	nsp	1.199	nsp
	$F(\text{X}-\text{X})^{[c]}$	4.035	9.551	nsp	17.301	nsp
Si-Si	$E_{\text{tot}}^{[a]}$	-582.63864	-581.37580 ^[d]	-581.37706	-580.08511 ^[f]	-580.11845
	$r(\text{X}-\text{X})^{[b]}$	2.354	2.139	2.173 ^[e]	1.967	2.106 ^[g]
	$F(\text{X}-\text{X})^{[c]}$	1.617	3.030	2.127	5.039	2.654
C-Si	$E_{\text{tot}}^{[a]}$	-331.25362	-329.98423	nsp	-328.67656 ^[f]	-328.68670
	$r(\text{X}-\text{X})^{[b]}$	1.884	1.708	nsp	1.588	1.649 ^[h]
	$F(\text{X}-\text{X})^{[c]}$	2.744	5.402	nsp	8.818	5.464

[a] Total energies in Hartree. [b] Å. [c] $\text{aJ}\text{\AA}^{-2}$. The actual unit of a compliance stretching force constants is $\text{\AA}^2\text{aJ}^{-1}$. Nevertheless, the values are given as reciprocal values (relaxed force constants) for comparability reasons. [d] nimag (number of imaginary frequencies) = 1. [e] Out-of-plane angle: 30.81° . [f] nimag (number of imaginary frequencies) = 2. [g] H-Si-Si angle: 124.82° . [h] H-Si-C angle: 120.42° ; H-C-Si angle: 154.11° . [i] nsp = no stationary point.

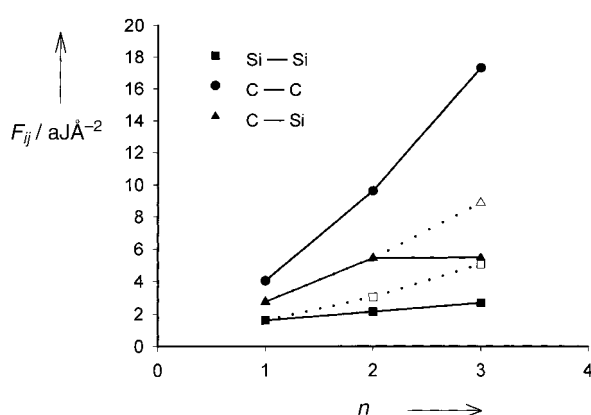


Figure 1. Reciprocal compliance force constants (relaxed force constants) of the five systems (see Table 1) containing single and multiple C-C, C-Si, and Si-Si bonds at the B3LYP/6-311++G(d,p) level of theory as a function of the formal bond order (n). The dotted lines correspond to theoretical ethylene- or acetylene-like geometries for the C-Si and Si-Si series (see text).

Figure 2 compares real-space and compliance force constants. According to real-space force constants, which are used exclusively in the literature, the C-Si bond strength in the *trans*-bent HCSiH minimum geometry reaches $6.447\text{ aJ}\text{\AA}^{-2}$. This seems to be in line with an interpretation as a triple bond (C=Si double bond: $5.495\text{ aJ}\text{\AA}^{-2}$; real space coordinates). The reason for the discrepancy between real-space force constants and reciprocal compliance force constants is to be found in Table 2. The strong coupling between the C-Si stretching and the H-Si-C angle bending ($0.431\text{ aJ}\text{\AA}^{-1}\text{rad}^{-1}$) excessively

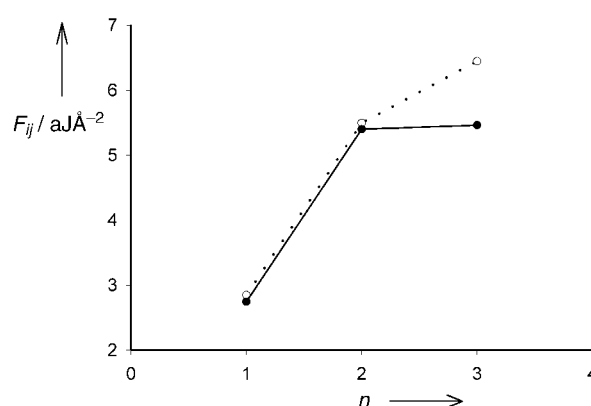
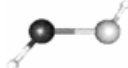


Figure 2. Comparing reciprocal compliance force constants (relaxed force constants) and real space force constants of the C-Si bond in $\text{H}_3\text{C-SiH}_3$, $\text{H}_2\text{C-SiH}_2$, and HC-SiH at the B3LYP/6-311++G(d,p) level of theory. $\circ$ = real-space force constants, $\bullet$ = compliance force constants.

raises the numerical values of the diagonal elements (C-Si bonds). Since compliance matrices do not depend on the definition of the coordinate system and there is no such strong coupling in the force fields of $\text{H}_3\text{C-SiH}_3$ and $\text{H}_2\text{C-SiH}_2$, the difference between real-space force constants and reciprocal compliance force constants is most pronounced in *trans*-bent HCSiH.

To summarize, the major results of this study are as follows: 1) In contrast to real-space force constants, compliance force constants provide a unique description of bond strengths. 2) Pyramidalization (Si-Si) or *trans*-bent distortion (C-Si) of the atoms involved in (Si-Si or C-Si) multiple bonds has a

Table 2. B3LYP/6-311++G(d,p) matrix of force constants of the *trans*-bent HCSiH minimum geometry expressed in internal, real space coordinates.

	Si-H stretch [$\text{aJ}\text{\AA}^{-2}$]	C-H stretch [$\text{aJ}\text{\AA}^{-2}$]	C-Si stretch [$\text{aJ}\text{\AA}^{-2}$]	C-Si-H bend [aJrad^{-2}]	Si-C-H bend [aJrad^{-2}]	H-Si-C-H torsion [$\text{aJ}\text{\AA}^{-1}\text{rad}^{-1}$]
Si-H stretch	2.829	-0.006	-0.088	0.102	0.034	0.000
C-H stretch	-0.006	5.861	-0.131	0.043	0.073	0.000
C-Si stretch	-0.088	-0.131	6.447	0.431	0.218	0.000
C-Si-H bend	0.102	0.043	0.431	0.197	0.095	0.000
Si-C-H bend	0.034	0.073	0.218	0.095	0.330	0.000
H-Si-C-H torsion	0.000	0.000	0.000	0.000	0.000	0.035

strong influence on the bond strength. 3) There is no strengthening of the formal C–Si triple bond in a *trans*-bent HCSiH arrangement relative to a linear C=Si arrangement. Similar to the Ga–Ga multiple bonds, the notion “triple bond” is at least misleading.

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A New Type of Heteropolyoxometalates formed from Lacunary Polyoxotungstate Ions and Europium or Yttrium Cations**

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Polyoxometalates have found applications in catalysis, analytical chemistry, and separation science. A new area of interest is the preparation of novel materials based on polyoxometalate building blocks. Prominent examples in this area can be found in the work by Müller et al.^[1] on giant molybdates. Because of their multiple coordination requirements and oxophilicity, lanthanide (Ln) cations are suitable for linking polyoxometalate ions together to form new classes of materials with extended metal–oxygen frameworks. In the case of tungsten, lacunary XW_9 ($SbW_9O_{33}^{7-}$ and $AsW_9O_{34}^{9-}$) ions and $W_5O_{18}^{6-}$ ions have been linked by lanthanide ions to form complexes such as $[Eu_3(H_2O)_3(W_5O_{18})_3(SbW_9O_{33})]^{18-}$,^[2] and recently the largest heteropolyoxotungstate ion, containing a cyclic $[Ln_{16}As_{12}W_{148}O_{524}(H_2O)_{36}]^{76-}$, assembly was reported.^[3] Extended polymeric structures in the solid state were recently obtained from La and Ce complexes and the lacunary $SiW_{11}O_{39}^{4-}$ ions.^[4]

Here we report a new type of heteropolyoxometalates, stable in the solid state and in aqueous solution at pH 7–9, that are assembled from $(PW_9O_{34})^{9-}$ anions and Eu^{III} or Y^{III} cations. The formation of these species is dependent on the counteranion that is used. For example, ^{31}P NMR spectra of the $Eu^{3+}/PW_9O_{34}^{9-}$ (2/1) solution (pH 7.0; $PW_9O_{34}^{9-}$ as the Na salt) prior to addition of the new counteranion shows the presence of a precursor complex, as yet uncharacterized. Addition of K^+ results in the complex **1** reported herein. Addition of Cs^+ or Rb^+ to the precursor solution yields different products: $[Eu(PW_{11}O_{39})_2]^{12-}$ and a different unknown species, respectively. Addition of Al^{3+} results in

$[{Eu(H_2O)_3(\alpha_2-P_2W_{17}O_{61})_2}]^{14-}$. Complex **1** can be synthesized from either $A-PW_9O_{34}^{9-}$ or $B-PW_9O_{34}^{9-}$.

$$[(PM_2W_{10}O_{38})_4(W_3O_{14})]^{30-} \quad (M = Eu, Y; \mathbf{1})$$

Complex **1** is an assembly of $4PW_9O_{34}^{9-}$ anions, $8M^{3+}$ cations, and 7 additional tungsten atoms that form a $[M_8W_7O_{30}]^{6+}$ network (Figure 1). It can be viewed as composed of two V-shaped asymmetric entities that are symme-

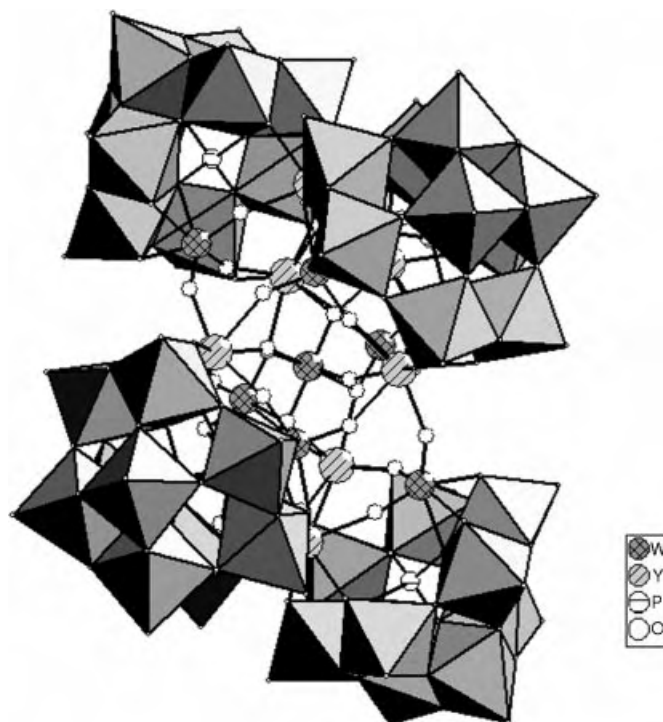


Figure 1. Complex ion **1** comprised of $4PW_9O_{34}^{9-}$ ions connected by a network of $M-O$ ($M = Y, W$) bonds. Eight Y ions and seven W atoms in a $[M_8W_7O_{30}]^{6+}$ network connect the $PW_9O_{34}^{9-}$ anions.

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try-related by a C_2 axis about a central tungsten atom. Each asymmetric entity (Figure 2) consists of two distorted Keggin-like parts (**L** and **R**), both composed of an $A-\alpha-PW_9O_{34}^{9-}$ cap^[5] (see Supporting Information) connected to a distorted M_2W six-membered ring comprising an eight-coordinate (square-antiprismatic) M^{III} , a seven-coordinate M^{III} , and a tungsten atom. The formulation of **1** as $[(PM_2W_{10}O_{38})_4(W_3O_{14})]^{30-}$ reflects the distorted Keggin-like structural parts. Parts **L** and **R** are connected to each other by two bridging WO_6 octahedra (W11 and W12) and the oxygen atoms coordinating the two M^{III} cations (Y1, Y1').^[6] The asymmetric entities are joined together by 6- and 8-membered $M-O$ ($M = W, Y$) rings about the central tungsten atom W12 (see Supporting Information). Rearrangements of A - and B - XW_9 building groups to form XW_{10} and Keggin structures have been observed previously.^[7] The stereochemical requirements of the metal atoms (transition metal, lanthanide or actinide), pH of the solution in which the reaction occurs, and the requirements of the heteroatom (P, As) appear to play a role in this transformation.^[8]

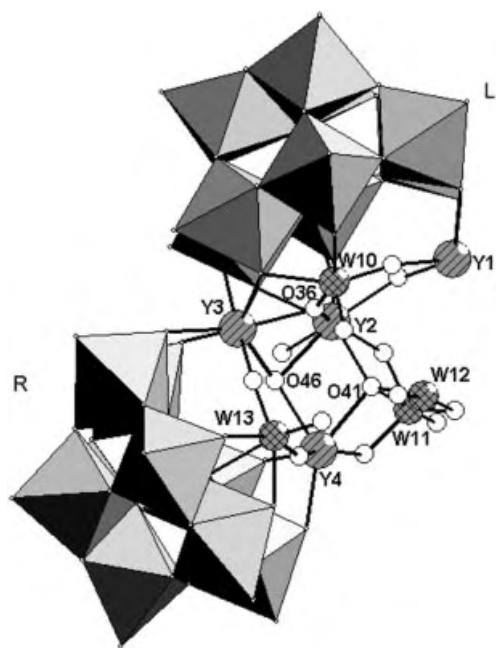


Figure 2. The asymmetric entity of **1** consists of two distorted Keggin-like parts $[(\text{PY}_2\text{W}_{10}\text{O}_{38})^{5-}]$ connected to each other and to the symmetry equivalent entity by bridging oxygen atoms and tungstate units.

The strong involvement of the potassium counteranions, seen in the three-dimensional “tertiary” structure of the complex salt, influences the formation of this particular structure. Packing of the anions perpendicular to the crystallographic *a* axis shows a zigzag ribbonlike geometry; potassium cations sew together the strands to form a two-dimensional network. Packing along the *c* axis shows an interlocking structure; potassium cations tie together the heteropolyanions to form linear strands, and tie together the strands as well (Figure 3)

The complex ion **1** bears a charge of -30 . This charge is compensated by 15 potassium and six sodium cations from the reaction mixture, as well as nine oxonium ions. On the basis of simple angular considerations, it is likely that three triply bridging hydroxo ligands ($\mu_3\text{-OH}$) connect the M and W ions in the M,W,O core of **1** (Figure 2). The sum of the M-O-M angles is close to the value of 328.4° expected for pure sp^3 -hybridized oxygen atoms (the three oxygen atoms connecting the $\text{PW}_9\text{O}_{34}^{9-}$ anions of **L** and **R** in each asymmetric entity).^[9] The sum of the M-O-M angles for the other triply bridging oxygen atoms is close to the 360° for a $\mu_3\text{-O}$ bonding situation. The M-O bond lengths for $\mu_3\text{-O}$, $\mu_3\text{-OH}$, $\mu_2\text{-O}$, and OH_2 are close to those found in other lanthanide oxygen clusters.^[10]

Both ^{183}W and ^{31}P NMR spectroscopy on $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$ provide evidence that the complex remains intact in aqueous solution. The $\text{PW}_9\text{O}_{34}^{9-}$ group itself is not stable under

aqueous conditions and forms other polyoxoanions upon decomposition.^[11] The $\text{M}^{\text{III}}, \text{W}, \text{O}$ network apparently holds the PW_9 units together tightly. Two signals are observed in the ^{31}P NMR spectrum, consistent with the C_2 symmetry. The ^{183}W NMR spectrum of the Y analogue shows 19 signals (see Supporting Information), one with a relative intensity of unity and three with about twice the intensity of the other fifteen; this suggests overlapping signals. In total, 22 signals are expected as the complex contains 22 nonequivalent tungsten atoms.

Complex **1** is stable at pH 7–9, according to ^{31}P NMR spectroscopy on the Eu compound. Below pH 6, decomposition to a species with one ^{31}P signal at $\delta = 5.3$ (structure unknown as yet), is observed; at pH 6, the two signals characteristic of **1** and the signal at $\delta = 5.3$ are observed; the signals for **1** alone are observed at pH 7–9. Above pH 10, signals attributed to phosphate are observed.

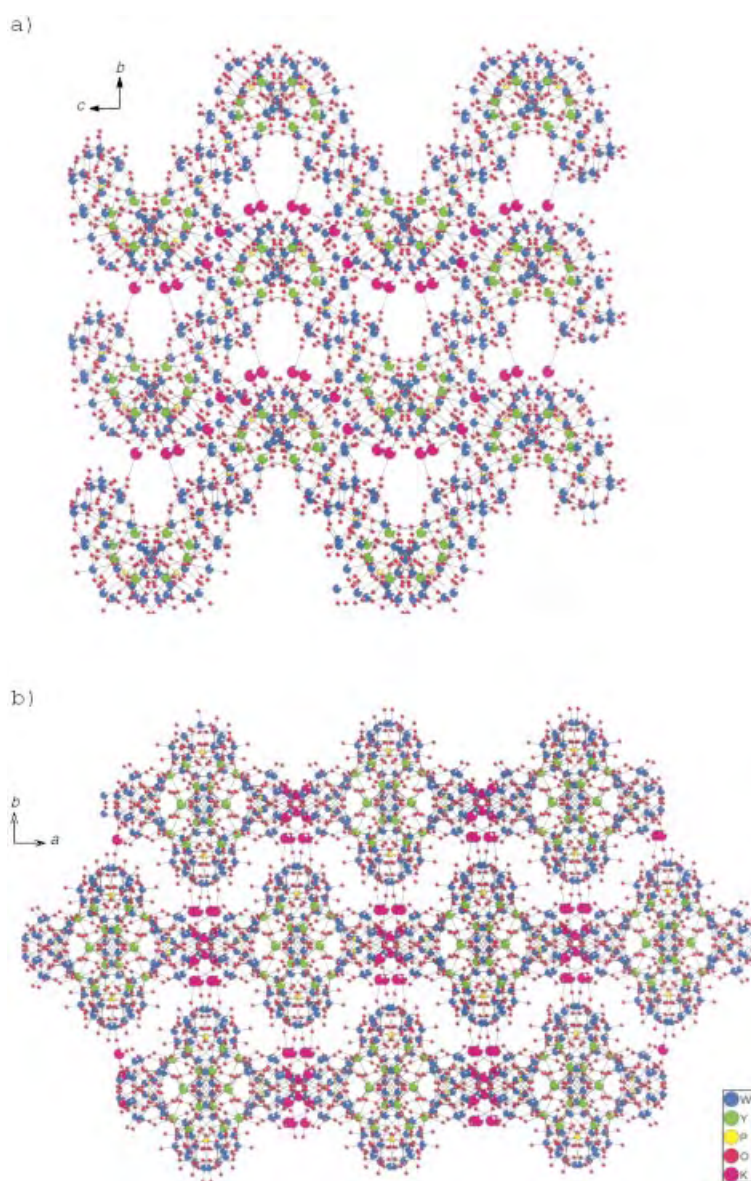


Figure 3. Packing of **1** and K^+ cations along the crystallographic *a* axis (a) and *c* axis (b). The K^+ counterions binding to the surface oxygen atoms of the complex ion link them to form the zigzag and rosette structures shown.

The excitation spectrum of the Eu^{III} compound in aqueous solution showed four transitions at 579.6, 579.9, 580.2, and 580.5 nm, corresponding to the ${}^7\text{F}_0$ to ${}^5\text{D}_0$ transitions of the four unique Eu^{3+} sites (Figure 4). Due to the overlap of the

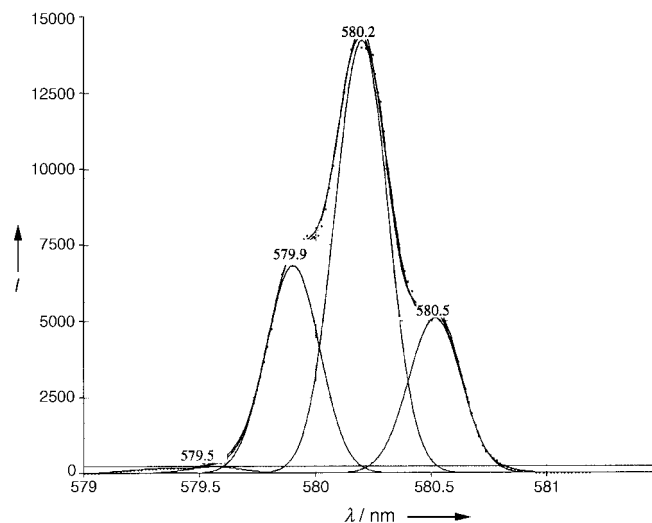


Figure 4. Laser excitation spectrum of the Eu^{3+} compound showing the overlapping excitation bands of the four different Eu^{3+} sites. The Eu^{3+} emission due to the ${}^5\text{D}_0$ to ${}^7\text{F}_2$ transition was monitored.

transitions, it was difficult to determine the lifetime of each Eu^{III} site in D_2O and H_2O solutions in order to calculate the number of coordinated H_2O molecules.^[12] Excitation into the tungsten bands of a solid sample of the Eu^{III} compound leads to Eu^{III} emission. The luminescence lifetimes for solid samples, prepared in H_2O and D_2O ($\lambda = 590$ nm), resulted in $q = 0.7 \pm 0.5 \text{H}_2\text{O}$ per Eu ion;^[12] this is consistent with the crystallographic data, which show two water molecules, one each bound to Eu_4 , per 8Eu^{III} ions in the molecule.

Experimental Section

$\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]^{30-}$: Solid powdered $\text{Na}_9\text{PW}_9\text{O}_{34} \cdot 15\text{H}_2\text{O}$ ^[13] (2.2 g, 0.81 mmol) was added to a solution of $\text{YCl}_3 \cdot 6\text{H}_2\text{O}$ (0.57 g, 1.9 mmol) in H_2O (7.5 mL). The resulting suspension was heated to about 80°C , and a clear solution formed. Solid KCl (1.4 g, 19 mmol) was added to the hot solution, and the solution heated for an additional 10 min. The resulting slurry was cooled to room temperature and then in an ice bath. The solid was collected by filtration, washed with cold H_2O , and recrystallized from hot H_2O (yield: 2.1 g, 72% based on YCl_3). X-ray-quality crystals of $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$ were grown at -10°C from a clear solution of $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$ in H_2O saturated with KCl . The europium complex was prepared in a similar manner from $\text{EuCl}_3 \cdot 6\text{H}_2\text{O}$.

Elemental analysis (%) calcd (based on crystal structure) for $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})] \cdot 9\text{H}_2\text{O}$: Y 5.71, W 63.40, P 0.99, K 4.71, Na 1.11; found: Y 5.7, W 62.8, P 1.0, K 5.9, Na 0.2. Elemental analysis (%) calcd (based on crystal structure) for $\text{K}_{16.5}(\text{H}_3\text{O})_{13.5}[(\text{PEu}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})] \cdot 26\text{H}_2\text{O}$: Eu 9.22, W 59.6, P 0.93, K 4.7%, H_2O 5.4; found: Eu 9.7, W 62.3, P 1.1, K 5.1, Na 0.3, H_2O 4.9. The elemental analyses are consistent with the formulations. The major differences between calculated and found weight percentages are for the counteranions and the water of hydration, as expected. IR (KBr disk) for both complexes showed metal–oxygen stretches at $\tilde{\nu} = 1092$ (m), 1055 (m), 1025 (m), 951 (s), 935 (s), 820 (vs), 790 cm^{-1} (s).

${}^{31}\text{P}$ NMR (161.8 MHz, D_2O) of $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$: $\delta = -9.68, -10.53$; ${}^{31}\text{P}$ NMR (D_2O) of $\text{K}_{16.5}(\text{H}_3\text{O})_{13.5}[(\text{PEu}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$:

$\delta = 31.76, 23.24$; ${}^{183}\text{W}$ NMR (16.7 MHz, D_2O) of $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$: $\delta = -30.8, -99.8, -103.4, -110.8, -124.2, -129.8, -131.1, -133.8, -134.6, -135.8, -139.2, -141.3, -145.9, -149.7, -157.9, -159.8, -174.7, -187.8, -225.7$.

Crystal structure analysis for $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})] \cdot 9\text{H}_2\text{O}$: Crystal dimensions $0.4 \times 0.2 \times 0.2$ mm, monoclinic, space group $C2/c$, $a = 22.236(8)$, $b = 34.264(12)$, $c = 26.698(9)$ Å, $\beta = 96.271(6)^\circ$, $V = 20219(18)$ Å³, $\rho_{\text{calcd}} = 4.08$ g cm^{-3} , total collected reflections 51 638, unique reflections 23 150, $R_{\text{int}} = 0.0725$, $\mu = 75.805$ mm⁻¹, $R_1 = 0.0824$ for $I < 2\sigma(I)$ and $wR_2 = 0.1999$ for all reflections, total parameters 709, max residual electron density 6.823 e Å⁻³.

Crystal structure analysis for $\text{K}_{16.5}(\text{H}_3\text{O})_{13.5}[(\text{PEu}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})] \cdot 26\text{H}_2\text{O}$: Crystal dimensions $0.3 \times 0.3 \times 0.2$ mm, triclinic, space group $P1$, $a = 20.27270(10)$, $b = 22.62970(10)$, $c = 25.88400(10)$ Å, $\alpha = 68.33$, $\beta = 85.21$, $\gamma = 85.52^\circ$, $V = 10982(8)$ Å³, $\rho_{\text{calcd}} = 3.98$ g cm^{-3} , total collected reflections 71 178, unique reflections 45 571, $R_{\text{int}} = 0.1046$, $\mu = 25.106$ mm⁻¹, $R_1 = 0.1448$ for $I < 2\sigma(I)$ and $wR_2 = 0.3439$ for all reflections, total parameters 1365, max residual electron density 8.977 e Å⁻³.

Differences in the anion charge and number of cations found in both $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$ and $\text{K}_{16.5}(\text{H}_3\text{O})_{13.5}[(\text{PEu}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$ of 9⁻ and 13⁻, respectively, are most likely compensated by protons. The high residual electron densities in both structures, due to W atom noise, are found within an Ångström of W atoms and are accompanied by other W atom noise peaks of similar intensity. Single crystal X-ray diffraction data on $\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$ and $\text{K}_{16.5}(\text{H}_3\text{O})_{13.5}[(\text{PEu}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$ were collected at 298 K and 153 K, respectively, on a Bruker P4 diffractometer equipped with a SMART CCD detector and a graphite monochromator ($\lambda(\text{MoK}\alpha) = 0.71073$ Å). The structures were solved by direct methods and standard difference-map techniques, and refined by full-matrix least-squares procedures (SHELXTL).^[14] No hydrogen atoms were included.

Further details on the crystal structure investigations 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-391092 ($\text{K}_{15}\text{Na}_6(\text{H}_3\text{O})_9[(\text{PY}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$) and CSD-411918 ($\text{K}_{16.5}(\text{H}_3\text{O})_{13.5}[(\text{PEu}_2\text{W}_{10}\text{O}_{38})_4(\text{W}_3\text{O}_{14})]$).

Elemental analysis was performed at Hunter College by inductively coupled plasma analysis on a Spectro Spectroflame M120 E spectrometer and by Kanti Technologies Inc, Tonawanda, NY. IR spectra were recorded on a Perkin Elmer Series 1600 FTIR spectrometer. ${}^{31}\text{P}$ and ${}^{183}\text{W}$ NMR were recorded on a JEOL 400 MHz with 85% H_3PO_4 and 2 M Na_2WO_4 , respectively, as external standards.

Laser luminescence studies were performed at Pennsylvania State University with a Continuum YG581 pulsed Nd:YAG laser, pumping a TDL50 tunable dye laser. The ${}^7\text{F}_0$ to ${}^5\text{D}_0$ transitions of the Eu^{3+} ions were excited while the ${}^5\text{D}_0$ to ${}^7\text{F}_2$ emission band was monitored. Measurements were carried out at $25.0 \pm 0.1^\circ\text{C}$. The commercially available Peakfit program, which employs a nonlinear regression method, was used for data analyses. The concentrations of the samples used to obtain the excitation and the luminescence decay lifetime spectra were 20 mM.

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- [6] A detailed description of the bonding in **L** and **R** (Figure 2) follows: Y1 (7-coordinate) and Y2 (8-coordinate) are both bound to oxygen atoms of **L**. Y1 is also bound to one oxygen atom in each of the symmetry-equivalent **L** (μ_2 -O (2.264(17) Å) to W10A) and **R** (μ_2 -O (2.275(19) Å) to W13A) and μ_2 -O (2.301(17) Å) to W12. The other four coordination sites of the eight-coordinate Y2, which connect **L** to **R**, are occupied by μ_3 -O (2.483(17) Å) to Y3 and Y4, μ_2 -O to W12 (2.310 Å), μ_2 -O to W11 (2.39 Å) and a terminal O atom (2.44 Å). Similarly, Y3 and Y4 are bound to O atoms of **R**. Y3 is connected to **L** by μ_3 -O (2.442(17) Å) to W4 and W5, μ_3 -O (2.556(18) Å) to W5 and W10, μ_3 -O (2.464 (18) Å) to W4 and Y2, and the fourth remaining site to μ_3 -O (2.337(17) Å) to Y2 and Y4. The three remaining coordination sites on Y4, connecting Y4 to **L**, are occupied by μ_2 -O (2.341(18) Å) to W12, μ_2 -O (2.368(19) Å) to W11, and μ_3 -O (2.335(17) Å) to W12 and Y2.
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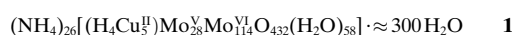
“Nanoobjects” by Self-Assembly Concomitant with Modifications under Alterable Boundary Conditions: Incorporation of Paramagnetic Metal Centers (Cu^{2+}) in Ring-Shaped Molybdenum-Oxide Based Clusters**

Achim Müller,* Erich Krickemeyer, Hartmut Bögge, Marc Schmidtman, Paul Kögerler, Christina Rosu, and Eike Beckmann

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

Until now it has been a tremendous and ongoing challenge to initiate a variety of chemical reactions at *well-defined* positions even of the same and structurally *well-defined* nanoobject, especially if significant property changes or novel functionalities are intended.^[1] This aim has now been achieved for giant ring-shaped molybdenum oxide based clusters of the type $\{Mo_{154}\}$ and $\{Mo_{176}\}$ which can be obtained in related crystalline salts in a facile high-yield synthesis and exhibit nanosized cavities, a variety of sites with different well-defined functional groups, and overall are comparable to a nanostructured landscape.^[2, 3] Here we report the incorporation of paramagnetic metal centers, that is, Cu^{2+} ions, in cavities of these rings—which are spanned by four O atoms and have the corresponding appropriate size—according to a basic type of self-assembly process leading to nanoobjects all of which have the ring topology. Important in this context is that this allows a variety of deliberate concomitant modifications under alterable boundary conditions—such as the pH, temperature, and/or presence of different substrates—corresponding to the different sites.^[4] The procedure opens perspectives not only for a new type of nanochemistry but also for an understanding of a basic reaction type of material organization (see below).

The reduction of an acidified aqueous polymolybdate solution with copper powder leads to the crystalline black compound **1**, which was characterized by elemental analyses



(including cerimetric titration to determine the formal number of Mo^V centers), thermogravimetry (to determine the amount of crystal water), spectroscopy (UV/Vis/NIR, infrared (IR), resonance-Raman, ESR), single-crystal X-ray structure analysis,^[5] and bond valence sum (BVS)^[6] calculations (to determine the positions of the H_2O molecules and to

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distinguish between the Mo^{VI} and Mo^{V} centers) as well as magnetic susceptibility measurements.

The crystal structure shows the abundance of the cluster anions $[\{\text{Mo}_8^{\text{V/VI}}\text{O}_{26}(\mu_3\text{O})_2\text{X}_i(\text{H}_2\text{O})_3\text{Mo}^{\text{V/VI}}\}_{14}\{\text{Mo}_2^{\text{V}}\text{O}_5(\text{H}_2\text{O})_2\}_8]^{26-}$ ($\Sigma\text{X}_i = 4\text{H} + 5\text{Cu}$) (**1a**) which are derivatives of the aforementioned prototypal tetradecameric $\{\text{Mo}_{154}\} \equiv \{\text{Mo}_8\}_{14}\{\text{Mo}_1\}_{14}\{\text{Mo}_2\}_{14}$ type species.^[2, 3] In comparison to the $\{\text{Mo}_{154}\}$ anion, **1a** lacks six $\{\text{Mo}_2\}$ -type building blocks and shows fascinating novel features: In the tetrahedral cavities spanned by four oxygen atoms (two μ_3 and two terminal, abundant and within the $\{\text{Mo}_8\}$ building blocks)—that is, at well-defined sites underneath the cluster surface—five Cu^{2+} centers are incorporated, but interestingly are not uniformly distributed in the cavities, the largest occupation number being 0.73. These replace some of the 14H atoms of the parent cluster **2a** which are bonded to one of the two above-mentioned μ_3 -O atoms that form the cavities (Figure 1). Whereas with high H^+ ion concentrations the maximum 14-fold protonation of the tetradecameric cluster is obtained,^[3] an increased pH value—here because of buffering with HCOONH_4 —leads to lower degrees of protonation and to Cu^{2+} coordination to the basic μ_3 -O atoms.

Whereas the resonance-Raman ($\lambda_{\text{e}} = 1064\text{ nm}$ excitation line) and IR spectra are nearly identical with that of the parent cluster **2a**, the electronic spectrum of solid **1** shows, as a result of the abundance of Cu^{2+} centers, an additional band at $\approx 520\text{ nm}$ and a blue shift of the higher energy intervalence charge transfer (IVCT) transition, localized in the $\text{Mo}_5^{\text{V/VI}}\text{O}_6$ -type compartments (see ref. [3]), each of which contains two delocalized Mo (4d) electrons. The change of the charge transfer is caused by the fact that the encapsulated Cu^{2+} ions are coordinated to the μ_3 -O atoms which belong to the Mo_5O_6 compartments and therefore influence the electronic struc-

ture/distribution. Furthermore, the room-temperature ESR powder spectrum (Figure 2)—which is similar to that of tetrahedral complexes containing CuX_4 and in particular CuO_4 groups^[7, 8]—shows nicely the abundance of the $\text{Cu}^{2+}(\text{d}^9)$

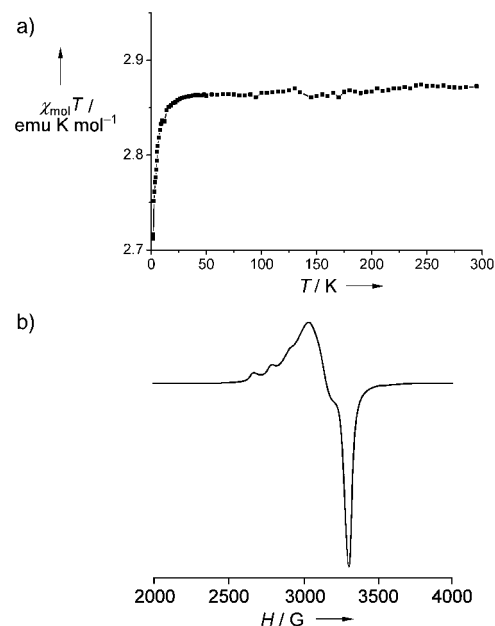


Figure 2. Magnetic susceptibility as function of temperature (a) and ESR spectrum, X-band, room temperature (b) of solid **1**.

centers with the characteristic $g_x = 2.07$, $g_y = 2.15$, and $g_z = 2.37$, and a hyperfine splitting constant $A_z = 125\text{ G}$ (because of the nuclear spin of $^{63/65}\text{Cu}$ with $I = 3/2$), thus showing that the $\text{Cu}^{2+} \cdots \text{Cu}^{2+}$ magnetic interactions ($\text{Cu} \cdots \text{Cu} \approx 6.2\text{ Å}$) are

practically negligible (see also ref. [7]). This observation is also supported by the measured susceptibility data (Figure 2). Upon correction of the diamagnetic and temperature independent paramagnetism (TIP) contributions (that sum up to $-2.5 \times 10^{-4}\text{ emu mol}^{-1}$), $\chi_{\text{mol}}T$ at high temperatures displays a constant value of approximately $2.86\text{ emu K mol}^{-1}$ at a plateau which corresponds to around 6 Cu^{2+} centers per formula unit for $g = 2.2$ (compare with ESR results). Accordingly there is a small error limit of ± 1 in the number of Cu atoms while one more Cu^{2+} ion can directly replace 2NH_4^+ ions in the lattice or can be localized in the cluster anion. (The number of Cu atoms in the formula corresponds to the sum of their occupation factors.) The observed antiferromagnetic cou-

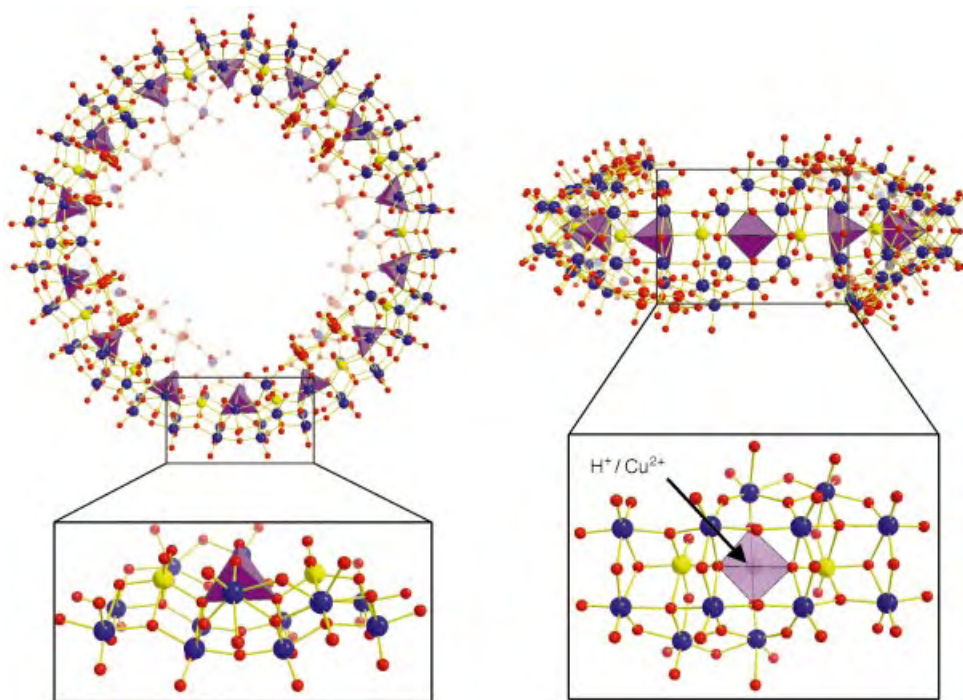


Figure 1. Molecular structure of the cluster anion **1a** (top and side view) in crystals of **1** in ball and stick representation while the $\text{O}_4(\text{Cu})$ tetrahedra (violet) are given in polyhedral representation; additionally, one relevant segment is highlighted separately.

pling interactions—of inter- and intramolecular nature—are very weak and the susceptibility can be modeled using a Curie–Weiss term with a very low Weiss temperature of $\theta \approx -0.5$ K. Consequently, $\chi_{\text{mol}}T$ decreases only below about 20 K.

Interestingly, the thermogravimetric analysis shows that it is possible to remove most of the crystal water by heating **1** to around 300 °C (weight loss approximately 20 %), and thus in principle(!) to generate a mesoporous magnetic material. This is new for this type of wheel-shaped clusters since to date we have never succeeded in isolating pure salts with NH_4^+ ions which may be easily decomposed on heating; important in this context: crystal water molecules in the channels are fixed by the cations.^[8] (According to the IR spectrum the compound heated to 300 °C does not contain NH_4^+ ions.)

The remarkable integration of the paramagnetic Cu^{2+} ions into the cluster cavities under certain self-assembly conditions leading to the giant wheel-type parent species is possible because the dimensions of the aforementioned O_4 -type cavities in **2a** provide the exact characteristic Cu–O distances (2.0 ± 0.1 Å). The assembly route leads in principle from the simple mononuclear MO_n -type units via intermediate building blocks (abundant in a virtual library), by molecular recognition processes for Cu^{2+} centers at the surface/interface of these building blocks, and by selection/addition, to an organized complex mesoscopic ring-shaped structure with a variety of functionalities.^[2, 3] The highly symmetrical mesoscopic $\{\text{Mo}_{154}\}$ parent ring structure, which in the present case is the primary aim of the self-assembly process, can undergo a variety of modifications by altering the boundary conditions, or in other words, because of environmental influences, as for example, the presence of Cu^{2+} ions. In this context, it is important to realize that assembly processes based on simple linkable units lead preferably to highly symmetrical species,^[9, 10] such as rings, corresponding to many observations in cluster chemistry (for general aspects, see also ref. [11]). A relevant aspect in this context is that mesoscopic (i.e. giant) systems can, in spite of a high overall symmetry, exhibit a manifold of highly reactive substructures with related functionalities, for example, on the (large) surface or inside cavities, as in the present case. This feature is noteworthy as the accepted view is that higher symmetry leads to a decrease in structural details and reactivities, which applies, however, to smaller discrete species as well as crystalline systems with macroscopic homogeneity and microscopic translational invariance, but not to discrete mesoscopic molecular-type species. Interestingly, the spherical virus situation also provides a relevant example, as mentioned in most biochemistry textbooks.

Our results show that the molybdenum oxide based wheel-shaped nanoclusters can be considered as nanostructured landscapes with well-defined functional groups.^[2, 3] This allows different types of reactions, also catalytic ones, at well-defined positions, among others, 1) the coordination of (activated) ligands including amphiphilic and multiphilic ones even at electron-rich sites with the option of generating unusual surfaces within cavities,^[12] 2) the generation of different types of defects (supported as in the present case by relatively high pH values), and 3) as in the present case, the incorporation of metal centers in appropriate cavities. A

further perspective based on this work is that reactivities and electron distributions of nanoobjects can be modulated by defect generations as well as by incorporated open-shell heterometal atoms. In the present case, the influence of the Cu^{2+} centers on the distribution of delocalized electrons within compartments can be nicely demonstrated by a shift of the IVCT band from approximately 750 nm of the parent $\{\text{Mo}_{154}\}$ anion^[3] to around 680 nm for **1a**. The general aspect of this observation is that the change of electron distribution can influence/tune the reactivity and even the catalytic activity of the present nanoobjects, which can show selective oxidations.^[13]

Experimental Section

1: Copper powder (0.50 g, 7.87 mmol; Merck, p.a., $\langle 63 \mu\text{m} \rangle$ 230 mesh American Society for Testing and Materials) and 32 % HCl (7.0 mL, p.a.) were added to a solution of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ (18.20 g, 14.73 mmol; p.a.) in H_2O (450 mL) resulting in a color change to blue. The reaction mixture was stirred vigorously for 30 min in an open 500 mL (wide-necked) conical flask. After filtration, HCOONH_4 (0.70 g, 11.10 mmol; Aldrich, 97 %) was dissolved in the deep blue filtrate and the solution was kept for 8 days (covered with a watch glass and without stirring) for crystallization. The precipitated small black crystals of **1** were collected by filtration, washed with ice-cold water, and dried over CaCl_2 in an inert gas atmosphere. Yield: 1.7 g (8.5 % based on Mo; correct analysis). If 1.0 g copper powder is used, crystals can be obtained after 3–4 days as shown in a later experiment.

Characteristic IR bands for **1** (KBr pellet; $1800\text{--}500\text{ cm}^{-1}$): $\tilde{\nu} = 1616$ (m, $\delta(\text{H}_2\text{O})$), 1400 (m, $\delta_{\text{as}}(\text{NH}_4^+)$), 988 (sh), 971 (m), ca. 940 (sh), 907 (m, $\nu(\text{Mo=O})$), 796 (m), 746 (m), 667 (sh), 630 (s), 554 (s) cm^{-1} ; characteristic resonance Raman bands (KBr pellet; $\lambda_{\text{ex}} = 1064\text{ nm}$; $1000\text{--}200\text{ cm}^{-1}$): $\tilde{\nu} = 792$ (m), 534 (s), 463 (s), 324 (m-s), 215 (s) cm^{-1} ; UV/Vis (solid-state reflectance spectrum measured vs. cellulose as white-standard): $\lambda \approx 500$ (sh), ≈ 680 (br) nm.

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- and $-2.04 \text{ e} \text{ \AA}^3$ (SADABS, SHELXS/L by G. M. Sheldrick, Universität Göttingen, Germany, 1993 and 1997; structural graphics with DIAMOND 2.1 from K. Brandenburg, Crystal Impact GbR, 1999). Several individual crystals were measured. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-411939.
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Structure of $\text{Ca}_{13}\text{Cd}_{76}$: A Novel Approximant to the $\text{MCd}_{5.7}$ Quasicrystals ($\text{M} = \text{Ca}, \text{Yb}$)*

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The compound $\text{Ca}_{13}\text{Cd}_{76}$ has been synthesized and its structure has been solved from single crystal X-ray diffraction data.^[1] The discovery of the stable binary icosahedral quasicrystals $\text{YbCd}_{5.7}$ and $\text{CaCd}_{5.7}$ opens the doors to new possibilities for understanding quasicrystalline structures.^[2, 3] A stable quasicrystalline phase has the obvious advantage that large, single-grain crystals can be grown, which allow detailed investigations of physical properties in the bulk, structural studies with neutron radiation, etc. Most stable quasicrystals

are ternary or multinary, and this leads to uncertainties in the occupancy of different atomic sites in the structure. A binary quasicrystal thus offers the additional advantage of simplicity in its structural description. The uniqueness of the $\text{MCd}_{5.7}$ ($\text{M} = \text{Ca}, \text{Yb}$) quasicrystals lies in the combination of these features. Although icosahedral approximants are ubiquitous,^[4] the $\text{MCd}_{5.7}$ compounds are the only known icosahedral quasicrystals that exhibit both these characteristics.

The structures of the quasicrystal approximants play a key role in understanding quasicrystals, since they are expected to display the same local arrangements as the true quasicrystals, and their long-range order facilitates their structural determination by standard methods. Thus, they provide a link to the underlying mechanism of quasicrystal formation.

Modeling quasicrystals is a very attractive way to predict thermodynamic stability, but large multinary approximants containing several different d- or f-block elements do not easily lend themselves to calculations. $\text{Ca}_{13}\text{Cd}_{76}$ is even better suited in this context; not only is it a well-ordered, binary system with accurately defined sites for the two types of metal atoms, it is for all practical purposes composed of elements with closed-shell cores.

The classic approximants to the $\text{MCd}_{5.7}$ quasicrystals are the long known CaCd_6 and RECD_6 ($\text{RE} = \text{rare earth metal}$) phases;^[5, 6] recent investigations conducted at our department, however, show that their true structures have yet not been well characterized. The characterization of $\text{Ca}_{13}\text{Cd}_{76}$ (or $\text{CaCd}_{5.85}$) shows that it is a more closely related approximant to the $\text{MCd}_{5.7}$ quasicrystals than any other so far known. The relation between the structures of CaCd_6 , $\text{Ca}_{13}\text{Cd}_{76}$, and the icosahedral $\text{MCd}_{5.7}$ quasicrystals is implicitly evident from the diffraction patterns of the two approximants; the tenfold symmetry of the patterns is clearly enhanced in $\text{Ca}_{13}\text{Cd}_{76}$ compared to that of CaCd_6 (Figure 1). The recurring structural building blocks seen in the RECD_6 phases, CaCd_6 , and the $\text{RE}_{13}(\text{Zn}, \text{Cd})_{58}$ phases can be found in $\text{Ca}_{13}\text{Cd}_{76}$, but in a new, spectacular arrangement.^[7, 8] A comparison of the $\text{Yb}-\text{Cd}$ and the $\text{Ca}-\text{Cd}$ binary phase diagrams reveals that the systems are very similar; several isostructural phases are present. The compounds $\text{CaCd}_{5.7}$ and $\text{YbCd}_{5.7}$ were earlier reported in these two systems (as $\text{Ca}_3\text{Cd}_{17}$ and $\text{YbCd}_{5.7}$) but in no other.^[5, 9] However, their structures had not previously been characterized. Furthermore, a comparison of atomic radii shows that Yb and Ca are almost identical in size; not even the neighboring lanthanides match the size of Yb better than Ca . The atomic size apparently must be restricted to a narrow span to allow the formation of the $\text{CaCd}_{5.85}$, $\text{CaCd}_{5.7}$, and $\text{YbCd}_{5.7}$ phases. This could explain why no other lanthanides form these phases in combination with Cd , though the 1:6 approximants exist in almost all $\text{RE}-\text{Cd}$ systems. Furthermore, both Yb and Ca have two s electrons in their outer shell and form divalent ions. All these similarities between the elements make Ca the perfect candidate for the formation of a compound that is next of kin to the $\text{MCd}_{5.7}$ quasicrystals.

$\text{Ca}_{13}\text{Cd}_{76}$ crystallizes in the cubic space group $P\bar{6}3$ (no. 205), with $a = 25.339(2) \text{ \AA}$. A convenient way to describe the structure is to identify a unique structural building block and then further describe the cell content in terms of the

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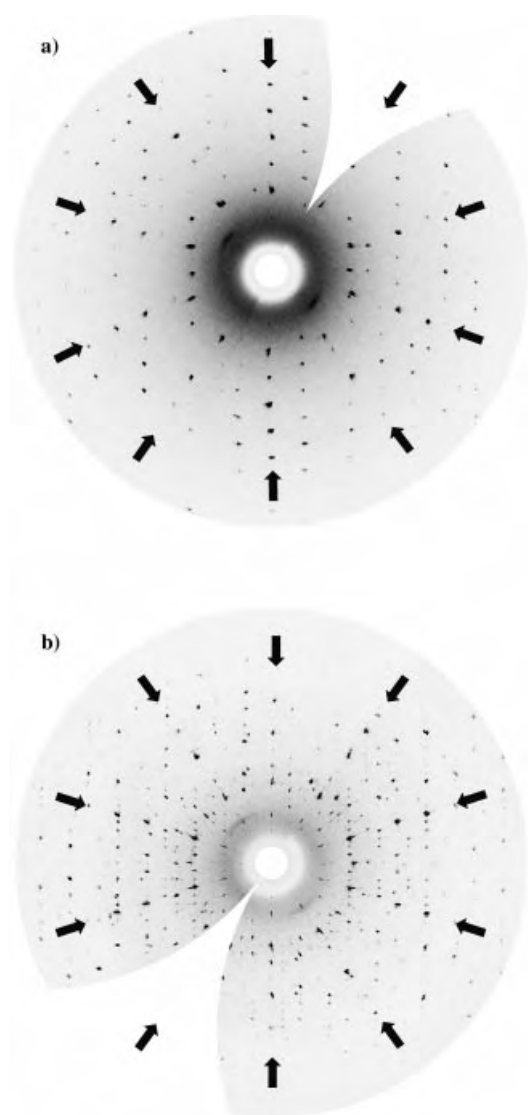


Figure 1. The diffraction pattern of a RECd_6 approximant is seen in a) a section through the origin of reciprocal space perpendicular to $[850]$. The diffraction pattern of $\text{Ca}_{13}\text{Cd}_{76}$ is seen in b) a section through the origin of reciprocal space, perpendicular to $[21130]$. The directions were chosen to give a good approximation to the ideal $[\tau10]$, where $\tau = (\sqrt{5} + 1)/2$. The strong main reflections exhibit an accentuated tendency to tenfold symmetry in (b). This feature is present but less apparent and has stronger deviations from perfect decagonality in (a). An interesting feature in comparing the cell parameter of CaCd_6 with that of $\text{Ca}_{13}\text{Cd}_{76}$ is that they relate as $1:\tau$. The data presented in (b) were collected on a macroscopically twinned crystal.

distribution of such building blocks. The central core of the basic building block consists, in analogy with CaCd_6 and the RECd_6 phases, of a Cd_{20} pentagonal dodecahedron that encloses a disordered Cd_4 tetrahedron.

The Cd atoms are arranged in two ways around the Ca atoms. The first is a monocapped, double pentagonal antiprism (CaCd_{16} polyhedron; Figure 2a), an arrangement that is known from $\text{Ce}_6\text{Cd}_{37}$, CaCd_6 , the RECd_6 and $\text{RE}_{13}(\text{Zn},\text{Cd})_{58}$ phases.^[10] The second arrangement is a double Friauf polyhedron (Figure 2b), which is known from several other intermetallic compounds.^[11] The construction of the basic building block from CaCd_{16} polyhedra, Cd_8 cubes, and double Friauf polyhedra is illustrated in Figure 3. The presence of Cd_8

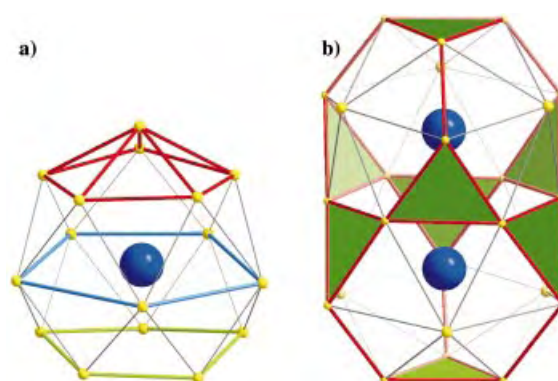


Figure 2. The different arrangements of Cd atoms (yellow) around Ca atoms (blue) in $\text{Ca}_{13}\text{Cd}_{76}$. a) The CaCd_{16} polyhedron, a monocapped double pentagonal antiprism. b) The double Friauf polyhedron, two truncated tetrahedra sharing a hexagonal face. All hexagonal faces are capped by Cd atoms, except for the shared face, in which the Ca atoms mutually serve as capping atoms for one another.

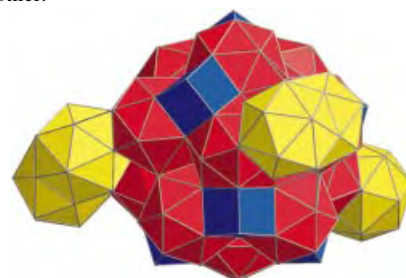


Figure 3. Polyhedral model of the basic building block in $\text{Ca}_{13}\text{Cd}_{76}$. The CaCd_{16} polyhedra (red), the three surrounding double Friauf polyhedra (yellow), and the vacant Cd_8 cubes (blue) have been combined to construct the building block. Cd atoms are the corners of all polyhedra in the figure.

cubes is not unique to $\text{Ca}_{13}\text{Cd}_{76}$; once again the kinship to the RECd_6 and $\text{RE}_{13}(\text{Zn},\text{Cd})_{58}$ phases is apparent. In $\text{Ca}_{13}\text{Cd}_{76}$ all cubic interstices are vacant.

An alternative way of constructing the basic building block is displayed in Figure 4. This representation is preferable for describing the structures of $\text{Ca}_{13}\text{Cd}_{76}$ and CaCd_6 as the simple packings of triacontahedral clusters seen in Figure 5a and b. The main difference between the structure of $\text{Ca}_{13}\text{Cd}_{76}$ and that of the closely related compound CaCd_6 is the packing of the triacontahedra. The triacontahedron is not a space-filling polyhedron, and in $\text{Ca}_{13}\text{Cd}_{76}$ this problem is solved by interpenetration of the triacontahedral clusters and by the creation of cavities. Two Ca atoms are fitted into each of these cavities to form the double Friauf polyhedron (Figure 6). In CaCd_6 the problem of space filling is solved solely by interpenetration of the triacontahedra.

The unforeseen introduction of a double Friauf polyhedron allows for new ways to arrange the triacontahedral clusters; this knowledge could prove useful in modeling the structures of the $\text{MCD}_{5,7}$ quasicrystals.

Experimental Section

Crystals of $\text{Ca}_{13}\text{Cd}_{76}$ were obtained by placing a mixture of Cd metal (1.0101 g; splinters from a rod of pure metal, purified by melting) and Ca (0.0736 g; STREM 99.9%) in a steel ampoule that was sealed under argon atmosphere. The sample was first preheated in a high-frequency induction furnace (two 5-s bursts, well above 1300 K). The ampoule was then inserted into a regular furnace for 1 min at 1133 K, quenched to ambient temper-

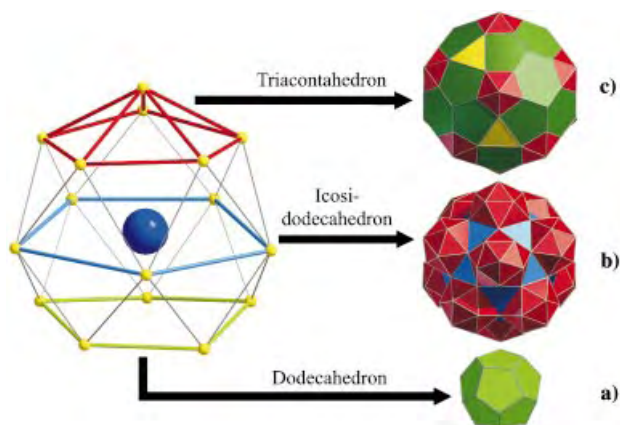


Figure 4. Spherical representation of the basic building block. The spherical layers are created by interconnecting the different pentagonal planes of the CaCd_{16} polyhedra. To emphasize this and the relation with the polyhedral model in Figure 3, the CaCd_{16} polyhedra are included in (b) and (c). Interconnection of the basal pentagonal planes (green) yields the pentagonal dodecahedron in (a); it is somewhat distorted by the disordered Cd_4 tetrahedron residing inside. Interconnection of the intermediate pentagonal planes (blue) gives an icosidodecahedron, a polyhedron composed entirely of equilateral triangles and regular pentagons, shown in blue in (b). The outermost shell of the basic building block is generated by connecting the pentagonal pyramids (red) through the equidistant Cd atoms located in between. This results in a defect rhombic tricontahedron (c). A few of the corner atoms are missing; this is represented by two yellow triangular faces in (c). These vacant positions correspond to positions inside the Cd_8 cubes in Figure 3. Occupation of the cubic interstices by Cd atoms would yield the complete tricontahedron. Occupied and vacant Cd_8 cubes have been observed before in $\text{Ce}_6\text{Cd}_{37}$, $\text{Dy}_{13}\text{Zn}_{57}$, and several other RECd_6 and $\text{RE}_{13}(\text{Zn,Cd})_{58}$ phases.^[7] However, the single-crystal data collected for $\text{Ca}_{13}\text{Cd}_{76}$ do not support a structure with filled cubic interstices.

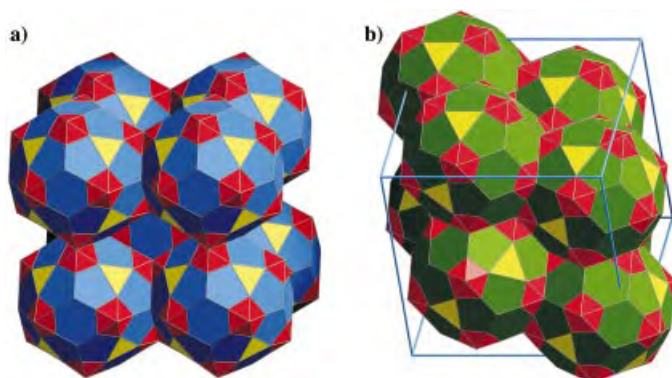


Figure 5. The structure of CaCd_6 (a) can be described as a body-centered cubic arrangement of partially interpenetrating tricontahedra. The cell content of $\text{Ca}_{13}\text{Cd}_{76}$ (b) can similarly be described as a cubic close-packed arrangement of partially interpenetrating tricontahedra. The yellow triangles indicate missing corner atoms.

ature, reinserted at 858 K, and held at that temperature for 90 h. The furnace was then turned off, and the sample was left inside to cool down to ambient temperature (cooling rate ca. 3° min^{-1}).

The diffraction data were collected on a STOE IPDS single-crystal X-ray diffractometer with a rotating-anode $\text{MoK}\alpha$ X-ray source, and the determination of the structure by direct methods was performed with the program SHELXS-86.^[12] The refinement of the structure was performed on a twinned crystal by using the program JANA98.^[13] The intensities of the reflections were integrated with the STOE software, and the numerical absorption correction was performed with the programs X-RED and X-SHAPE.^[14]

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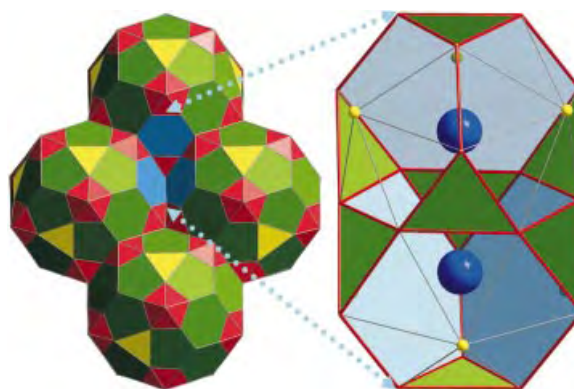


Figure 6. The double Friauf polyhedron is located at the junction where eight of the tricontahedral clusters meet. Four of these clusters have been removed in the figure, and the hexagonal faces of the double Friauf polyhedron are highlighted in blue for clarity.

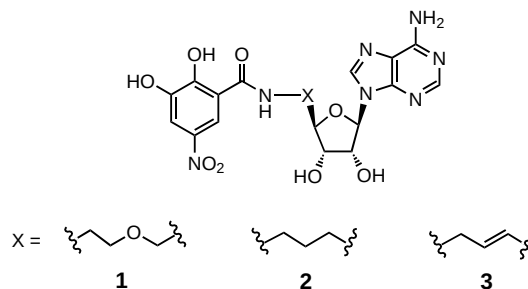
- [1] Crystallographic data for $\text{Ca}_{13}\text{Cd}_{76}$: $M_r = 9063.4$, cubic, space group $Pa\bar{3}$ (no. 205), $a = 25.339(2) \text{ \AA}$, $V = 16270(1) \text{ \AA}^3$, $Z = 8$, $\rho_{\text{calc}} = 7.401 \text{ g cm}^{-3}$, $F(000) = 31226$, $\mu(\text{MoK}\alpha) = 20.19 \text{ mm}^{-1}$, crystal dimensions $0.3 \times 0.27 \times 0.25 \text{ mm}$. Diffraction data were collected on a STOE IPDS at 298 K; $2\theta = 3.9\text{--}51.9^\circ$, 5242 independent reflections, 1965 observed reflections ($I > 3\sigma(I)$), $R_{\text{int}}(\text{obs/all}) = 0.109/0.139$, 258 parameters, $R(F) = 0.0525$, $R_w(F) = 0.0496$, numerical absorption correction from X-SHAPE, $T_{\text{min}}/T_{\text{max}} = 0.0301/0.0737$, $\Delta\rho_{\text{min}}/\Delta\rho_{\text{max}} = 4.985/-3.912 \text{ e \AA}^{-3}$, $\Delta/e.s.d. = 0.0004$. Further details on the crystal structure investigations 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 depositary number CSD-411887.
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X-ray Crystal Structure of a Bisubstrate Inhibitor Bound to the Enzyme Catechol-*O*-methyltransferase: A Dramatic Effect of Inhibitor Preorganization on Binding Affinity**

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Although many drugs are based on single-substrate analogues, it is well appreciated that enzymes often require, in addition to a substrate, a cofactor for function. The rational design of inhibitors, where a substrate analogue and a cofactor analogue are covalently linked to form a bisubstrate inhibitor, may provide innovative new lead structures in medicinal chemistry that feature both enhanced binding affinity and binding-site selectivity. Some attempts have been made to construct bisubstrate inhibitors for kinases which target both the ATP and the substrate binding sites.^[1, 2] Other important targets are methyltransferases that depend on *S*-adenosyl-methionine (SAM). The enzyme catechol-*O*-methyltransferase (COMT) catalyzes the methylation of biologically active catechols, such as l-dopa and dopamine, in the presence of SAM and Mg²⁺ ions. The addition of COMT inhibitors to levodopa reduces the extracerebral catabolism of levodopa and increases its elimination half-life, thus ensuring that a higher quantity of orally administered L-dopa reaches its target in the brain.^[3] This situation produces a stronger and longer lasting therapeutic effect in patients with Parkinson's disease. Nitro-substituted catechols were found to be potent COMT inhibitors, and two derivatives (tolcapone (Tasmar) and entecapone (Comptan)) have been introduced into the marketplace.^[3] Recently, we described the first effective bisubstrate inhibitor **1** for COMT (IC₅₀ = 2 μM; IC₅₀ = concentration of inhibitor at which 50 % inhibition of the enzyme is observed) which was developed by rational design using the crystal structure of the quaternary complex between the enzyme, SAM, 3,5-dinitrocatechol, and a Mg²⁺ ion.^[4–6] ¹H NMR analysis of a cytosine analogue of **1**^[4] in D₂O revealed a strong nuclear Overhauser effect (NOE) between the catechol protons and H-C(5) of the nucleobase and indicates a hydrophobic collapse of the inhibitor.^[7] This collapse results in a favorable conformation of the free inhibitor which reduces the binding free energy. Guided by

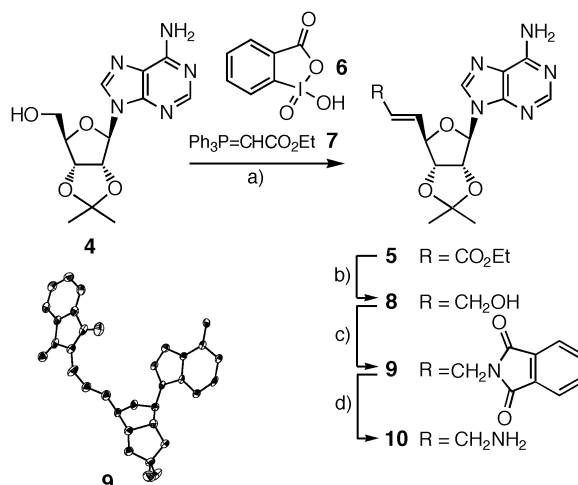
computer modeling studies,^[8] we designed compounds **2** and **3** with shorter and conformationally less flexible linkers between the adenine and catechol moieties (Scheme 1). Here,



Scheme 1. Bisubstrate inhibitors **1–3** for COMT with different linkers X.

we show that **3** is the most potent bisubstrate inhibitor of COMT introduced thus far and describe the X-ray crystal structure of its ternary complex with COMT and a Mg²⁺ ion.

The synthesis of **2** and **3** started from protected adenosine **4**^[9] (Scheme 2).^[10] The unsaturated ester **5**^[11] was prepared by a convenient one-pot^[12] 5'-oxidation with *o*-iodoxybenzoic



Scheme 2. Synthesis of amine **10**: a) Me₂SO, 20 °C, 72 h, 70 %; b) DIBAL, CH₂Cl₂, –78 °C, 2 h, 98 %; c) phthalimide, DEAD, PPh₃, THF, 20 °C, 2.5 h, 68 %; d) MeNH₂, EtOH, 20 °C, 16 h, 95 %. DIBAL = diisobutylaluminum hydride. DEAD = diethyl azodicarboxylate.

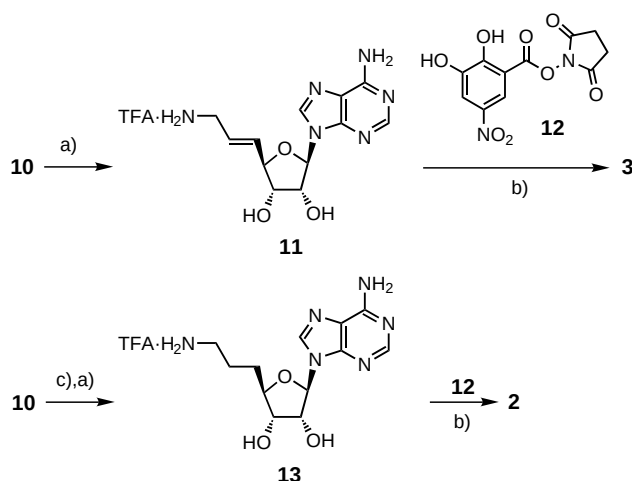
acid (IBX, **6**)^[13] and olefination with phosphorane **7**. Reduction with DIBAL gave allylic alcohol **8**, which was transformed into phthalimide **9** by a Mitsunobu reaction.^[14] The X-ray crystal structure of **9** (Scheme 2)^[15] showed a large spatial separation of the nucleobase and phthalimide moieties, which indicated that the alkene spacer would efficiently prevent the hydrophobic collapse in the free bisubstrate inhibitor **3**. Amine **10** was obtained in excellent yield by the cleavage of phthalimide **9** with methylamine.

Deprotection of **10** gave **11**, which reacted with the activated ester **12** to give target compound **3** (Scheme 3). Catalytic hydrogenation of **10** followed by deprotection afforded **13**, which was coupled to **12** to give the second target compound **2**.

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Scheme 3. Synthesis of bisubstrate inhibitors **2** and **3**: a) CF_3COOH (TFA)/ H_2O (5/2), 20°C , 2 h, 81%; b) Et_3N , DMF, 20°C , 24 h, 80%; c) H_2 , Pd/C, EtOH, 20°C , 2 d, then (a), 74% (from **10**).

The IC_{50} values, obtained in a radiochemical assay,^[4, 16] are listed in Table 1. Compound **2** (IC_{50} 199 nM) has a tenfold higher inhibitory potency than **1** (IC_{50} 2 μM). Removal of the 5'-oxygen atom in **1** produces a shorter, conformationally less-flexible linker which remains sufficiently long to allow the

Table 1. IC_{50} values (uncertainties $\pm 5\%$) determined by a radiochemical assay with incubation^[4, 16] for the bisubstrate inhibitors **1**–**3** of COMT.

Compound	IC_{50} [nM]
1	2000
2	199
3	9

docking of **2** in both SAM and catechol binding sites. Further rigidification of the spacer by the introduction of a double bond has a tremendous effect on the binding affinity. Compound **3**, which has an IC_{50} value of 9 nM, is the most potent bisubstrate inhibitor for COMT to date. Kinetic analysis^[4] shows a competitive inhibition mechanism for **3** with regard to the SAM binding site and a more complex inhibition mechanism with regard to the catechol binding site.

In order to prove our bisubstrate binding model based on computer modeling studies, **3** was co-crystallized with COMT and Mg^{2+} ions. The X-ray structure of the ternary complex formed was then determined at 2.6 Å resolution (Figure 1a).^[17] The inhibitor occupies, as predicted, both the SAM and catechol binding sites. The structure of the ternary complex closely resembles that of the quaternary complex of COMT with SAM, 3,5-dinitro catechol, and a Mg^{2+} ion—this structure having been used for the rational design of **3**.^[4, 5] The protein structure is similar in both complexes, with an overall root mean square (r.m.s.) deviation of 0.4 Å for the C α atoms. In particular, the intermolecular contacts between the protein and adenosine and catechol moieties are conserved (Figure 1b). The side chain of Trp143 is not fully visible in the electron density, that is, its indole group, which shields the adenine and the linker part of the inhibitor from the exterior, is disordered in the ternary complex. The methyl group of

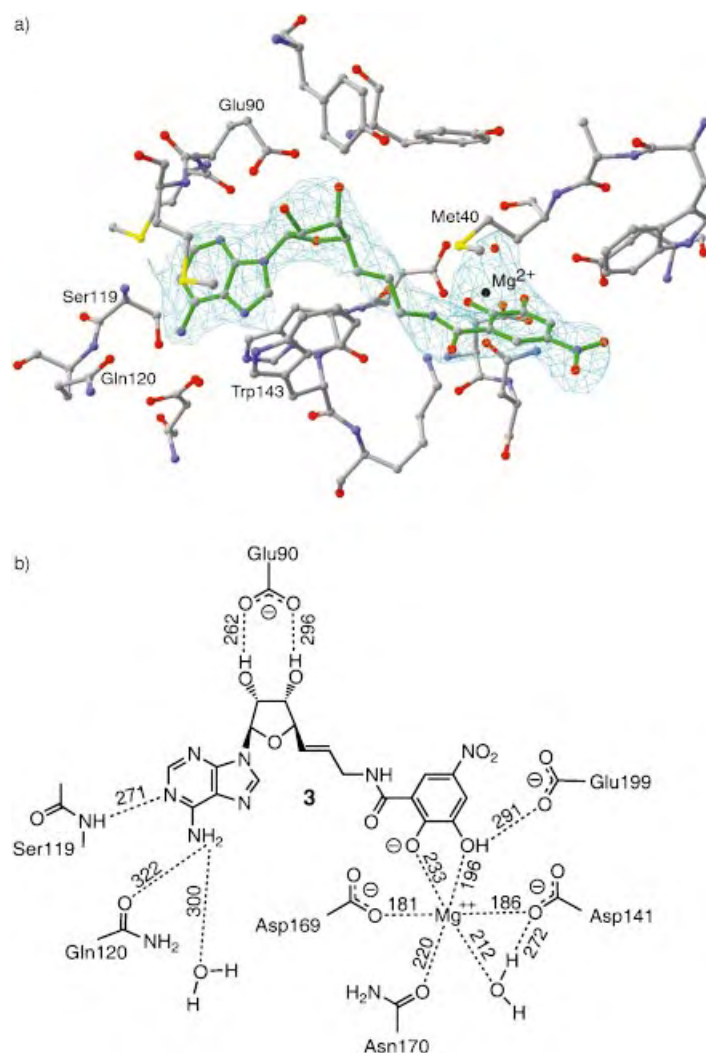


Figure 1. a) The bisubstrate inhibitor binding site in the refined X-ray structure. The $F_{\text{obs}} - F_{\text{calc}}$ electron density of **3** is shown contoured at the 2.5 σ level. This electron density was calculated after the first round of refinement when the inhibitor was not yet included into F_{calc} and is therefore unbiased. Coloring: C: gray, inhibitor framework: green, O: red, N: blue, S: yellow; H atoms omitted. b) Schematic drawing of the H-bonding interactions (dashed lines) in the ternary complex. Distances are given in pm.

Met 40 is rotated by 79° relative to the conformation of Met 40 found in the quaternary complex of COMT, thus making space for the linker of the bisubstrate inhibitor. In the design of next-generation bisubstrate inhibitors of COMT, the flexibility of the side chains of Met 40 and Trp 143 could be taken into account. With the insight gained from X-ray analysis into the molecular recognition principles at the active site of COMT, structural variations of the ribose, catechol, and nucleobase moieties in bisubstrate inhibitors are now targeted.

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- [17] Crystals of recombinant rat liver COMT^[5] were grown by the vapor diffusion method in space group *P*3₂21 with cell axes *a* = *b* = 50.6, *c* = 167.7 Å. The reservoir solution was 25 % polyethylene glycol (PEG) 8000, 100 mM ammonium sulfate, and 100 mM bis-Tris pH 5.5 (Tris = tris(hydroxymethyl)aminomethane). The hanging drop consisted of 1 μL of the reservoir solution and 3 μL of a solution containing 10 mg mL^{−1} COMT, 5 mM MgCl₂, and 1.6 mM **3**. A data set to 2.6 Å resolution with an *R*_{sym} value of 5.4 % and a completeness value of 97.8 % was collected using CuKα radiation from a rotating anode source. In the highest resolution shell the *R*_{sym} value was 27.9 % and the completeness value of 95.4 %. The starting model for refinement was the protein portion of an isomorphous quarternary COMT inhibitor complex in the crystal (F. K. Winkler, F. Hoffmann–La Roche, Basel, unpublished results, **1994**). The structure was completed using MOLOC^[8] and refined with CNX (A. T. Brünger, P. D. Adams, G. M. Clore, W. L. DeLano, P. Gros, R. W. Grosse-Kunstleve, J. S. Jiang, J. Kuszewski, M. Nilges, N. S. Pannu, R. J. Read, L. M. Rice, T. Simonson, G. L. Warren, *Acta Crystallogr. Sect. D* **1998**, *54*, 905–921) to an *R* factor of 22.3 % and a free *R* factor of 28.0 %. The refined model consists of protein residues 3 to 214, a Mg²⁺ ion, 16 water molecules, and **3**. 88.8 % of the residues are in the most favored regions of the Ramachandran plot. The atomic coordinates have been deposited to the Brookhaven Protein Databank, with the PDB entry code 1JR4.

A Blue Luminescent Star-Shaped Zn^{II} Complex that Can Detect Benzene**

Jun Pang, Eric J.-P. Marcotte, Corey Seward, R. Stephen Brown,* and Suning Wang*

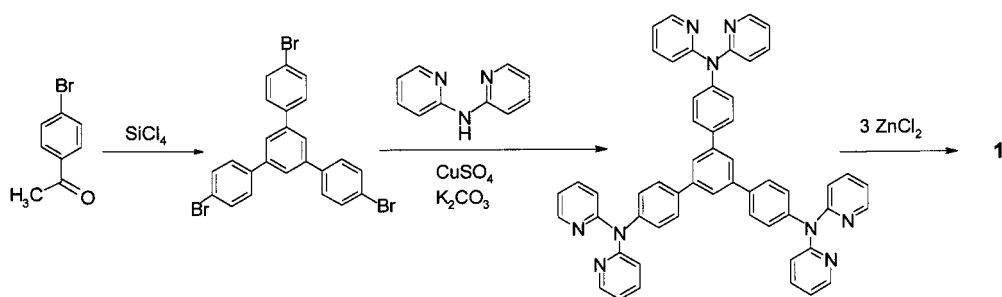
Luminescent metal complexes are a fascinating class of molecules that have found applications in many areas of chemistry and materials science. For example, it has been demonstrated that luminescent metal compounds can function as emitters in light-emitting devices.^[1] Luminescence is often used as a tool for the detection of a certain weak metal–metal interactions.^[2] There are several recent reports on the effect of organic solvents on the luminescence of transition metal compounds,^[2] of which most intriguing are the reports by Balch and co-workers that describe an unusual solvoluminescent phenomenon displayed by gold(I) cluster compounds.^[2c,d] The high sensitivity of the luminescence of metal complexes to their environment demonstrated in these reports makes such complexes possible fluorescent sensors for specific chemicals. Although there are abundant reports on the use of luminescent transition metal compounds as fluorescent sensors, information on the direct correlation between structures and sensor capability is still scarce. Blue luminescent compounds are a class of highly sought-after materials primarily, because of their potential application as emitters in electroluminescence displays.^[3–4] In addition, because most blue emitters have absorption bands in the UV or near-UV region where many aromatic molecules absorb, they have the potential to function as fluorescent sensors for the detection of aromatic molecules, such as benzene, that are an environmental concern.

During our investigation of blue luminescent compounds, we synthesized a new class of blue luminescent organic star-shaped molecules that contain either 7-azaindolyl or 2,2'-dipyridylamino groups. Some of the new star-shaped molecules have been found to be promising blue emitters in electroluminescence devices.^[4d, 5] Most interestingly, we found that the new star-shaped molecules are capable of coordinating to various metal centers, which results in the formation of novel coordination compounds. Some of these new compounds are capable of selectively detecting specific small molecules by functioning as fluorescent sensors, an example of which, the Zn^{II} complex of 1,3,5-tris(*p*-(2,2'-dipyridylamino)phenyl)benzene (TPDPB), is described herein.

The novel TPDPB ligand was obtained by a two-step synthesis in an overall 68 % yield. The first step is based on a literature procedure^[6] and the second step uses Ullmann condensation methods^[7] (Scheme 1). The TPDPB ligand displays a broad emission band at λ_{max} = 386 nm in solution

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Scheme 1.

(CH₂Cl₂) and at $\lambda_{\text{max}} = 400$ nm in the solid state when irradiated by UV light. The quantum efficiency of TPDPB in solution was determined to be 0.19, relative to that of 9,10-diphenylanthracene. The star-shaped complex, [(ZnCl₂)₃(TPDPB)] (**1**) was obtained from the reaction of TPDPB with three equivalents of ZnCl₂ in CH₂Cl₂/CH₃OH solution. Complex **1** is stable toward air and moisture in solution and in the solid state, and its fluorescence emission shows an unusually high selectivity to benzene vapor.

Single-crystal X-ray diffraction revealed that **1** adopts several different motifs of crystal lattices,^[8] which depend on the solvents used in crystallization. In the presence of CH₂Cl₂ and a small amount of benzene, crystals **A** with the composition of [(ZnCl₂)₃(TPDPB)] · 3 CH₂Cl₂ · 0.25 C₆H₆ were obtained. When a solution of CH₂Cl₂ and benzene in a 1:1 ratio was used, crystals **B** with the composition of [(ZnCl₂)₃(TPDPB)] · 3 C₆H₆ were formed. The molecular structure of **1** in both crystals is similar. The structure of **1** in the crystal lattice of **A** (Figure 1) has a crystallographically imposed C₃ symmetry with a bowl shape. In both **A** and **B** each ZnCl₂ unit is chelated by two 2-pyridyl groups and has a distorted tetrahedral geometry and normal bond lengths^[4e, 4f, 9] (**A**: Zn–N 2.017(8)–2.051(8), Zn–Cl 2.190(3)–2.198(3) Å; N–Zn–N 90.4(3)–90.6(3), Cl–Zn–Cl 116.85(16)–117.24(14), Cl–Zn–N 108.0(2)–116.4(2); **B**: Zn–N 1.969(11)–2.052(9), Zn–Cl 2.148(4)–2.212(3) Å;

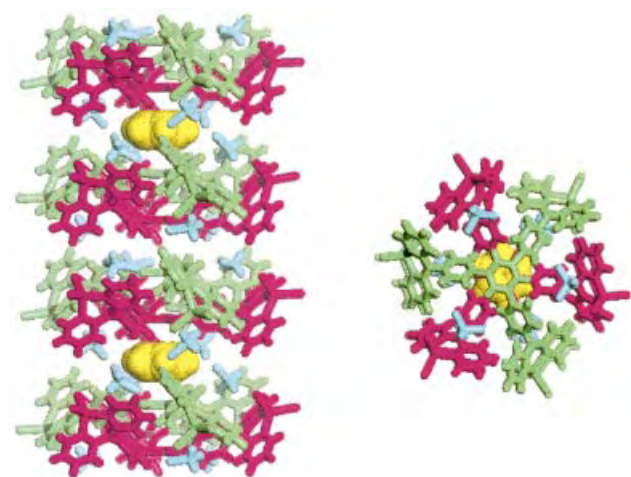


Figure 1. Stick/space-filling diagrams showing the sandwiched arrangement of benzene and **1** in crystal **A**, viewed along *c* axis (left) and viewed down the *c* axis (right). Benzene: yellow, space filling; CH₂Cl₂: light blue, stick. The interlocked pairs of molecules of **1** are shown as red and green, respectively

N–Zn–N 88.8(5)–90.1(4), Cl–Zn–Cl 119.58(15)–122.80(14), Cl–Zn–N 105.2(3)–116.0(3)°). In the crystal lattice of **A**, two neighboring molecules of **1** are paired and staggered in a face-to-face fashion with the separation between the central phenyl rings being 3.85(1) Å. These pairs stack along the *c* axis to form a hexagonal column. The benzene molecule is situated

directly above the central phenyl ring of **1** and sandwiched by two molecules of **1** (Figure 1). The separation between the benzene molecule and the two central phenyl rings of **1** is 3.60(1) Å, indicative of the presence of π – π stacking interactions. There are three benzene solvent molecules per molecule of **1** in the crystal lattice of **B**, which do not stack with compound **1** in the face-to-face manner observed in **A**. Two of the benzene molecules are nearly perpendicular to the TPDPB ligand while the remaining one is somewhat parallel to the TPDPB ligand shown (Figure 2), but is perpendicular to



Figure 2. Space-filling diagram of the molecular structure of **1** in crystal **B**. Green: chlorine, blue: nitrogen, red: zinc, gray: carbon, yellow: benzene.

a neighboring TPDPB ligand of an adjacent molecule in the lattice. The π – π interactions in **B** are therefore both edge-to-face and face-to-face. The crystals **A** and **B** demonstrate that in the solid state compound **1** has a high affinity for benzene, which makes **1** a possible fluorescent sensor for benzene.

Compound **1** shows a broad emission band ($\lambda_{\text{max}} = 417$ nm in solution and $\lambda_{\text{max}} = 432$ nm in the solid state) resembling that of TPDPB but red-shifted by ~ 30 nm. A similar red-shift as a consequence of Zn^{II} coordination is observed for tris(2-pyridyl)amine Zn^{II} complexes^[4f] where the Zn^{II} ion is chelated by two 2-pyridyl groups in a similar fashion to that in **1**. The quantum efficiency of **1** is similar to that of the free ligand. To study the potential of **1** as a fluorescence sensor, we prepared a modified optical-fiber tip by attaching a freshly prepared prepolymerized polydimethylsiloxane (PDMS) bead containing **1** (1.8 mm diameter, prepared by mixing prepolymerized PDMS (50 mg) with a CH₂Cl₂ (0.3 mL) solution of **1** (0.25 mg) and allowing the mixture to dry until sticky) to a fused silica optical fiber (0.6 mm in diameter). Fluorescent measurements were carried out by using an optical-fiber setup.^[10] Upon exposure to benzene, the intensity (integrated) of the

emission band of **1** decreases. The response curves in Figure 3 show both the absolute signal and the Stern–Volmer response. The linear Stern–Volmer response is consistent with well-behaved fluorescence quenching systems. After the removal of benzene vapor, the fluorescence of **1** recovers to the initial intensity. To study the selectivity of our sensor, we

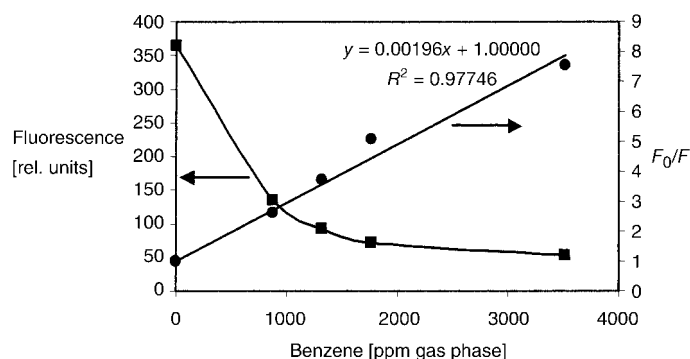


Figure 3. The response curves of **1** as an optical sensor for benzene; F_0/F = Stern–Volmer.

placed our sensor in contact with 500 ppm of selected compounds and examined the change of fluorescent intensity. For each compound, five measurements were carried out. The averaged results given in Figure 4 show that compound **1** has a remarkably high selectivity for benzene. Most noteworthy is that of the four aromatic molecules examined (benzene, toluene, ethyl benzene, and xylene) benzene stands out in terms of fluorescence response. A similar fluorescent response was not observed by using the free ligand TDPBP as the probe.

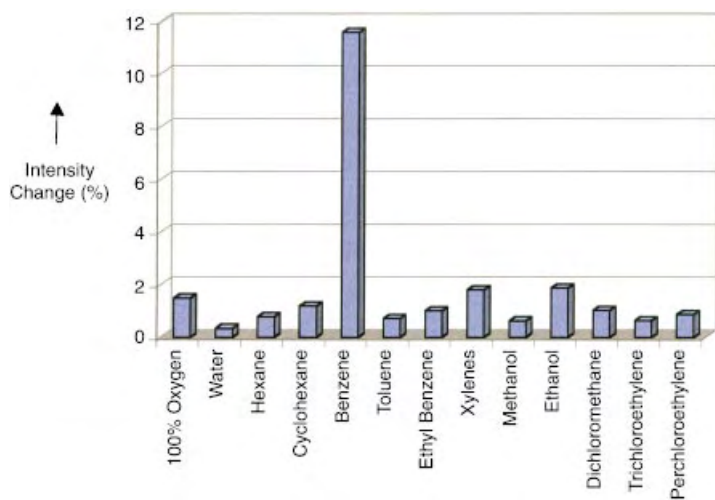


Figure 4. A diagram showing the change of fluorescent intensity of **1** in the optical sensor upon exposure to 500 ppm selected molecules.

Although the precise nature of the interactions between the benzene molecule and compound **1** in PDMS cannot be established at this time, the high selectivity of the fluorescence of compound **1** towards benzene could be attributed to the high affinity of **1** for benzene as demonstrated in the crystals **A** and **B**. Fluorescence quenching by π – π stacking interac-

tions is well documented.^[11] Therefore, π – π interactions, face-to-face or edge-to-face, between benzene and **1** as observed in **A** and **B** are most likely to be responsible for the fluorescent quenching.

Chemical sensors, based on fiber-optic devices, for benzene have been reported.^[12] Fiber-optic sensors based on fluorescence have some advantages over other strategies, these are ease of operation and use, low sensitivity to defects in coatings, insensitivity to electrical interference, and use in gas and liquid phases. However, fluorescence sensors based on solid-state materials for the selective detection of benzene vapor are still rare. Although the response of the optical sensor **1** towards benzene is still far from being suitable for practical applications, it demonstrates that complexes based on the novel TDPBP ligand are promising as fluorescent sensors for specific organic molecules.

Experimental Section

TPDPB: A mixture of 1,3,5-tris-(*p*-bromophenyl)-benzene (0.98 g, 1.8 mmol), 2,2'-dipyridylamine (1.54 g, 9.0 mmol), K_2CO_3 (1.24 g, 9.0 mmol), and $CuSO_4$ (0.13 g, 0.518 mmol) in water (20 mL) and CH_2Cl_2 (100 mL) was stirred well, and evaporated to dryness in vacuum. The residue was heated at 210 °C for 8 h under N_2 . After being cooled to ambient temperature, the mixture was dissolved in CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was purified by column chromatography using THF/hexane (3/1) as the eluent to obtain colorless crystalline solid of TPDPB (1.24 g, yield 85 %). M.p. 177–180 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.42 (d, ^3J = 5.1 Hz, 6H, py), 7.79 (s, 3H, ph), 7.71 (d, ^3J = 8.6 Hz, 6H, ph), 7.63 (dd, $^3J_1$ = 8.6 Hz, $^3J_2$ = 6.9 Hz, 6H, py), 7.32 (d, ^3J = 8.6 Hz, 6H, ph), 7.08 (d, ^3J = 8.6 Hz, 6H, py), 7.00 (dd, $^3J_1$ = 6.9 Hz, $^3J_2$ = 5.1 Hz, 6H, py); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 158.0, 148.7, 144.5, 141.7, 138.1, 128.6, 126.9, 118.4, 118.3, 117.8, 117.5. Elemental analysis calcd (%) for $C_{54}H_{39}N_9/H_2O$: C 77.97, H 4.93, N 15.16; found: C 78.51, H 4.75, N 14.64.

1: A solution of TPDPB (0.050 g, 0.0614 mmol) in CH_2Cl_2 (5 mL) was added to a solution of anhydrous $ZnCl_2$ (0.0276 g, 0.203 mmol) in CH_3OH (10 mL) at ambient temperature under N_2 . The solution was left to stand for three days and a colorless powder of **1** was obtained (0.066 g, 72 %). M.p. > 300 °C; ^1H NMR (300 MHz, $[D_4]methanol$, 25 °C): δ = 8.26 (dd, ^3J = 5.1 Hz, ^4J = 0.9 Hz, 6H, py), 7.92 (s, 3H, ph), 7.83 (d, ^3J = 8.4 Hz, 6H, ph), 7.75 (ddd, ^3J = 7.8 Hz, $^3J'$ = 7.2 Hz, ^4J = 1.8 Hz, 6H, py), 7.31 (d, ^3J = 8.4 Hz, 6H, ph), 7.13 (dd, ^3J = 7.2 Hz, $^3J'$ = 5.1 Hz, 6H, py), 7.11 (d, ^3J = 7.8 Hz, 6H, py). Elemental analysis calcd (%) for $C_{38.5}H_{46.5}N_9Cl_{12}Zn_3$: C 46.93, H 3.13, N 8.42, found: C 46.61, H 2.94, N 8.80.

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- [8] Crystal data for crystal **A**: $C_{54}H_{39}N_9Cl_6Zn_3 \cdot 3CH_2Cl_2 \cdot 0.25C_6H_6$, rhombohedral, $R\bar{3}$, $a = b = 33.517(4)$, $c = 19.167(3)$ Å, $V = 18647(4)$ Å³, $Z = 12$. Crystal data for crystal **B**: $C_{54}H_{39}N_9Cl_6Zn_3 \cdot 3C_6H_6$, triclinic, $P\bar{1}$, $a = 13.805(4)$, $b = 14.848(5)$, $c = 17.384(5)$ Å, $\alpha = 87.208(6)$, $\beta = 88.569(6)$, $\gamma = 77.828(8)^\circ$, $V = 3478.7(18)$ Å³, $Z = 2$. Data were collected on a Bruker CCD1000 X-ray diffractometer at 24 °C. Structural solution and refinements were carried out using Bruker AXS SHELXTL NT software. Convergence to final $R_1 = 0.1283$ and $wR_2 = 0.3320$ by using 10089 reflections and 495 parameters for **A** and $R_1 = 0.0991$ and $wR_2 = 0.1079$ by using 16047 reflections and 791 parameters for **B** were achieved. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-163379 (**A**) and -163380 (**B**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Lamellae-Nanotube Isomerism in Hydrogen-Bonded Host Frameworks**

Matthew J. Horner, K. Travis Holman, and Michael D. Ward*

The supramolecular organization displayed by surfactant assemblies (SAs) and block copolymers (BCs) is often characterized by various ordered microstructures—spherical, lamellar, hexagonal, and cubic phases—that exhibit different curvatures of a common interface that defines the boundary between dissimilar segments of the molecular components. The ultimate microstructure reflects a delicate balance of forces on opposite sides of the interface.^[1, 2] Though typically described by smaller length scales, analogous architectures are evident in crystalline small-molecule assemblies,^[3] such as the hexagonal urea^[4] and perhydrotriphenylene^[5] inclusion compounds, supramolecular hydrogen-bonded nanotubes formed by cyclic peptides^[6] and cyclodextrins,^[7] high-symmetry metal–organic coordination networks,^[8] and lamellar organic salts.^[9] To the best of our knowledge, however, structural isomerism in organic single crystals based on the curvature of a common two-dimensional supramolecular interface is unknown.

We previously reported that, depending on the identity of the organic substituent, guanidinium organomonosulfonates typically crystallize as either bilayered or continuously layered (CL) architectures. The organic substituents form interdigitated arrays between “quasi-hexagonal” hydrogen-bonded sheets of the guanidinium ions (**G**) and sulfonate (**S**) moieties (Figure 1).^[10] The two architectures differ with respect to the projection of the organic substituents from each **GS** sheet—whereas substituents project from the same side of each sheet in the bilayer form they project from both sides in the CL architecture, thereby accommodating substituents with a larger steric “footprint”. The **GS** sheet can be described as one-dimensional **GS** ribbons fused by hydrogen bond “hinges” that allow the sheets to pucker (about an angle θ_{IR}) in the CL architectures in order to optimize the packing of the organic substituents.^[11] Guanidinium salts of appropriately chosen organodisulfonates form analogous bilayer and continuous “brick” host architectures in which the organic substituents serve as “pillars” and generate guest-filled inclusion cavities between the **GS** sheets.^[12] The preference for a given host architecture depends upon the shape and relative sizes of the pillars and guests, the latter behaving as templates that direct the formation of a particular **GS** host architecture.

We have now discovered that guanidinium organomonosulfonates can also form inclusion compounds, with their

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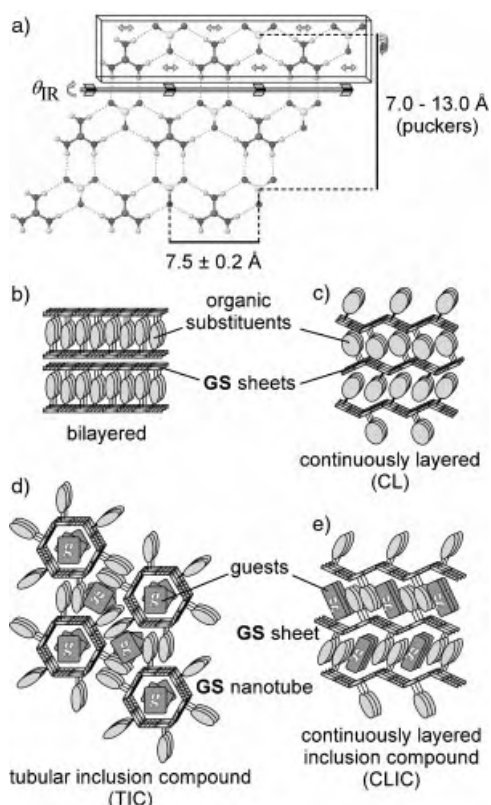
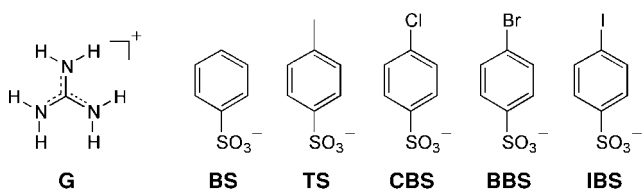


Figure 1. a) Schematic representation of the “quasi-hexagonal” hydrogen-bonded **GS** sheet consisting of 1D ribbons (boxed), which are fused along their edges by hydrogen bond “hinges” about which the sheet can pucker (by an angle θ_{IR}) in the CL architectures. b–e) Schematic representations of the various architectural isomers of the guest-free and guest-included guanidinium organomonosulfonates.

GS frameworks exhibiting bilayered, continuously layered, and hexagonal tubular architectures that are reminiscent of SA and BC microstructures. Guest-free **G**[benzenesulfonate], **G**[*p*-toluenesulfonate], **G**[4-chlorobenzenesulfonate], and **G**[4-bromobenzenesulfonate], herein referred to as **GBS**, **GTS**, **GCBS**, and **GBBS**, respectively, crystallize in the



bilayered form, and **G**[4-iodobenzenesulfonate] (**GIBS**) crystallizes in the CL architecture (Table 1). When crystallization is performed in the presence of certain aromatic molecules, however, these molecules template new **GS** host architectures, either a CL inclusion compound (CLIC) with one guest included per **GS** unit or a tubular inclusion compound (TIC) with two-thirds of a guest per **GS** unit (Figure 1).

The **GS** sheets in the guest-free and inclusion compounds in Table 1 all exhibit identical supramolecular connectivity, that is, the quasi-hexagonal **GS** hydrogen-bonding motif depicted in Figure 1a.^[13] Therefore, for a given organomonosulfonate the three frameworks can be regarded as architectural

Table 1. Summary of architectures observed in guest-free and guest-included guanidinium organomonosulfonates.

Guest	GBS	GTS	GCBS	GBBS	GIBS
none	bilayer ^[a]	bilayer ^[a]	bilayer ^[b]	bilayer^[b]	CL ^[c]
<i>p</i> -xylene	CLIC ^[b]	CLIC ^[b]	CLIC ^[b]	CLIC^[b]	CLIC ^[b]
<i>m</i> -xylene	TIC ^[d]	CLIC ^[b]	CLIC ^[b]	CLIC ^[b]	CLIC ^[b]
<i>o</i> -xylene	TIC ^[c]	TIC ^[c] /CLIC ^[b]	TIC ^[c]	CLIC ^[b]	CLIC ^[b]
2-chlorotoluene	TIC ^[c]	CLIC ^[d]	TIC ^[c]	TIC^[b]	CLIC ^[c]
1,2-dichlorobenzene	CLIC ^[b]	CLIC ^[d]	TIC ^[c]	TIC ^[c]	CLIC ^[d]
<i>N,N</i> -dimethylaniline	CLIC ^[b]	CLIC ^[b]	TIC ^[c]	TIC ^[c]	CLIC ^[b]

[a] Structures previously reported.^[10a,b] [b] Completely refined single-crystal structures reported here.^[14] [c] Assignment based on partially refined single-crystal X-ray diffraction data because of poor quality crystals. [d] Preliminary assignment based upon crystal morphology and ¹H NMR data only. The entries in bold correspond to examples depicted in Figure 2.

isomers. For example, guest-free **GBBS** crystallizes in the bilayered architecture, whereas **GBBS**·(*p*-xylene) and **GBBS**· $\frac{2}{3}$ (2-chlorotoluene) crystallize as a CLIC and TIC, respectively (Figure 2).^[14] The guests in the CLICs are interdigitated with the organomonosulfonate substituents, thus generating a herringbone motif that resembles the packing commonly observed in single crystals of simple arenes. Rather than forming the guest-free bilayer phase, the added bulk introduced by the guests forces the formation of the CLIC architecture. This effect is similar to the role of bulky organomonosulfonates that promote the formation of guest-free CL phases. The CLICs, similar to the guest-free CL phases, optimize molecular packing through accordionlike puckering of the **GS** sheet, with puckering angles in the range of $124^\circ < \theta_{\text{IR}} < 144^\circ$. This puckering affords a lamellar architecture in which the **GS** sheets have zero mean curvature.

In contrast to the CLICs, the **GS** sheets in the TICs exhibit curvature, curling into six-sided *discrete* tubes, each comprising six **GS** ribbons. The tubes assemble into a hexagonal array through dispersive interactions between the organosulfonate substituents that line the outer surface of each tube. The hexagonal symmetry of the nanotubes mandates a puckering angle of $\theta_{\text{IR}} = 120^\circ$, which is within the range of values observed for other **GS** compounds. The guest molecules occupy both the tube interior ($\frac{1}{3}$ guest per **GS** unit) and the region between the tubes (the remaining $\frac{1}{3}$). The guest molecules in the tube are disordered, but the structural data reveal that these guests are stacked cofacially with interplanar separations of approximately 3.8 Å. This value is equivalent to one-half of the *c* lattice constant along the tube, which is defined by the nearest neighbor S...S distance along the **GS** ribbon. The center–center intertube distance is $d_{\text{tt}} = 16.3$ Å for **GBS** and ranges from 19.2–19.6 Å for the other three hosts. The values reflect the shorter length of the benzene substituent in **GBS**. The inner diameter of the nanotubes, after accounting for the van der Waals radii, is approximately 8 Å. With the exception of **GBBS**· $\frac{2}{3}$ (2-chlorotoluene), crystals of the TICs appear to be slightly twinned and preliminary structural refinements tend to be poor, although assignment of the tubular architecture is unambiguous.

The CLIC and TIC architectures are distinguished by the projection topology of the organic substituents about their

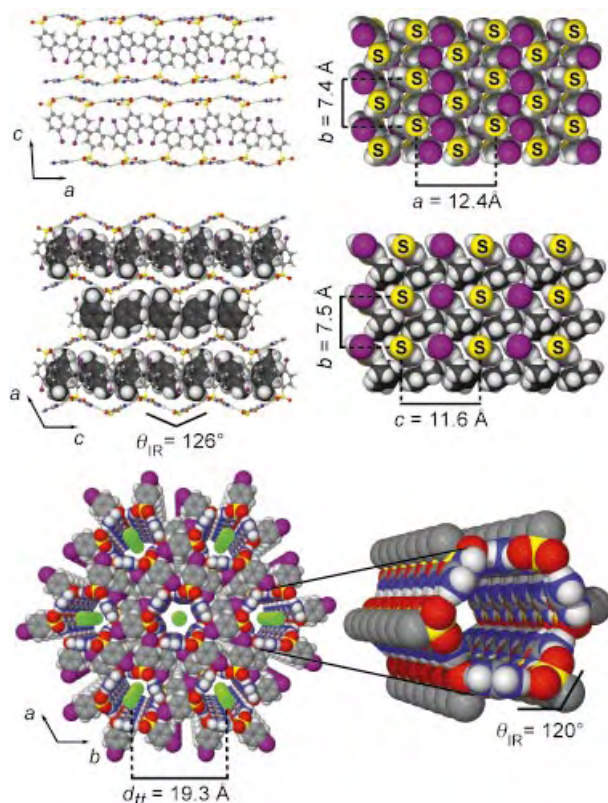


Figure 2. Architectural isomers of the **GBBS** framework. Top: The guest-free bilayer structure as viewed parallel (left) to the hydrogen-bonded **GS** sheets. The packing of the organic substituents between the layers, as viewed normal to the **GS** sheets, is depicted on the right. To better illustrate the packing, the **G** ions and the sulfonate oxygen atoms have been removed and the sulfur atoms labeled. Middle: The CLIC structure observed for **GBBS**·(*p*-xylene) as viewed parallel (left) to the puckered ($\theta_{IR} = 126^\circ$) **GS** sheets. The packing of the *p*-xylene guests and the bromobenzene substituents of sulfonate anions are depicted to the right. The sulfur atoms are labeled and the *p*-xylene guests shaded darker. Bottom: The hexagonal packing of the six-sided **GS** nanotubes in **GBBS**·2/3(2-chlorotoluene) as viewed parallel to the long axes of the tubes. For clarity, the guest molecules are depicted as green circles within the nanotubes, but are omitted from the intertube regions. A single nanotube is illustrated on the right. The organic substituents, with the exception of the carbon atom attached to the sulfonate moiety, are removed for clarity. The hydrogen-bonded surface of the nanotube is described by the same quasihexagonal motif as the guest-free and CLIC phases.

respective **GS** sheets. Whereas an equivalent number of organic substituents project from each side of a given sheet in the CLIC architecture, all the substituents in the TIC architecture project outward from the surface of each tube, enforcing curvature of the **GS** sheet and tube formation. The organic substituents on the tube surface exhibit a twofold disorder and suggest herringbone-like packing in the interdigitated regions of adjacent tubes. In general, however, the guests in this region are so highly disordered that an unambiguous assignment of their orientation is not possible.

The three crystal architectures are also reflected in their dramatically different crystal habits, which are illustrated here by the **GTS** phases (Figure 3). The guest-free bilayered crystals form as plates with large (001) faces and the CLICs form rectangular rafts with prominent (010) faces, both forms reflecting fastest growth along the **GS** ribbons (the

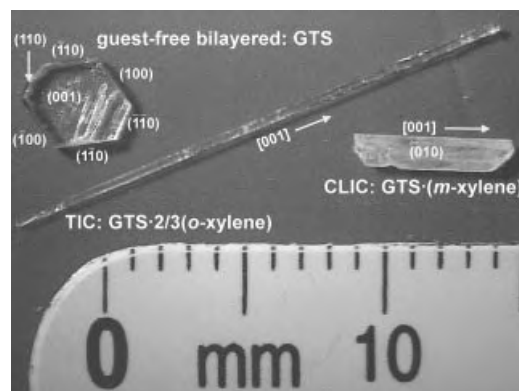


Figure 3. Photograph of single crystals of **GTS**, **GTS**·(*m*-xylene), and **GTS**·2/3(*o*-xylene) which crystallize in the bilayer, CLIC, and TIC architectures, respectively.

[010] direction in the bilayered phase and the [001] in the CLICs). The TICs, however, grow as needles along [001], which coincides with the **GS** ribbons and the long axis of the tubes. Optical microscopy reveals that the tubes have six well-defined sides corresponding to the hexagonal symmetry of the crystals.

Table 1 reveals that the host architecture depends on the specific combination of host and guest. To date, **GTS** is the only host that exhibits both architectures for the same guest (*o*-xylene). Attempts to form inclusion compounds of **G**[4-fluorobenzenesulfonate] afforded only a guest-free crystalline phase with oblong **GS** tubes wherein two of the fluorobenzene substituents project into the tube interior.^[15]

The number of examples in this study is not yet sufficient to construct an unambiguous explanation for the preference of the various architectures for specific host–guest combinations. Though kinetic contributions, such as those related to concentration effects, have not yet been thoroughly investigated, the architectural selectivity observed for the CLICs and TICs in Table 1 most likely is governed by subtle differences in the intermolecular packing of the organic substituents and/or guests between the **GS** sheets or tubes. The observation of both a CLIC and TIC for *o*-xylene inclusion compounds of **GTS** suggests similar lattice energies for these architectural isomers. Notably, the host with the largest organomonosulfonate substituent, **GIBS**, only forms CLICs for the guests in Table 1. This may reflect unfavorable steric interactions between the large iodo group and arene rings on adjacent tubes in putative TICs based on this host. Alternatively, the larger iodo substituent may satisfy a dense packing requirement in the CLIC architecture that is not always achieved with hosts endowed with smaller substituents. Inspection of Table 1 suggests that the shape of the guests also plays a role in the selectivity.

The inclusion compounds described here illustrate an architectural isomerism that resembles the morphological behavior observed for SAs and BCs, albeit at a reduced length scale. The isomerism relies on the curvature of a common, flexible yet robust, two-dimensional interface, namely the **GS** sheet. Like SAs and BCs, the energetic penalty for this curvature must be sufficiently small that the hexagonal tube architecture can be achieved.

In principle, the **GS** tubes are expandable because a continuous quasihexagonal tube surface can form with any number of **GS** ribbons greater than three, thereby producing tubes of various diameters^[15] that can accommodate a range of guest molecules. Molecular models also reveal that tubes constructed from an odd number of ribbons will be chiral. Though it remains to be determined whether volume fraction and frustration models used to explain the microstructures of SAs and BCs can be applied here, we anticipate that the different tube diameters can be achieved through judicious tuning of the steric balance between the guest templates and the organic substituents. The ability to modify the **GS** sheet with different organic substituents provides a distinct advantage over most other organic hosts, which typically cannot be modified in a systematic manner without complete loss of their host architecture. The discrete nature of these self-enclosed nanotubes suggests that, with suitable organic substituents, the isolation of single nanotubes may be possible. The discovery of the new CLIC and TIC architectural isomers, which have substantially different inclusion cavity shapes and dimensionality, also suggests new opportunities in molecular separations^[16] and materials design.

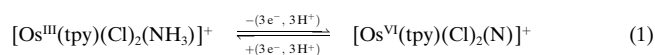
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- [13] Single crystals of the guest-free **GS** phases were grown by evaporation from their methanolic solutions. Single crystals of the inclusion compounds were grown either from methanol solutions containing an excess of the guest or by layering a methanol solution of a **GS** host on neat liquid guest.
- [14] A full hemisphere of data were collected on a Siemens SMART diffractometer with MoK α radiation ($\lambda = 0.71073$ Å). Data were corrected for absorption, and decay using SADABS. Structures were solved by direct methods (SHELXS) and refined with full-matrix least-squares based on $|F^2|$ (SHELX-97-2). H atoms were placed in calculated position using a riding model. X-ray data for **GBBS**: C₁₄H₂₀N₆O₆S₂Br₂, $0.36 \times 0.24 \times 0.14$ mm, monoclinic, $P2_1/c$ (no. 14), $a = 12.391(1)$, $b = 7.4245(6)$, $c = 26.110(2)$ Å, $\beta = 95.498(2)^\circ$, $Z = 4$, $V = 2391.0(3)$ Å³, $\rho_{\text{calcd}} = 1.645$ g cm⁻³, $\mu = 3.605$ mm⁻¹, $1.57 < 2\theta < 27.0^\circ$, $T = 173$ K, $R_1 = 0.0448$ and $wR_2 = 0.0943$ for 2907 ($I > 2\sigma(I)$) of 5218 unique reflections and 271 parameters. **GBBS**·(*p*-xylene): C₁₅H₂₀N₃O₃SBr, $0.45 \times 0.10 \times 0.05$ mm, monoclinic, $P2_1/n$ (no. 14), $a = 7.5357(5)$, $b = 20.809(2)$, $c = 11.6326(8)$ Å, $\beta = 91.463(1)^\circ$, $Z = 4$, $V = 1823.5(2)$ Å³, $\rho_{\text{calcd}} = 1.465$ g cm⁻³, $\mu = 2.385$ mm⁻¹, $2.0 < 2\theta < 27.0^\circ$, $T = 173$ K, $R_1 = 0.0387$ and $wR_2 = 0.0886$ for 2521 ($I > 2\sigma(I)$) of 3971 unique reflections and 210 parameters. **GBBS**· $\frac{2}{3}$ (2-chlorotoluene): C_{112/3}H_{142/3}N₃O₃SBrCl_{2/3}, $0.46 \times 0.22 \times 0.22$ mm, hexagonal, $P6_3/m$ (no. 176), $a = b = 19.305(1)$, $c = 7.6998(6)$ Å, $Z = 6$, $V = 2485.2(3)$ Å³, $\rho_{\text{calcd}} = 1.53$ g cm⁻³, $\mu = 2.724$ mm⁻¹, $2.4 < 2\theta < 52^\circ$, $T = 173$ K, $R_1 = 0.0352$ and $wR_2 = 0.0983$ for 1649 ($I > 2\sigma(I)$) of 1761 unique reflections and 142 parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-164111–164126 and -164280–164282. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Isolation and Characterization of the Osmium(v)–Imido Complex [Os^V(Tp)(Cl)₂(NH)]⁺

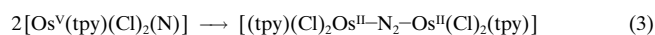
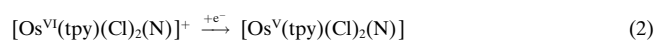
My Hang V. Huynh,* Peter S. White, Kevin D. John, and Thomas J. Meyer*

In the redox chemistry of high oxidation state osmium(vi)-nitrido (Os^{VI}≡N) complexes, a reversible 3 e[−]/3 H⁺ reduction in water gives osmium(III)–NH₃ [Eq. (1)]. Evidence has been found for osmium(IV) amido intermediates, Os^{IV}–NH₂⁺, which are unstable with respect to disproportionation.^[1]



tpy = 2,2':6',2''-terpyridine

One-electron reduction of Os^{VI}≡N⁺ to Os^V≡N in non-aqueous solvents is followed by rapid N⋯N coupling [Eqs. (2), (3)].^[2]



Laser flash photolysis of [Os^{VI}(NH₃)₄(N)]³⁺ in the presence of electron donors such as 1,4-dimethoxybenzene gives evidence for Os^V≡N as a short-lived transient that also undergoes N⋯N coupling [Eq. (4)].^[3]



Thus in both cases where osmium dimers form, an Os^V≡N complex has been invoked as a transient intermediate but not isolated. We report here conditions that allow Os^V≡N species to be trapped either in acidic–aqueous solution as a neutral osmium(v) imido complex (Os^V=NH) or in non-aqueous solvents by N[−] ion transfer before coupling can occur.

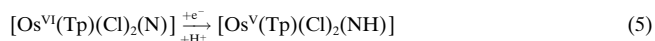
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

One-electron electrochemical reduction of 2.05 × 10^{−2} M [Os^{VI}(Tp)(Cl)₂(N)] (**1**) (Tp = hydrotris(pyrazol-1-yl)borate) in CH₃CN 3.5 M in HPF₆ at *E*_{app} = −1.05 V (versus the sodium saturated calomel electrode (SSCE), *E*_{app} = applied potential) results in formation of [Os^V(Tp)(Cl)₂(NH)] (**2**) [Eq. (5)].



The neutral Os^V=NH complex (**2**) has been isolated (yield = 47 %) and characterized by infrared (IR) spectroscopy (ν(¹⁴N–H) = 3257 cm^{−1} and ν(¹⁵N–H) = 3250 cm^{−1}),^[4a] elemental analysis,^[4b] and X-ray crystallography (Figure 1).^[4c] Crystals of **2** were grown by slow evaporation of CH₃CN with

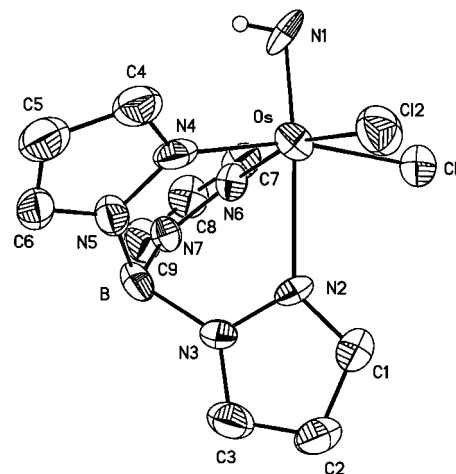


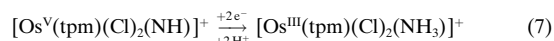
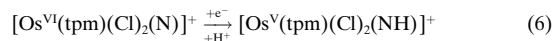
Figure 1. ORTEP diagram (thermal ellipsoids set at 30 % probability) and labeling scheme for **2**.

a stream of nitrogen from a strongly acidic CH₃CN solution containing the salts prepared by one-electron electrolytic reduction. The same synthetic method was also used to generate [Os^V(bpy)(Cl)₃(NH)] (bpy = 2,2'-bipyridine) which was isolated (yield = 56 %) and characterized by IR spectroscopy (ν(N–H) = 3315 cm^{−1}) and elemental analysis.^[5]

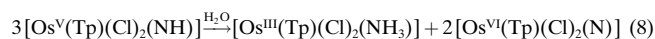
In the structure of **2**, the distorted octahedral arrangement of ligands around the Os center in the parent Os^{VI}≡N complex is retained. The Os–Cl bond lengths of 2.320(3) and 2.329(3) Å are about the same length as the nondisordered Os–Cl length in the starting Os^{VI}≡N complex, **1**.^[6] There is evidence for an imido structural *trans* effect in the elongated Os–N(Tp) bond of 2.291(8) Å *trans* to the NH^{2−} ligand compared to 2.053(8) and 2.063(9) Å for the Os–N(Tp) bonds in the coordination sites *cis* to NH^{2−}. The d³ Os–N(imido) bond of 1.749(7) Å is the longest reported for transition metal parent imido (M–NH) complexes which fall in the range of 1.638–1.749 Å.^[7] This is the first structurally characterized example of a late transition metal parent imido complex. Others have been reported for d⁰ molybdenum(vi)^[8a–d] and vanadium(v);^[8e] for d² rhenium(v),^[9a] molybdenum(IV),^[9b] and tungsten(IV);^[9c] and d⁴ rhenium(III).^[10]

The importance of protonation at the N atom in trapping osmium(v)-nitrido is evident from previous electrochemical results.^[1c] One-electron reduction of [Os^{VI}(tpm)(Cl)₂(N)]⁺ (**3**⁺) (tpm = tris(1-pyrazolyl)methane) in CH₃CN gives the

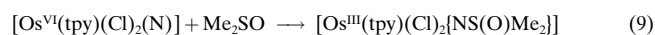
Os^{II}-N₂-Os^{II} dimer [cf. Eqs. (2), (3)]. In CH₃CN with added HPF₆, three-electron reduction leads to the osmium(III)–ammine complex as indicated by cyclic voltammetry.^[1c] These observations suggest that a small amount of added HPF₆ is sufficient to change the chemistry from N⋯N coupling to reduction with the key step being protonation of the osmium(v)–nitrido unit [Eqs. (6), (7)].



In aqueous solution, [Os^V(Tp)(Cl)₂(NH)] is not observed as a transient because it is unstable with regard to disproportionation.^[1a] Disproportionation was confirmed in strongly acidic CH₃CN solution to which water was added. Addition of water led to the appearance of [Os^{III}(Tp)(Cl)₂(NH₃)] and [Os^{VI}(Tp)(Cl)₂(N)] in a 1:2 ratio as shown by the ratio of peak currents at 0.80 V (the Os^{IV/III} couple of the ammine complex) to –0.97 V (versus SSCE) (the Os^{VI/V} irreversible couple of the nitrido complex). This observation is consistent with the disproportionation reaction shown in Equation (8).^[11]



It is also possible to capture [Os^V(tpy)(Cl)₂(N)] (**4A** = *trans* and **4B** = *cis*) in dry organic solvents before dimerization occurs by adding appropriate reductants at high concentrations as trapping agents. For example, electrochemical reduction of [Os^{VI}(tpy)(Cl)₂(N)]⁺ (**5A**⁺ = *trans* and **5B**⁺ = *cis*) in dimethylsulfoxide (DMSO; Me₂SO) under nitrogen at a potential past that of the Os^{VI/V} reduction waves, *E*_{pc}(*cis*) = –0.31 V and *E*_{pc}(*trans*) = –0.45 V (*E*_{pc} = cathodic peak potential versus SSCE), gives the corresponding osmium(III)–sulfoximido complexes, [Os^{III}(tpy)(Cl)₂{NS(O)Me₂}] (**6A** = *trans* and **6B** = *cis*) [Eqs. (2) and (9)].



During workup, the osmium(III) products (*E*_{1/2} [Os^{IV/III}] = 0.24 V for **6A** and 0.23 V for **6B** versus SSCE) undergo air oxidation to give [Os^{IV}(tpy)(Cl)₂{NS(O)Me₂}]⁺ (**7A**⁺ = *trans* and **7B**⁺ = *cis*) which were isolated as their Cl[–] (77% yield) and PF₆[–] (74% yield) salts, respectively. [**7A**]Cl was fully characterized by elemental analysis,^[12] X-ray crystallography (Figure 2),^[13] cyclic voltammetry, and UV/Vis spectroscopy (Supporting Information).

The reaction of the starting osmium(vi)–nitrido complex with DMSO is slow or nonexistent at room temperature. It is notable that one-electron reduction to osmium(v)–nitrido enhances oxidative reactivity much as for many free radicals compared to their precursors.^[14] One-electron reduction of d² Os^{VI}≡N⁺ occurs at a dπ* level that is antibonding with regard to the Os–N interaction.^[15] This activates the osmium(v)–nitrido group toward N[–] ion transfer. “Reductive activation” opens the possibility of exploring N[–] ion transfer with reagents that have slow or no reactivity towards Os^{VI}≡N.

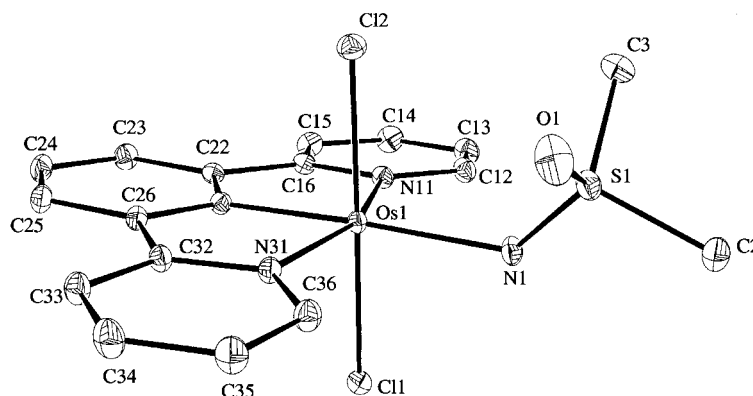


Figure 2. ORTEP diagram (thermal ellipsoids set at 30% probability) and labeling Scheme for [**7A**]Cl.

The chemistry of capturing osmium(v)–nitrido in dry organic solvents appears to be general. Depending on the reduction potentials for the Os^{IV/III} couples of the products, they are formed as osmium(III) or undergo further air oxidation to osmium(IV) species. As examples, electrochemical reduction of **5**⁺ in the presence of high concentrations (1.0 M) of 3,5-Me₂C₆H₃OH or HNPh₂ in CH₃CN under nitrogen gives [Os^{III}(tpy)(Cl)₂{N(H)OC₆H₃Me₂}] (**8** = *trans*) or [Os^{III}(tpy)(Cl)₂{N(H)NPh₂}] (**9** = *cis*). The osmium(IV) analogues, [Os^{IV}(tpy)(Cl)₂{N(H)OC₆H₃Me₂}]⁺ (**10**⁺ = *trans*) or [Os^{IV}(tpy)(Cl)₂{N(H)NPh₂}]⁺ (**11**⁺ = *cis*), have been isolated as PF₆[–] salts (**10**⁺ = 53% and **11**⁺ = 62%) and characterized by IR^[16] and UV/Vis spectroscopy and cyclic voltammetry (Supporting Information), and elemental analysis.^[17]

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- [12] Elemental analysis calcd (%) for **7A**Cl: $\text{OsC}_{17}\text{H}_{17}\text{N}_4\text{SOCl}_3 \cdot (\text{H}_2\text{O}$ and $\text{Me}_2\text{SO})$: C 31.78, H 3.51, N 7.80; found: C 31.95, H 3.64, N 8.12. **7B**PF₆ elemental analysis calcd (%) for $\text{OsC}_{17}\text{H}_{17}\text{N}_4\text{SOCl}_2\text{PF}_6$: C 27.91, H 2.34, N 7.66; found: C 28.23, H 2.52, N 7.87.
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- [17] **10**PF₆: elemental analysis calcd (%) for $\text{OsC}_{23}\text{H}_{20}\text{N}_4\text{Cl}_2\text{OPF}_6 \cdot \text{CH}_3\text{CN}$: C 36.82, H 2.84, N 8.59; found: C 37.14, H 3.04, N 8.75. **11**PF₆: elemental analysis calcd (%) for $\text{OsC}_{27}\text{H}_{22}\text{N}_5\text{Cl}_2\text{PF}_6$: C 39.42, H 2.70, N 8.51; found: C 39.63, H 2.86, N 8.69.

Chiral Recognition of *O*-Phosphoserine by Mass Spectrometry**

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Reversible protein phosphorylation is involved in a multitude of regulatory mechanisms for the control of intracellular protein functionality.^[1–4] Serine, threonine, tyrosine, and a number of other amino acid residues can be modified by the attachment of a phosphate group. The exact site of the modification has to be determined to elucidate the physiological impact of this event. This can be a very difficult task since only a small fraction of a given protein may be phosphorylated and phosphorylation may occur at multiple sites, thus giving rise to various phosphorylated forms. Although sensitive analytical methods are available for the detection and quantification of phosphorylation sites,^[5–9] there is still a great need for further improvements, especially in view of the fact that both *O*-phosphoserine and -threonine cannot be unambiguously assigned by Edman sequencing.^[10]

In recent years, tandem mass spectrometry (MSⁿ) has gained wide recognition as a powerful tool for peptide sequencing and for the identification of modified amino acids within the sequence tag.^[11] This capability has encouraged the exploration of a mass spectrometric methodology for gas-phase discrimination of chiral analytes (A_R and A_S) through the measurement of the stability^[12–14] and the reactivity^[12, 15] of the diastereomeric complexes formed with a chiral reference molecule (ref). The kinetic method proved particularly useful for this task and was exploited by the research groups of Cooks,^[13, 14, 16] Tao,^[13, 14] and others.^[17] The method is based on the collisionally induced dissociation (CID) of the diastereomeric cluster ions $[\text{M} \cdot (\text{ref})_2 \cdot A_R]^+$ and $[\text{M} \cdot (\text{ref})_2 \cdot A_S]^+$ ($\text{M} = \text{H}$ or metal; Figure 1). It is convenient to define the cluster ions as “homo” when the analyte and reference have the same configuration, and “hetero” in the opposite case.

According to the foundations of the kinetic method used by Cooks and co-workers,^[13, 16] CID of $[\text{M} \cdot (\text{ref})_2 \cdot A_R]^+$ and $[\text{M} \cdot (\text{ref})_2 \cdot A_S]^+$ may produce different fragmentation patterns that reflect the stability of $[\text{M} \cdot \text{ref} \cdot A_R]^+$ (and $[\text{M} \cdot \text{ref} \cdot A_S]^+$) relative to $[\text{M} \cdot (\text{ref})_2]^+$ (ΔG_R and ΔG_S , respectively).

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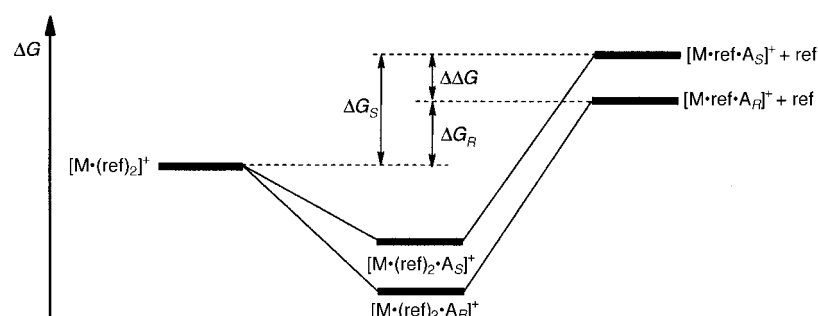


Figure 1. Free-energy diagram for the dissociation of trimeric cluster ions.

Measurement of the ratio of the “homo” versus “hetero” ion abundance ratios provides the chiral selectivity R_{chiral} [Eq. (1)]

$$R_{\text{chiral}} = \frac{R_{\text{homo}}}{R_{\text{hetero}}} = \frac{[\text{M} \cdot \text{ref} \cdot \text{A}_S]^+ / [\text{M} \cdot (\text{ref})_2]^+}{[\text{M} \cdot \text{ref} \cdot \text{A}_R]^+ / [\text{M} \cdot (\text{ref})_2]^+} \quad (1)$$

if the *S* enantiomer of the reference is employed, and R'_{chiral} [Eq. (2)] if the *R* enantiomer of the reference is employed. The

$$R'_{\text{chiral}} = \frac{R'_{\text{homo}}}{R'_{\text{hetero}}} = \frac{[\text{M} \cdot \text{ref} \cdot \text{A}_R]^+ / [\text{M} \cdot (\text{ref})_2]^+}{[\text{M} \cdot \text{ref} \cdot \text{A}_S]^+ / [\text{M} \cdot (\text{ref})_2]^+} \quad (2)$$

relative stability of the “homo” versus the “hetero” $[\text{M} \cdot \text{ref} \cdot \text{A}]^+$ cluster ion ($\Delta\Delta G$) is calculated from Equation (3), where T_{eff} is the effective temperature^[18] and R is the gas constant.

$$\ln R_{\text{chiral}} = \frac{\Delta\Delta G}{RT_{\text{eff}}} \quad (3)$$

We describe here the application of the kinetic method of Cooks and co-workers to the enantiodiscrimination of

O-phosphoserine (^{OP}Ser). The study is intended to demonstrate the sensitivity and the reproducibility of the method and its potential in quantifying the enantiomeric excess of ^{OP}Ser in biological specimens.

Singly charged trimeric clusters $[\text{M} \cdot (\text{ref})_2 \cdot \text{A}]^+$ ($\text{M} = \text{H}, \text{Na}$) were generated by electrospraying aqueous methanol solutions containing a pure enantiomer of ^{OP}Ser and a chiral reference compound, namely, (*R*)-(-)- (E_R), (*S*)-(+)- (1-aminoethyl)phosphonic acid (E_S), or *O*-phospho-L-threonine (^{OP}Thr_L). The use

of these reference compounds with size and functionality similar to those of the ^{OP}Ser analyte is dictated by the desirability to minimize entropy effects on $[\text{M} \cdot (\text{ref})_2 \cdot \text{A}]^+$ fragmentation.^[19] The CID of the selected trimeric cluster ions $[\text{M} \cdot (\text{ref})_2 \cdot \text{A}]^+$ ($\text{M} = \text{H}, \text{Na}$) was carried out in a triple-quadrupole mass spectrometer (QqQ). For comparative purposes, the CID spectra of both the homochiral $[\text{Na} \cdot (\text{OPThr}_L)_2 \cdot \text{OPSer}_L]^+$ and the heterochiral $[\text{Na} \cdot (\text{OPThr}_L)_2 \cdot \text{OPSer}_D]^+$ ions were further investigated with a Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometer.

The lower part of Figure 2 shows the QqQ-CID spectra of these latter species measured at a collision energy of 10 eV (lab frame). The FT-ICR-SORI-CID spectra (SORI = sustained off-resonance irradiation) of the same species are illustrated in the upper part of Figure 2. The closeness of the calculated R_{chiral} factors (0.67 (QqQ) and 0.69 (FT-ICR)) points to the methodology having a negligible effect on the enantiodiscrimination of the analyte. The R_{chiral} values show

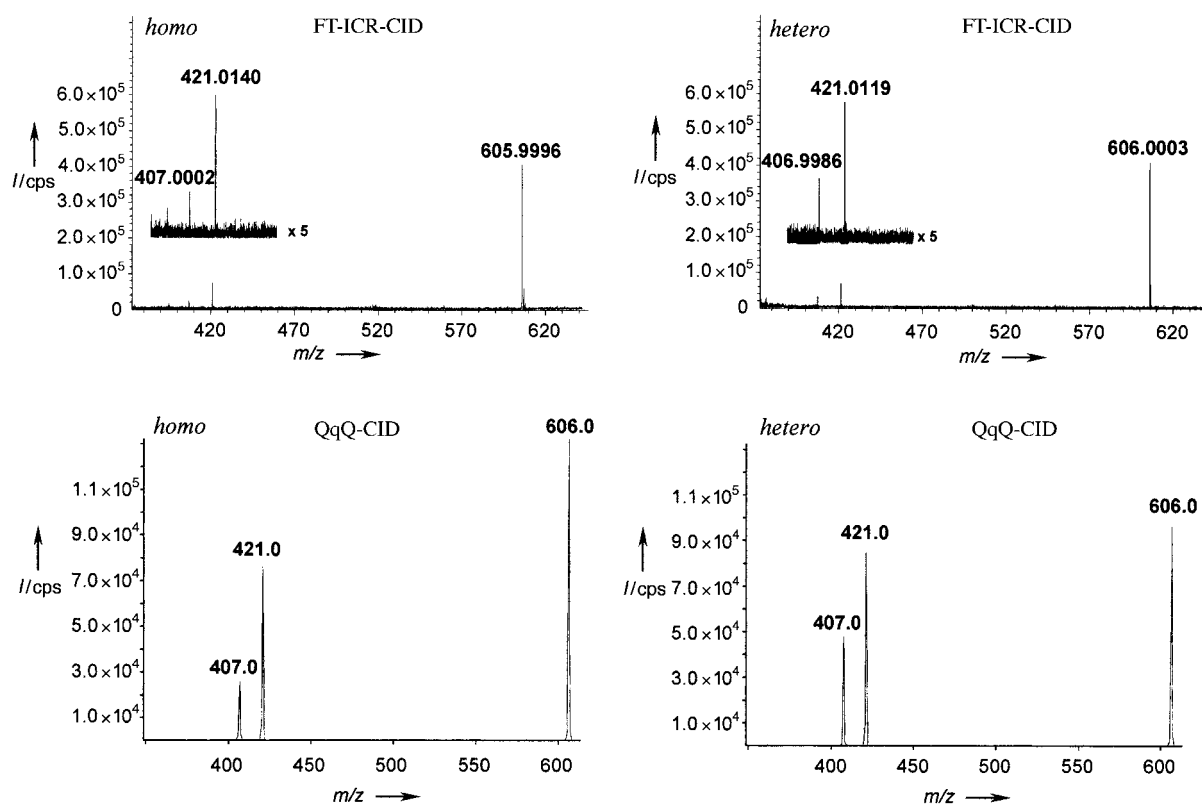


Figure 2. Top: SORI-CID spectra of $[\text{Na} \cdot (\text{OPThr}_L)_2 \cdot \text{OPSer}_L]^+$ (*homo*) and $[\text{Na} \cdot (\text{OPThr}_L)_2 \cdot \text{OPSer}_D]^+$ (*hetero*), obtained by FT-ICR mass spectrometry (m/z : 606 ($[\text{Na} \cdot (\text{OPThr}_L)_2 \cdot \text{OPSer}]^+$), 421 ($[\text{Na} \cdot (\text{OPThr}_L)_2]^+$), 407 ($[\text{Na} \cdot \text{OPThr}_L \cdot \text{OPSer}]^+$)). Bottom: CID-MS² spectra of $[\text{Na} \cdot (\text{OPThr}_L)_2 \cdot \text{OPSer}_L]^+$ (*homo*) and $[\text{Na} \cdot (\text{OPThr}_L)_2 \cdot \text{OPSer}_D]^+$ (*hetero*), using a triple quadrupole (QqQ; collision energy 10 eV; lab frame).

the homochiral $[\text{Na} \cdot (\text{OPSer}_\text{L})_2 \cdot \text{E}_\text{S}]^+$ fragment has a lower stability than the heterochiral $[\text{Na} \cdot (\text{OPSer}_\text{L})_2 \cdot \text{E}_\text{R}]^+$ one.

The results obtained from the QQQ-CID experiments on the homochiral $[\text{H} \cdot (\text{E}_\text{S})_2 \cdot \text{OPSer}_\text{L}]^+$ and the heterochiral $[\text{H} \cdot (\text{E}_\text{S})_2 \cdot \text{OPSer}_\text{D}]^+$ clusters as a function of the collision energy (6–10 eV (lab frame)) are summarized in Table 1. It should be noted that while both the R_hom and R_hetero terms from the CID of $[\text{H} \cdot (\text{E}_\text{S})_2 \cdot \text{OPSer}_\text{L}]^+$ tend to decrease on increasing the collision energy from 6 to 10 eV, their $R_\text{chiral} = R_\text{hom}/R_\text{hetero}$ ratios are scattered around the average value of 0.84 ± 0.07 . A similar average value (0.87 ± 0.06) is obtained for the $R'_\text{hom}/R'_\text{hetero}$ ratios from the CID of $[\text{H} \cdot (\text{E}_\text{R})_2 \cdot \text{OPSer}_\text{L}]^+$. The remarkable reproducibility of the measurements is further testified by the average $R_\text{hom}/R'_\text{hetero}$ and $R'_\text{hom}/R_\text{hetero}$ ratios (last two columns of Table 1), which are found to coincide with the $R_\text{hom}/R_\text{hetero}$ and $R'_\text{hom}/R'_\text{hetero}$ ratios within their combined experimental uncertainties.

The QQQ-CID spectra of the trimeric complexes $[\text{Na} \cdot (\text{E}_\text{S})_2 \cdot \text{OPSer}_\text{L}]^+$ and $[\text{Na} \cdot (\text{E}_\text{S})_2 \cdot \text{OPSer}_\text{D}]^+$ display features which prevent any quantitative evaluation of OPSer_L versus OPSer_D discrimination. Indeed, the fragmentation patterns of both diastereomers are characterized by the presence of a minor signal corresponding to the loss of two E_S molecules. Their abundance increases from about 7% (7 eV) to about 11% (12 eV) of the total ion current. Since it is not possible to assign firmly the origin of this fragment to a given precursor, either from $[\text{Na} \cdot \text{E}_\text{S} \cdot \text{OPSer}]^+$ after the loss of a first E_S molecule or directly from $[\text{Na} \cdot (\text{E}_\text{S})_2 \cdot \text{OPSer}]^+$, the corresponding R_chiral value could be affected by a systematic error. Such a drawback is absent in the fragmentation of the homochiral $[\text{Na} \cdot (\text{OPSer}_\text{L})_2 \cdot \text{E}_\text{S}]^+$ and the heterochiral $[\text{Na} \cdot (\text{OPSer}_\text{L})_2 \cdot \text{E}_\text{R}]^+$ clusters. Their fragmentation patterns as a function of the collision energy (7–12 eV) are illustrated in Table 2. The $R_\text{chiral} = R_\text{hom}/R_\text{hetero}$ terms from the CID of $[\text{Na} \cdot (\text{OPSer}_\text{L})_2 \cdot \text{E}]^+$ converge around the average value of 0.64 ± 0.14 . A similar average value (0.74 ± 0.04) is measured for the $R'_\text{hom}/R'_\text{hetero}$ ratios from the fragmentation patterns of the diaster-

omeric $[\text{Na} \cdot (\text{OPSer}_\text{D})_2 \cdot \text{E}_\text{R}]^+$ and $[\text{Na} \cdot (\text{OPSer}_\text{D})_2 \cdot \text{E}_\text{S}]^+$ cluster ions. Even in this case, the average $R_\text{hom}/R'_\text{hetero}$ and $R'_\text{hom}/R_\text{hetero}$ ratios (last two columns of Table 2) are found to coincide with the relevant $R_\text{hom}/R_\text{hetero}$ and $R'_\text{hom}/R'_\text{hetero}$ values within their combined experimental uncertainties.

A similar approach has been used to quantify OPSer enantiodiscrimination through the fragmentation spectra of their trimeric clusters with *O*-phospho-L-threonine ($[\text{M} \cdot (\text{OPThr}_\text{L})_2 \cdot \text{OPSer}]^+$; with $\text{M} = \text{H}$ or Na). The relevant results, combined with those from Tables 1 and 2, are summarized in Table 3. These values provide a measure of the reliability and the reproducibility of the MS^2 approach. The chiral selectivity factors can be further evaluated in terms of the underlying thermochemistry by using Equation (3). The difference be-

Table 3. Degree of chiral recognition of *O*-phosphoserine.

M	ref	Chiral selectivity factor	$\Delta\Delta G$ (KJ mol ⁻¹)
H	E_S	$R_\text{chiral} = 0.84 \pm 0.07$	-1.4 ± 0.7
H	E_R	$R'_\text{chiral} = 0.87 \pm 0.06$	-1.1 ± 0.6
H	OPThr_L	$R_\text{chiral} = 0.88 \pm 0.11$	-1.0 ± 0.9
Na	E_S	$R'_\text{chiral} = 0.65 \pm 0.08$	-3.4 ± 0.9
Na	E_R	$R'_\text{chiral} = 0.67 \pm 0.08$	-3.2 ± 0.9
Na	OPThr_L	$R_\text{chiral} = 0.75 \pm 0.12$	-2.3 ± 1.2

tween the change in free energy $\Delta\Delta G$ reflects the different attractive electrostatic and repulsive steric interactions operating in the diastereomeric $[\text{M} \cdot \text{ref} \cdot \text{A}]^+$ clusters, whose effective temperature T_eff is estimated as approximately 950 K from previous studies on strictly related systems.^[20] The negative $\Delta\Delta G$ values indicate that the heterochiral complexes are more stable than the homochiral analogues. Their stability difference is larger for the Na-bound complexes than for the proton-bound ones.^[21]

Although the chiral selectivity values of Table 3 are not particularly large,^[22] the accuracy and sensitivity of the MS^2 approach can nevertheless be used for quantifying the optical

Table 1. Fragment-ion abundance ratios $[\text{H} \cdot \text{ref} \cdot \text{A}]^+ / [\text{H} \cdot (\text{ref})_2]^+$ from CID of diastereomeric $[\text{H} \cdot (\text{ref})_2 \cdot \text{A}]^+$ complexes at various collision energies (lab frame).

Collision energy [eV]	ref	A = OPSer_L R_hom	A = OPSer_D R_hetero	R_chiral ($R_\text{hom}/R_\text{hetero}$)	ref	A = OPSer_D R'_hom	A = OPSer_L R'_hetero	R'_chiral ($R'_\text{hom}/R'_\text{hetero}$)	R'_chiral ($R_\text{hom}/R'_\text{hetero}$)	R''_chiral ($R'_\text{hom}/R_\text{hetero}$)
6	E_S	2.36	2.92	0.81	E_R	2.21	2.45	0.90	0.96	0.76
7	E_S	2.12	2.63	0.81	E_R	2.17	2.35	0.92	0.90	0.83
8	E_S	1.97	2.40	0.82	E_R	1.70	2.06	0.82	0.96	0.71
9	E_S	1.84	2.02	0.91	E_R	1.69	2.08	0.81	0.88	0.84
10	E_S	1.78	2.04	0.87	E_R	1.76	1.91	0.92	0.93	0.86
				Av: 0.84 ± 0.07					Av: 0.87 ± 0.06	Av: 0.93 ± 0.05
									Av: 0.80 ± 0.09	

Table 2. Fragment-ion abundance ratios $[\text{Na} \cdot \text{ref} \cdot \text{A}]^+ / [\text{Na} \cdot (\text{ref})_2]^+$ from CID of diastereomeric $[\text{Na} \cdot (\text{ref})_2 \cdot \text{A}]^+$ complexes at various collision energies (lab frame).

Collision energy [eV]	ref	A = E_S R_hom	A = E_R R_hetero	R_chiral ($R_\text{hom}/R_\text{hetero}$)	ref	A = E_R R'_hom	A = E_S R'_hetero	R'_chiral ($R'_\text{hom}/R'_\text{hetero}$)	R'_chiral ($R_\text{hom}/R'_\text{hetero}$)	R''_chiral ($R'_\text{hom}/R_\text{hetero}$)
7	OPSer_L	0.17	0.34	0.50	OPSer_D	0.20	0.30	0.67	0.57	0.59
8	OPSer_L	0.19	0.28	0.68	OPSer_D	0.21	0.26	0.81	0.73	0.75
9	OPSer_L	0.23	0.40	0.57	OPSer_D	0.27	0.36	0.75	0.64	0.67
10	OPSer_L	0.19	0.28	0.68						
11	OPSer_L	0.21	0.32	0.65						
12	OPSer_L	0.23	0.31	0.74						
				Av: 0.64 ± 0.14					Av: 0.74 ± 0.07	Av: 0.65 ± 0.08
									Av: 0.67 ± 0.08	

purity of ^{OP}Ser . A calibration curve can be derived from the analysis of the QqQ-CID spectra of trimeric $[Na \cdot (^{OP}Thr_L)_2 \cdot ^{OP}Ser]^+$ complexes containing variable $^{OP}Ser_L$ versus $^{OP}Ser_D$ proportions. The results show a linear relationship of $\ln([Na \cdot ^{OP}Thr_L \cdot ^{OP}Ser]^+ / [Na \cdot (^{OP}Thr_L)_2]^+)$ versus the molar fraction of the D enantiomer of ^{OP}Ser ($\% ^{OP}Ser_D$; Figure 3).

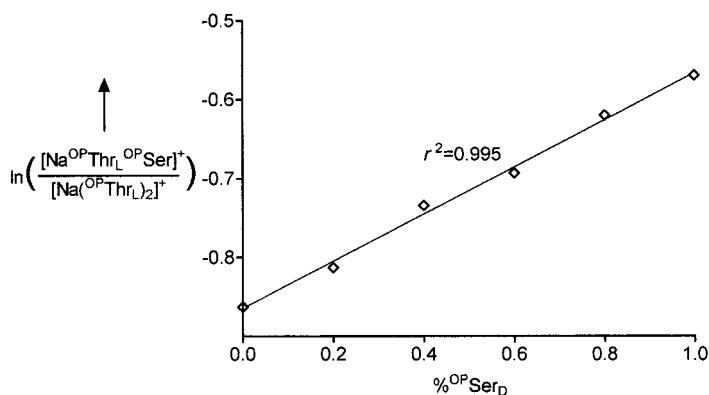


Figure 3. Calibration curve for the chiral analysis of *O*-phosphoserine.

The present study highlights several successful applications of the kinetic method of Cooks and co-workers to the enantiodiscrimination of chiral compounds. The studies demonstrate that the kinetic method is sufficiently precise and accurate to be potentially applicable for quantifying the enantiomeric excess of *O*-phosphoserine in proteomic analysis. The ESI-MS² procedure is fast and does not rely on any manipulation of the sample. The chiral selectivity factors also do not seem to depend upon the specific instrumentation used (FT-ICR or QqQ). Given the extremely high resolution normally attainable in FT-ICR experiments (full width at half height (FWHH) > 50000), the FT-ICR-SORI-CID procedure appears particularly suitable for the routine analysis of chiral *O*-phosphoserine and -threonine even in complex biological matrices. Extension of this work to other phosphorylated amino acids is in progress.

Experimental Section

ESI-MS² experiments: The CID experiments were performed by using both a commercial API 100/300 triple-quadrupole (QqQ) mass spectrometer from Perkin Elmer Sciex Instruments and a commercial APEX 47e FT-ICR mass spectrometer from Bruker Spectrospin. Both instruments were equipped with an ESI source and a syringe pump. Operating conditions for the ESI source: spray voltage: 3.8 kV, capillary temperature: 298 K, sheath gas (N₂) flow rate: 30 units (roughly 0.75 L min⁻¹). The selected gas-phase complexes were generated by electrospraying at a flow rate of 10 μL min⁻¹ solutions of water/methanol (50/50) containing equimolar amounts (10 μM each) of the optically pure *O*-phosphoserine and a chiral reference compound, that is, (*R*)-(-)-(1-aminoethyl)phosphonic acid, its *S* enantiomer, or *O*-phospho-L-threonine. The CID experiments on the so-formed diastereomeric complexes were conducted in the positive-ion mode.

QqQ-CID experiments: In the full-scan QqQ-MS² mode, the diastereomeric cluster ions were isolated in the first mass-analyzing quadrupole *Q*, excited in the second “rf-only” quadrupole *q* by collision with N₂ (pressure around 10 mbar, energy range 6–12 eV in the laboratory frame), and eventually analyzed in the third quadrupole *Q* of the instrument.

FT-ICR-CID experiments: In the FT-ICR-MS² mode, the same cluster ions were injected from the external source of the instrument into the analyzer, quenched by multiple collision with N₂, admitted into the analyzer through

a pulsed valve assembly (the nominal peak pressure was approximately 5 × 10⁻⁶ mbar), and eventually isolated by broad-band ejection of the unwanted fragments. SORI-CID experiments were carried out by accelerating the quenched ions with an activation frequency 0.25 kHz higher than the cyclotron frequency of the ion, and by allowing them to collide for 2 s with the N₂ present in the analyzer at a constant pressure of 2 × 10⁻⁸ mbar.

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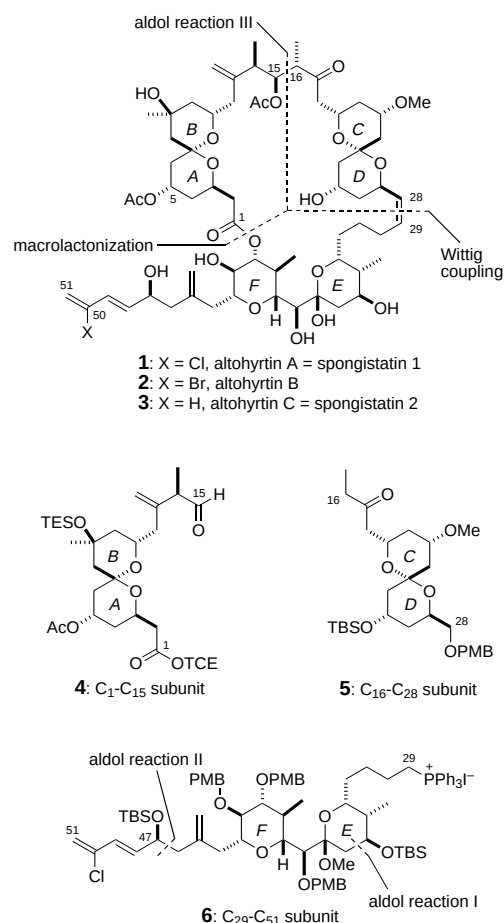
Stereocontrolled Total Synthesis of (+)-Altohyrtin A/Spongistatin 1**

Ian Paterson,* David Y.-K. Chen, Mark J. Coster, Jose L. Aceña, Jordi Bach, Karl R. Gibson, Linda E. Keown, Renata M. Oballa, Thomas Trieselmann, Debra J. Wallace, Andrew P. Hodgson, and Roger D. Norcross

First reported in 1993 by three groups (Kobayashi and Kitagawa, Pettit, and Fusetani),^[1] the altohyrtins/spongistatins/cinachyrolides are a unique family of antimetabolic macrolides^[2–5] which are obtained from marine sponges in trace amounts by bioassay-guided isolation and display exceptional potency against a wide variety of human cancer cell lines. They feature a highly substituted 42-membered macrolide ring which comprises two spiroacetals (*AB* and *CD* rings) and a bis(tetrahydropyran) unit (*E* and *F* rings), including a triene side chain, along with 24 stereogenic centers (Scheme 1, **1–3**). Initial discrepancies in the configurational assignments were resolved in 1997 by the first total synthesis of altohyrtin C (**3**) by the Evans group,^[6] and soon after altohyrtin A (**1**) by the Kishi group,^[7] which confirmed the full assignment proposed for the altohyrtins by Kobayashi and Kitagawa,^[2d] and that they were identical to spongistatins 2 and 1, respectively, as isolated by Pettit et al.^[3a,b] More recently, the Smith group has completed a second total synthesis of **3**.^[8]

Spongistatin 1 (**1**) constitutes one of the most potent cytotoxic compounds tested by the US National Cancer Institute (NCI),^[3a,b] having sub-nanomolar growth inhibitory activity (mean GI₅₀ = 0.03 nM) against highly chemoresistant tumor types (including lung, colon and brain cancers), while in vivo human melanoma and ovarian carcinoma xenograft experiments showed curative responses at extremely low doses.^[3g] It inhibits mitosis by binding to tubulin and blocking microtubule assembly.^[3h] Despite this highly promising profile, the unreliable and extremely meagre supply (3.4×10^{-7} % isolation yield for **1**)^[3a] has effectively halted further preclinical development in cancer chemotherapy.

The exceptional biological activity, combined with the supply problem, has provided an impetus to develop a practical route to these synthetically challenging bis-spiro-



Scheme 1. Representative structures of altohyrtins/spongistatins and key subunits employed for the synthesis of altohyrtin A/spongistatin 1 (**1**). TES = triethylsilyl, TCE = 2,2,2-trichloroethyl, TBS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl.

acetal macrolides.^[9, 10] Herein, we describe a highly stereocontrolled total synthesis of the most active congener, altohyrtin A/spongistatin 1 (**1**), which produces useful quantities for further biological evaluation, and enables access to novel analogues for SAR studies. Throughout our synthesis, asymmetric boron aldol reactions of ketones are exploited as a powerful bond-forming and stereodefining process.^[11]

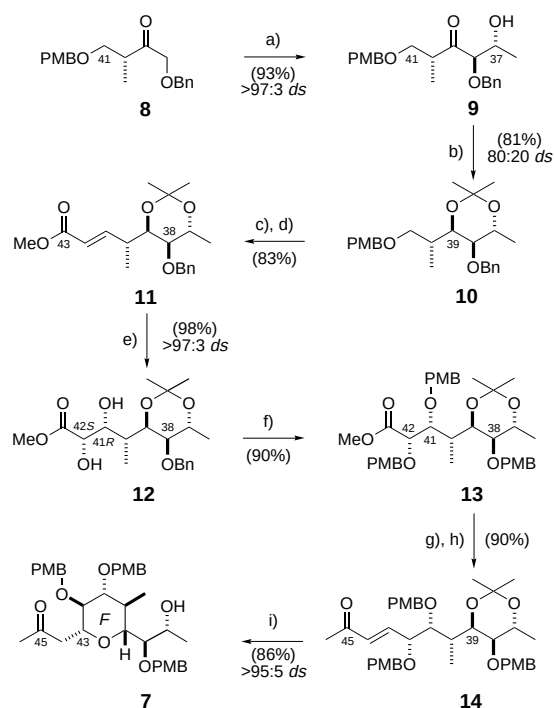
As shown in Scheme 1, our proposed synthetic route to **1**, which is based on a threefold disconnection of the 42-membered macrolide ring, employs macrolactonization as well as Wittig and aldol couplings. We planned^[9] a modular route based on the late-stage, sequential connection of the fully functionalized spiroacetal subunits **4** and **5**, followed by the bis(tetrahydropyran) subunit **6**. Introduction of the bridging chain between the *AB* and *CD* ring systems in **4** and **5**, and the connection of the *E* to the *F* ring in **6**, were identified as strategic aldol bond constructions (aldol reactions I and III), along with the installation of the terminal chlorodiene and isolated C47 stereocenter in **6** (aldol reaction II).

As outlined in Scheme 2, the synthesis of the *F* ring subunit **7** began with a boron-mediated *anti* aldol reaction between the readily available^[12] ketone (*R*)-**8** and acetaldehyde to give **9**, followed by reduction with Me₄NBH(OAc)₃^[13] to the 1,3-

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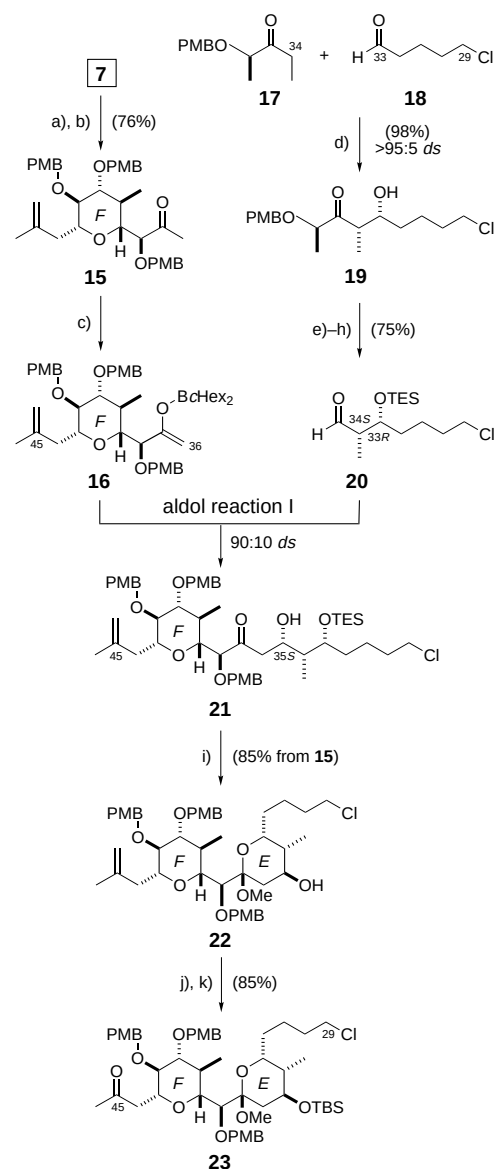
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 2. Synthesis of the C36–C46 subunit **7**: a) $c\text{Hex}_2\text{BCl}$, Et_3N , Et_2O , -78°C , 2 h; MeCHO , $-78 \rightarrow -20^\circ\text{C}$, 16 h; H_2O_2 , MeOH/pH 7 buffer, $0 \rightarrow 20^\circ\text{C}$, 3 h; b) 1. $\text{Me}_4\text{NBH}(\text{OAc})_3$, MeCN/AcOH , 4°C , 60 h; 2. PPTS, $\text{Me}_2\text{C}(\text{OMe})_2$, CH_2Cl_2 , 20°C , 16 h; c) 1. DDQ, $\text{CH}_2\text{Cl}_2/\text{pH}$ 7 buffer, 0°C , 90 min; 2. Dess–Martin periodinane, CH_2Cl_2 , 20°C , 3 h; d) $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, LiCl , $i\text{Pr}_2\text{NEt}$, MeCN , 20°C , 16 h; e) enriched AD-mix- β , MeSO_2NH_2 , $t\text{BuOH}/\text{H}_2\text{O}$, 20°C , 8 h; f) 1. H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, NaHCO_3 , MeOH , 20°C , 20 h; 2. $\text{PMBO}(\text{C}=\text{NH})\text{CCl}_3$, Ph_3CBF_4 , THF , 0°C , 2 h; g) DIBAL-H, CH_2Cl_2 , -78°C , 30 min; h) $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{COMe}$, $\text{Ba}(\text{OH})_2$, $\text{THF}/\text{H}_2\text{O}$, 20°C , 16 h; i) 1. AcOH , $\text{THF}/\text{H}_2\text{O}$, 20°C , 48 h; 2. KOH , MeOH , 20°C , 24 h. Bn = benzyl, PPTS = pyridinium *p*-toluenesulfonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride.

anti diol and formation of the acetone **10**. Following deprotection (and separation of the minor C39 epimer), Dess–Martin oxidation and chain extension by Horner–Wadsworth–Emmons (HWE) olefination furnished the (*E*)-enoate **11**. This alkene with a benzyloxy group at C38 proved to be an excellent substrate for Sharpless dihydroxylation^[14] with enriched AD-mix- β to give solely the (41*R*,42*S*)-diol **12** in 98% yield.^[15] For the remainder of the synthesis, we now chose to install PMB protecting groups at the C38, C41, and C42 hydroxy groups. Hydrogenolysis of **12** ($\text{Pd}(\text{OH})_2$, NaHCO_3), followed by PMB protection with *p*-(methoxybenzyl)-trichloroacetimidate under mild catalysis^[16] with Ph_3CBF_4 gave tris-PMB ether **13**. Reduction of **13** with DIBAL-H and HWE chain extension^[17] with dimethyl (2-oxopropyl)-phosphonate and $\text{Ba}(\text{OH})_2$ then provided the (*E*)-enone **14** exclusively (81% from **12**). Exposure of **14** to acetic acid in aqueous THF caused hetero-Michael cyclization by the C39 hydroxy group, to initially produce a mixture (ca. 1:1 at C43) of tetrahydropyrans. On treatment with KOH in MeOH , clean equilibration ($>95:5$) led to the desired *F* ring ketone **7** (86%), having all the substituents equatorial. This efficient 9-step sequence could be performed on a multigram scale and proceeded in high overall yield (34%).

Introduction of the *E* ring and chlorodiene side chain were now required to reach the fully elaborated C29–C51 segment **6** of althohyrin A. The control of the remote (47*S*)-stereocenter, as well as that at C35, turned out to be challenging; it proved best to first protect the C45 ketone then install the *E* ring before introducing the delicate side chain (Scheme 3). Thus, Petasis methylenation^[19] of ketone **7** with $[\text{Cp}_2\text{TiMe}_2]$ proceeded cleanly and was followed by TPAP/NMO oxidation^[20] to afford the methyl ketone **15** (76% overall). For the introduction of the *E* ring, the aldehyde **20** having a chloride



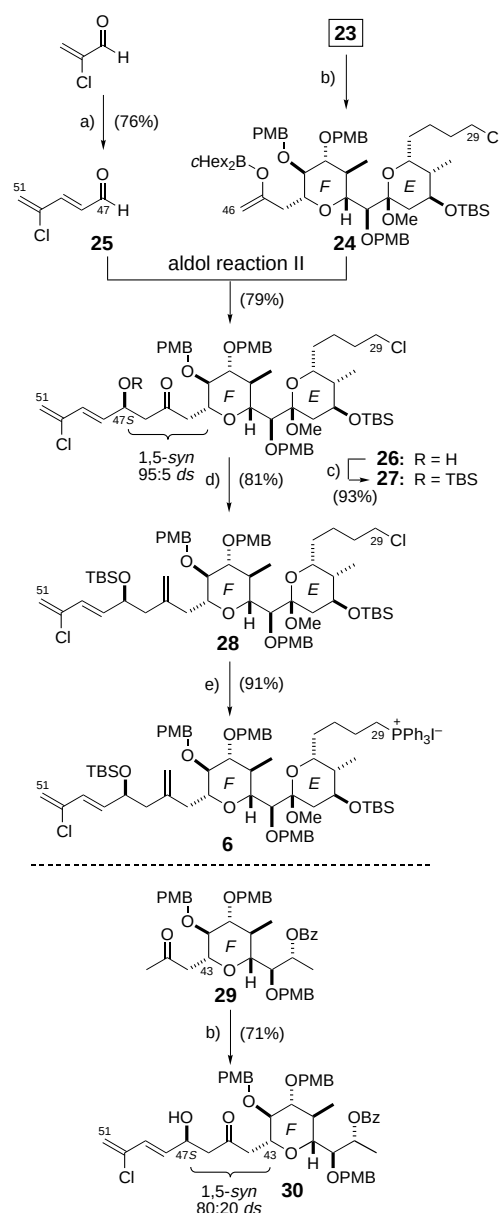
Scheme 3. Synthesis of the C29–C46 subunit **23**: a) $[\text{Cp}_2\text{TiMe}_2]$, PhMe , 120°C , 2 h; b) TPAP, NMO, 4 Å-MS, CH_2Cl_2 , 20°C , 30 min; c) $c\text{Hex}_2\text{BBR}$, Et_3N , Et_2O , -78°C , 2.5 h; **20**, $-78 \rightarrow -20^\circ\text{C}$, 16 h; H_2O_2 , MeOH/pH 7 buffer, $0 \rightarrow 20^\circ\text{C}$, 2 h; d) $c\text{Hex}_2\text{BCl}$, Et_3N , Et_2O , -78°C , 60 min; **18**, $-78 \rightarrow -20^\circ\text{C}$, 16 h; H_2O_2 , MeOH/pH 7 buffer, $0 \rightarrow 20^\circ\text{C}$, 2 h; e) TESOTf, 2,6-lutidine, CH_2Cl_2 , -78°C , 1 h; f) DDQ, $\text{CH}_2\text{Cl}_2/\text{pH}$ 7 buffer, 20°C , 16 h; g) LiAlH_4 , THF , -78°C , 30 min; h) $\text{Pb}(\text{OAc})_4$, Na_2CO_3 , CH_2Cl_2 , 0°C , 40 min; i) PPTS, $(\text{MeO})_3\text{CH}$, MeOH , 20°C , 1 h; j) TBSCl, Im, Et_3N , DMF , 20°C , 16 h; k) 1. OsO_4 , Me_3NO , $\text{acetone}/\text{H}_2\text{O}$, 20°C , 16 h; 2. $\text{Pb}(\text{OAc})_4$, Na_2CO_3 , CH_2Cl_2 , 0°C , 40 min. Cp = cyclopentadienyl, TPAP = tetrapropylammonium perruthenate, TESOTf = triethylsilyl trifluoromethanesulfonate, Im = imidazole, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves.

at C29 was selected to enable direct formation of the phosphonium salt for Wittig coupling. By using our lactate methodology,^[18] a boron-mediated *syn* aldol reaction between the PMB-protected ketone **17** and the aldehyde **18** produced the adduct **19** (98%; >95:5 *ds*). Following a straightforward four-step sequence, the (3*R*,3*S*)-aldehyde **20** was obtained cleanly (75%).

The successful boron aldol coupling between ketone **15** and aldehyde **20** (aldol reaction I) necessitated the use of freshly prepared *c*Hex₂BBr^[21] as a more reactive enolizing reagent than the chloride. Exposure of **15** to *c*Hex₂BBr/Et₃N at –78 °C in Et₂O, followed by addition of the aldehyde **20**, led to a 90:10 mixture of adducts with (3*S*)-alcohol **21** as the major isomer. Subjection to PPTS in MeOH/CH(OMe)₃ then induced TES removal and concomitant formation of the *E* ring as the methyl acetal **22**.^[22] Following TBS protection of **22**, oxidative cleavage of the alkene by dihydroxylation and brief exposure to Pb(OAc)₄ regenerated the methyl ketone in **23**; this could be prepared on a gram scale in 72% yield over four steps from **15**.

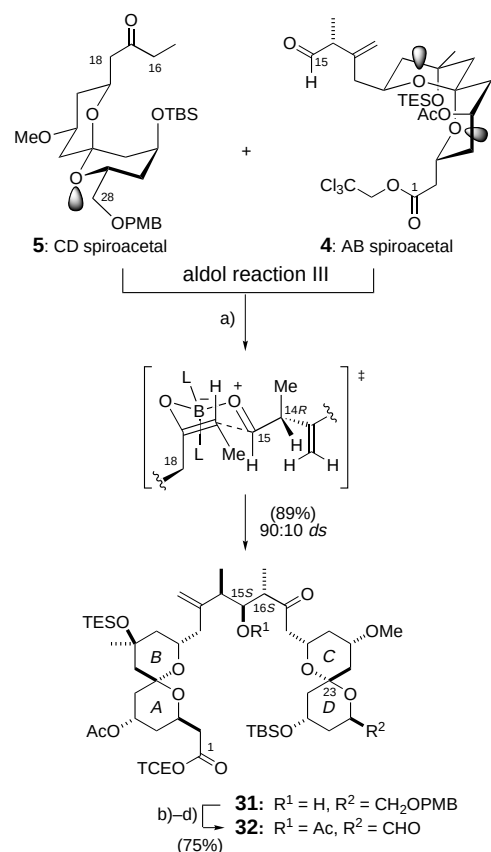
Introduction of the chlorodiene terminus of altohyrtin A, with control of the isolated C47 stereocenter, was now required in aldol reaction II (Scheme 4). Ultimately, this proved remarkably effective using solely substrate control from the ketone component **23**. Here the addition of the dicyclohexylboron enolate **24** to the chlorodienal **25**^[10b] (prepared in three steps from 2-chloroacrolein) proceeded selectively at –78 °C. After oxidative workup, the (4*S*)-adduct **26** was isolated in 80% yield with 95:5 *ds*.^[23] Notably, this result is in the 1,5-*syn* sense, opposite to 1,5-*anti* stereoinduction observed for boron aldol reactions of simple β-alkoxy methyl ketones,^[24] indicating the overriding contribution in this special case from the more remote stereocenters. A reinforcing effect from the *E* ring is apparent, as the analogous reaction with the ketone **29** proceeded with reduced 80:20 *ds* in favor of **30**. In both these cases, the corresponding lithium aldol reaction (LiHMDS) gave no measurable induction. To complete the fully elaborated *EF* segment **6**, TBS protection gave **27** and methylenation of the highly functionalized C45 ketone was achieved using a modified Takai procedure.^[25] Overall, this new method for introducing the altohyrtin/spongistatin side chain proceeds in high overall yield (60% for **23**→**28**) and should be applicable to other congeners, as in altohyrtins B and C (**2** and **3**), simply by changing the aldehyde. In preparation for the final Wittig coupling, direct conversion of **28** into the phosphonium salt **6** was achieved in 91% yield by heating with Ph₃P in the presence of NaI. Thus, the fully functionalized C29–C51 subunit **6** was obtained efficiently in high overall yield (54% from **23**).

Scale up of our previously described aldol-based syntheses^[9d–f] of the *AB* and *CD* spiroacetal units **4** and **5** led to multi-gram quantities,^[26] in readiness for an *anti*-selective aldol coupling (aldol reaction III) to produce the *ABCD* segment **31** (Scheme 5). Notably, the *AB* spiroacetal ring is stabilized by a double anomeric effect, while the *CD* spiroacetal subunit benefits from only a single anomeric effect, and thus epimerizes readily at C23 such that acidic conditions must be avoided. While both boron^[9d] and lithium-



Scheme 4. Synthesis of the C29–C51 phosphonium salt **6**: a) 1. (EtO)₂P(O)CH₂CO₂Et, NaHMDS, catechol, –78 → –20 °C 40 h; 2. DIBAL-H, CH₂Cl₂, –78 °C, 2 h; 3. oxalyl chloride, DMSO, –78 °C, 1 h; Et₃N, –78 °C, 1 h; b) *c*Hex₂BBr, Et₃N, Et₂O, –78 → –40 °C, 90 min; **25**, –78 °C, 16 h; MeOH/pH 7 buffer then H₂O₂/pH 7 buffer, 0 °C, 2.5 h; c) TBSCl, Im, DMF, 20 °C, 3 h; d) Zn, CH₂I₂, TiCl₄, PbI₂, THF/CH₂Cl₂, 20 °C, 4 h; e) PPh₃, NaI, *i*Pr₂NEt, MeCN/MeOH, Δ, 20 h. NaHMDS = sodium bis(trimethylsilyl)-amide, DMSO = dimethylsulfoxide, Bz = benzoyl.

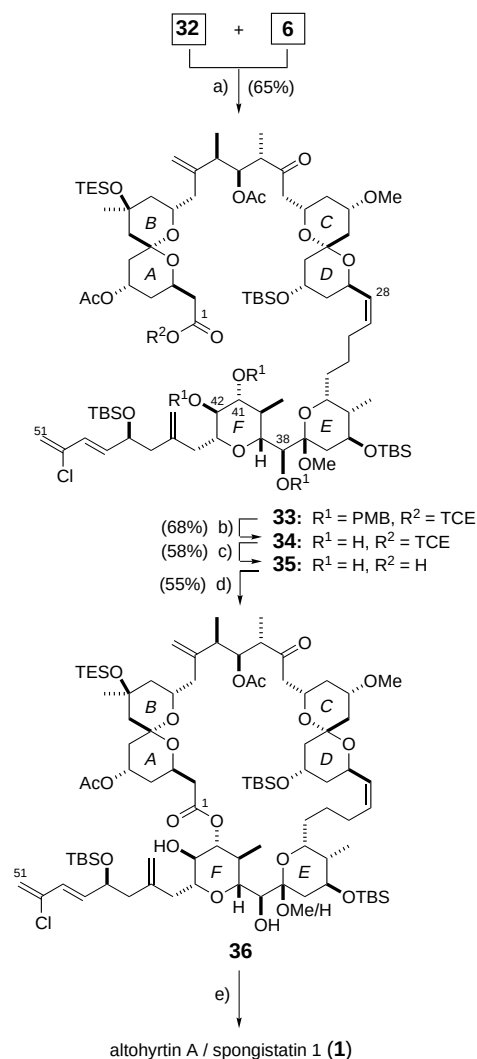
mediated protocols^[9f] were explored to produce the required (1*S*,16*S*)-adduct **31**, the former (as used independently by Evans et al.^[6c,d]) proved superior on a larger scale. Controlled (*E*)-enolization of **5** with *c*Hex₂BBr/Et₃N in Et₂O and addition of aldehyde **4** led to the formation of **31** (90:10 *ds*) in 89% yield,^[27] corresponding to preferential Felkin–Anh attack. A three-step sequence of acetylation of the C15 hydroxy group, PMB ether deprotection by DDQ (CH₂Cl₂, pH7 buffer), and TPAP oxidation then led to the fully functionalized C1–C28 aldehyde **32** (75% overall), without compromising the configurational integrity at C23 in the acid-labile *CD* spiroacetal.



Scheme 5. Synthesis of C1–C28 aldehyde **32**: a) $cHex_2BCl$, Et_3N , Et_2O , $-78 \rightarrow 0^\circ C$, 20 min; **4**, $-78^\circ C$, 16 h; SiO_2 , $20^\circ C$, 40 min; b) Ac_2O , DMAP, pyr, $20^\circ C$, 2 h; c) DDQ, CH_2Cl_2/pH 7 buffer, $0^\circ C$, 90 min; d) TPAP, NMO, 4 Å-MS, CH_2Cl_2 , $20^\circ C$, 10 min. DMAP = 4-(dimethylamino)pyridine.

Realization of an efficient and reproducible Wittig coupling of the fully elaborated C1–C28 and C29–C51 subunits, **32** and **6**, was now crucial (Scheme 6).^[28] Deprotonation of the phosphonium salt **6** with LiHMDS in THF/HPMA at $-78^\circ C$ gave an intense orange-colored ylide solution, whereupon the aldehyde **32** was added, leading on warming to clean Wittig coupling and isolation of the (*Z*)-alkene **33** (*Z*:*E* > 97:3 by 800 MHz ^1H NMR) in 65% yield, representing the fully protected *seco*-acid of altohyrtin A/spongistatin 1 (**1**).

In preparation for macrolactonization, rapid deprotection of the three PMB ethers was achieved in the presence of the potentially labile unsaturated side chain,^[29] by exposure to excess DDQ in CH_2Cl_2/pH 7 buffer, to give the triol **34** (68%; obtained as a ca. 1.3:1 mixture of the *E* ring methyl acetal and its hemiacetal hydrolysis product).^[30] Subjection of this mixture to Zn powder in THF/ NH_4OAc induced deprotection^[31] of the trichloroethyl (TCE) ester to give the *seco*-acid **35**. Regioselective macrolactonization^[6c, 7b, 8b, 32] of the triol **35**, which engaged the C41 hydroxy group (in preference to those at C42 and C38), was performed under modified Yamaguchi conditions^[33] to produce the 42-membered macrolide **36** in 55% yield. Finally, exposure to HF/MeCN led to deprotection of the four silyl ethers and hydrolysis of the remaining methyl acetal to provide (+)-altohyrtin A/spongistatin 1 (**1**) in 36% yield.^[34] The spectroscopic data [^1H NMR (CD_3CN and CD_3OD , 500 and 800 MHz), ^{13}C NMR (CD_3CN), IR,



Scheme 6. Final steps of the total synthesis of altohyrtin A/spongistatin 1 (**1**): a) LiHMDS, THF/HPMA, $-78^\circ C$, 10 min; **32**, $-78 \rightarrow 20^\circ C$, 40 min; b) DDQ, CH_2Cl_2/pH 7 buffer, $0^\circ C$, 60 min; c) Zn, THF/1M NH_4OAc , $20^\circ C$, 30 min; d) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, $20^\circ C$, 3 h; DMAP, PhMe, $100^\circ C$, 20 h; e) HF, MeCN/ H_2O , $0^\circ C$, 4 h. LiHMDS = lithium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide. Compounds **34**, **35**, and **36** were mixtures of the methyl acetal and hemiacetal in ca. 1.3:1 ratio.

HRMS),^[35] along with specific rotation [$[\alpha]_D^{20} = +21.0$ ($c = 0.44$, MeOH); cf. Kobayashi^[2a] $[\alpha]_D^{20} = +21.7$ ($c = 1.20$, MeOH) and Pettit^[3a] $[\alpha]_D^{20} = +26.2$ ($c = 0.32$, MeOH)] of the synthetic material were in excellent agreement with that reported (and by comparison with the NMR spectra kindly provided by Professors Pettit and Kishi).^[36]

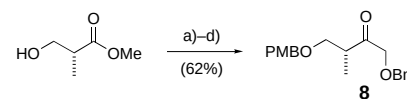
Overall, this highly stereocontrolled total synthesis of altohyrtin A/spongistatin 1 proceeds in 33 steps and 1.0% overall yield for the longest linear sequence (based on the AB subunit). Altogether, this constitutes one of the most testing applications of boron-mediated aldol methodology for polyketide synthesis, including its use for the side-chain installation (as in **23** → **26**) which benefits from a remarkable level of remote stereoinduction. To date, this synthesis has already provided useful quantities of altohyrtin A/spongistatin 1 and thus contributes to replenishing the largely exhausted natural

material from the initial isolation work^[37] and enables more detailed biological evaluation.

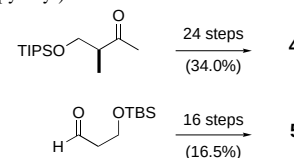
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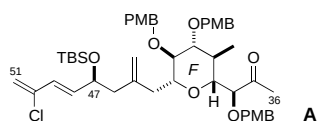


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- [36] We thank Professors Pettit and Kishi for kindly providing comparison NMR spectra.
- [37] Isolation from sponge sources: At present, we have synthesized 4.5 mg of **1** and 60 mg of its direct precursor **36**; optimum conditions for the final deprotection step are being developed. 13.8 mg from 400 kg of *Spongia* sp. by Pettit et al.^[3a] + 7.6 mg from 112 kg of *Hyrtios alium*. by Kobayashi et al.^[2c]

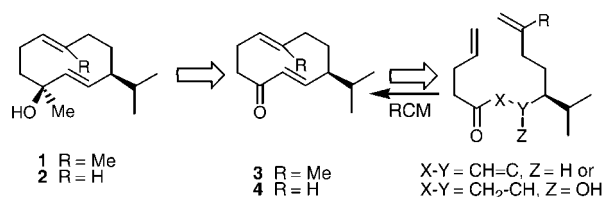
Synthesis of a 10-Membered Carbocycle By Olefin Metathesis**

Marta Nevalainen and Ari M. P. Koskinen*

Dedicated to Professor Henry Rapoport

The pine sawfly *Neodiprion sertifer* is a common pest in pine trees of the northern hemisphere.^[1] The population of larvae can cause extensive defoliation, resulting in serious economical damage. Therefore, great effort has recently been directed to monitor and control the population of sawfly species.^[2] It was shown that the resin secreted by pines interferes with the development of larvae.^[3] The main component of the sesquiterpene fraction of the resin of *Pinus sylvestris* is 1,6-germacradien-5-ol (**1**),^[4] first isolated by Bohlmann et al.^[5] from *Senecio phonolithicus*. On the other

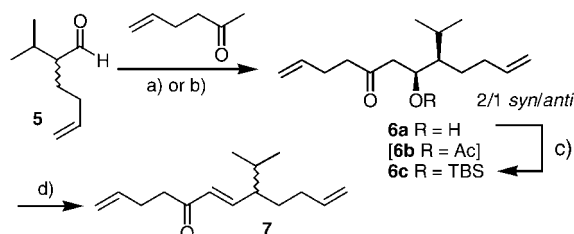
hand, 4α-hydroxygermacra-1(10),5-diene (4α-HDG, **2**) is a predominant foliage sesquiterpene in many pine trees (*Pinus radiata*).^[6] To date, no synthesis for **1** or **2** has yet been reported.^[7] Here we describe the synthesis of cyclodecenones (±)-**11** and (±)-**12**, which are direct precursors for (±)-**2** (Scheme 1), by ring-closing olefin metathesis (RCM). To the



Scheme 1. Retrosynthesis of 1,6-germacradien-5-ols **1** and **2**.

best of our knowledge, this is the first 10-membered carbocycle obtained by using the RCM methodology.^[8] Only a few examples of the formation of ten-membered rings by RCM have been reported,^[9] and all dealt with the synthesis of oxazoles or azacycles.

Among the many cyclization reactions, olefin metathesis has emerged as a very powerful tool for the formation of C=C bonds.^[9, 10] However, as a result of inherent ring strain, the formation of 8- to 11-membered rings is particularly difficult,^[9] and its success depends on the substitution pattern of the bis-olefin.^[11] The importance of restricted chain mobility is clearly illustrated by **6a** (Scheme 2), in which the conformational-control element is the aldol moiety. Conversion of this functional group into an enone completely inhibits the cyclization, as described hereafter.



Scheme 2. Synthesis of bis-olefins **6** and **7**. a) LDA, THF, −78 °C (61 %); b) LDA, THF, −78 °C; then Ac₂O (not isolated); c) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C (96 %); d) DBU, THF, 0 °C (56 % from **5**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LDA = lithium diisopropylamide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Aldehyde **5** was synthesized in 72 % overall yield from isovaleric acid. Condensation of **5** with 5-hexen-1-one delivered aldol **6a** with 3,4-*syn*/3,4-*anti* (Felkin) selectivity. In situ entrapment of **6a** with acetic anhydride followed by DBU-promoted elimination yielded enone **7** (Scheme 2).

The RCM reaction of enone **7** in the presence of the Grubbs catalyst provided only oligomers, along with unconverted starting material (Table 1, entry 1). In CH₂Cl₂ solution, enone **7** adopts a linear conformation in which the olefinic termini are located at a maximum distance from each other. Therefore, only acyclic diene metathesis polymerization takes place. We were thus pleased to observe that the aldol **6a** (*syn*/*anti* 2/1) underwent the RCM reaction to form 10-membered

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

Table 1. RCM reactions conducted on bis-olefins **6** and **7**.^[a]

Entry	Bis-olefin	Catalyst (mol %)	Additive (mol %)	t [h]	Product (%) ^[b]	Recovered bis-olefin [%] ^[b]
1	7	10	–	48	–	62
2	6a	15	–	48	8 (11)	25
3 ^[c]	6a	15	Me ₂ AlCl (100)	96	9 (34)	30
4 ^[d]	6a	10	Me ₂ AlCl (100)	96	4 (32) 7 (28) 10 (7)	–
5	6c	10	–	48	11 (35) 12 (16) 13 (11)	6
6	6c	10	Ti(OiPr) ₄ (10)	48	11 (47) 12 (21) 13 (8)	–

[a] All reactions were performed in CH₂Cl₂ at reflux (*c* = 0.56 mm). [Ru]-carbene (Grubbs catalyst) was added with a cannula as a solution in CH₂Cl₂. [b] Yields of isolated products. [c] Reaction quenched with 1N HCl. [d] The reaction mixture was treated with DBU (100 mol %) before quenching.

carbocycle **8** (Scheme 3). The *E-cis* ring was formed exclusively (the *cis* configuration of this isomer was assigned by analogy of its NMR data with that obtained for **13**; see below), but unfortunately in only 11% yield (Table 1, entry 2). Unconverted starting material was recovered in 25% yield, and the formation of oligomers was also observed. The reverse reaction of the free hydroxy group with the catalyst competes with the desired metathesis. Moreover, the hydroxy group is not large enough to template the bis-olefin towards ring closure.

In view of those results, we decided to treat aldol **6a** with an equimolar amount of Me₂AlCl and attempt the RCM reaction on the resulting metal complex (Scheme 3).^[13] We observed that the RCM reaction proceeded to form the target macrocycle. However, the drawback of this approach turned out to be the quenching of the reaction. Treatment of the reaction mixture with dilute hydrochloric acid gave retroaldol product **9** in 34% yield as a 9/1 *E/Z* mixture of diastereomers (Table 1, entry 3). The remainder consisted of oligomers and unconverted starting material (30% recovery yield). Clearly, the

retroaldol reaction occurred to release the transannular strain of the newly formed 10-membered ring. When the reaction mixture was treated under reflux with DBU (100 mol %) for 1 h, cyclic enone **4** (mixture of diastereomers) was obtained as an inseparable mixture along with acyclic enone **7** (Table 1, entry 4). The 20-membered enone **10** was isolated as a side product in 7% yield and as a diastereomeric mixture.

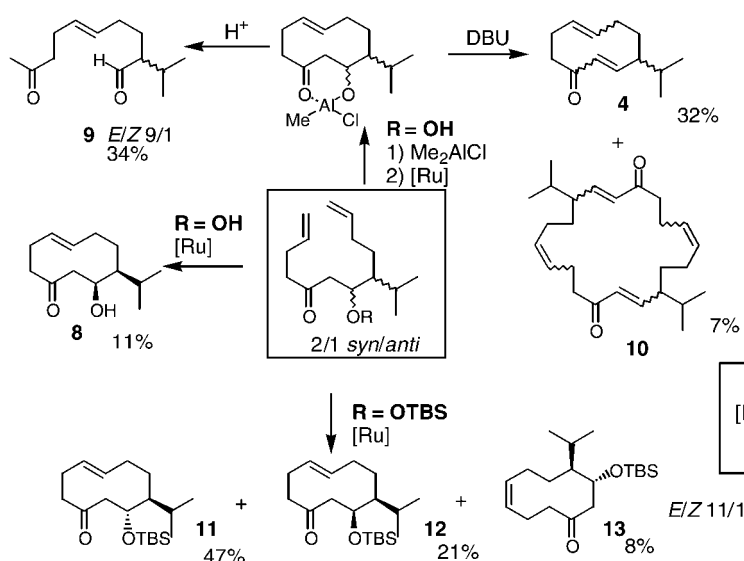
In light of these results, protection of the hydroxy group of aldol **6a** was envisaged as a possible solution. Indeed, *O*-TBS-protected bis-olefin **6c** (*syn/anti* 2/1) underwent the RCM reaction smoothly and provided 10-membered rings **11–13** in 62% total yield (Table 1, entry 5). Unconverted starting material was recovered in 6% yield. Careful inspection of the ¹H NMR spectrum of the crude reaction mixture revealed that only three of the four possible diastereomers were formed and that the *E/Z* ratio was 8/1. We tentatively assigned^[12] the relative C8,C9 configuration of the *Z* isomer (**13**) and of the major *E* isomer (**11**) to be *trans*. Both compounds showed similar spectral patterns for the characteristic signals. In contrast, the minor *E* isomer should have the *cis* configuration for those stereocenters. It can be concluded that both *syn* and *anti* aldols favor the formation of the *E* olefin. However, as the recovered bis-olefin was enriched in the *anti* isomer (1/3 *syn/anti* mixture), the *syn* aldol (leading to *trans* rings) must cyclize faster than the *anti* aldol. The *anti* aldol (leading to the *cis* ring) decomposes partially by oligomerization.

Finally, when the RCM reaction of **6c** was conducted in the presence of 10 mol % of Ti(OiPr)₄, the total yield of the cyclization increased to 76% and the *E/Z* ratio to 11/1 (Table 1, entry 6). Coordination of the Lewis acid to the carbonyl group of **6c**^[13] seems to confer further conformational restriction on the bis-olefin and thus favors the desired cyclization.

In summary, we have successfully synthesized (±)-9-(*tert*-butyldimethylsilyloxy)-8-isopropylcyclodec-4-enone as an 11:1 mixture of *E/Z* diastereomers in 76% yield by using the binary system Grubbs catalyst/Ti(OiPr)₄. This is the first example of a 10-membered carbocycle being formed by RCM.

The bulky TBS group acts as a conformational-control element that facilitates ring closure.^[11]

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Scheme 3. RCM reactions of aldol **6a** and silylated aldol **6c**.

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Experimental Detection of Tetraoxygen**

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The search for tetraoxygen, which dates back to a study by Lewis in 1924,^[1] is being actively pursued, owing to its fundamental interest, its potential role as a material of high energy density,^[2] and, in particular, the current upsurge of interest in excited states of O₂ with relevance to atmospheric chemistry and to terrestrial and Venusian nightglow.^[3] Numerous calculations at different levels of theory predict the existence of metastable O₄ molecules with a *D*_{2d} cyclic geometry^[4] or a *D*_{3h} “pinwheel” geometry.^[5, 6] Positive experimental detection of such species has not been reported, whereas weakly bonded (O₂)₂ van der Waals dimers, with dissociation enthalpies of less than 1 kcal mol^{−1}, have long

been known and thoroughly characterized.^[7] Indirect evidence for metastable tetraoxygen was derived from experiments involving electron transfer from Cs to O₄⁺, followed by the measurement of the kinetic energy spectrum of the O₂ fragments. The structure of the kinetic energy distribution was consistent with the intervention of some O₄ species that were not observable under the conditions of the experiment.^[8] Strong evidence for metastable O₄ was derived from studies involving the photoionization of O₂ excited by a DC discharge.^[9, 10] Interestingly, the results of both experimental studies were interpreted as suggestive of the existence of a third metastable O₄ species in addition to the theoretically predicted molecules, namely, a relatively long lived complex between a ground-state O₂ molecule and an O₂ molecule in the excited c¹Σ_u[−] electronic state.^[10]

To obtain conclusive proof, we have carried out an experiment aimed at detecting intact O₄. Our approach is also based, like previous studies,^[8] on the neutralization of O₄⁺ cations in the gas phase, but uses for the identification of the intact O₄ molecule neutralization reionization (NR) mass spectrometry^[11] on a highly sensitive instrument that allowed the detection of other elusive atmospheric species, such as hydrogen trioxide^[12] and the [H₂O⁺·O₂[−]] charge-transfer complex.^[13]

The O₄⁺ ions were generated in a chemical ionization (CI) source by association of O₂ molecules with O₂⁺ primary ions, formed both in the X²Π_g ground state and in electronically excited states by electron impact.^[14] The ions were then accelerated through 4–8 keV, magnetically mass resolved, and probed by collisionally activated dissociation (CAD) mass spectrometry. Whereas the CAD spectrum of ¹⁶O₄⁺ from the ionization of ¹⁶O₂ shows ¹⁶O₂⁺ as the charged fragment, ¹⁶O₂¹⁸O₂⁺ ions from ¹⁶O₂/¹⁸O₂ mixtures give ¹⁶O₂⁺ and ¹⁸O₂⁺ without the ¹⁶O¹⁸O⁺ ions^[15] that would suggest isotopic scrambling (Figure 1). This shows that the O₄⁺ ions probed contain two discrete O₂ units, each of which retains its original identity.

In the NR experiments the O₄⁺ ions were also accelerated to 4–8 keV and mass-selected before undergoing two consecutive collision events in separate cells aligned along the beam path. In the first cell a fraction of the ions undergoes electron transfer from a target gas to yield O₄ together with neutral and charged fragments. All O₄⁺ parent cations that escaped neutralization and any charged fragments were removed by a deflecting electrode, so that a beam containing only fast neutral species entered the second cell, where reionization by collision with a suitable target gas gives cations that are energy-selected, and their mass spectra are recorded. Detection of a “recovery” peak, that is, of a charged species with the same *m/z* ratio as the original O₄⁺ ions demonstrates the occurrence of the sequence of Equation (1) and hence the existence of a neutral O₄ species with a lifetime that exceeds the flight time from the neutralization to the reionization cell.



The NR spectra of the ¹⁶O₄⁺, ¹⁶O₂¹⁸O₂⁺, and ¹⁸O₄⁺ ions, illustrated in Figure 2, show significant recovery peaks at *m/z* = 64, 68, and 72, respectively, a result that positively

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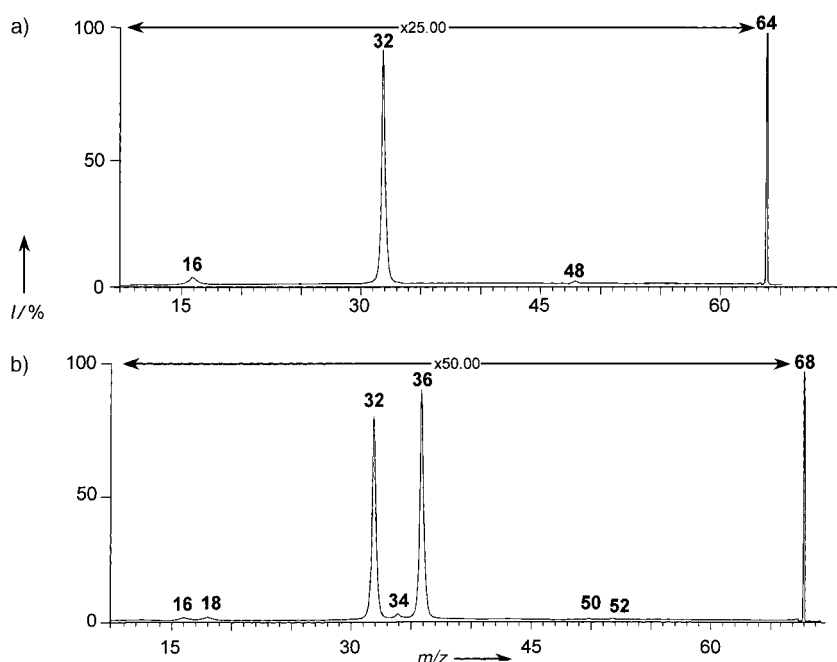


Figure 1. a) CAD spectrum of 8-kV $^{16}\text{O}_4^+$ ions, $m/z = 64$. Collision gas, He. b) CAD spectrum of $^{16}\text{O}_2^{18}\text{O}_2^+$ ions, $m/z = 68$.

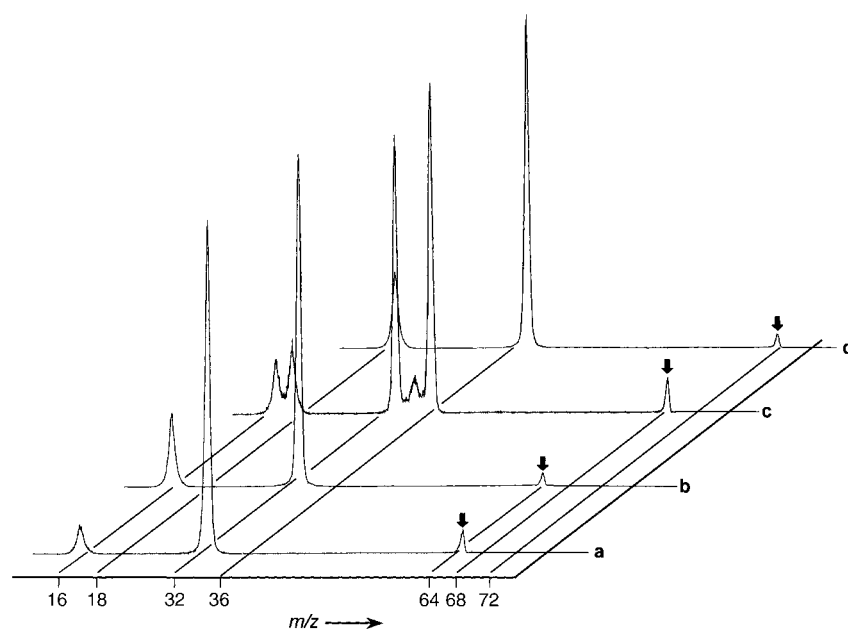


Figure 2. NR spectra of a) 4-kV $^{16}\text{O}_4^+$ ions, b) 6-kV $^{16}\text{O}_4^+$ ions, c) 6-kV $^{16}\text{O}_2^{18}\text{O}_2^+$ ions, and d) 6-kV $^{18}\text{O}_4^+$ ions. Note the recovery peaks at the appropriate m/z ratios in all spectra. Neutralizing gas, CH_4 ; reionizing gas, O_2 (see text).

establishes the existence of a neutral tetraoxygen species with a relatively long lifetime, whose lower limit of $0.95 \pm 0.15 \mu\text{s}$ is defined by the flight time of an $^{18}\text{O}_4$ molecule with a mass of 72 Da and a kinetic energy of 4 keV from the neutralization to the reionization cell of the NR spectrometer.

Structural insight is provided by the isotopic composition of the charged fragments revealed by the NR spectra, which can originate only from the neutral species formed in one of the following processes: 1) The collision undergone by O_4^+ in the neutralization cell; 2) the unimolecular fragmentation of O_4

during its flight time; and 3) the collision undergone by O_4 in the reionization cell. As expected, $^{16}\text{O}_4$ gives $^{16}\text{O}_2^+$, $^{18}\text{O}_4$ gives $^{18}\text{O}_2^+$, and $^{16}\text{O}_2^{18}\text{O}_2$ gives nearly equal amounts of $^{16}\text{O}_2^+$ and $^{18}\text{O}_2^+$ without isotopically mixed $^{16}\text{O}^{18}\text{O}^+$ fragments^[15] (Figure 2). This pattern strongly suggests, although it does not rigorously prove, that the neutral O_4 species detected contain two distinct O_2 units that become separated in the dissociation process(es) without exchanging their constituent atoms.

Having conclusively established the existence of long-lived metastable O_4 , it is legitimate to inquire whether it can be identified as one of the species so far suggested. The following criteria can be applied: in general, NR mass spectrometry allows detection of a neutral species only if its dissociation requires overcoming a sizable barrier, on the order of 10 kcal mol^{-1} . Furthermore, the vertical character of the neutralization process allows survival of the neutral molecule only if its geometry is not significantly different from that of its charged parent (adequate Franck–Condon overlap).^[11] Application of the above criteria to the O_4^+/O_4 system is particularly difficult, in view of the symmetry-breaking problem that affects the description of O_4^+ , even by the most robust theoretical methods.^[16] The structure of O_4^+ has been extensively investigated by IR and ESR spectroscopy in cryogenic Ne matrices^[17] and by theoretical methods.^[18] A comprehensive theoretical study indicates that a rectangular D_{2h} species and a *trans*-planar C_{2h} species are the most stable isomers, located 11.0 and $11.5 \text{ kcal mol}^{-1}$, respectively, below separated O_2^+ and O_2 .^[19] Symmetry-breaking problems were tackled by the complete active space state interaction (CASSI) method, which led to reassignment of the experimentally measured frequency of 1320 cm^{-1} to antisymmetric stretching of rectangular O_4^+ .^[20] A recent study of the performance of various theoretical methods weakened this assign-

ment and additionally pointed to the failure of otherwise reliable methods such as BLYP and BPW91, which predict no bound solution at all for O_4^+ , and further showed that the bond lengths calculated with a variety of methods by using both 6-31*G and cc-pVTZ basis sets show unusually wide variations.^[16] If one considers that similar problems may conceivably affect the theoretical description of neutral O_4 as well, structural assignment of the experimentally observed O_4 species on theoretical grounds is clearly difficult. In principle, the relatively long lived species detected by NRMS could be a

covalently bound molecule or some strongly bonded complex between two O₂ units. As to the first possibility, it appears that among the covalently bound O₄ molecules so far theoretically characterized, neither the D_{2d} quasisquare species nor the D_{3h} pinwheel species have a geometry sufficiently close to any of those assigned to the O₄⁺ precursors detectable by NR mass spectrometry, in view of the unfavorable Franck–Condon factors involved. Furthermore, the calculated barrier for dissociation of the D_{2d} tetraoxygen molecule of 5.6 kcal mol^{−1},^[4e] is somewhat lower than the threshold generally regarded as necessary to survive the vertical neutralization process. Finally, the fragmentation pattern in the NR spectrum is hardly consistent with those expected for either of the covalent molecules. Assuming a quasisquare D_{2d} structure in which all O–O bonds are equivalent, one would expect ¹⁶O₂¹⁸O₂ to give, in addition to ¹⁶O₂ and ¹⁸O₂, a comparable ¹⁶O¹⁸O fragment, which is not displayed by the NR spectra.^[15] As for the pinwheel D_{3h} molecule, its dissociation is expected to give, in addition to O and O₂, an O₃ fragment, also undetected in the NR spectrum.

Based on the above considerations, neither of the covalent molecules so far theoretically predicted is a particularly attractive candidate. Passing to O₄ complexes, that between a ground state O₂ molecule and one in the excited c¹Σ_u[−] state appears more compatible with the present results. As previously noted, its role has been stressed by Suits et al.,^[10] based on their photoionization study of O₂ excited by DC discharges, and supported by ab initio calculations^[9] and by Helm and Walter in a previous study of the neutralization of O₄⁺ by Cs.^[8] Consistent with their interpretation,^[8, 10] neutralization of the [c(¹Σ_u[−])O₂⋯O₂(X³Σ_g[−])] complex populates a Rydberg state built on a core of O₂⁺ in a [O₂ d¹Π_g(R)⋯O₂(X³Σ_g[−])] complex, that couples efficiently to the [O₂(1¹Π_g)⋯O₂(X³Σ_g[−])] complex, which eventually decays by a fully allowed transition to the metastable [O₂(c¹Σ_u[−])⋯O₂(X³Σ_g[−])] complex. This sequence accords well with the experimental finding that a fraction of the O₄⁺ ions survives dissociation in the vertical neutralization process, since the weakly bound Rydberg electron is not expected to appreciably affect the geometry or the relatively large binding energy (ca. 10 kcal mol^{−1})^[21] of the parent complex.^[10] We further note that intervention of Rydberg states and formation of metastable O₄ species other than covalently bound molecules (e.g. ion-pair structures) have been suggested by Helm and Walter to account for the kinetic energy distribution of O₂ fragments from the neutralization of O₄⁺ by Cs,^[8] and that the lifetime of up to a few hundred nanoseconds of the metastable O₄ species inferred from their data is consistent with that measured in this work.

In conclusion, whereas a definitive assignment is not allowed by the present results, we are inclined to tentatively identify the O₄ species now positively detected as a long-lived complex between an O₂ molecule in the electronically excited c¹Σ_u[−] state and a ground state O₂ molecule, whereas the theoretically calculated features of the covalently bound O₄ molecules so far predicted appear less consistent with the experimental picture, although other structures cannot be rigorously excluded. Clearly, additional theoretical work is required to fully characterize metastable O₄, and hopefully

the conclusive proof of its existence provided by this study will stimulate further calculations in this direction.

As a final note, the unabated interest in O₄ and its relevance to research areas other than atmospheric science are witnessed by recent studies on the red phase of solid oxygen at pressures of up to 63 GPa, whose IR spectrum is interpreted on the basis of a crystal composed by units formed by four atoms.^[22, 23]

Experimental Section

The experiments were performed with a multisector mass spectrometer of the EBE-TOF configuration (ZABSpec oa-TOF, VG Micromass Ltd, Manchester), modified by addition of two pairs of collision gas cells and a CI source equipped with a thoriated filament. Typical source conditions were as follows: source temperature 100 °C; repeller voltage 0.0 V; ion-extraction voltage 4–8 kV; source pressure 0.05–0.1 Torr. The CAD and NR experiments were performed in the first of the collision cell pairs, located between the magnet and the second electrostatic analyzer. CAD spectra were recorded by utilizing He as the target gas, admitted into the first cell to a pressure adjusted to achieve a 80 % transmittance. In the NR experiments CH₄, utilized as the neutralizing gas, was also admitted into the first cell to achieve a beam transmission of 80 %. All charged species were then removed by a high-voltage (1 kV) deflector, and the fast neutral species entered the second cell, where reionization was achieved with O₂ as the stationary target gas. The NR spectra were averaged over 50 acquisitions to achieve a satisfactory signal-to-noise ratio. The gases were research-grade commercial products with a stated purity exceeding 99.99 mol %. The highly enriched ¹⁸O₂ sample (99 atom % ¹⁸O) utilized in the NR experiments was obtained from IKON Stable Isotopes Inc.

In all NR experiments, and particularly in those where quite unusual species such as long-lived O₄ are observed, it is imperative to guard against conceivable interferences that are isobaric with the ionic parent(s) that are neutralized. In the case of interest, intervention of contaminants containing H, or other odd-mass atoms, can be safely excluded, based on the absence of detectable odd-mass fragments in the CAD and NR spectra of the ¹⁶O₄⁺, ¹⁶O₂¹⁸O₂⁺, and ¹⁸O₄⁺ ions utilized as the charged precursors. This leaves only impurities containing even-mass atoms such as S₂⁺, SO₂⁺, etc. These, and other conceivable, but much more unlikely candidates, were safely ruled out by the results of experiments involving O₄⁺ ions labeled with ¹⁸O; for example, no plausible impurity isobaric with ¹⁸O₄⁺ (*m/z* = 72) exists.

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Fundamental Zeolite Crystal Growth Rates from Simulation of Atomic Force Micrographs**

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Insight into zeolite crystal growth is afforded by a computer model that simulates atomic force microscopy (AFM) images^[1] of zeolite A crystallite surfaces. This leads to the first ever quantification of fundamental zeolite crystal growth processes. AFM enables imaging of nonconducting surfaces with atomic-scale vertical resolution and is ideal for probing the surface of inorganic crystals. The first AFM image of a zeolite, which depicted the cleaved (100) face of clinoptilolite,

was published by Weisenhorn et al. in 1990.^[2] This triggered a series of mineral zeolite studies^[3] that used extremely detailed topographical information obtained from AFM images to estimate unit cell parameters. At lower resolution the imaging of atomic corrugations is precluded; however, there still remains a great wealth of information to be garnered concerning crystal growth processes.

Zeolite growth often occurs by the deposition of successive layers thus creating surface terraces.^[1] Typically, terrace height, orientation, and shape are governed by the unit-cell structure and symmetry of the zeolite. Terrace separation usually decreases towards the extremity of the growing face, thus generating an overall parabolic cross-section. This quadratic relationship implies that it is terrace area and not size that grows at constant rate.^[1b] Constant-area-deposition growth therefore predominates and this has significant ramifications on the mode of transport of gel nutrient to the growing face, as will be discussed later. As an introduction, an overview is given of specific features observed on the surface of zeolite A, chosen owing to its paramount industrial importance, cubic symmetry (facilitating creation of the model), and the existence of high-quality AFM images of its surface.

Atomic force micrographs of the (100) face of zeolite A crystallites reveal square-shaped surface terraces of uniform height equal to 1.2 nm, that is half the unit-cell dimension (Figure 1; squares are distorted to parallelograms owing to

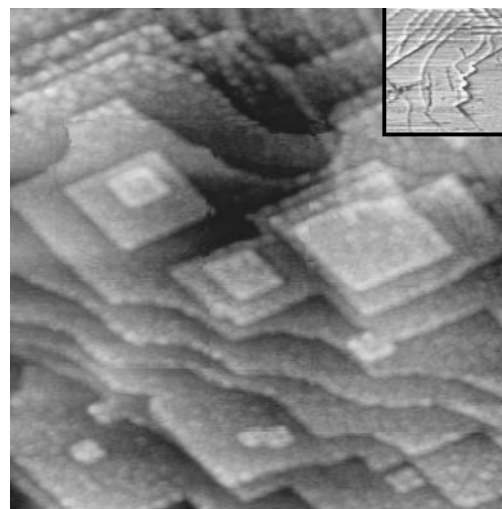


Figure 1. $1.0 \times 1.0 \mu\text{m}^2$ AFM Tapping Mode image of a portion of a $10.0 \times 10.0 \mu\text{m}^2$ (100) face of a zeolite A crystallite. Inset: phase image showing a section with a convex terrace growth front.

crystal tilt). The terrace edges run parallel to the edges of the crystal face. A further feature is that of curved terrace edges that have been postulated to arise during the coalescence of individual nucleation centers.^[1b] The shape and surface density of these terraces are a result of the crystal growth mechanism. This work is concerned with simulation of such AFM images using the rates of fundamental crystal growth processes as variables in the model.

These AFM observations serve both as a basis for creation of the computer code and also provide a means of testing the

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accuracy of different models. Herein we reveal the relative rates of individual crystal-growth processes in a zeolite for the first time, and thus make an important step towards understanding the crystallization of an extremely important class of open-framework inorganic materials.

The purpose of this study is to determine relative growth rates of surface terraces. It is not the purpose to determine the precise units of attachment at the face of a growing crystallite. The very existence of terraces implies stable surface terminations (possibly closed cages—but this is as yet undetermined). These surface structures can be achieved by addition of monomeric silica or alumina or oligomeric units. We concern ourselves only with the nature of the point of attachment.

Owing to the cubic symmetry of zeolite A, a two-dimensional grid may be employed to represent the (100) growing face—this study employed a 100 by 100 grid. During the simulation, the evolution in height of each position on the surface is measured in terms of the number of growth layers—each layer has been shown to comprise a beta cage and a double four-ring (D4R)—although the exact manner of surface termination remains as of yet unclear. The nature of the surface at a given position is defined by the relative presence of vicinal growth terraces. It is thus possible to define five sites, named arbitrarily. Initially, all sites on the surface are termed SURFACE sites, see Figure 2a. There are no vicinal terraces and any deposition must involve nucleation. The presence of one vicinal terrace is typical of sites found along the edge of an advancing terrace front. These sites, depicted in Figure 2b, are termed EDGE sites. A kink in a terrace front or a coalescence of two orthogonal terrace fronts will create a site, which has two vicinal terraces. These sites, depicted in Figure 2c, are termed KINK sites. The final two sites, depicted in Figure 2d and e, have three and four vicinal terraces and are termed U site and SURROUND site, respectively.

This simple representation of the (100) face as a grid and the definition of various types of surface site form the basis of the model used. It is noteworthy that such sites, for an open-framework material, are more complex than the usual definition for a dense-phase material where a neighboring site is usually an individual atom. Deposition of nutrient at the surface is simulated by incrementing the height variable of a given position on the surface and altering site geometries in the vicinity accordingly. Thus far the model is both ideologically trivial and easily programmed. Complexity arises from consideration of the method for allocating surface growth positions due to the inherent need for this process to be justified in a real physical sense.

The program works by defining growth times for the different site types—specific values will be discussed later. Every iteration, the program checks for growth at the different site types in the sequential order SURFACE, EDGE, KINK, U (in the final version of the code it was found to be unnecessary to differentiate between U and SURROUND sites). If no site type is destined for growth then the counter is incremented until a site type is primed. Once a type has been selected then one such site is chosen at random. After incrementing the surface height at that point by one

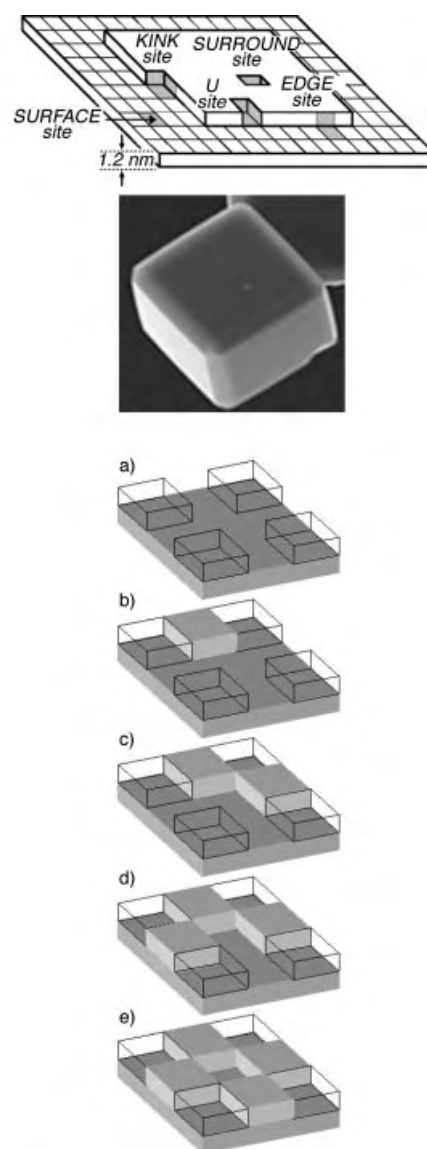


Figure 2. Scanning electron microscopy (SEM) image of the (100) face of a $10.0 \times 10.0 \times 10.0 \mu\text{m}^3$ zeolite A crystallite (center), the five possible sites considered in modeling the growth process (a–e), and a schematic of a typical surface arrangement (top). The five sites are termed: a) SURFACE site, b) EDGE site, c) KINK site, d) U site, and e) SURROUND site, with zero, one, two, three, and four adjacent growth units, respectively. In each case, the potential growth site is located in the center of the upper layer. Diagonally adjacent surface units do not influence site definition in this current model and are hence shown as wire frames.

unit, adjacent site geometries are recalculated and the iteration is repeated.

Transport of gel nutrient may now be considered. Diffusion-limited growth implies intermittent supply of nutrient to the crystal surface and is strongly influenced by population distribution of site types, as well as energetics of attachment. Thus growth is more probable at a large square-shaped terrace with many EDGE sites than at a small square-shaped terrace with fewer EDGE sites. Such growth, characterized by constant linear terrace advance, is refuted by experimental evidence, in images recorded on zeolites A, Y, and silicalite. These images are recorded on crystallites removed from gels at the end of synthesis, thus growth is not diffusion-limited

even when supersaturation levels of aluminate and silicate are low. This is in contrast to template transport which has been shown to be diffusion-limited in unstirred syntheses.^[4] Non-diffusion-limited growth implies that nutrient is present at all positions on the surface and growth is thus dependent solely on energetics of attachment. Such growth is characterized by the experimentally observed constant area terrace advance. Crucially, the computer model allows deposition at only one site on the surface per iteration. Though this might initially seem counter-intuitive, it prevents the influence of population distribution of site types, and thus leads to the correct growth patterns.

The final step in creating the model involved defining the relative growth times for the different site types. This process has profound impact on the ultimate nature of the growth observed. The growth times mirror intuitive site attachment energies, thus SURFACE sites have the longest growth time and U sites and SURROUND sites have the shortest growth time. To minimize the number of iterations required to see a reasonable degree of surface growth, these latter short growth times were chosen as one time unit. Other times have been optimized based upon the features observed in the experimental AFM images. The SURFACE site time was set at 1000 time units as this gave a reasonable degree of multiple nucleation. The EDGE site time dictates the speed at which a freshly nucleated site will commence growth. More importantly, the ratio of EDGE site/KINK site times dictates the overall shape of the terraces. If this ratio is too high then the terraces will tend to grow out in a circular fashion, since KINK site growth is the mechanism for blocking out terrace shape. The final ratio was chosen to be 30/2 time units. The evolution of growth produced by these times is illustrated in the fifteen frames of Figure 3. Frames 2–4, 7, and 14 highlight the

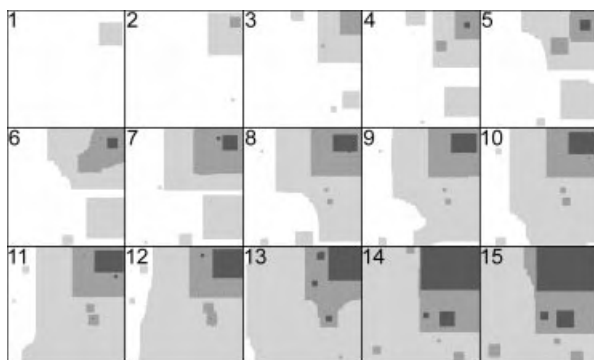


Figure 3. Fifteen frames that show the evolution of surface growth generated by the computer model. The frames are displayed in chronological order but were not necessarily taken at constant time intervals. Relative growth times, in arbitrary units, required to produce this simulation are, SURFACE 1000, EDGE 30, KINK 2, both U and SURROUND 1.

presence of multiple nucleation and the general square shape of the terraces. Frame 5 is taken shortly after the first terrace coalescence and highlights the formation of curved terrace edges. This phenomenon is repeated in further images though the curved terraces may be seen to grow out rapidly. The existence of convex terrace edges, as predicted by Monté

Carlo growth simulation,^[1b] is now confirmed in Figure 1. In terms of the most significant growth processes of surface nucleation, edge and kink growth the relative rates are:

$$500 \times \text{surface rate} = 15 \times \text{edge rate} = \text{kink rate}.$$

In conclusion, an accurate model of the surface growth of one of the most important industrial zeolites has been created. In conjunction with experimental data this model highlights the non-diffusion-limited nature of zeolite growth and furnishes the first rate data concerned with fundamental growth processes in zeolites.

Experimental Section

Atomic force micrographs were recorded on a Digital Instruments Nanoscope Multimode Microscope operating in TappingMode, recording height and phase information. The method used to prepare the samples for AFM and the synthesis procedure for the zeolite A crystals were reported in ref. [1b]. The computer simulation was written using the software package Mathematica 3.0 from Wolfram Research Inc. This package was chosen for ease of post-simulation image processing; however, future versions of the program will be coded in a high-level language.

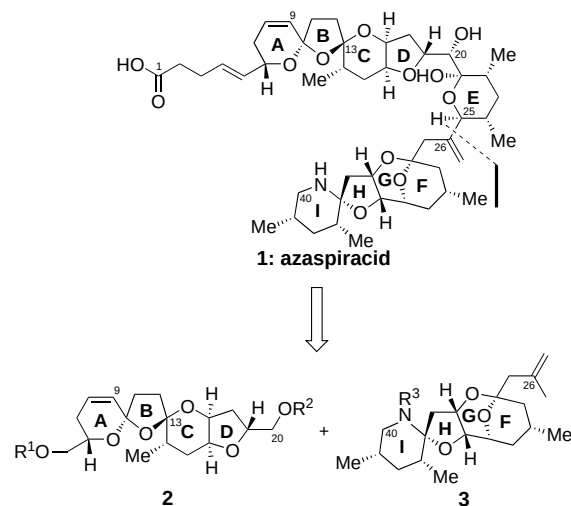
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Synthesis of the ABCD Ring System of Azaspiracid**

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Azaspiracid (**1**, Scheme 1) is a marine biotoxin^[1] whose structure and damaging effects on the environment and humans have recently stimulated considerable synthetic

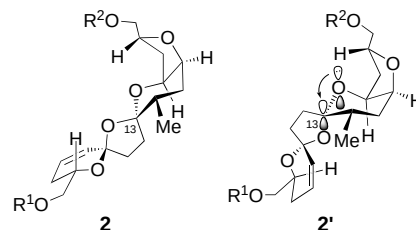


Scheme 1. Structure of azaspiracid (**1**) and retrosynthetic analysis leading to the ABCD and FGHI fragments **2** and **3**.

activities.^[2] Justification of endeavors directed towards its total synthesis has been given elsewhere in a report that also included the construction of the FGHI ring system of this molecule.^[3] Here we report the synthesis of the ABCD ring framework of azaspiracid (**1**) by a special strategy requiring a hydrogen bonding auxiliary group to establish the proper configuration of one of the spirocenters (C13).

According to our previously articulated retrosynthetic analysis,^[3] azaspiracid (**1**) is disconnected by rupturing the

C25–C26 bond leading to the ABCD and FGHI domains **2** and **3** as shown in Scheme 1. Considering that neither the absolute stereochemistry of **1** nor the relative stereochemistry of the two domains of this compound are known, we decided arbitrarily to develop routes to these systems which could be adaptable to either enantiomer. At the onset, it was clear that the anomeric effects^[4] within structure **2** will favor the undesired 13*S* configuration, thus providing a thorny challenge regarding this stereochemical problem (see Scheme 2).



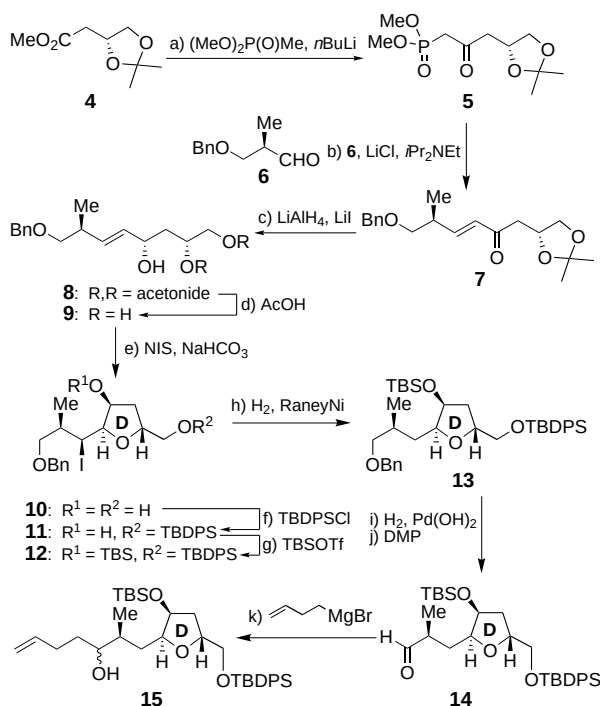
Scheme 2. Conformational arrangements of the ABCD ring system of azaspiracid (**2**, 13*R*, desired) and its C13 epimer (**2'**, 13*S*, undesired, favored by anomeric effect).

Indeed, a recent report^[2d] by the Forsyth group in which an attempted spirocyclization of an open-chain precursor led exclusively to the unwanted C13 diastereomer whose epimerization to the correct C13 stereoisomer proved impossible, confirmed these suspicions.

Our approach to addressing this problem invoked the use of a stereocontrolling group at C9 capable of driving the spirocyclization reaction toward the desired 13*R* configuration through favorable intramolecular interactions. The first attempt to solve this problem was inspired by the work of Williams and co-workers who utilized an optically active sulfoxide as an auxiliary group to construct spiroketals.^[5] The hypothesis to be tested was that a tolyl sulfoxide (ArSO) group installed at C9 might be influential in controlling the C13 stereochemistry at the spirocyclization step (see Scheme 4, **21** → **22**). Scheme 3 summarizes the synthesis of the first required building block for the projected synthesis of the ABCD ring system according to this plan. Thus, methyl ester **4**^[6] reacted with the lithium anion of dimethyl methylphosphonate to furnish β -ketophosphonate **5** in 84% yield. Treatment of **5** with LiCl and *i*Pr₂NEt^[7] followed by addition of aldehyde **6**^[8] led to enone **7** in 86% yield. Chelation-controlled 1,2-reduction of **7** using Mori's method^[9] (LiAlH₄, LiI, –100 °C) afforded allylic alcohol **8** in 98% yield accompanied by only traces of the undesired epimeric alcohol. Acid-catalyzed removal of the acetonide group from **8** gave triol **9** in 97% yield which set the stage for the cyclization to ring D. To this end, **9** was exposed to NIS in the presence of NaHCO₃ to yield tetrahydrofuran derivative **10** in 70% yield with the desired 2,5-*trans* stereochemistry.^[10] Selective protection of the primary hydroxy group in **10** was then accomplished by the use of TBDPSCI/Et₃N/4-DMAP (90%), and this was followed by protection of the secondary hydroxy group with TBSOTf/2,6-lutidine (100%) to furnish compound **12** via **11**. Reductive cleavage of the C–I bond in **12** with a suspension of Raney Ni in ethanol under a hydrogen

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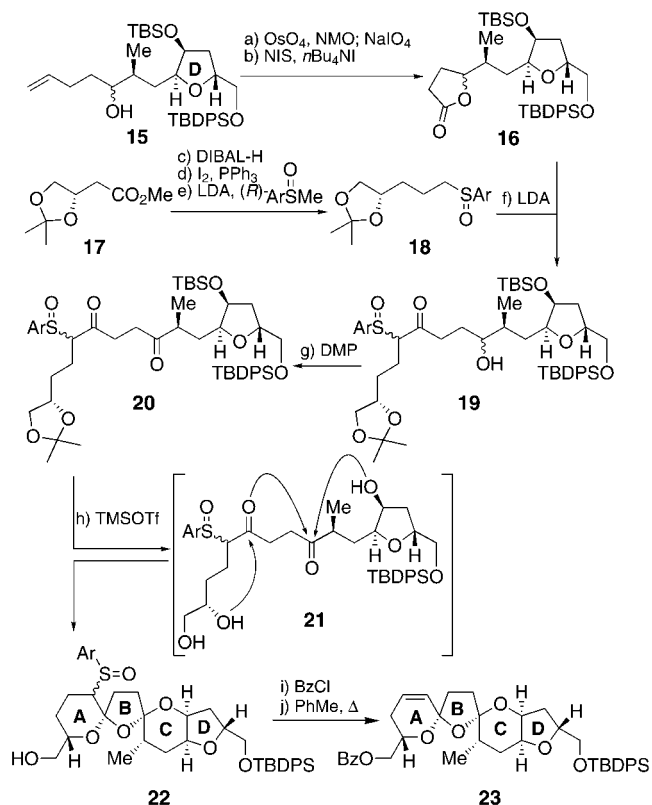
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Scheme 3. Construction of key intermediate **15**: a) (MeO)₂P(O)Me (2.2 equiv), *n*BuLi (1.6 M in hexanes, 2.2 equiv), THF, −78 °C, 1 h, 84%; b) **6** (0.67 equiv), LiCl (1.3 equiv), *i*Pr₂NEt (1.0 equiv), CH₃CN, 25 °C, 12 h, 86% based on **6**; c) LiAlH₄ (10.0 equiv), LiI (8.0 equiv), Et₂O, −100 °C, 30 min, 98%; d) AcOH/H₂O (2:1), 25 °C, 5 h, 97%; e) NIS (5.0 equiv), NaHCO₃ (10.0 equiv), THF, 0 °C, 2.5 h, 70%; f) TBDSO (1.4 equiv), Et₃N (3.0 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, −10 → 0 °C, 3 h, 90%; g) TBSOTf (1.6 equiv), 2,6-lutidine (4.0 equiv), CH₂Cl₂, −10 °C, 30 min, 100%; h) H₂, Raney Ni (100 equiv), EtOH, 25 °C, 1 h, 99%; i) H₂, Pd(OH)₂/C (10% by weight, 0.1 equiv), EtOH, 25 °C, 3 h, 88%; j) DMP (2.0 equiv), CH₂Cl₂, 25 °C, 2 h, 99%; k) 3-butenylmagnesium bromide (6.0 equiv), THF, −78 → −10 °C, 3 h, 87%. NIS = *N*-iodosuccinimide, TBDSO = *tert*-butyldiphenylsilyl, 4-DMAP = 4-(dimethylamino)pyridine, TBS = *tert*-butyldimethylsilyl, OTf = trifluoromethanesulfonate, DMP = Dess Martin periodinane.

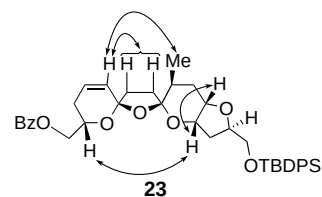
atmosphere produced compound **13** in 99% yield, while hydrogenolysis of the benzyl ether from the latter compound was facilitated by catalytic amounts of palladium hydroxide and hydrogen in ethanol (88%). The resulting primary alcohol was then oxidized with DMP leading to aldehyde **14** in 99% yield. Finally, treatment of **14** with excess 3-butenylmagnesium bromide afforded hydroxy olefin **15** in 87% yield as a mixture of diastereomers (ca. 1:1).

Scheme 4 summarizes the final drive toward the goal of this approach. Thus, dihydroxylation of the terminal olefin of **15** (NMO, cat. OsO₄) followed by cleavage of the resulting 1,2-diol (NaIO₄) gave the corresponding aldehyde–lactone mixture (96% overall yield) which was oxidized (NIS/*n*Bu₄NI)^[11] to afford the γ -lactone **16** in 98% yield (ca. 1:1 ratio of diastereomers). The fragment corresponding to azaspiracid's A ring was then introduced by using intermediate **18**, which also carried the required aryl sulfoxide moiety. This compound was constructed from **17** (*S* configuration)^[6] by DIBAL-H reduction, iodination of the resulting alcohol (Ph₃P/I₂, 99% overall yield), and coupling of the iodide with the lithium derivative (LDA) of (*R*)-(+)-methyl-*p*-tolyl sulfoxide (83% yield). Generation of the anion from sulfoxide **18**



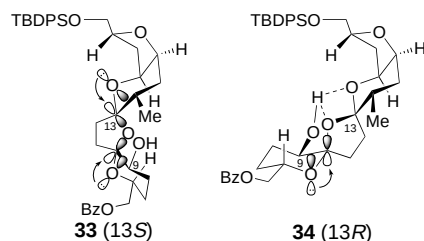
Scheme 4. Preparation of the C13-epimeric ABCD ring system (**23**; for selected physical data, see Table 1) by the sulfoxide method: a) OsO₄ (0.03 equiv), NMO (2.0 equiv), *n*BuOH/THF/H₂O (10:2:1), 25 °C, 12 h; then NaIO₄ (5.0 equiv), pH 7 buffer, 25 °C, 5 h, 96%; b) NIS (5.0 equiv), *n*Bu₄NI (2.0 equiv), CH₂Cl₂, 25 °C, 1 h, 98%; c) DIBAL-H (1.0 M in CH₂Cl₂, 2.5 equiv), THF, −78 → 25 °C, 1 h, 99% over two steps; d) I₂ (1.5 equiv), PPh₃ (1.5 equiv), imidazole (1.5 equiv), Et₂O, 25 °C, 1 h, 99%; e) LDA (1.0 equiv), (*R*)-(+)-methyl-*p*-tolylsulfoxide (1.0 equiv), THF, −78 °C, 30 min, 83%; f) LDA (1.0 equiv), **16** (1.5 equiv), THF, −78 °C, 15 min, 87%; g) DMP (3.0 equiv), CH₂Cl₂, 25 °C, 2 h, 92%; h) TMSOTf (3.0 equiv), CH₂Cl₂, −78 °C, 1 h; then 0 °C, 10 min, 62%; i) BzCl (4.0 equiv), py (100 equiv), CH₂Cl₂, 25 °C, 12 h, 96%; j) P(OMe)₃ (6.0 equiv), toluene, reflux, 45%. NMO = *N*-methylmorpholine *N*-oxide, DIBAL-H = diisobutylaluminum hydride, Ar = *para*-tolyl, LDA = lithium diisopropylamide, TMS = trimethylsilyl, Bz = benzoyl, py = pyridine.

with LDA followed by addition of lactone **16** gave coupling product **19** as a mixture of four diastereomers (ca. 1:1:1:1 ratio) and in 87% yield. Oxidation of the secondary hydroxy group in **19** with DMP furnished the coveted cyclization precursor, diketone **20**, in 92% yield (mixture of two diastereomers, ca. 1:1 ratio). Exposure of **20** to TMSOTf^[12] removed the acetonide and TBS groups, presumably forming intermediate **21** whose anticipated cascade cyclization to a tetracyclic system (**22**) was concomitantly realized under the reaction conditions (62% overall yield). Determination of the C13 stereochemistry of the obtained ABCD ring system was postponed until further elaboration. Thus, benzylation of the free hydroxy group in **22** (BzCl, py) furnished the corresponding benzoate in 96%



Scheme 5. Selected NOE enhancements observed for compound **23**.

yield (mixture of two sulfoxide diastereomers, ca. 1:1 ratio). Heating this sulfoxide mixture in refluxing toluene resulted in the formation of olefin **23** (45% yield) plus recovery of the equatorial sulfoxide (ca. 45%) which requires higher temperatures (refluxing xylenes) to eliminate and give the same olefin **23**. The spiroketal **23** was obtained as a single diastereomer; but, unfortunately, NMR analysis revealed (see Scheme 5 for NOEs) its incorrect stereochemistry at C13.

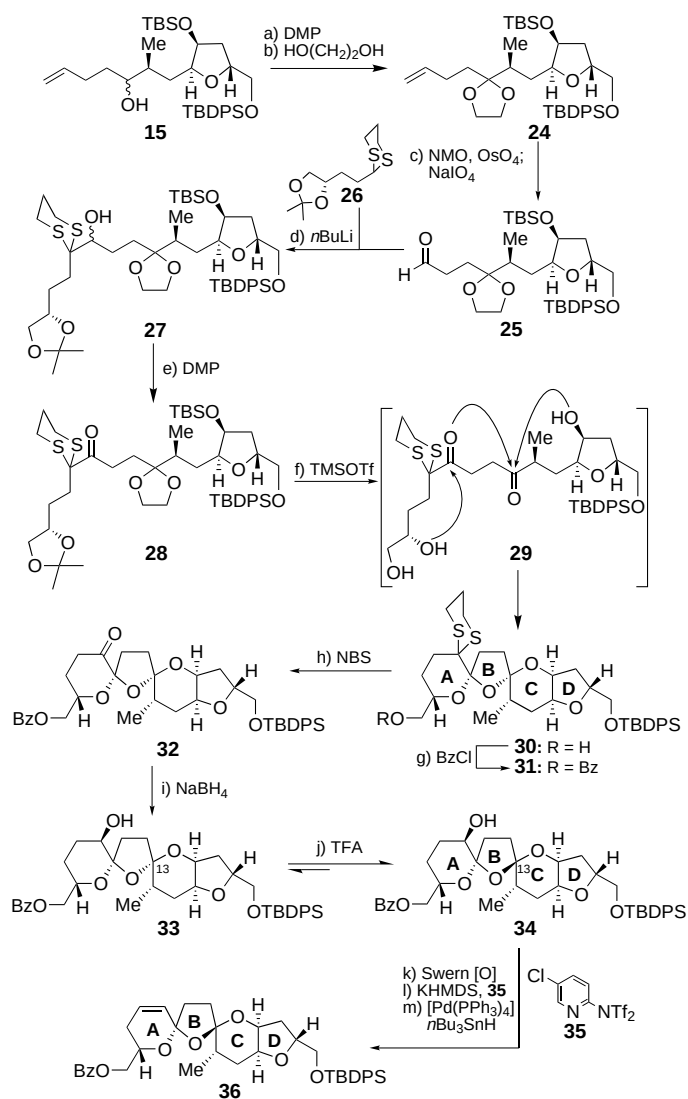


Scheme 6. Hydrogen bonding and anomeric effects in spiroketals **33** (13S, undesired) and **34** (13R, desired, favored by hydrogen bonding). For selected physical data of compounds **33** and **34**, see Table 1.

Apparently, the bulky tolyl sulfoxide group at C9 failed to overcome the anomeric effects forcing this spiroketal into the undesired configuration during the cyclization step (**20** → **21** → **22**). Furthermore, exposure of **23** to acid catalysis failed to change its stereochemistry, forcing us to seek an alternative approach to the desired 13R spiroketal fragment.

Based on a previous report,^[13, 14] it was reasoned that an equatorial free hydroxy group at C9 might be capable, by virtue of its hydrogen bonding ability, to invert the 13S configuration of the double spiroketal system of the ABCD azaspiracid system to its natural 13R form. The rationale for this hypothesis is shown graphically in Scheme 6 which depicts both the desired (13R) and the undesired (13S) stereoisomers of the targeted ABCD ring framework. Armed with this argument, a new sequence for this compound was devised and followed as shown in Scheme 7. Thus, DMP oxidation of alcohol **15** followed by ketalization furnished ethylene ketal **24** in 93% overall yield. A two-step oxidative cleavage of the terminal olefin within **24** as described above led quantitatively to aldehyde **25** which was coupled with the anion derived from dithiane **26**^[15] and *n*BuLi, to afford a diastereomeric mixture (ca. 1:1) of alcohols (**27**) in 87% yield. DMP oxidation of **27** led to ketone **28** (88% yield) whose cascade deprotection–cyclization reaction was induced by TMSOTf as described above for **20**, affording the double spiroketal **30** (85% yield), presumably via open chain precursor **29**. Benzoylation of **30** as before furnished benzoate **31** (93% yield), while exposure of the latter derivative (**31**) to NBS/2,6-lutidine in aqueous acetonitrile removed the dithiane group, leading to ketone **32** in 91% yield. Diastereoselective reduction of **32** with sodium borohydride in methanol furnished alcohol **33** (92% yield) in which the hydroxy group was found to reside in the desired equatorial position.

With tetracycle **33** at hand, we were now ready to attempt the crucial epimerization at C13 via acid catalysis. Gratifyingly, when **33** was exposed to TFA in CH₂Cl₂ at ambient temperature, an equilibrium mixture was soon reached from

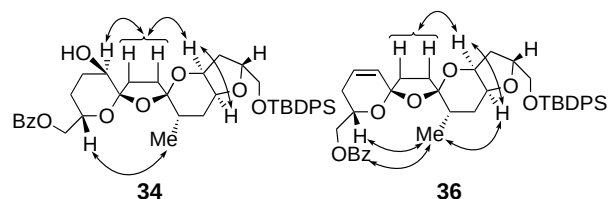


Scheme 7. Synthesis of the ABCD ring system (**36**) of azaspiracid by the hydroxy auxiliary method: a) DMP (2.0 equiv), CH₂Cl₂, 25 °C, 3 h, 95%; b) HO(CH₂)₂OH (7.0 equiv), triethyl orthoformate (3.0 equiv), *p*TsOH (cat.), 55 °C, 98%; c) OsO₄ (0.03 equiv), NMO (2.0 equiv), *t*BuOH/THF/H₂O (10:2:1), 25 °C, 14 h, then NaIO₄ (5.0 equiv), pH 7 buffer, 25 °C, 5 h, 100%; d) *n*BuLi (1.6 M in hexanes, 2.6 equiv), **26** (2.6 equiv), THF, –20 °C, 40 min, 87%; e) DMP (2.0 equiv), CH₂Cl₂, 25 °C, 1 h, 88%; f) TMSOTf (3.0 equiv), CH₂Cl₂, –78 → –30 °C, 1 h, 85%; g) BzCl (4.0 equiv), py, 25 °C, 2 h, 93%; h) NBS (8.0 equiv), 2,6-lutidine (16.0 equiv), aqueous CH₃CN, 25 °C, 2 h, 91%; i) NaBH₄ (1.0 equiv), MeOH, –5 °C, 5 min, 92%; j) TFA (3.0 equiv), CH₂Cl₂, 25 °C, 4 h, 56%; k) DMSO (20 equiv), (COCl)₂ (10 equiv), Et₃N (50 equiv), CH₂Cl₂, –78 °C, 1 h, 80%; l) **35** (10 equiv), KHMDS (0.5 M in toluene, 9.0 equiv), THF, –78 °C, 45 min, 83%; m) [Pd(PPh₃)₄] (0.2 equiv), *n*Bu₃SnH (10 equiv), THF, 25 °C, 45 min, 90%. *p*TsOH = *para*-toluene sulfonic acid, NBS = *N*-bromosuccinimide, DMSO = dimethylsulfoxide, KHMDS = potassium bis(trimethylsilyl)-amide.

which a 56% yield of a new compound (**34**, less polar on silica gel, hexanes/ethyl acetate 5:1) was isolated in addition to starting material (**33**, 44%). Recycling the starting material (**33**) twice raised the yield of **34** to 80%, making this step a practical method for obtaining the new isomer **34**. Even more delightful was the confirmation of the correct 13R configurations of **34** by NMR spectroscopy as shown by NOEs (see Scheme 8). Evident from these studies was also the stereo-

Table 1. Selected physical data for compounds **23**, **33**, **34**, and **36**.

23: Colorless oil; R_f = 0.64 (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20}$ = -31.7 (CHCl₃, c = 0.30); IR (film): $\tilde{\nu}_{\max}$ = 2928, 1724, 1462, 1378, 1273, 1113, 1070, 1032, 990, 710 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 8.07 (brd, J = 7.2 Hz, 2H), 7.66 (m, 4H), 7.47 (t, J = 7.2 Hz, 1H), 7.43–7.35 (m, 8H), 5.97 (ddd, J = 10.1, 5.7, 1.3 Hz, 1H), 5.65 (d, J = 10.1 Hz, 1H), 4.39 (m, 3H), 4.30 (m, 2H), 3.84 (d, J = 1.7 Hz, 1H), 3.64 and 3.60 (dd-like AB system, J = 10.6, 4.8/3.9 Hz, 2H), 2.25 (m, 1H), 2.10 (m, 3H), 2.06 (m, 1H), 1.99 (m, 1H), 1.93–1.70 (m, 5H), 1.03 (s, 9H), 0.86 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 166.6, 135.6, 133.6, 133.0, 130.1, 129.7, 129.6, 128.7, 128.4, 127.6, 126.5, 109.4, 104.9, 78.5, 76.5, 73.3, 67.5, 67.1, 66.3, 37.3, 35.9, 34.9, 31.1, 29.7, 26.8, 26.5, 19.3, 15.8; HRMS (MALDI): calcd for C₄₀H₄₈O₇SiNa⁺ [M+Na⁺]: 691.3061, found: 691.3044 33: Colorless oil; R_f = 0.27 (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20}$ = -2.8 (CHCl₃, c = 0.68); IR (film): $\tilde{\nu}_{\max}$ = 3483, 2929, 2856, 1722, 1453, 1273, 1112, 1070, 1028, 867, 710 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.16 (brd, J = 8.4 Hz, 2H), 7.77–7.71 (m, 4H), 7.59–7.54 (m, 1H), 7.52–7.42 (m, 8H), 4.43 (dd, J = 11.0, 3.7 Hz, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.39–4.25 (m, 3H), 4.01–3.98 (m, 1H), 3.74 and 3.68 (dd-like AB system, J = 10.6, 4.8/3.7 Hz, 2H), 3.62 (brdd, J = 11.4, 5.0 Hz, 1H), 2.38–2.31 (m, 1H), 2.27–2.04 (m, 5H), 1.99 (ddd, J = 13.9, 4.0, 2.2 Hz, 1H), 1.94–1.75 (m, 5H), 1.68–1.57 (m, 1H), 1.53 (d, J = 11.4 Hz, 1H), 1.12 (s, 9H), 1.02 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 166.5, 135.60, 135.58, 133.6, 133.0, 130.1, 129.7, 129.6, 129.5, 128.3, 127.6, 110.1, 108.4, 78.6, 76.3, 73.6, 71.4, 69.5, 67.1, 66.2, 36.0, 34.7, 34.3, 31.3, 30.8, 29.1, 27.4, 26.8, 19.3, 16.6; HRMS (MALDI): calcd for C₄₀H₅₀O₈SiNa⁺ [M+Na⁺]: 709.3167, found: 709.3183 34: Colorless oil; R_f = 0.39 (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +13.9 (CHCl₃, c = 1.24); IR (film): $\tilde{\nu}_{\max}$ = 3507, 2931, 1722, 1454, 1428, 1273, 1111, 997, 710 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 8.11 (brd, J = 8.4 Hz, 2H), 7.78–7.71 (m, 4H), 7.66–7.61 (m, 1H), 7.53–7.43 (m, 8H), 4.53–4.46 (m, 1H), 4.36 (dd, J = 11.0, 3.3 Hz, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.33–4.26 (m, 1H), 4.26–4.22 (m, 1H), 3.98–3.94 (m, 1H), 3.86 and 3.72 (dd-like AB system, J = 10.6, 4.0/3.7 Hz, 2H), 3.61–3.52 (m, 1H), 3.01 (d, J = 10.3 Hz, 1H), 2.61–2.52 (m, 1H), 2.37–2.27 (m, 1H), 2.23 (ddd, J = 13.2, 9.2, 4.4 Hz, 1H), 2.17 (ddd, J = 14.7, 2.9, 2.9 Hz, 1H), 2.14–2.06 (m, 2H), 2.04–1.88 (m, 3H), 1.86–1.77 (m, 2H), 1.70–1.56 (m, 1H), 1.50 (ddd, J = 14.7, 13.2, 3.3 Hz, 1H), 1.12 (s, 9H), 0.99 (d, J = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃): δ = 166.4, 135.60, 135.59, 133.5, 132.9, 130.1, 129.63, 129.60, 128.25, 127.64, 111.8, 108.7, 78.6, 76.6, 75.9, 68.9, 68.2, 67.2, 66.0, 36.1, 33.7, 31.2, 30.3, 29.7, 28.9, 26.9, 26.8, 19.3, 15.6; HRMS (MALDI): calcd for C₄₀H₅₀O₈SiNa⁺ [M+Na⁺]: 709.3167, found: 709.3191 36: Colorless oil; R_f = 0.54 (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20}$ = -17.0 (CHCl₃, c = 0.50); IR (film): $\tilde{\nu}_{\max}$ = 2926, 1723, 1454, 1379, 1272, 1112, 988, 824, 743, 710 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 8.04 (d, J = 7.5 Hz, 2H), 7.67 (m, 4H), 7.56 (t, J = 7.4 Hz, 1H), 7.45–7.35 (m, 8H), 6.00 (ddd, J = 10.1, 5.7, 1.7 Hz, 1H), 5.75 (dd, J = 10.1, 1.3 Hz, 1H), 4.47 (m, 1H), 4.39 (m, 1H), 4.36 (m, 2H), 4.17 (m, 1H), 3.87 (d, J = 2.2 Hz, 1H), 3.76 and 3.64 (dd-like AB system, J = 10.9, 4.2/3.5 Hz, 2H), 2.22 (m, 1H), 2.17–1.98 (m, 9H), 1.42 (m, 1H), 1.03 (s, 9H), 0.88 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃): δ = 166.5, 135.60, 135.58, 133.6, 133.0, 130.0, 129.7, 129.6, 129.5, 128.2, 127.6, 127.3, 111.7, 104.0, 78.6, 76.5, 76.0, 67.0, 66.7, 66.2, 36.2, 35.8, 33.9, 30.8, 29.7, 26.8, 26.4, 19.3, 15.8; HRMS (MALDI): calcd for C₄₀H₄₈O₇SiNa⁺ [M+Na⁺]: 691.3061, found: 691.3062



Scheme 8. Selected NOE enhancements observed for compounds **34** and **36** (hydrogen bonding not shown). For selected physical data of compounds **34** and **36**, see Table 1.

chemical integrity of the epimerizable C14 methyl group in these systems. Having established the correct stereochemistry of the ABCD ring system, the facilitating (but superfluous) hydroxy group had to be excised, a task assumed to require nonacidic conditions for stereochemical safety purposes. This goal was accomplished by oxidation [(COCl)₂, DMSO, Et₃N, 80 % yield], enol triflate formation (KHMDS, triflimide **35**, 83 % yield) and reduction (*n*Bu₃SnH, cat. [Pd(PPh₃)₄], 90 % yield) to furnish the desired ABCD azaspiracid fragment **36**. The structural assignment of this final product was also confirmed by observing the expected NOEs (see Scheme 8). The described chemistry provides a solution to one of the main obstacles remaining in the total synthesis of azaspiracid (**1**) and, as such, opens the way for the final drive toward this novel natural product.

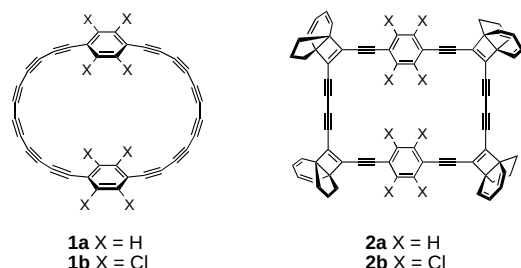
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- [15] Compound **26** was prepared from acetone methyl ester **17** and 1,3-dithiane by a similar route to that used to prepare **18** (see Scheme 4).

[12.12]Paracyclophanedodecaynes $C_{36}H_8$ and $C_{36}Cl_8$: The Smallest Paracyclophynes and Their Transformation into the Carbon Cluster Ion C_{36}^{-**}

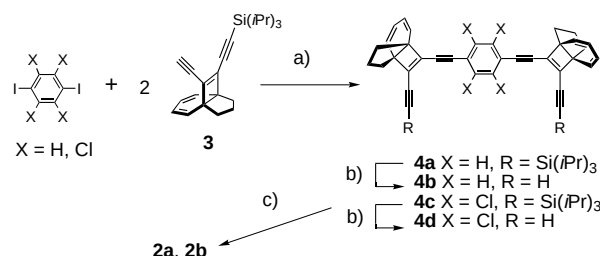
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Carbon clusters with magic numbers such as C_{20} and C_{36} have fullerene structures when they are produced from appropriate precursors or by vaporization of carbon materials under specific conditions. Thus the C_{20} fullerene cation was produced selectively by field evaporation of carbon nanotubes^[1] and the positive and negative ions, C_{20}^+ and C_{20}^- , were formed by debromination of polybrominated dodecahedrane under mass spectrometric conditions.^[2] A cage structure was characterized by photoelectron spectroscopy for the negative ion.^[2] On the other hand, there remains controversy regarding the structure of C_{36} ; C_{36} formed by arc discharge of graphite exists as a polymeric form with D_{6h} symmetry in solid state,^[3] while high-temperature laser ablation of metal-doped graphite resulted in the isolation of $C_{36}H_6$.^[4] However, no attempt has been made so far to produce C_{36} from an appropriate organic precursor. We and Rubin and co-workers have found independently that macrocyclic polyyne $C_{60}H_6$ formed C_{60} fullerene ions under mass spectrometric conditions, presumably by cyclization of the polyyne chain in an analogous manner to the mechanism proposed for fullerene formation from small carbon clusters.^[5, 6] We envisaged that a similar cyclization of polyyne-bridged paracyclophane **1a** and subsequent dehydrogenation would give D_{6h} -symmetric C_{36} . In addition, the key intermediate **1a** is of substantial interest as a member of the highly unsaturated, alkyne-bridged paracyclophanes coined cyclophynes.^[7, 8] In view of the fact that the



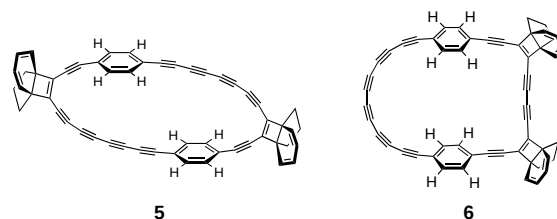
smaller [8.8]paracyclophynes was elusive,^[7] **1a** was expected to be too reactive for isolation, although the strain imposed on each sp carbon must be minimal (bending angle slightly larger than 10°).^[9] It may, on the other hand, be capable of existence at low temperature in an inert atmosphere. We planned to generate **1a** from precursor **2a**, which contains [4.3.2]propellatriene units, by [2+2] cycloreversion of the cyclobutene ring, the method we have employed in generation of highly reactive polyyynes such as cyclocarbons^[10] and the C_{60} precursors.^[5] Herein we report the synthesis of **2a** and its octachloro derivative **2b**, studies on the photolysis of **2a**, and generation of anions of **1a** ($C_{36}H_8^-$) and **1b** ($C_{36}Cl_8^-$) and subsequent formation of C_{36}^- under mass spectrometric conditions.

Palladium-catalyzed coupling of propellandiyne **3**^[5] with 1,4-diiodobenzene gave **4a** (Scheme 1).^[11] After removal of the protecting group of **4a**, the resulting compound **4b** was subjected to oxidative coupling under high dilution conditions to yield **2a** in good yield. Similarly, **2b** was prepared from **3** and 1,2,4,5-tetrachloro-3,6-diiodobenzene via **4c** and **4d**.



Scheme 1. a) For **4a**, [Pd(PPh₃)₄], CuI, (*i*Pr)₂NH, THF, RT, 93%; for **4c**, [Pd₂(dba)₃]·CHCl₃, CuI, PPh₃, Et₃N, 90°C, 65%; b) Bu₄NF, AcOH, THF, RT; c) Cu(OAc)₂, pyridine, RT, 79% for **2a**, 75% for **2b**. dba = *trans,trans*-dibenzylideneacetone.

When a solution of **2a** in [D₈]THF was irradiated with a low-pressure mercury lamp at 0°C, indan was formed quantitatively as judged by the integration of its aromatic protons relative to the residual proton of THF. However, the aromatic protons of **2a** became small, broad signals, indicating that the products formed by [2+2] cycloreversion were intractable polymeric materials.^[12] The photolysis was then carried out in furan with the aim of intercepting the reactive intermediates as Diels–Alder adducts of furan.^[10] To our surprise, however, the major product **5**, isolated in 18% yield



as a labile orange solid, did not possess furan unit(s). The structure of **5**, which lost two opposite indan fragments from **2a**, was elucidated on the basis of the spectroscopic properties.^[13] The alternative possibility **6** was excluded on stability grounds.^[14] The effect of furan which allowed the isolation of **5** only in its presence is not clear yet, although **5** was detected as

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one of products in the photolysis of **2a** in THF. At present, it appears that polyne **5** is not strained enough to react thermally with furan.

Irradiation of **2a** at 77 K in a matrix, composed of 2-methyltetrahydrofuran and ethanol (6/1, v/v), resulted in a remarkable change in the absorption band at 350–420 nm (Figure 1), together with the monotonic increase of the

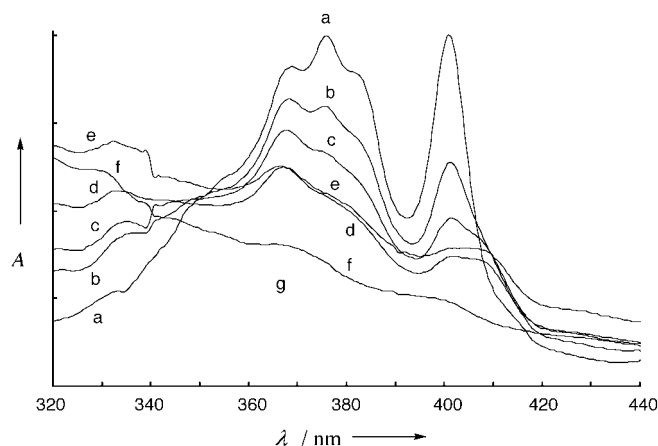


Figure 1. UV/Vis spectral changes for **1a** in a 2-methyltetrahydrofuran/ethanol (6:1) matrix at 77 K by irradiation with a low-pressure mercury lamp. a) before irradiation; b–e) after irradiation for 1, 3, 13, and 24 h, respectively; f) after irradiation for 24 h followed by thaw and refreeze; g) subtraction of line f from line e.

absorption band of indan at 258–280 nm. The new absorption band at 350–420 nm did not change after irradiation for 24 h, but it was completely lost when the matrix was thawed by warming to room temperature and then refreezed (77 K). Subtracting the spectrum recorded after the thaw/refreeze cycle from that measured before the thaw leaves absorption maxima at 408, 379 and 367 nm (dotted line g in Figure 1). We attribute the absorption of this highly reactive species to cyclophynone **1a**, although additional evidence is needed for its full characterization.

To generate the cyclophynone ions in the gas phase and to examine the possibility of their transformation into the carbon cluster C_{36} , laser-desorption time-of-flight mass spectra of **2a** and **2b** were measured. Figure 2a and 2b show the negative-mode mass spectra of **2a** and **2b**, respectively. As shown in Figure 2a, [2+2] cycloreversion of **2a** took place cleanly to form cyclophynone anion $C_{36}H_8^-$. However, in contrast to the case of $C_{60}H_6^-$,^[5,6] subsequent dehydrogenation leading to C_{36}^- was not observed. This can be ascribed to the difficulty of the structural rearrangement that would accompany the dehydrogenation for thermodynamic (C_{36} not as stable as C_{60}) and kinetic (the polyne chains of **1a** located at para positions) reasons. By contrast, the mass spectrum of **2b**, which contains weaker C–Cl bonds, exhibits not only the peak of **1b** ($C_{36}Cl_8^-$) but also the peaks due to the stepwise loss of chlorine atoms down to C_{36}^- (Figure 2b), in analogy with the degradation of $C_{60}Cl_6^-$.^[5b] Since the intensity of the C_{36}^- signal is considerably larger than those of $C_{36}Cl^-$, $C_{36}Cl_2^-$, and $C_{36}Cl_3^-$, we assume that the dechlorination is accompanied by a drastic skeletal change leading to possibly D_{6h} -symmetric

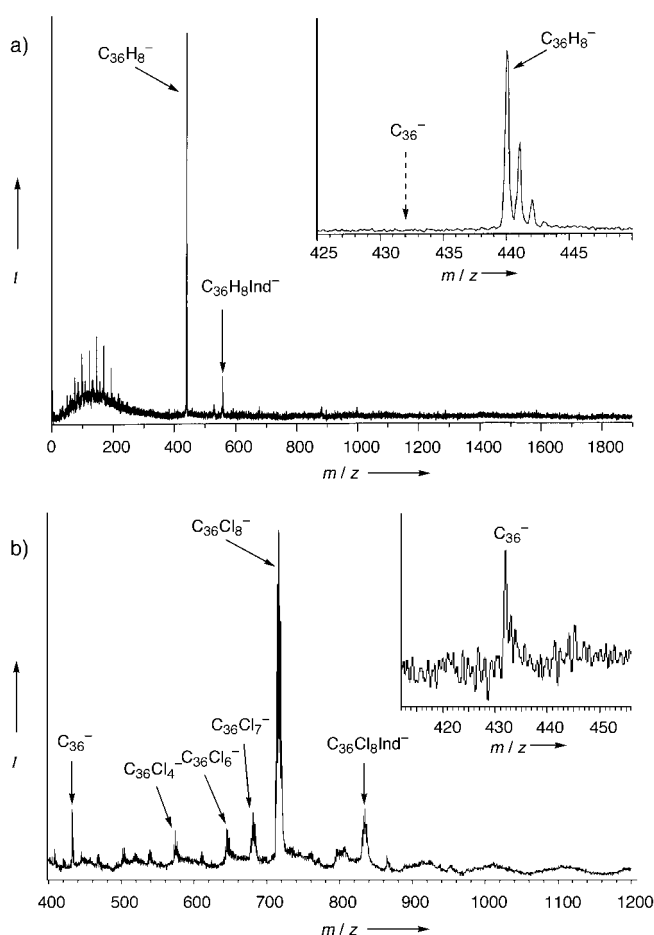


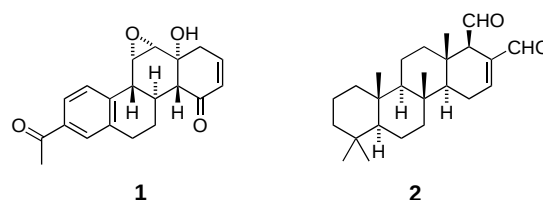
Figure 2. Laser-desorption time-of-flight mass spectra of a) **2a** and b) **2b** (Ind = indan). The compounds were dissolved in liquid paraffin as a matrix. For simultaneous desorption and ionization, the third harmonic of a Nd:YAG laser (355 nm) was focused on an area of 3 mm².

C_{36}^- . Further work is in progress to confirm this by ultraviolet photoelectron spectroscopy.

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- [9] The bond angles of the sp carbon atoms estimated from semiempirical AM1 calculations for the model compound of **1a**, in which the propellane units are substituted by cyclobutene, are 167.3–168.2°.

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- [11] Compounds **2a**, **b**, **4a–d**, and **5** were obtained as mixtures of diastereomers, which were not separated, due to orientation of the propellane units. Only one of the isomers is drawn for each of the structures.
- [12] Monitoring the reaction with HPLC showed several peaks during the initial stage of the photolysis, which then disappeared after prolonged irradiation, finally leaving only the peak of indan.
- [13] The ^1H NMR spectrum exhibits an AA'BB' pattern for the aromatic protons with the same integration value as that of the protons of the propelladiene unit. The ^{13}C NMR spectrum displays two signals for tertiary aromatic carbon atoms and ten signals for sp carbon atoms. The UV/Vis spectrum exhibits a few absorption maxima in the long wavelength region (λ_{max} (CHCl_3) 426 (ϵ 15 000), 397 (50 000), and 368 (90 000) nm) which are reminiscent of those of the diphenylotetrayne chromophore (λ_{max} (CH_2Cl_2) 415 (ϵ 18 600), 381 (33 400), and 353 (43 800) nm: M. M. Haley, M. L. Bell, S. C. Brand, D. B. Kimball, J. J. Pak, W. B. Wan, *Tetrahedron Lett.* **1997**, *38*, 7483). Finally, the mass spectrum exhibits a peak at m/z 677 [$M^+ + 1$], which is attributed to the molecular ion of **5**. See Supporting Information for details.
- [14] The ΔH_f° values (AM1) for the model compounds of **5** and **6**, in which the propellane units are substituted by cyclobutene, are 660 and 675 kcal mol $^{-1}$ and their bond angles around the sp carbon atoms are 173.1–173.7° and 164.1–170.2°, respectively.



The Zipper-Mode Domino Intramolecular Diels–Alder Reaction: A New 0 $\rightarrow$ ABCD Strategy for Steroids and Related Compounds**

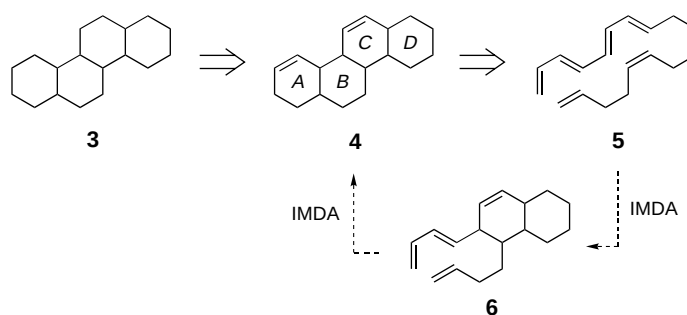
Marck Nörret and Michael S. Sherburn*

In the push towards more efficient syntheses of organic molecules, processes which lead to a rapid increase in structural complexity are playing an increasingly important role.^[1] Multiple bond-forming processes involving parallel transformations (e.g. two-directional synthesis,^[2] the generation of libraries of compounds) or sequential transformations^[3] (e.g. domino reactions, multiple component couplings) are often utilized to achieve this goal.

Herein we report an efficient strategy for the one-step stereoselective synthesis of tetracycles of the perhydrochrysene class (i.e. D-homosteroid)—found in many biologically active naturally products such as the nicandrenones (e.g. NIC-10 **1**)^[4] and scalarane sesterterpenes (e.g. scalarenedial **2**)^[5]—

from a simple and readily prepared acyclic precursor. This unprecedented domino sequence generates four rings, four C–C bonds, and eight contiguous stereocenters in a single operation and, as such, represents a new 0 $\rightarrow$ ABCD strategy for the synthesis of steroids and related compounds.^[6, 7]

The essence of our approach is depicted in Scheme 1. Retrosynthetic introduction of disubstituted alkenes into the A and C rings of saturated tetracycle **3** permits the implementation of two intramolecular Diels–Alder (IMDA) transformations.^[8–10] Thus, the tetracyclic diene **4** is retrosynthetically unzipped^[11] to furnish simple acyclic precursor **5**, carrying a linearly conjugated tetraene (the bis-diene) tethered to an internal dienophile which, in turn, is tethered to a second, terminal dienophile.



Scheme 1. The domino zipper-mode IMDA reaction of hexaenes **5** to fused tetracycles **4**.

For a successful realization of the synthetic transformation of an acyclic hexaene **5** into a tetracycle such as **4**, a regioselective intramolecular cycloaddition of the more proximate, internal diene-internal dienophile pair must occur first (i.e. **5** $\rightarrow$ **6**). The bicyclic system thus formed has pendant diene and dienophile “arms” attached to neighboring ring atoms which must come together for the second IMDA reaction to ensue (ie. **6** $\rightarrow$ **4**). Inspection of molecular models reveals that cycloaddition transition states are readily adoptable for both of the expected diastereomers of bicyclic intermediate **6**.

We were concerned with the potential for generating many stereoisomers of tetracycle **4**. The parent 1,3,9-decatriene, for example, undergoes an unselective IMDA reaction at 250 °C (*cis:trans*-fused product ratio = 53:47).^[12] Clearly, the judicious incorporation of functionality into unsubstituted system **5** was the key to obtaining stereocontrol in this domino reaction. Thus, we elected to prepare hexaene **12** to test this concept since both dienophile moieties of **12** carry activating groups which were anticipated to lead to facile and stereoselective IMDA reactions.^[8]

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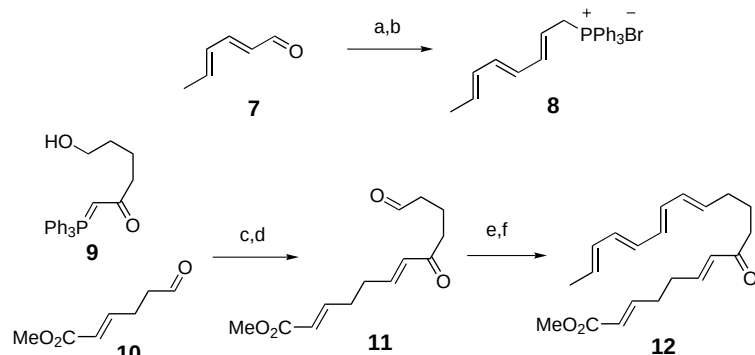
[**] We thank Dr. Simon Fielder (HortResearch New Zealand) and Mr. Leon Wong (University of Sydney) for preliminary experiments, Dr. Kelvin Picker (University of Sydney) for assistance with HPLC and GC analyses, and Dr. Ian Luck (University of Sydney) for 2D NMR experiments. This work was supported by The Australian Research Council and The University of Sydney.

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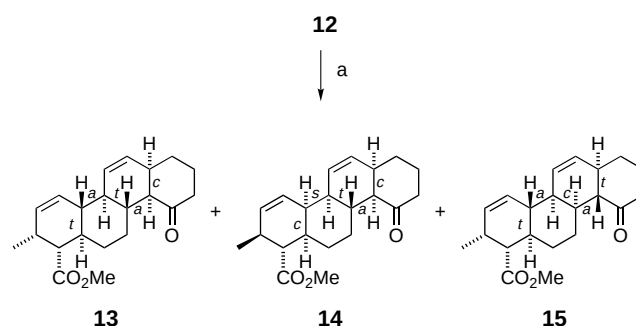
In light of the expected sensitivity of the conjugated tetraene moiety^[13] a short, doubly convergent synthetic approach to acyclic hexaene **12** was developed (Scheme 2). Thus, the stabilized ylide **9**, prepared by non-classical Wittig reaction^[14] of methylenetriphenylphosphorane with δ -valerolactone,^[15] was coupled with aldehyde **10**^[16] to give a primary alcohol^[17] which was oxidized to aldehyde **11**. The semi-stabilized ylide derived from phosphonium salt **8** was employed as the Wittig coupling partner for **11**. Phosphonium salt **8** was prepared by the addition of vinylmagnesium bromide to 3,5-hexadienal **7** followed by exposure of the resulting trienol^[18] to triphenylphosphane hydrobromide. The Wittig reaction between **11** and the ylide derived from **8** is best carried out at low temperatures; under these conditions **12** is formed as an approximate 2:1 (*E*:*Z*) mixture about the newly formed C=C bond. This mixture can be equilibrated to an approximately 5:1 (*E*:*Z*) mixture upon exposure to a sub-stoichiometric amount of iodine in dilute solution.^[19]

Cyclization of acyclic precursor **12** was examined under a variety of conditions (PhMe, PhH, CH₂Cl₂ solvents with and without various quantities of Lewis acid promoters from -78°C to 110°C) until optimum conditions were uncovered. After much experimentation, we were delighted to find that hexaene **12** undergoes the novel domino IMDA sequence in 79% yield upon exposure to 1.9 molar equivalents of Et₂AlCl in refluxing CH₂Cl₂ for 30 min (Scheme 3). Three chromatographically separable tetracyclic products **13**, **14**, and **15** are formed under these conditions in a 72:14:14 ratio.^[20] The stereochemistry of each of these three double cycloadducts was deduced from 2D NMR experiments (COSY, NOESY, HMBC, and HETCOR) and the stereochemistry of the major product was confirmed by single-crystal X-ray structure analysis.^[21] We were unable to observe putative bicyclic intermediates **16** and **17** (Scheme 4) during this reaction, irrespective of the reaction conditions employed. This observation points to the second Diels–Alder reaction (cf. **6**→**4**; Scheme 1) being significantly more facile than the first (cf. **5**→**6**; Scheme 1). We conclude that the conversion of **12**→**13**, **14**, and **15** is a true domino process.^[3a]

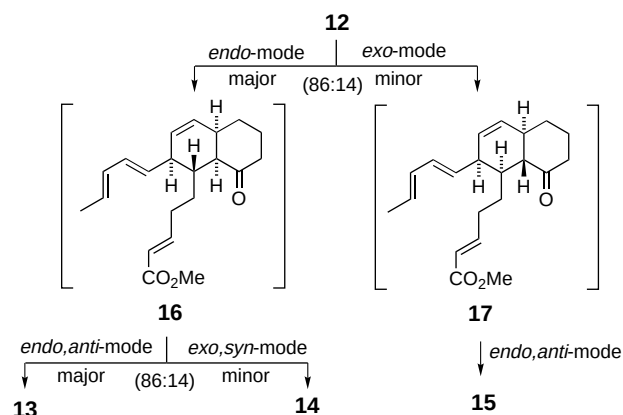
We note that, if both Diels–Alder reactions are concerted [4+2] cycloaddition events (i.e. if diene and dienophile



Scheme 2. Synthetic route to domino IMDA precursor **12**. Reagents and conditions: a) CH₂=CHMgBr (1.1 equiv), THF, RT, Ar, 4 h, then NH₄Cl/H₂O, 98%; b) Ph₃P·HBr, CH₂Cl₂, RT, Ar, 2 h, 92%; c) **9** (1.0 equiv) + **10** (1.0 equiv), CH₂Cl₂, RT, Ar, 48 h, 76%; d) Dess–Martin periodinane (1.8 equiv), CH₂Cl₂, RT, Ar, 48 h, 68%; e) **8** (2.8 equiv) + *n*BuLi (1.9 equiv), THF, -78°C , Ar, 5 min, then **11** (1.0 equiv), -78°C , 2 h, 62%; f) I₂ (0.05 equiv), CH₂Cl₂, RT, Ar, 2 h, 48%.



Scheme 3. The domino IMDA reaction. Reagents and conditions: a) Et₂AlCl (1.9 equiv), CH₂Cl₂, 40°C , 30 min, 79%; **13**:**14**:**15** = 72:14:14.



Scheme 4. IMDA stereoselectivities en route to the cycloadducts.

geometry is conserved in the double Diels–Alder reaction), eight diastereomeric tetracyclic products are possible. Clearly, for a complex mixture of stereoisomeric products to be avoided, *both* IMDA events in this domino sequence must be highly stereoselective processes. This is evidently the case for precursor **12** (Scheme 4). The *cis*-fused C/D ring system in products **13** and **14** results from an initial *endo*-docking mode, whereas the *trans*-fused C/D moiety in **15** indicates a minor *exo*-pathway for this first cycloaddition event.^[22] Both *cis*- and *trans*-fused monoadducts **16** and **17** undergo highly stereoselective IMDA reactions: of the four stereoisomers which may be formed in each case, **16** gives two^[23] and **17** furnishes only one. Moreover, the stereochemistry about the six contiguous stereocenters of the ring junction positions of **13** and **14** mirrors that seen naturally in cholic acids and the cardiac glycosides, respectively.^[24]

The work described herein represents a “proof-of-principle” study for the zipper-mode domino IMDA sequence depicted in Scheme 1. This extremely concise approach to tetracycles offers new opportunities for the preparation of steroids and steroid-like compounds. This strategy is particularly attractive for the preparation of biologically (and commercially) important 18- and 19-norsteroids, compounds which are currently prepared through lengthy stepwise synthetic routes.^[25] Studies towards this end, involving the use of enantiopure Lewis acid promoters to control the absolute

stereochemistry of the tetracyclic products,^[26] are currently under investigation in this laboratory.

Experimental Section

Domino IMDA reaction of **12**: A dry Ar-flushed Schlenk tube was charged with **12** (52.0 mg, 0.158 mmol) and dry, distilled CH₂Cl₂ (7 mL). To the stirred solution at reflux under Ar was added Et₃AlCl (0.301 mmol, 167 μ L (1.9 equiv) of a 1.8 M solution in toluene) in one portion. After 30 min at reflux the solution was cooled to ambient temperature, aqueous NaHCO₃ (10 mL) was added, and the product was extracted into Et₂O (3 $\times$ 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure to give a yellow oil (48 mg). Flash chromatography on silica gel, eluting with CH₂Cl₂/EtOAc (50:1), afforded **13** (R_f = 0.46 in CH₂Cl₂/EtOAc (10:1)) as a white solid (29.8 mg, 0.091 mmol, 57 %) and a mixture of **14** and **15** (R_f = 0.56 in CH₂Cl₂/EtOAc (10:1), 11.2 mg). The two minor tetracycles were separated on HPLC (Partisil 10, EtOAc/hexane (8:92), flow rate 3 mL min⁻¹) to give **14** (5.5 mg, 0.017 mmol, 11 %) as a colorless oil and **15** (5.6 mg, 0.017 mmol, 11 %) as a white solid.

Characterization data for **13**: m.p. 109–111 °C; ¹H NMR (600 MHz, C₆D₆, 25 °C, TMS): δ = 5.77 (d, J = 10.8 Hz, 1H; H-11), 5.75 (d, J = 10.9 Hz, 1H; H-1), 5.51 (ddd, J = 10.1, 4.4, 1.9 Hz, 1H; H-2), 5.48 (ddd, J = 10.1, 4.5, 1.5 Hz, 1H; H-12), 3.36 (s, 3H; H-21), 2.62 (dd, J = 11.6, 6.2 Hz, 1H; H-4), 2.55–2.47 (m, 1H; H-3), 2.38 (dd, J = 10.1, 5.6 Hz, 1H; H-14), 2.20 (ddt, J = 12.7, 3.2, 3.2 Hz, 1H; H-6 α), 2.27–2.23 (m, 1H; H-16), 2.09–2.04 (m, 1H; H-13), 1.80 (dt, J = 5.7, 13.6 Hz, 1H; H-16), 1.60–1.49 (m, 2H; H-5, H-17), 1.46–1.33 (m, 5H; H-7, H-8, H-9, H-10, H-18), 1.27–1.12 (m, 3H; H-7, H-17, H-18), 0.98 (d, J = 7.1 Hz, 3H; H-19), 0.78 (dq, J = 12.7, 3.7 Hz, 1H; H-6 β); ¹³C NMR (100.6 MHz, C₆D₆, 25 °C, TMS): δ = 210.9 (C=O), 173.3 (COOR), 132.8 (=CH), 131.4 (=CH), 126.9 (=CH), 125.9 (=CH), 56.6 (CH), 50.7 (OCH₃), 50.0 (CH), 46.0 (CH), 45.3 (CH), 39.8 (CH), 39.7 (CH₂), 38.0 (CH), 36.7 (CH), 32.5 (CH), 29.9 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 25.9 (CH₂), 18.0 (CH₃); IR (thin film): $\tilde{\nu}_{\text{max}}$ = 3028, 2924, 2861, 1737, 1704 cm⁻¹; MS (EI, 70 eV): m/z (%): 328 (100) [M^+]; elemental analysis (%) calcd for C₂₁H₂₈O₃: C 76.79, H 8.59; found: C 76.87, H 8.69.

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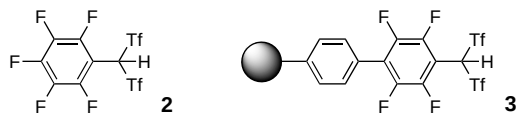
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Polystyrene-Bound Tetrafluorophenylbis(triflyl)methane as an Organic-Solvent-Swellable and Strong Brønsted Acid Catalyst**

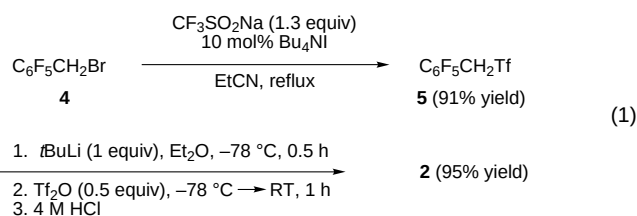
Kazuaki Ishihara, Aiko Hasegawa, and Hisashi Yamamoto*

Perfluororesinsulfonic acids such as Nafion are highly acidic solid catalysts, and they are superior to conventional resinsulfonic acids such as Dowex-50, Amberlite IR-112, and Permutit-Q with regard to catalytic activity, thermal stability, and chemical resistance.^[1, 2] However, like inorganic solid acids such as zeolites, they are not effectively swollen by most aprotic organic solvents.^[3] A resin-bound superacidic Brønsted acid that is effectively swollen by such solvents may offer several advantages over Nafion, including a broader range of applications, improved yields, improved selectivity, and milder reaction conditions.

The trifluoromethanesulfonyl (triflyl, Tf) group is one of the strongest neutral electron-withdrawing groups.^[4] In particular, it greatly increases the acidity of α -hydrogen atoms.^[5–7] For example, phenylbis(triflyl)methane (**1**, $pK_a = 7.83$ in MeCN)^[6] is a strong nonoxidizing acid. The steric and electronic effects of the aromatic ring in arylbis(triflyl)methanes are expected to greatly influence their Brønsted acidity and their catalytic activity and selectivity for organic reactions. We report here on concise syntheses of the new strong organic Brønsted acids pentafluorophenylbis(triflyl)methane (**2**) and polystyrene-bound tetrafluorophenylbis(triflyl)methane (**3**) and their catalytic applications in organic synthesis.



The synthetic strategy for **2** involves the preparation of 2,3,4,5,6-pentafluorobenzyltriflate (**5**) by nucleophilic substitution of 2,3,4,5,6-pentafluorobenzyl bromide (**4**) with sodium trifluoromethanesulfonate and subsequent reaction of **5** with triflic anhydride [Eq. (1)].^[8, 9] The first step was accomplished in 91 % yield by a slight modification of the method described by Hendrickson et al.^[4] The second step was achieved by successive addition of *t*BuLi (1 equiv) and triflic anhydride (0.5 equiv) to a solution of **5**. Thus, **2** was obtained in 95 % yield based on triflic anhydride, and **5** was recovered in ca.



50 % yield. When *t*BuLi (2 equiv) and triflic anhydride (1 equiv) were used with **5**, 4-*tert*-butyl-2,3,5,6-tetrafluorophenylbis(triflyl)methane (**6a**) was obtained instead of **2** as a major product.

To explore the generality and scope of the nucleophilic *para* substitution of **2**, the reaction was examined with several alkyl lithium reagents (Table 1). We confirmed that compound **6** was always produced as a single isomer by *para* substitution

Table 1. Regiospecific nucleophilic *para* substitution of **2**.

RLi ^[a]	Conditions	6	Yield [%]
<i>t</i> BuLi	– 78 °C, 1 h	6a	87
BuLi	– 78 °C, 1 h	6b	> 95
PhLi	– 78 °C → RT, 1 d	6c	> 95

[a] RLi (3 equiv) was added.

by ¹H, ¹³C, ¹⁹F, F-F COSY, and NOE difference NMR spectroscopy, and by single-crystal X-ray analysis on **6c**^[10] (Figure 1). The C13–H13 bond in **6c** is almost coplanar with

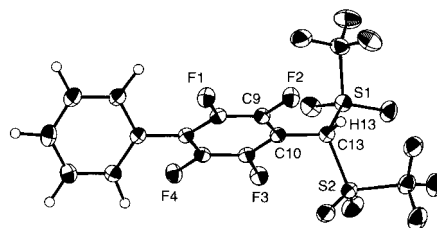


Figure 1. ORTEP plot of **6c**. Ellipsoids are drawn at 26 % probability. Selected distances [Å] and torsion angles [°]: C13–H13 0.993(4), H13...F2 2.2516; C9–C10–C13–H13 6.2(3), C9–C10–C13–S1 – 116.7(4).

the tetrafluorobenzene ring, and the torsion angle C9–C10–C13–H13 is 6.2°. Furthermore, **6** may prefer an asymmetrical conformation in CDCl₃ at room temperature, according to NMR spectroscopic data. These experimental results can be explained by conformational relaxation to avoid steric repulsion between the triflyl groups and the *ortho*-fluoro substituents of the tetrafluorobenzene moiety in **6**.

To understand the *para* selectivity of the nucleophilic substitution of **2**, we recorded the ¹³C NMR spectra of **2** and its lithium salt in CD₃OD, and compared the chemical shifts of the reaction sites. The ¹³C NMR signals of C4 were observed at $\delta = 143.0$.^[11] This means that conjugation between the anionic carbon center and the pentafluorobenzene ring is lost. In addition, the next lowest unoccupied molecular orbital (NLUMO) coefficients^[12] and charges on the pentafluorophenyl carbon atoms of the lithium salt were estimated by theoretical calculations (RHF/STO-3G) (Figure 2).^[13] The

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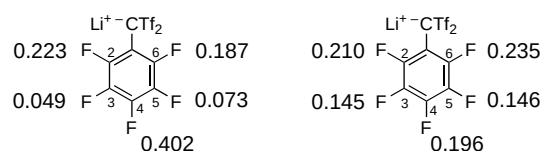


Figure 2. Frontier electron densities (left) and atomic charges (right) of the NLUMO at C2–C5 in the lithium salt of **2**.

frontier electron density of NLUMO and the positive charge at the C4 position are much greater than those at the C3 and C5 positions. Therefore, interception of the electron donation from the anionic carbon atom to the aromatic ring and the steric hindrance of triflyl groups on the *ortho* position cause higher reactivity at the *para* position.^[14]

To determine the acid strengths of **2** and **6c**, the ¹H NMR signals of their acidic protons were compared, and their pK_a values in glacial acetic acid were measured by the ¹H NMR method of Schantl et al. (Table 2).^[15] Their ¹H NMR signals were observed at a lower field in the order **1**, **2** ≈ **6c**, CHTf₃. If the pK_a values shown in Table 2 are valid, **2** is a remarkably strong acid (superacid). In addition, **6c** is still of equal acidity to concentrated sulfuric acid, although the *para* substitution of **2** by phenyllithium lowered the Brønsted acidity.

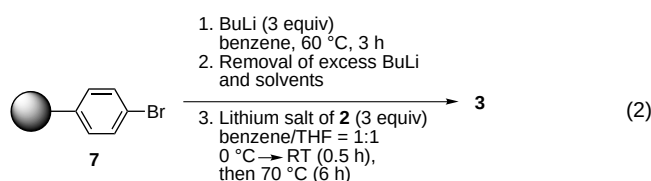
Table 2. ¹H NMR signals and pK_a for R_nCHTf_{3–n} (n = 0, 1; R = H, aryl).

	CH ₂ Tf ₂	1	H ₂ SO ₄	6c	2	CHTf ₃
δ ¹ H ^[a]	4.98	5.97	–	6.31	6.21	7.21
pK _a in AcOH ^[b]	13	12.5	7.5 (7.0) ^[c]	7.5	1.5	–

[a] ¹H NMR chemical shift for the acidic proton of R_nCHTf_{3–n} in CDCl₃.

[b] See ref. [15]. [c] Literature data.^[15]

Our goal was to develop a highly acidic heterogeneous catalyst that can be effectively swollen by organic solvents. Polystyrene, 1 or 2% cross-linked with divinylbenzene (DVB), is fully swollen by aprotic solvents such as aromatic solvents, chlorinated hydrocarbons, dioxane, and THF.^[16] We envisioned that the nucleophilic *para* substitution of **2** with an alkyl lithium could be adapted to prepare polystyrene-bound tetrafluorophenylbis(triflyl)methane **3** [Eq. (2)]. Three equivalents of the lithium salt of **2** were added to lithiated



polystyrene beads,^[16a] prepared from commercially available poly(4-bromostyrene) (**7**; 2.71 mmol Br g^{–1} resin, 2% DVB cross-linker, 200–400 mesh^[17]) in situ, and the reaction mixture was heated at 70 °C. After treatment with 4 M HCl, **3** was obtained as a brownish resin. The loading of **2** on the resin was estimated to be 1.01 mmol of Tf₂CHC₆F₄ units per gram of resin, based on fluorine content (elemental analysis).

The catalytic activities of Brønsted acids **2** and **3** were first tested in the acylation of alcohols with carboxylic anhydrides, which is known to be catalyzed by Lewis acids (Table 3).^[18] As expected, **3** exhibited an extremely high catalytic activity for

Table 3. Acetylation of (–)-menthol with carboxylic anhydrides (1.5 equiv).

Entry	Catalyst [mol % Tf ₂ CH units]	(RCO) ₂ O ^[a]	t [h]	Yield [%]
1	3 (0.1)	Ac ₂ O	< 1	> 99
2	2 (3)	Bz ₂ O	< 1	> 99
3	6c (3)	Bz ₂ O	< 1	> 99
4	3 (3)	Bz ₂ O	4	71
5	3 (6)	Bz ₂ O	17	> 99
6	Nafion SAC-13 ^[b]	Bz ₂ O	17	0

[a] Ac = acetyl, Bz = benzoyl. [b] Nafion SAC-13 (60 g mol^{–1}) was used.

the acetylation of (–)-menthol with acetic anhydride: the reaction was complete within 1 h in the presence of **3** (0.1 mol % Tf₂CH units, entry 1). Benzoic anhydride is much less reactive than acetic anhydride.^[18] Nevertheless, the benzoylation reaction proceeded quantitatively in the presence of **3** (6 mol % Tf₂CH units, entry 5). Moreover, **2** and **6c** were more active than **3** for the benzoylation (entries 2 and 3 vs entry 4). Surprisingly, Nafion-H/silica nanocomposite (Nafion SAC-13^[19]), which has a 10⁴-fold higher surface area than Nafion-H beads (Nafion NR50),^[19] was inert in the benzoylation (entry 6).

To demonstrate the usefulness and effectiveness of **3**, its catalytic activities in several important synthetic reactions were compared with those of Nafion SAC-13 (Equations (3)–(7) and Table 4). Catalyst **3** was highly active and reusable for all of the reactions examined: direct esterification [Eq. (3)],^[1] Friedel–Crafts acylation [Eq. (4)],^[1] acetalization [Eq. (5)],^[1] the Mukaiyama aldol reaction [Eq. (6)], and Sakurai–Hosomi allylation [Eq. (7)]. The catalytic activity of **3** in the reactions examined was superior to that of Nafion, which may be the strongest Brønsted acid among the known solid acids.

The polymer catalyst **3** was quantitatively recovered by simple filtration and could be reused.^[20] For example, **3**

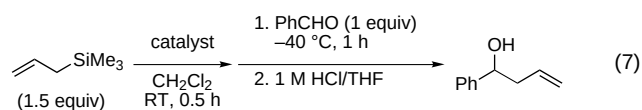
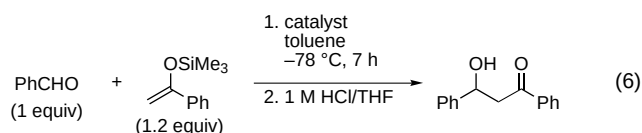
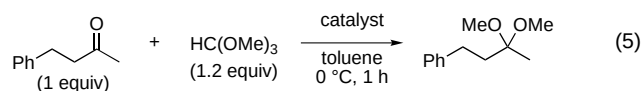
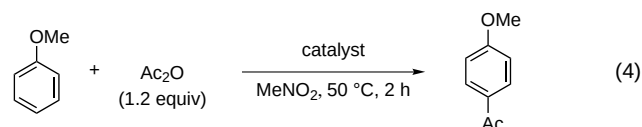
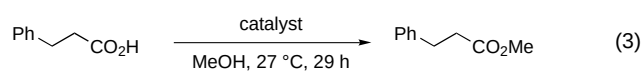


Table 4. Comparison of catalytic activities of **3** and Nafion SAC-13.

Reaction	3 [g mol ⁻¹ (mol % Tf ₂ CH)]	Yield [%]	Nafion SAC-13 [g mol ⁻¹]	Yield [%]
Eq. (3)	10 (1)	94	10	39
Eq. (4)	30 (3)	> 99	–	–
Eq. (4)	10 (1)	54	10	25
Eq. (5)	5 (0.5)	> 99	5	16
Eq. (6)	30 (3)	> 99	30	> 99
Eq. (7)	30 (3)	89	30	2

(0.1 mol % Tf₂CH units) was reused for acetalization [Eq. (5)] more than ten times, and no loss of activity was observed for the recovered catalyst.^[21] This means that the turnover number (TON) is greater than 10000 and the turnover frequency (TOF) exceeds 1000 h⁻¹.

In conclusion, a practical method for preparing a novel carbon Brønsted superacid **2** was developed and a resin-bound strong Brønsted acid **3** was obtained by *para* substitution of the lithium salt of **2** with lithiated polystyrenes. To the best of our knowledge, this is the first example of a highly acidic heterogeneous Brønsted acid catalyst that is effectively swollen by nonpolar organic solvents, and its catalytic activity is superior to that of Nafion SAC-13. Such superacids could make a major contribution to green chemistry.

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Steric Turnoff of Vibrationally Mediated Negative Differential Resistance in a Single Molecule**

Jennifer Gaudioso and Wilson Ho*

Understanding the flow of energy through a molecule is a problem of fundamental interest to chemical dynamics and of practical importance to molecular electronics. Examples abound of vibrational energy coupling to changes in molecular conformation.^[1] The scanning tunneling microscope (STM) has been used to study these processes at the single-molecule level.^[2, 3] Stipe et al. discovered that the CH stretching excitation couples to the reversible rotation of an acetylene molecule in the fourfold hollow site of Cu(001) at 8 K. We previously demonstrated that tunneling electrons could be used to excite the CH₂ stretch in single pyrrolidine molecules adsorbed on the Cu(001) surface at 9 K. This excitation energy coupled to the interconversion between two conformational states of the adsorbed molecule to produce negative differential resistance (NDR) by a new vibrationally mediated mechanism.^[4] In contrast, previous observations of NDR in the Esaki tunnel diode,^[5] quantum wells and dots,^[6] atomic impurities,^[7, 8] and adsorbed monolayers^[9, 10] can all be attributed to discrete states in the electronic structure. These discrete states are due to either size quantization or atomic localization. Negative differential resistance, that is, decreasing current with increasing voltage, is the basic operating principle behind a variety of high-speed semiconductor devices.^[11, 12] While the development of molecular-sized versions of conventional electronics will become important as we push towards ever smaller devices,^[13] these single-molecule studies also offer insights into the effects of structure and dynamics on electron transport and intramolecular and molecule–surface energy-transfer processes.

Here we report on the steric turnoff of the vibrationally mediated NDR effect by comparing *N*-methylpyrrolidine to pyrrolidine on Cu(001) at 9 K. The STM was used to further our understanding of the relationship between molecular structure and dynamics in single adsorbed molecules.

Experiments were performed with a homemade variable-temperature STM in an ultrahigh-vacuum chamber. Details of the apparatus and cleaning procedures for the Cu(001) sample and tungsten tips have been described elsewhere.^[14] For experiments, the sample and STM were cooled to 9 K. Pyrrolidine (Aldrich; 99.5 % purity), [2,2,3,3,4,4,5,5-*D*₈]pyrrolidine (Isotec, Inc.; 98 atom % purity), and *N*-methylpyrro-

lidine (Aldrich; 97 % purity) were further purified by multiple freeze–pump–thaw cycles. Coverages of about 0.001 monolayers were obtained by passing the molecules from the vapors above the room-temperature liquids through a capillary-array doser attached to a variable leak valve. Neither pyrrolidine nor *N*-methylpyrrolidine diffuses away from the tip under the conditions used in this study. The vibrational energies are reported in units of millielectron volts: 1 meV = 8.065 cm^{−1}.

Both pyrrolidine and *N*-methylpyrrolidine are adsorbed through the lone pair of electrons on nitrogen and appear as protrusions in the constant-current STM images (Figure 1 a). As the tip was scanned across the molecules, the pyrrolidine

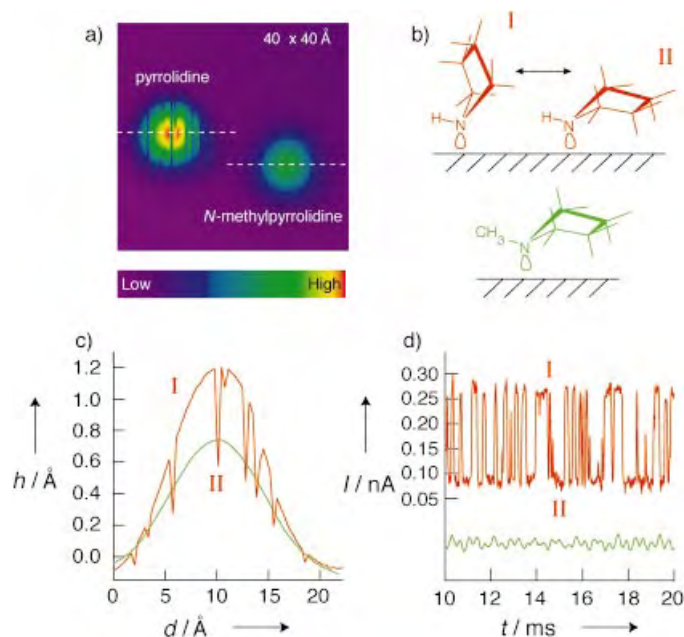


Figure 1. a) 40 × 40 Å constant-current STM images of pyrrolidine and *N*-methylpyrrolidine on Cu(001) at 9 K, taken at 50 pA and 30 mV sample bias. The pyrrolidine molecule flipped between two states (I and II) as the tip was scanned across the molecule, whereas *N*-methylpyrrolidine did not change. b) Schematic picture of the two proposed conformations of adsorbed pyrrolidine (top) and the single conformation of *N*-methylpyrrolidine (bottom). c) Cross sections of pyrrolidine (red) and *N*-methylpyrrolidine (green) images, taken along the dashed lines in (a). d) Current collected during a voltage pulse with the sample bias corresponding to 16 meV above the CD₂ (CH₂) stretching energy; the tip was positioned over the center of a [D₈]pyrrolidine (*N*-methylpyrrolidine) molecule. Two distinct current levels corresponding to states I and II are seen in the [D₈]pyrrolidine (red) current trace; only one current level is observed for *N*-methylpyrrolidine (green), with an average value of 0.14 nA (for clarity the current trace is offset from that of [D₈]pyrrolidine but shares the same y axis scale). The flipping rate of pyrrolidine is faster than that of [D₈]pyrrolidine.

molecule flipped between two states (I and II); the proposed conformations of these states are depicted in Figure 1 b.^[4] The occupation of these two states is determined by the sample bias voltage and the tunneling current. *N*-Methylpyrrolidine was never observed to change states. We believe that the methyl group pins the molecule in the bent conformation (Figure 1 b). Cross sections taken through the maxima in the molecular images (Figure 1 c) show that the apparent height

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of *N*-methylpyrrolidine is about 120% of that of conformation II of pyrrolidine. Changes in the electronic structure of the molecule due to the substitution of the methyl group for the hydrogen atom on the nitrogen atom could result in the observed height differences. The apparent height of conformation I of pyrrolidine is about 194% of that of conformation II. The conformational change in pyrrolidine can be studied by monitoring the time dependence of the tunneling current. With the tip fixed at a constant height over the maximum of the molecular protrusion, the tunneling current of the molecular junction changed as the pyrrolidine molecule flipped between the two conformations. This was evident as two levels in the current. The current trace displayed in Figure 1 d was collected over $[D_8]$ pyrrolidine, which flips at a slower rate than pyrrolidine. For all biases studied, the current collected with the tip over *N*-methylpyrrolidine exhibited only one level (Figure 1 d), which indicates that the molecule does not change states. This difference in molecular geometry between pyrrolidine and *N*-methylpyrrolidine produces a significant difference in the molecular conductivity of the two species. The current–voltage (*I*–*V*) characteristic for a single pyrrolidine molecule (Figure 2) shows regions of NDR at both

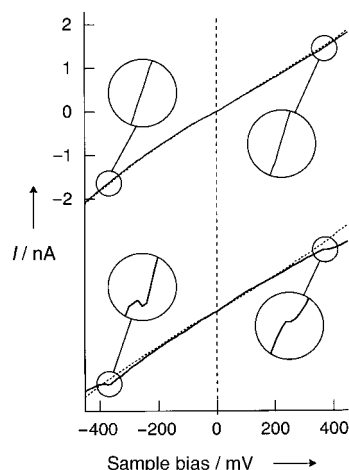


Figure 2. *I*–*V* measured with the same tip over *N*-methylpyrrolidine (upper curve) and pyrrolidine (lower curve). A spectrum was also collected over the clean Cu(001) surface (dashed line) for comparison. The NDR regions for pyrrolidine and the comparable regions for *N*-methylpyrrolidine are shown as expanded views ($\times 6$). NDR was observed at voltages corresponding to the CH_2 stretch in pyrrolidine. The spectra are averages of multiple scans from -450 to $+450$ mV and back down to -450 mV: 200 scans on *N*-methylpyrrolidine, 1000 scans on pyrrolidine, and 200 scans on Cu(001). The step size is 2.5 mV with a dwell time of 2 ms. Because the pyrrolidine molecule switches conformations, more averaging is required to achieve a signal-to-noise ratio that is comparable to that of the *N*-methylpyrrolidine curve.

positive and negative bias. The value of the current at each bias represents an average of both the high- (*I*) and low-current (*II*) levels weighted by the fractional occupation of the two conformations. When pyrrolidine ($[D_8]$ pyrrolidine) begins to spend more time in the low current state as the sample bias crosses the threshold voltage corresponding to the CH_2 (CD_2) stretch, the average current decreases.^[4] Since the methyl group constrains *N*-methylpyrrolidine to only one

state on Cu(001), the *I*–*V* characteristic for this molecule increases monotonically throughout the measurement.

Stark contrasts are also evident in the inelastic electron tunneling spectra (STM-IETS^[15]) collected over the single adsorbed molecules (Figure 3). Four vibrational modes are

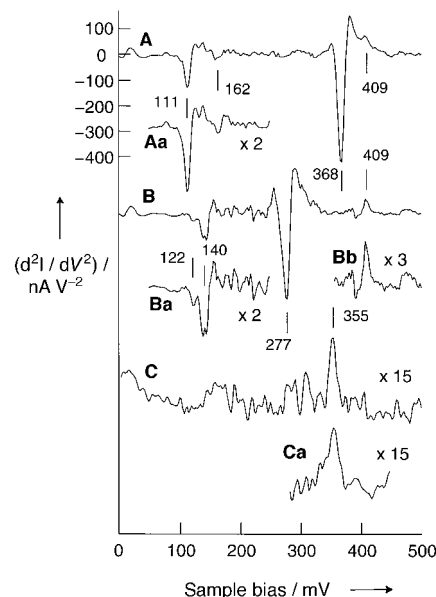


Figure 3. Single-molecule vibrational spectra obtained by STM-IETS for **A**) pyrrolidine, **B**) $[D_8]$ pyrrolidine, and **C**) *N*-methylpyrrolidine. The vertical lines indicate the positions of the dips or peaks associated with the vibrational modes. To clarify the lineshape in d^2I/dV^2 , portions of spectra for modes with smaller intensities are shown enlarged and with additional averaging. **A**) 235 scans from 0 to 500 mV and back down to 0 mV (0–500 mV), **Aa**) 1025 scans (50–250 mV); **B**) 533 scans (0–500 mV), **Ba**) 733 scans (50–250 mV), **Bb**) 533 scans (325–500 mV); and **C**) 112 scans (0–500 mV), **Ca**) 285 scans (250–450 mV). The step size is 2.5 mV with a dwell time of 300 ms.

observed by STM-IETS in the d^2I/dV^2 spectrum for pyrrolidine ($[D_8]$ pyrrolidine). Asymmetric dips are observed at 368 (277), 162 (140), and 111 (122 mV) and are associated with the CH_2 (CD_2) stretch, CH_2 (CD_2) wag or twist, and a ring mode, respectively. The second derivative of the NDR region of the *I*–*V* curves produces the observed lineshape for the CH_2 (CD_2) stretch. The symmetric, positive peak (409 mV) is assigned to the NH stretch. It appears in the shoulder of the CH_2 stretch but is clearly visible in the $[D_8]$ pyrrolidine spectrum. These mode assignments were based on isotopic shifts and comparison to previous infrared studies on gas- and liquid-phase pyrrolidine.^[16] A CH_2 stretch (355 mV), also a symmetric, positive peak, is the only vibrational mode detected by STM-IETS for *N*-methylpyrrolidine. This observed lineshape is indicative of an increase in the differential conductance dI/dV at the vibrational energy.^[17] In contrast to *N*-methylpyrrolidine, more vibrational modes are “tunneling-active” in pyrrolidine. This increase in the inelastic cross section is attributed to the coupling of the tunneling electrons to the different conformations of pyrrolidine.

For gaseous pyrrolidines, it is well known that substitution at the nitrogen atom only marginally affects the structure of the ring but strongly affects the preferred conformation.^[18, 19]

Substitution of a methyl group for the *N*-hydrogen atom turns a conformationally floppy adsorbate into a sterically constrained one. This alters the process of intramolecular vibrational energy redistribution (IVR). For pyrrolidine, the CH₂ stretch excitation can dissipate by coupling to the large-scale conformational change. This dissipation path is quenched for *N*-methylpyrrolidine. For both molecules, the CH₂ stretch can transfer its energy to other lower energy vibrations, substrate phonons, and electron–hole pairs.

Like the pyrrolidines, pyridine binds to copper predominantly through the lone pair electrons on nitrogen.^[20] Only the CH (CD) stretch mode of pyridine on Cu(001) at 377 (281) mV has been observed with STM-IETS,^[21] and the lineshape of this mode matches the lineshape of the *N*-methylpyrrolidine CH₂ stretch. The aromaticity of the pyridine ring constrains the molecule to a planar geometry. The rigid electronic backbone of pyridine acts like the bulky methyl group on *N*-methylpyrrolidine, keeping the molecule in just one conformation.

It is evident that molecular structure can have a significant impact on the dissipation of vibrational energy. Simple substitution of a methyl group for a hydrogen atom removes the NDR from the *I*–*V* curve. Thus, as we move to ever smaller devices, consideration must be given to the effect of molecular structure and conformation on the conductivity. By changing the functional groups in a molecule, different electronic functions can be realized at the molecular level. At a more fundamental level, understanding how molecular structure and dynamics alter electron transport through single molecules has important ramifications in chemical and biological systems.

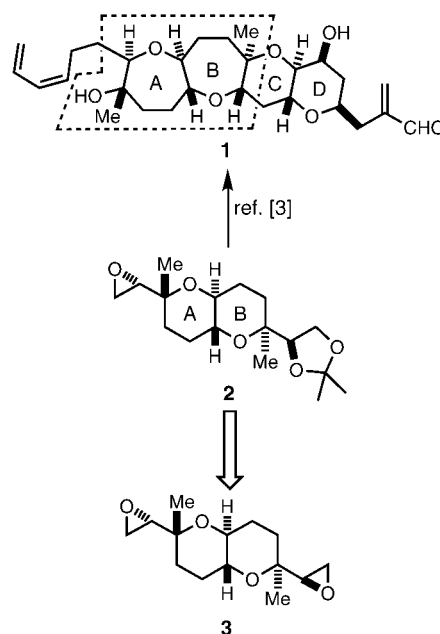
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First Desymmetrization of a Centrosymmetric Molecule in Natural Product Synthesis: Preparation of a Key Fragment in the Synthesis of Hemibrevetoxin B**

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Many polyether marine natural products, such as the ciguatoxins, brevetoxins, and yessotoxins, have embedded centrosymmetric fragments.^[1] For example, the AB ring system of hemibrevetoxin B (**1**) is a centrosymmetric dioxepane (see boxed fragment: **1**, Scheme 1). There are three reported syntheses of hemibrevetoxin B (**1**), but none of these approaches take advantage of this hidden symmetry.^[2, 3]



Scheme 1. Retrosynthetic analysis.

Our approach to hemibrevetoxin B is outlined in Scheme 1. Desymmetrization^[4] of the centrosymmetric diepoxide **3**, by selective hydrolysis^[5] of one of its enantiotopic epoxides and protection, would give the known^[3] acetone **2**. The symmetry of **3** demanded that a two-directional strategy^[6] be used, an approach which was expected to improve the efficiency of the synthesis of **2** considerably. The epoxide **2** has been prepared

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from geranyl acetate in 22 steps and 14% overall yield, and is a key early intermediate in a total synthesis of hemibrevetoxin B: it has been converted in 32 steps into hemibrevetoxin B by means of an elegant double tetrahydropyran (THP) $\rightarrow$ oxepane ring expansion.^[3]

The enedione **5** was prepared as a 2:1 mixture of *E*- and *Z*-geometric isomers by cross-metathesis of the available γ,δ -unsaturated ketone **4** (Scheme 2). An alternative approach to the enedione (*E*)-**5** involved reaction of the enamine **10** with (*E*)-1,4-dibromobut-2-ene, followed by hydrolysis and decarboxylation (70% yield). The enedione (*E*)-**5** was epoxidized with 3-chloroperoxybenzoic acid (*m*-CPBA) to give the epoxy diketone **6** in excellent yield.

The cyclization of the epoxy diketone **6**, catalyzed by pyridinium *p*-toluenesulfonate (PPTS), was central to the success of our synthesis;^[7] participation of one of the ketones of **6** initially gave the diacetals **11** which equilibrated to give the di-THP **7**. The transformation **6** $\rightarrow$ **7**, therefore, exhibits an

Ozonolysis of **8**, with reductive work-up, gave the dialdehyde **9** whose sulfur ylide-mediated epoxidation gave the diepoxide **3** as a 20:1 mixture of centrosymmetric and unsymmetrical isomers. The observation of a long-range coupling ($^4J = 1.6$ Hz) between the aldehyde proton (H^A) and the axial proton on C-3 (H^B) suggests that **9** largely populates a conformation with a characteristic *W*-arrangement between H^A and H^B (Figure 2). The isolation of the

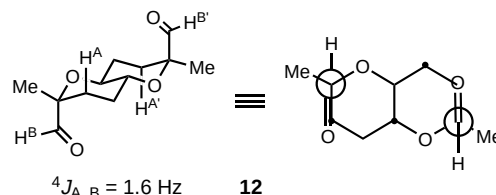
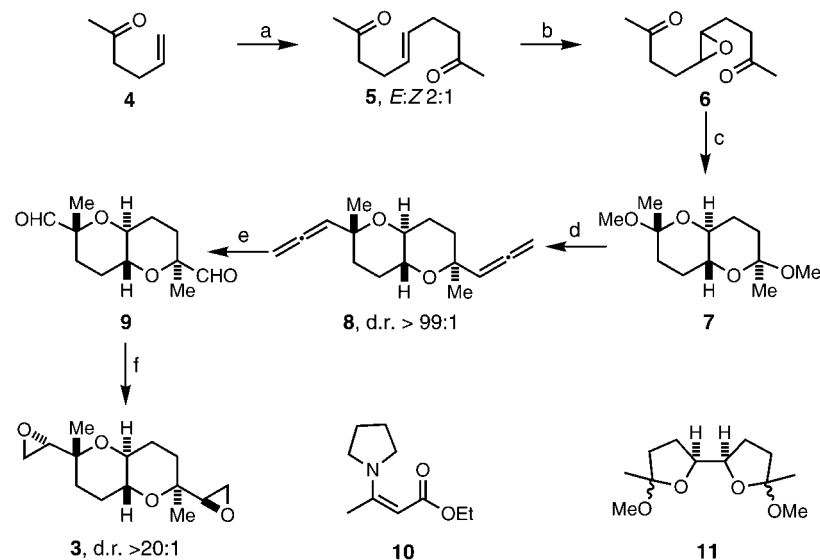


Figure 2. Ground-state conformation of the dialdehyde **9**.



Scheme 2. Synthesis of the centrosymmetric bisepoxide **3**: a) 5 mol % $[(\text{Cy}_3\text{P})_2\text{RuCHPh}]$, CH_2Cl_2 , 92%; b) *m*-CPBA, 96%; c) PPTS, MeOH, 85%; d) propargyl trimethylsilane, cat. Me_3SiOTf , 92%; e) O_3 , then Me_2S , 98%; f) $\text{Me}_3\text{S}(\text{O})\text{I}$, NaH, DMSO, 75%. Cy = cyclohexyl.

exquisite combination of thermodynamic and kinetic control: the stereochemistry of the ring junction derives from the stereospecific epoxide opening and the regiochemistry of the ring system and the stereochemistry of the anomeric centers are thermodynamically controlled.

Nucleophilic substitution of both acetals of **7** gave the centrosymmetric di-THP **8** in which both allenyl substituents had been introduced from an axial^[8] direction; the relative stereochemistry was determined by using a series of NOE experiments (see Figure 1 for diagnostic NOE enhancements). In the context of two-directional synthesis, the isolation of a >99:1 mixture of diastereoisomers **8** reflects >200:1 stereoselectivity for each substitution reaction.

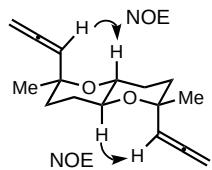


Figure 1. Proof of the stereochemistry of the bisallene **8**.

diepoxide **3** is consistent with attack of the dimethylsulfoxonium ylide on the Felkin–Anh^[9] conformation **13** (Figure 3).

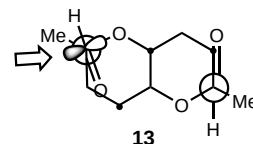
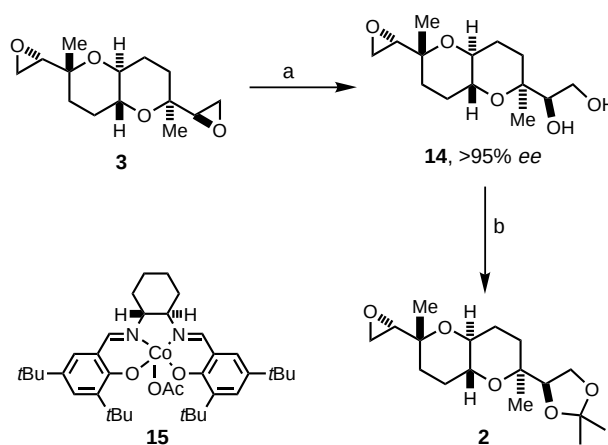


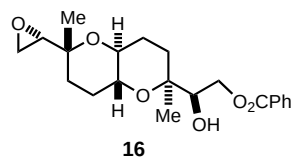
Figure 3. Diastereoselective epoxidation of the dialdehyde **9**.

The centrosymmetric diepoxide **3** was desymmetrized by enantioselective epoxide hydrolysis^[5] by using Jacobsen's chiral salen catalyst (*R,R*)-**15** (Scheme 3). Accordingly, treatment of a solution of **3** (1.0 M in 1:1 acetonitrile/dichloromethane) with 1.1 equivalents of water and 20 mol % (*R,R*)-**15** gave the diol **14** in >98% yield, which was converted into the corresponding acetonide **2**. The epoxy



Scheme 3. Desymmetrization of the bisepoxide **3** and synthesis of the key intermediate **2**: a) 20 mol % **15**, 1.1 equiv H_2O , MeCN/ CH_2Cl_2 , >98%; b) $(\text{MeO})_2\text{CMe}_2$, cat. PPTS, CH_2Cl_2 , 98%.

acetal **2**, $[\alpha]_D^{20} = -21.7$ ($c = 0.67$ in CHCl_3), was spectroscopically identical to that prepared previously^[3] ($[\alpha]_D^{20} = -22.2$ ($c = 1.15$ in CHCl_3)^[3]). The sense of asymmetric induction was the same as those observed in kinetic resolutions of terminal epoxides under similar reaction conditions. The enantiomeric excess of the desymmetrized product **14** was determined by chiral HPLC analysis of the corresponding benzoate **16**; comparison of **16** with a sample of low enantiomeric excess (prepared by mixing **16** with its enantiomer *ent*-**16**, also



synthesized by desymmetrization of **3**) showed that the desymmetrized product **2** had $> 95\%$ ee.

The key step of our synthesis was the desymmetrization of a centrosymmetric molecule, an approach which had not previously been exploited in natural product synthesis. This strategy has, however, been applied in the desymmetrization of a 2-pyridone [4+4] photodimer,^[10] the asymmetric reduction of a diketone,^[11] and in the preparation of syndiotactic polymers.^[12] The use of a desymmetrization, rather than a kinetic resolution strategy, enabled the product **2** to be obtained in high yield without compromising its enantiomeric excess. Our two-directional approach allowed the synthesis of the established intermediate **2** in eight steps and 34% overall yield. The key features of our synthesis of **2** include a) the use of no protecting groups, b) the use of only achiral reagents to control relative stereochemistry, and c) the use of a single chiral catalyst to induce asymmetry. The desymmetrization of centrosymmetric molecules, combined with a two-directional synthetic approach, is a powerful strategy which will find further application in the synthesis of natural products and biologically active compounds.

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Discrete Mixed-Valence Metal Chains: Iridium Pyridonate Blues**

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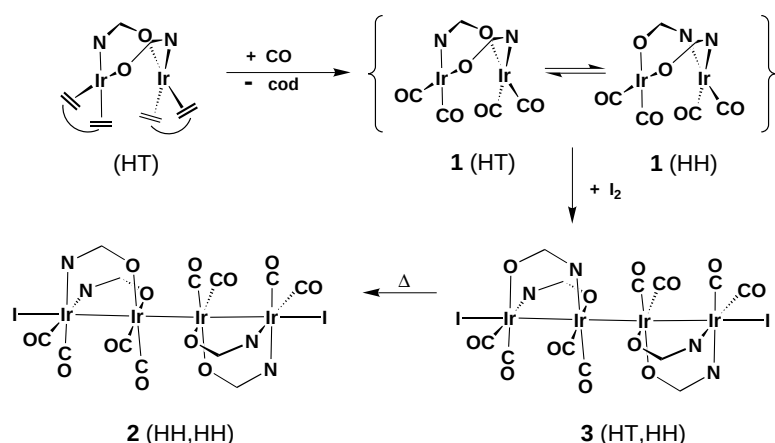
Discrete chains of metal atoms are of current interest from both theoretical and practical points of view. One synthetic approach to this type of compounds is based on ligand-assisted reactions using polydentate ligands, which is exemplified by several families of metal string complexes supported by oligo- α -pyridylamido ligands.^[1] A second approximation involves the formation of metal–metal bonds between partially oxidized d^8 square-planar complexes, for which the platinum blues are the most representative examples.^[2] Most of the reported platinum blues have been prepared from disymmetric square-planar dinuclear complexes with two amidate N-C-O-type ligands as bridges, and it has been claimed^[2a-c] that the head-to-head (HH) configurations are essential to achieve the tetrametallic platinum chains. Moreover, it has been argued that the head-to-tail (HT) structures do not dimerize for steric reasons. In fact, all the reported structures of platinum blues are based on HH dimers. Other metals, for which square-planar complexes are common, such as rhodium, iridium, and gold, are suitable for forming such metallic chains, but few examples for these metals are known.^[3] Herein we describe two new tetrametallic mixed-valence iridium compounds, which substantiate that dinuclear complexes with HT configurations are actually able to participate in metallic chains, while those with HH configurations generate the thermodynamically stable compounds.

An appropriate precursor for the formation of iridium pyridonate blues is the binuclear complex $[\{\text{Ir}(\mu\text{-OPy})(\text{CO})_2\}_2]$ (Opy = 2-pyridonate (**1**)). It was prepared, as purple microcrystals with metallic luster, by bubbling carbon monoxide through a solution of the complex $[\{\text{Ir}(\mu\text{-OPy})(\text{cod})\}_2]$ (cod = 1,5-cyclooctadiene) in toluene.^[4] While the HT configuration of the α -pyridonate ligands was found in the solid state and in solution for the diolefinic complex, a bridging ligand rearrangement occurs on carbonylation. Thus, complex **1** was found to be a 1:1 mixture of the HH and the HT isomers in solution (Scheme 1). Noteworthy, these configurational isomers were found to be in a chemical equilibrium, as shown by the ^1H two-dimensional exchange (EXSY) spectrum.

Oxidation of a solution of **1** in toluene with diiodine (in a 2:1 molar ratio) at 50 °C gives immediately an EPR-silent purple solution from which a crystalline blue solid (**2**) was isolated in excellent yield (95%) on addition of hexane.^[5] This

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Scheme 1.

intensely colored solid was found to be the mixed-valence tetrametallic compound $\text{HH,HH-}[\text{Ir}_2(\mu\text{-OPy})_2(\text{I})(\text{CO})_4]_2$ (**2**), which is structurally and chemically similar to the platinum blues, with the metallic core $\text{Ir}(1.50+)_4$. The X-ray crystal structure of **2** (Figure 1) showed two face-to-face dinuclear iridium complexes with a HH configuration joined together by an unsupported Ir–Ir bond between the *O,O*-coordinated Ir atoms.^[6]

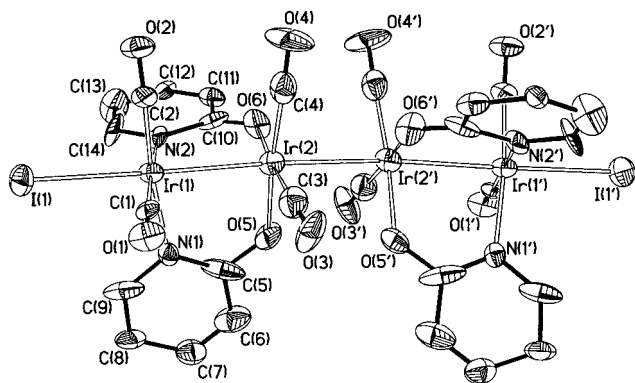


Figure 1. Molecular representation of the tetranuclear complex **2**. Primed atoms are related to the unprimed ones by the symmetry transformation $-x, y, -z + 1/2$. Selected bond lengths [Å] and angles [°]: Ir(1)–Ir(2) 2.7015(15), Ir(2)–Ir(2') 2.750(2), Ir(1)–I(1) 2.843(2), Ir(1)–N(1) 2.14(2), Ir(1)–N(2) 2.113(19), Ir(1)–C(1) 1.86(2), Ir(1)–C(2) 1.85(3), Ir(2)–O(5) 2.007(18), Ir(2)–O(6) 2.035(17), Ir(2)–C(3) 1.84(3), Ir(2)–C(4) 1.91(3); Ir(2)–Ir(1)–I(1) 176.89(5).

The result of this reaction was more relevant when the reaction was carried out at temperatures below 0 °C. Under these conditions, green crystals of the novel compound $\text{HT,HH-}[\text{Ir}_2(\mu\text{-OPy})_2(\text{I})(\text{CO})_4]_2$ (**3**), containing a dimeric unit with the HT configuration, were obtained in 75 % yield by crystallization from methanol. The X-ray crystal structure of **3**,^[7] (Figure 2) revealed the unsymmetrical tetrametallic chain formed by a linear stack of $\text{HT-}[\text{Ir}_2(\mu\text{-OPy})_2(\text{I})(\text{CO})_4]$ and $\text{HH-}[\text{Ir}_2(\mu\text{-OPy})_2(\text{I})(\text{CO})_4]$ units with an averaged oxidation state (1.50+) for the iridium atoms of the chain.

In both complexes, the two dinuclear moieties, which are linked through an unsupported Ir–Ir bond, are arranged in an almost transoid conformation (mean torsion angles around

the unsupported Ir–Ir bonds of 140(2)° in **2** and 142.3(8)° in **3**). All the Ir–Ir bond lengths within the metallic chains are similar, with those of the ligand-bridged metal–metal bonds (2.7015(15) Å in **2**, 2.6915(11) and 2.7114(11) Å in **3**) shorter than those of the central Ir–Ir bond (2.750(2) Å in **2**, 2.7793(11) Å in **3**). The three metal–metal bonds are nearly linear (168.20(6)° in **2**, 165.59(4)° and 168.17(4)° in **3**), and also the iodine atoms are linearly disposed with respect to these metal–metal bonds (176.89(5)° in **2**, 177.02(4)° and 168.83(5)° in **3**). This behavior has also been observed in the closely related pyrazolato-bridged complex $[\text{Ir}_2(\mu\text{-pz})_2(\text{I})(\text{CNtBu})_4]_2$, although in this complex the intermetallic distances are slightly longer (2.7268(8) and 2.8037(10) Å), probably due to the different electronic properties of the ancillary ligands.^[3e]

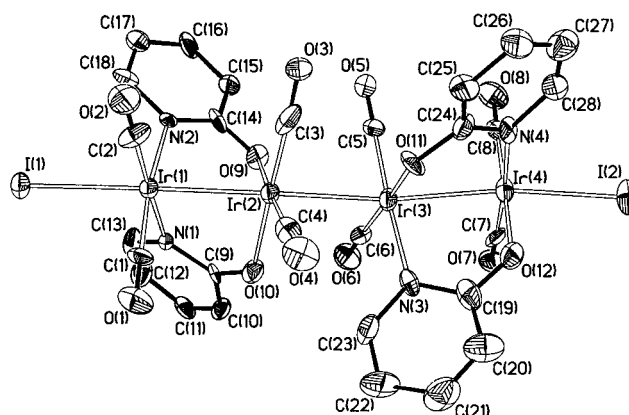


Figure 2. Molecular structure of the tetranuclear complex **3**. Selected bond lengths [Å] and angles [°]: Ir(1)–Ir(2) 2.6915(11), Ir(2)–Ir(3) 2.7793(11), Ir(3)–Ir(4) 2.7114(119), Ir(1)–I(1) 2.8470(15), Ir(4)–I(2) 2.8206(17), Ir(1)–N(1) 2.132(15), Ir(1)–N(2) 2.125(13), Ir(2)–O(9) 2.069(11), Ir(2)–O(10) 2.064(13), Ir(3)–N(3) 2.120(16), Ir(3)–O(11) 2.087(12), Ir(4)–N(4) 2.123(15), Ir(4)–O(12) 2.045(13), Ir–C(O) range 1.81(3)–1.885(18); Ir(2)–Ir(1)–I(1) 177.02(4), Ir(3)–Ir(4)–I(2) 168.83(5).

The stability found in solution for these diamagnetic tetrairidium chains is remarkable, and contrasts with most of the platinum blues, which disrupt upon dissolution.^[2a] The iridium compounds reported here remain as such in solution, giving the expected resonances in the ^1H NMR spectra. Thus, complex **2** showed equivalent α -pyridonate groups, while **3** showed four nonequivalent α -pyridonate bridging ligands. On the other hand, a solution of the green complex **3** (HT,HH) was found to evolve into the blue isomer **2** (HH,HH) on heating at 60 °C in less than five minutes. This transformation, quantitative by ^1H NMR spectroscopy, occurred also at room temperature, but slowly. Indeed, the isomerization process was avoided when the preparation and isolation of **3** was carried out at low temperature. From these experiments, it is now clear that complex **2** is the thermodynamic isomer, while complex **3** corresponds to the kinetic isomer.

As commented above, the metal–metal distances and bond angles were similar for the isomers **2** and **3**, and no relevant steric strain arises from the participation of the HT config-

uration in the formation of the unsupported metal–metal bond. Furthermore, the steric bulk of the pyridonate rings does not hinder the formation the unsupported metal–metal bond. Therefore, one could envisage the accessibility of a hypothetical tetrametallic chain made of two HT units.

With the experimental confirmation of the intervention of HT dimers in tetrametallic chains, it seems likely that the lack of HT-pyridonate dimers in the platinum blues complexes should be attributed mainly to thermodynamic reasons rather than to steric factors.

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- [6] a) Crystallographically imposed twofold symmetry was observed relating the two halves of the tetranuclear complex. Crystal data for **2**: $C_{28}H_{16}N_4O_{12}Ir_4$, $M_r = 1623.04$, laminar crystal ($0.14 \times 0.11 \times 0.06$ mm), monoclinic, space group $C2/c$, $a = 27.709(3)$, $b = 9.2163(10)$, $c = 16.9592(17)$ Å, $\beta = 124.274(2)^\circ$, $V = 3578.9(6)$ Å³, $Z = 4$, $\rho_{calcd} = 3.012$ g cm⁻³, $F(000) = 2888$, $T = 150(2)$ K, $MoK\alpha$ radiation ($\lambda = 0.71073$ Å, $\mu = 16.615$ mm⁻¹). Data collected with a Bruker SMART

APEX CCD diffractometer. Of 5545 measured reflections (2θ : $5–50^\circ$, ω scans 0.3°), 2662 were unique ($R_{int} = 0.0808$); a multiscan absorption correction was applied (PLATON program) with min./max. transmission factors of 0.204/0.436. Structure solved by Patterson and difference-Fourier maps; refined using SHELXTL. Final agreement factors were $R1 = 0.0808$ (1965 observed reflections, $F^2 > 4\sigma(F^2)$) and $wR2 = 0.2264$; data/restraints/parameters 2662/72/227; GOF = 1.039. Largest peak and hole in the final difference map 6.084 and -3.483 e Å⁻³. The limited quality of the structural data (also the merging and agreement factors, and the high residuals) should be necessarily associated to the diffracting weakness, to the anisotropic morphology, and to the high absorption of the crystals. b) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-165456 (**2**) and CCDC-165457 (**3**·2CH₄O). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [7] Crystal data for **3**·2CH₄O: $C_{28}H_{16}N_4O_{12}Ir_4$ ·2CH₄O, $M_r = 1687.13$, triclinic, space group $P\bar{1}$, $a = 10.2440(8)$, $b = 13.4751(10)$, $c = 15.2437(11)$ Å, $\alpha = 75.8696(15)$, $\beta = 71.2963(13)$, $\gamma = 78.1790(15)^\circ$, $V = 1914.4(2)$ Å³, $Z = 2$, $\rho_{calcd} = 2.927$ g cm⁻³, $F(000) = 1516$, $T = 150(2)$ K, $MoK\alpha$ radiation ($\lambda = 0.71073$ Å, $\mu = 15.541$ mm⁻¹). Data collected as described for **3** with an elongated block ($0.20 \times 0.06 \times 0.04$ mm). Of 10303 measured reflections (2θ : $5–50^\circ$, ω scans 0.3°), 6555 were unique; a multiscan absorption correction was performed (SADABS program) with min./max. transmission factors of 0.119/0.583. Structure solution and refinement as described for **2**. Final agreement factors were $R1 = 0.0656$ (4735 observed reflections) and $wR2 = 0.1606$. Data/restraints/parameters 6555/61/487; GOF = 1.049. Largest peak and hole in the final difference map 3.638 and -2.464 e Å⁻³.^[6b]

Enantiomeric Discrimination in a Reiterative Domino Coupling Process: Cu^I-mediated Syn Cyclotrimerization of Racemic Polycyclic Trimethylstannyl Bromonorbadienes**

Sergio Cossu,* Chiara Cimenti, Paola Peluso, Antonio Paulon, and Ottorino De Lucchi

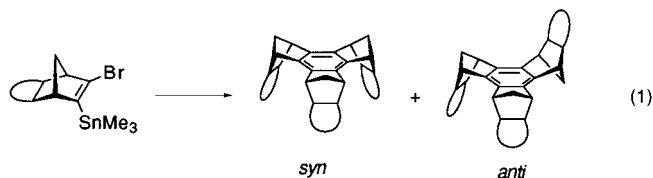
The fundamental concept of molecular discrimination considers the ability of a chemical object to identify, in the presence of alternative possibilities, a defined chemical counterpart through specific interactions.^[1] When discrimination depends on the chiral properties of the chemical partners, only one of the events that derive from the possible stereochemical combinations can be realized.^[1] In this context, a peculiar discrimination was observed during the self-coupling of racemic ketones that possess the bicyclo[2.2.1]heptene skeleton, either by means of aldol reactions or via organocuprate derivatives. The main feature of the reported

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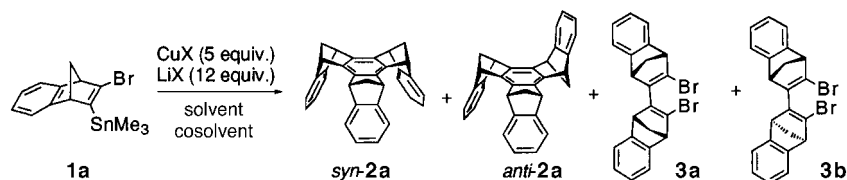
examples is that these enolate anions prefer to react with the reaction partner with the same absolute configuration.^[2]

Herein we report a new Cu^I-mediated cyclotrimerization of racemic 3-bromo-2-trimethylstannylalkenes which affords *syn* cyclotrimers through a reiterative enantiomeric discrimination process. Previously, these compounds were obtained as mixtures with the corresponding *anti* isomers, through cyclotrimerization processes of substituted polycyclic alkenes [Eq. (1)].^[3, 4] The reaction of polycyclic bromotrimethylstannyl alkenes in the presence of copper(II) nitrate in THF was



reported to afford a statistical 1:3 mixture of *syn* and *anti* isomers. On the other hand, only the Pd⁰-catalyzed *anti*-selective synthesis of the cyclotrimer has been achieved efficiently.^[3] Cyclotrimers with *syn* geometry have peculiar concave architectures and electronic potential surface (EPS) values,^[3d, 5] similar to those reported for a variety of nonplanar complexing molecules such as cyclooveratrylene,^[6] molecular tweezers,^[5] and others^[7] which also present interesting applications in the field of liquid crystals.^[8]

The benzonorbornadiene derivative **1a** was chosen as the model compound for the preliminary screening. The main results of the reaction depicted in Scheme 1 are summarized in Table 1. Under the reaction conditions of Piers et al.^[9] (Table 1, entry 2), which are known to promote the coupling of vinylstannanes by using CuCl as the sole catalyst, and also



Scheme 1. General synthesis of coupled products from benzonorbornadiene **1a**.

Table 1. Reagents, solvents, reaction conditions, products, and yields for the reaction of **1a**.

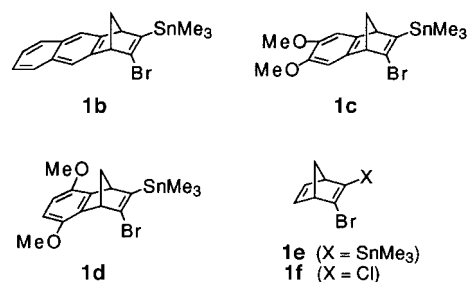
Entry	CuX	Solvent	Co-solvent	LiX	T	t [h]	<i>syn/anti</i> - 2a (% yield)	3a,b [%]
1	Cl	DMF	–	–	RT	1	1:2 (75)	traces
2	Cl	THF	–	Cl	RT	4	1:2 (5)	5
3	Cl	DMF	–	Cl	RT	19	1:1 (50)	50
4	Cl	DMF	DME	Cl	60 °C	4	2:1 (80)	–
5	Cl	DMF	DMDPE	Cl	RT	2	2:1 (70)	20
6	I	DMF	DME	Cl	RT	24	4.5:1 (80)	3
7	I	DMF	DME	Br	RT	360	3:1 (15)	35
8	Cl	DMF	DME	I	RT	168	1:1.5 (25)	25
9	I	DMF	DME	I	RT	12	–	–
10	I	NMP	DME	NO ₃	RT	24	9:1 (80)	–

DMF = *N,N*-dimethylformamide; DME = 1,2-dimethoxyethane; DMDPE = *rac* 1,2-dimethoxy-1,2-diphenylethane; NMP = *N*-methylpyrrolidone. All compounds were separated, purified, and characterized by using NMR spectroscopy, GC-MS, and in some instances X-ray techniques.

in the reaction carried out in presence of LiCl as co-catalyst (Table 1, entry 2), a 1:2 mixture of stereoisomeric *syn* and *anti* trimers **2** is obtained. These results already seemed significant to us because this was the first time that we observed a preferential formation of the *syn* isomer (rather than the statistical 1:3 ratio). The reaction gave a 1:1 *syn/anti* ratio in DMF (Table 1, entry 3), without the formation of protodes-tannylated or chlorodestannylated compounds **4** and **5**, respectively.

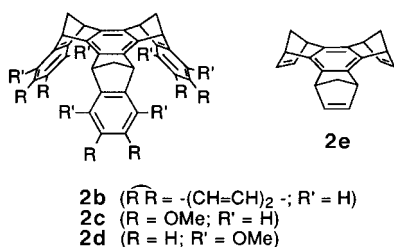
A further improvement in the yields of the trimers resulted from the use of dimethoxyethane as cosolvent, which led to a reaction mixture composed exclusively of the cyclotrimers, in a 2:1 *syn/anti* ratio (Table 1, entry 4). We reasoned that the diether formed a complex with the copper intermediates and therefore tested the effect of the chiral enantiopure diether (*R,R*)-1,2-dimethoxy-1,2-diphenylethane (Table 1, entry 5), but no significant variation in the *syn/anti* selectivity was observed. A final definite improvement was found when CuCl was replaced with CuI (Table 1, entry 6), which led to a reaction mixture enriched with the *syn* cyclotrimer (4.5:1) in 80 % yield. Other combination of salts (X = Cl, Br, I either in the copper or in the added lithium salt) did not improve the reaction further (Table 1, entries 7–9); instead, the reactivity of the system decreased, in agreement with the literature.^[9, 10, 11] An exception proved to be lithium nitrate in NMP (Table 1, entry 10), which gave a result comparable with that in entry 5, with the extra advantage that it required milder reaction conditions and that it completely suppressed the formation of halogenated derivatives **5**.

The 3-bromo-2-trimethylstannyl-substituted naphthonorbornadiene **1b**, 6,7-dimethoxybenzonorbornadiene **1c**, 5,8-dimethoxybenzonorbornadiene **1d**, and norbornadiene **1e** were tested under the reaction conditions of entries 6 and 10 of Table 1. Naphthonorbornadiene derivative **1b** exhibited the same selectivity as **1a**. The reaction of 6,7-dimethoxybenzonorbornadiene derivative **1c** proved to be totally stereoselective and afforded only the *syn* cyclotrimer **2c**. However, 5,8-dimethoxy-

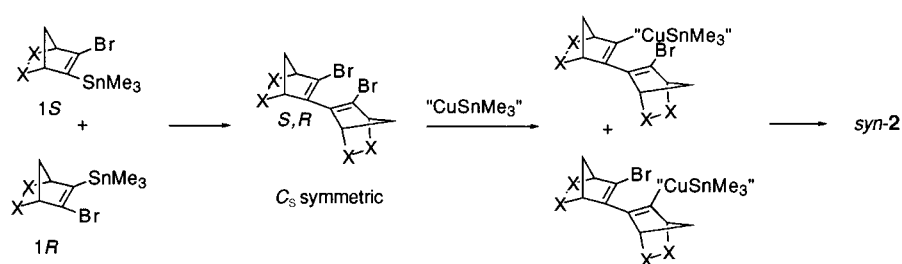


benzonorbornadiene derivative **1d** was much less reactive, probably as a result of the steric interactions between the methoxy groups. The norbornadiene derivative **1e** was subjected to the reaction conditions of entry 5 and predominantly afforded the chlorodestannylated product **1f** as well as

small amounts of cyclotrimers, with a preference for **2e** in a 3:1 *syn/anti* ratio.

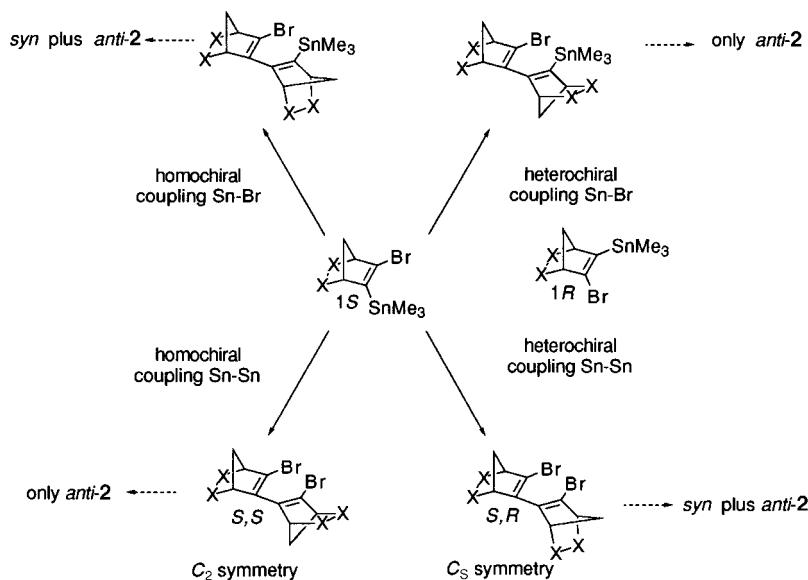


The predominant formation of the *syn* cyclotrimer requires an explanation, because the reaction of a racemic mixture of bromotrimethylstannyl alkenes **1** should afford a statistical 1:3 isomeric mixture. Taking into account that the coupling of **1** may occur between enantiomers of the same (homochiral) or opposite (heterochiral) configuration, and to establish if the mechanism proceeds through a Sn–Br or a Sn–Sn coupling process (Scheme 2), the reaction was carried out with the enantiomerically pure **1a**.^[12] The reaction was dramatically



Scheme 3. Stereoselective formation of *syn*-**2**.

regio- and chemoselective enantiomeric discrimination process, which involves the formation of diastereoisomeric intermediates, as a final result of a reiterative recognition between opposite enantiomers.^[14] From a conceptual point of view, the ability of a reagent to discriminate between the *Re* and *Si* faces, which in the present case are defined by the trimethylstannyl-substituted sp^2 carbon atoms of two different molecules (the enantiomers), is virtually equivalent to an enantiotopic discrimination between the sp^2 carbon atoms of “*meso*” compounds, which are typical substrates for stereoselective desymmetrization processes.^[15]



Scheme 2. Dimerization of bromotrimethylstannyl alkenes **1**.

slower than that of racemic **1a** and afforded only a small amount of dibromo dimer **3b** with C_2 symmetry and traces of *anti* cyclotrimer **2a**. This result suggests an Sn–Sn coupling process and an intrinsic reluctance of homochiral monomers to couple between themselves; it also suggests that the reaction cannot proceed *via* a symmetric alkyne metal complex in which the chiral information would be lost.^[13] Hence the mechanism has to proceed with a total selectivity of each enantiomer in choosing the reaction partner of opposite configuration, not only in the formation of the dimer but also in the further coupling to the trimer (Scheme 3).

The described methodology represents the first highly selective direct access to *syn* cyclotrimers: starting from a racemic mixture of reagents, *via* racemic reactive species generated in situ, the final product is obtained after a domino

Experimental Section

General cyclotrimerization: A 25-mL, two-necked, flame-dried flask, equipped with a magnetic stirring bar, was charged with lithium salt (6 equiv) and further dried (110°C , vacuum/argon) for 30 min. After cooling to room temperature, freshly dried DME (10 equiv), DMF (2 mL), and Cu^{I} salt (5 equiv) were added sequentially. After 15 min, the mixture was treated with a solution of **1a** (0.5 mmol) in dry DMF (1 mL) and stirred under argon at room temperature. The reaction was monitored by means of NMR spectroscopy. The crude reaction mixture was diluted with Et_2O (60 mL), washed with H_2O (3×40 mL), aqueous NH_4OH (10%, 4×30 mL), and brine (3×30 mL). The organic layer was separated and dried (Na_2SO_4). The residue was purified by flash chromatography (silica gel, eluant: gradient of *n*-hexane/ethyl acetate). Products were identified by comparison of their spectral data with those of the authentic samples.^[3] Selected data for **3a**, **3b**:^[3d] ^1H NMR (200 MHz, CDCl_3 , TMS): $\delta = 7.58\text{--}7.53$, $7.41\text{--}7.37$, $7.20\text{--}7.13$ (series of m, 16H; Ar, both isomers), 4.69 (br s, 2H; **3a**), 4.46 (br s, 2H; **3b**), 3.86 (br s, 4H; both isomers), 2.57 (dt, $J = 7.7$ and 1.7 Hz, 1/2 AB system, 1H; **3b**), 2.45 (dt, $J = 7.7$ and 1.7 Hz, 1/2 AB system, 1H; **3a**), 2.26 (dt, $J = 7.7$ and 1.7 Hz, 1/2 AB system, 1H; **3b**), 2.19 (dt, $J = 7.7$ and 1.7 Hz, 1/2 AB system, 1H; **3a**); ^{13}C NMR (CDCl_3 , 100 MHz): (both isomers) $\delta = 149.4$, 149.2, 149.0, 148.7, 145.2, 144.1, 132.3, 131.1, 125.2, 125.1, 124.8, 124.5, 122.8, 122.2, 121.8, 121.7; (**3a**): 65.8, 60.1, 52.7; (**3b**): 66.7, 59.7, 53.0.

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Yttrate Metathesis: Ligand Design for the Controlled Synthesis of f-Block Heterobimetallic Compounds**

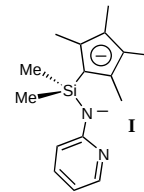
Michael S. Hill* and Peter B. Hitchcock

Heterobinuclear derivatives in which one of the constituent metals is a member of Group 3 or the lanthanide series display unusual cooperative properties for a variety of diverse applications.^[1] Approaches to bimetallic rare earth complexes that comprise metals other than those of Group 1 are however uncommon and usually inflexible with regard to the identity and coordination requirements of the second metal.^[2] We describe here a simple and readily modified ligand design that permits the synthesis of molecules containing a trivalent rare earth element with a defined and proximal disposition to a second metal center. Our adopted strategy exploits the tendency of these large cations to form uninegative “ate” complexes, through the attachment of two amido-cyclopentadienyl dianions, **I**. Further bimetallic systems may then be synthesized by metathesis of the initial alkali metal derivative with a metal halide.

For this approach to succeed, the ligand design must suppress fragmentation of the lanthanide ate anion. Kempe et al. have shown that metathesis of a variety of early and late transition metal halides with aminopyridinato-based lanthanide ate complexes results in complete ligand transfer (albeit via unstable bimetallic intermediates).^[3] This reactivity may be perturbed, however, permitting the synthesis of Nd/Rh and Nd/Pd bimetallic compounds, through the use of chelating bis-aminopyridinato ligands.^[2d]

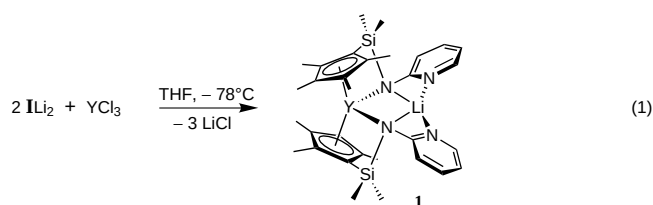
Dianion **I** is based upon the ligand framework applied by Bercaw et al. to the synthesis of “constrained geometry” olefin polymerization catalysts.^[4] Our ligand constitution is determined by the demonstrated ability of Bercaw’s and similar ligands to saturate the coordination sphere of Group 3 metals.^[5] The amido functionality of **I** results from the deprotonation of a 2-aminopyridine substituent, selected for the capacity of 2-aminopyridinato ligands to bind a wide variety of metal centers.^[6] For the initial investigation of the ligating properties of **I**, we chose to study the chemistry of trivalent yttrium derivatives, mindful of the diagnostic solution-state NMR data derived from observation of the ⁸⁹Y nucleus and its attendant internuclear couplings.

Reaction of YCl₃ and two equivalents of the dilithium derivative of **I** in THF afforded the colorless complex **1** [Eq. (1)]. Complex **1** is very soluble in THF and aromatic solvents but poorly soluble in aliphatic hydrocarbons. The



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observation of four ring methyl resonance signals in the ^1H and ^{13}C NMR spectra and five cyclopentadienyl ring signals, identified by their coupling to the yttrium nucleus ($^1J_{\text{Y,C}} = 0.5\text{--}2.0$ Hz), in the ^{13}C NMR spectrum were consistent with a C_2 -symmetric structure in which yttrium is bound by η^5 -cyclopentadienyl and η^1 -amido interactions.^[7] The ^6Li and ^7Li NMR spectra consist of a single resonance signal at $\delta = 3.1$. Cooling of a $[\text{D}_8]$ toluene solution of **1** to 248 K did not result in any perceptible changes to the NMR spectra, indicating a static solution geometry. The robust nature of **1** in solution was further reflected by a $^2J_{\text{Y,Si}}$ coupling of 2.1 Hz in the ^{29}Si NMR spectrum and in the vapor phase by a 100 % intensity molecular ion at 636 in the mass spectrum.

A bent metallocene structure for **1** was confirmed by a single-crystal X-ray diffraction analysis (Figure 1).^[8a] The yttrium atom is coordinated in a pseudotetrahedral fashion by two pairs of cyclopentadienyl and amido donors. The Y–C(Cp) bond lengths (2.576(3)–2.758(3) Å) and the $\text{Cp}_{\text{cent}}\text{--Y--Cp}_{\text{cent}}$ angle (137.0(1)°) are comparable to those in $\text{Li}[\text{Y}(\eta^5\text{-C}_5\text{Me}_4\text{SiMe}_2\text{NCH}_2\text{CH}_2\text{OMe})_2]$ (**II**).^[5d] The Y–N bond lengths (2.332(3), 2.349(3) Å) are only about 0.02 Å longer than those of **II**, despite the potential for enhanced delocalization of charge from the amido donors onto the

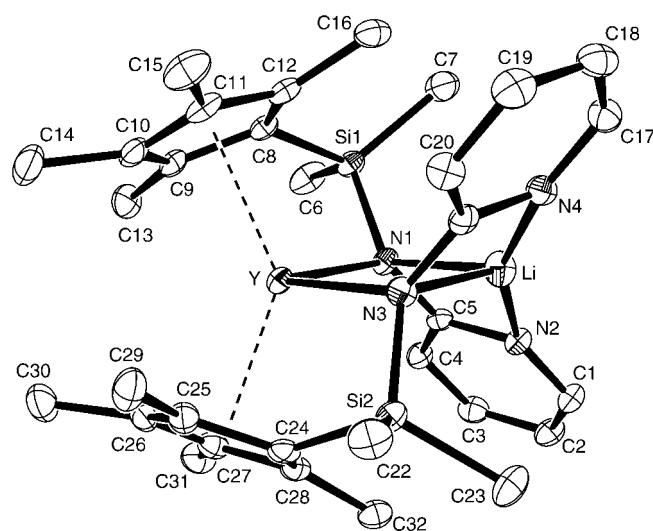
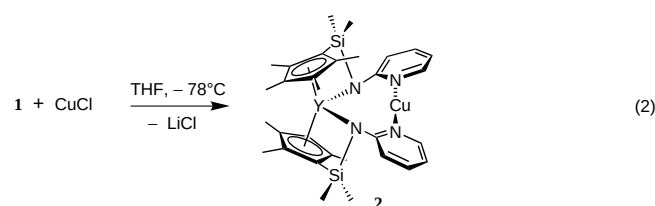


Figure 1. Structure of **1** (ORTEP plot; 30% probability ellipsoids). H atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Y–N1 2.349(3), Y–N3 2.332(3), Y–C8 2.576(3), Y–C9 2.617(3), Y–C10 2.734(3), Y–C11 2.752(3), Y–C12 2.673(3), Y–C24 2.588(3), Y–C25 2.599(4), Y–C26 2.722(4), Y–C27 2.758(3), Y–C28 2.704(3), Y–M1 2.380(4), Y–M2 2.385(4), Li–N1 2.308(7), Li–N2 1.995(6), Li–N3 2.256(7), Li–N4 1.990(6), Y...Li 3.136(6); N1–Y–N3 92.99(10), N1–Y–M1 95.2(1), N1–Y–M2 114.4(1), N3–Y–M1 114.3(1), N3–Y–M2 95.3(1), M1–Y–M2 137.0(1), N1–Li–N3 96.1(3), N1–Li–N2 65.0(2), N2–Li–N4 155.9(4), N4–Li–N3 66.0(2), N1–Li–N4 135.6(3), N2–Li–N3 132.0(3). M1 and M2 are the centroids of the C8 to C12 and C24 to C28 rings respectively.

2-pyridyl substituents. The pendant aminopyridinato groups both chelate the lithium counteranion. In contrast to other lithiated aminopyridines,^[6a] the lithium center is preferentially bound by the pyridyl nitrogen atoms of the N_4 -donor set (Li–N1 2.308(7), Li–N3 2.256(7), Li–N2 1.995(6), Li–N4 1.990(6) Å). This results in a displacement of the lithium atom away from the yttrate anion and a Y–Li separation of 3.136 Å. Evidently the steric demands of the yttrate fragment and the “bite” provided by the pendant aminopyridinato substituents are such that further coordination of THF solvent is prevented.

Reaction of **1** with one equivalent of CuCl in THF provided, after crystallization from toluene, the colorless heterobinuclear compound **2** [Eq. (2)]. The formation of this



unusual Y/Cu species was indicated by a strong peak for the molecular ion at m/z 692 in the mass spectrum. Furthermore, retention of the C_2 symmetry of the molecule was deduced from the similarity of the solution-state NMR spectra to those of **1**. The ^{89}Y chemical shift of **2** is little altered from that of **1** ($\Delta\delta = 10.1$ ppm) indicating that substitution of copper for lithium causes little disruption to the yttrium coordination environment.^[9]

An X-ray structural analysis confirmed the incorporation of copper into the pendant aminopyridinato coordination environment of the yttrate anion (Figure 2).^[8b] The structural parameters relating to the yttrium coordination sphere are

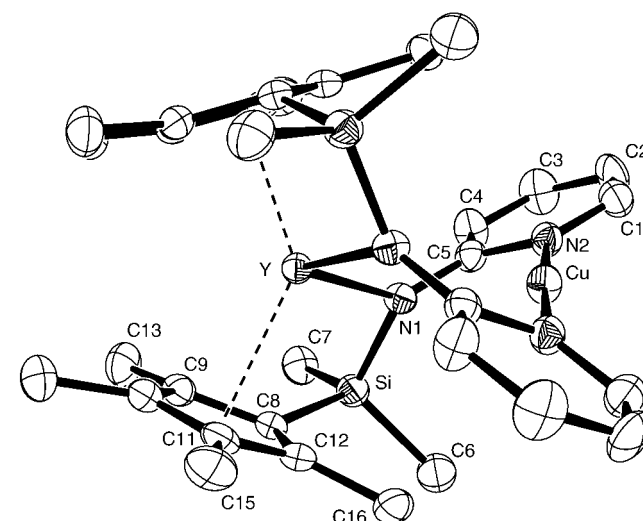


Figure 2. Structure of **2** (ORTEP plot; 50% probability ellipsoids). H atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Y–N1 2.358(3), Y–C8 2.585(4), Y–C9 2.678(4), Y–C10 2.759(4), Y–C11 2.732(4), Y–C12 2.630(4), Y–M1 2.388(4), Cu–N2 1.879(3), Y...Cu 3.458(6); N1–Y–N1' 107.8(2), N1–Y–M1 94.4(2), N1'–Y–M1 111.9(2), M1–Y–M1' 135.2(2), N2–Cu–N2' 177.6(2). M1 is the centroid of the C8 to C12 ring.

very similar to those of **1** apart from a widening of the N1-Y-N1' angle to 107.8(2)° (from 92.99(10)° for the equivalent N1-Y-N3 measurement in **1**). This adjustment to the yttrate configuration is due to the almost linear (N-Cu-N 177.6(2)°) 2-coordination of the copper atom provided exclusively by the pyridyl N donors of the aminopyridinato substituents. This also results in a lengthening of the intermetallic Y-Cu distance to 3.458 Å.

In conclusion, the isolation of **2** indicates that the kinetic stabilization afforded by the sterically demanding architecture of **1** is suitable for the intact metathetical transfer of an yttrium-centered anion. This simple synthetic method holds promise for the assembly of a range of unusual and unprecedented combinations of metal centers. To further understand the pendant coordination environment of **1**, we are exploring the generality of its metathesis reactions with a range of main group and d-block metal halides. Preliminary mass spectral studies indicate that reactions of **1** with AlCl₃, FeBr₂ and PdCl₂ also result in the replacement of lithium and the formation of mixed-metal species. This is most clearly apparent for the reaction with AlCl₃, which displays a strong peak for the molecular ion at *m/z* 726. However in this case each signal in the ¹H NMR spectrum splits into two demonstrating that the C₂ symmetry of **1** and **2** is lost, due, most likely, to coordination by a single aminopyridine. This latter observation indicates that "tuning" of the pendant donor environment to the coordination requirements of particular metal centers will be a major consideration in the realization of certain combinations of metals. With this in mind, the simplicity of **1** allows straightforward modification of ligand bite and donor identity by, for example, the inclusion of methylene spacers between the amido nitrogen atoms and the pyridyl substituents.

Experimental Section

All reactions and manipulations were performed under rigorous exclusion of water and oxygen, either on a double manifold vacuum line or a N₂-filled drybox operating at < 1 ppm O₂. All reagents and solvents were purified by standard procedures.

1: YCl₃ (0.34 g, 1.76 mmol) and Li₂(C₅Me₄SiMe₂NC₅H₄N-2) (1.0 g, 3.52 mmol) were combined in a flask, and precooled THF (30 mL) was added at -78 °C with stirring. The resulting mixture was allowed to warm to room temperature and stirred for 14 h to give a pale yellow solution. The solvent was removed and the resultant pale yellow glass extracted with toluene (30 mL). This was filtered from LiCl, and the clear pale yellow solution concentrated to 5 mL. Storage at -30 °C for one week resulted in the formation of mono-toluene solvated **1** as air-sensitive colorless crystals suitable for an X-ray diffraction study. The included toluene was removed by storage of a ground sample under vacuum: yield; 0.95 g, 85%. M.p. 138 °C (decomp); elemental analysis: C₃₂H₄₄LiN₄Si₂Y: calcd: C 60.29, H 6.90, N 8.79; found: C 60.39, H 7.00, N 8.68; ¹H NMR (300.1 MHz, C₆D₆, 25 °C): δ = 0.47, 0.60 (s, 6H; SiMe), 1.55, 1.85, 2.13, 2.26 (s, 6H; C₅Me₃), 6.29 (t, 2H; 4-H, C₅H₄N), 6.61 (d, 2H; 3-H, C₅H₄N), 7.06 (m, 2H; 5-H, C₅H₄N), 7.85 (d, 2H; 6-H, C₅H₄N); ¹³C{¹H} NMR (125.8 MHz, C₆D₆, 25 °C): δ = 4.1, 5.8 (SiMe), 10.4, 11.5, 13.1, 13.2 (ring CH₃), 104.4 (ring C attached to SiMe₂), 114.2 (4-C; C₅H₄N), 119.1 (3-C, C₅H₄N), 121.4 (¹J_{YC} = 2.0 Hz, ring C), 122.2 (¹J_{YC} = 0.5 Hz, ring C), 122.4 (¹J_{YC} = 0.8 Hz, ring C), 126.8 (¹J_{YC} = 1.9 Hz, ring C), 138.0 (5-C, C₅H₄N), 146.7 (6-C, C₅H₄N), 171.6 (2-C, C₅H₄N); ²⁹Si{¹H} NMR (99.4 MHz, C₆D₆, 25 °C): δ = -16.46 (²J_{YSi} = 2.2 Hz); ⁶⁷Li NMR (194.5 MHz, C₆D₆, 25 °C): δ = 3.1; ⁸⁹Y{¹H} NMR (24.5 MHz, C₆D₆, 25 °C): δ = -82.4; MS (70 eV): *m/z* (%): 636 (100) [*M*⁺], 509 (60), 458 (15), 359 (55) [RY], 277 (6), 151 (35).

2: Precooled THF (20 mL) was added at -78 °C to a solid mixture of **1** (0.35 g, 0.55 mmol) and CuCl (0.06 g, 0.57 mmol) to give a pale yellow solution that turned deep red-brown on warming to room temperature. After stirring for a further 2 h the solvent was removed to give a red-brown glass. This was extracted with toluene (15 mL) and filtered. Concentration to about 5 mL followed by storage at -30 °C for one week provided **2** as colorless block crystals suitable for an X-ray diffraction study: yield 0.22 g, 58%. M.p. softens 175 °C, melts 225 °C (decomp); elemental analysis: C₃₂H₄₄CuN₄Si₂Y: calcd: C 55.38, H 6.35, N 8.08; found: C 55.48, H 6.32, N 7.96; ¹H NMR (300.1 MHz, C₆D₆, 25 °C): δ = 0.56, 0.73 (s, 6H; SiMe), 1.84, 1.85, 2.17, 2.32 (s, 6H; C₅Me₃), 6.10 (t, 2H; 4-H, C₅H₄N), 6.68 (d, 2H; 3-H, C₅H₄N), 6.91 (m, 2H; 5-H, C₅H₄N), 7.20 (d, 2H; 6-H, C₅H₄N); ¹³C{¹H} NMR (125.8 MHz, C₆D₆, 25 °C): δ = 3.7, 6.0 (SiMe), 11.1, 11.8, 14.1, 14.7 (ring CH₃), 104.8 (ring C attached to SiMe₂), 113.1 (4-C, C₅H₄N), 119.4 (³J_{YC} = 1.1 Hz, 3-C, C₅H₄N), 121.2 (¹J_{YC} = 0.7 Hz, ring C), 122.9 (¹J_{YC} = 1.8 Hz, ring C), 123.7 (¹J_{YC} = 0.5 Hz, ring C), 125.3 (¹J_{YC} = 1.9 Hz, ring C), 137.6 (5-C, C₅H₄N), 147.4 (6-C, C₅H₄N), 171.8 (2-C, C₅H₄N); ²⁹Si{¹H} NMR (99.4 MHz, C₆D₆, 25 °C): δ = -17.91 (²J_{YSi} = 2.1 Hz); ⁸⁹Y{¹H} NMR (24.5 MHz, C₆D₆, 25 °C): δ = -72.3; MS (70 eV): *m/z* (%): 692 (60) [*M*⁺], 509 (35), 359 (15) [RY], 285 (98), 207 (20), 151 (100), 120 (20).

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methods (SHELXS-97) and refined against all F^2 using SHELXL-97) with non hydrogen atoms anisotropic and hydrogen atoms in riding mode. a) Crystallographic data for **1** at 173(2) K: ($C_{39}H_{52}LiN_4Si_2Y$, $M_r = 728.88$) crystal dimensions $0.4 \times 0.4 \times 0.3$ mm³: triclinic, space group $P\bar{1}$ (no. 2), $a = 11.2801(6)$, $b = 12.5170(8)$, $c = 14.0742(9)$ Å, $\alpha = 106.916(3)$, $\beta = 92.003(4)$, $\gamma = 93.380(3)^\circ$, $V = 1895.1(2)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.28$ Mg m⁻³, $\mu = 1.63$ mm⁻¹. Of 12 364 reflections measured ($3.75 < \theta < 24.10^\circ$), 5977 were independent ($R_{\text{int}} = 0.051$). $wR2 = 0.093$ (all data), $R1 = 0.045$ (for 4962 reflections with $I > 2\sigma(I)$), 436 parameters, GOF = 1.049. b) Crystallographic data for **2** at 173(2) K: ($C_{32}H_{44}CuN_4Si_2Y$, $M_r = 693.34$) crystal dimensions $0.1 \times 0.1 \times 0.1$ mm³: orthorhombic, space group $Pbcn$ (no. 60), $a = 11.9268(5)$, $b = 17.0281(6)$, $c = 16.0764(7)$ Å, $V = 3265(2)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.41$ Mg m⁻³, $\mu = 2.52$ mm⁻¹. Of 15 424 reflections measured ($3.84 < \theta < 25.01^\circ$), 2872 were independent ($R_{\text{int}} = 0.079$). The molecule lies on a twofold rotation axis. $wR2 = 0.098$ (all data), $R1 = 0.041$ (for 1907 reflections with $I > 2\sigma(I)$), 188 parameters, GOF = 1.025. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-168596 and CCDC-168597 for **1** and **2**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Helical Chiral Polyisocyanides Possessing Porphyrin Pendants: Determination of Helicity by Exciton-Coupled Circular Dichroism**

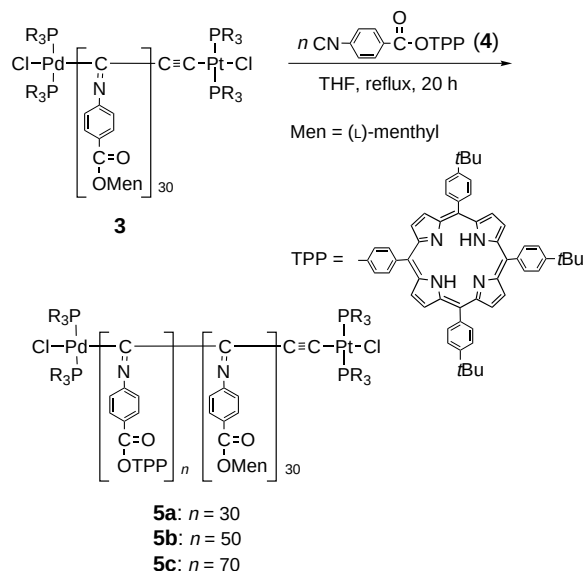
Fumie Takei, Hiroko Hayashi, Kiyotaka Onitsuka, Nagao Kobayashi, and Shigetoshi Takahashi*

There has been considerable interest in helical chiral polymers because of their unique functions that are applicable to a wide range of scientific disciplines, such as molecular recognition and asymmetric syntheses.^[1] Although the helical structure is often found in biopolymers, only a limited number of artificial polymers that maintain a stable helical conformation in solution have so far been reported. Polyisocyanide with bulky substituents is a representative example of such helical polymers.^[2] In recent years, interesting studies on the selective syntheses of single-handed helical polyisocyanides using chiral monomers, chiral initiators, and chiral additives have been reported.^[3–6] Many problems associated with helical

polymers, however, still remain to be solved. One such problem is the determination of the helical sense. Although theoretical circular dichroism (CD) calculations provide useful information on the helical sense, experimental determination of the helical sense is quite rare.^[7, 8] We previously developed a living polymerization of aryl isocyanides by the use of a Pd/Pt μ -ethynediyl complex (**1**) as an initiator.^[9] This living polymerization system is applicable to aryl isocyanides bearing various kinds of substituents, and poly(aryl isocyanide)s with porphyrin pendants in their side chains have been prepared.^[10] Herein we present a novel method of determining the helical sense of poly(aryl isocyanide)s that is based on exciton-coupled CD of the porphyrin Soret band.

It is well-known that the CD sign arising from exciton coupling is a useful probe for the assignment of the absolute configuration of chiral organic molecules.^[11] Porphyrin derivatives are one of the best candidates since they exhibit a sharp and intense absorption band (the Soret band) at around 420 nm.^[12] Thus, we started our study from the preparation of helical chiral poly(aryl isocyanide)s having porphyrin pendants. Since we had already shown that helical chiral poly(aryl isocyanide)s are selectively synthesized by block copolymerization between chiral and achiral isocyanides^[13], aryl isocyanide (**4**), which has a tetraphenylporphyrin derivative linked through an ester group,^[10] was polymerized using a helical chiral initiator (**3**; $M_n = 7000$, $M_w/M_n = 1.12$, $\Delta\epsilon_{364} = 9.60$ dm³ cm⁻¹ mol⁻¹) prepared from complex **1** and 30 equivalents of the chiral isocyanide (**2a**) with a (L)-menthyl group.

Treatment of **4** with **3** in refluxing THF for 20 h resulted in the quantitative formation of block copolymers (**5a–5c**) with a narrow polydispersity index (Scheme 1). The CD spectra of



Scheme 1.

the resulting polymers **5a–5c** exhibited a Cotton effect at 364 nm, which is characteristic of helical chiral polyisocyanides and assignable to the $n-\pi^*$ transition of the imino chromophore.^[2] The $\Delta\epsilon_{364}$ values of **5a–5c** are smaller than that of the helical chiral initiator **3**, but almost constant and

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independent of the degree of polymerization (Table 1). Chiroptical properties of helical chiral poly(aryl isocyanide)s are strongly affected by substituents on the aromatic ring, while a decrease in the $\Delta\epsilon_{364}$ values with an increase in the degree of polymerization indicates that the helical sense of the

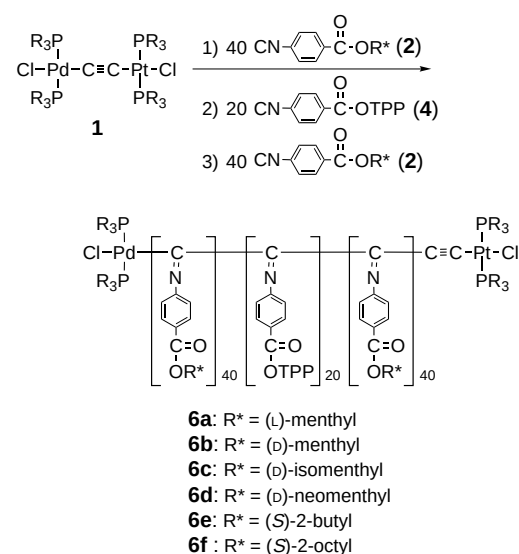
Table 1. Polymerization of porphyrin isocyanide **4** by chiral oligomer complex **3**.

polymer	<i>n</i>	$M_n^{[a]}$	$M_w/M_n^{[a]}$	$\Delta\epsilon_{364}$ [dm ³ cm ⁻¹] ^[b]
5a	30	10300	1.16	5.40
5b	50	15300	1.16	5.29
5c	70	19000	1.15	5.68

[a] Determined by gel-permeation chromatography using polystyrene standards. [b] In CHCl₃ at room temperature.

block copolymers is not well-controlled by the helical chiral initiator **3**.^[13] In the present case, the constant values of $\Delta\epsilon_{364}$, independent of the degree of polymerization, clearly show that porphyrin isocyanide **4** was polymerized with a high helical-sense selectivity to give block copolymer **5** having a predominantly single-handed helical structure. It is noteworthy that the polymer block composed of **4**, which possesses *para* substituents on the porphyrin ring forms a stable helical structure, whereas the analogous polymer block with cyclohexyloxycarbonyl pendants does not maintain a helical conformation as a result of insufficient steric bulkiness. An intense Cotton effect with exciton coupling arising from the Soret band was observed in the CD spectra of **5a–5c**. However, uncertainty remains in determining the helical sense of the main chain on the basis of the CD sign since the chain end of the polymer, in which the porphyrin chromophore is also situated, would be relatively flexible.^[13]

Thus, we have designed a triblock copolymer (**6**), in which porphyrin units line up as pendant groups only in the central part of the main chain, thus keeping a rigid helical conformation. This triblock polymer was prepared by successive polymerization of chiral and achiral monomers **2** and **4** (Scheme 2). Figure 1 shows the electronic absorption and the



Scheme 2.

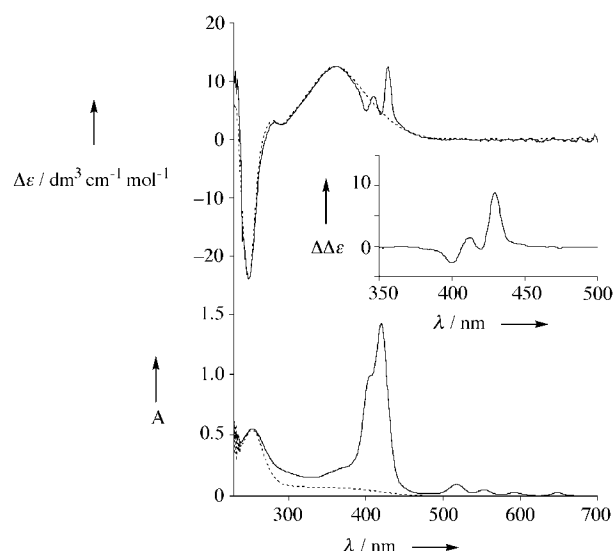
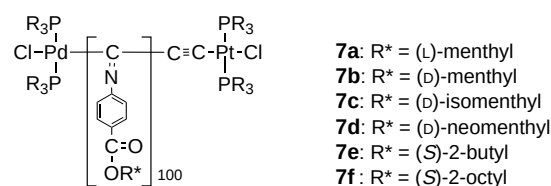


Figure 1. Electronic and CD spectra of triblock copolymer **6a** and homopolymer **7a** in CHCl₃ at room temperature (—: **6a**, ---: **7a**). The inset indicates the subtraction of the CD spectrum in the Soret band region ($\Delta\Delta\epsilon = \Delta\epsilon(\mathbf{6a}) - \Delta\epsilon(\mathbf{7a})$).

CD spectra of **6a** in chloroform along with those of homopolymer **7a** prepared from **2a**. Homopolymer **7a** has a weak broad absorption band between 300 and 500 nm in



addition to a definite peak at 253 nm.^[13] Copolymer **6a** containing tetraphenylporphyrin units, on the other hand, showed several absorption peaks characteristic of a metal-free porphyrin: namely, Soret bands at 405 and 419 nm and four weak bands between 500 and 670 nm (the so-called Q bands), in addition to a peak at 253 nm, which was also seen for **7a**.^[10] The CD spectrum of **7a** consists of a broad positive envelope and a sharp trough corresponding, respectively, to the absorption shoulder at 364 nm and peak at 253 nm. The CD spectrum of **6a** is essentially similar in shape except in the Soret region (380–450 nm), which indicates that the helicity of **6a** and **7a** is the same. Subtraction of the CD spectrum of **7a** from that of **6a** (the inset in Figure 1) showed a positive-to-negative pattern (the positive CD couplet) on going from longer to shorter wavelengths, and corresponds to the Soret band. Thus, the CD spectrum in this region of copolymer **6a** is produced by the superimposition of this positive CD couplet and the broad CD envelope originating from the homopolymer main chain. Triblock copolymers with a different composition of **2a** and **4** were systematically prepared down to **2a/4/2a** = 49/2/49. As the content of the porphyrin monomer **4** decreased, the intensity of the Soret band consequently decreased and the higher energy component of the two split Soret bands in the electronic spectra was lost. The triblock

copolymer (**2a/4/2a** = 49/2/49) showed a single positive couplet arising from the Soret band in the CD spectra at the same wavelength as the lower energy component of the split Soret band in **6a**, which suggests that the CD sign of the Soret band unambiguously reflects the helical sense of the main chain. Thus, the helicity of **6a**, and thus accordingly **7a**, can then be determined to be right-handed from the change of the CD sign in the Soret band region.^[11, 12]

This methodology using a triblock porphyrin copolymer has successfully been applied to the determination of the helicity of other helical chiral poly(aryl isocyanide)s (Table 2).^[14] For example, the CD spectrum of copolymer **6b** prepared from **2b** and **4** showed a negative Cotton effect at 364 nm (Figure 2). The differential CD spectrum obtained from **6b** and **7b** exhibits negative CD couplets of the Soret band. These CD

In conclusion, we have developed a novel method of determining the helical sense of poly(aryl isocyanide)s by using the porphyrin chromophore. This is the first example of the experimental determination of the helical sense of poly(aryl isocyanide)s and may be applicable to other helical polymers.

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Table 2. CD signs and helical sense of triblock copolymers **6**.

polymer	R*	$M_n^{[a]}$	$M_w/M_n^{[a]}$	$\Delta\epsilon_{364}^{[b]}$	2nd Cotton effect ^[c]	1st Cotton effect ^[c]	Helical sense
6a	(L)-menthyl	15 300	1.10	+	–	+	<i>P</i>
6b	(D)-menthyl	13 800	1.10	–	+	–	<i>M</i>
6c	(D)-isomenthyl	13 300	1.10	–	+	–	<i>M</i>
6d	(D)-neomenthyl	13 700	1.09	–	+	–	<i>M</i>
6e	(S)-2-butyl	13 700	1.14	–	+	–	<i>M</i>
6f	(S)-2-octyl	15 000	1.09	–	+	–	<i>M</i>

[a] Determined by gel-permeation chromatography using polystyrene standards.
[b] In CHCl₃ at room temperature. [c] The sign of the Soret band in the differential CD spectra between triblock copolymers **6** and homopolymers **7**.

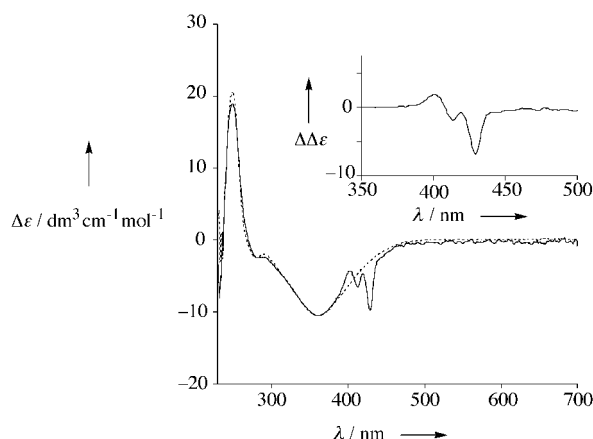


Figure 2. CD spectra of triblock copolymer **6b** and homopolymer **7b** in CHCl₃ at room temperature (—: **6b**, ---: **7b**). The inset indicates subtraction of the CD spectrum in the Soret band region ($\Delta\Delta\epsilon = \Delta\epsilon(\mathbf{6b}) - \Delta\epsilon(\mathbf{7b})$).

spectra are exactly mirror images of those of **6a** and **7a**, which suggests that **6b** has a left-handed helical structure. Comparison of the sign of the $\Delta\epsilon_{364}$ band to the helical sense determined by the CD sign of the exciton coupling of the Soret band reveals that the positive $\Delta\epsilon_{364}$ band is indicative of a right-handed helix, while the negative signal indicates a left-handed helix.^[11, 12] It should be noted that the present relationship between the sign of the $\Delta\epsilon_{364}$ band and the helical sense of poly(aryl isocyanide)s is opposite to that assigned in a previous study^[15] in which it was estimated from the theoretical CD calculation of poly(*tert*-butyl isocyanide)s.^[7]

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Redox Activation of a Polyaniline-Coated Cantilever: An Electro-Driven Microdevice**

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The integration of chemical activity with micromechanical force sensors has opened up fundamentally new approaches for the development of novel microdevices. While the atomic force microscopy (AFM) lever is a sensitive spring that undergoes mechanical bending and acts as a force sensor, the coupled chemical component may be used to activate the forces on the cantilever. The AFM optical detection system can be used as a sensitive detector for the cantilever movement or deflection as a result of forces exerted by the chemical element on the cantilever. With the development of micro-mechanical sensors over the past decade, it is now possible to measure forces below 1 pN (10^{-12} N). The advantages of using cantilever sensors lies in their dimensions: typically several hundred microns long and 0.5 to 1 μm thick. These miniature dimensions give rise to small spring constants (typically 0.1–10 N m^{-1}) and high resonance frequencies (10 kHz–1 MHz) which translate to high sensitivity and fast response times. The use of AFM cantilevers as sensors has already been demonstrated in various applications.^[1–3] Temperature, power, and surface-energy changes of 10^{-5} K, 10 pW, and 20 fJ, respectively, were detected with a bimetallic-strip coated cantilever.^[4] Mass changes occurring on the cantilever,^[5] down to 1 pg, measurement of the surface stress associated with an electrochemically deposited metal monolayer on the cantilever,^[6, 7] and the determination of binding energies^[8] enable the characterization of chemical reactions by force responses of the modified cantilevers. Recently, force interactions on cantilevers were employed to characterize protein binding^[9] and particularly the specific DNA hybridization^[10] on a cantilever surface.

In all of the described systems, the principle is that the cantilever will deflect when subjected to a force or moment. In systems where surface stress in layers adsorbed on one side of the cantilever exert the force on the cantilever, one may use the Stoney's formula [Eq. (1)] to relate the cantilever deflection to changes in the surface stress, where $\Delta\sigma$ is the stress difference between the two sides of the cantilever, ΔZ is the

$$\Delta\sigma = \frac{Et^2}{3(1-\nu)L^2}\Delta Z \quad (1)$$

tion to changes in the surface stress, where $\Delta\sigma$ is the stress difference between the two sides of the cantilever, ΔZ is the

deflection of the free-end of the cantilever, L is the length, t is the thickness, E is Young's modulus, and ν is the Poisson ratio of the cantilever.

Here we report the development of an electro-driven micromachine by the electrochemical deposition of polyaniline^[11, 12] on one side of the cantilever. Upon oxidation of the polymer, the cantilever is subjected to stress, a result of the electrostatic repulsion of the polymer chains and of a polymer swelling process that results in the deflection of the cantilever. Reduction of the oxidized polymer will release the stress and the cantilever will retract to its original position.

By the cyclic oxidation and reduction of the polymer, the cantilever is reversibly deflected from and restored to the original position, respectively. We are able to monitor the kinetics of swelling and shrinking of the polymer film by following the time-dependent deflection of the cantilever.

The electrochemical liquid cell depicted in Figure 1 consists of an Au-coated cantilever, a gold wire, and a silver wire which operate as a working electrode (WE), a counter electrode (CE), and a quasi-reference electrode (RE), respectively. The

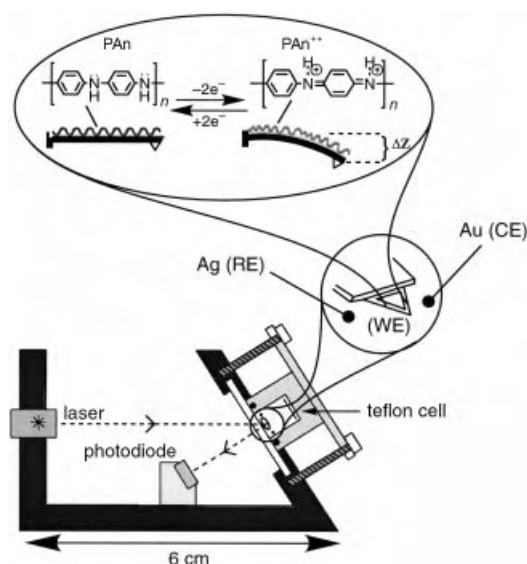


Figure 1. The system used for in situ electrochemically induced stress measurements on the cantilever. Inset shows the reversible electrochemical oxidation–reduction of the polyaniline film and the resulting lever deflection, see text for full details.

cantilevers employed in our experiments are commercially available triangular Si_3N_4 AFM cantilevers coated on one side with approximately 40 nm of Au. The cantilevers have a length of 160 μm and a thickness of 0.6 μm . Using Equation (1) we find that for these levers a deflection of the end of the lever by 1 nm (10^{-9} m) corresponds to a surface stress of 1.7 N m^{-1} . Given that the sensitivity of the deflection sensor is approximately 0.1 nm, then a practical limit for surface-stress measurements in liquids is about 0.2 N m^{-1} . The Au-coated cantilevers were cleaned by sonication in acetone then in isopropanol and rinsed with deionized water. The cantilevers were then subjected to a plasma etch (50:50 O_2 :Ar) to remove any residual contaminants. Electropolymerization of aniline on the Au surface of the cantilever was performed in a 0.1M

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$\text{H}_2\text{SO}_4/0.5\text{ M Na}_2\text{SO}_4$ solution in the presence of the aniline monomer (0.1 M) upon the application of a constant potential, $E = 0.8\text{ V}$ versus the Ag-quasi-reference electrode. Electrolysis was conducted for 10 seconds. By coulometric assay of the charge passed through the cell, and knowing the Au-surface area, the average thickness of the polyaniline (PAn) film was estimated to be 190 nm. This value is in excellent agreement with the estimated thickness of the PAn film prepared by a similar method, and measured using surface plasmon resonance spectroscopy.^[13a]

The PAn-functionalized cantilever was subjected to a multipotential-step chronoamperometric experiment in a mixture of 0.1 M $\text{H}_2\text{SO}_4/0.5\text{ M Na}_2\text{SO}_4$. The potential steps from -0.2 V to 0.8 V result in an electrochemically induced transition from the reduced polymer state, PAn, to the oxidized polymer state, PAn^{2+} , whereas the potential steps from 0.8 V to -0.2 V result in the polymer reduction ($\text{PAn}^{2+} \rightarrow \text{PAn}$). Figure 2A shows the chronoamperometric responses of the polymer film upon application of

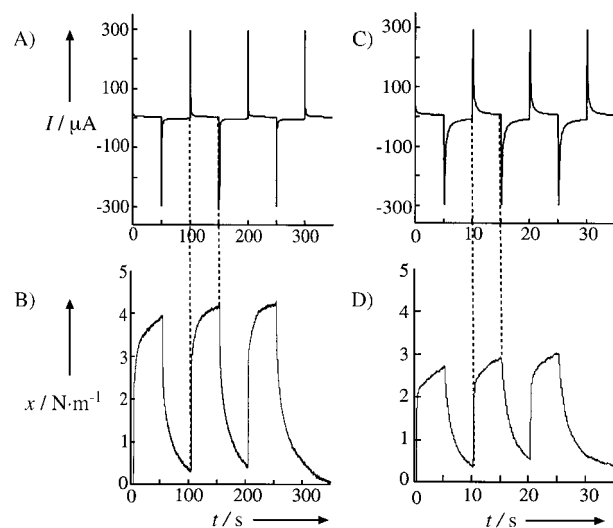


Figure 2. A) Chronoamperometric transients measured upon the multistep potential changes from -0.2 V to 0.8 V and from 0.8 V to -0.2 V with the time-gap of 50 s. B) Time-dependent cantilever stress generated upon the potential changes shown in (A). C) Chronoamperometric transients measured upon multistep potential changes from -0.2 V to 0.8 V and from 0.8 V to -0.2 V with the time-gap of 5 s. D) Time-dependent cantilever stress generated upon the potential changes shown in (C). The experiments were performed in a 0.1 M $\text{H}_2\text{SO}_4/0.5\text{ M Na}_2\text{SO}_4$ solution; anodic current is positive; (x = surface stress).

the potential steps that result in the oxidation and the reduction of the PAn film with a 50 second gap between the potential steps. Figure 2B shows the respective time-dependent stress on the cantilever resulting from the electrochemical oxidation–reduction process of the polymer. The stress values were calculated using Equation (1) from the experimental deflection signal measured simultaneously with chronoamperometric responses. It is evident that upon oxidation of the PAn film, the cantilever is deflected, which implies the development of stress on the lever. The reduction of the polymer releases the stress and the lever is restored to its original rest position. The stress on the lever and the

concomitant deflection, are reversibly stimulated by the cyclic multistep potential changes resulting in the electrochemical oxidation and reduction of the polymer film. Control experiments reveal that a bare Au-covered cantilever is not deflected upon performance of the similar multistep chronoamperometric experiment. Also, the application of the same potential step sequence on the PAn-modified cantilevers in 0.1 M phosphate buffer ($\text{pH} = 7.0$), conditions where the PAn is redox inactive, does not yield any stress (or deflection) on the lever. These results indicate that the oxidation and subsequent reduction of the polymer film control the cyclic stress exerted on the cantilevers upon the application of the multistep potential sequence on the electrode. Close examination of the stress developed on the lever (Figure 2B) reveals that upon oxidation of the polymer to the PAn^{2+} state, an instantaneous increase in the stress on the lever is observed to approximately 2.3 N m^{-1} followed by a time-dependent increase in the stress to about 3.9 N m^{-1} after approximately 50 seconds. The rapid increase in the stress on the lever is attributed to electrostatic repulsion between the oxidized, positively charged polymer chains. The slow increase in stress on the lever is attributed to swelling of the PAn^{2+} film. The swelling and shrinking of polyaniline films on electrode supports resulting from redox-transformations is well established.^[13] In a recent study^[13a] employing surface plasmon resonance (SPR) spectroscopy, we demonstrated that the oxidation of a PAn film to PAn^{2+} is accompanied by a swelling process exhibiting a rate constant of $k_{\text{sw}} = (3.0 \pm 0.3) \times 10^{-4}\text{ s}^{-1}$. Kinetic analysis of the time-dependent stress changes on the lever reveals that this is a first-order process with a rate constant corresponding to $k' = (2.8 \pm 0.3) \times 10^{-4}\text{ s}^{-1}$, very similar to the swelling rate constant observed by SPR. Similarly, the retraction of the lever to its original position upon the reduction of the film ($\text{PAn}^{2+} \rightarrow \text{PAn}$) reveals an instantaneous release of the stress, followed by a substantially slower time-dependent decrease in the stress, Figure 2B. Our SPR study has revealed that reduction of the PAn^{2+} polymer is accompanied by shrinking, $k_{\text{sh}} = (5.0 \pm 0.5) \times 10^{-4}\text{ s}^{-1}$. Kinetic analysis of the time-dependent stress release on the lever upon the reduction of PAn^{2+} to PAn reveals that it is a first-order process, $k'' = (6.0 \pm 0.5) \times 10^{-4}\text{ s}^{-1}$, very similar to the rate of shrinking of the reduced polymer. Thus, the stress induced on the levers upon oxidation of the polymer film to the PAn^{2+} state is attributed to electrostatic repulsions between charged polymer chains, and to the swelling of the polymer film as a result of its oxidation. The detailed kinetic analysis of the slow deflection and retraction processes of the lever are provided as Supporting Information.

Figures 2A and C show the transient-current responses of the PAn-modified cantilever upon application of the multistep potential changes using different intervals between the steps. Integration of the resulting current responses, indicates that the charge associated with the oxidation of PAn to PAn^{2+} is independent of the oxidation–reduction time width, which suggests that the PAn^{2+} content is similar in both systems. Figures 2B and D show the cyclic stress responses of the cantilever subjected to the multipotential pulses of different time widths. The immediate stress developed on the polymer-functionalized lever upon application of the 5 s potential-

pulse gap, around 2.3 Nm^{-1} , is almost identical to the instantaneous stress developed on the lever upon the application of the 50 s potential pulse gap. This is consistent with the electrostatic repulsive interactions in the two polymer films being similar because of identical surface coverage of the oxidized polymer. The stress on the polymer subjected to the 50 s potential step continues to increase with time as a result of the swelling process, whereas the swell-induced stress on the polymer-functionalized lever, on which the 5 s potential-step is applied, is prohibited.

The chronoamperometric transients observed upon the oxidation (or reduction) of the polymer (cf. Figure 2C), reveal, however, that the oxidation (or reduction) of the polymer film proceeds in about 5 s. Thus, further shortening of the potential-step time interval is anticipated to lead to incomplete oxidation of the polymer and to a decrease in the yield of the PAn^{2+} product. This would yield lower repulsive interactions and lower stress on the lever as the time interval of the potential step decreases. Figure 3 shows that the surface stress on the lever decreases, as the potential-step pulse is shorter. At pulse widths shorter than 10 ms no deflection of the lever is observed, which implies that the response-time of the electrochemically driven microdevice is $\tau = 10 \text{ ms}$.

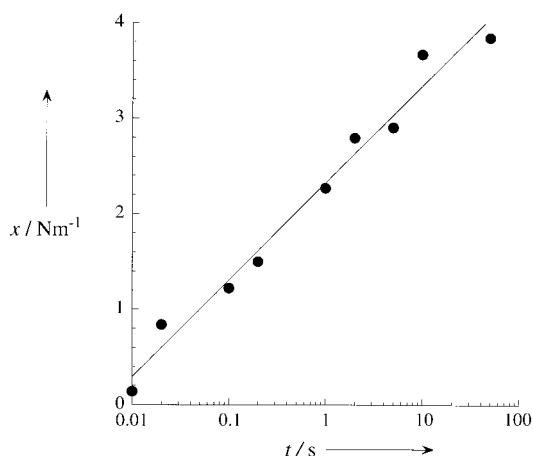


Figure 3. Saturated cantilever stress value as a function of the time between the potential steps. The potential steps from -0.2 V to 0.8 V and from 0.8 V to -0.2 V were applied on the polyaniline-modified cantilever immersed in a $0.1 \text{ M H}_2\text{SO}_4/0.5 \text{ M Na}_2\text{SO}_4$ solution; (x = surface stress).

In conclusion, we have designed an electrically driven micromachine where a polyaniline-functionalized cantilever is reversibly deflected and returned to a rest position as a result of cyclic potential steps. The degree of lever deflection (or stress) is controlled by the electrostatic repulsive inter-

actions in the polymer and the swelling of the film. One may envisage such electropowered levers as microactuators, micropumps, or microrobotic elements. As different other stimuli such as light,^[14] thermal,^[15] or chemical,^[16] may induce the swelling of polymer films, the tailoring of other signal-triggered microdevices is envisaged. The method presented here complements recent activities to fabricate microactuators^[17] and microrobots.^[18] With all these signal-triggered devices, new functional sensors, biosensors, and “smart” micromachine devices are envisaged.^[19]

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